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May 2014

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- A summary of the competitive landscape and how new drug candidates may fit into existing treatment paradigms.
- An analysis of drug characteristics and likelihood of approval (LOA) for drugs in development.
- Discussion of drug targets and promising experimental agents in development.

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May 2014

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- Dendritic cell (DC) therapies
- T-cell therapies (CAR-T)
- Cancer vaccines

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2014 Pre-ASCO Report

2014 ASCO Meeting
May 30 - June 3 | Chicago, Illinois

25,000+ attendees
1,000+ talks
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Top Talks @ ASCO
by Company

by Drug

Roche Novartis Bristol-Myers Squibb
AstraZeneca

Avastin Nivolumab MK-3475 Erbitux
Cyramza Rituxan

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Summary

Abstracts from the 50th Annual meeting of the American Society of Clinical Oncology (ASCO) were released May 14th at 5pm EDT. The 2014 ASCO meeting will be held in Chicago, Illinois from May 30 through June 3, 2014.

We have bulleted some key findings from the abstracts, highlighted some stocks to watch leading up to the meeting and stocks to watch during the meeting. Also included are numerous abstracts of particular interest for your perusal and an updated ASCO planner with links to the oral presentations via the abstract number. In addition to our typical coverage, we have included an overview of key abstracts surrounding companion diagnostics and biomarker data.

While this is just a brief overview, we will be available to discuss any data of interest in further detail. Please email BioMedTracker or call your sales representative. Additionally, keep an eye out for our ASCO weekend updates and live-coverage when the meeting takes place.
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COMPANIES TO WATCH

Clovis (CLVS)
- Oral Session on May 31, 2014 presenting updated Phase I/II CO-1686 NSCLC Data (Abstract #8010).
- Also to watch: competing EGFR inhibitor from AstraZeneca, AZD9291, presenting positive NSCLC data (Abstract #8009).
- CO-1686 received Breakthrough Status from FDA; Phase II/III Program to start in 2014.
- Updated Rucaparib (PARP Inhibitor) data in ovarian cancer positive as well.
- **Bottom line – Positive for CLVS**

Incyte (INCY)
- Strong, but expected, data for Jakafi in pivotal polycythemia vera study should lead to second approved indication.
- Positive data for Jakafi in pancreatic cancer, but concern over appropriateness of subgroup stratification. INCY continuing with Phase III study in with same stratification, but under FDA SPA.
- **Bottom line – Negative for INCY**
Seattle Genetics (SGEN)
- Top-line SGN-CD19A Phase I results demonstrate clinical efficacy in B-cell NHL.
- Several other presentations featuring Antibody-Drug-Conjugate (ADC) program (RG7599, Polatuzumab).
- Robust early-stage pipeline and continued strength of ADC technology.
- **Bottom line – Positive for SGEN**

Acceleron (XLRN)
- First data for key drug in Acceleron pipeline.
- Modest top-line data in both renal cell and head & neck cancer.
- Unclear efficacy for novel bone morphogenetic protein (BMP) target in oncology.
- **Bottom line – Neutral for XLRN; more information needed**

ImmunoGen (IMGN)
- IMGN853: some clinical efficacy in ovarian cancer, but recent vintafolide failure raises concerns about folate receptor mechanism of action.
- IMGN529: Preliminary data for non-Hodgkin's lymphomas suggests efficacy, but company needs to iron out safety questions.
- **Bottom line - Neutral for IMGN; questions about early-stage pipeline**

Pharmacyclics (PCYC)
- Robust Imbruvica median duration of response in patients from a PhIb/II trial after 3 years of follow-up.
- Preliminary ABT-199 data similar to Imbruvica, but associated tumor lysis syndrome is positive for PCYC.
- Poor AE profile of GS-9973+idelalisib combo closes the door on future development of combo. Positive for PCYC.
- **Bottom line – Positive for PCYC**
BIOMEDTRACKER ANALYSES

Here we provide our commentary on some selected presentations.

ANTI-PD-1 CHECKPOINT INHIBITORS

MEDI-4736 (AstraZeneca (AZN); Phase III)
Abstract #3001*: A phase 1 study of MEDI4736, an anti–PD-L1 antibody, in patients with advanced solid tumors.

Abstract #3002*: Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody.

MEDI-4736 is a relative newcomer to the anti-PD-1 crowd with its first Phase III study initiated just last month for NSCLC and little public data released. In the abstracts, updated data were released for a Phase I study providing the first quantitative response data, albeit from only 26 patients (13 NSCLC, 8 melanoma, and 5 other). Abstract #3001 reveals a reasonable 4 PRs, and a 46% disease control rate (RP + SD). These data are too early to extrapolate too much, but updated data from more patients could be available at the actual meeting presentation. Additionally, safety data from 105 patients are presented in Abstract #3002. Importantly, no discontinuations were reported despite 33% of patients experiencing a treatment-related AE (7% Grade 3 or above) suggesting an acceptable safety profile.

Along with the ASCO abstract releases, a collaboration was announced today to evaluate the combination of MEDI-4736 and INCB24360, an IDO inhibitor from Incyte. IDO inhibitors are an emerging class of immunotherapies gaining wide-spread attention although still in early development.

MK-3475 (Merck (MRK); BLA)
Abstract #LBA9000*: Efficacy and safety of the anti-PD-1 monoclonal antibody MK-3475 in 411 patients (pts) with melanoma (MEL).

MK-3475 is a PD-1 antibody for which a BLA has already been filed in melanoma. Although a number of minor updates were released, the primary abstract of interest is LBA9000 will present the first large dataset from 411 patients from either the Phase II – Study 002 evaluating the drug against chemotherapy or the Phase III Study 006 that has Yervoy as an active comparator.

Nivolumab (BMS-936558; Bristol-Myers Squibb (BMY); Phase III)
Abstract #LBA9003: Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL).
Nivolumab is an anti-PD-1 antibody being developed aggressively by BMY. Fewer major presentations for nivolumab are being featured at ASCO this year, but the first survival data from the Phase Ib - Study 004 of the combination with Yervoy (ipilimumab) in melanoma will be presented as a Late Breaking Abstract, so no data were available in advance (Abstract #LBA9003).

In renal cell cancer, some important data were released including the first Phase II data from a study in patients with clear cell RCC (Abstract #5009) as well as top-line data from the Phase I – CheckMate 016 combination study (Abstract #5010). The Phase II data show some characteristics of immune therapies including a lack of a strong dose response for PFS and ORR. Median overall survival was only reached in the lowest dose group (18.2 months), but the 2 and 10 mg/kg groups will likely have slightly higher, but roughly similar, OS numbers. Ultimately, if nivolumab efficacy in RCC is similar to its efficacy in other indications, these numbers will probably be secondary to the actual duration of response. So far, PD-1 inhibitors have resulted in modest median OS numbers, but have resulted in remarkably long survival for a fraction of patients. Thus, the shape of the actual survival curves (and a trend towards a long survival “tail”) will be key if presented at the meeting.

The CheckMate 016 study (Abstract #5010) evaluated a combination of nivolumab with sunitinib, pazopanib, or ipilimumab. The abstract shows early signs of activity with ORRs of 52% (with sunitinib) and 45% with pazopanib. PFS at 24 weeks was encouraging at 78% and 55% with sunitinib or pazopanib, respectively. Some dose-limiting toxicities were observed including 4 of 20 patients in an expanded pazopanib arm. Nevertheless, most AEs appeared manageable.

In lung cancer, top-line data were available from the Phase I – CheckMate 012 study evaluating nivolumab in chemotherapy-naïve patients either as a single agent or combination therapy with other agents including Yervoy. Abstract #8024 indicates an overall ORR of 30% which is impressive, especially considering many immunotherapies have not fared well in NSCLC. These results are also in-line with the early data from the Phase Ib – 003 study across tumor types that generated so much excitement at the last two ASCO meetings. Abstract #8023 focuses on the CheckMate 012 patients from the Yervoy combination arm of the study and reveals a 22% ORR which, of course, is derived from a smaller sample size and is thus generally in line with the overall results. Other details from the study are also described in Abstracts #8113 and #8022.

Along with the abstract releases, BMY announced a collaboration with Celldex to evaluate a combination of nivolumab with varlilumab, an anti-CD27 antibody in multiple tumor types. Nivolumab also gained Breakthrough Therapy Designation for Hodgkin’s Lymphoma.

Other nivolumab abstracts include #5012, #5511, #4504, 8112, and #9002.

**Pidilizumab (CT-011; CureTech; Phase II for Melanoma)**

Abstract #9001: Phase 2, multicenter, safety and efficacy study of pidilizumab in patients with metastatic melanoma.

Little information had been released for pidilizumab which is unique among the PD-1 therapies in its development for DLBCL which has already reached Phase II study. At ASCO, updated data will be presented from a Phase II study in melanoma patients. The abstract presents similar response (10%) and survival data (64.5% at 12 months) as a previous disclosure but also provides new details on various
subgroups including B-RAF V600 WT patients (69.3% survival at 12 months). The abstract also includes the first safety details.

It will be interesting to learn more details on pidilizumab in general and why it appears to be faring worse than other PD-1 antibodies. The low 10% response rate is concerning, and it should be noted that development was suspended in colorectal cancer last year (although, again, no clinical data were ever released).

**RG7446 (Roche; Phase II for Bladder Cancer)**

*Abstract #5011: Inhibition of PD-L1 by MPDL3280A and clinical activity in pts with metastatic urothelial bladder cancer (UBC).*

Unlike the other PD-1 therapies listed above which target the PD-1 receptor, RG7446 targets the PD-L1 ligand. RG7446 is already in Phase III trials for NSCLC, but the primary presentation of interest at this year’s ASCO reports new data on bladder cancer patients from the Phase I solid tumors. Positive data had long been released from the study showing early efficacy signals in melanoma and NSCLC patients. Abstract #5011 now reveals an impressive 50% ORR (1 CR and 9 PRs) in 31 urothelial bladder cancer patients. The abstract indicates that updated data will be presented at the meeting, including details on correlations with PD-L1 expression status.

**ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)**

**Blinatumomab (Amgen (AMGN); Phase III)**

*Abstract #7005*: Confirmatory open-label, single-arm, multicenter phase 2 study of the BiTE antibody blinatumomab in patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL).

Top-line results for the Phase II confirmatory trial of the bispecific antibody blinatumomab for r/r ALL were presented in an ASCO abstract. Of the 189 patients enrolled in the trial, 43% (82 patients) had a complete response or complete response with partial blood count recovery (CR/CRh), the primary endpoint of the study. CR/CRh rates of at least 30% were observed in all groups when patients were analyzed by number of prior salvage regimens, including the difficult subgroup of patients who had 2+ prior salvages or were primary refractory. This response rate compares favorably to late-line cytotoxic agents available for ALL, including Marqibo (~15% CR/CRh in patients failing 2+ lines of treatment, or 1+ lines of salvage).

Given the lack of treatment options for r/r, Ph-negative ALL patients, we are increasing the LOA by another 1%.

**BREAST CANCER**

**Neratinib (Puma (PBYI); Investigator Initiated)**

*Abstract #528: TBCRC 022: Phase II trial of neratinib for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer and brain metastases (BCBM).*
Neratinib had little effect on breast cancer brain metastases in this trial, with an overall CNS response rate of only 7.5%. Most of these patients failed previous Tykerb treatment; some physicians use Tykerb rather than HER2-directed antibodies in HER2+ patients with brain metastases in the belief that the EGFR inhibitor will cross the blood-brain barrier. Activity in brain mets would have been a differentiating factor for neratinib in the HER2-targeted therapy space, which is currently dominated by highly-effective, Roche-sponsored biologics.

We are lowering the LOA by 1% in breast cancer.

**Trebananib (Amgen (AMGN); Phase II)**

*Abstract #502: A phase 1b study of trebananib plus paclitaxel (P) and trastuzumab (T) in patients (pts) with HER2+ locally recurrent or metastatic breast cancer (MBC).*

Although the number of patients in this open-label, Phase Ib trial was low, AMGN reported highly positive results for trebananib in the first-line treatment of metastatic breast cancer. Patients receiving trebananib + Taxol + Herceptin had objective response rates of 80%; most responses were PRs, but 3/17 patients had CRs in the higher dose group. Patients in the higher dose group had a mPFS of 18.7 months. For comparison, patients receiving first-line Taxol + Herceptin (in Roche-sponsored trials) had an overall response rate of 38% with a median time-to-progression of 6.7 months, according to the Herceptin prescribing information.

Adverse events in this trial were generally consistent with those reported for Taxol + Herceptin, with the exception of relatively high rates of (low-grade) peripheral edema and peripheral neuropathy. Both of these are less common side effects of Taxol + Herceptin treatment. In larger trials for ovarian cancer, trebananib did not cause VEGF class-type adverse events, such as GI perforations and hypertension. Recurrent varian cancer patients receiving trebananib had a modest but statistically significant improvement in mPFS.

We are increasing the LOA by 10% and look forward to later-phase data on this drug.
CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) / SMALL CELL LYMPHOCYTIC LYMPHOMA (SLL)

ABT-199 (AbbVie (ABBV); Phase III)
Abstract #7013: ABT-199 (GDC-0199) combined with rituximab (R) in patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): Interim results of a phase 1b study.

ABBV released top-line data for a Phase Ib trial of ABT-199 + rituximab for CLL and updated data for a Phase I trial of monotherapy ABT-199 for CLL/NHL.

Top-line results for ABT-199 + rituximab were positive in CLL. CR/PR rates were 39%/39% in this limited number of patients, which is comparable to the overall response rate (ORR) seen in the Phase III trial of idealalisib + rituximab (81%) and somewhat higher than the ORR seen with Imbruvica + rituximab after a similar median follow-up time. As with these other two drugs, ABT-199 is effective in patients with the high-risk 17p deletion.

For monotherapy ABT-199, CLL patients also had high response rates (79%, with 22% CRs), with a median duration of response of >20 months. Though it is difficult to compare between trials, this DOR is lower than that reported for PCYC-1102 Phase Ib/II study of monotherapy Imbruvica (25 months for del17p patients and not reached in the overall patient population).

Tumor lysis syndrome (TLS) was a serious complication reported early in ABT-199 clinical development. The modified dosing scheme implemented by ABBV may have limited serious TLS events, but one death was reported in the trial of ABT-199 with rituximab. ABBV’s anticipated late-stage clinical trial program.
includes trials for ABT-199 monotherapy and ABT-199 in combination with monoclonal agents, including rituximab and Roche’s third-generation anti-CD20 agent obinutuzumab.

Given these data, we are increasing the LOA by 4%. ABT-199 has certainly demonstrated efficacy in early-phase trials, but this agent will need to compete with Imbruvica and idelalisib, which will both be marketed by the time pivotal ABT-199 clinical trials provide top-line data.

**Imbruvica (ibrutinib; Pharmacyclics (PCYC); Approved)**

*Abstract #7014: Independent evaluation of ibrutinib efficacy 3 years post-initiation of monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic leukemia including deletion 17p disease.*

A key question regarding Imbruvica is the patient duration of response (DOR), as this will affect predicted sales figures, may influence future prescribing practices, and provides a point of reference for drugs in the pipeline. Results from 3 years of Imbruvica monotherapy treatment (PCYC-1102 trial) showed that high-risk del17p patients had a mDOR of 25.0 months; the mOR was not reached for the study population overall. This mDOR sets a high bar for other CLL drugs, including idelalisib, ABT-199, and earlier-phase compounds.

**MELANOMA**

**INCB24360 (Incyte (INCY); Phase II)**

*Abstract #3010: Preliminary results from a phase 1/2 study of INCB024360 combined with ipilimumab (ipi) in patients (pts) with melanoma.*

Combination therapies are generating huge interest, especially with immunotherapies which may complement each other through multiple pathways of T-cell activation. These are top-line data from a study evaluating the IDO inhibitor, INCB24360, with the immune checkpoint inhibitor, Yervoy (BMY; approved). IDO (indoleamine 2,3-dioxygenase) catalyzes the rate-limiting step in tryptophan degradation and is proposed to inhibit T-cell activation in the tumor microenvironment, while Yervoy inhibits the well-characterized CTLA-4 immune checkpoint. These are limited data from a very small sample size but do show promising activity with 6 of 8 patients showing a tumor reduction by the first evaluation (especially promising considering immunotherapies typically have a long lag time for efficacy).

Other IDO inhibitors are in development including NLG-919 and indoximod (both NLNK), although only a Trial Progress abstracts are schedule for presentation on either drug and should have little new information. Nevertheless, ASCO may be a venue to gauge sentiment on IDO inhibitors in general as well as their suitability in combination therapies.

**PV-10 (Pro vectus (PVCT); Phase II)**

*Abstract #9027: Efficacy of intrale sional Rose Bengal in patients receiving injection of all existing melanoma in phase II study PV-10-MM-02.*
Provectus, like a few other companies, has been trying to latch on to the excitement surrounding immunotherapies in its promotion of PV-10. PV-10 is a formulation of the small molecule, rose bengal, which has long been used as a biological stain. Although the specific mechanism of action to kill tumor cells is not entirely clear, PV-10 is believed to accumulate in the lysosomes of rapidly growing tumor cells and cause cell lysis. However, more recently, the company has been promoting a tumor specific immune response associated with PV-10 that is most likely a secondary effect of lysing tumor cells.

It is perhaps not surprising, that the company’s press release accompanying its ASCO abstracts is somewhat hyperbolic in proclaiming the “exceptional complete response rates” in two PV-10 abstracts (both poster presentations). While the complete response rates are apparently quite high (near 50%), they are derived from a small subgroup of patients. Previously, the company disclosed an overall CR of 25%. While the market reaction appears to be quite favorable for PVCT, we will cautiously await more definite results. It is unclear, though, when those might be forthcoming as a Phase III study that was announced several years ago has yet to be initiated.

**NON-HODGKIN’S LYMPHOMA (NHL)**

**SGN-CD19A [Seattle Genetics (SGEN); Phase I]**

*Abstract #8505: Interim analysis of a phase 1, open-label, dose-escalation study of SGN-CD19A in patients with relapsed or refractory B-lineage non-Hodgkin lymphoma (NHL).*

These top-line Phase I results demonstrate that this antibody-drug conjugate has clinical efficacy in B-cell NHLs; we are increasing the LOA by 1%. We are interested in the breakdown of responses between the different NHL subtypes, as this will affect potential future development of the biologic.

**NON-SMALL CELL LUNG CANCER (NSCLC)**

**AZD9291 (AstraZeneca (AZN); Phase I/II)**
**CO-1686 (Clovis (CLVS); Phase I/II)**

*Abstract #8009: Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor–resistant non-small cell lung cancer (NSCLC).*

AZD9291 is an EGFR inhibitor which received the FDA’s Breakthrough Therapy Designation last month for TKI-refractory NSCLC patients, and Abstract #8009 is the first clinical data release for the drug. The fairly large Phase I/II study shows an impressive response rate (64%) and DCR (96%) in T790M+ patients. These results, along with a positive safety profile, should lead rapidly to the Phase II – AURA2 study and possibly even a Phase III study by year end. Regardless of its rapid development, AZD9291 will have to compete with CO-1686 (CLVS), another EGFR inhibitor that generated huge excitement at the last ASCO. CO-1686 is most striking in its proposed mechanism of sparing wild-type EGFR, thus avoiding the associated skin and GI toxicity. Abstract #8010 presents little new data from the very small Phase I/II study which has already had many data releases, but it will be interesting to hear audience questions and opinion regarding both EGFR inhibitors which are featured in back-to-back presentations.
OVARIAN CANCER

Rucaparib (Clovis (CLVS); Phase III)
Abstract #2573: Phase 1/2 study of oral rucaparib: Final phase 1 results.

Final results from the Phase I portion of the Phase I/II were released in an ASCO abstract. Of the breast and ovarian cancer patients enrolled in this study, only those with germline BRCA (gBRCA) mutations had a response to rucaparib, which validates the drug’s mechanism of action and helps define the patient population for later clinical trials. (Some PARP inhibitors may have activity in non-BRCA-mutated patients, and the rucaparib ARIEL2/3 trials include all high-grade ovarian cancer patients.) Robust disease control rates were observed for patients with gBRCA-mutated ovarian and breast cancer patients, particularly those who received the recommended Phase II/III dose.

We are increasing the LOA by 3% in ovarian cancer and 1% in breast cancer. We are increasing the LOA by a larger margin in ovarian cancer due to the unmet need and the responses that occurred in platinum-resistant patients.

PANCREATIC CANCER

Jakafi (ruxolitinib; Incyte (INCY); Phase III)
Abstract #4000: A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC).

Although Jakafi is well-known for its efficacy in myeloproliferative disorders (MF and PV, but not ET), it is also being developed for solid tumors and has reached Phase III study for pancreatic cancer. Initial data from the Phase II – RECAP study showed the study failed to reach its primary OS endpoint in the ITT population in combination with capecitabine. However, the company highlighted an impressive OS benefit in a pre-specified subgroup (6-month OS HR = 0.47, p=0.005) but oddly did not provide any information on the nature of that subgroup.

The ASCO abstract reveals that the study delineated the subgroup as patients with local and systemic inflammation (INFL) defined as serum C-reactive protein levels greater than the group median of 13 mg/L. In this subgroup, the OS hazard ratio was 0.47 (p=0.01) as opposed to 0.79 (p=0.25) for the ITT population. PFS was still non-significant in both the ITT and subgroup populations.

While these data are positive, we are concerned with the somewhat arbitrary stratification by the median CRP level and question whether some of the large difference between ITT population and INFL subgroup is a chance finding due to smaller sample size (n=60 for the INFL subgroup). Nevertheless, the company is moving forward with the Phase III – JANUS 1 study under a special protocol assessment (SPA) from the FDA. We look forward to discussion at ASCO on the appropriateness of this stratification.
POLYCYTHEMIA VERA (PV)

Jakafi (ruxolitinib; Incyte [INCY]; Phase III)
Abstract #7026: Results of a prospective, randomized, open-label phase 3 study of ruxolitinib (RUX) in polycythemia vera (PV) patients resistant to or intolerant of hydroxyurea (HU): the RESPONSE trial.

Jakafi made headlines as the first targeted therapy approved for the treatment of myelofibrosis. Now the Jak inhibitor is nearing approval for the related disorder, polycythemia vera (PV), which is important from a market perspective as PV is a chronic disorder with a long period of treatment. Jakafi is also set to face increased competition in MF from another Jak inhibitor, momelotinib (GILD) which has demonstrated impressive anemia responses in its Phase I/II study and could thus make inroads despite Jakafi’s sizeable developmental lead.

Incyte had already disclosed that the pivotal RESPONSE study met its primary endpoint of hematocrit control (HCT) and spleen volume (SV) reduction. The ASCO abstract now presents the first quantitative results from the study. The study demonstrated very strong efficacy with 21% of treated patients (vs 1% best available therapy) achieved both HCT with phlebotomy (PBT) and a 35% or greater reduction in spleen volume (p<0.0001) with a long duration of response (91% response at week 48). Jakafi was impressive in secondary measure as well, including complete hematologic response (24% vs 9% BAT, p=0.003). Finally, Jakafi resulted in a positive reduction in grade 3/4 anemia.

Ultimately, these results should lead to a fairly smooth approval for Jakafi in PV.
ADRENOCORTICAL CANCER

**Linsitinib, Astellas**

International randomized, double-blind, placebo-controlled, phase 3 study of linsitinib (OSI-906, L) in patients (pts) with locally advanced or metastatic adrenocortical carcinoma (ACC).

Abstract #4507

Author(s): David I. Quinn, Eric Baudin, Michael J. Demeure, Martin Fassnacht, Gary D Hammer, Srinivasu Poondru, Tanya Fleeger, Ramona Rorig, Alfredo Berruti; Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA; Institut Gustave Roussy, Villejuif, France; TGen, Phoenix, AZ; Department of Internal Medicine I – Endocrine Unit, University Hospital of Wuerzburg, Wuerzburg, Germany; University of Michigan, Ann Arbor, MI; Astellas Pharma Global Development (APGD), Northbrook, IL; Astellas Pharma Global Development, Clinical Study Manager, Northbrook, IL; Astellas Pharma, Northbrook, IL; Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Medical Oncology, University of Brescia, Brescia, Italy

**Background:** ACC is an uncommon but frequently fatal cancer. For pts with metastatic or recurrent nonoperable ACC, there are very limited treatment options. Insulin-like growth factor 2 (IGF2) overexpression occurs in >90% of ACC, hence the IGF pathway is a potential therapeutic target. We assessed the activity of a potent IGF-1 receptor TKI linsitinib in ACC.

**Methods:** In a double-blind phase III trial accruing over 21 months, pts with measurable locally advanced or recurrent ACC following 1st- or 2nd-line treatment were randomly assigned to linsitinib 150mg BID orally or best supportive care & placebo (P), in a 2:1 ratio, respectively. The primary endpoint was overall survival (OS; power 80% for ñOS from 9 to 15.6 months); secondary endpoints: PFS, disease-control & objective response rate (blinded central review by RECIST 1.1), QoL & safety/toxicity (CTCAEv4.02).

**Results:** 139 pts (median age 50yrs, 67% female, ECOG 0/1: 44.6, 51.1%) were enrolled with 90 assigned to linsitinib & 49 to P. Prior therapies included surgery: 90.6%; radiotherapy: 30.9%; mitotane: 100% & cytotoxic chemotherapy: 73.4%. The median time from diagnosis to trial initiation was 26.5 months. There was no difference between linsitinib and placebo in overall survival (median 323 vs 356d (10.8 vs 11.8); p=0.77, HR 0.94); PFS (44 vs 46d; p=0.3, HR 0.83) & DCR (32.2 vs 34.7%). However, 3 pts on linsitinib experienced PR and 8 had prolonged PFS >100d (4 on drug >400d), whereas these events did not occur with placebo. Dose modification: L: 43.3, P 29.2%. Treatment-emerged adverse events (TEAEs) occurred in 97.8 vs 93.8%, grade 5: 10.1 vs 10.4%, grade 4: 10.1 vs 2.1%, grade 3: 45.6 vs 31.3% for L vs P respectively. Common TEAEs: fatigue (33.3 vs 22.9%), nausea (26.7 vs 31.3%), vomiting (20.0 vs 20.8%), QTc prolonged (20 vs 6.3%) for L vs P.

**Conclusions:** Targeting the IGF pathway with linsitinib did not improve overall or progression-free survival in adrenocortical cancer patients, although a small subgroup of patients seemed to benefit from this drug. Timely and efficient accrual to phase III trials in rare cancers is internationally feasible. Clinical trial information: NCT00924989.
BILIARY TRACT CANCER

Recentin, AstraZeneca (AZN)

ABC-03: A randomized phase II trial of cediranib (AZD2171) or placebo in combination with cisplatin/gemcitabine (CisGem) chemotherapy for patients (pts) with advanced biliary tract cancer (ABC).

Abstract #4002

Author(s): Juan W. Valle, Harpreet Wasan, Mark Jitlal, Alison Catherine Backen, Daniel H. Palmer, Marian Duggan, David Cunningham, David Alan Anthoney, Philippa Corrie, Srinivasan Madhusudan, Anthony Maraveyas, Paul J. Ross, Justin S. Waters, William P. Steward, Charlotte Rees, Sandy Beare, Caroline Dive, John A. Bridgewater; University of Manchester, Manchester Academic Health Science Centre; Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom; Hammersmith Hospital, Imperial College Healthcare Trust, London, United Kingdom; Cancer Research UK & UCL Cancer Trials Centre, London, United Kingdom; Paterson Institute for Cancer Research, Manchester, United Kingdom; Clatterbridge Centre for Oncology NHS Foundation Trust, Merseyside, United Kingdom; Cancer Research UK & University College London Cancer Trials Centre, London, United Kingdom; Royal Marsden Hospital, Sutton, United Kingdom; St James's University Hospital, Leeds, United Kingdom; Oncology Centre, Cambridge University Hospitals NHS Foundation Trust (Addenbrooke's Hospital), Cambridge, United Kingdom; Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; Castle Hill Hospital, Hull, United Kingdom; Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; Kent Oncology Centre, Maidstone Hospital, Maidstone, United Kingdom; Department of Oncology, University of Leicester, Leicester, United Kingdom; Southampton University Hospital NHS Foundation Trust, Southampton, United Kingdom; Cancer Research UK and University College London Cancer Trials Centre, London, United Kingdom; Cancer Research UK Manchester Institute, Manchester, United Kingdom; Department of Medical Oncology, University College London Cancer Institute, London, United Kingdom

Background: ABCs exhibit increased VEGF expression, correlating with metastatic disease. Combining cediranib (which inhibits VEGFR1, 2 and 3 tyrosine kinase and VEGF-induced signaling in endothelial cells) with CisGem may improve outcome.

Methods: Pts with histo-/cytologically confirmed ABC, aged ≥18 yrs, ECOG PS 0-1 and adequate bone marrow, liver and renal function were randomized to receive Cis (25mg/m²) followed by Gem (1000mg/m²) on days 1 and 8 of a 21-day cycle (up to 8 cycles), plus either cediranib (20mg once daily [OD]) or placebo (OD), until disease progression (PD). Tumor assessment was performed 12-weekly until PD. The target hazard ratio (HR) for progression-free survival (PFS, primary endpoint) was 0.64, requiring 136 pts (for 92 PFS events, 80% power, alpha=0.2, two-sided, ITT analysis).

Results: 124 pts were enrolled (62 per arm, Apr-11 to Sep-12, study closed early due to cessation of cediranib development). Pt characteristics (cediranib vs. placebo): median age 68.0 vs. 64.5 years; 45% vs. 55% female; 19% locally advanced and 81% metastatic vs. 13% and 87%; bile duct, gall bladder, ampulla (%): 61, 32, 6 vs. 63, 31, 6; prior adjuvant chemotherapy: 3% vs. 2%; ECOG PS 0, 1: 44, 56 vs. 45, 55%. The most common grade 3-4 non-haematological adverse events (AEs) were hypertension, diarrhea and fatigue; 50% and 45% of cediranib and placebo pts experienced grade 3-4 haematological AEs, predominantly neutropenia (40 vs. 39%). Response rate (RECIST, in evaluable pts): cediranib (23/55 [43%] vs. placebo 10/53 [19%], p=0.01. With a median follow-up of 11.9 mo, PFS was not different
(median (95%-CI)): 7.7 (6.3 – 9.3) vs. 7.4 (5.7 – 8.6) mo, HR (95% CI) 0.99 (0.78 – 1.26), p=0.95; with a trend for longer OS in the cediranib arm, median (95% CI): 14.1 (10.2 – 16.0) vs. 11.9 (9.2 – 13.4) mo, HR (95% CI) 0.76 (0.50 – 1.14), p=0.19. ELISA was performed for 15 potential plasma biomarkers of which Angiopoietin-2 (HR 0.65 (0.44 to 0.97) p=0.006) and Fibroblast Growth Factor-b (HR 0.83 (0.68 to 1.00) p=0.009) were the most significant.

Conclusions: Cediranib appears to improve response rate but not PFS; effect on OS may warrant further studies. Clinical trial information: NCT00939848.

BLADDER CANCER

Cometriq, Exelixis (EXEL)
Effect of cabozantinib on immunosuppressive subsets in metastatic urothelial carcinoma.
Abstract #4501

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Background: Myeloid-derived suppressor cells (MDSC) and regulatory T cells (Treg) are major components of the immune suppressive tumor microenvironment. Both cell types promote effector T-cell dysfunction and tumor progression. The effect of cabozantinib, a tyrosine kinase inhibitor primarily targeting MET and VEGFR2 on specific immunosuppressive subsets, is unclear. In this study we assess MDSC and Tregs in patients undergoing treatment with cabozantinib and correlate with clinical response to therapy.

Methods: Peripheral blood samples were obtained from patients with advanced/refractory metastatic urothelial carcinoma undergoing treatment with cabozantinib under a clinical trial at the National Cancer Institute (NCT01688999). MDSC (CD11b+CD33+CD14-) and Tregs (CD4+CD25hi Foxp3+) were measured in 24 patients at baseline and after 2 cycles of continuous cabozantinib treatment. MDSC and Tregs were further analyzed for CD40 and PD-1, respectively, as suppressive functional markers.

Results: Patients with low Tregs at baseline had an improved partial response (PR) rate (p=0.014), progression free survival (PFS) (p=0.059) and overall survival (OS) (p=0.0071). Tregs decreased with cabozantinib treatment (p=0.015). Overall, PD-1 expression in Tregs increased after cabozantinib (p=0.011). However, patients with a PD-1 change below the median showed a strong trend to improved PFS compared to those with increased PD-1 above the median (p=0.035). The percent MDSC did not change with treatment. However, MDSC CD40 expression was increased after cabozantinib treatment compared to baseline (p=0.0005). Though, a decrease in MDSC CD40 expression after treatment was associated with an improved PFS (p=0.020).
**Conclusions:** Treg levels prior to cabozantinib treatment are predictive of therapeutic responsiveness and OS. Changes in Treg PD-1 expression and MDSC CD40 expression may be prognostic markers in patients with advanced/refractory metastatic urothelial carcinoma treated with cabozantinib.

**RG7446, Roche**

**Inhibition of PD-L1 by MPDL3280A and clinical activity in pts with metastatic urothelial bladder cancer (UBC).**

Abstract #5011

Author(s): Thomas Powles, Nicholas J. Vogelzang, Gregg Daniel Fine, Joseph Paul Eder, Fadi S. Braiteh, Yohann Loriot, Cristina Cruz Zambrano, Joaquim Bellmunt, Howard A. Burris, Siew-leng Melinda Teng, Xiaodong Shen, Hartmut Koeppen, Priti S. Hegde, Daniel S. Chen, Daniel Peter Petrylak; Barts Cancer Institute, Queen Mary University Hospital of London, London, United Kingdom; University of Nevada School of Medicine and US Oncology/Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Genentech, Inc., South San Francisco, CA; Yale Cancer Center, New Haven, CT; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Gustave Roussy, Villejuif, France; Vall d'Hebron University Hospital, Barcelona, Spain; Bladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA; Sarah Cannon Research Institute, Nashville, TN; Genentech Inc., South San Francisco, CA

**Background:** Metastatic UBC is associated with a poor prognosis and limited treatment options. PD-L1 expression is prevalent in this disease and may protect cancer cells from immune-mediated destruction by binding to its receptors PD-1 and B7.1. MPDL3280A is a human anti-PD-L1 mAb with an engineered Fc-domain designed for optimized efficacy and safety.

**Methods:** In a Ph I study, UBC pts received MPDL3280A 15 mg/kg IV q3w for up to 1 y. Objective response rate (ORR; including unconfirmed responses) was assessed by RECIST v1.1. In parallel, tumor and circulating biomarkers were evaluated to study MPDL3280A immune correlates.

**Results:** As of Sep 19, 2013, 31 UBC pts were treated with MPDL3280A. Pts were 84% male, had a median age of 66 y (42-86), 57% were ECOG PS 1 and 68% had visceral metastases. 71% received ≥ 2 prior therapies; 97% received prior platinum-based chemotherapy. Pts had received MPDL3280A for a median duration of 43 d (1-153); the majority remained on treatment as of the data cutoff. The G1-4 treatment-related AEs occurring in ≥ 2 pts were pyrexia, anemia, decreased appetite, fatigue and nausea. Related G3-4 AEs occurred in 3.2% of pts. There were no immune-related AEs. 20 PD-L1+ pts were evaluable for efficacy at time of analysis with a median follow up of 2.8 m (1.4-5). The ORR was 50% (1 CR and 9 PRs) with a median time to response of 43 d (39-82), corresponding to the first radiographic assessment. Responders included pts with visceral metastases at baseline. All responders were still responding at the time of clinical cutoff. Treatment resulted in transient increases in circulating CD8+Ki-67+ T cells and plasma proteins (eg, IL-18) upstream of IFNγ signaling, representing pharmacodynamic biomarkers of activity. Gene expression data from pretreatment tumors showed that pts who progressed had a proportionally higher myeloid gene signature (eg, IL8, CCL2). Updated data will be presented, including data from PD-L1–neg pts.

**Conclusions:** MPDL3280A was well tolerated in this pretreated UBC population. 50% of pts treated responded to treatment. Responses were rapid and on-going. Biomarker analysis revealed
pharmacodynamic markers, as well as markers of potential mechanisms of resistance to therapy. Clinical trial information: NCT01375842.

**BONE DISEASE**

*Xgeva, Amgen (AMGN)*

**Effect of denosumab versus zoledronic acid (ZA) in preventing skeletal-related events (SREs) in patients with metastatic bone disease: Subgroup analyses by baseline characteristics.**

Abstract #9501

Author(s): Allan Lipton, Karim Fizazi, Alison Stopeck, David H. Henry, Matthew Raymond Smith, Neal D. Shore, Miguel Martin, Saroj Vadhan-Raj, Kefei Zhou, Arun Balakumaran, Ada H. Braun; Penn State Hershey Medical Center, Hershey, PA; Department of Cancer Medicine, Gustave Roussy, University of Paris Sud, Cancer Campus, Grand Paris, Villejuif, France; University of Arizona Cancer Center, Tucson, AZ; Pennsylvania Hospital, Philadelphia, PA; Harvard Medical School and Massachusetts General Hospital, Boston, MA; Carolina Urologic Research Center, Atlantic Urology Clinics, Myrtle Beach, SC; Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain; Section of Cytokines and Supportive Oncology, Department of Sarcoma Medical Oncology. The University of Texas MD Anderson Cancer Center, Houston, TX; Amgen, Thousand Oaks, CA; Amgen, Inc., Thousand Oaks, CA; Amgen Inc., Thousand Oaks, CA

**Background:** There is an interest in identifying patients at risk for SREs who may benefit most from treatment with bone-targeted agents (BTA). Previous results from a subgroup analysis of three phase 3 trials demonstrated denosumab was superior to ZA in preventing SREs (pathologic fracture, radiation or surgery to bone, or spinal cord compression) regardless of baseline clinical pain symptoms or prior SRE status. This analysis assesses if denosumab is superior to ZA in delaying patients’ time to SREs across relevant baseline characteristics.

**Methods:** Patients with metastatic bone disease were randomized 1:1 to receive either SC denosumab 120 mg + IV placebo (n=2,862) or IV ZA 4 mg (adjusted for CrCl) + SC placebo Q4W (n=2,861) in double-blinded phase 3 studies. Time to first on study SRE and time to first and subsequent SREs were evaluated in patients by several baseline variables: location of skeletal metastases (mets) (axial vs appendicular), presence of visceral mets (yes/no), urinary N-telopeptide (uNTx) level (median; ≥43.5 vs <43.5 nmol/mmol), number of bone mets(<2 or ≥2), and ECOG performance status (0 or ≥1).

**Results:** Denosumab significantly delayed time to first SRE compared to ZA regardless of patients’ baseline characteristics. Similar results were noted in preventing first and subsequent SREs in all subgroups.

**Conclusions:** Denosumab significantly delayed patients’ time to SREs compared to ZA regardless of patient’s baseline status. Clinical trial information: NCT00321464, NCT00330759, NCT00321620.
Benefit of denosumab vs ZA on time to first on-study SRE.

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial bone mets only (n=1,422)</td>
<td>0.83 (0.70,1.00)</td>
<td>0.046</td>
</tr>
<tr>
<td>Appendicular bone mets only (n=753)</td>
<td>0.78 (0.61,0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td>Both axial &amp; appendicular bone mets (n=1,695)</td>
<td>0.83 (0.71,0.97)</td>
<td>0.022</td>
</tr>
<tr>
<td>≥2 bone mets (n=2,234)</td>
<td>0.81 (0.71,0.93)</td>
<td>0.003</td>
</tr>
<tr>
<td>&lt;2 bone mets (n=3,489)</td>
<td>0.84 (0.74,0.94)</td>
<td>0.003</td>
</tr>
<tr>
<td>Visceral mets (n=2,341)</td>
<td>0.80 (0.69,0.93)</td>
<td>0.003</td>
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<tr>
<td>No visceral mets (n=3,382)</td>
<td>0.84 (0.75,0.94)</td>
<td>0.002</td>
</tr>
<tr>
<td>High uNTx (n=2,553)</td>
<td>0.86 (0.76,0.98)</td>
<td>0.028</td>
</tr>
<tr>
<td>Low uNTx (n=2,553)</td>
<td>0.75 (0.65,0.86)</td>
<td>&lt;0.001</td>
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<tr>
<td>ECOG 0 (n=2,312)</td>
<td>0.82 (0.71,0.94)</td>
<td>0.006</td>
</tr>
<tr>
<td>ECOG ≥1 (n=3,398)</td>
<td>0.84 (0.75,0.94)</td>
<td>0.002</td>
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BRAIN CANCER

**Apocept, Apogenix**

Final results of APG101_CD_002: APG101 plus reirradiation versus reirradiation in the treatment of patients with progressive glioblastoma.

Abstract #2006^

Author(s): Michael Platten, Harald Fricke, Klaus Junge, Grigory Kobyakov, Tobias Martens, Oliver Heese, Benedikt Wiestler, Maximilian G Schliesser, Andreas von Deimling, Josef Pichler, Elena Vetlova, Inga Harting, Juergen Debus, Christian Hartmann, Claudia Kunz, Martin Bendszus, Stephanie E. Combs, Wolfgang Wick; Neurooncology, University of Heidelberg Medical Center, Heidelberg, Germany; Apogenix GmbH, Heidelberg, Germany; Premier Research, Darmstadt, Germany; N. N. Burdenko Neurosurgical Institute, Moscow, Russia; University of Hamburg, Hamburg, Germany; Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; CCU Neurooncology, DKFZ, Heidelberg, Germany; Institute of Pathology, Dept Neuropathology, University of Heidelberg, INF 224, and CCU Neuropathology German Cancer Research Center (DKFZ), Heidelberg, Germany; Landesnervenklinik Linz, Linz, Austria; NSI, Moscow, Russia; Department of Neuroradiology, University of Heidelberg Medical Center, Heidelberg, Germany; University Hospital Heidelberg, Heidelberg, Germany; Department of Neuropathology, Institute of Pathology, Medizinische Hochschule, Hannover, Germany; Department of Neuroradiology, University Hospital Heidelberg, Heidelberg, Germany.
Background: Preclinical data indicate antiinvasive activity of APG101, a CD95-ligand (CD95L)-binding fusion protein, and synergistic activity with radiotherapy in glioblastoma. In healthy volunteers, single doses of up to 20 mg/kg APG101 are safe.

Methods: Patients (N=91) with progressive glioblastoma after standard radiochemotherapy (± 1 second-line chemotherapy), provided a tumour diameter of 1-4 cm and time since the end of radiotherapy ≥ 8 months, were randomised 1:2 stratified for tumour diameters ≤ or > 2.5 cm between radiotherapy (36 Gy; 5 times 2 Gy per week; rRT) or rRT+APG101 (400 mg weekly i.v.) to be continued until progression. CD95L was evaluated in tumour tissue. This open-label, non-comparative phase II trial (NCT01071837) sought to demonstrate a doubling in the 6-months progression-free survival (PFS-6) rate with rRT+APG101 assuming a 15% PFS-6 rate with rRT alone. The control arm with rRT alone was added to calibrate for the PFS-6 assumption.

Results: Patient characteristics in the intention-to-treat population [N=84 (26 patients rRT, 58 patients rRT + APG101)] were balanced. The PFS-6 rates were 3.8% (95%-CI: 0.1 - 19.6) rRT and 20.7% (95%-CI: 11.2 - 33.4) for rRT+APG101 (p=0.04). Median PFS was 2.5 (95%-CI: 2.3-3.8) months and 4.5 (95%-CI: 3.7-5.4) months with a hazard ratio (HR) of 0.49 (95% CI: 0.27-0.88, p=0.0162). Cox regression analysis adjusted for tumour size revealed a HR for rRT+APG101 for death of any cause of 0.60 (95% CI: 0.36-1.01) (p=0.0559). Patients with lower methylation levels at CpG2 in the CD95L promoter in the tumour tissue had a stronger risk reduction (HR=0.13 95% CI: 0.03-0.52) when treated with APG101.

Conclusions: CD95 pathway inhibition in combination with rRT is an innovative concept with clinical efficacy. It warrants further clinical development. CD95L promoter methylation in the tumour may be developed as a biomarker. Clinical trial information: NCT01071837.

Avastin, Roche
Validation of rano criteria: Contribution of T2/FLAIR assessment in patients with recurrent glioblastoma treated with bevacizumab.
Abstract #2007

Author(s): Raymond Yi-kun Huang, Rifaquat Rahman, Whitney B. Pope, Benjamin M. Ellingson, S. Keith Anderson, Sara J Felten, Karla V. Ballman, Wenting Wu, Lakshmi Nayak, Eudocia Quant Lee, Lauren E. Abrey, Ewantiha Galanis, David A. Reardon, Timothy Francis Cloughesy, Patrick Y. Wen; Dana-Farber Cancer Institute/Brigham and Women's Cancer Center, Boston, MA; Harvard Medical School, Boston, MA; Department of Radiological Sciences, University of California, Los Angeles, Los Angeles, CA; Department of Radiological Sciences, Biomedical Physics, and Bioengineering; University of California, Los Angeles, Los Angeles, CA; Mayo Clinic, Rochester, MN; Dana-Farber Cancer Institute, Boston, MA; F. Hoffmann-La Roche, Basel, Switzerland; Dana-Farber Cancer Center Institute, Boston, MA; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA

Background: Since its introduction, the RANO criteria have been widely adopted in clinical trials for evaluating treatment response in high-grade gliomas. To date, the criteria have not been validated using outcome data from prospective trials. We examined the radiologic data of patients with recurrent glioblastoma treated with bevacizumab from the randomized phase II BRAIN trial (AVF3708g) to determine the effect of including T2/FLAIR evaluation in the RANO criteria on measurements of objective response rates (ORR) and progression free survival (PFS).
Methods: The imaging data of 163 patients with recurrent glioblastoma from the BRAIN trial were evaluated by 6 readers blinded to clinical information. The ORR and median PFS were determined using the RANO criteria and compared to those obtained without evaluating the T2/FLAIR abnormality (Macdonald criteria). Landmark analyses were performed at 2, 4 and 6 months, and Cox proportional hazard models were used to determine the associations between OR and progression with subsequent survival.

Results: The ORRs were 0.433 (95% CI: 0.373 - 0.494) and 0.451 (95% CI: 0.391 – 0.513) by RANO and Macdonald criteria, respectively (p = 0.78). The median PFS was 4.21 months (95% CI: 3.68-5.49) using RANO criteria, compared to 5.52 months (95% CI: 4.27-6.83) as determined by Macdonald criteria (p=0.04). At 2-, 4-, and 6-month landmarks, both OR status and PFS determined by RANO criteria were predictive of overall survival (OS) (hazard ratios for 4-month landmark; OR HR= 2.12, p = 0.0003, PFS HR=4.08, p<0.0001).

Conclusions: The inclusion of T2/FLAIR assessment in the RANO criteria results in a small difference in median PFS but no significant difference in ORR. The associations of OR and PFS with survival using the RANO criteria at 6 months and earlier time points following therapy potentially support their possible roles as surrogates for OS.

Avastin, Roche
Correlation of molecular subtypes with survival in AVAglio (bevacizumab [Bv] and radiotherapy [RT] and temozolomide [T] for newly diagnosed glioblastoma [GB]).
Abstract #2001^

Author(s): Heidi Phillips, Thomas Sandmann, Congfen Li, Timothy Francis Cloughesy, Olivier L. Chinot, Wolfgang Wick, Ryo Nishikawa, Warren P. Mason, Roger Henriksson, Frank Saran, Albert Lai, Nicola Moore, Priti S. Hegde, Lauren E. Abrey, Richard Bourgon, Josep Garcia, Carlos Bais; Genentech Inc., South San Francisco, CA; University of California, Los Angeles, Los Angeles, CA; Aix-Marseille University, AP-HM, Service de Neuro-Oncologie, CHU Timone, Marseille, France; Neurooncology, University of Heidelberg Medical Center, Heidelberg, Germany; Saitama Medical University, Saitama, Japan; Princess Margaret Cancer Centre, Toronto, ON, Canada; Regional Cancer Centre Stockholm Gotland, Stockholm, Sweden; The Royal Marsden NHS Foundation Trust, Surrey, United Kingdom; UCLA Neuro-Oncology Program, Los Angeles, CA; F. Hoffmann-La Roche, Basel, Switzerland; Genentech, Inc., South San Francisco, CA

Background: Factors that correlate the extent of clinical benefit with anti-VEGF therapy are poorly understood. Two phase 3 trials in newly diagnosed GB (AVAglio and RTOG-0825) reported that Bv+RT/T prolonged PFS but not OS v placebo (P)+RT/T. Specific GB pt subgroups may derive OS benefit from 1st-line Bv; tumor profiling has uncovered intrinsic and prognostic GB molecular subtypes. Bv efficacy in molecular subtypes was evaluated as an exploratory objective in AVAglio.

Methods: An 800 gene platform capable of reliable gene expression (GE) measurement in formalin-fixed, paraffin-embedded samples was developed/validated. In AVAglio, randomized pts (n=921) received: RT/T+Bv or P, 6 wks; 28-day break; maintenance T+Bv or P (x6); Bv or P until PD/unacceptable toxicity. Samples from 342 AVAglio pts (Bv/P; biomarker evaluable population) were profiled and classified into known GB molecular subtypes (pre-defined hypothesis); assigned subtypes were
correlated with OS. An exploratory outcome-driven analysis to discover novel predictor subtypes more directly associated with OS benefit from Bv was then performed.

**Results:** Per recent data from The Cancer Genome Atlas (TCGA), pts with proneural tumors with wild-type isocitrate dehydrogenase 1 (IDH1) had the worst prognosis among all GB subtypes (defined by TCGA [Verhaak, Cancer Cell 2010]/Phillips, Cancer Cell 2006). Importantly, this analysis uncovered a relationship between molecular subtype and extent of OS benefit in Bv-treated pts. Exploratory outcome-driven GE analyses identified novel gene clusters associated with prolonged OS with Bv v P. Pt groups predicted to derive Bv benefit in the outcome-driven method overlapped with, but were not identical to, groups defined by known GB subtypes; thus, novel OS-associated candidate predictors may more precisely identify pts likely to derive benefit from Bv.

**Conclusions:** Candidate molecular predictors were identified in AVAglio, suggesting that a subgroup of newly diagnosed GB pts may derive OS benefit from Bv; these data could impact pt stratification and therapy and give insights into Bv mode of action, and warrant further validation in other datasets. Clinical trial information: NCT00943826.

**ICT-107, ImmunoCellular (IMUC)**
A randomized, double-blind, placebo-controlled phase 2 trial of dendritic cell (DC) vaccination with ICT-107 in newly diagnosed glioblastoma (GBM) patients.
Abstract #2005

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**Background:** The trial investigated whether adding tumor-antigen-loaded DC vaccine to surgery and chemoradiation would improve overall survival (OS) or progression free survival (PFS).

**Methods:** HLA-A1+ and/or -A2+ resected patients with residual tumor <1 cm³ received 6 weeks of concurrent temozolomide (TMZ) and radiation. 124 patients were randomized 2:1 to receive ICT-107 (autologous PBMC-derived DC pulsed with 6 synthetic peptide CTL epitopes targeting the GBM tumor and tumor stem cell-associated antigens MAGE-1, HER-2, AIM-2, TRP-2, gp100, and IL-13Rα2) or its matching control (unpulsed DC). Patients then received induction ICT-107 or control QWx4 followed by maintenance TMZ, 5 days/mo for 12 mos. Booster vaccinations occurred at 1, 3, and 6 mos after induction, and every 6 mos thereafter. The trial concluded and data were evaluated at 67 events.
Results: ICT-107 was generally safe and well tolerated, with no imbalance in AEs between the treated and control groups. PFS improved by 2 mos in the ICT-107 ITT group (p=0.02 two-sided, hazard ratio (HR)=0.56). In the per-protocol (PP) group (117 patients receiving all 4 induction vaccinations), p=0.01 two-sided, HR=0.53, and the difference in median PFS increased to 3 mos. The median OS favored ICT-107 by 2 mos in the ITT and 3 mos in the PP groups. However, the number of events was small and OS did not reach statistical significance (p=0.58 two-sided, HR=0.87, and p=0.40 two-sided, HR=0.79, respectively). Median follow-up from randomization was 13.6 mos. In the ICT-107 group, vaccine activation markers IL12 and HLA-DR were predictive of OS (p-values < 0.05). There were no correlations in the placebo group.

Conclusions: This is the first randomized, placebo-controlled immunotherapy trial in GBM to positively affect a clinical outcome, PFS. Although OS improvement was not statistically significant at the 67/124 event point, patients continue to be followed for OS, allowing periodic updating of the primary endpoint and assessment of long-term survival. Analysis of QOL, and correlation of both tumor antigen expression and vaccine immunologic response with OS are in process.

Nuvigil, Teva (TEVA)

A randomized, placebo-controlled pilot trial of armodafinil for fatigue in patients with gliomas undergoing radiotherapy.

Abstract #2004

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Background: Fatigue is a common symptom among glioma patients and affects quality of life. Armodafinil, a wakefulness-promoting medication, benefits patients with fatigue of various causes. This study evaluates the effects of armodafinil on fatigue in glioma patients undergoing radiation therapy (RT).

Methods: Eligibility criteria included age ≥ 18; Karnofsky Performance Status (KPS) ≥ 60; grade 2-4 glioma undergoing RT to a total dose of 50-60 Gy with or without chemotherapy. Patients were randomized 1:1 to armodafinil (A) or placebo (P). Fatigue assessments were made at baseline, Day 22, Day 43, and Day 56 with the FACIT-F Fatigue Scale, Brief Fatigue Inventory (BFI), and Cancer Fatigue Scale (CFS). The primary aim is to detect a difference in the 42-day change in FACIT-F fatigue subscale scores between the two groups using a 2-sample Wilcoxon statistic. Secondary outcomes include a 42-day change in CFS and BFI.

Results: Data is available for 77 of the 80 patients (40 in A and 37 in P). In the armodafinil arm, median age was 56 (25-79), median KPS was 90 (70-100), 57.5% had glioblastoma (GBM), 35% had anaplastic
glioma (AG), 7.5% had another glioma histology. In the placebo arm, median age was 54 (19-78), median KPS was 90 (70-100), 51.4% had GBM, 32.4% had AG, and 16.2% had another glioma histology. The median 42-day change in the FACIT-F fatigue subscale scores in the armodafinil arm was 2 (range -40 to 26) and in the placebo arm was -6.665 (range -65 to 28) with Wilcoxon p-value of 0.066. There was a statistically significant improvement in fatigue in the armodafinil arm vs. the placebo arm based on median 42-day change in the BFI (Wilcoxon p-value of 0.008). Toxicity was rare and similar between arms. There were no cardiac toxicities attributed to treatment. One patient experienced insomnia in the armodafinil arm.

Conclusions: Treatment with armodafinil is well tolerated in glioma patients undergoing RT. There is a trend towards fatigue reduction in the armodafinil group. Updated results will be presented. Study Sponsored by: Cephalon, Inc., a wholly owned subsidiary of Teva Pharmaceuticals, and the National Brain Tumor Society. Clinical trial information: NCT00766467.

**Torisel, Pfizer (PFE)**

**Radiation therapy and concurrent plus adjuvant temsirolimus (CCI-779) versus chemoirradiation with temozolomide in newly diagnosed glioblastoma without methylation of the MGMT gene promoter.**

Abstract #2003

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**Background:** Preclinical data indicate activity of mammalian target of rapamycin inhibitors and synergistic activity together with radiotherapy in glioblastoma. The aim of this trial is to assess the therapeutic activity of temsirolimus (CCI-779), an intravenous mTOR inhibitor, in patients with newly diagnosed glioblastoma with unmethylated \textit{O6 methylguanine-DNA-methlytransferase} (MGMT)promoter.

**Methods:** Patients (n=257) with newly diagnosed glioblastoma after open surgical biopsy or resection fulfilling basic eligibility criteria underwent a central MGMT promoter analysis using quantitative methylation specific PCR. Patients with glioblastoma harboring an unmethylated \textit{MGMT} promoter (n=111) were randomized 1:1 between radiotherapy (60 Gy; 5 times 2 Gy per week) plus concomitant and six cycles of maintenance temozolomide or radiotherapy plus weekly temsirolimus at 25 mg flat dose to be continued until progression or undue toxicity. Primary endpoint was overall survival at 12 months (OS12). Sample size of the investigational treatment arm required 54 patients to assess adequacy of temsirolimus activity set at 80%. More than 38 patients alive at 12 months in the per
protocol population was considered a positive signal. A control arm of 54 patients treated with the standard of care was implemented to evaluate the assumptions on OS12.

**Results:** Between December 2009 and October 2012, 111 pts in 14 centers were randomized and treated. Median age was 55 and 58 years in the temsirolimus and standard arm, respectively. Most patients (95.5%) had a WHO performance status of 0 or 1. Both therapies were properly administered with a median of 13 cycles of maintenance temsirolimus. In the per protocol population, exactly 38 patients treated with temsirolimus (out of 54 eligible) reached OS12. In the intention to treat population OS12 was 72.2% (95% CI (58.2, 82.2)) in the temozolomide arm and 69.6% (95% CI (55.8, 79.9) in the temsirolimus arm [HR=1.16 95% CI (0.77, 1.76), p=0.47].

**Conclusions:** The therapeutic activity of temsirolimus in patients with newly diagnosed glioblastoma with an unmethylated MGMT promoter is too low. Clinical trial information: NCT01019434.

**BREAST CANCER**

**Aromasin, Pfizer (PFE)**

**Arobase: A phase III trial of exemestane (Exe) and bevacizumab (BEV) as maintenance therapy in patients (pts) with metastatic breast cancer (MBC) treated in first line with paclitaxel (P) and BEV—A Gineco study.**

Abstract #501

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**Background:** Combination of P+BEV significantly improves progression-free survival (PFS) in MBC pts, but is associated with adverse events (AEs), mainly neuropathy and fatigue worsening over time. Endocrine therapy (ET) combined to BEV has been proven tolerable and may be an option as maintenance therapy after P+BEV.

**Methods:** in this prospective, randomized, open label, phase III study, pts with histologically confirmed ER+ HER2- locally advanced or MBC, who had not progressed after 16-24 weeks of 1st-line P+BEV therapy, were randomized to P+BEV continuation vs ET+BEV (Exe 25 mg/d+BEV 15 mg/kg q3w). Primary
endpoint was PFS. To demonstrate an improvement in the 6-month PFS rate (PFS-6m) from 50% with P+BEV to 65% with ET+BEV (2-sided α=5%) with 80% power, 141 events were required and 198 pts were planned. An interim analysis (IA) was planned after 40% of required events. Secondary endpoints included overall survival (OS) and toxicity.

Results: At the cut-off date for the IA (May 2013), 113 pts were included, 98 were analyzable. Median age was 55 (range 35-86). ET was given as adjuvant therapy in 64% of pts and in the metastatic setting in 24%. Median follow up was 9.7 months (range 0.8-28.3). PFS-6m was 70% (95% confidence interval (CI) 54, 81.5) with P+BEV and 54% (95% CI 38.5, 67.2) with ET+BEV (HR 1.2, 95% CI (0.7, 1.9), p=0.56). Given these interim results, the probability to show statistically significant PFS at the end of the study was 7%. Deaths were reported for 11 pts in the P+BEV arm vs 6 pts in the ET+BEV arm (median OS not reached). Grade 3-4 AEs rates were lower with ET+BEV (fatigue: 4% of pts vs 14%; neuropathy: 0% vs 12%; pain: 2% vs 8%; neutropenia: 0% vs 12%), as well as serious AEs related to treatment (13% vs 24%). Based on both safety and efficacy results, the IDMC decided to definitely stop the enrollment and to keep patients under tretment in the protocol. Follow-up data will be updated for the final analysis.

Conclusions: The efficacy hypothesis was not reached, despite a better safety profile of the ET+BEV maintenance therapy. Exploratory analyses are planned to identify potential subgroups benefiting from it. Clinical trial information: NCT01303679.

Buparlisib, Novartis (NVS)
Phase I study of oral BKM120 and oral olaparib for high-grade serous ovarian cancer (HGSC) or triple-negative breast cancer (TNBC).
Abstract #2510

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Background: In vivo synergy of the PI3-kinase inhibitor BKM120 and the PARP inhibitor olaparib is seen using a mouse model of BRCA1-related breast cancer (BrCa) and sporadic TNBC (Juvekar et al and Ibrahim et al, Cancer Discovery 2012). The PI3kinase pathway is activated in both TNBC and HGSC (www.cancergenome.nih.gov). Olaparib is active in HGSC and germlineBRCA mutation (gBRCAm) ovarian cancer (OvCa) and gBRCAm BrCa. These data were the rationale for this phase I, multi-center study (NCT01623349) combining BKM120 and olaparib in patients (pts) with recurrent HGSC or TNBC.

Methods: This study has a 3 + 3 design, escalating dose levels (DL) if 0/3 or 1/6 pts have a dose limiting toxicity (DLT) during the first cycle (1st 28 days). Objectives are to determine the MTD and RP2D of daily oral olaparib (tablet formulation) and BKM120, assess toxicities, preliminary activity of this combination, and PK profiles of both drugs. Planned translational endpts include PI3kinase pathway effects, BRCA1 immunostaining/methylation, IL-8/circulating DNA levels, and somatic mutations in BRCA1/2 using FFPE
Results: 34 pts to date have received study drugs; 9 pts w/TNBC and 25 pts w/HGSC. 26 have known gBRCAm. Dosing started at DL1 (BKM120 60 mg and olaparib 100 mg BID); 2 DLTs were observed (1 gr 3 LFTs and 1 gr 3 hyperglycemia). A lower dose (-1) was pursued followed by re-escalation as below. DL 6 was not feasible because of of grade 3 LFTs and grade 3 depression early in cycle 2. Evidence of clinical benefit by RECIST 1.1 was observed on all DL’s, and AEs seen were compatible with AE profile of BKM120 and olaparib. Expansion cohorts are accruing.

Conclusions: Combined BKM120 and olaparib is feasible with evidence of clinical benefit seen at all DL’s. Further studies combining PA

**Herceptin, Roche**

Association of genomic analysis of immune function genes and clinical outcome in the NCCTG (Alliance) N9831 adjuvant trastuzumab trial.

Abstract #509

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Background: Some 20-25% of patients with HER2+ disease relapse after adjuvant trastuzumab (H). We used a genomic approach to define biological processes that predict benefit from H.

Methods: Whole genome DASL technology was used to identify genes associated with relapse-free survival (RFS) among 1,282 patients enrolled in the N9831 adjuvant H trial (NCT00005970). Cox proportional hazard ratios (HR), adjusted for significant clinical/pathological risk factors, were used to determine the association of each gene with RFS (median follow-up 6years, 11months) for 433 patients who received chemotherapy alone and 849 patients who received chemotherapy plus H. Functional ontology analysis and network modeling were used to identify key biological processes associated with RFS in patients who received chemotherapy alone or chemotherapy plus trastuzumab.

Results: Using probes with HR p<0.01, 10/13 significantly enriched biological processes associated with increased RFS (p<0.01) were linked to immune functions. These 10 processes defined a cohort of 87 immune function genes. Patients defined as immune function positive based on the 87 genes experienced a favorable outcome when treated with H (HR=0.55, p=0.0005). Patients who did not exhibit immune function enrichment and were treated with H did not have better RFS than patients with immune function enrichment who were treated with chemotherapy alone (HR=0.93, p=0.72). Among patients who received chemotherapy alone, enriched immune function was not associated with increased RFS (HR=1.01, p=0.96).

Conclusions: Improved RFS following treatment with adjuvant H appears to be associated with a heightened state of immunological function. This observation may define a significant biological process.
that is linked to the efficacy of HER2-targeted therapy, may provide a means of predicting probability of relapse following adjuvant trastuzumab, and suggests possible routes of therapeutic enhancement.

**Iniparib, Sanofi (SNY)**
Association of increased tumor-infiltrating lymphocytes (TILs) with immunomodulatory (IM) triple-negative breast cancer (TNBC) subtype and response to neoadjuvant platinum-based therapy in PrECOG0105.
Abstract #1000^

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**Background:** Increased TILs are prognostic and predictive of therapy response in TNBC. PrECOG 0105, a neoadjuvant trial of carboplatin, gemcitabine and iniparib, enrolled 80 pts with clinical stage I-IIIA TN or BRCA1/2 mutation-associated BC. This correlative study was designed to assess the association of pre-therapy TILs in PrECOG 0105 with pathologic response, germline BRCA1/2 genotype & gene expression profiles, including TNBC subtypes.

**Methods:** Evaluable pts had TNBC and completed at least 4 of 6 planned cycles of therapy. H and E stained tumor sections from pre-therapy biopsies were evaluated by a central pathologist for density of stromal (sTILs) and intratumoral (iTILs) lymphocytes. Pathologic response was assessed by the residual cancer burden (RCB) index. All patients had comprehensive BRCA1/2 genotyping. TNBC subtypes were derived from Affymetrix U133 plus 2.0 arrays.

**Results:** 70 pts were included in this analysis. Median age = 47 yrs, median T size = 3.2 cm, 20% BRCA1/2 mutant & 48% node positive. 76% of tumors had at least 10% sTILs (range 10-80%) & 31% at least 10% iTILs (range 10-40%). Lymphocyte-predominant BC (LPBC), defined as ≥50% sTILs, was seen in 13%. pCR rate was highest (56%) in LPBC, though not significantly different from the non-LPBC group (38%, p=0.47). sTILs were significantly associated with TNBC subtype; median sTIL = 40% in the IM subtype, 15% in BL1, 20% in BL2, 10% in LAR, 0% in M, and 10% in MSL (p=0.0005). iTILs were also significantly associated with TNBC subtypes (p=0.0003); iTIL>0 for 10/14 (71%) in IM subtype, 1/7 (14%) in BL1, and 0 in others. Association with BRCA1/2 mutation status was not significant. In a multivariate model, each 10% increase in iTILs (OR 2.62 [95% CI 1.08 – 6.35]; p=0.03), but not sTILs (OR 1.17 [95% CI 0.87 – 1.58];p=0.28) was independently associated with pCR (RCB=0). However, both sTILs (p=0.02) and iTILs (p=0.009) were significantly associated with continuous RCB value.

**Conclusions:** Both sTILs and iTILs are predictive of response to platinum-based neoadjuvant therapy and are significantly associated with TNBC subtypes, with the highest frequency in the IM subtype. Clinical trial information: NCT00813956.
Neratinib, Puma (PBYI)
TBCRC 022: Phase II trial of neratinib for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer and brain metastases (BCBM).
Abstract #528

Author(s): Rachel A. Freedman, Rebecca Sue Gelman, Jeffrey Scott Wefel, Ian E. Krop, Michelle E. Melisko, Alarice Lowe, Nathalie Agar, Kimberly L. Blackwell, Roisin M. Connolly, Polly Ann Niravath, Catherine H. Van Poznak, Shannon Puhalla, Nicole Ryabin, Elizabeth S Lawler, Nuhad K. Ibrahim, Minetta C. Liu, Antonio C. Wolff, Eric P. Winer, Nancy U. Lin, on behalf of the Translational Breast Cancer Research Consortium (TBCRC); Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Brigham and Women’s Hospital, Boston, MA; Duke Cancer Institute, Durham, NC; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Baylor College of Medicine, Houston, TX; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; University of Pittsburgh Medical Center, Women’s Cancer Program at Magee-Womens Hospital of UPMC, Pittsburgh, PA; Mayo Clinic, Rochester, MN; The Johns Hopkins Hospital and The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: Evidence-based treatments for metastatic, HER2+ breast cancer to the central nervous system (CNS) are limited. Neratinib is an irreversible inhibitor of erbB1, HER2, and erbB4 with promising activity in HER2+ disease. Preclinical evidence suggests it may cross the blood brain barrier. We evaluated neratinib in pts with HER2+ BCBM in a multicenter, phase II open label trial. We report the results of cohort 1 here.

Methods: Pts with measurable BCMC (>/= 1 cm in longest dimension) who progressed after receipt of local CNS therapy were eligible. Pts received neratinib 240 mg orally once daily over 28 day cycles. Brain MRI and non-CNS imaging were obtained at baseline and every two cycles. Circulating tumor cell collections and neurocognitive evaluations were performed serially. The primary endpoint was composite CNS objective response rate (ORR). CNS ORR required all of the following: >/=50% reduction in volumetric sum of target CNS lesions, no progression of non-target lesions, no new lesions, no escalating steroids, no progressive neurologic signs/symptoms, and no non-CNS progression by RECIST 1.1. If patients progressed outside the CNS, the addition of trastuzumab was offered. We used a two-stage design to distinguish between ORR 6% vs 20% (responses in >/=1/18 pts to enter 2nd stage; responses in >/=5/40 pts to be promising).

Results: 40 pts were enrolled between 2/12-6/13; median age was 51. Most pts (80%) had received 2+ lines of therapy for metastatic disease, 85% had prior lapatinib, and 75% had prior WBRT. As of 1/10/14, 0 patients remain on protocol therapy and 22 patients have died. Three women experienced a response (CNS ORR=7.5%; 95% CI 2-27%). The median number of cycles received was 2 (range 1-15+); 6 women (15%) received 6+ cycles of therapy. The most common grade 3+ event was diarrhea (25%); this event decreased after an amendment mandated 2 mg loperamide prophylaxis once daily during cycle 1 (33% grade 3+ diarrhea pre-prophylaxis vs. 21% post-prophylaxis).

Conclusions: Neratinib is associated with a low CNS ORR in pts with BCBM but provided durable disease control in some pts. Updated results will be presented at the meeting. Clinical trial information: NCT01494662.
**Paraplatin, Bristol-Myers Squibb (BMY)**

Pathological complete response (pCR) rates after carboplatin-containing neoadjuvant chemotherapy in patients with germline BRCA (gBRCA) mutation and triple-negative breast cancer (TNBC): Results from GeparSixto.

Abstract #1005

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**Background:** We previously showed in participants with TNBC of the neoadjuvant phase II GeparSixto study (NCT01426880) that the addition of carboplatin can substantially improve the pCR rates from 36.9% with weekly paclitaxel/non-pegylated liposomal doxorubicin (PM) to 53.2% with PM plus weekly carboplatin (AUC2) (PMCb) (von Minckwitz et al, Proc ASCO 2013). We aimed to assess how far this benefit is correlated with gBRCA mutation or with a family history for breast or ovarian cancer.

**Methods:** Full blood samples with sufficient amount of DNA were available in 295 (94%) out of 315 participants of GeparSixto with TNBC. We searched for gBRCA mutations by MLPA and Fluidigm screening for recurrent pathogenic BRCA1/2 alterations. In combination, both methods enable us to detect approximately 60% of all expected mutation carriers. Participants with so far undetected mutations are currently under investigation by employing next generation sequencing (NGS) techniques to detect additional pathogenic germline alterations in BRCA1/2 or other breast cancer predisposing genes.

**Results:** At total of 38 mutation carriers (35 BRCA 1, 3 BRCA 2) have so far been identified (31 by central testing and 7 known results from local testing). Additional 78 patients have a known family breast cancer history. 179 patients have so far neither a mutation nor a family history. Overall pCR (ypT0 ypN0) rate increased from 40.2% in patients with no identified risk, to 44.9% in patients with family history only, to 57.9% for patients with gBRCA mutation. Adding carboplatin to PM increased the pCR rate by 14% (odds ratio, OR 1.79) in patients without increased risk, by 20% (OR 2.29) in patients with family history only, and by 25% (OR 2.75) for patients with gBRCA mutation.

**Conclusions:** gBRCA mutation and family history are predictors for higher pCR rates after neoadjuvant anthracycline/taxane based chemotherapy in TNBC. Additive effect of carboplatin is most prominent in
patients with gBRCA mutation. Updated results after complete gBRCA mutation analysis will be presented at the meeting. Clinical trial information: NCT 01426880.

**Paraplatin, Bristol-Myers Squibb (BMY)**

Expression of immunologic genes in triple-negative and HER2-positive breast cancer in the neoadjuvant GEPARSIXTO trial: Prediction of response to carboplatin-based chemotherapy.

Abstract #510

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**Background:** We have recently described tumor-infiltrating lymphocytes (TILs) as predictors of pathological complete response (pCR = ypT0ypN0) to neoadjuvant carboplatin-based chemotherapy in the GeparSixto breast cancer (BC) trial. To further dissect the immunological status in tumor tissue we have evaluated a total of 12 immunologically relevant genes, including T-cell markers, B-cell markers, chemokines and immunoregulatory factors, in 481 pretherapeutic FFPE samples.

**Methods:** GeparSixto investigated the addition of carboplatin to a doxorubicin/taxane combination in HER2-positive (HER2+) or triple-negative (TN) primary BC. Trastuzumab and lapatinib were added for HER2+ disease and bevacizumab for TN disease. Expression of 12 immunologically relevant genes (CXCL9, CCL5, CD8A, CD80, CXCL13, IGKC, CD21, IDO1, PD-1, PDL1, CTLA4, FOXP3) was evaluated by quantitative RT-PCR in 481 core biopsies.

**Results:** All immune mRNA markers showed a strong positive correlation with each other and with the stromal lymphocyte infiltrate. Hierarchical clustering revealed three different immune-subtypes of tumors with different expression of immunological genes and different amounts of tumor infiltrating lymphocytes. In the GeparSixto cohort all 12 immune markers were significantly linked to increased pCR rates in univariate analysis. 11 of the markers were also significant in multivariate analysis including clinical parameters. Some markers, such as CCL5, IDO1 and PDL1 provided predictive information even if controlled for TILs. CCL5, CD8A, CTLA4, IDO1 and PD1 showed a significant interaction with treatment (carboplatin vs. control) in the complete cohort. In TN disease CCL5 and CD8A provided predictive information for carboplatin response even after adjustment for TILs.

**Conclusions:** Expression of immune marker mRNAs in BC is predictive for response to neoadjuvant chemotherapy. In GeparSixto, these immunological parameters can be used in addition to TILs to
identify patients with increased response rates to carboplatin. The results should be validated in other breast cancer trials evaluating carboplatin therapy.

**Rucaparib, Clovis (CLVS)**

RNA-sequencing of residual triple-negative breast cancers after neoadjuvant chemotherapy compared to matched pretreatment biopsies from the Hoosier Oncology Group trial BRE09-146.

Abstract #1002

Author(s): Milan Radovich, Bradley Allen Hancock, Jeffreay Peter Solzak, Rutuja Atale, Sunil S. Badve, Kathy D. Miller, Bryan Paul Schneider; Indiana University School of Medicine, Indianapolis, IN; Indiana University Simon Cancer Center, Indianapolis, IN

**Background:** Residual disease after neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) patients entails a high risk of disease recurrence. We investigated the transcriptomes of residual disease versus matched pre-treatment biopsies from a post-neoadjuvant TNBC trial to understand mechanisms of treatment resistance and to identify potential therapeutic interventions.

**Methods:** RNA-sequencing of 44 TNBC tumors with high tumor cellularity (22 matched pre- and post-neoadjuvant specimens) was performed using the Ion Proton Next Generation Sequencer. RNA-seq data was aligned to the genome followed by expression and network analysis.

**Results:** Statistical analysis resulted in 1,022 genes differentially expressed between matched pre- and post-neoadjuvant chemotherapy samples (p<0.01). Pathway analysis identified significant down-regulation of immune genes (P<1x10^{-5}), which correlated with histologic observation of the depletion of lymphocytic cells in the post-neoadjuvant specimens (p=0.018). To identify novel therapeutic modalities, we employed upstream regulator analysis which predicts transcriptional regulators that are activated based on differentially expressed genes. Our top activated regulator in post-neoadjuvant specimens is MAPK1 (p=1.13x10^{-4}), a key component of the MEK/ERK pathway. To further identify novel markers of residual disease, we analyzed for precursor microRNAs. Differential expression identified significant up-regulation of our top hit, miR-663B (P=2x10^{-4}, Fold-Change=3.4) in residual disease tumors.

**Conclusions:** RNA-seq and histology identified significant depletion of immune cells in residual disease, which has been previously associated with poor prognosis in breast cancer. We further identified a highly activated MAPK1 network, suggesting the potential use of MEK/ERK inhibitors in clinical trials for this population. Lastly, we identified a novel clinical biomarker, miR-663B, which is known to mediate in vitro TNBC resistance to doxorubicin, cyclophosphamide, and docetaxel.

**Taltorvic, Ariad (ARIA)**

**MK-2206, Merck (MRK)**

Safety/efficacy of MK-8669 (ridaforolimus) plus MK-2206 (AKT inhibitor) in patients with advanced breast cancer with low RAS signature and PTEN deficient prostate cancer.

Abstract #2509

Author(s): Shilpa Gupta, Pamela N. Munster, Antoine Hollebecque, Guillem Argiles, Olav Dajani, Jonathan D. Cheng, Ann M. Swift, Alessandra Tosolini, Sarina Anne Piha-Paul; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Stanford Cancer Institute, Stanford, CA; University of Texas MD Anderson Cancer Center, Houston, TX; ocean Health Ventures, Inc, Los Angeles, CA; Ariad Pharmaceuticals, Cambridge, MA; MD Anderson Cancer Center at The University of Texas, Houston, TX; Aastrom Biosciences, South San Francisco, CA; AstraZeneca, Minneapolis, MN; Stony Brook University, Stony Brook, NY; Eli Lilly and Company, Indianapolis, IN; Memorial Sloan-Kettering Cancer Center, New York, NY; MedImmune, Gaithersburg, MD; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; MSKCC, New York City, NY; University of Southern California, Los Angeles, CA; H. Lee Moffitt Cancer Center, Tampa, FL; University of Wisconsin-Madison, Madison, WI; AstraZeneca, Cambridge, MA; AstraZeneca, Whippany, NJ; Stanford University, Stanford, CA; Fredrickson Institute of Cancer Research, University of Washington, Seattle, WA; University of Florida, Gainesville, FL; European Cancer Institute, Milan, Italy; University of California, Los Angeles, Los Angeles, CA; MD Anderson Cancer Center, Houston, TX; University of California, San Francisco, San Francisco, CA; University of Southern California, Los Angeles, CA; Dana-Farber Cancer Institute, Boston, MA; City of Hope National Medical Center, Duarte, CA; Cleveland Clinic, Cleveland, OH; AstraZeneca, Macclesfield, UK; University of California, Irvine, CA; Memorial Sloan Kettering Cancer Center, New York, NY; MD Anderson Foundation, Houston, TX; and Ariad Pharmaceuticals, Cambridge, MA; Indianapolis, IN; Los Angeles, CA; Houston, TX; San Francisco, CA; NYC, NY; Minneapolis, MN; and Somerville, MA; UC San Francisco 1230 33rd Street, San Francisco, CA.
Background: The PI3K/AKT/mTOR signaling pathway is aberrantly activated in a variety of cancers. The combination of ridaforolimus (mTOR inhibitor) and MK-2206 may lead to blockade of the PI3K pathway.

Methods: We conducted a phase 1 study with ridaforolimus + MK-2206 in advanced solid tumors (n=35). Part A defined the maximum-tolerated dose (MTD); part B evaluated preliminary clinical efficacy in enriched breast cancer (BCa) and prostate cancer (PCa) patients. BCa patients had low RAS gene signature; ER+ BCa patients required a high Ki67 index. PCa patients had evidence of PTEN deficiency.

Results: Eleven patients were in part A and 24 patients were in part B (16 BCa/8 PCa patients). In addition, 1 BCa patient from part A was found to be biomarker-eligible when tested after a clinical response. Total of 124 BCa patients were prescreened: 98 tissues were evaluable; 51 were biomarker-eligible. Sixty-eight PCa patients were prescreened: 40 tissues were evaluable; 24 had loss of PTEN. The MTD was 10 mg qd ridaforolimus 5 days/wk + 90 mg weekly MK-2206; 1/17 patients had a dose limiting toxicity of G3 rash. For BCa patients, investigator-assessed objective responses were seen in 2/16 (2 partial responses [PR], 12.5%), centrally read objective responses were seen in 2/14 (2 complete responses [CR], 14.3%), and objective responses using volumetric 3-D assessment were seen in 4/14 (2 PR + 2 CR, 28.6%). In addition, stable disease (SD) ≥ 6 months was seen in 1 patient by the investigator assessment and 1 patient by central read. For PCa patients, 1/8 patient had SD for > 6 months. No responses were seen in other non-biomarker-tested tumors in part A (although one subject with colorectal cancer had SD for 7 months). At the MTD, the following drug-related AEs were seen: rash (44.4%); stomatitis (38.9%); diarrhea and decreased appetite (27.8%); asthenia, nausea and fatigue (22.2%).

Conclusions: The combination of ridaforolimus and MK-2206 shows promising activity in BCa patients with low RAS. This combination was overall well tolerated with rash, stomatitis, diarrhea and asthenia being among the most common drug-related AEs. Clinical trial information: NCT01295632.

Trebananib, Amgen (AMGN)
A phase 1b study of trebananib plus paclitaxel (P) and trastuzumab (T) in patients (pts) with HER2+ locally recurrent or metastatic breast cancer (MBC).
Abstract #502

Author(s): Peter Andrew Kaufman, Gilles Freyer, Margaret Kemeny, Anthony Goncalves, Guy Heinrich Maria Jerusalem, Alison Stopeck, Nandogopal Vrindavanam, Florence Dalenc, Nuwan Nanayakkara, Benjamin Wu, Cheryl Ann Pickett-Gies, Hans Wildiers; Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH; Centre Hospitalier Lyon-Sud, Lyon, France; Queens Cancer Center of Queens Hospital, Jamaica, NY; Institut Paoli Calmettes, Marseille, France; Centre Hospitalier Universitaire Sart Tilman Liege and University of Liege, Liege, Belgium; University of Arizona Cancer Center, Tucson, AZ; Signal Point Hem/Onc, Middletown, OH; Institut Claudius Regaud, Toulouse, France; Quintiles, San Diego, CA; Amgen Inc., Department of Pharmacokinetics and Drug Metabolism, Thousand
Background: Trebananib (AMG 386) suppresses tumor angiogenesis by neutralizing the interaction between the Tie2 receptor and its ligands, angiopoietin-1 and -2. This study evaluated the tolerability and efficacy of trebananib plus P and T as first-line treatment in HER2\(^+\) MBC.

Methods: Pts in cohorts A1 and A3 received open-label trebananib (A1, 10 mg/kg; A3, 30 mg/kg) IV QW plus P 80 mg/m\(^2\) IV QW and T (loading dose of 8 mg/kg, then 6 mg/kg Q3W). If dose-limiting toxicity (DLT) criteria were not met, each cohort was expanded to 20 pts. A3 enrollment was initiated if DLT criteria were not met for A1. Results describing trebananib plus capecitabine and lapatinib will be reported elsewhere. Endpoints were the incidence of DLTs and treatment-emergent adverse events (AEs; primary); and efficacy and pharmacokinetics (PK).

Results: Of 40 enrolled pts in A1 (n = 20) and A3 (n = 20), two DLTs occurred across A1 (grade 3 transient ischemic attack, n = 1) and A3 (grade 3 increased gamma-glutamyltransferase, n = 1). The most common (> 50%) AEs in A1/A3 were peripheral edema (n = 13/15), diarrhea (n = 13/14), alopecia (n = 13/13), fatigue (n = 15/9), nausea (n = 11/13), nail disorder (n = 12/7), and rash (n = 12/6). Grade ≥ 3 AEs occurring in > 10% of pts were peripheral neuropathy (n = 4/4), peripheral sensory neuropathy (n = 4/0), and dyspnea (n = 3/1). In evaluable pts (A1/A3, n = 20/17), confirmed objective response rates (ORRs) were 80% (complete responses [CRs], n = 0; partial responses [PRs], n = 16) in A1 and 88.2% (CRs, n = 3; PRs, n = 12) in A3. The median duration of response (DOR; 95% CI) was 12.6 (4.3 – 20.2) months in A1 and 16.8 (8.2 – not evaluable) months in A3. Median (95% CI) progression-free survival (PFS) was 14.5 (6.9 – 20.6) months and 18.7 (10.4 – not evaluable) months in A1 and A3, respectively. No apparent PK drug-drug interaction was observed. Trebananib exposure appeared dose proportional with intersubject variability of 40.5% and 28.6% in A1 and A3, respectively.

Conclusions: In this phase 1b study, trebananib at 10 mg/kg and 30 mg/kg plus P and T appeared tolerable. The ORR, DOR, and PFS observed in this study suggest that further investigation of trebananib in this setting is warranted. Clinical trial information: NCT00807859.

CANCER

**ABT-700, AbbVie (ABBV)**

Phase 1, open-label, dose-escalation, and expansion study of ABT-700, an anti-C-met antibody, in patients (pts) with advanced solid tumors.

Abstract #2507

Author(s): John H. Strickler, Patricia LoRusso, Chia-Jui Yen, Chia-Chi Lin, Yoon-Koo Kang, Patrick Kaminker, Peter Ansell, Anahita Bhathena, Shekman Wong, Matthew W. Dudley, Louie Naumovski, Ramesh K. Ramanathan; Duke University Medical Center, Durham, NC; Karmanos Cancer Institute, Wayne State University, Detroit, MI; National Cheng Kung University Hospital, Tainan, Taiwan; Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; Asan Medical Center, Seoul, South Korea; AbbVie, Inc., North Chicago, IL; AbbVie Biotherapeutics, Redwood City, CA; Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Scottsdale, AZ
**Background:** *MET* amplification (MA) is an oncogenic driver in multiple malignancies. MA is relatively rare in primary tumors (~1-5%), but may increase after treatment with inhibitors of the EGFR pathway or cytotoxic chemotherapy. We are developing ABT-700 (hz224G11), an antagonistic antibody directed against c-Met, as monotherapy in MA tumors.

**Methods:** In a 3+3 dose escalation design, ABT-700 was administered at doses of 5, 10, 15 and 25 mg/kg once every 21 days. ABT-700 was then studied at the recommended single-agent dose of 15 mg/kg (chosen based on safety, pharmacokinetic (PK), and biomarker analyses) in 26 pts with advanced solid tumors (10 colorectal, 5 non-small cell lung, 4 ovarian, 3 gastric, 2 esophageal, 1 renal, 1 uterine). MA was assessed by fluorescence in situ hybridization (FISH).

**Results:** As of Dec 17, 2013, 41 pts received between 1-12 doses of ABT-700. The PK demonstrated target-mediated disposition with a mean T1/2 of 13.9 days at 15 mg/kg. (n=10, cycle 1 of expansion cohort). There were no acute infusion reactions. Common toxicities at the 15 mg/kg dose occurring in ≥15% of pts included constipation (24%), fatigue (24%), decreased appetite (21%), peripheral edema (21%), hypoalbuminemia (17%), hypokalemia (17%) and vomiting (17%). There was no dose limiting toxicity and no maximum tolerated dose identified. By RECIST, 3/5 (60%) of pts with MA tumors had a partial response (1 each ovarian, gastric and esophageal). Among these 3 pts, the duration of response was 19, 23, and 24 weeks, respectively. Two other pts with MA did not respond: 1 pt with papillary renal cancer treated at 5 mg/kg (considered to be sub-therapeutic based on preclinical studies) and 1 pt with gastric cancer treated at 15 mg/kg. Among pts with non-amplified tumors (n=36), no objective responses were observed, however 5 pts had stable disease at the 12 week assessment.

**Conclusions:** ABT-700 is well tolerated at the recommended single-agent dose of 15mg/kg. ABT-700 monotherapy has demonstrated promising anti-tumor activity in pts with MA solid tumors. The study has been expanded to identify and enroll pts with MA tumors to better define predictive biomarkers of clinical benefit. Clinical trial information: NCT01472016.

**AMG 337, Amgen (AMGN)**

First-in-human study of AMG 337, a highly selective oral inhibitor of MET, in adult patients (pts) with advanced solid tumors.

Abstract #2508

Author(s): David S. Hong, Patricia LoRusso, Omid Hamid, Darrin M. Beaupre, Filip Janku, Rabia Khan, Muaiad Kittanah, Robert D. Loberg, Benny Amore, Isaac Caudillo, Yuying C. Hwang, Rui Tang, Gataree Ngarmchanmanrith, Eunice Lee Kwak; The University of Texas MD Anderson Cancer Center, Houston, TX; Karmanos Cancer Institute, Wayne State University, Detroit, MI; The Angeles Clinic and Research Institute, Los Angeles, CA; Pharmaciescics, Sunnyvale, CA; Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas MD Anderson Cancer Center, Houston, TX; Molecular Sciences & Computational Biology, Amgen, Inc., Thousand Oaks, CA; Amgen Inc., Seattle, WA; Amgen Inc., Thousand Oaks, CA; Biostatistics – Medical Sciences, Amgen, Inc., Thousand Oaks, CA; Amgen Inc, Thousand Oaks, CA; Massachusetts General Hospital Cancer Center, Boston, MA
**Background:** Dysregulation of the MET pathway can promote tumor growth and metastasis, making MET an attractive target for cancer therapy. AMG 337 is an investigational, oral inhibitor of MET kinase activity. This study evaluated the safety, tolerability, pharmacokinetics, and efficacy of AMG 337.

**Methods:** Key eligibility: age ≥ 18 years, advanced solid tumors, measurable disease, ECOG ≤ 2, adequate organ function. AMG 337 was administered orally QD or BID on D1 and D3–28. After 1 week without AMG 337 in the absence of dose-limiting toxicity (DLT) or progression, pts resumed AMG 337 until progression. The starting dose of AMG 337 was 25 mg with planned dose escalation of 50-500 mg QD and 100-200 mg BID (3-9 pts/cohort) until the maximum tolerated dose (MTD, highest dose at which < 33% of pts/cohort had a DLT) was reached or the highest dose was tested. Pts with MET overexpression/amplification/mutation could enroll to the highest dose deemed safe at any time.

**Results:** As of OCT 2013, 66 pts (QD escalation: 3 at 25 mg, 4 at 50 mg, 14 at 100 mg, 9 at 150 mg, 15 at 200 mg, 8 at 300 mg, 6 at 400 mg; BID escalation: 5 at 100mg, 1 at 150mg; expansion: 1 at 300 mg) received ≥ 1 dose of AMG 337. Median age, 59 (19-79) years; men, 56%; ECOG ≤ 1, 96%. See Table for treatment-related AEs in >10% pts. 8 pts had DLTs: grade (G) 3 headache (150 mg QD, n=1; 200 mg QD, n=2; 300 mg QD, n=1; 400 mg QD, n=2); G3 hypertension (200 mg QD, n=1); G3 increased amylase (400 mg QD, n=1). QD MTD is 300 mg; BID MTD not yet reached. AMG 337 exposures increased with dose, with minimal accumulation after 28 days; half-life, 4.6-7.4 h. Tumor-response data (central read) were available for 45 pts: 1 complete response (CR), 4 partial response (PR), 28 stable disease (SD), 12 progressive disease (PD). Of these, 8 pts had known MET amplification, 7 with gastroesophageal cancer (1 CR [duration of response, 100 weeks], 4 PR, 1 SD, 1 PD) and one with renal cell carcinoma (PD).

**Conclusions:** Responses were observed in a subset of pts with MET-amplified tumors. A dose-expansion phase will enroll up to 50 pts at the MTD (300 mg QD). Clinical trial information: NCT01253707.

<table>
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<tr>
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<td>Fatigue</td>
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AZD4547, AstraZeneca (AZN)

**Exploratory biomarker analysis of a phase I study of AZD4547, an inhibitor of fibroblast growth factor receptor (FGFR), in patients with advanced solid tumors.**

Abstract #11010

Author(s): Elaine Kilgour, David Ferry, Matilde Saggese, Hendrik-Tobias Arkenau, Claire Rooney, Neil R. Smith, Dawn Baker, Brian Dougherty, Chris Womack, Paul D. Smith, Dana C. Ghiorgiu, Elizabeth A.
Harrington, J. Carl Barrett, Nigel Brooks, Paul Stockman, Fabrice Andre; AstraZeneca Oncology Innovative Medicines, Macclesfield, United Kingdom; New Cross Hospital, Wolverhampton, United Kingdom; Sarah Cannon Research Institute, London, United Kingdom; AstraZeneca, Waltham, MA; Institute Gustave Roussy, Villejuif, France

**Background:** AZD4547 is a selective inhibitor of FGFR 1, 2, and 3, with activity in patient-derived explant models with FGFR gene amplification. Study 1C1 assessed safety and clinical activity of AZD4547 (80 mg bid continuous dosing), in patients with advanced solid tumors, prospectively selected for amplification of FGFR 1 or 2. FGFR gene amplification status was determined using fluorescent in situ hybridization (FISH) analysis of archival tumor tissue.

**Methods:** Analysis of FFPE diagnostic tumor samples included FGFR expression by IHC, expression analysis of ~200 pathway related genes by Nanostring and targeted Next Generation Sequencing (NGS) of a 287 gene panel at Foundation Medicine.

**Results:** Of 21 patients dosed with AZD4547, seven had high FGFR amplification (ratio FGFR:Centromeric probe ≥ 3.0) and three of these, a squamous NSCLC, breast and bladder cancer patients, had target lesion shrinkage or prolonged (≥24 weeks) disease stabilization. NGS analysis of tumor from a partial response squamous NSCLC patient, confirmed high FGFR1 amplification together with amplification of 11q13 genes FGF3/4/19 and CCND1. A breast cancer patient, with 25% reduction in target lesions, was highly FGFR1 amplified by NGS and expressed FGFR1 protein. Four patients with high FGFR gene amplification by FISH had little sign of efficacy. Of these, one patient was not confirmed FGFR amplified by NGS analysis, likely due to tumor heterogeneity. The other three patient tumors had an additional Receptor Tyrosine Kinase (RTK) amplification (IGF1R, HER2 or EGFR), with accompanying high expression. Two out of three bladder cancer patients experienced prolonged disease stabilization, both with marked FGFR1 and FGFR3 expression, one with high FGFR1 amplification while an FGFR3 ligand binding domain mutation was found in tumor from the other.

**Conclusions:** In this AZD4547 Phase I study, evidence of FGFR pathway expression was observed in tumor samples from advanced cancer patients with signs of efficacy. Co-amplification of RTKs may confer resistance to AZD4547. FGFR1/3 expression, amplification and mutation are potential selection markers for bladder cancer patients. Clinical trial information: NCT00979134.

**HOT, Cellectar (CLRB)**

A novel “diapeutic” molecular imaging agent for combined oncologic diagnosis and therapy in a broad spectrum of human cancers: Preliminary clinical experience with CLR1404.

Abstract #11000

Author(s): Perry J. Pickhardt, Lance T. Hall, Matthew Lee, Marc Longino, Anatoly Pinchuk, Maria Banash, Joe Grudzinski, Benny Titz, Christine Jaskowiak, John S. Kuo, Jamey Weichert; University of Wisconsin, Madison, WI; University Wisconsin Carbone Cancer Center, Madison, WI; University of Wisconsin, School of Medicine and Public Health, Madison, WI; Cellectar, Madison, WI; Cellectar Biosciences, Madison, WI; Novelos Therapeutics, Inc., Madison, WI; UWSMPH, Madison, WI

**Background:** Extensive preclinical investigation into CLR1404, an akylphosphocholine analog, has demonstrated highly selective uptake and prolonged retention within a variety of human cancer preclinical models. Radioiodine labeling using $^{124}$I and $^{131}$I may allow for combined oncologic imaging and
treatment in humans, respectively, potentially bridging the gap between cancer imaging and therapy. We report preliminary imaging experience with this “diapeutic” agent in early phase human trials.

**Methods:** Prospective imaging studies with $^{124}$I-CLR1404 PET/CT (n=14) and $^{131}$I-CLR1404 SPECT/CT (n=9) in 22 enrolled patients (mean age, 61 years; M:F 12:10) with proven metastatic cancer were analyzed and compared with $^{18}$FDG PET/CT and other imaging studies. Underlying primary cancer types included bronchogenic (n=7), colorectal (n=4), prostate (n=3), triple-negative breast (n=2), esophageal (n=2), head and neck (n=2), pancreatic (n=1), and melanoma (n=1).

**Results:** There is preferential uptake of $^{124}$I- and $^{131}$I-CLR1404 within a variety of metastatic foci in all cancer subtypes. Persistent retention within sites of disease coupled with progressive washout of background activity favored more delayed imaging phases, days-weeks after injection. Distinct advantages in oncologic imaging over FDG PET include greater conspicuity of brain metastases (FDG false-negatives) and lack of uptake in areas of post-treatment false-positive FDG activity. CLR1404 uptake was also evident in nodal, skeletal, pulmonary, hepatic, and other sites of active metastatic disease.

**Conclusions:** Selective tumor uptake with prolonged retention of CLR1404 was demonstrated within a broad spectrum of historically difficult-to-treat metastatic cancers. This novel molecular imaging agent appears to have distinct advantages over FDG for oncologic PET imaging. Combined diagnosis and therapy using same molecule (ie, a “diapeutic” approach with $^{124}$I and $^{131}$I labeling) could lead to truly personalized care by ensuring pre-treatment tumor-specific uptake, providing patient-specific dose planning, and enabling treatment-specific imaging surveillance.

**JNJ-42756493, Johnson & Johnson (JNJ)**

**Phase 1 study of JNJ-42756493, a pan-fibroblast growth factor receptor (FGFR) inhibitor, in patients with advanced solid tumors.**

Abstract #2501

Author(s): Rastislav Bahleda, Rodrigo Dienstmann, Barbara Adamo, Anas Gazzah, Jeffrey R. Infante, Bob Zhong, Suso J. Platero, Hans Smit, Timothy Perera, Kim Stuyckens, Jacqueline Bussoleari, Vijay Peddareddigari, Jean-Charles Soria, Feng Roger Luo, Josep Taberner; Drug Development Department (DITEP), Gustave Roussy Institute, Villejuif, France; Vall d’Hebron University Hospital, Barcelona, Spain; Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; Janssen Research and Development, Spring House, PA; Janssen Research and Development, Beerse, Belgium; Janssen Research and Development, Raritan, NJ

**Background:** JNJ-42756493 is an orally bioavailable FGFR 1, 2, 3 and 4 inhibitor with nanomolar antitumor activity in cell lines and in vivo models with FGFR pathway aberration.

**Methods:** This first in human study consists of 3 parts: dose escalation part 1 to determine the recommended phase 2 dose (RP2D), dose confirmation part 2 with focus on pharmacodynamic effects, and dose expansion part 3 to evaluate the antitumor activity in selected solid tumors with FGFR gene amplification, mutation or translocation at the RP2D. Biomarkers include tumor tissue genomic profiling, skin/tumor biopsies and soluble serum markers. Toxicity is graded with CTCAE-4 and antitumor activity is assessed using RECIST 1.1.
**Results:** As of 27 January 2014, 37 patients have been treated at 6 dose levels (0.5, 2, 4, 6, 9 and 12 mg daily continuously) in part 1. Most common (≥ 20% of patients) adverse events (AEs) were hyperphosphatemia (60%), asthenia (46%), dry mouth (30%), constipation (27%), abdominal pain (22%), stomatitis (22%), and vomiting (22%); all were ≤ Grade 2 in toxicity. Ten (27%) patients had ≥ Grade 3 AEs, and one dose limiting toxicity of Grade 3 AST/ALT elevation was noted at 12 mg dose. Daily 9 mg continuous dosing was declared the RP2D. Seven (19%) patients had serious AEs, including 1 death, but none were drug-related. Six (16%) patients had dose reductions due to drug-related hyperphosphatemia at 9 and 12 mg. Pharmacokinetics were linear, dose proportional and predictable with a half-life of 50 to 60 hours. Exposure dependent increases in phosphate blood levels were observed at doses up to 9 mg, thereafter reaching a plateau. Also a trend was seen for increase in FGF23 and decrease in PTH. Out of 8 patients enrolled to date with FGFR pathway aberration, we observed 1 partial response in a bladder cancer patient with FGFR3-TACC3 translocation and 1 near complete response in an urothelial cancer of renal pelvis harboring FGFR2 truncation at the RP2D. Four patients (2 lung cancer, 1 chondrosarcoma and 1 breast cancer patients with FGFR1 amplification) had stable disease.

**Conclusions:** JNJ-42756493 has favorable pharmaceutical properties, with manageable side effects at the RP2D and evidence of antitumor activity. Clinical trial information: [NCT01703481](https://clinicaltrials.gov/ct2/show/NCT01703481).

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**Lucitanib, Clovis (CLVS)**

*A phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors.*

Abstract #2500

Author(s): Jean-Charles Soria, Filippo G. De Braud, Ratislav Bahleda, Barbara Adamo, Roberta Cereda, Maria Gabriella Camboni, Renata Robert, Jeffrey D. Isaacson, Jason B. Litten, Andrew R. Allen, Lindsey Rolfe, Josep Taberner; Gustave Roussy, Villejuif, France; Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy; DITEP, Drug Development Department, Institut Gustave Roussy, Villejuif, France; Vall d'Hebron University Hospital, Barcelona, Spain; EOS S.p.A., Milan, Italy; Institut de Recherches Internationales Servier (I. R. I. S.), Suresnes, France; Clovis Oncology, Inc., Boulder, CO; Clovis Oncology, Inc., San Francisco, CA; Clovis Oncology, Inc., Cambridge, United Kingdom

**Background:** Lucitanib is a potent, oral inhibitor of the tyrosine kinase activity of FGFR1/2, VEGFR1-3 and PDGFRα/β. These well-described signaling pathways are essential for tumor growth, survival, migration, and angiogenesis. Further, several tumor types, including carcinoma of the breast, demonstrate amplification of FGFR-related genes. Currently, there are no approved drugs for patients (pts) with molecularly defined FGF-aberrant (*FGFR1* or *FGF3/4/19* amplified) tumors.

**Methods:** The first in human 3-part study is evaluating oral lucitanib monotherapy. Part 1 employed a 3+3 ascending cohort design in pts with advanced solid tumors to establish a recommended dose for further study. Parts 2 and 3 evaluated safety and efficacy of lucitanib in pts with FGFR aberrant or angiogenesis sensitive tumors using continuous (part 2) or intermittent schedules (part 3) of administration.

**Results:** 109 (part 1 n=17; part 2 n=59; part 3 n=33) pts were treated. Median age was 55 yrs [range 34-80]; 59 female; 105 stage IV; 29 breast cancer, 16 colon, 13 thyroid and 51 other tumor. Doses from 5 mg to 30 mg were evaluated with dose limiting toxicities (DLTs) dominated by VEGF-inhibition related toxicity at the 30 mg dose level. The most common adverse events (all grades, all cohorts, continuous
and intermittent dosing schedules) were hypertension (86%), asthenia (73%) and proteinuria (69%). Exposure increased with dose and a t1/2 of 25-40 hours, deemed suitable for once daily administration. Clinical activity was observed at all doses tested with durable RECIST PRs in a variety of tumor types. In evaluable FGF-aberrant breast cancer pts, 50% (6 of 12) achieved RECIST PR with a median PFS of 9.4 months for all treated patients. Additionally, 1 of 3 pts with advanced squamous NSCLC experienced SD for 8 months with lucitanib therapy.

Conclusions: Lucitanib demonstrated promising clinical activity and a tolerable side-effect profile in pts with advanced solid tumors, including those with FGF pathway aberrations. A phase 2 program in FGF aberrant breast and squamous NSCLC is underway in US and Europe. Clinical trial information: NCT01283945.

**MEDI-4736, AstraZeneca (AZN)**
A phase 1 study of MEDI4736, an anti–PD-L1 antibody, in patients with advanced solid tumors.
Abstract #3001^

Author(s): Jose Lutzky, Scott Joseph Antonia, Andy Blake-Haskins, Xia Li, Paul B. Robbins, Aiman M. Shalabi, Jim Vasselli, Ramy A. Ibrahim, Samir Khleif, Neil Howard Segal; Mount Sinai Comprehensive Cancer Center, Miami Beach, FL; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; MedImmune, Gaithersburg, MD; GRU Cancer Center, Augusta, GA; Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Immune-suppressing molecules such as PD-L1 can be co-opted by cancer cells to suppress the natural immune response to cancer. Upregulation of PD-L1 and inhibition of antitumor T-cell activation is observed in several tumor types. MEDI4736 is a human IgG1 antibody which binds specifically to PD-L1, preventing binding to PD-1 and CD80.

**Methods:** An ongoing phase 1 multicenter, open-label study (NCT01693562) is evaluating safety, pharmacokinetics (PK), and antitumor activity of MEDI4736 given IV every 2 (q2w) or 3 wks (q3w) in a 3+3 dose escalation with a 28-day (q2w) or 42-day (q3w) dose-limiting toxicity (DLT) window, followed by expansion in 8 solid tumors. Response was assessed by immune-related response criteria in escalation.

**Results:** As of Jan 17, 2014, 26 patients (pts) (13 NSCLC, 8 melanoma, 5 other) in dose escalation (median age 59 yrs; 35-77), all PS 0-1, with a median of 4 prior treatments, received a median of 5 (1-25) q2w and 4.5 (1-7) q3w doses of MEDI4736 across 6 cohorts (0.1 – 10 mg/kg q2w; 15 mg/kg q3w). MEDI4736 showed dose-dependent PK. Evidence of ADA impacted PK exposure in only 1 patient. No DLTs or maximum tolerated dose were identified for q2w or q3w dosing. Treatment-related AEs occurred in 34% of pts, all Grade 1-2; none led to discontinuation of study drug. The most frequent treatment-related AEs were diarrhea, fatigue, rash, and vomiting (12% each). No pneumonitis, colitis, or hyperglycemia occurred. Of 26 pts, 4 PRs (3 NSCLC, 1 melanoma) and 5 additional pts with tumor shrinkage not meeting PR were observed. Disease control rate (PR + SD ≥ 12 wks) was 46%. Tumor shrinkage, as early as 6 wks, was seen at all dose levels, and benefit was durable; 11 pts remain on study as of the data cutoff (2+ to 14.9+ mos). Expansion cohorts opened Sep 2013 using a 10 mg/kg q2w dose; 151 pts have been dosed, with the opportunity to enroll > 600 pts. Preliminary clinical activity has been observed with acceptable safety across a range of tumors including SCCHN, pancreatic, gastric, NSCLC, and melanoma.
Conclusions: MEDI4736 has demonstrated an acceptable safety profile and durable clinical activity in this dose-escalation study. Expansion in multiple cancers and development of MEDI4736 as monotherapy and in combination is ongoing. Clinical trial information: NCT01693562.

MEDI-4736, AstraZeneca (AZN)

Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody.
Abstract #3002^

Author(s): Neil Howard Segal, Scott Joseph Antonia, Julie R. Brahmer, Michele Maio, Andy Blake-Haskins, Xia Li, Jim Vasselli, Ramy A. Ibrahim, Jose Lutzky, Samir Khleif; Memorial Sloan Kettering Cancer Center, New York, NY; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; University Hospital of Siena, Siena, Italy; MedImmune, Gaithersburg, MD; Mount Sinai Comprehensive Cancer Center, Miami Beach, FL; GRU Cancer Center, Augusta, GA

Background: Checkpoint blockade of the PD-1/PD-L1 and CTLA-4 pathways has shown to be active in multiple tumor types. MEDI4736 is a human IgG1 monoclonal antibody which binds specifically to PD-L1, preventing binding to PD-1 and CD80. In phase I, MEDI4736 showed acceptable safety (no maximal tolerated dose identified). With evidence of clinical activity in phase I, an expansion study was initiated in multiple cancer types including NSCLC, melanoma (cutaneous and ocular), gastroesophageal, hepatocellular carcinoma, pancreatic, SCCHN and triple negative breast cancer.

Methods: 10 - 20 pts were initially enrolled per tumor type, with expansion allowed upon observation of clinical activity. MEDI4736 was administered as 10 mg/kg IV every 2 weeks for 12 months. Retreatment was permitted for progression after 12 months of therapy. Response was assessed by RECIST v1.1.

Results: The expansion cohorts were initiated in Sep 2013. As of Jan 17, 2014, 151 pts had received ≥1 dose of MEDI4736. Safety data are available for 105 pts (median age 60y; 36-84), 59% male, ECOG 0/1 (27%/71%), with a median of 3 (1-8) prior treatments, who received a median of 3 (1-8) doses. The safety profile was consistent with previous reports. Treatment-related AEs occurred in 33% of pts, with related ≥ Grade 3 AEs in 7%; none led to discontinuation of study drug. The most frequently observed treatment-related AEs were fatigue (13%), nausea (8%), rash (6%), vomiting (5%), and pyrexia (5%). One pt developed Grade 2 pneumonitis which resolved with drug interruption and steroids. There were no reports of colitis or hyperglycemia of any grade. With a median follow-up of 6 weeks, tumor shrinkage is already detectable in multiple tumor types including pts with melanoma, pancreatic, head and neck, and gastroesophageal cancer. The study continues to enroll pts and generate more mature follow-up data.

Conclusions: Preliminary data in expansion suggest the safety of MEDI4736 is acceptable, even in heavily pre-treated pts. Early evidence of clinical activity was reported in multiple tumor types. Further evaluation of MEDI4736 as monotherapy and in combination with a variety of immunomodulators and targeted agents is ongoing. Clinical trial information: NCT01693562.

MK-1775, AstraZeneca (AZN)

Phase I trial of AZD1775 (MK1775), a wee1 kinase inhibitor, in patients with refractory solid tumors.
Abstract #2503
Background: Wee1 tyrosine kinase phosphorylates and inactivates Cdk1, causing G2 cell cycle arrest in response to DNA damage. AZD1775 is a novel inhibitor of Wee1 kinase with single-agent anti-tumor activity in preclinical models. Objectives of this study were to establish the safety, toxicity, maximum tolerated dose (MTD) of single agent AZD1775; determine the pharmacokinetics (PK) of AZD1775; evaluate for target modulation in paired tumor biopsies.

Methods: Eligible adult patients (pts) had refractory cancers that had progressed on standard therapy; ECOG PS 0-2; adequate organ function. Dose level (DL) 1 was 225 mg BID x 5 doses, q 21d cycles. Dose escalation: 225 mg (DL 2) or 300 mg (DL 3) BID x 5 doses for 2 wks, q21d cycles; 3 + 3 design. Blood sampling for PK and circulating tumor cells (CTCs) occurred on C1D1 and C1D3. Tumor biopsies at MTD were performed at baseline and C1D3 (2-5 hrs post-drug) and were evaluated for pTyr15-Cdk to assess target modulation.

Results: 18 pts treated; median age 54; median # of prior therapies 4; cancer dx (#pts): sarcoma (8); NSCLC (2); head and neck (3); fallopian tube (1); cervical (1); granulosa cell tumor (1); breast (1); appendiceal cancer (1). One pt with BRCA mutated head and neck cancer had a confirmed PR. Common toxicities were myelosuppression and diarrhea. Two DLTs occurred at DL 3: 1 pt had Gr 4 myelosuppression, developed pneumonia, and died; a second pt had SVT. At the MTD of DL 2, average Cmax was 1650 nM on D3; total exposure on D3 was 2-3 fold higher than on D1. Reduction in phosphorylated Tyr15-Cdk levels was shown in 3 of 5 paired tumor biopsies; quantitation of γH2AX, a DNA damage marker, is ongoing in CTCs and tumor biopsies.

Conclusions: This is the first single-agent trial of AZD1775 in pts with refractory solid tumors. MTD was established at 225mg BID x 5 doses/week, 2 of 3 wks, with evidence of antitumor activity in a pt with BRCA mutated head and neck cancer. Accrual is ongoing for BRCA+ pts. The accumulation of drug on the BID regimen is consistent with a t1/2 of ~ 24 hrs, which supports a QD schedule for future trials. Target modulation was demonstrated in paired tumor biopsies. CTCs were isolated from 2 pts with non-epithelial cancers. Analysis of tumor biopsies and CTCs for γH2AX is ongoing. Clinical trial information: NCT01748825.

OMP-54F28, OncoMed (OMED)
A first-in-human phase 1 study of anticancer stem cell agent OMP-54F28 (FZD8-Fc), decoy receptor for WNT ligands, in patients with advanced solid tumors.
Abstract #2505

Author(s): Antonio Jimeno, Michael S. Gordon, Rashmi Chugh, Wells A. Messersmith, David S. Mendelson, Jakob Dupont, Robert J. Stagg, Ann Kapoun, Lu Xu, Rainer Karl Brachmann, David C. Smith; University of Colorado Denver, Aurora, CO; Premiere Oncology of Arizona, Scottsdale, AZ; University of Michigan, Ann Arbor, MI; University of Colorado Cancer Center, Aurora, CO; Pinnacle Oncology
Background: The WNT/FZD signaling pathway is implicated in tumor cell de-differentiation and cancer stem cell (CSC) function in numerous cancer types. As a first-in-class recombinant fusion protein, OMP-54F28 binds WNT ligands and blocks WNT signaling through its domain of an extracellular part of human Frizzled 8 receptor (fused to a human IgG1 Fc fragment). In patient-derived xenograft models, OMP-54F28 inhibits growth and CSC frequency, promotes differentiation of tumor cells, and synergizes with chemotherapy in a broad spectrum of malignancies.

Methods: A 3+3 design was used; OMP-54F28 was given intravenously every 3 weeks. Objectives were determination of maximum tolerated dose (MTD), safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy.

Results: 25 patients were treated in 7 dose-escalation cohorts (0.5, 1, 2.5, 5, 10, 15 and 20 mg/kg). No further dose escalation was pursued as animal data and PK modeling indicated 10 mg/kg as the target efficacious dose. Most common related Grade 1 and 2 adverse events (AEs; ≥20% of patients) were dysgeusia, decreased appetite, fatigue, muscle spasms, nausea, and vomiting. No related Grade ≥3 AEs were reported. OMP-54F28 had a half-life of ~4 days at ≥10 mg/kg. Consistent with WNT pathway inhibition in bone, 5 patients had doubling from baseline of bone turnover marker β-C-terminal telopeptide (β-CTX), an event that was reversible (β-CTX return to baseline) upon treatment with a single dose of zoledronic acid. PD modulation of WNT pathway genes was shown in hair follicles at ≥2.5 mg/kg. Two desmoid tumor patients have experienced stable disease (SD) for >6 months. 4 of 4 patients at 20 mg/kg with ≥1 on-study tumor assessment continue on study with SD.

Conclusions: OMP-54F28 is well tolerated up to 20 mg/kg, double the target efficacious dose. PD modulation in bone and hair follicles was observed. Several patients experienced prolonged SD. Dose escalation is completed, and 3 Phase 1b studies are ongoing (pancreas cancer with nab-paclitaxel and gemcitabine, ovarian cancer with carboplatin and paclitaxel, and hepatocellular cancer with sorafenib). Detailed efficacy, safety, PK and PD results will be presented. Clinical trial information: NCT01608867.

PF-05082566, Pfizer (PFE)
A phase 1 study of PF-05082566 (anti-4-1BB) in patients with advanced cancer.
Abstract #3007

Author(s): Neil Howard Segal, Ajay K. Gopal, Shailender Bhatia, Holbrook Edwin Kohrt, Ronald Levy, Michael J. Pishvaian, Roch Houot, Nancy Bartlett, Paul Nghiem, Stephanie Anne Kronenberg, Aron D. Thall, Ganesh Mugundu, Bo Huang, Craig Davis; Memorial Sloan Kettering Cancer Center, New York, NY; University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA; University of Washington/Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, Seattle, WA; Department of Medicine, Division of Oncology, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA; Department of Medicine, Division of Oncology, Stanford University, Stanford, CA; Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; Centre Hospitalier Universitaire Pontchaillou, Rennes, France; Siteman Cancer Center, Washington University School of Medicine in St. Louis, St. Louis, MO; University of Washington, Seattle, WA; Memorial-Sloan...
Background: 4-1BB agonists markedly enhance cytotoxic T-cell responses, resulting in anti-tumor activity in several models. PF-05082566 is a fully humanized IgG2 agonist monoclonal antibody targeting 4-1BB. This portion of the first-in-human phase I study assessed the safety, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of PF-0508256 monotherapy in patients with advanced cancer.

Methods: An open-label, dose escalation study was conducted in patients with advanced malignancies for which no curative therapy was available. Cohorts of 3-6 patients were enrolled initially using a 3+3 design (0.006 to 0.3 mg/kg), then a Time-To-Event CRM design for higher doses (0.6 to 5 mg/kg). Patients received PF-05082566 via intravenous infusion every 4 weeks (one cycle) with an 8 week period for assessment of dose-limiting toxicity (DLT). Radiographic assessments were conducted every 8 weeks, using RECIST 1.1.

Results: 27 patients have been treated with PF-05082566 up to the 0.3 mg/kg dose level, including colorectal cancer (n=11), Merkel cell carcinoma (n=6), pancreatic adenocarcinoma (n=2), and one each of nasopharyngeal cancer, ampullary cancer, squamous cell lung cancer, carcinoma of unknown primary, melanoma, sarcoma, follicular lymphoma, and lymphocytic lymphoma (SLL). 25 patients completed the DLT assessment period and 7 patients remain on therapy. All discontinuations from treatment were due to disease progression. Median number of cycles ranged from 2 (at 0.006 mg/kg) to 7 (at 0.24 mg/kg). There was no apparent relationship between increasing doses and the frequency or severity of treatment emergent adverse events, which were mostly Grade 1. One patient treated at 0.06 mg/kg had Grade 3 elevation in alkaline phosphatase. No additional significant elevations in liver enzymes and no DLTs have occurred to date. Preliminary PK data suggests a linear increase in drug exposure with increasing dose, and a half life of ~10 days. A best overall response of stable disease was observed in 22% (6/27) patients.

Conclusions: PF-05082566 was well tolerated, with evidence of disease stabilization in multiple patients. Enrollment continues at higher dose levels to obtain additional safety, PK, PD, and efficacy data. Clinical trial information: NCT01307267.

RXDX-101, Ignyta (RXDX)
Phase 1 open label, dose escalation study of RXDX101, an oral pan-trk, ROS1, and ALK inhibitor, in patients with advanced solid tumors with relevant molecular alterations.
Abstract #2502

Author(s): Filippo G. De Braud, Lorenzo Pilla, Monica Niger, Silvia Damian, Benedetta Bardazza, Antonia Martinetti, Giuseppe Pelosi, Giovanna Marrapase, Laura Palmeri, Giulio Cerea, Emanuele Valtorta, Silvio Veronese, Andrea Sartore-Bianchi, Elena Ardini, Marcella Martignoni, Arturo Galvani, Paul Pearson, David Luo, James L. Freddo, Salvatore Siena; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Niguarda Cancer Center, Ospedale Niguarda Ca' Granda, Milan, Italy; Niguarda Cancer Center, Ospedale Niguarda Ca' Granda, Milano, Italy; Nerviano Medical Sciences, Nerviano, Italy; CLInical Organization for Strategies & Solutions (ClioSS), NMS Group, Nerviano, Italy; Ignyta, Inc., San Diego, CA; Ignyta, Inc, San Diego, CA
Background: RXDX-101 is an oral small molecule inhibitor of TrkA, TrkB and TrkC, as well as ROS1 and ALK, with high potency and selectivity. RXDX-101 has demonstrated potent pharmacological activity in preclinical studies and has the potential to be first-in-class against the Trk family of kinases. This study aims to determine the MTD, PD, PK, and anti-tumor activity in patients with advanced cancer with applicable molecular alterations.

Methods: Phase 1 dose escalation in patients with advanced solid tumors. Patients were treated with RXDX-101, dosed orally once each day in a 4 day on, 3 day off schedule for 3 weeks, followed by a 7 day rest period, in continuous 28-day cycles. A minimum of 3 patients were enrolled at each dose level. Endpoints include safety, PK, and tumor response by RECIST.

Results: 17 patients have been treated at 5 dose levels (100, 200, 400, 800, and 1200 mg/m2). RXDX-101 has been well tolerated to date; the MTD has not been reached in this trial. The most common AEs (all grade 1-2), considered possibly treatment-related, included paresthesias, nausea, dysgeusia, and diarrhea. No treatment related grade 3/4 AEs or SAEs were observed; one patient had grade 3 dyspnea considered to be disease-related. No DLTs seen to date. A patient with neuroblastoma (ALK+) has a PR and is in cycle 13. Two patients have prolonged stabilization of their disease and remain on treatment; a patient with NSCLC (ALK+) in cycle 11, and a patient with pancreatic cancer (ROS1+) in cycle 8. PK analysis shows maximum concentrations of RXDX-101 were generally achieved within 2 to 4 hours following dosing. Despite a degree of variability, RXDX-101 exposure (Cmax and AUC) increased with dose, with minimal accumulation following multiple doses. Average terminal half-life was ~21 hours across the dose range of 100 to 400 mg/m2/day, but increased to 32 hours in patients treated with 800 mg/m2/day; steady state was reached within 4-days.

Conclusions: RXDX-101 has been well tolerated in patients with advanced solid tumors. Continued clinical development is supported by the tolerability and early evidence of antitumor activity in patients with relevant molecular alterations.

SAR125844, Sanofi (SNY)
A first-in-human (FIH) phase I study of SAR125844, a novel selective MET kinase inhibitor, in patients (pts) with advanced solid tumors: Dose escalation results.
Abstract #2506

Author(s): Eric Angevin, Gianluca Spitaleri, Antoine Hollebecque, Tommaso De Pas, Jean-Charles Soria, Marzia Harnois, Florent Mazuir, Sylvie Assadourian, Filippo De Marinis; Institut Gustave Roussy, Villejuif, France; European Institute of Oncology, Milan, Italy; Drug Development Department (DITEP), Gustave Roussy, Cancer Campus, Grand Paris, Villejuif, France; Instituto Europeo di Oncologia, Milan, Italy; Drug Development Department (DITEP), Gustave Roussy Institute, Villejuif, France; Sanofi R&D, Vitry-sur-Seine, France; Sanofi R&D, Chilly-Mazarin, France; 1st Oncological Pulmonary Unit, San Camillo, High Specialization Hospital, Rome; and European Institute of Oncology, Milano, Italy

Background: SAR125844 (SAR) is a potent and highly selective MET kinase inhibitor (IC50= 4.2 nM; Ki = 2.8 nM) demonstrated to be effective in MET-driven tumors with a good safety and pharmacokinetics (PK) profiles in preclinical models. This FIH phase I study was designed to determine the maximum tolerated dose (MTD), assess tolerance, PK and pharmacodynamics of SAR.
**Methods:** Escalating doses of SAR, using a standard 3+3 escalation scheme, were administered intravenously (IV) every week in solid tumor pts with either high membrane total-MET protein expression or cMET-gene amplification.

**Results:** 33 heavily pre-treated pts were enrolled: 17M/16F, median age 56 [range 27-75], ECOG-PS 0/1:10/23 with a variety of solid tumors including 9 colorectal and 9 lung adenocarcinomas. A total of 434 infusions (median 10 [range 1-57]) of SAR was administered across 9 Dose Levels (DLs) ranging from 50 to 740 mg/m². DLTs were observed in 2 pts during the first 4 weeks consisting in grade (Gr) 3 transaminase increase (TI): 1 pt at 740mg/m² and 1 pt at 570mg/m². Recovery was obtained with dose omission and dose reduction. A Gr2 creatinine increase in 1 pt at 740mg/m² was also taken into account for dose selection. No dose-dependent adverse events (AE) were observed. No Gr≥3 related clinical toxicity was observed. Main drug-related Gr1-2 toxicities included: nausea/vomiting (33.3%), fatigue (18.2%), diarrhoea (15.2%), headache (12.1%), infusion site phlebitis (12.1%), pyrexia (9.1%). Blood exposure PK parameters (AUC and Cmax) increased in proportion with the dose, with a mean clearance of 32.2 L/h associated with a large volume of distribution (528L). Preliminary anti-tumor activity was observed at 570mg/m² with one partial response among a cMET-gene amplification lung adenocarcinoma pt. Seven pts with tumors not harbouring cMET-gene amplification experienced a long lasting stabilization over 3 months.

**Conclusions:** SAR is well tolerated with early evidence of activity. SAR 570 mg/m² is currently being confirmed in 2 extension cohorts. Clinical trial information: NCT01391533.

**CASTLEMAN’S DISEASE**

**Sylvant, Johnson & Johnson (JNJ)**

**Efficacy of siltuximab in patients with previously treated multicentric Castleman’s disease (MCD).**

Abstract #8514

Author(s): Frits Van Rhee, Nikhil C. Munshi, Raymond Wong, Xiaoyan Ke, Alexander Fossa, David Simpson, Angela Dispenzieri, Mary Jo Lechowicz, John Kuruvilla, Rajesh Bandekar, Xiang Qin, Ming Qi, Jessica Vermeulen, Corey Casper; Myeloma Institute for Research and Therapy, Little Rock, AR; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, Hong Kong; Peking University Third Hospital, Beijing, China; Oslo University Hospital, Oslo, Norway; North Shore Hospital, Takapuna Auckland, New Zealand; Mayo Clinic, Rochester, MN; The Winship Cancer Institute of Emory University, Atlanta, GA; University Health Network, Princess Margaret Cancer Centre, Toronto, ON, Canada; Janssen Research and Development, Spring House, PA; Janssen Research and Development, Leiden, Netherlands; Fred Hutchinson Cancer Research Center, Seattle, WA

**Background:** Siltuximab is a chimeric anti−IL-6 monoclonal antibody under investigation for treatment of MCD. A randomized, double-blind, placebo-controlled study in MCD showed significant improvement in durable tumor and symptomatic response (34.0% vs 0.0% with placebo; P = 0.001), superior response in the secondary endpoints of tumor response rate, time to treatment failure, MCD symptom improvement, and no increased frequency of adverse events compared with placebo. A prespecified subanalysis evaluated the efficacy of siltuximab among patients who had received prior systemic therapy.
Methods: Adults with confirmed symptomatic MCD were randomized 2:1 to siltuximab 11 mg/kg (n = 53) or placebo (n = 26) IV every 3 weeks and were stratified by corticosteroid use at randomization. All patients received best supportive care, and treatment was continued until treatment failure.

Results: The majority (siltuximab, n = 29 [54.7%]; placebo, n = 17 [65.4%]) of patients had received prior systemic treatment for MCD. The most frequently used agents included corticosteroids 93.5%, cyclophosphamide 50%, vincristine 26.1% and rituximab 17.4%. Durable tumor and symptomatic responses were similar for pretreated and treatment naïve subgroups (34.5 % vs 0% and 33.3 % vs 0% respectively). Secondary endpoints consistently favored siltuximab in both subgroups as presented in the Table. Frequencies of adverse events (AE) and serious (S) AEs were similar across pretreated and treatment naïve subjects.

Conclusions: Siltuximab is an active agent in both newly diagnosed MCD and patients who have insufficient response to or failed other therapies. Clinical trial information: NCT01024036.

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<th>Pretreated MCD patients</th>
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<td>Durable tumor and symptom response by investigator</td>
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<td>0%</td>
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<td>Median time to treatment failure</td>
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<td>Hemoglobin increase &gt; 1.5 g/dL in anemic subjects</td>
<td>59% (n = 17)</td>
<td>0% (n = 7)</td>
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<td>Durable complete symptomatic response</td>
<td>17%</td>
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CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

NEPA, Helsinn
Phase 3 study of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting during repeated moderately emetogenic chemotherapy (MEC) cycles.
Abstract #9502

Author(s): Matti S. Aapro, Meinolf Karthaus, Lee Steven Schwartzberg, Giorgia Rossi, Giada Rizzi, Maria Elisa Borroni, Marco Palmas, Hope S. Rugo; Clinique de Genolier, Genolier, Switzerland; Klinikum Neuperlach, Munich, Germany; The University of Tennessee Health Science Center, Memphis, TN;
Background: Antiemetic guidelines recommend co-administration of targeted prophylactic medications aimed at inhibiting several molecular pathways involved in emesis. NEPA is a novel, fixed-dose combination of a new NK₁ receptor antagonist (RA), netupitant (NETU 300 mg), and palonosetron (PALO 0.50 mg), a pharmacologically distinct 5-HT₃RA. NEPA was previously shown to be superior to PALO after a single chemotherapy (CT) cycle in this study; maintenance of efficacy/safety over continuing cycles has been evaluated as a secondary objective.

Methods: This multinational, randomized, double-blind, parallel group study assessed the efficacy/safety of single oral doses of NEPA versus PALO in chemotherapy-naive patients (pts) receiving multiple cycles of anthracycline-based CT. All pts also received oral dexamethasone (DEX) 12 mg (NEPA) or 20 mg (PALO) on Day 1. Efficacy endpoints were complete response (CR: no emesis, no rescue medication) and no significant nausea (<25 mm on 100 mm VAS).

Results: 1,455 pts were randomized; 1286 participated in the multiple cycle extension. Patients participated in 5969 total CT cycles; 76% completed at least 4 cycles. Treatment groups were comparable; female (98%), white (80%), mean age of 54 yrs. The superiority of NEPA over PALO for overall (0-120 hr) CR during Cycle 1 was maintained over multiple CT cycles. A greater proportion of NEPA-treated pts also had no significant nausea over repeated cycles. Most frequently reported study drug-related adverse events (AEs) for NEPA included headache (3.5%) and constipation (2.0%) during the multiple cycle extension. The type/incidence of AEs were similar for NEPA and PALO.

Conclusions: NEPA, a novel, fixed-dose combination targeting dual antiemetic pathways, is highly effective and safe over multiple cycles of MEC. A single dose of NEPA + DEX on Day 1 of CT offers guideline-based prophylaxis with a convenient, single-day treatment. Clinical trial information: NCT01339260.

Overall CR rates (% patients) | NEPA | PALO | P value
--- | --- | --- | ---
Cycle 1 | N = 724 | 74.3% | 66.6% | 0.001
Cycle 2 | N = 635 | 80.3% | 66.7% | <0.0001
Cycle 3 | N = 598 | 83.8% | 70.3% | <0.0001
Cycle 4 | N = 551 | 83.8% | 74.6% | <0.0001
COLORECTAL CANCER

Avastin, Roche
Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine + bevacizumab versus observation after induction treatment with chemotherapy + bevacizumab in metastatic colorectal cancer (mCRC).
Abstract #3504

Author(s): Miriam Koopman, Lieke Simkens, Anne Maria May, Linda Mol, Harm van Tinteren, Cornelis J. A. Punt; University Medical Center Utrecht, Utrecht, Netherlands; Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; Integraal Kankercentrum Nederland, Nijmegen, Netherlands; Department of Statistics, The Netherlands Cancer Institute, Amsterdam, Netherlands

Background: We investigated the efficacy of maintenance treatment with capecitabine (cap) + bev versus observation in mCRC patients (pts) not progressing during induction treatment with cap, oxaliplatin and bev (CAPOX-B).

Methods: Previously untreated mCRC pts with stable disease or better after 6 cycles of CAPOX-B were randomized between observation (arm A) or maintenance treatment with cap 625 mg/m2 bid daily continuously + bev 7.5 mg/kg iv q 3 weeks (arm B). Upon first progression (PFS1), pts in both arms were to be treated with CAPOX-B until 2nd progression (PFS2, primary endpoint). Secondary endpoints were overall survival (OS) and time to 2nd progression (TTP2), which was defined as the time to progression on any treatment following PFS1, and quality of life (QoL). Preplanned subset analyses were performed.

Results: A total of 558 pts were randomized. Upon PFS1, CAPOX-B was reintroduced in 61% of pts in arm A and 47% in arm B. There was a significant benefit for maintenance treatment for PFS1, TT2PD and PFS2 with a median of 8.5 m vs 11.7 m, respectively (HR 0.67, p < .0001). Multivariable analysis showed a significant interaction for treatment with OS. Subgroup analysis showed a significant interaction for treatment in pts with synchronous metastases with resected primary tumor (n=180): median OS 18.0 m (A) vs 25.0 m (B) (p <0.0001), and for pts with complete/ partial response to induction treatment before randomization (n=366) with median OS of 18.8 m (A) and 24.1 m (B; p < .0001). QoL was maintained during maintenance treatment, and was clinically not inferior compared to QoL in the observation arm.

Conclusions: Final CAIRO3 results establish the benefit of maintenance treatment with cap + bev after first-line induction treatment in pts with mCRC. Multivariable analysis shows a significant interaction of treatment with OS. Our finding that the positive effect on survival for maintenance treatment is most pronounced in pts with synchronous disease and resected primary tumor and with PR/CR to induction treatment should be confirmed.

Erbitux, Eli Lilly (LLY)
Treatment outcome according to tumor RAS mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab.
Abstract #3505

Author(s): Carsten Bokemeyer, Claus-Henning Kohne, Fortunato Ciardiello, Heinz-Josef Lenz, Volker Heinemann, Ute Klinkhardt, Frank Beier, Klaus Duecker, Sabine Tejpar; Department of Oncology,
Background: The addition of cetuximab to FOLFOX4 significantly improved progression-free survival and response in the first-line treatment of patients (pts) with \textit{KRAS} codon 12/13 (hereinafter exon 2) wild-type (wt) mCRC. Pts with \textit{KRAS} exon 2 tumor mutations showed no such cetuximab benefit, with a trend for worse outcome.

Methods: Available \textit{KRAS} exon 2 wt tumors from OPUS study pts were screened for 26 mutations (new \textit{RAS}) in 4 additional \textit{KRAS} codons (exons 3 and 4) and 6\textit{NRAS} codons (exons 2, 3 and 4) using BEAMing technology (5\% sensitivity cutoff selected for analysis). Outcome was assessed according to \textit{RAS} mutation status (\textit{KRAS} exon 2 + new \textit{RAS}).

Results: Mutation status was evaluable in 118/179 (66\%) pts with \textit{KRAS} exon 2 wt tumors. New \textit{RAS} mutations were detected in 31/118 (26\%) pts. In those with \textit{RAS} wt tumors, response was significantly improved by the addition of cetuximab to FOLFOX4 (Table). The treatment effect for those with new \textit{RAS} tumor mutations could not be definitively assessed due to low pt numbers. In pts with any tumor \textit{RAS} mutation (\textit{KRAS} exon 2 + new \textit{RAS}), no benefit from the addition of cetuximab to FOLFOX4 was seen, with a clear trend for worse outcome.

Conclusions: Pts with mCRC harboring any activating \textit{RAS} mutation are unlikely to benefit from the addition of cetuximab to FOLFOX4. Restricting cetuximab administration to pts with tumors wt at all such loci might help further tailoring of therapy to maximize pt benefit. Clinical trial information: NCT00125034.
### Treatment outcome according to tumor RAS mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab.

**Abstract #3506**

Author(s): Fortunato Ciardiello, Heinz-Josef Lenz, Claus-Henning Kohne, Volker Heinemann, Sabine Tejpar, Ivan Melezinek, Frank Beier, Christopher Stroh, Eric Van Cutsem; Medical Oncology, Second University of Naples, Naples, Italy; Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Onkologie Klinikum Oldenburg, Oldenburg, Germany; Department of Medical Oncology, Klinikum Grosshadern, University of Munich, Munich, Germany; University of Leuven, KUL, Leuven, Belgium; Merck KGaA, Darmstadt, Germany; University Hospitals Leuven, Leuven, Belgium

<table>
<thead>
<tr>
<th>Parameter</th>
<th><strong>RAS wt</strong> (all loci)</th>
<th><strong>New RAS mt</strong></th>
<th><strong>RAS mt</strong> (any locus)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOLFOX4 + cet</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Response rate, %</td>
<td>57.9</td>
<td>26.6</td>
<td>53.3</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>3.33</td>
<td></td>
<td>1.50</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.36–8.17</td>
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<tr>
<td>P value‡</td>
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<tr>
<td>Median progression-free survival, months</td>
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<td>7.5</td>
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<tr>
<td>HR</td>
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<td>95% CI</td>
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<tr>
<td>95% CI</td>
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<td>P value§</td>
<td>0.80</td>
<td>0.86</td>
<td>0.157</td>
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</tbody>
</table>

Abbreviations: cet, cetuximab; HR, hazard ratio; mt, mutant; *RAS evaluable population, N=118; †Subset of the OPUS KRAS evaluable population, N=315; ‡Cochran-Mantel-Haenszel; §log-rank.

**Erbitux, Eli Lilly (LLY)**

**Treatment outcome according to tumor RAS mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab.**

**Abstract #3506**

Author(s): Fortunato Ciardiello, Heinz-Josef Lenz, Claus-Henning Kohne, Volker Heinemann, Sabine Tejpar, Ivan Melezinek, Frank Beier, Christopher Stroh, Eric Van Cutsem; Medical Oncology, Second University of Naples, Naples, Italy; Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Onkologie Klinikum Oldenburg, Oldenburg, Germany; Department of Medical Oncology, Klinikum Grosshadern, University of Munich, Munich, Germany; University of Leuven, KUL, Leuven, Belgium; Merck KGaA, Darmstadt, Germany; University Hospitals Leuven, Leuven, Belgium
Background: The addition of cetuximab to FOLFIRI significantly improved progression-free survival, overall survival and response in the first-line treatment of patients (pts) with KRAS codon 12/13 (hereinafter exon 2) wild-type (wt) mCRC. Pts with KRAS exon 2 tumor mutations showed no cetuximab treatment benefit.

Methods: Available KRAS exon 2 wt tumors from CRYSTAL study pts were screened for 26 mutations (new RAS) in 4 additional KRAS codons (exons 3 and 4) and 6 NRAS codons (exons 2, 3 and 4) using BEAMing technology (5% sensitivity cutoff selected for analysis). Outcome was assessed according to RAS mutation status (KRAS exon 2 + new RAS).

Results: Mutation status was evaluable in 430/666 (65%) pts with KRAS exon 2 wt tumors. New RAS mutations were detected in 63/430 (15%) pts. In those with RAS wt tumors, a significant benefit across all endpoints was associated with the addition of cetuximab to FOLFIRI (Table). In pts with newRAS tumor mutations, no clear difference in efficacy outcomes between treatment groups was seen. In pts with any tumorRAS mutation (KRAS exon 2 + new RAS), no benefit from the addition of cetuximab to FOLFIRI was apparent.

Conclusions: In the first-line treatment of mCRC, pts with RAS wt tumors derived a marked benefit from the addition of cetuximab to FOLFIRI; pts with RAS tumor mutations did not benefit. This finding may allow the further tailoring of cetuximab therapy to maximize pt benefit. Clinical trial information: NCT00154102.

<table>
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<tr>
<th>Parameter</th>
<th>RAS wt* (all loci)</th>
<th>New RAS mt*</th>
<th>RAS mt† (any locus)</th>
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<td>Parameter</td>
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<tr>
<td>Response rate, %</td>
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<td>31.7</td>
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<td>P value‡</td>
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<td>7.4</td>
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<tr>
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<td>18.2</td>
<td>16.4</td>
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<tr>
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<td>0.69</td>
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<tr>
<td>95% CI</td>
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</tr>
<tr>
<td>P value§</td>
<td>0.0024</td>
<td>0.50</td>
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ESOPHAGAEL CANCER

Erbitux, Eli Lilly (LLY)
RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery.
Abstract #4007

Author(s): David H. Ilson, Jennifer Moughan, Mohan Suntharalingam, Adam Dicker, Lisa A. Kachnic, Andre A. Konski, Bapsi Chakravarthy, Chris Anker, Harish V. Thakrar, Naomi Horiba, Vivek Kavadi, Melvin Deutsch, Adam Raben, Kevin S. Roof, John H. Suh, Jonadavid Pollock, Howard Safran, Christopher H. Crane; Memorial Sloan Kettering Cancer Center, New York, NY; Statistical Center, Radiation Therapy Oncology Group, Philadelphia, PA; University of Maryland Greenebaum Cancer Center, Baltimore, MD; Department of Radiation Oncology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; Boston University Medical Center, Boston, MA; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Vanderbilt-Ingram Cancer Center, Nashville, TN; University of Utah, Salt Lake City, UT; John H. Stroger Jr. Hospital of Cook County, Chicago, IL; University of Maryland, Baltimore, MD; USOR-Texas Oncology, Sugarland, TX; University of Pittsburg Medical Center, Pittsburgh, PA; Helen F. Graham Cancer Center, Wilmington, DE; Southeast Radiation Oncology, Charlotte, NC; Cleveland Clinic, Cleveland, OH; Schiffler Cancer Center, Wheeling, WV; Brown University Oncology Research Group, Providence, RI; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: RTOG 0436 is a randomized Ph III trial evaluating cetuximab added to concurrent chemoradiation for patients (pts) undergoing non-operative management of esophageal carcinoma (EC).

Methods: Pts with biopsy proven squamous cell or adenocarcinoma of the esophagus (T1N1M0; T2-4 AnyN M0; Any T/N M1a) were randomized to weekly concurrent cisplatin (50 mg/m2), paclitaxel (25 mg/m2) for 6 weeks and daily radiation 50.4 Gy/1.8 Gy fractions ± weekly cetuximab (400 mg/m2 day 1 then weekly 250 mg/m2) for 6 weeks. Pts were stratified by histology, tumor size (< 5 cm vs > 5cm) and the status of celiac lymph nodal involvement. Overall survival (OS) was the primary endpoint, with a planned accrual of 420 pts to detect an increase in 2-year OS from 41% to 53%; 80% power and 1-sided 0.025 alpha. An interim analysis of cCR was planned for the first 150 of each histology.

Results: The study accrued 344 pts from 2008-2013 and 328 were eligible. Based on interim analyses, the study stopped accruing adeno pts in 5/2012 and SCC pts in 1/2013. Pts were well matched for pretreatment characteristics: 80% T3/4 disease, 66% N1, and 19% celiac nodes. Grade 3/4/5 treatment (tx) related AEs were 45%, 22%, 4% in Arm 1 (cetuximab) and 49%, 17%, 1% in Arm 2 (no cetuximab). A cCR rate of 56% was observed in Arm 1 vs 59% in Arm 2 [p=0.72]. No differences were seen in cCR between tx arms for either histology. The 12 and 24 mo OS rates for cCR pts were 79% and 58% vs 53% and 30% for those with residual disease [p<0.0001]. Median follow-up for all pts is 15.4 mos. The 12 and 24 mo OS (95% CI) for Arm 1 is 64% (56%, 71%) and 44% (36%, 52%) vs 65% (57%, 72%) and 42% (34%, 50%) for Arm 2 [p=0.70]. Adeno pts (n=203) had a 12 and 24 mo OS of 65% and 43% for Arm 1 vs 64%
and 41% for Arm 2 [p=0.37]. The 12 and 24 mo OS for the 125 SCC pts was 62% and 46% for Arm 1 vs 67% and 43% for Arm 2 [p=0.97].

**Conclusions:** Cetuximab added to chemoradiation did not improve OS. There were no differences in cCR rates by tx arm. These results add to the growing body of literature indicating no benefit for current EGFR targeted agents in the tx of unselected patients with EC. Supported by RTOG CA21661 and CCOP CA3742 NCI grants and Bristol Myers Squibb. Clinical trial information: NCT00655876.

**GASTRIC CANCER**

**Apatinib, LSK BioPartners**  
Phase III study of apatinib in advanced gastric cancer: A randomized, double-blind, placebo-controlled trial.  
Abstract #4003

Author(s): Shukui Qin; PLA Cancer Center of Nanjing Bayi Hospital, Nanjing, China

**Background:** Molecular targeted therapy has made great progress in the treatment of gastric cancer. This paper reports the outcome of a phase III clinical study of apatinib, as an oral small molecular of VEGFR-2 tyrosine kinase inhibitor, in the treatment of patients with advanced gastric cancer who prior failure to second-line chemotherapy. This study may provide a new treatment options and leading a new hope for these patients.

**Methods:** This is a multicenter, randomized, double-blind, placebo-controlled phase 3 trial. Apatinib or matching placebo, 850 mg, po, qd, 28 days as one cycle. Primary outcomes were overall survival. Study randomization was centralized and stratified according to the number of metastatic sites (≤2 or >2). Planned to enroll 270 cases: 180 of apatinib and 90 of placebo. This trial was registered with ClinicalTrials.gov, number NCT01512745.

**Results:** The patient baseline characteristics were similar in two arms in regards to age, historical of the disease, gender, ECOG scores, number of metastatic sites, pathological grading, clinical stage and therapy history(P>0.05). As the efficacy, median overall survival (mOS) was significantly prolonger in the apatinib group compare with in the placebo group (195 days versus 140 days ; HR= 0.71; 95% CI (0.54~0.94); p< 0.016). Median progression-free survival (mPFS) was also prolonged in the apatinib group compared with the placebo group (78 days versus 53 days, HR= 0.44, 95%CI (0.33~0.61), P<0.0001). The objective response rates (ORR) of apatinib group and placebo group were 2.84% and 0.00% respectively. As the safety, Treatment of apatinib group was generally well tolerated. Most of the adverse reaction could be managed by dose interruptions or reductions. Grade 3/4 adverse reactions that occurred in more than 2% of patients were hypertension, hand-and-foot syndrome, proteinuria, fatigue, anorexia, elevated aminotransferase.

**Conclusions:** This study further confirmed the efficacy and safety of apatinib in the patients with advanced gastric cancer. 850 mg, qd is the recommended dose for clinical use. Clinical trial information: NCT01512745.
**Cyramza, Eli Lilly (LLY)**

**Ramsirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial.**

Abstract #4004

Author(s): Harry H. Yoon, Johanna C. Bendell, Fadi S. Braiteh, Irfan Firdaus, Philip Agop Philip, Allen Lee Cohn, Nancy Lewis, Daniel M. Anderson, Edward Arrowsmith, Jonathan D. Schwartz, Yihuan Xu, Minoru Koshiji, Steven R. Alberts, Zev A. Wainberg, Mayo Clinic, Rochester, MN; Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Sarah Cannon Research Institute/Oncology Hematology Care, Inc, Cincinnati, OH; Karmanos Cancer Center, Detroit, MI; Rocky Mountain Cancer Center/US Oncology, Denver, CO; Kimmel Cancer Center of Thomas Jefferson University, Philadelphia, PA; Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, MN; Sarah Cannon Research Institute/Tennessee Oncology, Chattanooga, TN; ImClone Systems, a wholly-owned subsidiary of Eli Lilly & Co, Branchburg, NJ; ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, Kobe, Japan; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA

**Background:** RAM, an anti-VEGFR2 monoclonal antibody, improved overall survival (OS) in 2 phase 3 trials in patients (pts) with previously treated gastric/gastroesophageal junction (GEJ) AC. We report the first assessment of RAM as 1st-line Rx for GE-AC.

**Methods:** Pts with untreated metastatic or locally advanced unresectable GE-AC (PS ≤1) were randomized 1:1 to mFOLFOX6 plus RAM (8 mg/kg IV) v placebo (PL), q14d. Primary endpoint was progression-free survival (PFS), with 80% power to detect HR 0.71 (α = .3). Secondary endpoints included OS, response rate (RR), disease control rate (DCR), and safety.

**Results:** 168 pts (RAM 84 v PL 84) enrolled at 47 US sites, 04/11 – 08/12. Pt characteristics: age (65 v 60); male (75% v 73%); gastric (23% v 24%), GEJ (31% v 27%), esophageal (46% v 49%); metastatic (95% v 94%). Median PFS 6.4 v 6.7 m (HR 0.98 [95% CI 0.69 – 1.37]; p = .89) and OS 11.7 v 11.5 m (HR 1.08 [0.73-1.58]). Subgroup analyses by primary tumor location: for esophageal, median PFS was 5.6 v 6.1 m (HR 1.30); for gastric/GEJ, PFS was 8.7 v 7.1 m (HR 0.77 [0.48 – 1.24]; p = .28) and OS 14.6 v 12.5 m. PFS rate at 3 m was higher in RAM v PL (89% v 75%, p = .020), but not at 6, 9, or 12 m. RR (CR, PR) 45% v 46%. DCR (SD, CR, PR) 85% v 67% (p = .008). Most common grade ≥3 adverse events (AEs): neutropenia (27% v 36%), fatigue (18% v 15%), neuropathy (9% v 11%). Grade ≥3 AEs of special interest were uncommon, except hypertension. Median cycles of OX were similar among arms (8.5 v 9.5), but cycles of 5FU or RAM/PL (both 9 v 11) were lower in RAM arm. Rx discontinuation for non-progressive disease (PD) was more common in RAM: pt/physician decision (27% v 10%), AEs (21% v 6%). In exploratory analyses that censored PFS at Rx discontinuation for non-PD, HR for PFS favored RAM arm (HR 0.76; p = .194), mainly in gastric/GEJ pts (PFS 9.3 v 7.6 m; HR 0.53 [0.29 – 0.97]; p = .036).

**Conclusions:** Addition of RAM to FOLFOX did not improve median PFS but showed PFS difference at 3 m and improved DCR. Longer PFS in RAM v PL was observed in gastric/GEJ cancer pts. A higher non-PD discontinuation rate and lower drug exposure in RAM arm may have impacted PFS assessment. These data are critical for clinical development of RAM in gastric cancer. Clinical trial information: NCT01246960.
**Cyramza, Eli Lilly (LLY)**

RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy—Efficacy analysis in Japanese and Western patients.

Abstract #4005

Author(s): Shuichi Hironaka, Yasuhiro Shimada, Naotoshi Sugimoto, Yoshito Komatsu, Tomohiro Nishina, Kensei Yamaguchi, Yoshihiko Segawa, Yasushi Omuro, Takao Tamura, Toshihiko Doi, Seigo Yudisawa, Hirofumi Yasui, Fumio Nagashima, Masahiro Gotoh, Taito Esaki, Michael Emig, Kumari Chandrawansa, Kei Muro, Hansjochen Wilke, Atsushi Ohtsu; Clinical Trial Promotion Department, Chiba Cancer Center, Chiba, Japan; Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan; Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; Department of Cancer Center, Hokkaido University Hospital, Sapporo, Japan; Department of Gastroenterology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; Division of Gastroenterology, Saitama Cancer Center, Kita-adachi-gun, Japan; Department of Medical Oncology, Saitama Medical University International Medical Center, Hidaka, Japan; Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan; Nara Hospital Kinki University Faculty of Medicine, Ikoma, Japan; Division of Digestive Endoscopy/Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Tochigi Cancer Center, Utsunomiya City, Japan; Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; Kyorin University Hospital, Tokyo, Japan; Cancer Chemotherapy Center, Osaka Medical College Hospital, Osaka, Japan; Eli Lilly and Company, Heidelberg, Germany; Eli Lilly and Company, Bridgewater, NJ; Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; Kliniken Essen Mitt

**Background:** RAINBOW, a global phase III trial, demonstrated significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in patients (pts) with mGC receiving RAM, a human IgG1 VEGF-receptor-2 targeted antibody, plus PTX compared with PL plus PTX. In global trials for mGC, regional differences in survival outcomes have been reported. Here, we analyzed clinical outcomes of Japanese (JP) pts and Western (Europe, US, Australia) pts.

**Methods:** Eligibility included Eastern Cooperative Oncology Group performance status ≤1, adequate organ function, and disease progression during or within 4 months of the last dose of first-line therapy. OS and PFS were compared using a stratified log-rank test. ORR was analyzed using a Cochran-Mantel-Haenszel test.

**Results:** Of 665 patients randomized worldwide, 140 were JP pts and 398 were Western pts. Efficacy results are shown in the Table.

**Conclusions:** Benefit was seen in PFS, ORR, and the 6-mos OS rate in the JP population, which was consistent with the Western population. Prolonged post-progression survival in JP pts may be due to higher use of post-discontinuation treatment (PDT) and may have masked the potential OS benefit. Clinical trial information: NCT01170663.
### GASTROINTESTINAL STROMAL TUMORS (GIST)

**Gleevec, Novartis (NVS)**

Long-term disease control of advanced gastrointestinal stromal tumors (GIST) with imatinib (IM): 10-year outcomes from SWOG phase III intergroup trial S0033.

Abstract #10508

Author(s): George D. Demetri, Cathryn J Rankin, Robert S. Benjamin, Ernest C. Borden, Christopher W. Ryan, Dennis A. Priebat, William D. Tap, Margaret von Mehren, Martin E. Blackstein, Michael C. Heinrich

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<table>
<thead>
<tr>
<th></th>
<th>Japanese</th>
<th>Western</th>
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<tbody>
<tr>
<td></td>
<td>RAM+PTX n=68</td>
<td>PL+PTX n=72</td>
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<tr>
<td>mPFS, mos</td>
<td>5.6</td>
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<tr>
<td>HR, 95% CI</td>
<td>0.503 (0.348-0.728) P=0.0002</td>
<td>0.631 (0.506-0.786) P&lt;0.0001</td>
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<tr>
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<td>11.5</td>
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<td>HR, 95% CI</td>
<td>0.880 (0.603-1.284) P=0.5113</td>
<td>0.726 (0.580-0.909) P=0.0050</td>
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<tr>
<td>mOS, mos</td>
<td>6-mos OS, %</td>
<td>12-mos OS, %</td>
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<tr>
<td>ORR, %</td>
<td>47.1</td>
<td>48.6</td>
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<td>2.51 (1.49-4.23) P=0.0004</td>
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<tr>
<td>HR, 95% CI</td>
<td>0.338 (0.124-0.922) P=0.0298</td>
<td>0.685 (0.518-0.906) P=0.0076</td>
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</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; m, median; mos, months; PDT, postdiscontinuation therapy.
Background: S0033 was designed to study the impact of IM, randomized between two doses, in patients (pts) with incurable GIST.

Methods: Full accrual to this phase III trial occurred over 8 months, ending 01SEP2001. A study amendment allowed collection of additional clinical information on long-term survival outcomes and annotation of any therapies subsequent to IM.

Results: Of 695 eligible patients, 180 (26%) survived 8 years or longer [94 on IM 400 mg/day arm and 86 on IM 800 mg/d arm]. The 10-year estimate of overall survival (OS) across both study arms combined is 22% (95% confidence interval (CI)=19-26%). Additional therapy information was obtained for 137 long-term survivors: IM was the sole therapy, administered continuously, in 49%; fifty-four (39%) received subsequent systemic agents, including sunitinib (41) and sorafenib (16). Local therapies, including surgical resection of metastases, radiofrequency ablation, and radiation therapy were also utilized in subsets. Univariate analyses with long-term survival data show that pts whose tumors harbored a KIT exon 9 mutation had a significantly shorter OS than those with KIT exon 11 mutations (p=0.0013) or KIT/PDGFRA wild-type (WT) genotypes (0.047).

Conclusions: A significant subset of pts with metastatic GIST achieved durable long-term overall survival with single-agent IM. Further investigation of what enables pts to live progression-free for more than a decade is warranted to optimize treatment approaches in this oncogene-driven disease, as well as to improve outcomes for more challenging molecular subsets, including KIT exon 9 or SDH-deficient (KIT/PDGFRα WT) GIST. Clinical trial information: NCT00009906.

Inclusig, Ariad (ARIA)
A phase 2 study of ponatinib in patients (pts) with advanced gastrointestinal stromal tumors (GIST) after failure of tyrosine kinase inhibitor (TKI) therapy: Initial report.
Abstract #10506

Author(s): Michael C. Heinrich, Margaret vonMehren, George D. Demetri, Jonathan A. Fletcher, Jichao Sun, J. Graeme Hodgson, Victor M. Rivera, Christopher D. Turner, Suzanne George; OHSU Knight Cancer Institute and Portland VA Medical Center, Portland, OR; Fox Chase Cancer Center, Philadelphia, PA; Dana-Farber Cancer Institute, Boston, MA; Brigham and Women’s Hospital/Harvard Medical School, Boston, MA; Ariad Pharmaceuticals, Inc., Cambridge, MA; ARIAD Pharmaceuticals, Inc., Cambridge, MA
Background: Ponatinib is an oral TKI that has potent preclinical activity against several mutant isoforms of KIT, including secondary exon 17 resistance mutants, and PDGFRA. Its preclinical activity against a broad spectrum of clinically-relevant resistance mutations suggests it may provide clinical benefit in pts with GIST resistant to standard approved TKI therapies.

Methods: This phase 2 single arm trial evaluates efficacy and safety of ponatinib at 45 mg QD in advanced GIST pts after TKI failure. Cohorts are enrolled based on the presence (A) or absence (B) of primary mutations in KIT exon 11. Primary end point: clinical benefit rate (CBR=CR+PR+SD ≥16 wks) by modified RECIST 1.1 in Cohort A. Secondary end points include CBR in Cohort B, ORR, safety/tolerability. Enrollment of new pts is on hold due to safety observations in other ponatinib trials; enrollment criteria are being revised to include only pts with failure of all 3 TKIs approved for GIST. NCT01874665.

Results: From June to Oct 2013, 35 of a planned 45 pts have been enrolled (24 in Cohort A). Baseline characteristics: median age 58 yrs; 46% 2 prior approved TKIs, 46% 3 prior approved TKIs. 74% of pts had ≥4 prior cancer regimens. The median time since diagnosis was 6 yrs. 17 pts discontinued (8 PD, 5 AE, 4 other). As of 6 Jan 2014, median follow-up: Cohort A 4 mos, Cohort B 3 mos. Cohort A CBR at ≥16 wks: 55% (11/20 pts) 1 PR and 10 SD. Cohort A ORR: 8% (2/24). All 5 Cohort A pts with matched PET scans (BL v. C1) had decreased FDG uptake in active lesions and remain on study with SD or better. Cohort B CBR: 22% (2/9); Cohort B ORR: 0%. Most common (≥30%) treatment-emergent AEs of any grade are: rash (54%), fatigue (46%), myalgia (46%), dry skin (40%), headache (40%), abdominal pain (34%), constipation (34%). Treatment-emergent serious AEs (SAEs) occurring in ≥2 pts are: abdominal pain (11%), nausea (6%), vomiting (6%), fatigue (6%). One pt had myocardial ischemia. There was 1 death (pneumonia) possibly ponatinib-related.

Conclusions: Initial analysis of this ongoing trial suggests that ponatinib has activity in pts with advanced GIST after failure of prior TKI therapy. Clinical trial information: NCT01874665.

Linsitinib, Astellas

Results of SARC 022, a phase II multicenter study of linsitinib in pediatric and adult wild-type (WT) gastrointestinal stromal tumors (GIST).

Abstract #10507

Author(s): Margaret von Mehren, Suzanne George, Michael C. Heinrich, Scott Schuetze, Martin G. Belinsky, Katherine A. Janeway, Lori Rink, Kristen N. Ganjoo, Jian Qin Yu, Jeffrey T. Yap, John Joseph Wright, Annick D. Van Den Abbeele; Fox Chase Cancer Center, Philadelphia, PA; Dana-Farber Cancer Institute, Boston, MA; OHSU Knight Cancer Institute and Portland VA Medical Center, Portland, OR; University of Michigan, Ann Arbor, MI; Stanford University, Palo Alto, CA; Huntsman Cancer Institute, Salt Lake City, UT; National Cancer Institute, Rockville, MD

Background: Most GISTs have activating mutations of KIT/PDGFRA, with rare cases of B-RAF/RAS mutations. 15% of GIST in adults and 85% in children are WT and commonly have high expression of IGF1R likely due to loss of succinate dehydrogenase (SDH) function. We tested the clinical benefit of linsitinib (L), an oral TKI with in vitro efficacy against IGF1R in WT GIST patients (pts).

Methods: A multi-center phase II trial of L using Clopper-Pearson two-stage design was conducted by SARC. All eligible pts signed consent, were >18 yo, had KIT/ PDGFRA WT GIST, RECIST1.1 measurable disease, ECOG PS of 0-2, and adequate organ function including: fasting glucose of < 150 mg/dL,
hemoglobin A1c < 7%, and a QTcF interval of < 450 msec. The trial's primary endpoint was objective response rate (ORR) and secondary endpoints were clinical benefit rate (CBR): CR, PR and SD≥9 mos, and qualitative and quantitative FDG metabolic response (MR) at 8 weeks.

**Results:** 20 pts were accrued to stage I of the study from 11/12-4/13 (Table). Treatment with L was well tolerated. Of the toxicities reported, 8.5% were grade 3/4. 36% were possibly related to L with nausea/vomiting (7.3%), fatigue (3.6%), and elevated LFTs (3.2%) being the most common. No objective responses were seen. Qualitative partial and stable MR were seen in 6/17 (35%) respectively. As of 1/5/2014, the average days on study was 231 (range 49-318+) with 5 patients remaining on L. CBR at 9 mos was 45% and MR was seen in 2/13 (15%); PFS and OS Kaplan Meier estimates at 9 months were 52% and 80% respectively. Correlative studies of SDHB immunohistochemistry and mutational testing, serum levels of insulin, IGF1R, its ligands and inhibitors at baseline, week 2, 4 and 8 on therapy will be presented.

**Conclusions:** L is well tolerated in patients with WT GIST. While the CBR with L was 45% and PFS at 9 mos was 52%, no objective responses have been observed. Rapid accrual to this study demonstrates clinical studies in selected subtypes of GIST are feasible. Clinical trial information: NCT01560260.

**HEAD AND NECK CANCER**

**Erbitux, Eli Lilly (LLY)**

**The KRAS-variant and cetuximab response in RTOG 0522.**

Abstract #6000

Author(s): Joanne B. Weidhaas, Jonathan Harris, Rita Axelrod, Adel K. El-Naggar, Anurag Singh, Thomas Galloway, David Raben, Dian Wang, Terence S. Herman, R. Jeffrey Lee, Rafael Ricardo Manon, Omar Yumen, Qiang Zhang, Christine H. Chung; Yale School of Medicine, New Haven, CT; Radiation Therapy Oncology Group, Philadelphia, PA; Department of Medical Oncology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; The University of Texas MD Anderson Cancer Center, Houston, TX; Roswell Park Cancer Institute, Buffalo, NY; Fox Chase Cancer Center, Philadelphia, PA; University of Colorado Denver, Aurora, CO; Medical College of Wisconsin, Milwaukee, WI; Oklahoma University Health Sciences Center, Oklahoma City, OK; Intermountain Medical Institute, Salt Lake City, UT; MD Anderson Cancer Ctr, Houston, TX; Geisinger Medical Center CCOP, Danville, PA; Statistical Center, Radiation Therapy Oncology Group, Philadelphia, PA; The Johns Hopkins University School of Medicine, Baltimore, MD

**Background:** The KRAS-variant, a germ-line mutation in a microRNA-binding site in KRAS, predicts increased cancer risk and unique cancer biology for many cancers. RTOG 0522 is a phase III trial of cisplatin/radiation +/- cetuximab for patients with locally advanced head and neck cancer. Here we tested the hypothesis that the KRAS-variant would predict cetuximab response for these patients.

**Methods:** Germline DNA was isolated from blood or buffy coat and tested for the KRAS-variant in Mira Dx’s CLIA-certified laboratory. Hazard ratios (HR) were estimated by Cox model. Where proportional hazards assumption was invalid, models included time-dependent covariates.
Results: 413/891 eligible patients on 0522 (46.4%) were tested for the KRAS-variant, and 70/413 were positive (16.9%). For progression-free survival (PFS) in the KRAS-variant group, there was a significant cetuximab benefit in year 1 (HR 0.31, p=0.04) and a significant interaction between treatment and time (p=0.02), confirming different effects in the first year and after. HR after year 1 was 1.76, but this did not reach statistical significance (p=0.29). The number of events in the KRAS-variant group (32) was too small for formal multivariate analysis, but HRs were stable after adjustment for single covariates (age, pack-years, Zubrod, site, p16, stage). In the KRAS-wildtype group, HRs for cetuximab effect were 1.00/1.07 with/without adjustment for covariates, similar to the overall trial (1.08). For overall survival (OS) in the KRAS-variant group there was a significant cetuximab benefit in years 1-2 (HR 0.19, p=0.03) and a significant interaction between treatment and time (p=0.02) confirming different cetuximab effects in years 1-2 and after. The HR after year 2 was 2.34, but this did not reach statistical significance (p=0.23). HRs were stable after adjustment for single covariates. In the KRAS-wildtype group, HRs for cetuximab effect were 0.90/0.93 with/without adjustment for covariates, similar to the overall trial (0.95).

Conclusions: Our findings suggest that locally advanced head and neck cancer patients with the KRAS-variant appear to positively respond to cetuximab, resulting in better short-term PFS and OS. These results warrant further validation through a prospective study. Clinical trial information: NCT00265941.

MK-3475, Merck (MRK)
A phase Ib study of MK-3475 in patients with human papillomavirus (HPV)-associated and non-HPV-associated head and neck (H/N) cancer.
Abstract #6011

Author(s): Tanguy Y. Seiwert, Barbara Burtness, Jared Weiss, Iris Gluck, Joseph Paul Eder, Sara I Pai, Marisa Dolled-Filhart, Kenneth Emancipator, Kumudu Pathiraja, Christine Gause, Robert Iannone, Holly Brown, Jennifer Houp, Jonathan D. Cheng, Laura Quan Man Chow; The University of Chicago Medicine and Biological Sciences, Chicago, IL; Fox Chase Cancer Center, Philadelphia, PA; Lineberger Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; Sheba Medical Center, Ramat Gan, Israel; Yale Cancer Center, New Haven, CT; The Johns Hopkins University School of Medicine, Baltimore, MD; Merck & Co., Inc., Whitehouse Station, NJ; University of Washington, Seattle, WA

Background: The PD-1 receptor-ligand pathway can be used by tumors to evade immune surveillance, thereby allowing neoplastic growth. MK-3475 is a highly selective, humanized IgG4/kappa isotype mAb designed to block PD-1 interaction with its ligands PD-L1 and PD-L2, to reactivate the immune system to eradicate the host tumor.

Methods: Pts with recurrent/metastatic H/N cancer were enrolled in this multi-center, non-randomized trial in two cohorts (HPV and non-HPV associated). Pts were prescreened for PD-L1 expression by immunohistochemistry (22C3), and if positive allowed to proceed with treatment of single agent MK-3475 given intravenously at 10 mg/kg every 2 wks. Primary objectives are to determine (1) safety and tolerability and (2) anti-tumor activity of MK-3475 assessed by RECIST 1.1. Secondary objectives include progression-free survival, overall survival and response duration.

Results: All results are based on preliminary, unaudited data as of Jan. 27, 2014. 77.9% of patients expressed PD-L1, defined as ≥1% of stained cells in the tumor microenvironment (Table). Of 60 patients (11 female, 49 male) enrolled in the study, 19 had an ECOG status of 0, and 40 had an ECOG status of 1.
(1 unknown); 23 were HPV+ and 37 were HPV-; 9 had no prior systemic treatment, 10 had 1, 16 had 2, 13 had 3, and 7 had ≥4 prior regimens of treatment (5 unknown). Of the patients treated with MK-3475, 78.3% experienced ≥1 AE, and 46.7% reported a drug-related (DR) AE. The most common DR AEs reported were pruritis (6, 10%), fatigue (4, 7%), rash (4, 7%), and diarrhea (3, 5%). At least one Grade 3-5 AE was reported in 55.0% of patients, with 13.3% reporting a DR Gr 3-5 AE. Grade 3-5 AEs considered DR were hyponatremia, lymphopenia, rash, diarrhea, musculoskeletal pain, abscess (neck), and atrial fibrillation. Tumor shrinkage was observed in several patients, but protocol-specified efficacy analyses are not yet available.

Conclusions: To date, treatment with MK-3475 has been well tolerated overall, with few serious DR AEs. Protocol-specified efficacy analyses are not yet available. Clinical trial information: NCT01848834.

**PD-L1 staining in tumors of screened patients (n=104)**

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**Tarceva, Astellas**

**Randomized placebo-controlled trial (RCT) of erlotinib for prevention of oral cancer (EPOC).**

Abstract #6007

Author(s): William Nassib William, Vassiliki Papadimitrakopoulou, J. Jack Lee, Li Mao, Heather Lin, Ann M. Gillenwater, Jack W Martin, Ezra E.W. Cohen, Mark W. Lingen, Jay Boyle, Dong Moon Shin, Nadarajah Vigneswaran, Nancy Shinn, Jeffrey Myers, Adel K. El-Naggar, Scott Michael Lippman; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Maryland Dental School, Baltimore, MD; Moores Cancer Center, University of California at San Diego, La Jolla, CA; The University of Chicago Medicine and Biological Sciences, Chicago, IL; Memorial Sloan Kettering Cancer Center, New York, NY; The Winship Cancer Institute of Emory University, Atlanta, GA; The University of Texas at Houston, School of Medicine, Houston, TX; University of California, San Diego, La Jolla, CA

**Background:** Loss of heterozygosity (LOH) profiles predict oral cancer (OC) risk in patients (pts) with oral premalignant lesions (OPL). We conducted a randomized, multi-center, double-blind, placebo-controlled, personalized medicine trial of the EGFR inhibitor erlotinib in pts with OPLs defined as high risk by molecular criteria. Our primary hypothesis was that erlotinib would improve oral cancer-free survival (OCFS) in the high-risk, LOH+ population.

**Methods:** Pts with histological evidence of an OPL (with or without a prior history of invasive OC) underwent LOH profiling at 3p14, 9p21, 4q, 8p, 11p, 13q, 17p. LOH+ pts were defined as those with prior OC and LOH at 3p14 and/or 9p21; or those without prior OC and LOH at 3p14 and/or 9p21 plus an additional chromosomal site. LOH- pts received no treatment. LOH+ pts were stratified by history of OC, then randomized (1:1) to erlotinib 150 mg po daily for 12 months or placebo and were assessed every 3-6 months for development of invasive OC. Primary endpoint was OCFS in the intent-to-treat (ITT)
population. With a planned sample size of 150, the study had 85% power to detect a hazard ratio (HR) of 0.47 with a 5% 2-sided type I error rate (stratified logrank).

**Results:** Of 375 pts evaluated for LOH, 254 were LOH+, of which 150 were randomized to erlotinib (N=75) or placebo (N=75). After a median follow up of 2.9 years, 44/179 LOH+ pts not randomized or randomized to placebo developed OC, versus 15/121 LOH- pts (HR=2.1, 95% CI 1.2-3.8, p=0.01). Among the randomized, LOH+, ITT population, 18/75 (24%) placebo-treated pts developed OC versus 22/75 (29%) erlotinib-treated pts. The HR for OCFS was 1.2 (95% CI 0.7-2.3, p=0.51) in the ITT population, 0.6 (95% CI 0.2-1.7) in 66 pts without prior OC, and 1.9 (95% CI 0.9-4.2) in 84 pts with prior OC (p=0.08 for interaction). Dose reductions were implemented in 34/75 and 1/75 erlotinib and placebo-treated pts, respectively, mostly due to expected, low-grade toxicities.

**Conclusions:** EPOC is the first personalized RCT in cancer prevention and prospectively confirmed LOH as an OC risk marker. Erlotinib did not reduce OCFS in this high-risk population, although the trend of reduced OCFS in pts without prior OC suggests that the timing of this intervention may be important. Clinical trial information: NCT00402779.

**Tykerb, Novartis (NVS)**

**Final analysis:** A randomized, blinded, placebo (P)-controlled phase III study of adjuvant postoperative lapatinib (L) with concurrent chemotherapy and radiation therapy (CH-RT) in high-risk patients with squamous cell carcinoma of the head and neck (SCCHN).

**Abstract #6005**

Author(s): Kevin J. Harrington, Stéphane Temam, Anil D'Cruz, Minish Mahendra Jain, Ida D'Onofrio, Georgy M. Manikhas, Geza Horvai, Yan Sun, Stefan Dietzsch, Pavol Dubinsky, Petra Holeckova, Hisham Mehanna, Iman El-Hariry, Natalie Franklin, Nigel Biswas-Baldwin, Philippe Legenne, Paul Stephen Wissel, Thelma Netherway, Sergio Santillana, Jean Bourhis; Institute of Cancer Research and Royal Marsden Hospital, London, United Kingdom; Institut Gustave Roussy, Villejuif, France; Tata Memorial Hospital, Mumbai, India; Ruby Hall Clinic, Pune, India; Hôpital Forcilles, Paris, France; St. Petersburg City Oncology Dispensary-, St Petersburg, Russia; Szent Imre University Teaching Hospital, Budapest, Hungary; Beijing Cancer Hospital, Beijing, China; Hospital and Policlinic for Radiation Therapy and Radio-oncology, Leipzig, Germany; East Slovakia Cancer Institute, Kosice, Slovakia; Institut of Radiation Oncology Hospital Na Bulovce, Prague and 1st Medical Faculty of Charles University Prague, Prague, Czech Republic; Institute of Head and Neck Studies and Education, University of Birmingham, Birmingham, United Kingdom; Synta Pharmaceuticals, Inc., Lexington, MA; GlaxoSmithKline, Uxbridge, United Kingdom; GlaxoSmithKline, Philadelphia, PA; GlaxoSmithKline, Philadelphia, PA; CHUV, Lausanne, Switzerland

**Background:** Epidermal growth factor receptor (EGFR) and ErbB2 are overexpressed in up to 90% and 40% of SCCHN, respectively. L, a tyrosine kinase inhibitor (TKI) of both EGFR and ErbB2, demonstrates tumor responses in SCCHN.

**Methods:** Patients with resected stage II-IVA SCCHN, with a surgical margin ≤5mm and/or extracapsular extension were randomized to CT-RT with either P or L. RT was 66Gy (2Gy per day, 5 days per week).100 mg/m² of cisplatin was administered on days 1, 22 and 43 of RT. P or L 1500 mg/day was given for up to one week prior to CT-RT, during CT-RT and for up to 12 months as monotherapy maintenance. Patients were stratified by nodal status, primary tumor location, geographical region and ErbB1 expression. The
study had 80% power to detect a 10% absolute difference in disease free survival (DFS) rate (55% to 65%).

**Results:** 688 patients were in the ITT population, 346 L and 342 P. Treatment arms were well balanced for prognostic factors. Median total doses of cisplatin (266.5 and 280 mg/m², L and P respectively) and median doses and duration of RT were similar in both arms. At the time of unblinding, recurrence/death from any cause was seen in 35% in L and 32% in P by independent review committee (IRC): Median DFS (95% CI) L: 53.6 mo (45.8, Not Reached [NR]); P: NR (54.6, NR), HR (95% CI) = 1.10 (0.85, 1.43) 2-sided p value = 0.45. Investigator results confirmed the IRC assessment: HR 1.03 (0.81, 1.30), p=0.82. No significant differences were observed in DFS for any of the pre-specified subgroups, including HPV. Death occurred in 30% L and 32% P; HR (95% CI) = 0.96 (0.73, 1.25). At least one adverse event was seen in 99% L and 98% P (SAEs 48% L/40% P, fatal AEs 7% L/5% P). AEs seen more in L were those expected with a TKI: diarrhea 42% vs 12%, rash 49% vs 30%, vomiting 46% vs 35%. Decrease in left ventricular ejection fraction SAEs were noted in 10 (3%) subjects L vs 3 (<1%) P.

**Conclusions:** In patients with resected SCCHN at high risk for recurrence, L, when added to standard therapy RT/CDDP, does not extend DFS. DFS in both treatment arms exceeded adjuvant CT-RT compared with historical randomized data. Clinical trial information: NCT00424255.

**LEUKEMIA**

**ABT-199 (AbbVie (ABBV); Phase III)**

ABT-199 (GDC-0199) combined with rituximab (R) in patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): Interim results of a phase 1b study.

Abstract #7013

Author(s): Shuo Ma, John Francis Seymour, Mark C. Lanasa, Thomas J. Kipps, Jacqueline Claudia Barrientos, Matthew Steven Davids, Tanita Mason-Bright, Nikita Rudersdorf, Jianning Yang, Wijith Munasinghe, Ming Zhu, Elisa Cerri, Sari H. Enschede, Rod Humrickhouse, Andrew Warwick Roberts; Northwestern University Medical School, Chicago, IL; Peter MacCallum Cancer Center, Melbourne, Australia; Duke University Medical Center, Durham, NC; University of California, San Diego, School of Medicine, San Diego, CA; Hofstra North Shore-LIJ School of Medicine, Hempstead, NY; Dana-Farber Cancer Institute, Boston, MA; AbbVie, Inc., North Chicago, IL; Royal Melbourne Hospital, Melbourne, Australia

**Background:** ABT-199 is a selective, orally bioavailable Bcl-2 antagonist that induces rapid apoptosis of CLL cells and > 80% response rate as monotherapy in pts with R/R CLL. R synergizes with ABT-199 in preclinical models of CD20+ve lymphoid cancers.

**Methods:** Objectives were to assess safety, pharmacokinetics (PK) and preliminary efficacy of ABT-199 + R and to determine a recommended phase 2 dose. Daily ABT-199 began at 50mg (modified to 20mg), with weekly increases to a final cohort dose (200-600mg). R was then initially dosed at 375 mg/m² then 500mg/m² monthly for 6 months (cohort 1-2 had 8 doses) with daily ABT-199 until progressive disease (PD).
**Results:** As of Jan 17, 2014, 37 pts were enrolled in 5 cohorts (median age 68, 14/23 F/M) with a median time on study: 4.8 (range 0 - 15.2) months, median number of prior therapies: 2 (range 1 - 5); 9 pts were fludarabine-refractory, 9 R-refractory, and 9 had del(17p). Six pts discontinued: 4 due to PD (3 Richter’s transformation, 1 CLL), 1 withdrew consent (WC), 1 due to fatal hyperkalemia in the setting of tumor lysis syndrome (TLS) at 1st dose (50mg). The most common treatment-emergent adverse events (AEs, >25% pts) were neutropenia (43%), nausea (38%), diarrhea (30%). The most common grade 3/4 AEs were neutropenia (43%), thrombocytopenia (16%), and anemia (11%). Two dose limiting toxicities occurred with ABT-199 + R: thrombocytopenia (300mg/375mg/m²) and hemophagocytic syndrome (300mg/500mg/m²). Preliminary PK data suggest a negligible effect of R on ABT-199 exposure. Of 18 pts who have completed combination therapy or discontinued prior to completion, 7 (39%) achieved CR/CRi and 7 (39%) PR, 2PD, 1WC, 1 fatal event. Minimal Residual Disease (MRD) was quantified locally in 6/7 CR pts: 5 pts were MRD negative. Of the 19 yet to complete combination therapy, 4 have confirmed PR, 9 have unconfirmed PR, and 6 are not yet evaluable.

**Conclusions:** To date, the addition of R to ABT-199 has identified no new toxicities. The combination is active in R/R CLL with a substantial CR rate. A fatal episode of TLS occurred during the ABT-199 lead-in period; with dosing modifications and increased monitoring no further TLS events occurred. Clinical trial information: NCT01682616.

**Alvocidib, Tolero**

Randomized multicenter phase II trial of timed-sequential therapy with flavopiridol (alvocidib), cytarabine, and mitoxantrone (FLAM) versus “7+3” for adults with newly diagnosed acute myeloid leukemia (AML).

Abstract #7002

Author(s): Joshua F. Zeidner, Matthew C. Foster, Amanda Blackford, Mark Robert Litzow, Lawrence Morris, Stephen Anthony Strickland, Jeffrey E. Lancet, Prithviraj Bose, M. Yair Levy, Raoul Tribes, Ivana Gojo, Christopher D Gocke, Gary L. Rosner, Jacqueline Greer, Joan M Cain, Richard F. Little, John Joseph Wright, L. Austin Doyle, B Douglas Smith, Judith E. Karp; The Johns Hopkins Hospital and The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Mayo Clinic, Rochester, MN; BMT Group of Georgia, Atlanta, GA; Vanderbilt University Medical Center, Nashville, TN; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; VCU Masey Cancer Center, Richmond, VA; Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; Mayo Clinic, Scottsdale, Scottsdale, AZ; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; National Cancer Institute, Rockville, MD

**Background:** Serial studies have demonstrated that induction therapy with flavopiridol (50 mg/m² days 1-3), a multi-serine-threonine cyclin-dependent kinase inhibitor, followed by cytarabine (667 mg/m²/days 6-8) and mitoxantrone (40 mg/m² day 9) yields complete remission (CR) rates of nearly 70% in pts with newly diagnosed, poor-risk AML. This trial compares “FLAM” with 7+3 in newly diagnosed AML pts.

**Methods:** Between May 2011-July 2013, 165 (FLAM, n=109; 7+3, n=56) newly diagnosed AML pts (18-70 years) with non-favorable cytogenetics were randomized 2:1 to receive FLAM or 7+3 (cytarabine 100 mg/m²/day, daunorubicin 90 mg/m²) across 10 institutions. Randomization was stratified by age, secondary AML and leukocyte count. Pts with residual leukemia on day 14 received 5+2 on the 7+3 arm, whereas pts treated with FLAM were not retreated on day 14. The primary endpoint was to compare CR
rates between 1 cycle of FLAM and 1 cycle of 7+3. Secondary endpoints were safety, CR rates after 1 cycle of FLAM vs 7+3 + 5+2, overall survival (OS), and disease-free survival (DFS).

**Results:** The majority of pts on both arms had at least 1 poor-risk feature, excluding age (FLAM=77%, 7+3=68%). FLAM resulted in higher CR rates compared to 7+3 (70% vs 46%, p=0.003), though this difference was less when compared to 7+3 + 5+2 (70% vs 57%, p=0.08). FLAM also produced higher CR rates in pts with secondary AML (60% vs 35%, p=0.05), pts with >1 poor-risk feature (61% vs 34%, p=0.01), pts without poor-risk features (100% vs 72%, p=0.009), and pts <60 years (79% vs 52%, p=0.02). Relapse rates as of this analysis were similar (FLAM: 36% vs 7+3: 38%). Toxicities were similar between both arms, including grade >3 toxicities, early treatment-related mortality, and time to count recovery.

**Conclusions:** FLAM induction results in significantly higher CR rates compared with 7+3 without increased toxicity. FLAM appears to be more active than 7+3 in pts <60 years of age and those with poor-risk features. Although follow-up is too early to assess OS and DFS, these results are promising and a phase 3 comparison of FLAM vs 7+3 is being explored. Clinical trial information: NCT01349972.

**Blinatumomab, Amgen (AMGN)**

Confirmatory open-label, single-arm, multicenter phase 2 study of the BiTE antibody blinatumomab in patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL).

Abstract #7005^  

**Background:** Blinatumomab, an investigational bispecific T-cell engaging (BiTE) antibody that directs cytotoxic T-cells to CD19-expressing target cells, has shown antileukemia activity in an exploratory study in adult r/r B-precursor ALL. We evaluated blinatumomab efficacy and toxicity in a large confirmatory phase 2 study.

**Methods:** Pts (≥18 yrs) with Ph-negative r/r ALL (refractory; 1st relapse <12 mo; relapse post HSCT <12 mo; ≥2ndsalvage) were eligible. Blinatumomab was given by continuous IV infusion (4 wks on/2 wks off) for up to 5 cycles (cycle 1 only: 9 μg/d days 1-7; then 28 μg/d). The primary endpoint was complete remission (CR) or CR with partial hematological recovery (CRh*) within the first 2 cycles.

**Results:** 189 pts were enrolled and received blinatumomab for a median (range) of 2 (1–5) cycles. Median age was 39 (18–79) yrs. As of Jan 2014 (primary analysis in Feb 2014), 43% of pts achieved CR/CRh*; 80% of responses occurred within cycle 1. CRs/CRh* were seen in all subgroups (Table). Regardless of causality, the most frequent adverse events (AEs) were pyrexia (59%), headache (35%) and febrile neutropenia (29%). The most frequent gr ≥3 AEs were febrile neutropenia (26%), anemia (15%)
and neutropenia (15%); 2% had gr ≥3 cytokine release syndrome. The most common gr ≥3 nervous system disorders were headache (4%), encephalopathy (3%) and ataxia (2%). 3 (2%) pts had gr 5 AEs considered treatment-related (sepsis, n=2; candida infection, n=1).

**Conclusions:** This large phase 2 study confirmed the antileukemia activity of single-agent blinatumomab in a difficult-to-treat population with r/r ALL. Clinical trial information: NCT01466179.

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<thead>
<tr>
<th>Endpoint</th>
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<tr>
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<td>Primary</td>
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<td>Prior aHSCT (n=64)</td>
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<td>1 prior salvage (n=47)</td>
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<td>≥2 prior salvages or primary refractory (n=53)</td>
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Secondary

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<td>N=189</td>
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<tr>
<td>CR, n (%)</td>
<td>64 (34)</td>
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<tr>
<td>CRh*, n (%)</td>
<td>18 (10)</td>
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<td>Median relapse-free survival, mo (95% CI)</td>
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<td>Median OS, mo (95% CI)</td>
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Exploratory

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<td>n=82</td>
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<tr>
<td>Minimal residual disease (MRD) response, n (%)</td>
<td>61 (74)</td>
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Abbreviation: aHSCT, allogeneic stem cell transplantation. a First two cycles (central review).

**GS-9973, Gilead (GILD)**

Phase 2 trial of GS-9973, a selective Syk inhibitor, in chronic lymphocytic leukemia (CLL).

Abstract #7007

Author(s): Jeff Porter Sharman, Leonard M. Klein, Michael Boxer, Kathryn S. Kolibaba, Esteban Abella-Dominicis, Michael J. Hawkins, Julie Di Paolo, Jing Hu, Anita Reddy, Feng Jin, Flordelia Melchor-Khan, Christopher A. Yasenchak; Willamette Valley Cancer Institute and Research Center/US Oncology Research, Springfield, OR; Illinois Cancer Specialists, Niles, IL; Arizona Oncology Associates, Tucson, AZ; Compass Oncology, Vancouver, WA; Gilead Sciences, Foster City, CA; Gilead Sciences, Branford, CT; Compass Oncology, P.C., Tualatin, OR

**Background:** Spleen tyrosine kinase (Syk) is a mediator of B-cell receptor signaling in normal and transformed B-cells. GS-9973 is an orally bioavailable, selective inhibitor of Syk (Kd 7.6 nM, no other kinase < 100 nM).
**Methods:** This Phase 2 trial enrolled 44 subjects with CLL treated with GS-9973 800 mg BID. Tumor imaging occurred at weeks 8, 16, 24 and then every 12. Response was independently evaluated according to Hallek 2008 as modified by Cheson 2012. GS-9973 plasma levels were obtained concurrently with plasma chemo/cytokine levels and phospho flow analysis of circulating leukemic cells.

**Results:** 27 subjects are still on treatment (Rx) for a median of 22 weeks. Median age was 73 (range 51 - 89), 66% were male. The median number of prior Rx regimens was 3 (range 1-8). Prior Rxs included anti-CD20 antibodies (95%), alkylating agents (86%; bendamustine 64%) and fludarabine (68%); 9 subjects had 17p deletions/TP53 mutations and 17 had other poor prognosis mutations/deletions. Results: 41 subjects were treated for at least 8 weeks and had ≥ 1 efficacy assessment. Per investigator, 40 (91%) subjects experienced reduced tumor bulk; 28 (64%) achieved a decrease of ≥ 50%. Results of the independent response assessments are pending and will be presented. GS-9973 was generally well tolerated. Rx emergent adverse events occurring in ≥ 10% of subjects are listed in the Table. Reversible Grade 3 or 4 ALT/AST elevations occurred in 2 (4.5%) subjects. 2 subjects died while on study: 1 from progressive disease, 1 from sepsis. The mean absolute lymphocyte count increased from 46,410 to 68,850/uL by day 8 and then declined; in 38 paired samples, mean leukemic cell pSyk MdFI levels decreased from 222 (D1) to 186 (D8).

**Conclusions:** GS-9973 given on this dose and schedule was generally well tolerated and demonstrated substantial activity in subjects with CLL, including those with poor prognostic features. Clinical trial information: NCT01799889.

**Imbruvica, Pharmacyclics (PCYC)**

Independent evaluation of ibrutinib efficacy 3 years post-initiation of monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic leukemia including deletion 17p disease.

Abstract #7014

Author(s): Susan Mary O'Brien, Richard R. Furman, Steven E. Coutre, Ian Flinn, Jan Andreas Burger, Kristie A. Blum, Jeff Porter Sharman, Jeffrey Alan Jones, William G. Wierda, Weiqiang Zhao, Nyla A. Heerema, Amy J. Johnson, Anh Tran, Cathy Zhou, Elizabeth Bilotti, Danelle Frances James, John C. Byrd; The University of Texas MD Anderson Cancer Center, Houston, TX; Weill Cornell Medical College, New York, NY; Stanford Cancer Center, Stanford University School of Medicine, Stanford, CA; Sarah Cannon Research Institute, Nashville, TN; The Ohio State University, Columbus, OH; Willamette Valley Cancer Institute and Research Center/US Oncology Research, Springfield, OR; Pharmacyclics, Inc., Sunnyvale, CA; Pharmacyclics, Inc, Sunnyvale, CA

**Background:** CLL/SLL is generally very responsive to chemoimmunotherapy. However, relapses occur and resistance develops. In particular, del(17p) is associated with poor outcomes using all currently available treatments. Effective targeted therapies are needed. Ibrutinib, a first-in-class covalent inhibitor of Bruton tyrosine kinase, showed single-agent activity and mild toxicity in treatment-naïve (TN) (Lancet Oncology 2013) and relapsed/refractory (R/R) CLL (NEJM 2013) in the phase 1b/2 study (PCYC-1102). We present independent assessment of efficacy data 3 years following initiation of therapy to confirm and further characterize the durability of response.

**Methods:** Analyses are based upon all patients (pts) treated from first dose on PCYC-1102 until data cut-off on the long-term follow-up study PCYC-1103. Patients received 420 or 840 mg ibrutinib daily. Best overall response rate (ORR) was assessed using iwCLL criteria.
**Results:** Of 132 CLL/SLL (31 TN, 101 R/R) pts evaluated, the median age was 68 years (range, 37–84), with 61% aged ≥ 65 years; 36 (27.3%) pts (2 TN, 34 R/R) had del(17p) and 36 (27.3%) had del(11q). R/R pts including 34 with Del(17p) had a median of 4 (range, 1–12) prior therapies. The updated ORR (by independent review) was 78.0% for all-treated pts (83.9% TN-, 76.2% R/R and 55.9% for those R/R with del(17p)). Additionally, 5 R/R pts, 2 with del(17p), had a best response of PR with lymphocytosis. Median DOR was not reached for all-treated pts, and was 25.0 months (range, 4.8–34.3) in pts with del(17p). Median time on study was 29.4 months (range, 0.7–38.1) for all-treated pts, and 27.3 months (range, 0.9–37.5) for R/R pts with del(17p). More pts receiving prior therapy experienced serious or ≥ Grade 3 adverse events that decreased after 1 year on treatment. No new safety signals were observed in long-term follow-up; 64% of pts remain on treatment with ibrutinib.

**Conclusions:** Single-agent ibrutinib showed durable responses in pts with TN or R/R CLL/SLL including those with del(17p), as independently confirmed with 3 years of follow-up.

**LIVER CANCER**

**Nexavar, Amgen (AMGN)**

**STORM: A phase III randomized, double-blind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of hepatocellular carcinoma (HCC)**

Abstract #4006^

**Author(s):** Jordi Bruix, Tadatoshi Takayama, Vincenzo Mazzaferrro, Gar-Yang Chau, Jiamei Yang, Masatoshi Kudo, Jianqiang Cai, Ronnie Tung-Ping Poon, Kwang-Hyub Han, Won-Young Tak, Han Chu Lee, Tianqiang Song, Sasan Roayaie, Luigi Bolondi, Kwan Sik Lee, Masatoshi Makuuchi, Fabricio Souza, Marie-Aude Le Berre, Gerold Meinhardt, Josep M. Llovet, STORM Investigators; BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain; Nihon University School of Medicine, Department of Digestive Surgery, Tokyo, Japan; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Taipei Veterans General Hospital, Taipei, Taiwan; Eastern Hepatobiliary Hospital, Shanghai, China; Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka, Japan; Cancer Institute and Hospital CAMS, Chinese Academy of Medical Sciences, Beijing, China; Queen Mary Hospital, Hong Kong, China; Severance Hospital, Seoul, South Korea; Kyungpook National University Hospital, Daegu, South Korea; Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Tianjin Medical University Cancer Hospital Huanhuxilu, Tianjin, China; Mount Sinai Medical Center, New York, NY; Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy. Center for Applied Biomedical Research (CRBA), S.Orsola-Malpighi Hospital, Bologna, Italy; Gangnam Severance Hospital, Seoul, South Korea; University of Tokyo, Tokyo, Japan; Bayer HealthCare Pharmaceuticals, São Paulo, Brazil; Bayer Healthcare Pharmaceuticals, Loos, France; Bayer HealthCare Pharmaceuticals, Whippany, NJ; Mount Sinai School of Medicine, New York, NY

**Background:** Sorafenib is a multikinase inhibitor with proven efficacy in unresectable HCC. We evaluated the efficacy and safety of adjuvant sorafenib for HCC.

**Methods:** Patients who had undergone surgical resection or local ablation with curative intent and had an intermediate or high recurrence risk were eligible. Main inclusion criteria were Child-Pugh score 5–7, ECOG PS 0, and no residual disease confirmed by CT or MRI. Exclusion criteria included recurrent HCC, ascites, extrahepatic spread, macrovascular invasion, and prior systemic therapy for HCC. Patients were
stratified by curative treatment, geographic region, recurrence risk, and Child-Pugh status and randomized 1:1 to treatment with sorafenib 400 mg orally twice a day or placebo for a maximum of 4 yrs. The primary endpoint was recurrence-free survival (RFS) by independent review. Secondary endpoints included time to recurrence (TTR) and overall survival (OS).

**Results:** A total of 1114 patients were randomized (n=556 sorafenib; n=558 placebo). Baseline characteristics were balanced between groups. Median age was 59 yrs, 62% were Asian, 81% had resection, 97% were Child-Pugh A, and 46% had high recurrence risk. The analysis was based on a total of 464 RFS events. No differences in RFS, TTR, and OS were observed (Table). The sorafenib group had a shorter median treatment duration (12.5 vs 22.2 mos) and lower mean daily dose (578 vs 778 mg). Discontinuation rates with sorafenib were higher due to treatment-emergent adverse events (TEAE) (24% vs 7%) and consent withdrawal (17% vs 6%). Most common grade (Gr) 3–4 sorafenib TEAEs occurring more frequently vs placebo were hand-foot skin reaction (28%), hypertension (7%), and diarrhea (6%).

**Conclusions:** The primary endpoint of the trial was not met. Adverse events are consistent with the known sorafenib safety profile and no new safety findings were observed. Clinical trial information: NCT00692770.

<table>
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<tr>
<th>Sorafenib</th>
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<tr>
<td><strong>Median, mos</strong></td>
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<tr>
<td>RFS</td>
<td>33.4</td>
<td>33.8</td>
<td>0.940 (0.780 – 1.134)</td>
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<td>TTR</td>
<td>38.6</td>
<td>35.8</td>
<td>0.891 (0.735 – 1.081)</td>
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<tr>
<td>OS</td>
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<td>NR</td>
<td>0.995 (0.761 – 1.300)</td>
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<td><strong>TEAE, %</strong></td>
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<tr>
<td>All Gr</td>
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<tr>
<td>Gr 5</td>
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*One sided; NR, not reached.
LUNG CANCER

AZD9291, AstraZeneca (AZN)
Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor–resistant non-small cell lung cancer (NSCLC).
Abstract #8009^

Author(s): Pasi A. Janne, Suresh S. Ramalingam, James Chih-Hsin Yang, Myung-Ju Ahn, Dong-Wan Kim, Sang-We Kim, David Planchard, Yuichiro Ohe, Enriqueta Felip, Claire Watkins, Mireille Cantarini, Serban Ghiorghiu, Malcolm Ranson; Dana-Farber Cancer Institute, Boston, MA; The Winship Cancer Institute of Emory University, Atlanta, GA; National Taiwan University, Graduate Institute of Oncology, Taipei, Taiwan; Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Seoul National University Hospital, Seoul, South Korea; Asan Medical Center, Seoul, South Korea; Gustave Roussy, Villejuif, France; National Cancer Center Hospital East, Kashiwa, Japan; Vall d’Hebron University Hospital, Barcelona, Spain; AstraZeneca, Macclesfield, United Kingdom; University of Manchester, Christie Hospital, Manchester, United Kingdom

Background: AZD9291 is a selective, third generation EGFR-TKI, effective against both EGFR-TKI sensitizing and resistance T790M mutations in preclinical models. We are conducting a phase I study of AZD9291 in EGFR mutant (EGFRm+) NSCLC pts.

Methods: EGFRm+ NSCLC pts, with acquired resistance to EGFR-TKIs, were enrolled in a multicenter trial (NCT01802632) into dose escalation and expansion cohorts. AZD9291 was administered orally, at doses of 20–240 mg once daily. Stable brain metastases were allowed. All pts were assessed for pharmacokinetics (PK), response to therapy, and adverse events (AEs). Prospective mandatory central T790M testing was required in the expansion cohorts and was optional for dose escalation cohorts.

Results: As of 16 January 2014, 199 pts (62% female, median age 60, Asian/Caucasian 65%/32%, immediate prior EGFR-TKI therapy: 57%) were enrolled including 31 across 5 dose levels in the dose escalation and 168 in 8 dose expansion cohorts. Median number of prior EGFR therapies: 1 (range, 1-5). PK was dose proportional, median t1/2 ~50 h. Plasma exposures achieved at all doses are predicted to be efficacious in preclinical models. Among all evaluable pts to date, the confirmed+unconfirmed overall response rate (c+uORR) was 51% (91/177). RECIST responses were observed at all dose levels and in brain metastases. In 132 pts with centrally confirmed T790M, the c+uORR in 89 EGFR T790M+ pts was 64% (95% CI; 53%, 74%) and in 43 EGFR T790M- pts was 23% (95% CI; 12%, 39%). The overall disease control rate (CR+PR+SD) in T790M+ pts was 96% (85/89). Among the 60 pts with a confirmed response, 97% (58/60) were ongoing at data cut-off; longest duration of response to date >8 months. No dose limiting toxicities were observed. Most common AEs (≥15%), mostly CTCAE Grade 1, were: diarrhea (30%), rash (24%), and nausea (17%). Grade 3/4 AEs occurred in 16% of pts. Six pts (3%) had dose reductions. Five reports of ILD-like events are under investigation.

Conclusions: AZD9291 has robust efficacy and is well tolerated in EGFRm+ NSCLC pts with acquired resistance to EGFR-TKIs. Pts with EGFR T790M+ tumors have higher ORR with AZD9291 compared with those with EGFR T790M- tumors. Clinical trial information: NCT01802632.
**Caprelsa, AstraZeneca (AZN)**

A randomized double-blind phase II trial of platinum (P) plus etoposide (E) with or without concurrent ZD6474 (Z) in patients (pts) with previously untreated extensive-stage (ES) small cell lung cancer (SCLC): Hoosier Oncology Group LUN06-113.

Abstract #7506

Author(s): Rachel E. Sanborn, Jyoti D. Patel, Gregory A. Masters, Nagesh Jayaram, Anthony W. Stephens, Michael J. Guarino, Jamal Ghazi Misleh, Corinne E. Williams, Jingwei Wu, Nasser H. Hanna; Earle A. Chiles Research Institute and Providence Cancer Center, Portland, OR; Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University, Chicago, IL; Thomas Jefferson University University Medical School, Medical Oncology Hematology Consultants, PA, Newark, DE; Southeastern Medical Oncology, Jacksonville, NC; Onc/Hem Assoc of SW Indiana, Jacksonville, NC; Christiana Care Health Services, Inc, Newark, DE; Med Onc Hem Consults PA, Newark, DE; Hoosier Oncology Group, Indianapolis, IN; Indiana University, Indianapolis, IN; Melvin and Bren Simon Cancer Center, Indiana University, Indianapolis, IN

**Background:** Standard treatment with P + E results in median survival for ES SCLC 10 months. Dose escalation, addition of third cytotoxic agents, and maintenance therapy have failed to improve outcomes. Overexpression of VEGF is associated with poor prognosis in SCLC. This trial evaluated the efficacy and tolerability with the addition of Z (dual VEGF and EGFR inhibitor) to PE.

**Methods:** Randomized, double blind, placebo controlled study of P (cisplatin 60 mg/m² or carboplatin AUC 5) day 1, E (120 mg/m² with cis or 100 mg/m² with carbo) IV days 1-3, with Z (100 mg) or placebo po daily, q3 wks for 4 cycles. 6 pts were initially enrolled on P+E+Z for safety assessment. Pts with untreated ES SCLC or high grade poorly differentiated neuroendocrine tumors and ECOG 0-1 were eligible. Pts with symptomatic brain metastases (mets) or prolonged QTc were ineligible. 1°endpoint was time to disease progression (TTP). Secondary endpoints were safety, response rate (RR), disease control rate (DCR), and overall survival (OS). VEGF polymorphisms were also evaluated.

**Results:** 74 pts enrolled (33 placebo, arm A; 41 Z, arm B) Median age 63/64 A/B; female/male 48.5%/51.5% A, 41.5%/58.5% B; ECOG 0/1 36%/64% A, 34%/66% B. Brain mets at diagnosis, 30% A, 39% B. Median number of cycles received was 4 (both arms). Cisplatin/carboplatin 51.5%/48.5% A, 61%/39% B. All Grade (Gr) 3-4 toxicity: 37% A, 69% B (heme, 20% A; 30% B, mainly neutropenia both arms; non-heme, 17% A; 33% B). Gr 5 toxicity, 1 each: A, 3 (cardiac infarct, pulmonary hemorrhage, pneumonitis); B, 2 (infection, respiratory failure). No differences were seen in bleeding/hemorrhage (1 gr 3/4 each, 1 gr 5 A). 3 pts had Gr 3/4 hypertension in B (0 in A). RR 65.4% A, 51.4% B; P=0.31. DCR 73% A, 74% B; P=1.0. Median OS 10.2 months (mo) A, 10.7 mo B; P=0.90; HR 0.78 (B v A). Median TTP 5.6 mo A, 5.5 mo B; P=0.66; HR 1.13 (B v A).

**Conclusions:** The addition of Z to PE did not improve TTP, RR, DCR, or OS for patients with extensive SCLC. An increase in toxicity was seen with Z compared with placebo. Z in combination with PE cannot be recommended for further study in unselected pts with ES SCLC. Clinical trial information: NCT00613626.

**CO-1686, Clovis (CLVS)**

First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M).

Abstract #8010^
Author(s): Lecia V. Sequist, Jean-Charles Soria, Shirish M. Gadgeel, Heather A. Wakelee, D. Ross Camidge, Andrea Varga, Benjamin J. Solomon, Vassiliki Papadimitrakopoulou, Sarah S. Jaw-Tsai, Lisa Caunt, Paramjit Kaur, Lindsey Rolfe, Andrew R. Allen, Jonathan Wade Goldman; Massachusetts General Hospital, Boston, MA; Gustave Roussy Institute, Villejuif, France; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Stanford Cancer Institute, Stanford, CA; University of Colorado Cancer Center, Aurora, CO; Gustave Roussy, Villejuif, France; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; The University of Texas MD Anderson Cancer Center, Houston, TX; Clovis Oncology, Inc., Boulder, CO; UCLA Santa Monica Hematology-Oncology, Santa Monica, CA

**Background:** Efficacy of existing EGFR tyrosine kinase inhibitors (TKIs) in NSCLC is limited by emergence of the T790M mutation in approximately 60% of patients, and significant skin rash and diarrhea, caused by wild-type (WT)-EGFR inhibition. CO-1686 is an oral, covalent TKI that targets common activating EGFR mutations and T790M, while sparing WT-EGFR.

**Methods:** This is a completed dose finding study in patients with EGFR mutated advanced NSCLC. Patients were previously treated with EGFR TKI and had a tumor biopsy in screening for central EGFR genotyping. CO-1686 was administered twice daily. Endpoints included safety, pharmacokinetics (PK), and efficacy.

**Results:** As of 17th January 2014, 88 patients were treated: 57 with CO-1686 free base (up to 900 mg BID); 31 with CO-1686 HBr (500 to 1000 mg BID). 10 transitioned from free base to HBr. 63% were T790M+, median age 61 years, 77% female, 76% white, and 72% ECOG 1. Median number of previous therapies was 3 (1-7); 40% had >1 prior line of EGFR TKI. PK of the CO-1686 HBr formulation was dose proportional with three times greater exposure than the equivalent free base dose. The dose limiting toxicity (DLT) rate at all doses was <33%. Related AEs (all grades) in ≥ 20% patients were: nausea (25%), fatigue (21%), impaired glucose tolerance/hyperglycemia (21%). Hyperglycemia was well managed with oral hypoglycemics and/or dose reduction. A recommended phase 2 dose of 750 mg BID has been selected. Nine T790M+ patients treated with 900 mg BID (free base) were evaluable for response; 6 (67%) achieved PRs, 2 (22%) achieved SD, one of whom subsequently achieved a PR after transition to CO-1686 HBr. Eight of nine progressed on EGFR TKI immediately before CO-1686. PRs have occurred among patients treated with CO-1686 HBr, however the majority of patients have not reached the first restaging. Efficacy data for at least 41 patients on CO-1686 HBr will be presented at the meeting.

**Conclusions:** CO-1686 has demonstrated promising efficacy against T790M+ EGFR mutant NSCLC. CO-1686 HBr delivered higher exposures than free base and was equally well tolerated. Dose-related WT-driven diarrhea and rash has not been seen. The phase 2/3 program will open in 2014. Clinical trial information: NCT01526928.

**HM61713, Hanmi**
Clinical activity and safety of HM61713, an EGFR-mutant selective inhibitor, in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations who had received EGFR tyrosine kinase inhibitors (TKIs).
Abstract #8011

Author(s): Dong-Wan Kim, Dae Ho Lee, Jin Hyoung Kang, Keunchil Park, Ji-Youn Han, Jong-Seok Lee, In-Jin Jang, Hyo-Yeon Kim, Jeewoong Son, Joo-Hang Kim; Seoul National University Hospital, Seoul, South Korea; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul,
Background: HM61713 is a novel, oral, selective inhibitor for EGFR mutations including both activating mutations and T790M, but not EGFR wild-type. This phase 1 trial was conducted to evaluate the safety, pharmacokinetics, and preliminary efficacy of HM61713 in the pts with advanced NSCLC harboring EGFR mutations who had failed to previous EGFR-TKIs (NCT01588145).

Methods: EGFR TKIs pre-treated, advanced NSCLC pts with EGFR mutation positive tumors were enrolled. The 3+3 dose-escalation scheme was used in dose-escalation cohort. Expansion cohort was implemented at the dose 300mg qd; pts were assigned to either arm A or B according to elapsed time interval after prior EGFR-TKIs (Arm A: <4 weeks; Arm B: ≥4 weeks) and underwent mandatory tissue biopsy at baseline to analyze EGFR T790M mutation status.

Results: To date, a total of 93 pts have been enrolled in both dose escalation and expansion cohorts (35:58 respectively). These pts received HM61713 up to 500 mg/day and maximum tolerated dose has not been determined yet and subsequent dose escalation is ongoing. Drug-related adverse events (AEs) reported in ≥10% of pts were skin exfoliation, nausea, diarrhea, rash, decreased appetite and pruritus. Most of AEs were typically Gr 1/2, easily manageable and reversible without interruption of dosing. Two cases of Gr3 or more drug-related AEs were reported. A total of 7 unconfirmed partial responses (uPR) were observed so far out of 42 evaluable pts (arm A: 3/16; arm B: 4/26) in expansion cohort. Disease control rate was 76.5% and 73.1% in arm A and B, respectively. Among 27 patients who had T790M mutation at baseline biopsy, 18 pts showed decreased size in the target lesions and all the uPR observed were T790M mutation positive cases.

Conclusions: HM61713 showed good safety profile and promising anti-tumor activity in pts with EGFR mutated NSCLC who failed to EGFR-TKIs, especially in pts with T790M mutation. Clinical trial information: NCT01588145.
**Background:** A placebo-controlled, phase II trial of erlotinib + onartuzumab, a humanized monovalent antibody to the MET receptor, demonstrated a benefit in progression-free survival (PFS) when compared with erlotinib in patients with MET-positive NSCLC (JCO 2013;31;4105). The aim of the METLung trial was to confirm the efficacy and safety of onartuzumab + erlotinib in MET-positive NSCLC.

**Methods:** This prospective, randomized, double-blind, placebo-controlled trial enrolled patients with previously treated MET-positive stage IIIb/IV NSCLC. MET diagnostic status was determined by an immunohistochemistry (IHC) assay using the CONFIRM anti-total MET SP44 monoclonal antibody (Ventana). Eligibility criteria included: ECOG PS 0–1, 1–2 prior lines of chemotherapy, and normal organ function. Stratification factors: *EGFR* mutation status (activating mutation vs negative; cobas *EGFR* assay), MET IHC (2+ vs 3+), number of prior treatments (1 vs 2), and histology (squamous vs non-squamous). Patients were randomized (1:1) to receive erlotinib 150mg PO daily + placebo or onartuzumab 15mg/kg IV every 21 days. Tumor assessments occurred every 6 weeks. The primary endpoint was overall survival (OS). The sample size (n=490) was based on the assumption that adding onartuzumab to erlotinib would improve OS by 41% with 90% power (one-sided alpha 0.025). An interim analysis was planned when 67% (244 events) of the final events were reached.

**Results:** 499 patients were enrolled between Jan 2012 and Aug 2013. An independent data review committee recommended to stop the trial for futility, as the addition of onartuzumab to erlotinib did not improve OS (HR 1.27, p=0.068; median OS 6.8 mos vs 9.1 mos), PFS (HR 0.99, p=0.92; median PFS 2.7 mos vs 2.6 mos), or overall response rate (8.4% vs 9.6%; p=0.63). The most frequent adverse events that were higher in the combination arm were peripheral edema, hypoalbuminemia, back pain, dyspnea, nausea, acneiform dermatitis, and rash.

**Conclusions:** The phase III study did not confirm the efficacy results observed in the phase II study. Exploratory analyses based on molecular subgroups are pending. Clinical trial information: NCT01456325.

**MK-3475, Merck (MRK)**

Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lung cancer (NSCLC).

Abstract #8007

Author(s): Naiyer A. Rizvi, Edward B. Garon, Amita Patnaik, Leena Gandhi, Natasha B. Leighl, Ani Sarkis Balmanoukian, Jonathan Wade Goldman, Joseph Paul Eder, Elizabeth Johnson, George R. Blumenschein, Matthew A. Gabens, Kyriakos P. Papadopoulos, Gregory M. Lubinecki, Jin Zhang, Michelle Niewood, Kenneth Emancipator, Marisa Dolled-Fihlart, Mary Elizabeth Hanson, Rina Hui; Memorial Sloan Kettering Cancer Center, New York, NY; University of California, Los Angeles, Los Angeles, CA; START Center for Cancer Care, San Antonio, TX; Dana-Farber Cancer Institute, Boston, MA; Princess Margaret Cancer Centre, Toronto, ON, Canada; The Angeles Clinic and Research Institute, Los Angeles, CA; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; AstraZeneca, Waltham, MA; Mayo Clinic, Jacksonville, FL; Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; University of California, San Francisco, San Francisco, CA; Merck & Co., Inc., Whitehouse Station, NJ; Westmead Hospital, University of Sydney, Sydney, Australia
Background: Programmed death-1 (PD-1) receptor-ligand interaction inhibits T cell activation against tumor cells. MK-3475 is a potent and highly selective humanized monoclonal antibody against PD-1 designed to directly block its interaction with its ligands, PD-L1 and PD-L2, thus removing the inhibition of T cell activation against cancer. MK-3475 led to prolonged anti-tumor activity in previously treated NSCLC patients. This Phase I study evaluated the safety, tolerability, and clinical activity of MK-3475 as initial therapy in patients with locally advanced or metastatic NSCLC.

Methods: Patients with no prior systemic therapy for metastatic disease whose tumors expressed PD-L1 by a preliminary immunohistochemical assay were randomized to MK-3475 10 mg/kg every 2 or 3 wks (Q3W). The first 11 patients were randomized to 2 mg/kg and 10 mg/kg Q3W. At least 1 measurable tumor lesion, ECOG performance status of 0 to 1, adequate organ function and adequate tumor biopsy were required for enrollment. Prior adjuvant therapy was allowed if it preceded relapse by at least a year. Tumor response was assessed every 9 weeks until confirmed disease progression per immune related response criteria (irRC; investigator review); RECIST 1.1 by independent central review will also be performed.

Results: 84 patients submitted tissue for PD-L1 assessment and 57 patients had tumors that expressed PD-L1. Between Feb 2013 and Oct 2013, 45 patients started treatment (n=6 2Q3W, n=23 10Q3W, n=16 10Q2W). Preliminary data indicate an ORR (confirmed and unconfirmed) of 36% (67% 2 mg/kg Q3W, 27% 10 mg/kg Q3W, 35% 10 mg/kg Q2W) by irRC. 25 patients (55%), including all but 2 responders, remain on treatment (treatment duration from 12+ to 48+ wks). 52% of patients experienced a drug-related adverse event (AE), usually grade 1-2 in severity, most commonly fatigue (14%), pruritus (8%), dermatitis acniform (6%), diarrhea (6%) and dyspnea (6%). There was a single drug-related grade 3-5 AE, a grade 3 pericardial effusion.

Conclusions: These data suggest that MK-3475 is generally well-tolerated and provides robust antitumor activity in a first-line setting in

Necitumumab, Eli Lilly (LLY)
A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC).
Abstract #8008^
Background: Necitumumab (N), a human IgG1 anti-EGFR monoclonal antibody, inhibits ligand-binding and receptor activation. EGFR is detectable in the vast majority of advanced sq-NSCLC tumors.

Methods: Pts with pathologically proven stage IV sq-NSCLC were randomized 1:1 to GC (G=1250 mg/m² iv, days 1 and 8; C=75 mg/m² iv, day 1) plus N (800 mg iv, days 1 and 8) (GC+N arm), or GC alone (GC arm) every 21 days for up to 6 cycles. GC+N pts with no progression continued on N alone until progressive disease or intolerable toxicity. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety. EGFR protein expression level by immunohistochemistry (H-score) in tumor tissue was an exploratory analysis. Planned sample size was 1080 pts, with 90% power and a 2-sided alpha level of 0.05.

Results: 1,093 pts were randomized (n=545, GC+N; n=548, GC). Baseline characteristics were balanced between GC+N and GC, respectively, including males (82.6% and 83.6%), ECOG PS 0/1 (91.0% and 91.2%), and PS 2 (9.0% and 8.6%). Exposure to chemotherapy was similar in both arms; median dose intensity (DI) for G and C was 86% and 95%, respectively, and DI for N was 94%. 51% of GC+N pts continued N alone for a median of 4 additional cycles. The addition of N to GC statistically significantly improved OS (HR=0.84, \( p=0.012 \)) and PFS (HR=0.85, \( p=0.020 \)); mOS was 11.5 vs 9.9 mo in GC and mPFS was 5.7 vs 5.5 mo in GC. ORR was 31% vs 29% in GC (\( p=0.400 \)), and the disease control rate (DCR) was 82% vs 77% in GC (\( p=0.043 \)). Post-progression anticancer therapy was similar (47% vs 45%). Several prespecified subgroup analyses of OS and PFS showed a consistent treatment effect, including pts with ECOG PS 2. Grade ≥3 adverse events with GC+N (measured by preferred MedDRA terms) that showed a >2% increase over GC were hypomagnesemia (8.7% vs 1.1%) and skin rash (3.7% vs 0.2%).

Conclusions: The addition of N to GC statistically significantly improved OS, PFS, and DCR. The safety profile of GC+N is acceptable. Clinical trial information: NCT00981058.

RG7599, Roche

A phase I study of DNIB0600A, an antibody-drug conjugate (ADC) targeting NaPi2b, in patients (pts) with non-small cell lung cancer (NSCLC) or platinum-resistant ovarian cancer (OC).

Abstract #2504

Author(s): Howard A. Burris, Michael S. Gordon, David E. Gerber, David R. Spigel, David S. Mendelson, Joan H. Schiller, Yulei Wang, Younjeong Choi, Robert S. Kahn, Katie Wood, Daniel J. Maslyar, Jeffrey R. Infante; Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN; Premiere Oncology of Arizona, Scottsdale, AZ; The University of Texas Southwestern Medical Center, Dallas, TX; Sarah Cannon Research Institute, Nashville, TN; Pinnacle Oncology Hematology, Scottsdale, AZ; Genentech Inc, South San Francisco, CA; Genentech, Inc., South San Francisco, CA; Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN

Background: NaPi2b (SLC34A2) is a multi-transmembrane, sodium-dependent phosphate transporter expressed in ~70% non-squamous NSCLC and ~90% OC. DNIB0600A is an ADC consisting of a humanized IgG1 anti-NaPi2b monoclonal antibody conjugated to an anti-mitotic agent MMAE that shows anti-proliferative activity in xenograft models.
Methods: This study evaluated safety and activity of DNIB0600A (0.2-2.8 mg/kg) given by intravenous infusion every 3 weeks (q3w) to pts with NSCLC or platinum-resistant OC. A traditional 3+3 design was used for dose escalation followed by expansion at the recommended Phase 2 dose (RP2D) of 2.4 mg/kg in patients with NSCLC and OC. Tumor NaPi2b expression was evaluated by immunohistochemistry (IHC) in archival tissue.

Results: As of 10 Dec 2013, 73 pts have enrolled (43 NSCLC; 30 OC), median age 62 (range 39-85), PS 0-1, median number of prior regimens 3 (1-10) in NSCLC, and 5 (1-12) in OC. Pts received a median of 4 (range 1-28) cycles of DNIB0600A. One pt experienced a DLT (Grade 3 dyspnea) at 1.8 mg/kg; no additional DLTs occurred through the maximally administered dose of 2.8 mg/kg. The most common related AEs (all grades) were fatigue (55%), nausea (40%), peripheral neuropathy (36%), decreased appetite (34%), vomiting (26%), and alopecia (19%). Related Grade 3/4 adverse events included neutropenia (8%), anemia, peripheral neuropathy, and pneumonia (each 3%), dehydration, dyspnea, fatigue, hyperglycemia, hyperkalemia, hypertension, transaminitis, and URI (each 1%)—only dyspnea led to study treatment discontinuation. At the RP2D of 2.4 mg/kg q3w, 7/17 (41%) of IHC 2/3+ pts with OC had confirmed PRs (DoR range 1.4+ to 9.4+ months). In NSCLC, 2/21 (10%) of IHC 2/3+ pts had confirmed PRs (DoR 4.3 and 4.8 months), and 5/21 (24%) had unconfirmed PRs for best response. No pt with an IHC Score of 0 showed clinical response by RECIST criteria. + : censored.

Conclusions: DNIB0600A administered q3w has an encouraging safety profile and evidence of anti-tumor activity in both OC and NSCLC. These data support Phase 2 development in OC with further clinical evaluation of DNIB0600A in NSCLC. Clinical trial information: NCT01375842.

Rucaparib (Clovis (CLVS); Phase III)
Phase 1/2 study of oral rucaparib: Final phase 1 results.
Abstract #2573

Author(s): Rebecca Sophie Kristeleit, Howard A. Burris, Patricia LoRusso, Manish R. Patel, Uzma Saddia Asghar, Fatima El-Khoudy, Alan Hilary Calvert, Jeffrey R. Infante, John Frederick Hilton, Sara M. Tolaney, Muaiad Kittaneh, Heidi Giordano, Jennifer Borrow, Sarah S. Jaw-Tsai, Geoffrey Shapiro; University College London Cancer Institute, London, United Kingdom; Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Florida Cancer Specialists and Research Institute, Sarasota, FL; University College Hospital, London, United Kingdom; UCL Cancer Institute, London, United Kingdom; Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; Dana-Farber Cancer Institute, Boston, MA; Clovis Oncology, Inc., San Francisco, CA; Clovis Oncology, Inc., Boulder, CO

Background: Rucaparib is a potent, oral PARP inhibitor (PARPi) that induces synthetic lethality in homologous recombination deficient (HRD) tumors (e.g. BRCA mutation). The primary objectives of the Phase 1 portion were to define the MTD, RP2D and PK of continuous rucaparib.

Methods: A 3+3 dose escalation design was used. Intra-patient dose escalation was allowed. Patients (pts) aged ≥18 with advanced solid tumors that had progressed on standard treatments were recruited. Measurable disease was not required. Rucaparib was taken orally QD or BID continuously. Plasma PK assessments included full profile and trough levels.
**Results:** Phase 1 is complete with 56 pts (median age 51 yrs [range 21-71]; 51 female; 29 ECOG PS=0; 27 breast cancer (BC), 20 ovarian/peritoneal cancer (OC), 9 other tumor) enrolled in 10 dose cohorts (40 QD-840 mg BID). 600 mg BID was identified as the optimal RP2/3D based on maximum exposure, manageable toxicity and promising clinical activity. Exposures exhibited dose proportional kinetics up to the RP2/3D with low inter- and intra-pt variability, an important attribute for uniform flat dosing strategies. At 360 mg BID, 1 pt had a DLT of Grade (G) 3 nausea, with no others at higher dose levels. The incidence and severity of myelosuppression, a known PARPi effect, was dose-dependent with ~50% of pts at the RP2/3D having at least one G2 or G3 event (% G2/G3): anemia (29%/29%), thrombocytopenia (0/14%), neutropenia (29%/0). All G3 events were post-Cycle 1 and were successfully managed with dose reduction. Treatment-related AEs (mostly G1/2) reported in ≥10% of all pts include fatigue (30%), nausea (30%), vomiting (23%), diarrhea (13%), anorexia (11%). No G4 AEs have occurred. RECIST and CA-125 responses occurred at doses ≥ 300 mg QD (2 CRs, 7 PRs, 3 CA-125). At these doses, disease control rate (CR+ PR + SD≥24 weeks) was 70% (7/10) in gBRCA OC pts. At the RP2/3D, 4/5 (80%) OC (3/4) and BC (1/1) pts had a RECIST or CA125 response. All responders had a BRCA 1/2 mutation. Responses were seen in platinum-sensitive and platinum-resistant OC pts.

**Conclusions:** Rucaparib has a desirable PK profile and is well tolerated with promising clinical benefit in OC, BC, and pancreatic cancer. Three studies are ongoing in OC pts (ARIEL2, ARIEL3, Phase 2 portion of this trial). Clinical trial information: NCT01482715.

**Tarceva, Astellas**

A randomized, double-blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB-IIIA EGFR positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results.

Abstract #7501

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**Background:** The proven efficacy of E in advanced NSCLC warranted its evaluation in the adjuvant setting. BR.21 data suggested pts with EGFR positive tumors (IHC/FISH) were more likely to benefit from E.
**Methods:** Completely resected IB-IIIA NSCLC pts were randomized 2:1 to receive E 150 mg qd or P for 2 years. Pts were stratified according to stage, histology, prior adjuvant chemotherapy, smoking status, EGFR FISH status, and country. The primary endpoint was disease free survival (DFS) in the full analysis set (FAS). Secondary endpoints included overall survival (OS) in the FAS and DFS and OS in the EGFR mutation (EGFR M+) subset (del19/L858R). Hierarchical testing procedure was used.

**Results:** Between NOV 2007 and JUL 2010, 973 pts were randomized. Baseline characteristics were balanced between arms (age > 65 41%; female 41%; stage IB 51%, II 33%, IIIA 16% [AJCC 6th ed]; adenocarcinoma 59%; prior adjuvant chemotherapy 53%; never smoker 20%; Asian 17%; EGFR FISH+72% and EGFR M+ 16.5%). The planned number of events (410) for the final DFS analysis was reached in APR 2013; 277 (28%) pts had died. Median follow-up was 47 months (m). No statistically significant difference in DFS was observed in FAS; hierarchical testing rendered all secondary endpoints non-significant. The median treatment duration was 12 m for E and 22 m for P in FAS. Rash and diarrhea occurred in 58% and 52% pts for E vs 17% and 16% for P. Grade ≥3 rash and diarrhea occurred in 12.6% and 6.2% pts for E vs 0.3% and 0.3% for P. No drug-related adverse events led to death.

**Conclusions:** Adjuvant E did not prolong DFS in the overall population. Further investigation in EGFR M+ pts is warranted. The safety profile of E was consistent with that in advanced disease. Clinical trial information: NCT00373425.

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<th>Median (m)</th>
<th>HR (95% CI)</th>
<th>P value</th>
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<td>E (N=623)</td>
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<tr>
<td><strong>DFS</strong></td>
<td>50.5</td>
<td>0.90 (0.741-1.104)</td>
<td>0.3235</td>
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<td>1.13 (0.881-1.448)</td>
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<td><strong>DFS</strong></td>
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Abbreviations: HR, hazard ratio; NR, not reached. *Not significant due to hierarchical testing.
Xalkori, Pfizer (PFE)

Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC).

Abstract #8001

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Background: c-Met-amplified NSCLC defines a subset of NSCLC that may be sensitive to the small-molecule tyrosine kinase inhibitor crizotinib, approved multinationally for the treatment of advanced ALK-positive NSCLC. Efficacy and safety data are presented for crizotinib in patients with advanced c-Met-amplified NSCLC within 3 categories of amplification MET/CEP7 ratio ≥1.8-≤2.2 (Low), >2.2-<5 (Intermediate) and ≥5 (High).

Methods: c-MET amplification status was determined by FISH, with 10-12 patients to be enrolled into each amplification category. If 2 or more objective responses occur in a category, 19 additional patients are to be enrolled. This study is part of an ongoing phase 1 crizotinib study (NCT00585195). Patients received crizotinib 250 mg BID. Responses were assessed using RECIST v1.0.

Results: At data cut-off, 16 patients were enrolled; 3 were subsequently determined not to have an amplification meeting MET/CEP7 criteria. 13 patients with c-MET-amplified NSCLC [Low (n=1), Intermediate (n=6) and High (n=6)] enrolled and received crizotinib, with 12 evaluable for response. Median age was 63 years (range 42-79), 92% of patients were ECOG 0 or 1 and 77% were ex-smokers. To date 4 PRs (33%; 95% CI: 10,65) have been observed (Low (n=0), Intermediate (n=1; 20%) and High (3; 50%). Median duration of response was 35 weeks [95% CI: 16,112]. Median treatment duration was 15.7 weeks (range 4-188), and 6 patients were on treatment at the data cut-off; 5 patients have died (all disease-related). 75% of the 16 patients enrolled had treatment-related adverse events (AEs): most commonly diarrhea (50%), nausea (31%), vomiting (31%), peripheral edema (n=25%) and visual impairment (25%). Most AEs were grade 1 in severity. There were no treatment-related serious AEs or treatment-related permanent discontinuations. Accrual of patients with c-Met-amplified NSCLC is ongoing.

Conclusions: Crizotinib appears to have antitumor activity in patients with c-Met-amplified NSCLC and a generally tolerable and manageable AE profile. These findings warrant further study of crizotinib in advanced c-MET-amplified NSCLC and ongoing exploration of the MET/CEP7 ratio associated with clinical benefit. Clinical trial information: NCT00585195.
Zykadia, Novartis (NVS)

Ceritinib in advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): Results of the ASCEND-1 trial.
Abstract #8003^

Author(s): Dong-Wan Kim, Ranee Mehra, Daniel Shao-Weng Tan, Enriqueta Felip, Laura Quan Man Chow, D. Ross Camidge, Johan F. Vansteenkiste, Sunil Sharma, Tommaso De Pas, Gregory J. Riely, Benjamin J. Solomon, Juergen Wolf, Michael Thomas, Martin H. Schuler, Geoffrey Liu, Armando Santoro, Margarida Geraldes, Anthony Boral, Alejandro Javier Yovine, Alice Tsang Shaw; Seoul National University Hospital, Seoul, South Korea; Fox Chase Cancer Center, Philadelphia, PA; National Cancer Centre, Singapore, Singapore; Vall d'Hebron University Hospital, Barcelona, Spain; University of Washington, Seattle, WA; University of Colorado Cancer Center, Aurora, CO; University Hospital KU Leuven, Leuven, Belgium; University of Utah Huntsman Cancer Institute, Salt Lake City, UT; Instituto Europeo di Oncologia, Milan, Italy; Memorial Sloan Kettering Cancer Center, New York City, NY; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; University Hospital Cologne, Cologne, Germany; Thoraxklinik, University of Heidelberg, Translational Lung Research Center Heidelberg, Member of the German Center for Lung Research, Heidelberg, Germany; University Hospital Essen, University Duisburg-Essen, Essen, Germany and German Cancer Consortium, Heidelberg, Germany; Ontario Cancer Institute, Princess Margaret Cancer Centre, Toronto, ON, Canada; IRCCS Institute Clinico Humanitas, Milan, Italy; Novartis Pharma, East Hanover, NJ; Novartis Institutes for BioMedical Research, Cambridge, MA; Novartis Pharma AG, Basel, Switzerland; Massachusetts General Hospital, Boston, MA

Background: ALK+ NSCLC is sensitive to crizotinib (CRZ) but patients (pts) invariably progress. Ceritinib (LDK378) is a novel ALK inhibitor (ALKi) more potent than CRZ in enzymatic and cell-based assays and CRZ-resistant animal models. Prior results from this Phase I study (ASCEND-1) established a MTD of 750 mg/d. Methods: Adult pts with advanced ALK+ cancers received oral ceritinib q.d. After MTD determination, pts were enrolled to expansion groups: ALKi pretreated (PT) NSCLC; ALKi naive NSCLC; non-NSCLC diseases. Results are reported for all NSCLC pts receiving ceritinib at the recommended dose (750 mg/d). Results: 255 pts from 11 countries were treated at 750 mg/d. 246 pts had ALK+ NSCLC, with 4.5 months' median follow-up; of these, 67% had received ≥2 anticancer therapies; ORR was ≥60% in each subgroup of pts with 0, 1, 2, and 3 prior anticancer regimens. 83 pts were ALKi naïve. All 163 ALKi PT pts had received CRZ – 78% as their last prior therapy – and 92% had progressive disease on prior ALKi. Investigator efficacy assessments are presented for 180 NSCLC pts who received first dose of ceritinib ≥18 wks prior to cut-off (2 Aug 2013). Of all 255 pts, the most common AEs were diarrhea (84%), nausea (77%), vomiting (57%), fatigue (36%), and ALT increased (36%). The most common Grade 3/4 AEs were ALT increased (21%), and AST increased (8%). Ceritinib treatment is ongoing for 58% of pts. During the dosing period dose reductions occurred in 133 pts (52.2%), all due to an AE. Only 24 (9.4%) pts discontinued ceritinib due to an AE. Conclusions: Ceritinib 750 mg/d has rapid, durable and high antitumor activity in ALK+ NSCLC pts, regardless of prior treatment with ALKi, providing effective treatment in this pt population. Clinical trial information: NCT01283516.
LYMPHOMA

**Adcetris, Seattle Genetics (SGEN)**

A pilot phase II study with brentuximab vedotin followed by ABVD in patients with previously untreated Hodgkin lymphoma: A preliminary report.

Abstract #8507

Author(s): Massimo Federico, Emanuela Anna Pesce, Francesco Merli, Stefano Luminari, Stephane Chauvie, Cinzia Pellegrini, Luigi Marcheselli, Isabella Capodanno, Fiorella Ilariucci, Massimiliano Salati, Lisa Argnani, Pier Luigi Zinzani; Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy; Hematology, Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia, Italy; Medical Physics Unit, S. Croce e Carle Hospital, Cuneo, Italy; Institute of Hematology “L. e A. Seràgnoli”, University of Bologna, Bologna, Italy

**Background:** In the majority of patients with relapsed or refractory Hodgkin Lymphoma (HL) Brentuximab vedotin (BV) has shown significant activity, with a manageable safety profile. We aimed to assess the role of 2 cycles of BV before starting the standard treatment with ABVD +/- RT in patients with previously untreated HL.

**Methods:** Patients with previously untreated CD30-positive HL, stage IA or IIA or IIA, absence of bulky disease, defined as a mediastinal mass greater than one-third of the maximum chest diameter, or any other mass greater than or equal to 10 cm, received 2 cycles of BV 1.8 mg/Kg intravenously every 3 weeks over 30 minutes, as an outpatient infusion, followed by 3-6 cycles of ABVD depending on stage. Decision on radiotherapy was at physician’s discretion. The primary endpoint of the study was the response to BV assessed by FDG/PET, defined as reduction of Deauville score or, in case of no change in Deauville score, as any reduction in SUV intensity compared to basal SUV. PET results (baseline and after 2 cycles of BV) were assessed by a panel of three external independent reviewers. The sample size was fixed at 12 patients. The treatment was considered promising if 10 or more responses were observed (response rate 83%, 95%CI 52-98%).
**Results:** Between April and October 2013, 12 patients with a median age of 36 years (age range: 19-70 years), eleven in stage II (Early favorable 7, early unfavorable 4, according to EORTC criteria) and one in stage III, were enrolled. BV was administered as scheduled and at the full dose in all patients. After the 2 cycles of BV, all patients but one (91%) responded, ten with complete (83%) and one (8%) with partial metabolic response. Of note, all seven patients with early favorable disease achieved a complete metabolic response. The only non responding patient had stage III and showed a new lesion at PET2. The only grade 3 adverse events were transient and asymptomatic increase in liver transaminases (n=3, 25%) and gamma glutamyl transpeptidase (n=2, 17%).

**Conclusions:** Two cycles of BV induced a complete metabolic response in the majority of patients with previously untreated, limited stage HL, and warrant further studies in first line therapy.

**Polatuzumab, Roche**

Preliminary results of a phase II randomized study (ROMULUS) of polatuzumab vedotin (PoV) or pinatuzumab vedotin (PiV) plus rituximab (RTX) in patients (Pts) with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL).

Abstract #8519

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**Background:** PoV and PiV, antibody drug conjugates (ADC) containing the anti-mitotic MMAE targeting CD79b (PoV) and CD22 (PiV), showed clinical activity in Phase I. The current study aims to compare PoV and PiV + RTX in R/R DLBCL and R/R follicular lymphoma (FL).

**Methods:** Pts were randomized to receive PoV or PiV + RTX (ADC 2.4 mg/kg + RTX 375 mg/m²) every 21 days. Tumor assessments were performed every 3 months.

**Results:** As of 8 November 2013, 58 received PoV + RTX (38 DLBCL; 20 FL), 63 PiV + RTX (42 DLBCL; 21 FL). Median prior therapies [DLBCL, 3 (1-10); FL, 2 (1-8)] were balanced between treatment arms; 46% were RTX refractory. Median treatment (tx) cycles in DLBCL: 5 for both ADC (1-15); FL: 8.5 PoV (3-15) and 6 PiV (1-13). Overall safety profiles of both regimens were similar. Tx-emergent adverse events (AE) >25%: fatigue (52%), diarrhea (42%), nausea (37%), peripheral neuropathy (PN) (32%), constipation (26%). Grade ≥ 3 AE >3%: neutropenia (21%), diarrhea (6%), dyspnea (4%), febrile neutropenia (4%),
hyperglycemia (4%) and PN (4%). Serious AE reported in 36%. Thirty-eight discontinued tx for AE after median 5 doses (range 1-14), including 16 for PN. Tx delays and ADC dose reductions reported in 27% and 22%. Two of 7 deaths (sepsis, urosepsis) unrelated to NHL were attributed to PiV. Complete (CR) and partial (PR) responses, n (%) [% 95% CI] (see Table).

Conclusions: PoV and PiV + RTX were generally well-tolerated with similar toxicity. Neutropenia, PN and diarrhea were principal toxicities. Similar efficacy was observed with both ADCs in heavily pretreated pts with DLBCL. The higher CR rate with PoV + RTX suggests greater clinical activity in R/R FL. Combination studies of R + PoV with chemotherapy and with ADC schedules to reduce PN are ongoing or in planning. Clinical trial information: NCT01691898.

<table>
<thead>
<tr>
<th>R/R DLBCL</th>
<th>PoV (CD79b) + RTX</th>
<th>PiV (CD22) + RTX</th>
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<tbody>
<tr>
<td>N</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>ORR</td>
<td>19 (51%) [34, 68]</td>
<td>20 (54%) [37, 71]</td>
</tr>
<tr>
<td>CR</td>
<td>5 (14%) [5, 29]</td>
<td>7 (19%) [8, 35]</td>
</tr>
<tr>
<td>PR</td>
<td>14 (38%) [23, 55]</td>
<td>13 (35%) [20, 53]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R/R FL</th>
<th>PoV (CD79b) + RTX</th>
<th>PiV (CD22) + RTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>ORR</td>
<td>12 (60%) [36, 81]</td>
<td>14 (67%) [43, 85]</td>
</tr>
<tr>
<td>CR</td>
<td>6 (30%) [12, 54]</td>
<td>1 (5%) [0.1, 24]</td>
</tr>
<tr>
<td>PR</td>
<td>6 (30%) [12, 54]</td>
<td>13 (62%) [38, 82]</td>
</tr>
</tbody>
</table>

Pharmacokinetic profiles were similar for both ADCs across DLBCL and FL with no free MMAE accumulation.

Revlimid, Celgene (CELG)

Effect of lenalidomide combined with R-CHOP (R2CHOP) on negative prognostic impact of nongerminat center (non-GCB) phenotype in newly diagnosed diffuse large B-cell lymphoma: A phase 2 study.
Abstract #8520

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Background: The non-germinal center B-cell like (non-GCB) subtype of diffuse large cell lymphoma (DLBCL) is associated with a worse outcome when treated with RCHOP chemotherapy. Lenalidomide has significant single-agent activity in relapsed DLBCL and might be particularly active in non-GCB DLBCL. We have previously reported that lenalidomide can safely be combined with RCHOP (R2CHOP). This phase 2 study evaluated the efficacy of this combination in newly diagnosed DLBCL and analyzed the outcomes based on DLBCL subtype.

Methods: Eligible patients were adults with newly diagnosed, untreated, stages II-IV CD20 positive DLBCL. Patients received oral lenalidomide 25 mg days 1-10 with standard dose R-CHOP every 21 days.
for 6 cycles. All patients received pegfilgrastim on day 2 of each cycle and aspirin prophylaxis throughout. DLBCL molecular subtype was determined by tumor immunohistochemistry (Hans algorithm) and classified as germinal center B-cell (GCB) vs non-GCB in the R2CHOP patients and 87 control DLBCL patients from the Mayo Clinic Lymphoma Database meeting the same inclusion criteria and treated with conventional RCHOP.

**Results:** 64 DLBCL patients were enrolled. Median age was 65 years (22-87) and 34 patients (53%) had IPI intermediate-high or high. 60 were evaluable for response. The overall response rate was 98% (59/60) with 80% (48/60) complete response (CR). 24 month EFS and OS rates (95% CI) were 59% (48%-74%) and 78% (68-90%), respectively. In RCHOP patients, 24 months PFS and OS were 28% vs 64%, p<0.001 and 46% vs 78% p<0.001 in non-GCB patients vs GCB patients respectively. In contrast, there was no difference in 24 months PFS or OS for R2CHOP treated patients based on non-GCB and GCB subtype, 60% vs. 0.59%, p= 0.83 and 83% vs. 75%, p=0.61 at 2 years respectively.

**Conclusions:** R2CHOP shows promising efficacy in DLBCL. The addition of lenalidomide to RCHOP appears to mitigate the negative impact of non-GCB phenotype on the outcome. A randomized phase 2 study of RCHOP vs. R2CHOP utilizing gene expression profiling classification of DLBCL subtype and led by the Eastern Cooperative Oncology Group (E1412) is currently ongoing. Clinical trial information: NCT00670358.

**Rituxan, Roche**

**Increased rituximab (R) doses and effect on risk of elderly male patients with aggressive CD20+ B-cell lymphomas: Results from the SEXIE-R-CHOP-14 trial of the DSHNHL.**

Abstract #8501

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**Background:** Elderly male patients have significantly lower R serum levels, shorter exposure times and a worse outcome in RICOVER-60, RICOVER-noRTh, and Pegfilgrastim trials (Blood 2012, 119:3276; Blood 2014, 123:640-646).

**Methods:** To test increasing R doses, male patients received 500 instead of 375 mg/m² in the SEXIE-R-CHOP-14 trial which also compared six cycles of CHOP-14 in combination with eight 2-week applications with eight upfront dose-dense applications of R (days -1, 0, 3, 7, 14, 21, 28, 42) in a randomized phase-II trial. 271 patients (61-80 years) were randomized, 268 patients are evaluable. 148 patients males received 500 mg/m², 120 females 375 mg/m² R.

**Results:** Protocol adherence was excellent with median relative doses of R and myelosuppressive drugs >98%. During the treatment period, the increased R dose in males resulted in slightly higher trough serum levels than in females; however, R levels dropped faster in males resulting in nearly identical...
serum levels thereafter and a very similar overall R exposure time. The increased R dose in males was not associated with increased toxicities. 3-year PFS was 74% in males and 68% in females (p=0.396), 3-year OS was 80% in males and 72% in females (p=0.111). In a multivariable analysis adjusting for IPI factors, male hazard was 0.9 (p=0.817) for PFS, and 0.8 for OS (p=0.317). In a historical comparison by multivariable analysis adjusting IPI risk factors and age >70 years, of 148 elderly males who received 500 mg/m² in SEXIE-R-CHOP-14 and 250 males who received 375 mg/m² in RICOVER-60, the increased dose of R was associated with a reduced risk for an event in PFS (HR=0.7; p=0.128) and 0.7 in OS (p=0.223).

**Conclusions:** Increasing R dose by one third from 375 mg/m² to 500 mg/m² eliminated the increased risk of elderly males. That the increased R dose significantly improves outcome not only of elderly male patients, but also in young male and female patients who have a R pharmacokinetics similar to elderly males should be confirmed in a larger randomized study of these subpopulations with aggressive CD20⁺ B-cell lymphomas. Supported by Roche and Deutsche Krebshilfe. Clinical trial information: NCT00290667.

**Rituxan, Roche**

Final results of a randomized phase II GELA/LYSA study of rituximab plus ACVBP or CHOP, using a PET-driven consolidation strategy, in patients with high-risk diffuse large B-cell lymphoma (DLBCL).

Abstract #8503

Author(s): Rene-Olivier Casasnovas, Loic Ysebaert, Catherine Thieblemont, Bertrand Coiffier, Serge Bologna, Gerard Lepeu, Alain Delmer, Isabelle Plantier, Jean Gabarre, Marc Andre, Delphine Senecal, Christophe Fruchart, Michel Meignan, Alina Berriolo-Riedinger, Stephane Bardet, Thierry Jo Molina, Jean-Philippe Jais, Corinne Haïoun, Herve Tilly, Franck Morschhauser; Hôpital Le Bocage, Dijon, France; CHU Toulouse, Toulouse, France; Assistance Publique–Hôpitaux de Paris, Hôpital Saint Louis, Paris, France; Lyon Sud University Hospital, Pierre-Bénite, France; Centre Hospitalier Universitaire, Nancy, France; Centre Hospitalier d’Avignon, Avignon, France; Hôpital Robert Debré, Reims, France; CH Roubai, Roubaix, France; Hopital Pitié Salpêtrière, Paris, France; Centre Hospitalier Universitaire Mont-Godinne, Dinant, Belgium; CH Chambery, Chambery, France; Centre François Baclesse, Caen, France; Hôpital Henri Mondor, Créteil, France; Department of Nuclear Medicine, Centre Georges-Francois Leclerc, Dijon, France; Centre Francois Baclesse, Caen, France; Hotel Dieu, Paris, France; Université Paris Descartes, Paris, France; Hôpital Henri Mondor, Creteil, France; Centre Henri Becquerel, Rouen, France; Hôpital Claude Huriez, Lille, France

**Background:** GELA standard for young patients (pts) with high-risk DLBCL (aaIPI 2-3) is R-ACVBP induction plus consolidative BEAM and autologous stem cell transplantation (ASCT). R-CHOP induction might be as efficient and possibly less toxic than R-ACVBP. Also, early PET-negative patients may not need first-line ASCT. A phase II randomized trial was designed in 2007 to test both induction regimen and a PET-driven consolidation strategy (NCT00498043).

**Methods:** Eligible pts were 18-59 years with a previously untreated CD20⁺ DLBCL, an aaIPI 2-3. Pts were randomly assigned to 4 cycles of either R-ACVBP14 or R-CHOP14 induction. Consolidation treatment was driven by centrally reviewed PET assessment (IHP visual criteria) after 2 (PET2) and 4 (PET4) induction cycles. Pts classified as PET2-/PET4- received a sequential immuno-chemotherapy consolidation; PET2+/PET4- pts underwent ASCT; PET4+ pts were considered as induction treatment failure and eligible for a salvage therapy. Primary endpoint was to evaluate the complete response (CR) rate after 4 induction cycles according to IWG 07 criteria.
Results: 222 pts (R-ACVBP: 114; R-CHOP: 108) with a median age of 46 yrs were included: 97% had stage III/IV, 95% elevated LDH, 24% ECOG≥2. After induction treatment, 47% of the R-ACVBP arm and 39% of the R-CHOP arm pts achieved a CR. PET2 and PET4 were negative in 30% and 53% of pts in the R-ACVBP arm, and 25% and 40% in the R-CHOP arm, respectively. PET2-/PET4- pts were 27% and 24% in the R-ACVBP and R-CHOP arms respectively. Due to more frequent PET4+, pts in the R-CHOP arm more often received salvage therapy as post-induction treatment (39%) than pts in the R-ACVBP arm (27%) (p = 0.048). With a median follow-up of 45 months, PFS and OS were similar in both arms (4y-PFS=75%; 4y-OS=83%).

Conclusions: A PET driven treatment of high risk DLBCL pts is feasible in a multicenter trial setting. Based on PET visual criteria at 4 cycles, CR rate was higher in the R-ACVBP arm and salvage was more frequently used after R-CHOP, possibly explaining similar PFS and OS in the two induction arms. 25% of pts found to be PET2-/PET4- do not require ASCT. Clinical trial information: NCT00498043.

**SAR3419, Sanofi (SNY)**
Starlyte phase II study of coltuximab rautansine (CoR, SAR3419) single agent: Clinical activity and safety in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL; NCT01472887).
Abstract #8506

Author(s): Marek Trneny, Gregor Verhoef, Martin JS Dyer, Dina Ben Yehuda, Caterina Patti, Miguel Canales, Andrés López, Farrukh Awan, Paul Montgomery, Andrea Janikova, Anna Maria Barbui, Kazimierz Sulek, Maria José Terol, John A. Radford, Laure Siraudin, Laurence Hatteville, Sandrine Schwab, Corina Oprea, Alessandro M. Gianni; Charles University Hospital, Department of Hematology, Prague, Czech Republic; UZ Leuven, Leuven, Belgium; Leicester University, Leicester, United Kingdom; Hadassah Medical Center, Jerusalem, Israel; Azienda Ospedali Riuniti Villa Sofia, Palermo, Italy; Hospital Universitario La Paz, Madrid, Spain; Hospital Universitari Vall d'Hebron, Barcelona, Spain; The Ohio State University, Columbus, OH; St. Lukes/Mountain States Tumor Institute, Boise, ID; University Hospital Brno, Brno, Czech Republic; Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; Military Medical Institute, Warszawa, Poland; Hospital Clínico Universitario de Valencia, Valencia, Spain; University of Manchester/Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Lincoln, Boulogne-Billancourt, France; Sanofi R&D, Vitry-sur-Seine, France; Sanofi R&D, Chilly-Mazarin, France; Fondazione IRCCS Istituto Nazionale Tumori and Università degli Studi di Milano, Milan, Italy

Background: CoR is an anti-CD19 antibody maytansinoid conjugate. CD19 is expressed in the majority of B cell lymphomas. Phase I program showed clinical activity in pts with both indolent and aggressive lymphomas.

Methods: Pts withCD19+ R/R DLBCL after at least one standard treatment including rituximab and not candidate for transplantation were eligible. Primary refractory pts were excluded. Biopsy was required at baseline. CoR 55 mg/m² was administered weekly for 4 weeks then bi-weekly until disease progression or other study discontinuation criteria. The primary objective was to demonstrate an overall response rate (ORR) of at least 20% following Cheson 2007 criteria. Tumor assessments were done every 12 weeks. Secondary objectives were: safety, pharmacokinetics (PK), duration of response (DOR), progression free and overall survival (PFS, OS). Assessment of correlation between biomarkers (BM) status and disease outcome was an exploratory objective.
Results: 41 pts were evaluable. Median age was 71 (39:85), 53.7% were male; 92.7% had ECOG performance status 0-1. 31.7% had received ≥ 3 prior regimens for DLBCL. The ORR was 43.9% (90% CI: 30.6% to 57.9%, p-value<0.0001) including 5 complete responses (12.2%). DOR, OS and PFS data are not mature (11 pts ongoing). The most common (>10%) all grades (gr) non-hematologic treatment-emergent adverse events (TEAEs) were nausea (23.0%), diarrhea (19.7%), fatigue and cough (18.0%), vomiting and decrease appetite (13.1%), asthenia, abdominal and back pain (11.5%). TEAEs led to treatment discontinuation in 4 pts. Only gr 1-2 eye disorders were reported, including 1 pt with unrelated gr 2 keratitis. Peripheral neuropathies were observed in 5 pts, all were gr 1-2. Hematological toxicity was moderate, with gr 3-4 neutropenia, thrombocytopenia and anemia in 26.4%, 9.9% and 6.6% pts respectively. PK assessment and investigations on BM expression are ongoing.

Conclusions: CoR as single agent demonstrated significant activity in R/R DLBCL pts and reached its primary endpoint for ORR, with acceptable safety profile. Trial funded by Sanofi. Clinical trial information: NCT01472887.

Selinexor, Karyopharm (KPTI)
A phase 1 dose-escalation study of the oral selective inhibitor of nuclear export (SINE) KPT-330 (selinexor) in patients (pts) with heavily pretreated non-Hodgkin lymphoma (NHL).
Abstract #8518

Author(s): Martin Gutierrez, Andre Goy, John C. Byrd, Joseph M. Flynn, Morten Sorensen, Peter Brown, Nashat Y. Gabrail, Michael Savona, Ian Flinn, Rachid C. Baz, Bijal D. Shah, Richard M. Stone, Eric Jacobsen, Vishal Kukreti, Roger E. Tiedemann, Tami Rashal, Mansoor Raza Mirza, Sharon Shacham, Michael Kauffman, John Kuruvilla; John Theurer Cancer Center, Hackensack, NJ; The Ohio State University, Columbus, OH; Rigshospitalet, Copenhagen, Denmark; H:S Rigshospitalet, The Finsen Centre, KAT, Haematology Department 4241, Copenhagen, Denmark; Gabrail Cancer Center, Canton, OH; Tennessee Oncology, Nashville, TN; Sarah Cannon Research Institute, Nashville, TN; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Center Institute, Boston, MA; Princess Margaret Cancer Centre, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON; Karyopharm Therapeutics, Newton, MA; University Health Network, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: KPT-330 (Selinexor) is a SINE XPO1 antagonist that forces nuclear retention and activation of >10 tumor suppressor proteins (TSP) and associated with reduction in c-myc and Bcl-XL. Anti-NHL activity was observed in murine models and in spontaneous canine aggressive lymphomas.

Methods: Oral KPT-330 was given at 8-10 doses / 28-day cycle. XPO1 inhibition leads to rapid elevations in XPO1 mRNA, representing a pharmacodynamic (PDn) marker for KPT-330. Tumor biopsies were performed. Response evaluation was done in cycles 1, 2, and every 2 cycles. All pts had heavily pretreated NHL with progressive disease (PD) on study entry.

Results: Thirty-two pts (18 M, 14 F; median age 68 yrs; ECOG PS 0/1: 9/23; median prior regimens: 3 range 1-11) received KPT-330 across 8 dose levels (3 to 60 mg/m²). Dosing at 60 mg/m² twice weekly (BIW) is ongoing and MTD has not been reached. Cycle 1 (DLT period) Grade 3/4 events in >1 pt included thrombocytopenia (20%) and neutropenia (20%). The most common grade 1/2 AEs in cycle 1: anorexia (53%), nausea (50%), fatigue (50%), and vomiting (43%). Supportive care with appetite stimulants and anti-emetics diminished constitutional symptoms. Increases in XPO1 mRNA levels were observed at 4-48
hours, supporting BIW dosing. Tumor biopsies confirmed TSP nuclear localization, c-myc reduction, and apoptosis. Objective responses were observed in all histologies of NHL (Table). 5/16 pts have remained on therapy for an average of 9 months (>5-17) months without clinically significant toxicities.

**Conclusions:** KPT-330 is generally well tolerated and can be administered over prolonged periods. The recommended phase 2 dose is ≥45 mg/m² BIW. Durable single agent activity was observed in heavily pretreated NHL pts, and phase 2 studies in DLBCL and Richter’s Syndrome are planned. Clinical trial information: NCT01607892.

**Response in 28 evaluable pts.**

<table>
<thead>
<tr>
<th>NHL</th>
<th>N</th>
<th>PR+SD (%)</th>
<th>PR (%)</th>
<th>[%Change in LN Size]</th>
<th>PD</th>
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<tbody>
<tr>
<td>Follicular (FL)</td>
<td>6</td>
<td>6 (100%)</td>
<td>1 (17%)</td>
<td>[-17% to -44%]</td>
<td></td>
</tr>
<tr>
<td>Mantle Cell</td>
<td>2</td>
<td>2 (100%)</td>
<td>1 (50%)</td>
<td>[-36%]</td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>14</td>
<td>9 (64%)</td>
<td>3 (21%)</td>
<td>[-12% to -19%]</td>
<td>5  (36%)</td>
</tr>
<tr>
<td>Transformed FL</td>
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<td>1 (33%)</td>
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<td>2  (67%)</td>
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<td>Richter’s</td>
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<tr>
<td>Total</td>
<td>28</td>
<td>21 (75%)</td>
<td>7 (25%)</td>
<td></td>
<td>7  (25%)</td>
</tr>
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</table>

**SGN-CD19A, Seattle Genetics (SGEN)**

Interim analysis of a phase 1, open-label, dose-escalation study of SGN-CD19A in patients with relapsed or refractory B-lineage non-Hodgkin lymphoma (NHL).

Abstract #8505

Author(s): Andres Forero-Torres, Craig Moskowitz, Ranjana H. Advani, Bijal D. Shah, Ana Kostic, Tina M. Albertson, Larissa Sandalic, Baiteng Zhao, Michelle A. Fanale; The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; Memorial Sloan Kettering Cancer Center, New York, NY; Stanford University Medical Center, Stanford, CA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Seattle Genetics, Inc., Bothell, WA; The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** CD19, a member of the immunoglobulin superfamily, is expressed in most patients with B-cell NHL. SGN-CD19A is a novel antibody-drug conjugate composed of a humanized anti-CD19 monoclonal antibody conjugated to the microtubule-disrupting agent monomethyl auristatin F (MMAF) via a maleimidocaproyl linker.
Methods: This phase 1, open-label, dose-escalation study investigates the safety, tolerability, pharmacokinetics (PK), and antitumor activity of SGN-CD19A in patients with relapsed or refractory B-cell NHL with at least 1 prior systemic regimen (NCT01786135). Patients with DLBCL or follicular lymphoma grade 3 (FL3) must have received intensive salvage therapy. A modified continual reassessment method is used for dose allocation and maximum tolerated dose (MTD) estimation. SGN-CD19A is given by IV on Day 1 of 21-day cycles.

Results: To date, 22 patients with a median age of 63 years (range, 33 to 81) with DLBCL (18), MCL (3), and FL3 (1) have been treated with SGN-CD19A. 50% of patients were refractory to their last treatment; 6 patients received prior autologous SCT. Patients have received a median of 2 cycles (range, 1 to 9) at dose levels from 0.5 mg/kg to 6 mg/kg. 11 patients remain on treatment and 11 have discontinued due to progressive disease (10) and patient decision (1). No dose-limiting toxicity (DLT) has been reported in 21 DLT-evaluable patients; the MTD has not yet been identified. Adverse events occurring in ≥10% of patients are fatigue (27%), blurred vision (27%), dry eye (23%), constipation (23%), dyspnea (14%), and keratitis (14%). Of the 20 patients evaluated, objective responses were observed in 8 patients (40%), 6 CRs (30%) and 2 PRs (10%); 3 patients had SD (15%) and 9 had PD (45%). SGN-CD19A ADC plasma exposures were approximately dose-proportional in preliminary PK analysis with mean terminal half-lives between 9-30 days.

Conclusions: To date, SGN-CD19A has shown evidence of clinical activity with an objective response rate of 40% (8 of 20 patients) and an observed CR rate of 30% (6 of 20 patients). No DLTs have been reported in tested dose levels; enrollment is ongoing to identify the optimal dose of SGN-CD19A for future studies. Clinical trial information: NCT01786135.

Velcade, Roche
Randomized phase 3 study of rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in newly diagnosed mantle cell lymphoma (MCL) patients (pts) ineligible for bone marrow transplantation (BMT).

Abstract #8500

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Background: R-CHOP is standard therapy for newly diagnosed, BMT-ineligible MCL pts. Bortezomib (V) is approved in the US for relapsed MCL. This study evaluated whether replacing vincristine with V in R-CHOP improves outcomes in newly diagnosed, BMT-ineligible MCL pts (NCT00722137).

Methods: Adults with treatment-naive, measurable stage II–IV MCL and ECOG PS 0–2 were randomized 1:1 (stratified by IPI score and disease stage) to 6–8 21-d cycles of rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², all IV d 1, and prednisone 100 mg/m² PO d 1–5, plus V 1.3 mg/m² IV d 1, 4, 8, 11 (VR-CAP) or vincristine 1.4 mg/m²(max 2 mg) IV d 1 (R-CHOP). Primary endpoint was PFS by independent radiology review (IRC); secondary endpoints included TTP, TTNT, OS, response by modified IWRC criteria, and safety. 486 pts were planned for 295 total PFS events, to provide 80% power (α=.05, 2-sided) to detect 40% PFS improvement with VR-CAP.
**Results:** 487 pts were randomized (244 R-CHOP, 243 VR-CAP; median age 66 yrs, 74% male, 74% stage IV MCL, 54% IPI ≥3). Pts received a median of 6 cycles. After 40 mos’ median follow-up (298 PFS events), median PFS by IRC was 14.4 (R-CHOP) vs 24.7 mos (VR-CAP) (ITT analysis: HR=.63* [.50, .79], P<.001**). Secondary efficacy data are below. Rates of grade ≥3 AEs were 85% (R-CHOP) vs 93% (VR-CAP), serious AEs 30% vs 38%, discontinuations due to AEs 7% vs 9%, and on-treatment drug-related deaths 3% vs 2%.

**Conclusions:** VR-CAP significantly prolonged PFS and consistently improved secondary efficacy endpoints vs R-CHOP in newly diagnosed, BMT-ineligible MCL pts, with additional but manageable toxicity. Clinical trial information: NCT00722137.

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<table>
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**MELANOMA**

**Cobimetinib, Roche**

Metabolic tumor burden for prediction of overall survival following combined BRAF/MEK inhibition in patients with advanced BRAF mutant melanoma.

**Abstract #9006**

Author(s): Grant A. McArthur, Jason Callahan, Antoni Ribas, Rene Gonzalez, Anna C. Pavlick, Omid Hamid, Thomas Gajewski, Igor Puzanov, Adil Daud, Ming Yin, Nicholas Choong, Jinay K Shah, Jill

See all of the reports, analysis and real-time email alerts that BioMedTracker offers. Get a free demo of BioMedTracker at goo.gl/0P10uY
Background: BRAF mutation is a common and potent oncogenic driver of ERK signalling in melanoma. Abrogation of pERK reduces 18-F-fluorodeoxyglucose (FDG) uptake on PET with recovery in glycolytic metabolism being a hallmark of resistance. FDG-PET also allows accurate quantification of melanoma burden. In a Ph1b trial (BRIM7), combining vemurafenib (vem) with a MEK inhibitor, cobimetinib (cobi), BRAFi-naïve patients (pts) with advanced $BRAF^{V600E}$-mutated melanoma attained 87% confirmed response rate, by RECIST and median progression-free survival of 13.7 months. We evaluated FDG-PET response as predictor of clinical outcome in BRAFi/MEKi naïve patients (pts) treated with this combination.

Methods: FDG-PET scanning was performed in cycle 1 (C1) (day 10-15) and in C2 (day 35-49) of BRIM7. The percentage of the injected dose (%ID) of FDG and metabolic tumor volume (MTV), as measures of tumor burden, and maximum standardized uptake value (SUVmax) in up to 5 target lesions, as an indicator of metabolism, were assessed at baseline, C1 and C2. PFS and OS were analysed by the log rank method.

Results: 35 evaluable BRAFi-naïve pts (mean %ID 1.6±2.9% and mean `MTV 166±251 ml) demonstrated a mean reduction in %ID, MTV and SUVmax of 86±14%, 72±23% and 76±18% at C1, respectively, and 95±10%, 92±12% and 89±14% at C2, respectively. All pts achieved a partial metabolic response (PMR) (>30% decrease in SUVmax) by C1 with 5 complete metabolic responses (CMR) (14%) in C1 and 17 CMR (51%) in C2. Pts achieving a CMR in C1 had longer PFS when compared to Pts achieving PMR. Although tumor burden at baseline was not correlated with metabolic response, both %ID and MTV were predictors of OS. Pts with a baseline %ID <median (0.36%) or MTV <median (47.5 ml) had better OS (HR 0.19, p<0.02 and 0.14, p=0.03) compared to pts with >median values.

Conclusion: Independent of tumor burden, BRAFi/MEKi naïve pts treated with vem/cobi achieved a marked, early and progressive metabolic response on FDG-PET consistent with successful inhibition of ERK-signaling. Tumor burden was a predictor of clinical outcome in this small patient cohort with low baseline %ID or MTV associated with longer overall survival; further validation is warranted. Clinical trial information: NCT01271803.
Background: Indoleamine 2,3-dioxygenase 1 (IDO1) is a tryptophan-catabolizing enzyme that is overexpressed in cancers and induces immune tolerance by suppressing T-cell responses. INCB024360, a potent, selective IDO1 inhibitor, was generally well tolerated as monotherapy up to 700 mg BID. Preclinical data support anti-tumor synergy for INCB024360 when administered with antibody antagonists to checkpoint receptors.

Methods: This is an ongoing dose-escalation study of INCB024360 combined with ipi (3 mg/kg IV q 3 wks x 4) in pts with metastatic melanoma. Enrollment in 2 cohorts (300 mg BID, 25 mg BID) is complete. Toxicity, ORR (irRC), Duration of Response (DoR), and OS were evaluated. The DLT evaluation period was 8 wks and assessments for response were every 9 wks.

Results: Seven pts were enrolled at 300 mg BID. When 5 pts developed clinically significant ALT elevations after 30–76 days on treatment, enrollment was stopped. ALT elevations were reversible with corticosteroids and treatment discontinuation. Six of 7 pts had evaluable on-study scans prior to discontinuation and all showed irSD. Time to subsequent therapy was >90 days in all 7 pts and >180 days in 4 of 7 pts. Enrollment was restarted at 25 mg BID (n=8), where 1 pt with progression of prior extensive liver metastases had a DLT (G3 AST elevation). Immune-related AEs (irAEs) were generally G1/2 and manageable with continued dosing or temporary dose interruption; 1 pt each discontinued for G3 colitis and G3 salivary amylase elevation. Six of 8 pts had tumor reduction by the 1st evaluation. Confirmed disease control rate was 75% (6/8). Three pts had confirmed irPR (2 occurred by the 1st or 2nd scan); DoR was 179, 148, and >127 (ongoing) days. Three pts had irSD for 116, >173 (ongoing), and >187 (ongoing) days. Pharmacodynamic effects at 25 mg BID were similar to those that were sufficient in preclinical models to achieve maximal therapeutic effect. A 50 mg BID cohort is enrolling.

Conclusions: INCB024360 25 mg BID with ipi was generally well tolerated and irAEs previously observed with ipi were reversible with appropriate management. Tumor response and duration data suggest the potential for enhanced melanoma patient outcomes compared to ipi monotherapy. Clinical trial information: NCT01604889.

LEE011, Novartis (NVS)
Binimetinib, Novartis (NVS)
A phase 1b/2 study of LEE011 in combination with binimetinib (MEK162) in patients with NRAS-mutant melanoma: Early encouraging clinical activity.
Abstract #9009

Author(s): Jeffrey Alan Sosman, Muaiad Kittaneh, Martijn P. J. K. Lolkema, Michael Andrew Postow, Gary Schwartz, Catherine Franklin, Alessandro Matano, Suraj Bhansali, Sudha Parasuraman, Kevin Kim; Vanderbilt University Medical Center, Nashville, TN; Center for Translational Therapeutics, Karmanos Cancer Institute, Detroit, MI; University Medical Center Utrecht, Utrecht, Netherlands; Memorial Sloan Kettering Cancer Center, New York, NY; Columbia University Medical Center, New York, NY; Novartis Institutes for Biomedical Research, Cambridge, MA; Novartis Pharma AG, Basel, Switzerland; Novartis
Background: NRAS-mutant melanoma has poor prognosis with no approved targeted therapies. Enhanced MAPK pathway signaling and cell cycle checkpoint dysregulation are frequent in NRAS-mutant melanoma. Thus, simultaneous inhibition of MEK and CDK4/6 could further suppress pathway activation. The MEK inhibitor binimetinib (MEK162) showed clinical activity in patients (pts) with NRAS-mutant melanoma. In preclinical studies, the selective CDK4/6 inhibitor LEE011 demonstrated tumor growth inhibition, and in combination with binimetinib led to regressions in NRAS-mutant melanoma models, warranting clinical study.

Methods: This is a phase 1b/2, open-label study of LEE011 + binimetinib in pts with NRAS-mutant melanoma. The primary objective of the phase 1b part is to estimate the MTD/RP2D of the combination, using a Bayesian logistic regression model (BLRM) with overdose control. Secondary objectives include safety, pharmacokinetics (PK), and preliminary efficacy. LEE011 is administered once daily for 21 days of each 28-day cycle and binimetinib is administered twice daily continuously.

Results: As of Dec 20, 2013, 14 pts were enrolled (93% stage M1c; ECOG PS 0/1/2 [43%/50%/7%]; median 2 prior lines) and were treated with LEE011 at 200 mg (dose level [DL] 1, n = 8) or 300 mg (DL 2, n = 6) and with binimetinib 45 mg. DLTs occurred at DL 1 (grade 3 acute renal injury, n = 1) and DL 2 (grade 4 asymptomatic creatine phosphokinase [CPK] elevation and grade 3 edema plus grade 4 atrial fibrillation, 1 pt each). Common treatment-related toxicities included CPK elevation, rash, edema, anemia, nausea, diarrhea, and fatigue. Preliminary PK was consistent with single-agent data for either drug, with no evidence of drug-drug interaction. Six pts achieved partial response (43%; 1 confirmed, 5 unconfirmed) and 6 had stable disease (4 with tumor shrinkage > 20%). Several pts experienced early tumor shrinkage with major symptomatic improvement; 8 pts remain on treatment (duration 2-8 mo).


Mekinist, Novartis (NVS)
Tafinlar, Novartis (NVS)
Phase 1 study of the BRAF inhibitor dabrafenib (D) with or without the MEK inhibitor trametinib (T) in combination with ipilimumab (Ipi) for V600E/K mutation–positive unresectable or metastatic melanoma (MM).
Abstract #2511

Author(s): Igor Puzanov, Margaret K. Callahan, Gerald P Linette, Sapna Pradyuman Patel, Jason J. Luke, Jeffrey Alan Sosman, Jedd D. Wolchok, Omid Hamid, David R. Minor, Keith W. Orford, Bruce A. Hug, Bo Ma, Gemma M. Matthys, Axel Hoos; Vanderbilt-Ingram Cancer Center, Vanderbilt University, School of Medicine, Nashville, TN; Memorial Sloan Kettering Cancer Center, New York, NY; Division of Oncology, Washington University School of Medicine in St. Louis, St. Louis, MO; The University of Texas MD Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute, Boston, MA; The Angeles Clinic and Research Institute, Los Angeles, CA; California Pacific Medical Center Research Institute, San Francisco, CA; GlaxoSmithKline Research and Development, Collegeville, PA; GlaxoSmithKline Research and Development, Collegeville, PA, and Research Triangle Park, NC
Background: D, T, and Ipi are each indicated for treatment of patients (pts) with MM (D+T in BRAF V600 mutation–positive MM). D and T can be safely combined and prolong progression-free survival compared with monotherapy. Combining D+T with the CTLA-4 antibody Ipi has the potential to improve treatment outcomes, but the safety profile is unknown. A recent report suggested caution in combining the BRAF inhibitor vemurafenib (V) with Ipi; V+Ipi resulted in G3 elevations of ALT in 6/10 pts leading to study discontinuation (NEJM2013 368; 14). The present study will characterize the safety of D±T+Ipi, select recommended phase 2 doses (RP2Ds), and report efficacy.

Methods: Pts with stage IIIc/IV BRAF V600E/K mutation–positive MM and ≤1 prior treatments are eligible. Dose escalation occurs in cohorts of 3-6 pts followed by expansion (≤30 pts) at the RP2D. At data cutoff (Nov 8, 2013), 10 pts were enrolled: 4 received D+Ipi (doublet), 2 received D only (withdrawn before Ipi treatment), and 4 received D+T+Ipi (triplet).

Results: Median age of the 10 pts was 59.5 y (range, 32-75 y). Doublet: D 150 mg bid + Ipi 3 mg/kg q3w × 4 doses was well tolerated and selected as RP2D. No G3/4 ALT elevations or dose-limiting toxicities (DLTs) were observed. The most frequent adverse events (AEs; ≥2) were chills, fatigue, hand-foot syndrome, pyrexia, and maculopapular rash. Of 4 pts, 2 are ongoing and 2 stopped treatment (disease progression). Pts are currently being enrolled at this dose level in the expansion. Triplet: At current doses (D 100 mg bid/T 1 mg qd+Ipi 3 mg/kg q3w × 4), no G3/4 ALT elevations and 1 DLT (G3 colitis; associated with Ipi) occurred. The most frequent AEs (≥2) were pyrexia, chills, arthralgia, insomnia, and maculopapular rash. One pt had G4 renal insufficiency that reversed rapidly. Of 4 pts treated, 1 stopped treatment (DLT), and 3 are ongoing. Updated safety data and preliminary efficacy data will be presented for both cohorts.

Conclusions: To date the combinations of D+Ipi and D+T+Ipi appear to be tolerable and have not been associated with significant hepatotoxicity in MM, suggesting differences between BRAF inhibitors when combined with Ipi. Clinical trial information: NCT01767454.

Mekinist, Novartis (NVS)
Tafinlar, Novartis (NVS)
COMBI-d: A randomized, double-blinded, Phase III study comparing the combination of dabrafenib and trametinib to dabrafenib and trametinib placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAFV600E/Kmutation-positive cutaneous melanoma
Abstract #9011^
Diderot, Paris, France; Papa Giovanni XIII Hospital, Bergamo, Italy; Sir Charles Gairdner Hospital, Perth, Australia; GlaxoSmithKline, Research Triangle Park, NC; GlaxoSmithKline, Collegeville, PA; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

**Background:** As monotherapies, the BRAF inhibitor dabrafenib (D) and the MEK inhibitor trametinib (T) demonstrated superior progression-free survival (PFS) v chemotherapy in pts with BRAF\textsuperscript{V600} mutant, metastatic melanoma (MM). Resistance develops in most pts, and oncogenic toxicities (e.g., cutaneous squamous carcinoma (cuSCC)) are associated with BRAF inhibition. Simultaneous inhibition of BRAF and MEK mitigated these effects in the Phase I/II study of D+T v D (NCT01072175), with an improvement in overall response rate (ORR), PFS and reduced frequency of cuSCC. This Phase III study (NCT01584648) was conducted to confirm the superiority of D+T over D in pts with BRAF\textsuperscript{V600E/K} mutant MM.

**Methods:** Pts were randomized 1:1 to receive D (150 mg twice daily) + T (2 mg once daily) or D+ placebo (P) as first-line therapy. Eligible pts were ≥18 years and ECOG performance status ≤1, with histologically confirmed unresectable stage IIIIC or IV, BRAF\textsuperscript{V600E/K} mutant cutaneous melanoma. The primary endpoint was investigator-assessed PFS; secondary endpoints were overall survival (OS), ORR, duration of response, and safety. Cross over was prohibited. The study has 95% power and a one-sided α=0.025 to detect a PFS hazard ratio (HR) of 0.59.

**Results:** From May 2012 to Jan 2013, 423 pts were randomized (211 to D+T, 212 to D+P). Median follow up was 9 mo (0-16 mo). HR for investigator-assessed PFS was 0.75 (95% CI: 0.57, 0.99; p=0.035), in favor of D+T with a median PFS of 9.3 v 8.8 mo with D+P. The confirmed ORR was 67% (complete response [CR] 10%) for D+T and 51% (CR 9%) for D+P (p=0.0015). HR for interim OS was 0.63 (95% CI 0.42, 0.94; p=0.023), in favor of D+T (40 v 55 deaths). Rates of AEs were similar for both arms. More pts had AEs leading to dose modifications with D+T v D+P. Increased incidence (51% v 28%) and severity (grade 3, 6% v 2%) of pyrexia occurred with D+T v D+P. Fewer cutaneous hyperproliferative events occurred with D+T v D+P (CuSCC 2% v 9%; hyperkeratosis 3% v 32%).

**Conclusions:** D+T demonstrated a significant improvement in PFS compared to D+P in pts with BRAF\textsuperscript{V600E/K} mutant MM. Clinical trial information: NCT01072175.

**MK-3475, Merck (MRK)**

Randomized comparison of two doses of the anti-PD-1 monoclonal antibody MK-3475 for ipilimumab-refractory (IPI-R) and IPI-naive (IPI-N) melanoma (MEL).

Abstract #3000

Author(s): Omid Hamid, Caroline Robert, Antoni Ribas, Jedd D. Wolchok, F. Stephen Hodi, Richard Kefferd, Anthony M. Joshua, Wen-Jen Hwu, Tara C. Gangadhar, Amita Patnaik, Peter Hersey, Jeffrey S. Weber, Richard Wayne Joseph, Kevin Gerigch, Xiaoyun (Nicole) Li, Patrick Chun, Scot Ebbinghaus, Soonmo Peter Kang, Adil Daud; The Angeles Clinic and Research Institute, Los Angeles, CA; Institut Gustave Roussy, Paris, France; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Westmead Hospital and Melanoma Institute Australia, University of Sydney, Westmead, Australia; Princess Margaret Cancer Centre, Toronto, ON, Canada; The University of Texas MD Anderson Cancer Center, Houston, TX; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; South Texas Accelerated Research Therapeutics (START) Center for Cancer Care, San Antonio, TX;
Background: MK-3475 has shown durable antitumor activity in MEL across multiple doses and schedules. We compared the efficacy and safety of 2 MK-3475 doses in MEL patients (pts).

Methods: In separate cohorts, IPI-N and IPI-R pts were randomized 1:1 to MK-3475 2 or 10 mg/kg every 3 wk (2 Q3W or 10 Q3W). IPI-N pts received ≤2 prior systemic therapies. IPI-R pts had any number of prior therapies and unequivocal or confirmed PD per immune-related response criteria (irRC) after ≥2 IPI doses; all BRAF-mutant pts were previously treated with BRAF inhibitors. Primary endpoint was ORR assessed by RECIST 1.1 every 12 wk by independent central review. Investigator-assessed response by irRC was also obtained.

Results: A total of 276 pts were randomized (103 IPI-N [2 Q3W, n = 51; 10 Q3W, n = 52] and 173 IPI-R [2 Q3W, n = 89; 10 Q3W, n = 84]). In both cohorts, treatment arms were well balanced for known prognostic factors. As of the 10/18/2013 cutoff, all IPI-N and 47% of IPI-R pts had ≥9 mo of follow-up. Among evaluable pts, no significant differences in ORR by RECIST were observed between doses in IPI-N (33% vs 40%) or IPI-R (26% vs 26%) pts. By RECIST, response duration ranged from 6+ wk to 39+ wk in both cohorts (median not reached), with ~90% of responses ongoing. PFS by RECIST was similar between doses. The safety profile was generally similar between pts treated with 2 Q3W and 10 Q3W. There were no drug-related deaths.

Conclusions: MK-3475 2 mg/kg Q3W and 10 mg/kg Q3W provided similar efficacy and safety in both IPI-N pts and IPI-R pts. Treatment was well tolerated with acceptable toxicity profile. The high ORR provided by MK-3475 comes with long durability in both IPI-N and IPI-R MEL. Clinical trial information: NCT01295827.
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<td>10 Q3W</td>
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<td>2 Q3W</td>
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**MK-3475, Merck (MRK)**

Clinical efficacy and correlation with tumor PD-L1 expression in patients (pts) with melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475.

Abstract #3005^
Whitehouse Station, NJ; Merck & Co, Inc, North Wales, PA; Merck & Co, Inc, Rahway, NJ; The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** MK-3475 demonstrated antitumor activity and acceptable safety in a phase I MEL cohort. We provide updated efficacy data and correlation with tumor PD-L1 expression.

**Methods:** 135 pts received MK-3475 10 mg/kg Q2W (n = 57), 10 mg/kg Q3W (n = 56), or 2 mg/kg Q3W (n = 22). Response was assessed every 12 wk by RECIST 1.1 by independent central review and by immune-related response criteria (irRC) by investigator. Biopsy was required in the 60 d before MK-3475. Tumor PD-L1 expression was assessed by IHC. A preliminary cutoff of 1% of stained tumor cells defined PD-L1 positivity.

**Results:** As of 10/18/2013, all pts had ≥13 mo follow-up. Median time on treatment was 23 wk (range, 1 dose to 97 wk). In pts with measurable disease, ORR was 41% by RECIST (Table). Objective responses were observed as late as 64 wk, with some conversions to CR seen as late as 72 wk. Median response duration was not reached; responses were ongoing for 87% of responders. Median PFS was 31 wk. Median OS was not reached, and OS rate at 1 y was 81%. Tumor PD-L1 expression was evaluable in 71 pts with measurable disease and ≥1 tumor evaluation (77% PD-L1+). Of these pts, PD-L1 expression was associated with improved ORR by RECIST (51% vs 6%, P = .0012 [Fisher’s exact]) and PFS (median 12 vs 3 mo, HR 0.31, 95% CI 0.16-0.61, P = .0004 [log-rank]). 1-y OS rate was 84% in PD-L1+ and 69% in PD-L1− pts (P = .2146 [log-rank]). There were no treatment-related deaths; 14% of pts experienced drug-related grade 3/4 AEs.

**Conclusions:** MK-3475 induces durable responses and favorable 1-y OS with acceptable safety in MEL. Although tumor PD-L1 positivity was associated with improved ORR and PFS, antitumor activity was also observed in pts with low baseline PD-L1 expression. These preliminary data require confirmation.

Clinical trial information: NCT01295827.

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**MK-3475, Merck (MRK)**
Evaluation of immune-related response criteria (irRC) in patients (pts) with advanced melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475.
Abstract #3006^
Author(s): F. Stephen Hodi, Antoni Ribas, Adil Daud, Omid Hamid, Caroline Robert, Richard Kefferd, Wen-Jen Hwu, Tara C. Gangadhar, Anthony M. Joshua, Peter Hersey, Jeffrey S. Weber, Roxana Stefania Dronca, Andrea Marie Perrone, Linda Gammage, Darcy Hille, Dahai Xue, Soonmo Peter Kang, Patrick Chun, Scot Ebbinghaus, Jedd D. Wolchok; Dana-Farber Cancer Institute, Boston, MA; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; University of California, San Francisco, San Francisco, CA; The Angeles Clinic and Research Institute, Los Angeles, CA; Institut Gustave Roussy, Paris, France; Westmead Hospital and Melanoma Institute Australia, University of Sydney, Westmead, Australia; The University of Texas MD Anderson Cancer Center, Houston, TX; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Princess Margaret Cancer Centre, Toronto, ON, Canada; University of Sydney, Sydney, Australia; Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL; Mayo Clinic, Department of Medical Oncology, Rochester, MN; Merck, West Point, PA; Merck & Co., West Point, PA; Merck & Co., North Wales, PA; Merck & Co, Inc, Rahway, NJ; Merck/MRL, Kenilworth, NJ; Merck & Co, Inc, North Wales, PA; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Unique response patterns have been observed with immunotherapies, and both objective response and prolonged disease stabilization can occur after an initial increase in tumor size. irRC were developed to better characterize response to immunotherapy, but it is unclear how irRC perform in pts treated with PD-1 blockade. Here, we describe unique patterns of response to MK-3475 in MEL pts and evaluate irRC as an alternative criterion for comprehensive response assessment.

Methods: Source population was pts from 3 MEL cohorts treated with MK-3475 2 mg/kg every 3 wk (Q3W), 10 mg/kg Q3W, or 10 mg/kg Q2W in a phase I trial. Tumor imaging was performed every 12 wk. Response was assessed by irRC and RECIST 1.1 by central review; irRC was used for pt management. Tumor flare and atypical delayed response were identified by using centrally assessed irRC data among pts on MK-3475 for ≥28 wk. Tumor flare was defined as unconfirmed PD at assessment 1 (ie, wk 12) and non-PD at assessment 2. Atypical delayed response was defined as PD at any time point followed by non-PD and then response. Survival data were analyzed in pts who had PD by RECIST but CR/PR/SD by irRC.

Results: Among the 411 pts enrolled across the 3 MEL cohorts, 192 were on MK-3475 for ≥28 wk as of the analysis cut-off of 10/18/2013. Tumor flare was seen in 7 (3.6%) pts. In these pts, best overall response per irRC was CR (n = 1), PR (n = 4), and SD (n = 2). Atypical delayed response was seen in 6 (3.1%) pts. The 51 pts with PD by RECIST but CR/PR/SD by irRC had favorable OS compared with the 145 pts with PD by both criteria (Table).

Conclusions: MEL pts treated with MK-3475 may experience unique patterns of response and should be managed accordingly. Similar to what has been observed with ipilimumab, conventional criteria such as RECIST may underestimate the benefit of MK-3475 in approximately 10% of treated pts. An updated version of response criteria that incorporate new data on PD-1 inhibitors may be appropriate for future consideration. Clinical trial information: NCT01295827.
Nivolumab, Bristol-Myers Squibb (BMY)

Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial.

Abstract #9002

Author(s): F. Stephen Hodi, Mario Sznol, Harriet M. Kluger, David F. McDermott, Richard D. Carvajal, Donald P. Lawrence, Suzanne Louise Topalian, Michael B. Atkins, John D. Powderly, William Howard Sharman, Igor Puzanov, David C. Smith, Philip D. Leming, Evan J. Lipson, Janis M. Taube, Robert Anders, Christine E. Horak, Georgia Kolliia, Ashok Kumar Gupta, Jeffrey Alan Sosman; Dana-Farber Cancer Institute, Boston, MA; Yale Cancer Center, Yale School of Medicine, New Haven, CT; Beth Israel Deaconess Medical Center, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Massachusetts General Hospital Cancer Center, Boston, MA; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; Carolina BioOncology Institute, Huntersville, NC; Vanderbilt-Ingram Cancer Center, Vanderbilt University, School of Medicine, Nashville, TN; University of Michigan, Ann Arbor, MI; The Christ Hospital Cancer Center, Cincinnati, OH; Bristol-Myers Squibb, Princeton, NJ; Vanderbilt University Medical Center, Nashville, TN

Background: We have shown that nivolumab, a fully human IgG4 PD-1 immune-checkpoint inhibitor antibody, is tolerable and active in pts with advanced solid tumors in a large phase I trial (Topalian et al. N Eng J Med 366:2443-54, 2012). For the MEL pts in this trial, we report long-term clinical activity, pts’ response off therapy, tumor PD-1 ligand (PD-L1) expression associated with survival endpoints, and for the first time, 3-y overall survival (OS).

Methods: Previously treated advanced MEL pts with no prior ipilimumab therapy received nivolumab (0.1, 0.3, 1, 3, or 10 mg/kg IV) Q2Wk for ≤96 wk and were evaluated for OS and progression-free survival (PFS). PD-L1 tumor cell membrane expression was retrospectively assessed in archival specimens by a Dako immunohistochemistry assay with ≥5% tumor cells designated as PD-L1(+)..

Results: From 2008-2012, 107 MEL pts initiated treatment with nivolumab; 25% had ≥3 prior therapies. Across doses, the 2- and 3-y OS rates were 48 and 41%, respectively (Table). For the 34/107 (32%) pts with objective responses (OR; RECIST), median response duration was 22.9 mo. Twenty-four OR pts stopped nivolumab for reasons other than disease progression; 11 (46%) maintained responses for ≥24 wk off drug (range: 24, 56+ wk). Four (4%) pts had unconventional "immune-related" responses. In a
subset of pts with evaluable tumor samples (41/107), pts with PD-L1(+) and (–) tumors (n=18 and 23, respectively) had median OS of not reached and 12.5 mo; median PFS was 9.1 mo and 1.9 mo. Safety has been previously reported (Sznol et al. J Clin Oncol 31:abs CRA9006, 2013).

**Conclusions:** In advanced MEL pts, nivolumab demonstrated favorable 2- and 3-y OS rates, durable responses with a number persisting off therapy, and an acceptable safety profile. Additional analyses will be presented by pts’ characteristics across the full population, the long-term survival subgroup, and the PD-L1(+/–) tumor subgroups. Ongoing phase III trials are further evaluating nivolumab for MEL pts and PD-L1 as a potential predictive biomarker for response to nivolumab. Clinical trial information: NCT00730639.

<table>
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<tr>
<th>OS rate*</th>
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<tr>
<td>n=107</td>
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*September 2013 analysis.

**Pidilizumab, CureTech**
**Phase 2, multicenter, safety and efficacy study of pidilizumab in patients with metastatic melanoma.** Abstract #9001

Author(s): Michael B. Atkins, Ragini Reiney Kudchadkar, Mario Sznol, David F. McDermott, Michal Lotem, Jacob Schachter, Jedd D. Wolchok, Walter John Urba, Timothy Kuzel, Lynn Mara Schuchter, Craig L. Slingluff, Marc S. Ernsto, Joseph W. Fay, Philip Adam Friedlander, Thomas Gajewski, Hassane M. Zarour, Rinat Rotem-Yehudar, Jeffrey Alan Sosman; Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC; University of South Florida, H. Lee Moffitt Cancer Center, Tampa, FL; Yale University, New Haven, CT; Beth Israel Deaconess Medical Center, Boston, MA; Sharett Institute of Oncology, Hadassah Hebrew University Medical Center, Jerusalem, Israel; Ella Institute for Research and Treatment of Melanoma, Sheba Medical Center, Affiliated to Sackler Faculty of Medicine Tel Aviv University, Ramat-Gan, Israel; Memorial Sloan Kettering Cancer Center, New York, NY; Earle A. Chiles Research Institute and Providence Cancer Center, Portland, OR; Feinberg School of Medicine, Northwestern University, Chicago, IL; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; University of Virginia School of Medicine, Charlottesville, VA; Dartmouth Hitchcock Medical Center/Norris Cotton Cancer Center, Lebanon, NH; Baylor Medical Center, Dallas, TX; Mount Sinai Medical Center, Ruttenberg Cancer Clinic, New York, NY; The University of Chicago, Chicago, IL; University of Pittsburgh Cancer Institute, Pittsburgh, PA; CureTech Ltd, Yavne, Israel; Vanderbilt University Medical Center, Nashville, TN

**Background:** Pidilizumab (CT-011), a humanized anti PD-1 IgG1k, was studied in two Phase 2 studies in aggressive and indolent lymphomas showing clinical activity correlated with PD-1/PD-L1+ lymphocytes.
Thus, we initiated a Phase 2 multicenter, randomized, open-label, study to evaluate the safety and efficacy of pidilizumab in patients (pts) with metastatic melanoma (MM).

**Methods:** Eligibility criteria: measurable disease; Stage IV clearly progressive; ECOG 0-1; ≤ 3 prior systemic therapies for MM; stabilized brain mets allowed; 6 weeks from prior ipilimumab (Ipi), no prior PD-1/PD-L1/PD-L2 blockade. Pts were randomized to 2 dose levels (1.5 or 6 mg/kg IV q2 wk X 27), each with 50 pts and each balance stratified by prior Ipi (yes/no).

**Results:** 103 pts were randomized; 75% M1c, 15.5% brain mets, 30% elevated LDH, 33% disease spread to ≥ 3 organs. 77% received prior systemic therapy for MM; 51% prior Ipi, 7.8% prior Braf inhibitor, 44% prior biologics (cytokines). 45% did not respond to most recent therapy. 45% received pidilizumab less than 4 months after prior therapy. ORR using irRC for all pts was 5.9% [90% CI: 2.3, 12.0] and 10.0% [90% CI: 1.8, 28.3] for 1.5mg/kg & prior Ipi. Pts with prior Ipi had higher irSD (53.7% vs 20.5%) and slightly longer median PFS (2.8 vs 1.9 months). Overall Survival at 12 months (12mo survival) was 64.5% (90% CI: 55.6, 72.0), with insignificant differences between strata or doses and irrespective of therapies given before study entry or after study withdrawal; 12mo survival for pts without prior or post-study Ipi (n=26) was 55.7% [90% CI: 35.6, 71.8], 12mo survival for pts with B-RAF V600 WT tumors (n=63) was 69.3% [90% CI: 58.2, 78.1]. The most frequent AEs were fatigue (43%), diarrhea (22.5%), arthralgia (21%) and SAEs of pneumonia (5%) and dyspnea (3%).

**Conclusions:** Despite low response rates, pidilizumab therapy results in substantial 12mo survival in heavily pretreated pts. The 12mo survival appears comparable to that of other anti-PD-1 MAbs. Treatment is very well tolerated. Further studies of pidilizumab in pts with MM are warranted, preferably in combination with other therapeutics. Clinical trial information: NCT01435369.

**PV-10, Provectus**

Abstract #9027: Efficacy of intralesional Rose Bengal in patients receiving injection of all existing melanoma in phase II study PV-10-MM-02.

Author(s): Sanjiv S. Agarwala, John F Thompson, B Mark Smithers, Merrick I. Ross, Charles Raben Scoggins, Brendon J Coventry, Susan J Neuhaus, David R. Minor, Jamie M Singer, Eric Andrew Wachter; St. Luke’s Hospital and Health Network, Easton, PA; Melanoma Institute Australia, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia; Princess Alexandra Hospital, Brisbane, Australia; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Louisville, Louisville, KY; Royal Adelaide Hospital, Adelaide, Australia; University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia; California Pacific Medical Center Research Institute, San Francisco, CA; Provectus Biopharmaceuticals, Inc., Knoxville, TN

**Background:** The safety and efficacy of intralesional (IL) treatment of refractory cutaneous melanoma with rose bengal disodium (PV-10) was evaluated in an 80 patient international, multicenter, single arm phase II trial (NCT00521053). Overall, PV-10 was well tolerated and 41 of 80 ITT patients (pts) met the primary endpoint of objective response (CR+PR) in their injected target lesions (51% ORR CI 40-63%, 26% CR).

**Methods:** Refractory pts (median of 6 previous interventions, 6.3 cm median sum lesion diameter in biopsy confirmed melanoma) received PV-10 into up to 20 cutaneous and subcutaneous lesions up to 4
times over a 16-week period and were followed for 52 weeks. Best overall response rate (BORR) was assessed by RECIST in up to 10 injected target lesions. Secondary endpoints included assessment of duration of response, BORR of untreated bystander lesions, overall survival and adverse events. Confidence intervals for response rates were based on the exact cumulative probabilities of the binomial distribution (95% confidence intervals).

**Results:** In the subgroup of 28 pts who received PV-10 into all existing melanoma lesions (i.e., no uninjected lesions), ORR by-patient was 71% (CI 51-87%) with 50% CR (CI 31-69%). In these pts with all disease injected plus 26 pts with uninjected disease limited to bystanders (i.e. 54 pts with all disease monitored), CR was achieved in 232 of the 363 injected lesions (64% CR): 121 lesions required a single injection for CR, 84 required 2 injections, 22 required 3 injections and 5 required 4 injections. Additionally, 10 of 28 uninjected bystander lesions achieved CR.

**Conclusions:** Recurrent locoregional melanoma can be a source of persistent morbidity, including disfigurement frequently accompanied with pain, ulceration, bleeding and infection. The high rate of symptom control in refractory patients, manifest in CR of injected lesions after minimal intervention, is the basis for a breakthrough therapy application based on the 28 patient “all treated” subgroup. Although the primary ablative effect is responsible for CR in injected tumors, durability of response and bystander response implicate an immunologic mechanism of action secondary to ablation. Clinical trial information: NCT00521053.

**Tafinlar, Novartis (NVS)**

**Combinatorial effect of dabrafenib, trametinib, and adoptive cell transfer (ACT) in an immune-competent murine model of BRAFV600E mutant melanoma.**

**Abstract #2512**

Author(s): Siwen Hu-Lieskovski, Stephen Mok, Lidia Robert Faja, Lucas Goedert, Begonya Comin-Anduix, Richard C. Koya, Antoni Ribas; UCLA Johnsson Comprehensive Cancer Center, Los Angeles, CA; University of California, Los Angeles, Los Angeles, CA; University of California, Los Angeles David Geffen School of Medicine, Los Angeles, CA; Division of Surgical Oncology, Department of Surgery, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA

**Background:** The first clinical trial testing the combination of BRAF targeted therapy with vemurafenib and immunotherapy with ipilimumab was terminated early due to significant liver toxicities, possibly due to paradoxical activation of cells with wild type BRAF. MEK inhibitors can potentiate the MAPK inhibition in tumor, while alleviating the unwanted paradoxical MAPK activation. We hypothesized that addition of a MEK inhibitor would enhance the immunosensitization effects of BRAF inhibition, with decreased toxicity.

**Methods:** A mouse model of syngeneic $BRAF^{V600E}$ driven melanoma (SM1) was developed. C57BL/6 mice treated with myeloid-depleting total body irradiation and bone marrow transplantation, were implanted SM1 tumors subcutaneously, followed by iv injection of $3 \times 10^6 gp100$ peptide-activated pml-1 splenocytes when tumors reach 4-5mm. For bioluminescent imaging (BLI), splenocytes were transduced with luciferase-transfected retrovirus. Activated splenocytes from wild type C57 BL/6 mice were controls. BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), vehicle (V), or D+T, were given daily by oral gavage from the day of ACT.
Results: Combination of D+T with pmel-1 ACT showed complete tumor regression, not observed in any other groups, including D+T with control ACT (mean volume of 0 mm² pmel+D+T, vs 30 C57+D+T, 118 pmel +D on day 20, P<0.0001 by one way ANOVA). BLI showed increased T cell infiltration to tumors with the triple combination, compared to ACT with D, or V. Intracellular IFNγ staining of the tumor infiltrating T cells did not show significant difference among groups, indicating trametinib is not detrimental to the effector functions. No significant toxicity observed with the triple combination by weight.

Conclusions: The MEK inhibitor trametinib, when combined with the BRAF inhibitor dabrafenib and ACT immunotherapy, enhances the antitumor effect, with increased infiltration and preserved function of effectors. Our findings support the testing of this combination in patients with BRAF V600E mutant metastatic melanoma.

Tafinlar, Novartis (NVS)
Updated overall survival (OS) for BRF113220, a phase 1-2 study of dabrafenib (D) alone versus combined dabrafenib and trametinib (D+T) in pts with BRAF V600 mutation-positive (+) metastatic melanoma (MM).
Abstract #9010^
Results: Updated OS for pts in Parts B and C with median follow-up of 28 and 24 months (mo) presented in Table 1. In Part C, median OS for 150/2 pts is 23.8 mo (HR=0.73 vs. D mono, p-value=0.24); 18-mo OS rate is 63%, reflective of paradigm shifting improvements in OS in this population. OS for D mono is confounded by cross-over to 150/2; 45 (83%) pts crossed over at time of analysis. In 150/1 and 150/2, 43 (80%) and 24 (44%) continued to receive D+T beyond RECIST PD. Subsequent systemic therapies were similar across arms; 38 (23%) pts received immune checkpoint inhibitors (19% ipilimumab and 8% PD-1/PD-L1), and 19 (12%) received vemurafenib.

Conclusions: Updated median OS is 23.8 mo for 150/2. Contribution of treatment beyond PD or post-treatment therapy is unknown. Follow-up continues; updated OS and safety data analysis will be performed in the final analysis after 30 mo follow-up or 75% events. Clinical trial information: NCT01072175.

<table>
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<th>Treatment</th>
<th>Number of deaths n (%)</th>
<th>Med OS, mo (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
<th>12-mo OS rate (%)</th>
<th>18-mo OS rate (%)</th>
</tr>
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<tbody>
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<td>Part B</td>
<td></td>
<td></td>
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<tr>
<td>150/2 (N=24)</td>
<td>8 (33)</td>
<td>NR (12.9, NR)</td>
<td></td>
<td>NA</td>
<td>73</td>
<td>67</td>
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<tr>
<td>Part C</td>
<td></td>
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<tr>
<td>D mono (N=54)</td>
<td>31 (57)</td>
<td>20.2 (14.5, 25.9)</td>
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<td>150/1 (N=54)</td>
<td>27 (50)</td>
<td>18.7 (13.7, NR)</td>
<td>0.96 (0.57, 1.60)</td>
<td>0.8683</td>
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<tr>
<td>150/2 (N=54)</td>
<td>25 (46)</td>
<td>23.8 (17.5, NR)</td>
<td>0.73 (0.43, 1.24)</td>
<td>0.2436</td>
<td>80</td>
<td>63</td>
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Abbreviations: NR, not reached; NA, not applicable.

T-VEC, Amgen (AMGN)
Primary overall survival (OS) from OPTiM, a randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIIB/C and IV melanoma.
Abstract #9008a

Author(s): Howard L Kaufman, Robert Hans Ingemar Andtbacka, Frances A. Collichio, Thomas Amatruda, Neil N. Senzer, Jason Chesney, Keith A. Delman, Lynn E. Spitler, Igor Puzanov, Yining Ye, Ai Li, Jennifer L. Gansert, Robert Coffin, Merrick I. Ross; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; The University of North Carolina at

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Background: T-VEC is an oncolytic immunotherapy derived from herpes simplex virus type-1 designed to selectively replicate in tumors and produce GM-CSF to enhance systemic antitumor immune responses. OPTiM is a randomized, phase 3 trial of T-VEC or GM-CSF in patients (pts) with unresected melanoma with regional or distant metastases (NCT00769704). OPTiM met the primary endpoint of a statistically significant improvement in durable response rate (DRR) with T-VEC vs GM-CSF (Andtbacka et al. ASCO 2013). The primary analysis of OS is reported here.

Methods: Key entry criteria were age ≥ 18 yrs, ECOG ≤1, unresectable melanoma stage IIIB/C or IV, injectable cutaneous, SC, or nodal lesions, LDH ≤1.5X ULN, ≤ 3 visceral lesions (excluding lung), none > 3 cm. Pts were randomized 2:1 to intralesional T-VEC (initially ≤ 4 mL x10^6 pfu/mL then after 3 wks, ≤ 4 mL x10^8 pfu/mL Q2W) or SC GM-CSF (125 µg/m^2 qd x 14 days q28d). The primary endpoint was DRR: partial or complete response continuously for ≥ 6 mos starting within 12 mos. Responses were per modified WHO by blinded central review. The primary analysis of OS (290 planned events) had 90% power to detect a HR of 0.67 with two sided α=0.05.

Results: 436 pts are in the ITT set: 295 (68%) T-VEC, 141 (32%) GM-CSF. 57% were men; median age was 63 yrs. An increase of 4.4 mos in OS with T-VEC vs GM-CSF was observed (p =0.051): HR 0.787 (95% CI: 0.62, 1.00); median (95% CI) OS was 23.3 (19.5, 29.6) mos with T-VEC vs 18.9 (16.0, 23.7) mos with GM-CSF. Objective response rate with T-VEC was 26% (95% CI: 21%, 32%) with 1% CR, and with GM-CSF was 6% (95% CI: 2%, 10%) with 1% CR. DRR for T-VEC was 16% (95% CI: 12%, 21%) and 2% for GM-CSF (95% CI: 0%, 5%), p<0.0001. Most common adverse events (AEs) with T-VEC were fatigue, chills, and pyrexia. No ≥ grade 3 AE occurred in ≥ 3% of pts in either arm.

Conclusions: In pts with unresectable Stage IIIB-IV melanoma, T-VEC demonstrated a significant improvement in the DRR vs GM-CSF with a tolerable safety profile. An improvement in OS approaching statistical significance was seen in the ITT population. Clinical trial information: NCT00769704.

MYELOMA

**Daratumumab, Johnson & Johnson (JNJ)**

Dose-dependent efficacy of daratumumab (DARA) as monotherapy in patients with relapsed or refractory multiple myeloma (RR MM).

Abstract #8513

Author(s): Henk M. Lokhorst, Jacob Laubach, Hareth Nahi, Torben Plesner, Peter Gimsing, Markus Hansson, Monique Minnema, Ulrik Niels Lassen, Jakub Krejcirk, Tahamtan AHmadi, Steen Lisby, Linda Basse, Nikolai C. Brun, Paul G. Richardson; UMC Utrecht, Utrecht, Netherlands; Harvard Medical School, Boston, MA; Karolinska Universitetssjukhuset-Huddinge, Huddinge, Sweden; Vejle Hospital, Vejle,

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Denmark; Copenhagen University Hospital, Copenhagen, Denmark; Skåne University Hospital, Lund, Sweden; Department of Oncology, Rigshospitalet, Copenhagen, Denmark; Janssen Research and Development, Spring House, PA; Genmab A/S, Copenhagen, Denmark; Dana-Farber Cancer Institute, Boston, MA

**Background:**Pts with RR MM received DARA for 9 wks in doses of 0.005-24mg/kg in the GEN501 dose-escalation part (Lokhorst: EHA 2013 abstract S576). The purpose of the GEN501 expansion part, which has completed enrollment, was to evaluate safety and efficacy of 2 doses of DARA for up to 24 mths using alternate dose schedules.

**Methods:**Pts ≥18 yrs, RR to at least 2 prior lines of therapy, incl. IMiDs and proteasome inhibitors, and ineligible for ASCT were enrolled at 2 dose levels: A: 8mg/kg +/- pre-dose (10mg) wkly for the first 8 infusions.B: 16mg/kg without pre-dose with a 3-wk washout period between the first 2 doses followed by 7 wkly doses. Then all pts were dosed every 2nd wk for 16 wks followed by dosing every 4th wk until disease progression, toxicity or for max 24 mths.

**Results:**Data from 30 pts in the 8mg/kg cohort and 15 pts in the 16mg/kg cohort recruited into the GEN501 expansion part are presented. Median age was 58.2 (35.1-76.9) and 64.1 (50.5-75.0) years, prior treatment lines were 5 (3-11), and 4 (2-8) and time since diagnosis was 5.5 (2.1-15.2) and 7.1 (0.4-13.3) years, respectively. Median number of DARA infusions was 10.5 vs 7.0, reflecting the more recent initiation of the 16mg/kg cohort. Infusion times were 3.5 vs 3.4 hours in the 8 and 16mg/kg groups, respectively. Safety: No dose-related increase in adverse events (AEs) was observed. Most common AEs reported (in ≥20% of all pts) were pyrexia, allergic rhinitis, fatigue, upper respiratory tract infection, diarrhea, dyspnea and cough. Only mild (Gr 1 and 2) infusion-related reactions (IRRs) were reported with 27% in the 16mg/kg group vs 20% in the 8mg/kg group. 2 SAEs, 1 in each group, were assessed as related to DARA (1 thrombocytopenia, 1 lymphocytopenia). One pt was withdrawn after 1st full dose due to thrombocytopenia Gr 3. Omission of the pre-dose increased neither the incidence nor the severity of IRRs.

**Conclusions:**DARA monotherapy in RR MM pts resulted in high single agent activity when administered at 16 mg/kg (46% ORR). The safety profile was manageable. Full response data will be presented at the meeting incl. bone marrow assessments. Clinical trial information: NCT00574288.

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<th>SD</th>
<th>MR</th>
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<td>16 mg/kg</td>
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^PR or better. ^b2 pts only had 1st dose at data cutoff.
**Panorama 1: A randomized, double-blind, phase 3 study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma.**

Abstract #8510^<sup>1</sup>

Author(s): Paul G. Richardson, Vania T.M. Hungria, Sung-Soo Yoon, Meral Bekzac, Meletios A. Dimopoulos, Ashraf Elghandour, Wieslaw W. Jedrzejczak, Andreas Guenther, Thanyaphong Na Nakorn, Noppadol Siritanaratkul, Robert L. Schlossman, Jian Hou, Philippe Moreau, Sagar Lonial, Jae Hoon Lee, Hermann Einsele, Monika Sopala, Bourras-Rezki Bengoudifa, Claudia Corrado, Jesus F. San-Miguel; Dana-Farber Cancer Institute, Boston, MA; Irmandade da Santa Casa de Misericordia de Sao Paulo, Sao Paulo, Brazil; Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea; Ankara University School of Medicine, Ankara, Turkey; Department of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece; Alexandria University, Alexandria, Egypt; Medical University of Warsaw, Warsaw, Poland; Division of Stem Cell Transplantation and Immunotherapy, 2nd Department of Medicine, University Hospital Schleswig-Holstein and University of Kiel, Kiel, Germany; Chulalongkorn University, Bangkok, Timor-Leste; Siriraj Hospital, Bangkok, Thailand; Chang Zheng Hospital, Shanghai, China; University Hospital of Nantes, Nantes, France; Winship Cancer Institute of Emory University, Atlanta, GA; Department of Internal Medicine, Gachon University Gil Hospital, Incheon, South Korea; Medizinische Klinik und Poliklinik II, University of Wuerzburg, Wuerzburg, Germany; Novartis Pharma AG, Basel, Switzerland; Universidad de Navarra, Pamplona, Spain

**Background:** Panobinostat (PAN) is a potent pan-deacetylase inhibitor that demonstrates synergistic antimyeloma activity when combined with bortezomib (BTZ) + dexamethasone (Dex). Early studies demonstrated durable responses in patients (pts) with relapsed (Rel) and relapsed/refractory (RR) multiple myeloma (MM) treated with PAN + BTZ + Dex. This initiated the PANORAMA 1 study, presented herein.

**Methods:** Eligible pts had Rel or RR (excluding BTZ- and primary-ref MM) following 1-3 prior regimens. Pts received oral PAN (20 mg) or placebo (pbo) 3 x/wk + IV BTZ (1.3 mg/m²; D 1, 4, 8, 11) during wks 1-2 with oral Dex (20 mg) on the days of and after BTZ in treatment phase (TP) 1, eight 3 wk cycles. Pts demonstrating benefit could proceed to TP2, with PAN dosing maintained and BTZ/Dex less frequent. The primary endpoint was progression free survival (PFS) with response assessed by modified EBMT criteria. Other endpoints included overall survival (OS), overall response rate (ORR), near complete/complete response (nCR/CR) rate, duration of response (DOR), and safety. PFS/ORR was confirmed by an independent review committee.

**Results:** A total of 768 pts (PAN + BTZ + Dex [n = 387]; pbo + BTZ + Dex [n = 381]) were randomized. Median age was 63 y (42% ≥ 65 y) and 48% received ≥ 2 prior regimens. Prior therapies included BTZ (43%), thalidomide (51%), lenalidomide (20%), and 25% received both prior BTZ + IMiDs. The primary endpoint was met with median PFS of 12 mo vs 8.1 mo (P < .0001; HR 0.63, 95% CI [0.52, 0.76]) for pts treated on the PAN vs pbo arm. In the PAN and pbo arms, ORR was 61% vs 55% and nCR/CR rate was 28% vs 16%, with DOR of 13.1 mo vs 10.9 mo, respectively. OS data is not mature. Adverse events (AEs) led to discontinuation in 36% in the PAN arm and 20% in the pbo arm. Common grade 3/4 lab abnormalities and AEs (regardless of study drug relationship) in the PAN vs pbo arms included thrombocytopenia (67% vs 31%), neutropenia (35% vs 11%), and diarrhea (26% vs 8%); these were generally manageable with dose reduction/supportive care. On-treatment deaths occurred in 8% and 5%, respectively.
**Conclusions:** PAN + BTZ/Dex significantly improves PFS in pts with Rel or RR MM, with manageable toxicity. Clinical trial information: NCT01023308.

**Revlimid, Celgene (CELG)**

**E1A06: A phase III trial comparing melphalan, prednisone, and thalidomide (MPT) versus melphalan, prednisone, and lenalidomide (MPR) in newly diagnosed multiple myeloma (MM).**

Abstract #8511

Author(s): A. Keith Stewart, Susanna J. Jacobus, Rafael Fonseca, Matthias Weiss, Natalie Scott Callander, Asher Alban Akmal Chanan-Khan, Vincent Rajkumar; Mayo Clinic, Scottsdale, AZ; Dana-Farber Cancer Institute, Boston, MA; Marshfield Clinic, Marshfield, WI; University of Wisconsin, Madison, WI; Mayo Clinic, Jacksonville, FL; Mayo Clinic, Rochester, MN

**Background:** Melphalan, prednisone and thalidomide (MPT) is an accepted regimen in newly diagnosed MM. Early studies suggested that lenalidomide (R) might be substituted for thalidomide (T) with equal efficacy and less toxicity. We present E1A06, a randomized, multicenter phase 3 trial comparing MPT vs. MPR in pts with untreated, symptomatic, transplant ineligible MM.

**Methods:** The primary objective was PFS differences between pts receiving MPT: M 9 mg/m² and P 100 mg p.o. each on days 1-4 with T 100 mg daily vs. MPR: M 5 mg/m² and P 100 mg p.o. each on days 1-4 with R 10 mg p.o. on days 1-21. MPT or MPR therapy was continued for twelve 28 day cycles followed by T 100mg or R 10mg daily until relapse. Aspirin prophylaxis was required. Pts were stratified by ISS stage (I-II vs. III) and age (<65 vs. ≥65). Inferiority of MPR was defined as a PFS treatment hazard ratio (HR) of MPT/MPR ≤ 0.82. Secondary objectives included OS between the arms, toxicities, response rates, depth of response and quality of life (QoL) change.

**Results:** 306 pts were enrolled. Treatment arms were balanced for age, ISS stage and other major prognostic factors. Median age was 75.7y. The median follow-up was 40.7 months (m). Median time on therapy was 12m, and 23m for the 46% of pts on maintenance therapy, with no differences by arm. Per protocol partial response rate was 62% (MPT) vs. 61% (MPR) with no difference in VGPR/CR rates (18.8% vs. 23%). Grade ≥3 toxicity was 71.6% (MPT) vs. 56.7% (MPR); p=0.008. By ITT, the median PFS was 21m on MPT and 18.7m on MPR; HR 0.84 [95%CI: 0.64, 1.09]. The null hypothesis of inferiority of MPR was not rejected. Three year OS was identical by arm at 63% and median OS was not significantly different; p=0.476. Second primary malignancies were observed in 17 (MPT) vs. 14 (MPR) pts with incidence rates of 3.47 and 2.01 (/100 person years). DVT/PE occurred in 8.8% vs. 6.7% of pts. QoL analysis favored MPR by induction end; p=0.007.

**Conclusions:** This phase III trial compares the efficacy of MPT and MPR in elderly patients with newly diagnosed MM. Response rates, PFS and OS were similar between the two arms; however, there was significantly better QOL at 12m and lower toxicity with MPR. Clinical trial information: NCT00602641.

**SAR650984, Sanofi (SNY)**

**A phase Ib dose escalation trial of SAR650984 (Anti-CD-38 mAb) in combination with lenalidomide and dexamethasone in relapsed/refractory multiple myeloma.**

Abstract #8512
Author(s): Thomas G. Martin, Karl Hsu, Eric Charpentier, Ravi Vij, Rachid C. Baz, Don M. Benson, Nikoletta Lendvai; University of San Francisco, San Francisco, CA; Sanofi-Aventis, Cambridge, MA; Multiple Myeloma Research Consortium, Norwalk, CT/Washington University School of Medicine, St. Louis, MO; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; The Ohio State University, Columbus, OH; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: SAR650984 (SAR) is a humanized IgG1 monoclonal antibody that binds selectively to a unique epitope on human CD38 receptor. SAR kills tumor cells via antibody-dependent cellular-mediated cytotoxicity, complement-dependent cytotoxicity, direct apoptosis induction without secondary crosslinking and allosteric inhibition on CD38 enzymatic activity. We present data on the dose escalation phase of the study (NCT01749969).

Methods: Three dose levels (DL) of SAR 3, 5 and 10 mg/kg were evaluated in combination with lenalidomide (LEN) and dexamethasone (Dex). LEN 25 mg was given on days (d) 1 – 21 and D 40 mg on d 1, 8, 15 and 22 every 28 d’s. SAR was given IV on d 1 and 15 and escalated using the classic 3+3 design.

Results: 13 patients (pts) with RRMM were treated; median age 61 yrs (48 - 73); median prior treatment regimens 6 (2 - 12), 100% had received prior LEN (23% prior pomalidomide) and 92.3% previously received bortezomib (38.5% prior carfilzomib). The median time from diagnosis to first SAR dosing was 4.5 yrs (3 - 11). The maximum tolerated dose was not reached. The most frequent adverse events included nausea, cough (n = 6 each); fatigue, muscle spasm, infection (n = 5 each); vomiting, diarrhea, dehydration and insomnia (n = 4 each). Grade (G) ≥ 3 hematologic abnormalities were neutropenia (n = 4) and thrombocytopenia (n = 3). One pt discontinued therapy (cycle 1, d 1) due to an infusion reaction (bronchospasm G 3). The ORR (≥ PR), according to IMWG criteria, among 12 evaluable pts was 58 %. Responses occurred at each DL of 3mg/kg (1PR), 5mg/kg (1PR, 1 VGPR) and 10 mg/kg (1PR, 3 VGPR). Clinical benefit response (≥ MR) was 67 % with 1 MR at 3 mg/kg. Median time on treatment was 20.6 weeks (0 - 35) and 7 pts remain on therapy. PK showed non linearity at select dose levels, SAR plasma trough levels were above target for tumor eradication from preclinical data.

Conclusions: The combination of SAR with LEN/Dex was tolerated and no DLT’s were reported at any DL. SAR + LEN/Dex demonstrated encouraging efficacy in pts with heavily pretreated RRMM. An expansion cohort of 18 pts recently enrolled on the trial and the results will be reported at the meeting. Clinical trial information: NCT01749969.

OVARIAN CANCER

Avastin, Roche

Molecular subgroup of high-grade serous ovarian cancer (HGSOC) as a predictor of outcome following bevacizumab.

Abstract #5502

of Oncology, St. James’s University Hospital, Leeds, United Kingdom; University of Glasgow, Glasgow, United Kingdom; Ninewells Hospital, Dundee, United Kingdom; University of Edinburgh Cancer Research UK Centre, Edinburgh, United Kingdom; Division of Pathology, University of Edinburgh, Edinburgh, Scotland; Department of Pathology, Belfast Health and Social Care Trust, Belfast, Northern Ireland; MRC Clinical Trials Unit, London, United Kingdom; MRC Clinical Trials Unit at UCL, London, United Kingdom; Almac Diagnostics Ltd., Craigavon, United Kingdom; Almac Diagnostics, Craigavon, Northern Ireland; Almac Diagnostics Ltd., Craigavon, Northern Ireland; Centre for Cancer Research and Cell Biology, Queen’s University Belfast, Belfast, Northern Ireland; Centre for Cancer Research and Cell Biology, Queen’s University Belfast, Belfast, United Kingdom

**Background:** HGSOC is a histopathological diagnosis and may represent multiple diseases at a molecular level. We investigated whether distinct molecular subgroups may influence treatment choice.

**Methods:** mRNA was extracted from 265 macrodissected formalin fixed paraffin embedded HGSOCs from Scottish patients (pts) treated with primary debulking then platinum based chemotherapy. Transcriptional analysis was performed using the Ovarian DSA microarray. This was repeated using 283 UK samples from the ICON7 study [first line paclitaxel/carboplatin +/- concomitant and maintenance bevacizumab (bev) for 12 months].

**Results:** Unsupervised hierarchical clustering (Scottish tumours) identified three major subgroups, two with angiogenic gene upregulation and one with angiogenic gene repression and immune gene upregulation. This latter ‘immune’ subgroup had a superior overall survival (OS) compared to the other two subgroups combined [HR = 0.66 (0.46-0.94)]. A 63-gene expression signature to prospectively identify this subgroup was generated and validated as prognostic for OS in an independent dataset [HR = 0.32 (0.19-0.54)]. As the immune subgroup had repressed angiogenesis-related gene expression we hypothesised that these pts would benefit less from bev [power to detect interaction > 2 in predicted direction for progression free survival (PFS) in ICON7 was 88% (α=0.1, one-tail)]. In ICON7 the gene signature showed a difference in impact of bev on PFS between the immune and proangiogenic subgroups (1-sided test for interaction, p=0.016). For the immune group (41% of cases), the addition of bev conferred a worse PFS [HR = 1.73 (1.12-2.68)] and OS [HR = 2.00 (1.11-3.61)] compared to chemotherapy alone. In the proangiogenic group there was a non-significant trend to improved PFS for the addition of bev (median 17.4 vs 12.3 months in controls).

**Conclusions:** An immune molecular subgroup of HGSOC has superior survival to other HGSOC. The addition of bev appears to significantly reduce PFS and OS in this subgroup. Patients in the proangiogenic subgroups have a trend towards a PFS benefit from bev. These data suggest a mechanism for stratification of bev therapy and should be validated in additional datasets.

**Buparlisib, Novartis (NVS)**

*Phase I study of oral BKM120 and oral olaparib for high-grade serous ovarian cancer (HGSC) or triple-negative breast cancer (TNBC).*

Abstract #2510

Author(s): Ursula Matulonis, Gerburg M. Wulf, Michael J. Birrer, Shannon Neville Westin, Philippa Quy, Katherine M. Bell-McGuinn, Brian Lasonde, Christin Whalen, Carol Aghajanian, David B. Solit, Gordon B. Mills, Lewis Cantley, Eric P. Winer; Department of Medical Oncology, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA;
Background: In vivo synergy of the PI3-kinase inhibitor BKM120 and the PARP inhibitor olaparib is seen using a mouse model of BRCA1-related breast cancer (BrCa) and sporadic TNBC (Juvekar et al and Ibrahim et al, Cancer Discovery 2012). The PI3kinase pathway is activated in both TNBC and HGSC (www.cancergenome.nih.gov). Olaparib is active in HGSC and germlineBRCA mutation (gBRCAm) ovarian cancer (OvCa) and gBRCAm BrCa. These data were the rationale for this phase I, multi-center study (NCT01623349) combining BKM120 and olaparib in patients (pts) with recurrent HGSC or TNBC.

Methods: This study has a 3 + 3 design, escalating dose levels (DL) if 0/3 or 1/6 pts have a dose limiting toxicity (DLT) during the first cycle (1st 28 days). Objectives are to determine the MTD and RP2D of daily oral olaparib (tablet formulation) and BKM120, assess toxicities, preliminary activity of this combination, and PK profiles of both drugs. Planned translational endpts include PI3kinase pathway effects, BRCA1 immunostaining/methylation, IL-8/circulating DNA levels, and somatic mutations in BRCA1/2 using FFPE tissue. Eligibility included: recurrent TNBC or HGSC or any histology of OvCa or BrCa with presence of a gBRCAmut, PS 0-1, and measurable/evaluable cancer. Prior PARP inhibitor use was allowed.

Results: 34 pts to date have received study drugs; 9 pts w/TNBC and 25 pts wHGSC. 26 have known gBRCAm. Dosing started at DL1 (BKM120 60 mg and olaparib 100 mg BID); 2 DLTs were observed (1 gr 3 LFTs and 1 gr 3 hyperglycemia). A lower dose (-1) was pursued followed by re-escalation as below. DL 6 was not feasible because of of grade 3 LFTs and grade 3 depression early in cycle 2. Evidence of clinical benefit by RECIST 1.1 was observed on all DL’s, and AEs seen were compatible with AE profile of BKM120 and olaparib. Expansion cohorts are accruing.

Conclusions: Combined BKM120 and olaparib is feasible with evidence of clinical benefit seen at all DL’s. Further studies combining PARP and PI3kinase inhibitors are warranted. Clinical trial information: NCT01623349.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Olaparib dose BID (mg)</th>
<th>BKM120 dose qD (mg)</th>
<th># of patients</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>-1</td>
<td>50</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>40</td>
<td>6</td>
</tr>
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<td>40</td>
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</tr>
<tr>
<td>4B</td>
<td>150</td>
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<td>3</td>
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</tr>
<tr>
<td>5B</td>
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<td>3</td>
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<tr>
<td>6 (DLT dose)</td>
<td>300</td>
<td>60</td>
<td>3</td>
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</tbody>
</table>
**CVac, Prima BioMed (PBMD)**

**Progression-free survival in ovarian cancer patients in second remission with mucin-1 autologous dendritic cell therapy.**

Abstract #5504

Author(s): Heidi J. Gray, Sharron Erna Gargosky, CAN-003 Study Team; Department of Obstetrics and Gynecology, University of Washington, Seattle, WA; PrimaBioMed, Sydney, Australia

**Background:** CVac is an autologous cellular therapy made by culturing autologous dendritic cells with a mucin 1 fusion protein and is intended to elicit a killer T cell response that is specific to mucin 1 over-expressing ovarian cancer cells. CAN-003 is an open label phase 2 study evaluating CVac as compared to standard of care (SOC) with the efficacy endpoints of progression free (PFS) and overall survival (OS), as well as safety and immune monitoring.

**Methods:** Eligible patients were stage III or IV epithelial ovarian cancer (EOC) who obtained a complete response to standard first (CR1) or second line chemotherapy (CR2). The first 7 patients were non-randomized and received CVac (NR CVac) for manufacturing comparison. Thereafter patients were randomized to either CVac (10 doses over 52 weeks) or to SOC.

**Results:** 63 patients were enrolled into the trial; 7 NR CVac, and 29 CVac and 27 SOC randomized. 42 patients were CR1 and 21 CR2. Overall CR1 and CR2 demographics were similar regarding tissue histology, optimal debulking and staging. 9 SAEs were reported in total. None were unexpected and only one (small bowel obstruction) was classified as unlikely-related to CVac. PFS was not improved in CR1 with CVac over SOC (HR=1.18, p=0.69) where as in CR2, CVac demonstrated a significant improvement in PFS; median PFS for SOC was 4.94 months; the median PFS for CVac was not reached but is greater than 12.91 months (p=0.04). Patient blood was assessed for antibodies to mucin 1; as anticipated, none were detected. Peripheral PBMC were assessed for T cell responses to mucin 1. Mucin 1 specific CD4 and CD8 T cell responses were observed, though without a significant correlation with PFS.

**Conclusions:** CVac treatment was safe and showed a significant improvement in PFS in 20 EOC patients in CR2. This strong efficacy signal in the CR2 population warrants further investigation in a larger trial. Clinical trial information: NCT01068509.

**Nivolumab, Bristol-Myers Squibb (BMY)**

**Efficacy and safety of anti-PD-1 antibody (Nivolumab: BMS-936558, ONO-4538) in patients with platinum-resistant ovarian cancer.**

Abstract #5511

Author(s): Junzo Hamanishi, Masaki Mandai, Takabumi Ikeda, Manabu Minami, Atsushi Kawaguchi, Noriomi Matsumura, Kaoru Abiko, Tsukasa Baba, Ken Yamaguchi, Akihiko Ueda, Masashi Kanai, Yukiko Mori, Shigemi Matsumoto, Toshinori Murayama, Shunsuke Chikuma, Satoshi Morita, Masayuki Yokode, Akira Shimizu, Tasuku Honjo, Ikuo Konishi; Kyoto University, Kyoto, Japan; Kinki University, Osaka, Japan; Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

**Background:** Programmed death-1 (PD-1) is a co-inhibitory receptor expressed on activated T cells which regulates antitumor immunity. Nivolumab is a fully-humanized IgG4 that blocks the engagement
of PD-1 by PD-1 ligands. Here we report the first trial for clinical application of nivolumab in ovarian cancer patients.

**Methods:** Nivolumab was administered every 2 weeks to patients with advanced or relapsed, platinum–resistant ovarian cancer, at the doses of 1 or 3 mg/kg during two cohort examination (10 patients each). The phase II efficacy trial defined 1st endpoint of response rate, and second endpoints of safety, and disease control rate. Patients received nivolumab up to 6 cycles (4 doses/cycle) of treatment or until PD or disease progression. Response rate was assessed by RECIST v1.1, and adverse events were evaluated by CTCAE v4.0. The data were cut-off on January 1, 2014.

**Results:** Fifteen patients were treated with nivolumab (1 mg/kg: n=10, 3 mg/kg: n=5), and evaluated. Median duration of therapy was 14 wks. There was one patient who had severe adverse drug reaction with fever, disorientation and gait disturbance. Clinical response rates were shown in Table. At the time of data cut off, one of the three responders had responses for 5 months, and the other two were on study with response for 4 and 10 months.

**Conclusions:** Nivolumab at 1 mg/kg cohort is well tolerated and has encouraging clinical efficacy for advanced or relapsed, platinum-resistant ovarian cancer patients. 3 mg/kg cohort is now under investigation. Clinical trial information: UMIN000005714.

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Total (n)</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>RR</th>
<th>DCR</th>
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<tbody>
<tr>
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<td>10</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>2/10 (20%)</td>
<td>5/10 (50%)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1/3 (33%)</td>
<td>2/3 (67%)</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>0</td>
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<td>4</td>
<td>5</td>
<td>1</td>
<td>3/13 (23%)</td>
<td>7/13 (54%)</td>
</tr>
</tbody>
</table>

Abbreviations: RR: response rate; CR+PR; DCR: disease control rate; CR+PR+SD.

**PM01183, PharmaMar**

Lurbinectin (PM01183), an active compound in platinum-resistant/refractory ovarian cancer (PRROC) patients: Results of a two-stage, controlled phase II study.

Abstract #5505

Author(s): Andres Poveda, Dominique Berton-Rigaud, Isabelle Laure Ray-Coquard, Jérôme Alexandre, Magali Provansal, Arturo Soto, Carmen Maria Kahatt, Sergio A. Szylbergmajn, Antonio Nieto, Cristian Fernandez, Eva Guerra Alia, Antonio Casado, Antonio Gonzalez-Martin, Jose Maria Del Campo; Instituto Valenciano de Oncologia, Valencia, Spain; ICO Centre René Gauducheau, Saint-Herblain, France; Centre Léon Bérard, Lyon, France; Cochin Hospital, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France; Institut Paoli Calmettes, Marseille, France; PharmaMar, Madrid, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; Hospital Clinico San Carlos, Madrid, Spain; Medical Oncology Service, Centro Oncologico M. D. Anderson International Spain, Madrid, Spain; Vall D'Hebrón Institute of Oncology, Barcelona, Spain
Background: PM01183 is a new anticancer agent that blocks the trans-activated transcription and induces the formation of double-strand breaks in a wide range of cancer cell lines, including platinum-resistant (Pt-res).

Methods: PRROC patients (pts) with less than 3 prior chemotherapy (CT) containing lines, adequate organ function and performance status (PS) 0-2 were included. The primary endpoint was overall response rate (ORR) (by RECIST v1.1 and/or Rustin criteria). Secondary endpoints were progression free survival (PFS), overall survival (OS) and safety. Pts were treated with i.v. PM01183 (P1), 7 mg flat dose, q3wk in the first stage. In the second stage, pts were randomized (1:1) to PM01183 (P2) or topotecan (T) (standard or weekly regimen). Cross-over to the P2 arm was allowed after progression to T.

Results: 81 pts were included (P1/P2/T: 22/30/29). Global median characteristics of pts were balanced: age 61 years; PS 1; Pt-res (P1/P2/T: 16/17/16 pts); prior bevacizumab: 18.5% of pts, median prior advanced chemotherapy lines: 1 in each arm. Efficacy results are summarized in the Table. The most common PM01183 related AEs were neutropenia (Gr 3-4, 85%), febrile neutropenia (23%), thrombocytopenia (Gr 3-4, 29%), nausea/vomiting (Gr 3, 16%) and fatigue (Gr 3, 37%)

Conclusions: PM01183 is an active drug in Pt-res/Pt-ref ovarian cancer. The study has met the primary endpoint, showing statistically significant superiority over T in terms of ORR, PFS and OS. The safety profile is predictable and manageable; prophylactic G CSF is recommended. A phase III study in Pt-res ovarian cancer is planned.

<table>
<thead>
<tr>
<th></th>
<th>PM01183 (n=51)</th>
<th>Topotecan (T) (n=29)</th>
<th>p-value</th>
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<tr>
<td></td>
<td>First stage (P1)</td>
<td>Second stage (P2)</td>
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<tr>
<td>OR [n (%)]</td>
<td></td>
<td>(n=22)</td>
<td>(n=29)</td>
</tr>
<tr>
<td>CR</td>
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<td>ORR (%) (95% CI)</td>
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<td>Pt-ref</td>
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<td>DCR (%)</td>
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<td>PFS (months) *</td>
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<td>(n=22)</td>
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<tr>
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<td>7.0</td>
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<tr>
<td>Pt-ref</td>
<td>12.6</td>
<td>8.7</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Abbreviations: Pt-ref, platinum-refractory; DCR, disease control rate. §2 PRs by Rustin criteria, *events: 81%; +events: 64%.

**PANCREATIC CANCER**

**Jakafi, Incyte (INCY)**

A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capetitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC).

Abstract #4000

Author(s): Herbert Hurwitz, Nikhil Uppal, Stephanie Ann Wagner, Johanna C. Bendell, J. Thaddeus Beck, Seborn Wade, John J. Nemunaitis, Philip J. Stella, J. Marc Pipas, Zev A. Wainberg, Robert Manges, William M. Garrett, Deborah S. Hunter, Jason Clark, Lance Leopold, Richard S. Levy, Victor Sandor; Duke University Medical Center, Durham, NC; NYU Langone Arena Oncology, Lake Success, NY; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; Sarah Cannon Research Institute, Nashville, TN; Highlands Oncology Group, Fayetteville, AR; Virginia Cancer Institute, Richmond, VA; Mary Crowley Cancer Research Centers, Dallas, TX; St. Joseph Mercy Health System - Alexander Cancer Care Center, Ann Arbor, MI; Dartmouth Hitchcock Medical Center Section of Hematology and Oncology, Lebanon, NH; UCLA Division of Hematology-Oncology, Los Angeles, CA; Investigative Clinical Research of Indiana, LLC, Indianapolis, IN; Incyte Corporation, Wilmington, DE

**Background:** Local and systemic inflammation (INFL) are hallmarks of cancer, including PC, that adversely impact prognosis. Given the role of JAK-STAT signaling in cancer INFL, the efficacy and safety of RUX, a JAK1/JAK2 inhibitor, given with CAPE in pts with mPC refractory to initial therapy was explored.

**Methods:** Pts with adequate performance status and organ function who progressed after gemcitabine treatment were included. RUX + CAPE was well tolerated in a 9 pt safety run-in. Subsequently, 127 pts were randomized to CAPE 1000 mg/m² BID days 1–14 with either RUX 15 mg BID or PBO on days 1–21 of a 21-day cycle. The primary endpoint was OS; secondary endpoints included PFS and ORR. To detect a HR ≤0.6 with 2-sided α=0.2 and β<0.2, final analysis was planned to occur after 97 deaths. Subgroup analyses were prespecified to explore treatment heterogeneity and a hypothesis that RUX would preferentially benefit pts with evidence of INFL.
Results: In the randomized population, OS and PFS favored RUX (Table). Confirmed ORR was 7.8% for RUX and 0% for PBO. In a prespecified subgroup of pts with INFL, as measured by serum C-reactive protein (CRP > group median of 13 mg/L), OS significantly favored RUX over PBO (Table). In this subgroup, 3 and 6 month survival was 48% and 42% with RUX vs 29% and 11% with PBO, respectively. In pts with CRP ≤13 mg/L, significant benefits in OS or PFS were not observed (HR = 0.89 and 0.82, respectively). OS benefit was also seen in pts classified by modified Glasgow Prognostic Score (mGPS), a measure of INFL in cancer (HRs 0.91, 0.71, 0.49 for mGPS 0, 1, 2, respectively). The combination of RUX and CAPE was generally well tolerated. Grade 3 or 4 (G3/4) adverse events occurred in 75% and 82% of RUX and PBO pts, respectively. G3/4 neutropenia and thrombocytopenia were uncommon in RUX pts (1.7% and 0%, respectively). G3/4 anemia occurred more frequently on RUX (15.3%) than PBO (1.7%).

Conclusions: RUX may improve OS and PFS in mPC pts with INFL characterized by elevated CRP or mGPS of 1 or 2. Clinical trial information: NCT01423604.

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>RUX</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, n</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>OS</td>
<td>0.79 (0.53–1.18) p=0.25</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>0.75 (0.52–1.10) p=0.28</td>
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</tr>
<tr>
<td>CRP &gt;13 mg/L, n</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>OS</td>
<td>0.47 (0.26–0.85) p=0.01</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>0.62 (0.35–1.1) p=0.20</td>
<td></td>
</tr>
</tbody>
</table>

PIGMENTED VILLONDULAR SYNOVITIS (PVNS)

**PLX3397, Daiichi Sankyo**

A pilot study of PLX3397, a selective colony-stimulating factor 1 receptor (CSF1R) kinase inhibitor, in pigmented villonodular synovitis (PVNS).

Abstract #10503^

Author(s): William D. Tap, Stephen Patrick Anthony, Bartosz Chmielowski, Arthur P. Staddon, Allen Lee Cohn, Geoffrey Shapiro, Igor Puzanov, Eunice L Kwak, Andrew J Wagner, Charles Peterfy, Henry H Hsu, Carolyn Gee, Paul S. Lin, Sandra Tong, Zev A. Wainberg; Memorial Sloan Kettering Cancer Center, New York, NY; Evergreen Hematology and Oncology/US Oncology Research Affiliate, Spokane, WA; University of California, Los Angeles, Los Angeles, CA; University of Pennsylvania School of Medicine, Philadelphia, PA; Rocky Mountain Cancer Center/US Oncology, Denver, CO; Dana-Farber Cancer Institute, Boston, MA; Vanderbilt-Ingram Cancer Center, Vanderbilt University, School of Medicine, Nashville, TN; Massachusetts General Hospital, Boston, MA; Spire Sciences, Inc., Boca Raton, FL; Plexxikon Inc., Berkeley, CA; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA

**Background:** PLX3397 is a novel, oral small molecule that potently and selectively inhibits CSF1R, Kit, and Flt3 kinases. CSF1R and Kit regulate key components of both the tumor and its microenvironment.
PVNS is a rare proliferative neoplasm involving the synovium of joints or tendon sheaths. Tumors contain CSF1R-bearing macrophages recruited by local overexpression of CSF-1 due to a gene translocation.

**Methods:** Patients (pts) with advanced PVNS were enrolled onto an expansion cohort of an ongoing single-arm, multicenter, clinical study. PLX3397 was given orally, 1000 mg daily (600 mg AM, 400 mg PM – 28 day cycles). MRI assessment by a central musculoskeletal radiologist blinded to chronology was performed every 2 cycles using a novel Tumor Volume Score (TVS) developed specifically for PVNS. Partial response (PR) was defined as ≥50% decrease in TVS compared to screening and progressive disease was ≥30% increase relative to lowest score. Patients remained on treatment until disease progression or intolerability.

**Results:** 17 PVNS pts have been enrolled to date. Median exposure 166 days (range 23-264). 59% pts were women; median age 46 yrs (range 22-80). Tumor locations: knees (12), ankles (2), feet (2), elbow (1). Of the 11 pts with evaluable MRI scans at this interim analysis, 7 pts (64%) achieved a PR and 4 pts (36%) had stable disease (SD). Mean tumor size reduction was 51% (range: -10% to -88%). Clinical improvements were seen in pain, stiffness, and overall function. Common AEs (>10%): fatigue, nausea, hair color changes, and diarrhea. Treatment-related AEs ≥Grade 3: anemia (1), hyponatremia (2), elevated ALT and AST (1), fatigue (1) and diarrhea (1).

**Conclusions:** PLX3397 was well tolerated and demonstrated profound activity as measured by a novel response criterion in pts with advanced PVNS. PLX3397 warrants further study in a larger clinical trial. Clinical trial information: NCT01004861.

---

**Percent change in TVS compared to screening.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cycle</th>
<th>3</th>
<th>5</th>
<th>7</th>
<th>9</th>
<th>Best response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>-64%</td>
<td>-40%</td>
<td>-68%</td>
<td>-64%</td>
<td>PR</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>-85%</td>
<td>-85%</td>
<td>-87%</td>
<td>-88%</td>
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</tr>
<tr>
<td>3</td>
<td>7</td>
<td>-50%</td>
<td>-50%</td>
<td>-50%</td>
<td>-58%</td>
<td>PR</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>-60%</td>
<td>-75%</td>
<td>-</td>
<td>-83%</td>
<td>PR</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>-13%</td>
<td>-13%</td>
<td>-13%</td>
<td>-</td>
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<tr>
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<td>6</td>
<td>-42%</td>
<td>-50%</td>
<td>-58%</td>
<td>-</td>
<td>PR</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>-5%</td>
<td>-10%</td>
<td>-</td>
<td>-</td>
<td>SD</td>
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<tr>
<td>8</td>
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<td>-39%</td>
<td>-</td>
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<td>-</td>
<td>SD</td>
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</tbody>
</table>
RG7155, Roche

Phase 1 study of RG7155, a novel anti-CSF1R antibody, in patients with locally advanced pigmented villonodular synovitis (PVNS).

Abstract #10504^

Author(s): Philippe Alexandre Cassier, Carlos Alberto Gomez-Roca, Antoine Italiano, Michael Cannarile, Carola Ries, Anne Brilliant, Claudia Mueller, Georgina Meneses-Lorente, Monika Baehner, Jayantha Ratnayake, Ross Harding, Keelara Abiraj, Nathalie Gass, Karen Noh, Randolph D. Christen, Mario Campone, Christophe Le Tourneau, Jean-Pierre Delord, Dominik Ruettinger, Jean-Yves Blay; Centre Léon Bérard, Lyon, France; Institut Claudius Regaud, Toulouse, France; Institut Bergonié, Bordeaux, France; Roche Pharma Research & Early Development Oncology, Penzberg, Germany; Roche Pharma Research & Early Development Oncology, Basel, Switzerland; Roche Pharma Research & Early Development Oncology, Welwyn, United Kingdom; Institut de Cancérologie de l'Ouest, Nantes, France; Department of Medical Oncology, Clinical Trial Unit, Institut Curie, Paris, France

Background: PVNS, also known as tenosynovial giant cell tumor (TGCT), is a rare disease mainly affecting young adults. This neoplastic disease is driven in most cases by a t(1;2) translocation resulting in fusion of COL6A3 and M-CSF genes encoding for colony-stimulating factor 1 (CSF1). The bulk tumor mass consists of CSF1 receptor (CSF1R) positive cells. RG7155 is a monoclonal antibody that potently inhibits the dimerization of CSF1R.

Methods: In this dose-escalation and –extension phase I study, we treated patients with locally advanced PVNS, who were not amenable to surgical treatment. Primary objectives were to assess safety, tolerability, pharmaco-kinetics and -dynamics. Clinical activity was evaluated using FDG-PET (at 4 weeks after treatment start; EORTC criteria) and MRI (at 6 weeks; RECIST 1.1). Pre- and on-treatment biopsies of tumor and surrogate skin tissue as well as peripheral blood PD markers were analyzed.

Results: Between September 2012 and October 2013, 11 PVNS patients (median age 38 (range 18-64)) were treated at three French institutions at four different dose levels (q2w). Three patients had previously been treated with nilotinib and imatinib, respectively. Seven patients had undergone previous surgeries. RG7155 induced a sustained increase of CSF1 associated with a decrease of CD14⁺CD16⁺ monocytes in peripheral blood in all 10 evaluable patients. RG7155 led to striking reductions of CSF1R⁺ and CD163⁺ macrophages in tumor tissue associated with rapid onset of objective clinical responses in 7/9 patients (78%; partial metabolic response at 4 weeks; FDG-PET) and 7/10 patients (70%; PR at 6 weeks; MRI). All patients showed tumor shrinkage associated with symptomatic improvement. 9/10 patients remained clinically progression-free with a longest follow-up of 17 months. RG7155 was well tolerated with only two patients experiencing grade 3 adverse events (periorbital edema; mucositis).

POLYCYTHEMIA VERA (PV)

Jakafi, Incyte (INCY)

Results of a prospective, randomized, open-label phase 3 study of ruxolitinib (RUX) in polycythemia vera (PV) patients resistant to or intolerant of hydroxyurea (HU): the RESPONSE trial

Abstract #7026

Author(s): Srdan Verstovsek, Jean-Jacques Kiladjian, Martin Griesshammer, Tamás Masszi, Simon T. S. Durrant, Francesco Passamonti, Claire N. Harrison, Fabrizio Pane, Pierre Zachée, Ruben A. Mesa, Shui He, Mark Jones, William M. Garrett, Jingjin Li, Ulrich Pirrin, Tomasz Lawniczek, Alessandro M Vannucchi; The University of Texas MD Anderson Cancer Center, Houston, TX; Hôpital Saint-Louis et Université Paris Diderot, Paris, France; Johannes Wesling Academic Medical Center, University of Hannover Teaching Hospital, Minden, Germany; St. István and St. László Hospital, Budapest, Hungary; Royal Brisbane and Women’s Hospital, Brisbane, Australia; Ospedale di Circolo e Fondazione Macchi, Varese, Italy; Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom; University of Naples Federico II, Naples, Italy; ZNA Stuivenberg, Antwerp, Belgium; Mayo Clinic, Scottsdale, AZ; Incyte Corporation, Wilmington, DE; Novartis Pharmaceuticals Corporation, Florham Park, NJ; Novartis Pharma AG, Basel, Switzerland; University of Florence, Florence, Italy

Background: PV is a myeloproliferative neoplasm characterized by increased erythrocytosis, disease-related symptom burden (eg, pruritus), and risk of vascular events (thrombosis and/or hemorrhage). Maintaining hematocrit (HCT) control is a key therapeutic goal. RESPONSE is the first phase 3 study to evaluate a JAK inhibitor (RUX) in treating PV.

Methods: Phlebotomy (PBT)-dependent patients (pts) with splenomegaly (> 450 cm³) and HU resistance/intolerance were randomized 1:1 to RUX 10 mg bid or best available therapy (BAT). The primary endpoint was the proportion of pts who achieved both HCT control without PBT from wk 8 to 32 (with ≤ 1 PBT from wk 0 to 8) and a ≥ 35% reduction in spleen volume (SV) from baseline (BL) by MRI at wk 32. Key secondary endpoints included the proportion of pts who maintained the primary response at wk 48 and the proportion of pts who achieved complete hematologic response (CHR) at wk 32. Other endpoints were duration of response, symptom improvement by MPN-SAFT diary, and safety. BAT-treated pts could cross over to RUX from wk 32. The primary analysis occurred when all pts reached wk 48 or discontinued.

Results: 110 and 112 pts were randomized to RUX and BAT, respectively (median exposure: RUX, 81 wk; BAT, 34 wk); 17 (15%) RUX and 108 (96%) BAT pts discontinued randomized treatment (96 crossed over to RUX). The primary endpoint was achieved in 21% of RUX vs 1% of BAT pts (P < .0001); 91% of RUX pts maintained their response at wk 48. Overall, 77% of RUX pts met ≥ 1 component of the primary endpoint: 60% of RUX and 20% of BAT pts achieved HCT control without PBT; 38% of RUX and 1% of BAT pts achieved a ≥ 35% SV reduction (median BL SV, 1195 cm³ in RUX and 1322 cm³ in BAT pts). CHR was achieved in 24% and 9% of RUX and BAT pts (P = .003); 49% vs 5% had a ≥ 50% improvement in MPN-SAFT 14-item total symptom score at wk 32. During the first 32 wk, grade 3/4 anemia or thrombocytopenia occurred in 1.8% and 5.5% of RUX pts, respectively, vs 0% and 3.6% of BAT pts; thromboembolic events occurred in 1 RUX and 6 BAT pts.
**PROSTATE CANCER**

**Orteronel, Takeda**  
Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) (ELM-PC 4 trial)  
Abstract #5008

**Author(s):** Ronald De Wit, Karim Fizazi, Viorel Jinga, Eleni Efstatiou, Peter C.C. Fong, Manfred Wirth, Kazuhiro Suzuki, Susan Moran, Ling Wang, Hideyuki Akaza, Joel Nelson, Howard I. Scher, Robert Dreicer, Niels Geert Borgstein, Fred Saad; Erasmus University Medical Center, Rotterdam, Netherlands; Institut Gustave Roussy, University of Paris Sud, Villejuif, France; UMF Bucharest, Bucharest, Romania; Alexandria General Hospital of Athens, Oncology Department, Department of Clinical Therapeutics, Medical School, University of Athens, Athens, Greece; Auckland City Hospital, Auckland, New Zealand; University Hospital Carl Gustav Carus Dresden, Dresden, Germany; Gunma University Graduate School of Medicine, Gunma, Japan; Takeda Pharmaceuticals International Co., Cambridge, MA; The University of Tokyo Research Center for Advanced Science and Technology, Tokyo, Japan; University of Pittsburgh, School of Medicine, Pittsburgh, PA; Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, New York, NY; Cleveland Clinic, Cleveland, OH; University of Montréal Hospital Center, Montréal, QC, Canada

**Background:** Orteronel, an investigational, non-steroidal, selective 17,20-lyase inhibitor, demonstrated improved radiographic PFS (rPFS) but not OS in men with mCRPC post-docetaxel (Dreicer et al, ASCO GU 2014, Abstract 7). The double-blind ELM-PC 4 trial (NCT01193244) evaluated orteronel in pts with chemotherapy-naïve mCRPC.

**Methods:** Men with progressive mCRPC (rising PSA and/or radiographic evidence) and testosterone < 50 ng/dL (post-orchiectomy or with maintained GnRH suppression) were randomized 1:1 to orteronel 400 mg twice daily (BID) + prednisone 5 mg BID (O+P) or placebo + prednisone (P), stratified by region and radiographic progressive disease at baseline. Co-primary endpoints were OS and rPFS. Based on 90% power to test OS (> 90% for rPFS), an initial HR of 1.25 in favor of orteronel was anticipated with 1454 pts and 900 deaths (pre-assigned alpha: OS 0.045, rPFS 0.005). The final analysis for rPFS was conducted at an interim analysis (IA) for OS; the final analysis for OS was conducted at 600 deaths, with 78% power.

**Results:** 1560 pts were randomized. The study met the co-primary endpoint of rPFS; at the IA (final for rPFS), median rPFS with O+P v P was 11 v 8.3 months (HR 0.7; 95% CI: 0.5–0.8; P < .001). At the final analysis for OS the updated median rPFS benefit with O+P v P had increased to 5.1 months (median 13.8 v 8.7 mo; HR 0.7; 95% CI: 0.6–0.8; P < .00001). The co-primary endpoint of OS was not met. Median OS with O+P v P was 31.4 v 29.5 months (HR 0.9; 95% CI: 0.8–1.1; P = .314), with no notable differences across regions. More pts had a ≥ 50% PSA decrease (43% v 25%, P < .00001) and a favorable circulating tumor cell count (15% v 9%, P = .00016) at 12 weeks with O+P v P. Common all-grade adverse events with O+P v P included nausea (36% v 15%), fatigue (34% v 20%), constipation (33% v 15%), and diarrhea.
(28% v 14%); 30% v 18% of pts discontinued due to AEs. In O+P v P groups, 45% v 51% of pts received subsequent therapy, including docetaxel/abiraterone/enzalutamide in 31%/14%/6% v 33%/20%/6%.

**Conclusion:** O+P demonstrated a significant improvement in rPFS but no statistically significant improvement in OS v P in chemotherapy-naive mCRPC. Clinical trial information: NCT01193244.

**Taltorvic, Ariad (ARIA)**
**MK-2206, Merck (MRK)**
**Safety/efficacy of MK-8669 (ridaforolimus) plus MK-2206 (AKT inhibitor) in patients with advanced breast cancer with low RAS signature and PTEN deficient prostate cancer.**
Abstract #2509

Author(s): Shilpa Gupta, Pamela N. Munster, Antoine Hollebecque, Guillem Argiles, Olav Dajani, Jonathan D. Cheng, Ann M. Swift, Alessandra Tosolini, Sarina Anne Piha-Paul; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Drug Development Department (DITEP), Gustave Roussy, Cancer Campus, Grand Paris, Villejuif, France; Vall d’Hebron University Hospital, Barcelona, Spain; Department of Oncology, Oslo University Hospital, Oslo, Norway; Merck & Co., Inc., Whitehouse Station, NJ; Merck & Co, North Wales, PA; Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** The PI3K/AKT/mTOR signaling pathway is aberrantly activated in a variety of cancers. The combination of ridaforolimus (mTOR inhibitor) and MK-2206 may lead to blockade of the PI3K pathway.

**Methods:** We conducted a phase 1 study with ridaforolimus + MK-2206 in advanced solid tumors (n=35). Part A defined the maximum-tolerated dose (MTD); part B evaluated preliminary clinical efficacy in enriched breast cancer (BCa) and prostate cancer (PCA) patients. BCa patients had low RAS gene signature; ER+ BCa patients required a high Ki67 index. PCA patients had evidence of PTEN deficiency.

**Results:** Eleven patients were in part A and 24 patients were in part B (16 BCa/8 PCA patients). In addition, 1 BCa patient from part A was found to be biomarker-eligible when tested after a clinical response. Total of 124 BCa patients were prescreened: 98 tissues were evaluable; 51 were biomarker-eligible. Sixty-eight PCA patients were prescreened: 40 tissues were evaluable; 24 had loss of PTEN. The MTD was 10 mg qd ridaforolimus 5 days/wk + 90 mg weekly MK-2206; 1/17 patients had a dose limiting toxicity of G3 rash. For BCa patients, investigator-assessed objective responses were seen in 2/16 (2 partial responses [PR], 12.5%), centrally read objective responses were seen in 2/14 (2 complete responses [CR], 14.3%), and objective responses using volumetric 3-D assessment were seen in 4/14 (2 PR + 2 CR, 28.6%). In addition, stable disease (SD) ≥6 months was seen in 1 patient by the investigator assessment and 1 patient by central read. For PCA patients, 1/8 patient had SD for > 6 months. No responses were seen in other non-biomarker-tested tumors in part A (although one subject with colorectal cancer had SD for 7 months). At the MTD, the following drug-related AEs were seen: rash (44.4%); stomatitis (38.9%); diarrhea and decreased appetite (27.8%); asthenia, nausea and fatigue (22.2%).

**Conclusions:** The combination of ridaforolimus and MK-2206 shows promising activity in BCa patients with low RAS. This combination was overall well tolerated with rash, stomatitis, diarrhea and asthenia being among the most common drug-related AEs. Clinical trial information: NCT01295632.
Xtandi, Astellas Pharma
Primary, secondary, and quality-of-life endpoint results from PREVAIL, a phase 3 study of enzalutamide in men with metastatic castration resistant prostate cancer (mCRPC).
Abstract #5007

Author(s): Andrew J. Armstrong, Bertrand Tombal, Cora N. Sternberg, Celestia S. Higano, Dana E. Rathkopf, Yohann Loriot, Fred Saad, Anthony M. Joshua, Johann Sebastian De Bono, Peter M. Venner, Joan Carles, Paul N. Mainwaring, Christopher P. Evans, Sarah B. Noorberg, Harry H. Mansbach, Suman Bhattacharya, Frank Perabo, De Phung, Tomasz M. Beer; Duke University, Durham, NC; Division of Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; Hospital San Camillo-Forlanini, Rome, Italy; Fred Hutchinson Cancer Research Center, Seattle, WA; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Cancer Medicine, INSERM U981, Gustave Roussy, Cancer Campus, Grand Paris, Villejuif, France; University of Montréal Hospital Center, CRCHUM, Montréal, QC, Canada; Princess Margaret Hospital, University Health Network, Toronto, ON, Canada; Division of Cancer Therapeutics and Division of Clinical Studies, The Institute of Cancer Research; Drug Development Unit, The Royal Marsden NHS Foundation Trust, Surrey, United Kingdom; Cross Cancer Institute, Edmonton, AB, Canada; Hospital Universitari Vall d’Hebron, Barcelona, Spain; ICON Cancer Care, South Brisbane, Australia; University of California, Davis, Sacramento, CA; Medivation, Inc., San Francisco, CA; Astellas Pharma Global Development, Inc., Northbrook, IL; Astellas Pharma Global Development, Inc., Leiderdorp, Netherlands; Oregon Health & Science University, OHSU Knight Cancer Institute, Portland, OR

Background: Enzalutamide (ENZ), an androgen receptor inhibitor, improved overall survival (OS) in men with mCRPC who had received prior docetaxel therapy (Scher, N Engl J Med 2012;367:13). The PREVAIL study examined whether ENZ could prolong OS and radiographic progression-free survival (rPFS) in men with mCRPC who had progressed on androgen deprivation therapy (ADT).

Methods: In this randomized double-blind, placebo-controlled, multinational study (NCT01212991), asymptomatic or mildly symptomatic patients were randomized 1:1 to ENZ 160 mg/day or placebo (PBO). OS and rPFS were co-primary endpoints and analyzed for the intent-to-treat population. Key prespecified secondary and exploratory endpoints are noted in the table below.

Results: 872 men were randomized to ENZ and 845 to PBO, with respective median treatment durations of 16.6 and 4.6 months. Based on a planned interim analysis at 540 deaths the Data Monitoring Committee recommended stopping the study and crossing PBO patients to ENZ. Efficacy results are shown in the Table. The most common adverse events with a higher incidence in the ENZ arm than PBO were fatigue (35.6% vs 25.8%), back pain (27.0% vs 22.2%), constipation (22.2% vs 17.2%), and arthralgia (20.3% vs 16.0%). Seizure was reported in 1 patient in each treatment arm (0.1%).

Conclusions: In men with mCRPC who progress on ADT, treatment with enzalutamide has a favorable safety profile and significantly improves OS, rPFS, and secondary measures of disease response and progression. Clinical trial information: NCT01212991.
### 2014 Pre-ASCO Report

#### Est. median (95% CI) months

<table>
<thead>
<tr>
<th>Co-primary endpoints</th>
<th>ENZ</th>
<th>PBO</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>32.4 (31.5, NYR)</td>
<td>30.2 (28, NYR)</td>
<td>0.71 (0.60, 0.84)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>rPFS</td>
<td>NYR (13.8, NYR)</td>
<td>3.9 (3.7, 5.4)</td>
<td>0.19 (0.15, 0.23)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

#### Other efficacy endpoints

| Time to cytotoxic chemotherapy | 0.35 (0.30, 0.40) | < 0.0001 |
| Time to antineoplastic treatment<sup>a</sup> | 0.27 (0.24, 0.31) | < 0.0001 |
| Time to first SRE              | 0.72 (0.61, 0.84) | < 0.0001 |
| Time to PSA progression        | 0.17 (0.15, 0.20) | < 0.0001 |
| Time to FACT-P degradation     | 0.63 (0.54, 0.72) | < 0.0001 |

#### Best objective response (CR+PR)

| ENZ = 58.8%                   | PBO = 5.0%         | < 0.0001 |

#### PSA decline from baseline

<table>
<thead>
<tr>
<th>ENZ</th>
<th>PBO</th>
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<th></th>
<th>≥ 90%</th>
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<tr>
<td>78.0%</td>
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<td></td>
<td>46.8%</td>
<td>1.2%</td>
</tr>
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<td>80%</td>
<td>4%</td>
<td></td>
<td></td>
<td>50%</td>
<td>5%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Cytotoxic, hormonal, or investigational therapy.

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**Xtandi, Astellas Pharma**  
**Zytiga, Johnson & Johnson (JNJ)**

Enzalutamide (ENZA) in combination with abiraterone acetate (AA) in bone metastatic castration resistant prostate cancer (mCRPC).

Abstract #5000

Author(s): Eleni Efstatiiou, Mark Anton Titus, Sijin Wen, Aileen SanMiguel, Anh Hoang, Angela De Haas-Amatsaleh, Frank Perabo, De Phung, Patricia Troncoso, Taoufik Ouatas, Christopher Logothetis;  
Alexandra General Hospital of Athens, Oncology Department, Department of Clinical Therapeutics, Medical School, University of Athens, Athens, Greece; The University of Texas MD Anderson Cancer Center, Houston, TX; West Virginia University Health Science Center, Morgantown, WV; Astellas Global Development, Northbrook, IL; Astellas Pharma Global Development, Inc., Northbrook, IL; Astellas Pharma Global Development, Inc., Leiderdorp, Netherlands; Astellas Pharma Global Development, Leiden, Netherlands

**Background:** Co-targeting the androgen receptor (AR) and paracrine androgen biosynthesis in mCRPC may be more effective than either alone. This study aims to evaluate safety, pharmacokinetic (PK) drug-
drug interactions (DDI), androgen signaling and steroid metabolome modulation and efficacy of ENZA with AA in mCRPC

Methods: We enrolled patients (pts) with progressive bone mCRPC, castrate level serum testosterone (≤ 50 ng/dl) consenting to bone marrow (BM) biopsy. Pts were treated with ENZA 160 mg QD and AA 1g QD + prednisone 5 mg bid and monitored every 4-week with CBC, chemistry, physical exams. mCRPC was assessed clinically by PSA, ALP and imaging. Tumor was characterized by IHC and LC mass spectrometry (blood and BM). C_{t rough} Plasma concentrations of AA were measured on days 4 & 29, and ENZA and its active metabolite M2 on d29 in pt subset.

Results: We enrolled (07/12-09/13) 60 pts with median age 66 yrs (range 40-82), PS-ECOG 1 (range 0-2) and PSA 20.8 ng/ml (range1-670). Gleason Score (GS) at diagnosis ≥ 8 in 38/53 (72%), [GS ≥ 9 29/53 (55%)]/7 unknown. Thirty (50%) had > 20 bone lesions, 19/60 (32%) lymph node lesions and 2/60 (3%) visceral metastases. Interim data on evaluable pts: PSA changes for 49 pts: maximum PSA decline ≥ 50% (37/49 [76%]), ≥ 90% (22/49 [45%]), PSA ≤ 0.1ng/ml (5/49 [10%]) and PSA progression (6 [12%]). Grade 3 adverse events: ALT rise (5), hypertension (5), ALP rise (4 ), arthralgia (3), bone pain (2). No Grade 4 AEs reported. At ENZA steady state (d29), C_{t rough} of AA was ~23% lower than d4 (pt n=14; LS means ratio 77.67 %; 90% CI 47.51-126.98) and C_{t rough} for ENZA, M2, and the sum of both (pt n=15) were comparable to those reported previously. Following 8 weeks treatment, serum and BM testosterone were undetectable (<1pg/ml) in 29/39 (74%) and 31/36 (86%) evaluated pts respectively, and androstenedione in all pts. Nuclear AR expression was reduced following treatment in 5/6 of evaluable paired tumor specimens.

Conclusions: ENZA+ AA combination has a favorable safety profile, without clinically meaningful PK DDI. Feedback mechanisms observed by either agent are dissipated. These promising findings are indicative of more efficacious androgen signaling inhibition in men with mCRPC. Clinical trial information: NCT01650194.

RENAL CELL CANCER

Afinitor, Novartis (NVS)

Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (The ESPN Trial): A multicenter randomized phase 2 trial.

Abstract #4505

Author(s): Nizar M. Tannir, Eric Jonasch, Emre Altinmakas, Chaan S. Ng, Wei Qiao, Pheroze Tamboli, Priya Rao, David F. McDermott, Christopher G. Wood, Toni K. Choueiri; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA

Background: In a single-arm phase II trial of sunitinib in non-clear cell RCC (nccRCC) we previously reported (Tannir et al. Eur Urol 2012), objective response rate [ORR] was 5% and median progression-free survival [PFS] was 2.7 months. Temsirolimus was previously shown to produce overall survival (OS) benefit in poor-risk RCC including nccRCC (Hudes et al. NEJM 2007).
Methods: This is a randomized phase II trial of everolimus (E) vs. sunitinib (S) with crossover design in metastatic nccRCC. Primary endpoint was PFS in first-line (1L). Secondary endpoints were PFS in second-line (2L), safety, and OS. A sample size calculation of 108 pts (54/arm) was based on an assumption of improved median PFS from 12 weeks with S to 20 weeks with E. Pts were stratified by histology (papillary vs. others), and MSKCC risk groups. Kaplan-Meier curves were used to estimate unadjusted time-to-event distributions. Stratified log rank tests were used to compare each time-to-event variable between groups.

Results: Seventy-three pts were enrolled. Sixty-eight pts were eligible and evaluable (median age 59, 43 males [63%], 52 pts [77%] had prior nephrectomy). Twenty-seven pts had papillary, 11 pts had chromophobe, 9 pts had unclassified, 7 pts had translocation, 13 pts had sarcomatoid, and 1 pt had oncocytic RCC. Thirty-five pts received E (good-risk 4, intermediate-risk 29, poor-risk 2). Thirty-three pts received S (good-risk 4, intermediate-risk 29). ORR with S in 1L was 12% (2 pts had chromophobe, 1 pt had papillary type 1 and 1 pt had 99% sarcomatoid); ORR with E in 1L was 0%. Median PFS in 1L with S was 6.1 mos (95% CI: 4.7, 10.8) and 4.1 mos with E (95% CI: 2.7, 7.4); p = 0.25. Thirty-eight pts received 2L therapy (S 19, E 19). Median PFS in 2L with S was 1.8 mos (95% CI: 1.5, NA) and 4.3 mos with E (95% CI: 1.4, NA). A total of 27 pts have died (8 had S and 19 had E). Median OS with E in 1L was 10.5 mos (95% CI: 7.4, NA); median OS with S in 1L was not reached; p=0.01. Toxicity was consistent with previous reports of E and S.

Conclusions: Based on futility analysis for PFS and inferior OS with E compared to S in 1L, the DSMB recommended termination of further pt accrual on this trial. E cannot be recommended as 1L option in nccRCC.

Nivolumab, Bristol-Myers Squibb (BMY)

Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC).
Abstract #4504

Author(s): Hans J. Hammers, Elizabeth R. Plimack, Jeffrey R. Infante, Marc S. Ernstoff, Brian I. Rini, David F. McDermott, Albiruni R. A. Razak, Sumanta Kumar Pal, Martin Henner Voss, Padmanee Sharma, Christian K. Kollmannsberger, Daniel Yick Chin Heng, Jennifer L. Spratlin, Yun Shen, John F. Kurland, Paul Gagnier, Asim Amin; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Fox Chase Cancer Center, Philadelphia, PA; Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN; Dartmouth Hitchcock Medical Center, Geisel School of Medicine, Norris Cotton Cancer Center, Lebanon, NH; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA; Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; City of Hope Comprehensive Cancer Center, Duarte, CA; Memorial Sloan Kettering Cancer Center, New York, NY; MD Anderson Cancer Center, University of Texas, Houston, TX; British Columbia Cancer Agency, Vancouver, BC, Canada; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; Bristol-Myers Squibb, Princeton, NJ; Levine Cancer Institute, Charlotte, NC

Background: There is a need for agents that result in durable responses and improved tolerability in patients (pts) with mRCC. Nivolumab, a fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, has shown activity in mRCC. Combining nivolumab + ipilimumab, a fully human monoclonal antibody to CTLA-4, showed encouraging clinical activity and acceptable safety in advanced melanoma. We report preliminary results of the combination in mRCC.
Methods: Pts with mRCC (favorable/intermediate MSKCC score; Karnofsky performance status ≥80%; untreated or any number of prior therapies) were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm N1 + I3) IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W until progression/toxicity. The primary objective was to assess safety/tolerability; secondary objective was to assess antitumor activity.

Results: Pts were randomized to N3 + I1 (n=21) and N1 + I3 (n=23). Most pts (n=34; 77%) had prior systemic therapy (N3 + I1: 16; N1 + I3: 18). Treatment-related adverse events (AEs) were seen in 39/44 pts (89%); 7 pts (16%; N3 + I1: 2; N1 + I3: 5) discontinued due to any-grade related AEs. Grade 3–4 related AEs occurred in 19 pts (43%; N3 + I1: 5; N1 + I3: 14), most commonly ↑ lipase (16%, n=7), ↑ ALT (11%, n=5), diarrhea (9%, n=4), colitis (5%, n=2), ↑ amylase (5%, n=2). No grade 3–4 pneumonitis was seen. Objective response rate (ORR) was 29% (N3 + I1) and 39% (N1 + I3) (Table). Duration of response (DOR) was 4.1+ to 22.1+ wks (all 6 responses ongoing) in N3 + I1, and 6.1+ to 18.3+ wks (8/9 responses ongoing) in N1 + I3. Responses occurred by first tumor assessment (wk 6) in 67% of responding pts in both N3 + I1 and N1 + I3. Stable disease (SD) was seen in 7 (33%) pts (N3 + I1) and 9 (39%) pts (N1 + I3).

Conclusions: Nivolumab + ipilimumab showed acceptable safety and encouraging antitumor activity in mRCC, with most responses ongoing. Follow-up, expansion cohorts at these doses and an additional dose cohort (nivolumab 3 mg/kg + ipilimumab 3 mg/kg) are being assessed. Clinical trial information: NCT01472081.

<table>
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<th>Arm</th>
<th>N3 + I1 n=21</th>
<th>N1 + I3 n=23</th>
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<tr>
<td>ORR, n (%)</td>
<td>6 (29)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>SD, n (%) [duration, wks]</td>
<td>7 (33) [6+ to 25+]</td>
<td>9 (39) [6+ to 26.1]</td>
</tr>
<tr>
<td>DOR, range (wks)</td>
<td>4.1+ – 22.1+</td>
<td>6.1+ – 18.3+</td>
</tr>
<tr>
<td>PFS, range (wks)</td>
<td>4.7+ – 28.1+</td>
<td>4.3 – 26.1</td>
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</table>

Nivolumab, Bristol-Myers Squibb (BMY)
Nivolumab for metastatic renal cell carcinoma (mRCC): Results of a randomized, dose-ranging phase II trial.
Abstract #5009

Author(s): Robert J. Motzer, Brian I. Rini, David F. McDermott, Bruce G. Redman, Timothy Kuzel, Michael Roger Harrison, Ulka N. Vaishampayan, Harry A. Drabkin, Saby George, Theodore F. Logan, Kim Allyson Margolin, Elizabeth R. Pлимак, Ian Waxman, Alexandre Lambert, Hans J. Hammers; Memorial Sloan-Kettering Cancer Center, New York, NY; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Northwestern University, Chicago, IL; Duke University Medical Center, Durham, NC; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Medical University of South Carolina, Charleston, SC; Roswell Park Cancer Institute, Buffalo, NY; Indiana University, Indiana Cancer Pavillion, Indianapolis, IN; Seattle Cancer Care Alliance, Seattle, WA; Fox...
Chase Cancer Center, Philadelphia, PA; Bristol-Myers Squibb, Princeton, NJ; Bristol-Myers Squibb, Paris, France; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

**Background:** Nivolumab, a fully human IgG4 programmed death-1 immune checkpoint inhibitor antibody, restores T-cell immune activity and showed objective responses in mRCC in a phase I trial (*NEJM* 366:2443). This phase II trial (NCT01354431) assesses three nivolumab doses in mRCC patients (pts) pretreated with agents targeting the VEGF pathway.

**Methods:** Pts with clear-cell mRCC (≥1 agent targeting VEGF pathway; ≤3 prior systemic therapies) were randomized (blinded 1:1:1) to nivolumab 0.3, 2 or 10 mg/kg IV Q3W until progression or toxicity. The primary objective was to evaluate the dose-response relationship measured by progression-free survival (PFS). Secondary objectives included overall survival (OS), objective response rate (ORR) and safety assessment.

**Results:** All pts (N=168) received prior systemic therapy (70% received ≥2) including VEGFR TKIs (98%), mTOR inhibitors (38%) and immunotherapy (24%). 25% were MSKCC poor risk. All had >16 months of follow-up. No dose-response relationship was noted for PFS (stratified trend test, \( P = 0.9 \)). PFS and ORR were similar across doses (Table). For 0.3 mg/kg, median duration of response was 15.7 months and median OS was 18.2 months; for other doses medians were not reached. Across doses 19/35 responders (54%) had objective responses lasting >12–20+ months. Rates of grade 3–4 related adverse events (AEs) were ≤17% for all doses (Table). There was no grade 3–4 pneumonitis. For 0.3, 2 and 10 mg/kg, 1 (2%), 6 (11%) and 4 (7%) pts, respectively, had treatment-related AEs that led to discontinuation.

**Conclusions:** Antitumor activity was observed with nivolumab in this pretreated mRCC population including objective responses of long duration. No dose-response relationship for PFS was noted and the safety profile was acceptable. Median OS was 18.2 months for the 0.3 mg/kg dose and was not reached for 2 or 10 mg/kg; updated OS will be presented. Clinical trial information: NCT01354431.

<table>
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<th>Treatment</th>
<th>0.3 mg/kg n=60</th>
<th>2 mg/kg n=54</th>
<th>10 mg/kg n=54</th>
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<tbody>
<tr>
<td><strong>Median PFS, months (80% CI)</strong></td>
<td>2.7 (1.9, 3.0)</td>
<td>4.0 (2.8, 4.2)</td>
<td>4.2 (2.8, 5.5)</td>
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<tr>
<td><strong>ORR, n (%)</strong></td>
<td>12 (20)</td>
<td>12 (22)</td>
<td>11 (20)</td>
</tr>
<tr>
<td><strong>Median OS, months (80% CI)</strong></td>
<td>18.2 (16.7, NR)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td><strong>Treatment-related AE, n (%)</strong></td>
<td>44 (75)</td>
<td>36 (67)</td>
<td>42 (78)</td>
</tr>
<tr>
<td><strong>Grade 3–4</strong></td>
<td>3 (5)</td>
<td>9 (17)</td>
<td>7 (13)</td>
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</table>

\( ^a \) Safety analysis included 59 treated pts; CI=confidence interval; NR=not reached.

**Nivolumab, Bristol-Myers Squibb (BMY)**

Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC).

Abstract #5010
Background: Antiangiogenic agents sunitinib (S) and pazopanib (P) are SOC for mRCC, but new therapies are needed as pts advance through therapy with limited survival benefit. We report preliminary results of a phase I trial of nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, in combination with S or P in pts with mRCC.

Methods: mRCC patients (≥1 prior systemic therapy) received nivolumab in combination with S (50 mg, 4 wks on, 2 wks off; arm S) or P (800 mg daily; arm P), until progression/unacceptable toxicity. Starting dose of nivolumab was 2 mg/kg IV Q3W (N2), with planned escalation to 5mg/kg IV Q3W (N5). Based on tolerability, arm S N5 cohort was expanded to treatment-naïve pts. Primary objectives were safety/tolerability and determination of maximum tolerated dose (MTD) for the combinations; secondary objective was antitumor activity (objective response rate [ORR] and duration of response [DOR]).

Results: 7 pts were assigned to each of arms S N2 and N5. No dose-limiting toxicities (DLTs) were observed and MTD was not reached thus N5 was expanded with 19 additional pts (total n=33). Arm P enrolled 20 pts at N2; 4 DLTs (elevated ALT/AST [n=3], fatigue [n=1]) were observed, leading to closure of this arm. Grade 3–4 related AEs were observed in 24/33 pts (73%) in arm S and 12/20 pts (60%) in arm P. Most common related grade 3–4 AEs included elevated ALT (18%), hypertension and hyponatremia (15% each) in arm S and elevated ALT/AST (20% each) and fatigue (15%) in arm P. Hepatotoxicities were manageable using treatment algorithms. Grade 3 pneumonitis occurred in 1 pt (arm S, N5). Grade 3–4 related AEs led to therapy discontinuation in 8/33 pts (24%; 1 N2, 7 N5) in arm S and 4/20 pts (20%) in arm P. ORR was 52% (17/33) in arm S and 45% (9/20) in arm P. Responses occurred by first assessment (6 wks) in 41% (arm S) and 56% (arm P) of responding pts and were durable (range: arm S: 12.1+ to 54 wks; arm P: 12.1 to 69.1+ wks). Stable disease rate was 33% (n=11) in arm S and 35% (n=7) in arm P. PFS rate at 24 wks was 78% for arm S and 55% for arm P.

Conclusions: Nivolumab plus S or P showed encouraging antitumor activity and a manageable safety profile in pts with mRCC. Additional follow up will be presented. Clinical trial information: NCT01472081.

Nivolumab, Bristol-Myers Squibb (BMY)
Immunomodulatory activity of nivolumab in previously treated and untreated metastatic renal cell carcinoma (mRCC): Biomarker-based results from a randomized clinical trial.
Abstract #5012
Author(s): Toni K. Choueiri, Mayer N. Fishman, Bernard J. Escudier, Jenny J. Kim, Harriet M. Kluger, Walter Michael Stadler, Jose Luis Perez-Gracia, Douglas G. McNeel, Brendan D. Curti, Michael Roger Harrison, Elizabeth R. Plimack, Leonard Joseph Appleman, Lawrence Fong, Charles G. Drake, Lewis J. Cohen, Shivani Srivastava, Maria Jure-Kunkel, Quan Hong, John F. Kurland, Mario Sznol; Dana-Farber Cancer Institute, Boston, MA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Institut Gustave Roussy, Villejuif, France; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Yale Cancer Center, New Haven, CT; University of Chicago Medicine, Chicago, IL; University Clinic of Navarra, Pamplona, Spain; Department of Medicine, University of Wisconsin-Madison, Madison, WI; Providence Cancer Center, Providence Portland Medical Center, Portland, OR; Duke University Medical Center, Durham, NC; Fox Chase Cancer Center, Philadelphia, PA; University of Pittsburgh Medical Center (UPMC) Cancer Pavilion, Pittsburgh, PA; University of California San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Bristol-Myers Squibb, Princeton, NJ

**Background:** Nivolumab, a fully human IgG4 programmed death-1 (PD-1) inhibitor antibody, has shown encouraging activity in mRCC. This trial assessed the immunomodulatory and clinical activity, and safety of nivolumab in patients (pts) with mRCC.

**Methods:** Ninety-one pts received nivolumab IV Q3W: pretreated pts (1–3 prior therapies; ≥1 anti-angiogenic agent) received 0.3 (n=22), 2 (n=22), or 10 mg/kg (n=23); 24 treatment-naïve pts received 10 mg/kg. Fresh biopsies and serum were obtained at baseline (BL) and nivolumab cycle 2 day 8 (C2D8; biopsy) and cycle 4 day 1 (C4D1; serum). Primary objective was to assess the immunomodulatory activity of nivolumab on serum chemokines (CXCL9, CXCL10) and tumor T cell infiltrates from BL to post treatment. Secondary/exploratory objectives included safety and tolerability, antitumor activity (ORR; RECIST 1.1), BL and treatment-induced changes in PD-1 ligand (PD-L1) expression (Dako immunohistochemistry assay; PD-L1 positivity: >5% tumor membrane staining at any intensity) and association of clinical activity with BL PD-L1 expression.

**Results:** Mean increase from BL to C4D1 was 191% for CXCL9 and 90% for CXCL10. T cell infiltrates increased by a median of 70% (CD3+; range 53–220%) and 88% (CD8+; 61–257%) from BL to C2D8. Of 56 evaluable fresh pretreatment biopsies, 18 (32%) were PD-L1+. ORR was 22% (4/18) for PD-L1+ pts vs 8% (3/38) for PD-L1−. In 5/27 (19%) matched biopsy pairs PD-L1 expression increased >5% by C2D8. For evaluable pts ORR was 16% (14/90); 16% in previously treated pts, 13% in untreated pts. Median duration of response was 15 months; 6 (43%) responses are ongoing. 14/91 (15%) pts had grade 3–4 related AEs, most commonly colitis and elevated AST (n=2 each), diarrhea and pneumonitis (n=1 each), all grade 3.

**Conclusions:** In this prospective biomarker-based study, nivolumab showed clinical activity and manageable safety in pts with previously treated and untreated mRCC. Responses were numerically higher in PD-L1+ pts but also seen in PD-L1− pts. Changes in biomarkers were consistent with PD-1 inhibition and provided evidence of immunomodulatory effects in serum and in the tumor microenvironment. Clinical trial information: NCT01358721.
**SARCOMA**

*Aldoxorubicin, CytRx (CYTR)*

Randomized phase 2b trial comparing first-line treatment with aldoxorubicin versus doxorubicin in patients with advanced soft tissue sarcomas.

Abstract #10502

Author(s): Sant P. Chawla, Zsuzsanna Papai, Kamalesh Sankhala, Leonid Vasylyev, Guzel Mukhametsina, Mamed Aliev, Kenneth Khamly, Scott Wieland, Daniel J. Levitt; Sarcoma Oncology Center, Santa Monica, CA; Oncology Department, State Health Center, Budapest, Hungary; CTRC Institute for Drug development, San Antonio, TX; Institute of Medical Radiology, Kharkiv, Ukraine; State Healthcare Institute Republican Clinical Oncological Center of the Ministry of Health of the Republic of Tatarstan, Kazan, Russia; Blokhin Cancer Research Center, Moscow, Russia; Epworth Healthcare and Clinical Trials Research Centre, Richmond, Australia; CytRx Corporation, Los Angeles, CA

**Background:** Doxorubicin (D) is the only approved first line therapy for most advanced soft tissue sarcomas (STS). Aldoxorubicin (A) consists of doxorubicin attached to an acid-sensitive linker that binds covalently to serum albumin. We compared the efficacy and safety of A to D as first line treatment for patients with advanced STS.

**Methods:** 31 site international trial; 123 patients ages 18-78 years with histologically confirmed metastatic, locally advanced or unresectable STS randomized 2:1 to receive either 350 mg/m² A (260 mg/m² D equivalents) or 75 mg/m² D, every 3 weeks for a maximum of 6 cycles. Tumor response by CT was monitored every 6 weeks until completion of treatment, 2 months post treatment, then every 3 months to progression or withdrawal from study. Primary endpoint: progression-free survival (PFS). Secondary endpoints: overall response rate (ORR), PFS at 6 months and overall survival (OS). Both a blinded, independent review and an investigator site review were performed for each scan.

**Results:** 83 patients were randomized to A and 40 to D. Groups were well-balanced for age, sex, race, performance status, and sarcoma pathology. Median (range) # of completed cycles: A = 6 (1-6); D = 4 (1-6). 30% of patients were from the U.S., 47% from Europe and 23% from Asia Pacific. Efficacy results are shown in the Table. Grade 3 or 4 adverse events that were increased in patients treated with A were neutropenia (28% vs 15%), nausea/vomiting (10% vs 0%), mucositis (12% vs 2%), fatigue (5% vs 0%) and anorexia (4% vs 0%). LVEF < 50%; A = 0, D = 9.5%. Grade 3/4 pain was increased in the D arm (2% vs 8%). Grade 3/4 febrile neutropenia (17% vs 18%), anemia (17% vs 20%) thrombocytopenia (7% vs 5%) were similar for patients receiving A or D.

**Conclusions:** Aldoxorubicin is more efficacious than doxorubicin in the treatment of advanced STS with an acceptable safety profile. Clinical trial information: NCT01514188.
### Investigator review

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<td>PFS, 6 months</td>
<td>67.1%</td>
<td>36.1%</td>
<td>0.008</td>
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<tr>
<td>ORR (%)</td>
<td>24.0</td>
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### Blinded independent review

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<td>HR (CI)</td>
<td>0.586 (0.358-0.960)</td>
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<tr>
<td>PFS, 6 months</td>
<td>46.8%</td>
<td>23.7%</td>
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<td>ORR (%)</td>
<td>23</td>
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**Avastin, Roche**

Randomized phase II trial of bevacizumab and temsirolimus in combination with vinorelbine (V) and cyclophosphamide (C) for first relapse/disease progression of rhabdomyosarcoma (RMS): A report from the Children’s Oncology Group (COG).

Abstract #10003

Author(s): Leo Mascarenhas, William H. Meyer, Elizabeth Lyden, David A. Rodeberg, Daniel Joseph Indelicato, Corrine M Linardic, James Robert Anderson, Douglas S. Hawkins, Soft Tissue Sarcoma Committee, Children's Oncology Group; Children's Hospital Los Angeles, Saban Research Institute, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; University of Oklahoma Health Sciences Center, Oklahoma City, OK; University of Nebraska College of Medicine, Omaha, NE; East Carolina University, Greenville, NC; University of Florida Proton Therapy Institute, Jacksonville, FL; Duke University Medical Center, Durham, NC; College of Public Health, University of Nebraska Medical Center, Omaha, NE; Seattle Children's Hospital, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA

**Background:** Patients with RMS have a poor prognosis at first relapse/disease progression. VC has activity in RMS and preclinical data supports the use of bevacizumab and temsirolimus in RMS.
Methods: Patients with biopsy proven RMS, < 30 years of age and unfavorable prognosis at first relapse/progression were eligible. Entry criteria were: life expectancy > 8 weeks, performance status < 2, adequate organ function and written informed consent. Patients were randomized between two regimens administered every 3 weeks for a maximum of 12 cycles: Regimen A- V 25 mg/m² intravenously (IV) days 1 & 8, C 1.2 gms/m² IV day 1, bevacizumab 15 mg/Kg IV day 1; b) Regimen B- VC identical to regimen A, temsirolimus 15 mg/m² IV days 1, 8 & 15. Primary endpoint was event free survival (EFS) at 6 months. Disease response at week 6 was assessed using RECIST. The study had a phase 2 screening design and was powered to detect a 15% difference in EFS between the two regimens (α=0.2, 1-β=0.8, 2-sided test). Interim analysis was planned when 30%, 50% and 75% of the expected events occurred.

Results: 87 of the 100 planned patients were enrolled when the trial was closed following the second interim analysis after 46 events occurred in 68 patients with sufficient follow-up. The O’Brien Flemming boundary at this analysis corresponded to a 2-sided p value of 0.0582 with an observed 2-sided p value of 0.0031 favoring the regimen with temsirolimus. The 6 month EFS for regimen A was 50% (95% CI 32%, 66%) and for regimen B was 65% (95% CI 44%, 79%). The response rate observed for regimens A and B were 32% and 47% respectively (p=0.22). The rate of progressive disease on regimen A was 26% compared with 9% on regimen B. Treatment was well tolerated. No unexpected toxicities were observed. Febrile neutropenia was the most common adverse event on both regimens. Oral mucositis and hypertriglycerideremia were noted only on regimen B.

Conclusions: Patients randomized to VC+ temsirolimus had a superior EFS compared to VC+ bevacizumab. Temsirolimus has been selected by COG for further investigation in newly diagnosed patients with intermediate risk RMS. Clinical trial information: NCT01222715.

Marqibo, Spectrum (SPPI)
Vincristine, dactinomycin, cyclophosphamide (VAC) versus VAC/V plus irinotecan (VI) for intermediate-risk rhabdomyosarcoma (IRRMS): A report from the Children’s Oncology Group Soft Tissue Sarcoma Committee.
Abstract #10004

Author(s): Douglas S. Hawkins, James Robert Anderson, Leo Mascarenhas, Geoffrey Brian McCowage, David A. Rodeberg, Suzanne L. Wolden, David Parham, Lynn Million, Sarah S. Donaldson, Andrea Anita Hayes-Jordan, Kenneth L.B. Brown, Lisa A. Teot, Sheri L. Spunt, William H. Meyer; Seattle Children’s Hospital, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA; College of Public Health, University of Nebraska Medical Center, Omaha, NE; Children’s Hospital Los Angeles, Saban Research Institute, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; Childrens Hospital at Westmead, Sydney, Australia; East Carolina University, Greenville, NC; Memorial Sloan Kettering Cancer Center, New York, NY; Children’s Hospital of Los Angeles, Los Angeles, CA; Stanford University, Palo Alto, CA; Stanford Cancer Center, Stanford, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; BC Children's Hospital, Vancouver, BC, Canada; Children’s Hospital Boston, Boston, MA; Lucile Packard Children's Hospital at Stanford, Palo Alto, CA; University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: The long-term event free survival (EFS) for IRRMS is 65%. Since VI had significant activity in metastatic and recurrent RMS, we tested whether adding VI to VAC would improve EFS for IRRMS.
Methods: Patients (pts) with alveolar (A) RMS or incompletely resected (Group III) embryonal (E) RMS arising in an unfavorable primary site (Stage 2/3), both without distant metastases, < 50 years, and adequate organ function were eligible to be randomized to 42 weeks of VAC (V=1.5 mg/m², A=0.045 mg/kg, C=1.2 g/m² every 3 weeks) vs VAC/VI (I=50 mg/m²/day x 5 days) intravenously; doses were adjusted for children < 3 years; radiation therapy (36-50.4 Gy) was started at week 4, with individualized local control for children < 2 years allowed. The primary study endpoint was EFS. The study was designed with 80% power (5% 1-sided alpha level) to detect an increase in 5 yr EFS from 65% to 76%, a relative risk of 0.64.

Results: 481 pts were entered between 12/2006-12/2012, with 461 confirmed eligible. Clinical features included ERMS 53%, ARMS 43%; age < 1 year 6%, 1-9 years 62%, 10+ years 32%; Group III 85%; Stage 3 61%. The most common primary tumor sites were parameningeal (44%), extremity (13%), and bladder/prostate (13%). With median follow up of 2.46 years in surviving pts, EFS and overall survival (OS) with 95% confidence intervals (CI) were similar overall and by histologic subtypes (Table). Grade 3/4 febrile neutropenia, anemia, and thrombocytopenia were less common with VAC/VI, particularly after the first 15 weeks of therapy, while diarrhea was more common with VAC/VI.

Conclusions: The addition of VI to VAC did not significantly improve EFS or OS compared to VAC alone for IRRMS. The lower rate of hematologic toxicity and cumulative C dose with VAC/VI (8.4 g/m² vs 16.8 g/m²) support the use of VAC/VI as the standard arm in future IRRMS trials. Clinical trial information: NCT00354835.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>2-year EFS (95% CI)</th>
<th>2-year OS (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>VAC</td>
<td>227</td>
<td>64% (56%, 70%)</td>
<td>84% (78%, 89%)</td>
</tr>
<tr>
<td>VAC/VI</td>
<td>234</td>
<td>64% (56%, 70%)</td>
<td>86% (80%, 90%)</td>
</tr>
<tr>
<td>ERMS: VAC</td>
<td>118</td>
<td>67% (56%, 76%)</td>
<td>86% (76%, 92%)</td>
</tr>
<tr>
<td>ERMS: VAC/VI</td>
<td>128</td>
<td>68% (58%, 76%)</td>
<td>89% (81%, 93%)</td>
</tr>
<tr>
<td>ARMS: VAC</td>
<td>102</td>
<td>58% (48%, 69%)</td>
<td>81% (71%, 88%)</td>
</tr>
<tr>
<td>ARMS: VAC/VI</td>
<td>95</td>
<td>57% (45%, 67%)</td>
<td>83% (72%, 90%)</td>
</tr>
</tbody>
</table>

SKIN CANCER

LDE225, Novartis (NVS)
Randomized, double-blind study of sonidegib (LDE225) in patients (pts) with locally advanced (La) or metastatic (m) basal-cell carcinoma (BCC)
Abstract #9009a^

Author(s): Michael Robert Migden, Alexander David Guminiski, Ralf Gutzmer, Luc Yves Dirix, Karl D. Lewis, Patrick Combemale, Robert Herd, Sven Gogov, Tingting Yi, Manisha Mone, Ragini Reiney Kudchadkar, Uwe Trefzer, John Lear, Daila B. Sellami, Reinhard Dummen; The University of Texas MD Anderson Cancer Center, Houston, TX; Royal North Shore Hospital, St Leonards, Australia; Medizinische Hochschule Hannover, Hannover, Germany; Sint-Augustinus Ziekenhuis, Wilrijk, Belgium; University of
Background: Pts with advanced BCC have limited treatment options. Sonidegib blocks the hedgehog pathway (overexpressed in ≥ 95% of BCCs) by selective inhibition of smoothened.

Methods: In this ph 2 study (BOLT; NCT01327053), pts with LaBCC, not amenable to curative surgery or radiation, or mBCC were randomized 1:2 to receive sonidegib 200 or 800 mg daily. The primary endpoint, objective response rate (ORR—histopathologically confirmed complete response [CR] + partial response [PR]—achieved if point estimate ≥ 30% and 95% CI lower bound > 20% [either arm]), and secondary endpoints duration of response (DoR), CR rate, time to tumor response (TTR), and PFS were assessed according to modified RECIST (mRECIST; LaBCC) or RECIST 1.1 (mBCC) by central review. Statistical comparison of arms was not planned. Safety was assessed up to ≈30 days post-last dose.

Results: Pts (194 LaBCC; 36 mBCC) were enrolled from Jul 2011-Jan 2013. The primary endpoint was met for both arms (Table; median follow-up 13.9 mo). Median exposure was 8.9 (200 mg) and 6.5 mo (800 mg). AEs were less frequent at 200 mg. AEs leading to discontinuation (200/800 mg) included muscle spasms (3.8%/8.7%), dysgeusia (2.5%/4.7%), weight decreased (2.5%/4.7%), and nausea (2.5%/4.0%).

Conclusions: Meaningful disease control with sustained DoR and prolonged PFS were achieved with both doses of sonidegib, with a more favorable benefit-risk profile for 200 mg. Clinical trial information: NCT01327053.

<table>
<thead>
<tr>
<th>Sonidegib (daily)</th>
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<th>800 mg</th>
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<td>LaBCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ORR</td>
<td>47.0</td>
<td>35.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>34.6-59.7</td>
<td>26.9-44.1</td>
</tr>
<tr>
<td>% CR</td>
<td>3.0</td>
<td>0</td>
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<tr>
<td>% PR</td>
<td>43.9</td>
<td>35.2</td>
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<tr>
<td>% Disease control rate (CR+PR+SD)</td>
<td>90.9</td>
<td>78.2</td>
</tr>
<tr>
<td>% ORR</td>
<td>42.9</td>
<td>37.6</td>
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<tr>
<td>95% CI</td>
<td>27.7-59.0</td>
<td>27.8-48.3</td>
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<tr>
<td>% ORR, a per investigator</td>
<td>65.2</td>
<td>57.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>52.4-76.5</td>
<td>48.0-65.7</td>
</tr>
</tbody>
</table>

a outcome evaluated by investigator

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Sonidegib (daily)

<table>
<thead>
<tr>
<th>TTR&lt;sup&gt;a&lt;/sup&gt;</th>
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<th>4.6</th>
<th>3.7</th>
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<td>1.8-7.4</td>
<td>2.6-3.8</td>
<td>1.0-2.1</td>
</tr>
<tr>
<td>95% CI</td>
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<tr>
<td>DoR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4/31</td>
<td>0/2</td>
<td>3/45</td>
<td>1/4</td>
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<tr>
<td>Median, mo</td>
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<tr>
<td>95% CI</td>
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<tr>
<td>PFS&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>10</td>
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<td>n&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Median, mo</td>
<td>5.6-13.1</td>
<td>NE</td>
<td>6.2-11.1</td>
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</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup> Full analysis set (intent-to-treat population)  
<sup>b</sup> Subset of pts (LaBCC w/tumor fully assessable per mRECIST [n=42, 200 mg; n=93, 800 mg] + mBCC per RECIST 1.1)  
<sup>c</sup> n=PFS events; N=responders NE, not estimable

STEM CELL TRANSPLANT

**TK, MolMed**


Abstract #7003

Author(s): Fabio Ciceri, Chiara Bonini, Arnon Nagler, Evangelia Yannaki, Maria Teresa Lupo Stanghellini, Attilio Bondanza, Giacomo Oliveira, Raffaella Greco, Eduardo Olavarria, Eva M Weissinger, Michael Stadler, Donald Bunjes, Dietger Niederwieser, Lutz Uharek, Wolfgang Bethge, John DiPersio, Michele Donato, Andrew Pecora, Antonio Lambiase, Claudio Bordignon; Hematology and BMT Unit, Department of Onco-Hematology, San Raffaele Hospital, Milan, Italy; Experimental Hematology Unit, Division of Regenerative Medicine, Stem Cells and Gene Therapy, San Raffaele Scientific Institute, Milan, Italy; Hematology Division, BMT and Cord Blood Bank, Chaim Sheba Medical Center, Tel-Hashomer, Israel; George Papanicolaou Hospital, Thessaloniki, Greece; Hematology and BMT Unit, San Raffaele Scientific Institute, Milan, Italy; Complejo Hospitalario de Navarra, Pamplona, Spain; Medizinische Hochschule, Hannover, Germany; Medizinische Klinik und Poliklinik, Ulm, Germany; University of Leipzig, Leipzig, Germany; Charité, Campus Benjamin Franklin, Berlin, Germany; Universitat Tubingen, Tubingen, Germany; Washington University School of Medicine in St. Louis, St. Louis, MO; John Theurer Cancer Center, Hackensack, NJ; MolMed, Milan, Italy.
Background: Haploidentical family donors represent the ideal solution to offer for every patient with high risk leukemia the potential cure of hematopoietic stem cell transplantation. Extensive application of haplo-HSCT is limited by high rate of late transplant related mortality (TRM) and relapse associated with the inadequate immune reconstitution (IR) due to ex vivo T cell depletion or in vivo post-transplant cyclophosphamide administration for severe graft-vs-host disease (GvHD) prevention.

Methods: In a haplo-HSCT phase III trial (TK008, NCT00914628), we infuse donor lymphocytes genetically engineered to express the suicide gene herpes simplex thymidine kinase (TK cells) to induce early IR after a T cell depleted graft. Key inclusion criteria are acute leukemia at high risk in patients lacking an HLA-matched donor. Control arms include T cell depleted or post HSCT cyclophosphamide haplo-HSCT. We enrolled 25 patients in 8 centres in Europe and US; 17 were assigned to experimental arm, 15/17 were in complete remission at HSCT. Hypothesis testing: 1-year disease free survival (DFS) 30% (control) vs 52% (TK arm).

Results: Results are presented only for patients enrolled in the experimental arm at November 2013 last follow-up. TK cells were given to 13 patients; IR was obtained in 9/13 patients after a median of 2 TK cell monthly infusions; median time from last infusion to IR (CD3+>100/µL) was 28 days (95% CI 24-41). Six pts developed GvHD (2 grade I, 2 grade II and 2 grade III) that was always abrogated by suicide gene induction; no progression from acute to chronic GvHD and no GvHD-related death occurred. IR obtained with TK cell infusion correlated with rapid development of a wide T cell repertoire and detection of high frequencies of T-cells specific for opportunistic pathogens. At a median follow-up of 473 days, by ITT analysis, 1-year overall survival is 89% (+ 10), DFS and immunosuppression-free survival is 80% (+ 10), 1-year TRM is 11% and relapse incidence is 8%.

Conclusions: Preliminary results of this ongoing phase III trial confirm safety and potential benefit in improving survival of the T-cell gene transfer technology integrated with T cell depleted haplo-HSCT. Clinical trial information: NCT00914628.
SELECT ABSTRACTS FOR BIOMARKERS AND COMPANION DIAGNOSTICS

**BRAIN CANCER**

*Delayed contrast MRI: A new paradigm in neuro-oncology.*

Abstract #2063

Author(s): Yael Mardor, David Guez, David Last, Dianne Daniels, Ouzi Nissim, Yuval Grober, Chen Hoffmann, Galia Tsarfaty, Dvora Nass, Alisa Talianksi, Sharona Salomon, Moshe Hadani, Roberto Spiegelmann, Zvi R Cohen, Leor Zach, TRAMs Authors Group; Sheba Medical Center, Ramat Gan, Israel

**Background:** Conventional MRI is unable to differentiate tumor progression from treatment-induced effects (pseudoprogression/radiation-necrosis) in brain tumor patients, thus significantly impacting patients’ management with no current solution.

**Methods:** We have applied a novel MRI-based methodology for high resolution depiction of tumor/non-tumor tissues. This unique model-independent technique is based on robust MRI sequences acquired...
with a delay, enabling complete separation between tumor (contrast clearance at the delayed time point) and treatment effects (contrast accumulation) with no overlap. 498 treatment response assessment maps were calculated for 149 patients with primary/metastatic brain tumors and 9 with AVM recruited/followed on study.

**Results:** The maps were validated by comparing pre-surgical maps of 51 patients with primary/metastatic brain tumors who underwent surgery with histology, resulting in 100% sensitivity and 94% specificity to active tumor. This validation confirms that contrast clearance in the maps represent morphologically active tumor while contrast accumulation represents non-tumor tissues. Following initial validation, the maps were used for making 231 clinical decisions. In 67 cases the decision was to continue follow-up (no treatment change) and in 164 cases to change treatment (including surgery, chemoradiation, radiation treatments, switch to Avastin, etc). Our data demonstrates the application for management of patients with various types of tumors after various treatments, for depiction of residual tumor post surgery, detection of tumor within hemorrhages and differentiating malignant transformation from treatment effects.

**Conclusions:** Our high resolution, easy to interpret, model-independent maps provide complete/clear differentiation between tumor/non-tumor tissues in patients with brain tumors. The increasing rate in which the maps are being used for clinical decisions making in Israel reflects their added value as an efficient/friendly tool for decision making in neuro-oncology. Excellent agreement between pre-surgical maps and histology suggests that the maps may be further applied for planning high precision procedures such as biopsies, resections, SRS and iMRT.

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**BREAST CANCER**

**BCI Genomic Signature, bioTheranostics, Trovagene (TROV)**

**Clinical impact of differential risk stratification by breast cancer index (BCI) versus recurrence score (RS) in HR+ early-stage breast cancer: A TransATAC study.**

Abstract #532

Author(s): Ivana Sestak, Yi Zhang, Catherine A. Schnabel, Brock Schroeder, Mark Erlander, Paul E. Goss, Jack M. Cuzick, Mitchell Dowsett, Dennis Sgroi; Queen Mary, University of London, London, United Kingdom; bioTheranostics, Inc., San Diego, CA; Trovagene, San Diego, CA; Massachusetts General Hospital Cancer Center, Boston, MA; Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, London, United Kingdom; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Massachusetts General Hospital, The Avon Foundation, Boston, MA

**Background:** BCI is a genomic signature that significantly predicts risk of both early (0-5y) and late (5-10y) distant recurrence (DR) in HR+, LN- breast cancer. Previous results from the TransATAC study showed that both BCI and Oncotype Dx RS added significant prognostic information for 10y DR risk. Here, pre-defined risk stratification with BCI vs RS and its potential clinical impact were comparatively evaluated.

**Methods:** 665 HR+, LN- patients were examined. BCI and RS risk groups were determined using pre-defined clinical cut-points. Kaplan-Meier estimates of 10y risk of DR and log-rank tests were used to
examine cross-stratification between BCI and RS. Likelihood Ratio (LR) tests were used to quantitate relative prognostic information beyond CTS.

**Results:** BCI re-stratification of the RS-Intermediate (RS-I) and RS-Low (RS-L) groups significantly impacted risk of 10y DR (P=0.003 and P<0.001), whereas RS did not significantly re-stratify BCI risk prediction (Table). BCI identified a small subset (20 pts in RS-L) with a high risk of DR (23.3%). Furthermore, BCI identified a large (95 pts in RS-I) and smaller (34 pts in RS-I) subset with 7.1% and 27.8% 10y DR risk, respectively. BCI added significant prognostic information beyond CTS+ RS (p=0.0009), whereas RS did not provide additional prognostic information beyond CTS+ BCI (p=0.1).

**Conclusions:** In this retrospective analysis evaluating individualized risk stratification, BCI identified subsets of RS-L and RS-I LN- patients with significant and clinically distinct rates of DR. BCI identified a small subset of RS-L and RS-I LN- patients that would potentially benefit from additional therapy.

### Risk Stratification and 10-year distant recurrence rates (%).

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>BCI risk groups</th>
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<th></th>
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<tbody>
<tr>
<td>RS risk groups</td>
<td>Low</td>
<td>Inter</td>
<td>High</td>
<td>Total</td>
<td>P value</td>
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<tr>
<td>Low</td>
<td>283</td>
<td>85</td>
<td>20</td>
<td>388</td>
<td>&lt;0.001</td>
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<tr>
<td>(3.9%)</td>
<td>(12.2%)</td>
<td>(23.3%)</td>
<td>(6.6%)</td>
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</tr>
<tr>
<td>Inter</td>
<td>95</td>
<td>49</td>
<td>34</td>
<td>178</td>
<td>0.003</td>
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<tr>
<td>(7.1%)</td>
<td>(24.3%)</td>
<td>(27.8%)</td>
<td>(15.8%)</td>
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<td>32</td>
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<td>99</td>
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<td>(10%)</td>
<td>(25.4%)</td>
<td>(31.5%)</td>
<td>(26.9%)</td>
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<td></td>
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</tr>
<tr>
<td>Total</td>
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<td>166</td>
<td>109</td>
<td>665</td>
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<td>(4.8%)</td>
<td>(18.3%)</td>
<td>(29.0%)</td>
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<td>0.07</td>
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</tbody>
</table>

**Herceptin, Roche**

Association of genomic analysis of immune function genes and clinical outcome in the NCCTG (Alliance) N9831 adjuvant trastuzumab trial.

Abstract #509

Author(s): Edith A. Perez, E. Aubrey Thompson, S. Keith Anderson, Yan W. Asmann, Krishna R. Kalari, Jeanette Eckel-Passow, Amylou C. Dueck, Kathleen S. Tenner, Jin Jen, Jian-Bing Fan, Xochiquetzal Geiger, Ann E. McCullough, Beiyun Chen, Michael Zschunke, Robert B. Jenkins, George W. Sledge, Eric P. Winer, Julie Gralow, Monica Madden Reinholz, Karla V. Ballman; Mayo Clinic, Jacksonville, FL; Mayo Clinic, Rochester, MN; Mayo Clinic, Scottsdale, AZ; Illumina, Inc., San Diego, CA; Stanford University, Palo Alto, CA; Dana-Farber Cancer Institute, Boston, MA; Seattle Cancer Care Alliance, Seattle, WA

**Background:** Some 20-25% of patients with HER2+ disease relapse after adjuvant trastuzumab (H). We used a genomic approach to define biological processes that predict benefit from H.
**Methods:** Whole genome DASL technology was used to identify genes associated with relapse-free survival (RFS) among 1,282 patients enrolled in the N9831 adjuvant H trial (NCT00005970). Cox proportional hazard ratios (HR), adjusted for significant clinical/pathological risk factors, were used to determine the association of each gene with RFS (median follow-up 6 years, 11 months) for 433 patients who received chemotherapy alone and 849 patients who received chemotherapy plus H. Functional ontology analysis and network modeling were used to identify key biological processes associated with RFS in patients who received chemotherapy alone or chemotherapy plus trastuzumab.

**Results:** Using probes with HR p<0.01, 10/13 significantly enriched biological processes associated with increased RFS (p<0.01) were linked to immune functions. These 10 processes defined a cohort of 87 immune function genes. Patients defined as immune function positive based on the 87 genes experienced a favorable outcome when treated with H (HR=0.55, p=0.0005). Patients who did not exhibit immune function enrichment and were treated with H did not have better RFS than patients with immune function enrichment who were treated with chemotherapy alone (HR=0.93, p=0.72). Among patients who received chemotherapy alone, enriched immune function was not associated with increased RFS (HR=1.01, p=0.96).

**Conclusions:** Improved RFS following treatment with adjuvant H appears to be associated with a heightened state of immunological function. This observation may define a significant biological process that is linked to the efficacy of HER2-targeted therapy, may provide a means of predicting probability of relapse following adjuvant trastuzumab, and suggests possible routes of therapeutic enhancement.

**Clinical and pathologic correlation of the activated form of the estrogen receptor beta (ERβ) in breast cancer (BC).**

**Abstract #3046**

Author(s): Emilie Hutt, Jacques Bosq, Erard M. Gilles, Alexander Zukiwski, Charline Alleaume, Barthelemy Octavius Gilles, Jacques Bonnetterre; Centre Oscar Lambret, Lille, France; Gustave Roussy Institute, Villejuif, France; Invivis Pharmaceuticals, Bridgewater, NJ; Arno Therapeutics, Flemington, NJ; Biodoxis, Romainville, France; Centre Oscar Lambret, Université Lille Nord de France, Lille, France

**Background:** ERβ is antagonized by anti-estrogens and has been associated with a better prognosis although its role is unclear. Experimentally, ERβ has a nuclear biology common to the steroid nuclear receptors. In the absence of estrogenic ligand, it is evenly distributed in nuclei; when exposed to ligand, ERβ migrates to form sub-nuclear aggregates that can be detected by immunofluorescence microscopy. Thus, two distinct nuclear patterns, diffuse (D) or aggregated (A) are observed which correspond to the receptors’ functional states. Similarly to previous work on ERα and PR (ASCO 2013 abstr. # e11535 & 593), an immunohistochemistry (IHC) method has been developed to characterize the nuclear distribution patterns which may indicate whether ERβ is transcriptionally active or not in PEFF tissues. The goal of the study is to analyze whether activated ERβ is associated with anti-estrogen treatment outcome.

**Methods:** 662 archived BC biopsies have been obtained along with clinical and pathological data. Biopsies were analyzed for standard HES, ERα, ERβ, PR and Ki67. ERβ positivity was determined with the 14C8 antibody (Abcam) and the nuclear distribution pattern analyzed at x1000 magnification.
Results: 392 cases have been analyzed to date. Mean Age: 57 (17-89). Median follow up 36 months (mo). Histology: ductal 82% lobular 15% other 3%; ERα\textsuperscript{pos} 78% PR\textsuperscript{pos} 78%. Adjuvant chemotherapy 46%, Hormone therapy 85%. Stage I 44%, II 48%, III 8%. Grade I 25%, II 50%, III 25%. ERβ was positive in 57% of the cases (ERβ\textsuperscript{pos}). ERβ was activated (A- ERβ) in 35% of the ERβ\textsuperscript{pos} biopsies, and non-activated (D-ERβ) in 65% ERβ\textsuperscript{pos}. A-ERβ was associated with higher grade (p < 0.000, p = 0.007); ERβ, PR, HER2, Ki67, staging were not associated with ERβ\textsuperscript{pos} nor A-ERβ. Local or distant Progressive disease (PD) was evident in 19% of cases and was not associated with ERβ\textsuperscript{pos} or A-ERβ (p=0.87). With DFS defined as time to PD or death (5 year cut-off), neither ERβ\textsuperscript{pos} nor A-ERβ were associated with a better DFS (HR: 1.02 and 0.98).

Conclusions: In contrast to ERα, preliminary results show that ERβ positivity and ERβ activation status were associated with higher pathological grade but not with other pathological or clinical variables.

Entinostat, Syndax
Phase 2 study investigating the safety, efficacy, and surrogate biomarkers of response to 5-azacitidine (5-AZA) and entinostat in advanced breast cancer.
Abstract #569

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Background: In breast cancer models, combination epigenetic therapy with a DNA methyltransferase inhibitor and a histone deacetylase inhibitor led to re-expression of genes encoding important therapeutic targets including the estrogen receptor. We conducted a multicenter phase II study of 5-AZA and entinostat in women with advanced breast cancer.

Methods: Women with advanced HER2-negative (triple-negative [TNBC] or hormone-resistant [HR]) breast cancer received 5-AZA 40 mg/m\textsuperscript{2} (SQ, ds 1-5, 8-10) and entinostat 7 mg (PO, ds 3,10) q28 ds. Primary endpoint: Objective response rate (ORR) in each cohort. Secondary endpoints: PFS, OS, safety. We obtained mandatory baseline and wk 8 tumor biopsies for gene methylation/expression, and blood samples for pharmacokinetics and pharmacogenetics. At progression, patients were offered optional continuation (OC) with the addition of endocrine therapy. We hypothesized that ORR would be >20% against null of 5% using Simon two-stage design. At least 1 response was required in 1\textsuperscript{st} of 13 patients per cohort to continue accrual to 27 per cohort. Type I error 4%, power 90%.

Results: TNBC data were presented at AACR 2013. From 08/2011-09/2013, 27 women enrolled in the HR cohort. Median age 55 ys (33-70), median prior endocrine and chemotherapies 3 each. Median cycles received 2 (1-16). Twelve women continued in OC phase and received median 2.5 additional cycles (range 1-9). We observed 1 partial response with epigenetic therapy alone (ORR 4%, 95% CI, 0-19%) and 1 in OC. At median follow up 6.3 ms, median PFS was 1.8 ms (95% CI, 1.7-1.9), and median OS 11.5 ms.
(95% CI, 5.5-16.3). In OC phase, median PFS was 1.9 ms (95% CI, 1.7-3.7) and median OS 15.6 ms (95% CI, 5.5-NA) vs PFS 1.8 ms (95% CI, 0.8-1.9) and OS 9.2 ms (95% CI, 2.3-16.3) for event monitoring. Therapy was well tolerated with few grade 3/4 events. We obtained 95% baseline core biopsies, and 58% matched samples. Correlative analyses will be presented.

**Conclusions:** Combination epigenetic therapy was well tolerated but our primary endpoint was not met. OC results suggest that some women benefit from epigenetic therapy and/or reintroduction of endocrine therapy beyond progression. Clinical trial information: NCT01349959.

**Oncotype DX, Genomic Health (GHDX)**

**Oncotype DX and proliferation response to short-term preoperative endocrine therapy for chemotherapy decision in early breast cancer: Biomarker data from the prospective multicenter phase II/III WSG-ADAPT trial.**

Abstract #524

Author(s): Oleg Gluz, Ulrike Nitz, Ronald Kates, Daniel Hofmann, Sherko Kümmel, Benno Nuding, Claudia Schumacher, Bahriye Aktas, Helmut Forstbauer, Nicolai Maass, Michael Wilhelm Braun, Mahdi Rezai, Manfred Kutsche, Albert von der Assen, Steven Shak, Christer Svedman, Rachel Wuerstlein, Nadia Harbeck, Hans Heinrich Kreipe, Matthias Christgen; West German Study Group; Evangelic Hospital Bethesda, Moenchengladbach, Germany; West German Study Group, Moenchengladbach, Germany; Kliniken Essen Mitte, Ev. Huysss Stiftung/Knappschaft, Essen, Germany; Ev. Hospital, Bergisch Gladbach, Germany; St. Elisabeth Hospital, Köln, Germany; Department of Gynecology and Obstetrics, University of Duisburg-Essen, Essen, Germany; Onkologie Troisdorf, Troisdorf, Germany; University of Aachen, Aachen, Germany; Rot-Kreuz-Klinikum München, Munich, Germany; Breast Center Duesseldorf, Louisen Hospital, Düsseldorf, Germany; Marienhospital Aachen, Women Clinics for Senology – Breast Center, Aachen, Germany; Niels-Stensen-Clinics - Franziskus-Hospital Harderberg, Georgsmarienhutte, Germany; Genomic Health, Inc., Redwood City, CA; University of Munich, Munich, Germany; Breast Center, University of Munich, Munich, Germany; Hannover Medical School, Hannover, Germany

**Background:** WSG-ADAPT aims to optimize early breast cancer therapy within a genomically classified (by OncotypeDX) intermediate-risk group using individual endocrine sensitivity.

**Methods:** WSG-ADAPT HR+/HER2- analyzes biomarker changes after 3 weeks of preoperative ET [aromatase inhibitors (AI) in postmenopausal, tamoxifen (Tam) in premenopausal women]. Overall, n=1760 patients (HR+/HER2-, pN0-1) with Recurrence Score (RS) 0-11 or RS 12-25 and post-Tx Ki-67<10% are treated by ET alone. Other RS 12-25 and all RS ≥26 patients are included in phase III CTx design (n=2200).

**Results:** 1118 patients from 61 centers have been enrolled (01/2014); run-in phase analysis included 383 patients (median age 54 years, 175 Tam, 208 AI). RS distribution (≤11/12-25/≥26) was 23%/57%/20%; median relative Ki-67 decreases were 0.67/0.60/0.40 by RS groups (p=0.017). Median relative Ki-67 decrease was more pronounced in post- vs. premenopausal patients (75% vs. 38%; p<0.001). Mean PR (not ER) expression changes were also more pronounced in postmenopausal patients (-39.5% -10.4%-units; p<0.001). Pre- and post-endocrine RS (n=187) are moderately correlated (rS = .70, p<.001); no significant RS change was seen (95% CI: -1.7 to 0.3). Absolute change in Ki-67 by IHC was correlated with change in RS proliferation (rS = .62, 95% CI: 0.52 to 0.7). Median ER expression by RT-PCR was higher.
Conclusions: Postmenopausal patients (mostly AI) and those with lower baseline RS showed stronger proliferation response to short preoperative endocrine therapy. The difference in outcome between early proliferation responders (>70%) treated with ET alone among pN0/N1 patients with RS 12-25 and those with RS<11 will be tested in the WSG-ADAPT HR+/HER2- main phase. Clinical trial information: NCT01779206.

Oncotype DX, Genomic Health (GHDX)
Prosigna, Nanostring (NSTG)
A pilot laboratory study comparing the 21-gene assay and PAM50-ROR.
Abstract #11003

Author(s): Oleg Gluz, Ulrike Nitz, Ronald Kates, Daniel Hofmann, Sherko Kümmel, Benno Nuding, Claudia Schumacher, Bahriye Aktas, Helmut Forstbauer, Nicolai Maass, Michael Wilhelm Braun, Mahdi Rezai, Manfred Kutsche, Albert von der Assen, Steven Shak, Christer Svedman, Rachel Wuerstlein, Nadia Harbeck, Hans Heinrich Kreipe, Matthias Christgen; West German Study Group; Evangelic Hospital Bethesda, Moenchengladbach, Germany; West German Study Group, Moenchengladbach, Germany; Kliniken Essen Mitte, Evang. Huysens Stiftung/Knappschaft, Essen, Germany; Ev. Hospital, Bergisch Gladbach, Germany; St. Elisabeth Hospital, Köln, Germany; Department of Gynecology and Obstetrics, University of Duisburg-Essen, Essen, Germany; Onkologie Troisdorf, Troisdorf, Germany; University of Aachen, Aachen, Germany; Rot-Kreuz-Klinikum München, Munich, Germany; Breast Center Duesseldorf, Louisen Hospital, Düsseldorf, Germany; Marienhospital Aachen, Women Clinics for Senology – Breast Center, Aachen, Germany; Niels-Stensen-Clinics - Franziskus-Hospital Harderberg, Georgsmarienhutte, Germany; Genomic Health, Inc., Redwood City, CA; University of Munich, Munich, Germany; Breast Center, University of Munich, Munich, Germany; Hannover Medical School, Hannover, Germany

Background: The Oncotype DX 21-gene Recurrence Score assay was developed in endocrine-treated patients (pts) and validated as a predictor of 10-yr distant recurrence risk and chemotherapy benefit in ER+ early-stage invasive breast cancer. The Prosigna assay (ROR) which uses 46 of the PAM50 genes, was validated on centrally processed samples as a prognostic assay only in endocrine treated, post-menopausal pts. To date no direct comparison data on paired samples from the same patients for these two assays has been reported and yet it’s frequently believed that these assays are interchangeable. We performed a pilot study comparing test results from the two assays obtained from the same tumor blocks.

Methods: Sequential breast cancer tumors from Marin Medical Laboratories with sufficient tumor material were tested with the standard 21-gene Recurrence Score assay. 40 cases stratified by the Recurrence Score (20 low, 10 intermediate and 10 high) were sent to an independent laboratory where the Prosigna assay for ROR and intrinsic subtype was performed with the operators blinded to the Recurrence Score results. Descriptive statistics were calculated for the results obtained from the two assays.
Results: Of the 40 pts, 3 were excluded due to low RNA signal in the Prosigna assay and 4 were ER(-) by RT-PCR. Of the 33 remaining cases, 24 were ductal, 7 lobular and 2 other; 27 were N- and 6 were N+. The Spearman rank correlation between Recurrence Score and ROR was 0.40 (95% CI 0.06 – 0.65). Risk group assignment (low/intermediate/high) between Recurrence Score and ROR was in agreement in 56% (15/27) of N(-) pts. Prosigna classified 19 as luminal A, 12 as luminal B, 2 as HER2 enriched and 0 as basal. In both the luminal A and B groups there was a wide range of Recurrence Score results.

Conclusions: Consistent with other comparisons between expression-based assays, it should not be assumed that these assays are interchangeable. While additional data from a larger independent analysis is needed, this pilot suggests that there is only a modest agreement between the Recurrence Score and ROR, with almost half of N(-), ER+ pts classified differently.

Prevalence of mutations in a panel of breast cancer susceptibility genes in patients with early onset breast cancer.
Abstract #1510

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Background: Approximately 5-10% of breast cancers are attributable to inherited single gene mutations. Clinical testing for germline variation in multiple cancer susceptibility genes is available using massively parallel sequencing. However, data is needed on the spectrum of mutations and variants of uncertain significance (VUSs) in defined patient populations.

Methods: We performed massively parallel sequencing using targeted capture of 19 cancer susceptibility genes in 277 BRCA1/2 negative patients with early onset breast cancer (EOBC).

Results: Excluding synonymous variants, 60% of patients were identified to have at least one rare variant. Twenty-eight patients (10%) were found to have a pathogenic mutation (Class 5 variant) or likely deleterious VUS (Class 4). Seven of these patients (2.5% overall) were found to have Class 4/5 variants in genes for which clinical guidelines exist for management, namely TP53 (4), CDKN2A (1) and MSH2 (2). Twenty-one patients (7.6%) had Class 4/5 variants in a moderate penetrance cancer susceptibility gene for which clinical guidelines are lacking. Four patients (1.4%) were heterozygous carriers of a pathogenic MUTYH mutation. In addition, 49 patients (18%) were found to carry a Class 3 VUS in a high penetrance or moderate penetrance gene.

Conclusions: These data show that massively parallel sequencing identifies reportable (Class 3, 4 or 5) variants in known cancer susceptibility genes in 30% of patients with early onset breast cancer. However, only rare patients (2.5%) have definitively actionable mutations given current clinical management guidelines. Large-scale cooperative group studies are therefore needed to determine the clinical utility of multiplex panel testing in patients with early onset breast cancer.
CANCER

**BRAF V600E Mutation Test, Trovagene (TROV)**  
Longitudinal monitoring of *BRAF* V600E mutation in urinary cell-free DNA of patients with metastatic cancers.  
Abstract #e22175

Author(s): Filip Janku, Cecile Rose T. Vibat, Gerald Steven Falchook, Sarina Anne Piha-Paul, Aung Naing, Vivek Subbiah, Veronica R. Holley, Jennifer J. Wheler, Funda Meric-Bernstam, Goran Cabrilo, Vanda M. T. Stepanek, Rajyalakshmi Luthra, Lorieta Leppin, Latifa Hassaine, Karena Kosco, Mark Erlander; Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas MD Anderson Cancer Center, Houston, TX; Trovagene, San Diego, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Investigational Cancer Therapeutics( Phase 1 program), The University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson, Houston, TX; Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Detection and monitoring of oncogenic mutations in urinary cell-free (cf) DNA opens the possibility of a new paradigm for a truly non-invasive method of individualized care for metastatic cancer patients, which would enable the quantitation of mutational tumor load and respective concordance to therapeutic responsiveness followed by detection of emerging genomic alterations underlying acquired resistance.

**Methods:** Multiple sequential urine samples were collected >/= 4 weeks apart from patients with advanced cancers harboring *BRAF* V600E mutation in the tumor tissue from a CLIA-certified laboratory before and after they started on systemic therapy. Quantitative assessment of *BRAF* V600E mutation in urinary cfDNA was developed using droplet digital PCR methodology (RainDance, MA) with enrichment of mutation-containing DNA fragments by pre-amplification of the *BRAF* gene. Detection limits were established as wild-type (<0.05% of mutant copies), low-mutant (0.05%-0.107%), mutant (>0.107%).

**Results:** Urinary cfDNA was extracted from 17 patients with advanced cancers (melanoma, n=7; non-small cell lung cancer, n=3; colorectal cancer, n=2; other, n=5) with *BRAF* V600E mutation in the tumor. Of these 17 patients, 15 (88%) had the same mutation in urinary cfDNA (mutant, n=11; low-mutant, n=4). Longitudinal analysis of sequentially (>/= 4 weeks) collected urine samples demonstrated that changes in the amount of *BRAF* V600E cfDNA correlated with response to BRAF/MEK targeted therapy defined as percentage change per RECIST 1.1 (r=0.69, p=0.002). In addition, patients with decrease in the amount of *BRAF* V600E cfDNA had longer median time-to-treatment failure (259 days, 95% CI 240-278 vs. 61 days, 95% CI 59-63; p=0.002).

**Conclusions:** Our data suggest that detecting *BRAF* V600E mutation in cell-free DNA from urine can offer a noninvasive tool for monitoring of therapeutic efficacy in patients with cancers and *BRAF* V600E mutation treated with BRAF/MEK targeted therapy.
**BRAF V600E Mutation Test, Trovagene (TROV)**

Detection of *BRAF* mutations in urine and plasma cell-free DNA: Application to the diagnosis and management of histiocytic disorder patients.

Abstract #11012

Author(s): Omar Ibrahim Abdel-Wahab, Eli L. Diamond, Minal Patel, Veronica R. Holley, Goran Cabrilo, Raajit Rampal, Latifa Hassaine, Karena Kosco, Jose Baselga, Razelle Kurzrock, Jason Poole, Cecile Rose T. Vibat, Mark Erlander, Filip Janku, David Michael Hyman; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson, Houston, TX; Trovagene, San Diego, CA; University of California, San Diego, San Diego, CA

**Background:** Histiocytosis patients (pts) have a high frequency of *BRAF* V600E mutations and respond to RAF inhibition but low tumor content and stromal contamination make detection in tissue biopsies challenging. Quantitative assessment of *BRAF*V600E mutations in tumor derived cell-free (cf) DNA may provide a convenient and reliable means of detecting this established biomarker and monitoring response to RAF targeted therapy. Here we compare the results of urine and plasma cfDNA *BRAF*V600E testing to tissue biopsy mutation testing in a large series of histiocytosis pts.

**Methods:** Quantification of *BRAF*V600E was performed in cfDNA using droplet digital (dd) PCR (Trovagene, San Diego, CA). *BRAF*V600E analysis in tumor tissue was conducted using a variety of highly sensitive methodologies including locked nucleic acid and next-generation sequencing in CLIA-certified labs. Concordance between mutational analysis in tissue, plasma, and urine was determined.

**Results:** 22 histiocytosis pts underwent cfDNA mutational analysis (18 Erdheim Chester Disease, 4 Langerhans Cell Histiocytosis). 20 pts also had CLIA-certified *BRAF*V600E mutational analysis in tissue (10 mutant, 6 wildtype, 4 test failure). All 10 *BRAF*-mutant pts based on tissue testing had a concordant positive cfDNA result in urine. Similarly, all 6 *BRAF*-wildtype pts based on tissue testing had a concordant negative cfDNA result in urine. 95% CI for concordance was 79-100%. Urine cfDNA was positive in 2 additional pts where tissue testing was unsuccessful. Plasma cfDNA testing did not identify *BRAF*V600E mutant pts who were not also positive by urine testing.

**Conclusions:** Detection of actionable *BRAF* mutations by ddPCR in cfDNA is feasible and was completely concordant with CLIA-certified tumor mutation testing. Moreover, the ability to detect *BRAF* mutations in the urine of pts with repeated tumor tissue testing failure is potentially practice changing and demonstrates the clinical utility of cfDNA technologies. Mutations in cfDNA should be further investigated for longitudinal assessment of RAF-targeted therapy in pts with histiocytoses.

**The EXACT trial: An individualized treatment protocol for solid tumors.**

Abstract #e14002

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**Background:** Currently approved novel targeted agents in the treatment of cancer are limited for certain subtypes of cancer and do not consider an individually expressed druggable target or an activated signaling pathway. To improve existing therapeutic strategies, there is increasing evidence of benefit by extension of treatment protocols focusing at molecular profile-based treatment decisions. To generate a scientific rationale for an individualized treatment approach, the current protocol was designed. We aim to prospectively validate treatment benefit of an individualized treatment concept based on molecular profiling from paraffin-embedded tumor tissue sections obtained by real time biopsy.

**Methods:** Patients with refractory metastatic cancer without any standard treatment options according to NCCN guidelines and/or ESMO guidelines are eligible for inclusion. Potential therapeutic targets in individual patients’ tumor sections are evaluated via a fully informative genomic tumor profile that analyses DNA via ultrahigh multiplex PCR. Suggested treatment benefit are evaluated to reject the null hypothesis, which is defined as follows: ≤ 40 % of this patient population have a progression free survival (PFS) ratio of ≥ 1.0. Thus, the individual patient serves as his own control for outcome parameters. The alternative proportion P1 (PFS ratio > 1.0) is set at least to 55% using a one-sided exact binomial test at a significance level of 0.0250. The null hypothesis, i.e. no benefit by using this strategy, can be rejected, if at least 30 out of 55 patients treated show a PFS ratio > 1.0. A potential correlation between overall response rate, PFS or overall survival will be assessed by RECIST criteria and evaluated as secondary end points. 10/55 patients have been included so far, allowing a first interim analysis.

**Results:** We aim to prospectively validate treatment benefit of an individualized treatment concept based on molecular profiling from paraffin-embedded tumor tissue sections obtained by real time biopsy.

**Conclusions:** This prospective translational study evaluates an individualized treatment concept based on prospective biomarkers assessed in a real-time biopsy for patients with treatment-refractory cancer.

**INCB24360, Incyte (INCY)**

Development of an IHC-based detection method for studying indoleamine 2,3-dioxygenase 1 (IDO1) expression in human cancers.

Abstract #3043

Author(s): Alton Hiscox, Heather Gustafson, Joseph Couto, Zhiming Liao, Yifei Zhu, Xiangdong Liu, Robert Charles Newton, James Hnatyszyn; Ventana Medical Systems, Tucson, AZ; Spring Biosciences, Pleasanton, CA; Incyte Corporation, Wilmington, DE

**Background:** Indoleamine 2,3-dioxygenase-1 (IDO1) mediates oxidative cleavage of tryptophan, an amino acid essential for cell proliferation and survival. The depletion of tryptophan and the generation of tryptophan metabolites have been shown to suppress immune functions via several cellular mechanisms, allowing tumor escape from host immune surveillance. IDO1 is induced by interferons and TLR agonists and is expressed in a variety of human cancers as well as the invading immune infiltrate and the tumor-draining lymph nodes. High IDO1 expression is significantly associated with more rapid disease progression and poor prognosis in multiple cancer types. Thus, inhibition of IDO1 activity may have therapeutic potential in cancer and furthermore, IDO1 expression could serve as a biomarker for selecting patients that are responsive to an IDO1 inhibitor-based treatment regimen.
Methods: We generated and selected an anti-human IDO1 rabbit monoclonal antibody. The specificity of the antibody for IDO1 was confirmed using Western blot analyses of lysates from cells expressing human IDO1, IDO2, or TDO.

Results: INCB024360, a novel IDO1-selective inhibitor, is currently being evaluated in clinical trials of cancer patients. To support the clinical development of INCB024360, we developed an immunohistochemistry (IHC)-based method for the detection of IDO1 protein in human tissues. To further evaluate the specificity and reactivity of the antibody against IDO1 in human tissues, an IHC staining protocol was established, standardized and used to stain various human normal and tumor tissues, as well as IDO1-expressing cells. We have examined IDO1 expression in several human tumors including lung, ovarian, melanoma, gastric, and pancreatic cancers.

Conclusions: In summary, we have developed and standardized an IHC-based method for the specific detection of IDO1 protein in human tissues. The method will be useful to determine the prevalence of IDO1 expression in a variety of human cancers. Furthermore, incorporating this detection method into ongoing clinical trials may identify patients that are likely responsive to IDO1 inhibitor-based treatment regimens.

CANCER GENETICS

Myriad Genetic (MYGN)
A study of ovarian cancer patients tested with a 25-gene panel of hereditary cancer genes.
Abstract #1510

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Background: With advances in next-generation sequencing, patients receiving hereditary cancer testing can be tested for more genes, more efficiently. Patients with ovarian cancer are at risk for several different hereditary cancer syndromes—Hereditary Breast and Ovarian Cancer (HBOC) and Lynch syndrome (LS) in particular.

Methods: We queried a laboratory database for patients affected with ovarian cancer and tested with a 25-gene hereditary cancer panel from September 4, 2013 through December 27, 2013. All patient data regarding clinical history was obtained by health care provider report on test requisition forms.

Results: We identified 263 patients with a personal history of ovarian cancer who received genetic testing using a 25-gene hereditary cancer panel. Of these patients, 77.2% met NCCN guidelines for HBOC, 0.8% met for NCCN guidelines for LS and 22.1% met guidelines for both syndromes. Deleterious or suspected deleterious mutations were identified in at least one gene in 16.3% of ovarian cancer patients. These included mutations in BRCA1 or BRCA2 (11%) and ATM (3.4%). Positive mutations were also identified in APC (3 patients), BRIP1 (2 patients), and 1 patient each in RAD51C, MSH6, CHEK2, and NBN. We detected 137 variants of uncertain significance (VUS) in 263 patients with a range of 0 to 4 VUS identified per patient. No VUS were detected in the majority (61.6%) of patients.
Conclusions: Testing patients using a 25-gene hereditary cancer panel increased the number of positive test results in ovarian cancer patients by 48% over BRCA1 and BRCA2 testing alone, showing the benefit of using a panel approach in this population.

CARCINOMA OF AN UNKNOWN PRIMARY (CUP)

CancerTYPE, Biomeriuex
GEFCAPI 04: A phase III trial comparing a treatment oriented by a molecular analysis with CancerTYPE ID test to cisplatin-gemcitabine in patients with carcinoma of an unknown primary (CUP).
Abstract #TPS11134

Author(s): Geraldine Martineau, Agnes Laplanche, Agnes W Van de Wouw, Gedske Daugaard, Carmen Balana, Nicolas Penel, Loic Chaigneau, Djelila Allouache, Bruno Chauffert, Stephane Cunie, Marine Gross-Goupil, Yacine Merrouche, Cristian Moldovan, Elodie Vauleon, Isabelle Borget, Fanny Wunder, Catherine A. Schnabel, Karim Fizazi; Clinical Research Department, Institut Gustave Roussy, Villejuif, France; Institut Gustave Roussy, Villejuif, France; Vieucri Medical Centre, Venlo, Netherlands; Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; Catalan Institute of Oncology Hospital Germans Trias i Pujol, Barcelona, Spain; Centre Oscar Lambret, Lille, France; Department of Medical Oncology, Besançon University Hospital, Besançon, France; Centre François Baconnes, Caen, France; University Hospital (CHU), Amiens, France; Department of Medical Oncology - Hospital Saint-Louis - APHP, Paris, France; Centre Hospitalo-Universitaire Saint André, Bordeaux, France; Inst De Cancerologie De La Loire, St Priest en Jarez, France; Centre Henri Becquerel, Rouen, France; Eugène Marquis Cancer Institute, Rennes, France; Clinical Research Department, Institut Gustave Roussy, Villejuif, France; bioTheranostics, Inc., San Diego, CA; Department of Cancer Medicine, Gustave Roussy, University of Paris Sud, Cancer Campus, Grand Paris, Villejuif, France

Background: Despite advances in tumor imaging and pathology, patients with CUP still account for about 2-3% of all cancer patients in European registries. Two randomized phase II trials: GEFCAPI01 (Culine, J Clin Oncol 2003) and GEFCAPI02 (Gross-Goupil, Eur J Cancer 2012) demonstrated that the combination of cisplatin and gemcitabine has anticancer activity and can be regarded as an acceptable comparator for new treatments. Recently, several groups have shown that molecular analysis can identify a likely primary cancer in up to 80% of patients with CUPs. This trial aims to assess whether the use of a molecular test-oriented systemic treatment improves progression-free survival (PFS) over cisplatin-gemcitabine in patients with CUPs.

Methods: GEFCAPI04 is a European randomized, phase III study comparing a diagnostic and therapeutic strategy based on molecular analysis followed by suspected primary cancer tailored specific therapy, to an empiric strategy by cisplatin and gemcitabine (NCT01540058). It was initiated in March 2012. Eligibility criteria include: patients presenting with CUP, confirmed by histo-pathological analysis, diagnostic work-up in keeping with guidelines (Lesimple et al., 2003), good or poor prognosis CUP, CUP not belonging to a subgroup requiring a specific treatment, no previous chemotherapy. Patients are stratified by prognostic factors (performance status and serum LDH level) and center. 223 patients will be randomized 1:1 to cisplatin-gemcitabine (A) or treatment according to the result of the molecular analysis (B). The primary endpoint is PFS based on central independent review. Imaging will be undertaken every 6 weeks, in each arm. A 0.05 level two-sided log-rank test for equality of PFS curves will have 80% power to detect a 3 months difference between PFS medians (5 months in group A and 8
months in Group B, (HR=0.62). Secondary endpoints include: overall survival, objective response rate, tolerance, and economic evaluation. The study is recruiting patients and 30 patients are included. Clinical trial information: NCT01540058.

COLORECTAL CANCER

A phase 1 mechanism of action study of intratumoral or intravenous administration of enadenotucirev, an oncolytic Ad11/Ad3 chimeric group B adenovirus in colon cancer patients undergoing resection of primary tumor.

Abstract #TPS3112

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Background: To date convincing clinical success with oncolytic viruses tends to be associated with intratumoral (IT) administration and evidence for successful systemic delivery of viruses to tumor cells by intravenous (IV) infusion remains sparse. Enadenotucirev (E or ColoAd1) is a tumor selective Ad11/Ad3 group B adenovirus that has demonstrated preclinical activity in a metastatic model of colorectal cancer (CRC) and in human tumor biopsies ex-vivo [Kuhn et al, PLoS ONE 2008; 3 (6):e2409]. Serological studies suggest that the prevalence of neutralising antibodies against group B adenoviruses is low, which may permit systemic delivery [Holterman et al, J Virol. 2004 Dec; 78(23):13207-15]. CRC patients (Pts) scheduled for resection of primary tumor present a pre-surgical window of opportunity to evaluate IV and IT delivery to tumor, lymph nodes and normal margins in resected tissues.

Methods: Pts with histologically confirmed CRC scheduled for surgical removal of primary tumor receive E delivered either IV on day (D) 1, 3 and 5 at a dose of 1e12 viral particles (vp) over 5 min (5 pts); or IT at a dose of 1e11 vp/mL with a variable volume injected based on the tumor surface area (5 pts). Surgery is performed 7 – 15 days post first dose of E. The primary objective is to assess the pattern and extent of E spread in the tumor, normal tissue and draining lymph nodes as visualised by IHC staining of E hexon protein. Evidence of immune modulation associated with virus activity is assessed by co-staining for markers including CD8, CD11b, CD57 and CD25. Additional staining includes the primary uptake receptors of E (CD46, DSG-2) and markers of endothelial cells (CD31) and myofibroablasts (SMA) that may influence viral delivery or spread. Additional analyses include electron microscopy and qPCR. Other objectives are assessment of safety, viral kinetics and immune response following IV and IT administration. Correlation with routine tumor biomarkers e.g. K-ras, BRAF, PI3K, PTEN, SPARC will also
be evaluated. To date 3 pts have been treated, 1 IT and 2 IV, and 3 pts are scheduled for treatment. Clinical trial information: EUDRACT 2013-000562-11.

**Efficiency of biomarker screening for enriched metastatic colorectal cancer trials: The ATTACC program experience.**

Abstract #3619

Author(s): Van Karlyle Morris, Michael J. Overman, Bryan K. Kee, David R. Fogelman, Cathy Eng, Arvind Dasari, Rachna T. Shroff, Laurel Deaton, Shanequa Manuel, Chris R. Garrett, Eduardo Vilar Sanchez, Constance S. Dennis, Imad Shureiqi, Gordon B. Mills, Kenna Rael Shaw, Stanley R. Hamilton, Robert A. Wolff, Funda Meric-Bernstam, Dipen M. Maru, Scott Kopetz; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX; Department of Investigational Cancer Therapeutics (Phase 1 program), The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Incorporation of multiple enrichment biomarkers into prospective clinical trials for metastatic colorectal cancer (mCRC) has been proposed or initiated by NSABP, EORTC, NCI Colon Task Force, and UK MRC. The feasibility of large scale screening efforts in mCRC has not been previously assessed.

**Methods:** Patients (pts) with 5-FU refractory mCRC at MD Anderson Cancer Center were offered screening in the Assessment of Targeted Therapies Against Colorectal Cancer (ATTACC) program to identify eligibility for companion phase I or II clinical trials with a therapy targeted to an aberration detected in the patient, based on FFPE testing by immunohistochemistry (IHC), 50-gene sequencing, and CpG island methylation phenotype (CIMP) assays. Ten unstained slides were required.

**Results:** Between 8/2010 and 1/2014, 506 pts were enrolled. Median time from consent to results was 28 days (interquartile range 22-37 days). Outside tissue was obtained after a median of 6 days (4-10 days). IHC, sequencing, and CIMP results required a median of 10, 13, and 20 days, respectively (Table), with 95% yield. During this 40 month period, between 20 and 40% of pts were eligible on the basis of screened tumor biomarkers for at least one of the 18 companion studies. Given trial-specific eligibility, study logistics, and intermittent study openings, only 14% of pts enrolled on an enriched companion trial, representing an approximate 50% efficiency of enrolling eligible patients. 66% received alternate treatments off protocol, 16% enrolled on unenriched studies, and 4% received no further therapy due to a declining performance status.

**Conclusions:** Even though dedicated screening infrastructures such as ATTACC represent an efficient strategy for enrichment studies, a majority of patients did not ultimately participate on a companion trial due to dropout of biomarker-eligible patients and a cumulative lack of trials targeting a majority of screened patients. Both of these hurdles need to be addressed to improve success of this strategy.

<table>
<thead>
<tr>
<th>Molecular aberration tested</th>
<th>Aberration present</th>
<th>Inadequate specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS mut</td>
<td>51%</td>
<td>0.9%</td>
</tr>
<tr>
<td>BRAF mut</td>
<td>8.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>PIK3CA mut</td>
<td>19%</td>
<td>1.3%</td>
</tr>
<tr>
<td>NRAS mut</td>
<td>6.6%</td>
<td>2.2%</td>
</tr>
<tr>
<td>CIMP high</td>
<td>37%</td>
<td>4.0%</td>
</tr>
<tr>
<td>PTEN loss</td>
<td>12%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
Next-generation sequencing (NGS) in metastatic colorectal cancer (CRC) patients (pts) in Israel.
Abstract #e14548

Author(s): Ayala Hubert, Ravit Geva, Amiel Segal, Baruch Brenner, Ronen M. Brenner, Sharon Pelles-Avraham, Alexander Beny, David Sarid, Shoshana P. Keren-Rosenberg, Salomon M. Stemmer, Alberto Gabizon, Ofer Purim, Esther Tahover, Moshe J. Inbar, Ido Wolf, Addie Dvir, Lior Soussan-Gutman, Jeffrey S. Ross, Phil Stephens, Vincent A. Miller; Sharett Institute of Oncology, Hadassah Hebrew University Medical Center, Jerusalem, Israel; Division of Oncology, Tel-Aviv Sourasky Medical center, Tel Aviv, Israel; The Oncology Institute, Shaare Zedek Medical Center, Jerusalem, Israel; Rabin Medical Center, Petach Tikva, Israel; Oncology Department, Wolfson Medical Center, Holon, Israel; Department of Oncology, Rambam Health Care Campus, Haifa, Israel; Department of Oncology, Lin Medical Center, Haifa, Israel; Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel; Division of Oncology, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel; Teva Pharmaceutical Industries, Ltd., Shoham, Israel; Foundation Medicine, Inc., Cambridge, MA

Background: Many metastatic CRC pts progress after exhausting all approved standard therapies but maintain a good performance status and could be candidates for further therapy. We hypothesized that a comprehensive NGS assay (FoundationOne) could identify novel therapy targets not routinely considered for CRC pts.

Methods: Hybridization capture of 3,769 exons from 236 cancer-related genes and 47 introns of 19 genes commonly rearranged in cancer was applied to ≥ 50 ng of DNA extracted from CRC FFPE specimens and sequenced to high, uniform coverage. Genomic alterations (GA) including base substitutions, small indels, copy number alterations, and select gene fusions, were characterized and reported for each pt sample. Actionable GAs were defined as those identifying anti-cancer targeted therapies on the market or in registered clinical trials.

Results: Thirty three CRC pts were included in the analysis (mean age, 54.2 years; range, 28-81; 52% male). Clinical samples used for NGS originated from colon (14, 42%), liver (10, 33%), lung (4, 9%), abdominal wall (2, 6%), and lymph nodes (2, 6%). At the time of NGS testing, 24 pts (73%) were pre-tested for KRAS (5 positive, 19 wild type [WT]). Thirty two cases harbored ≥1 GA, with a total of 117 GAs and a mean of 3.54 GAs per tumor. The most frequent currently non-actionable GAs were identified in TP53 (28, 85%), APC (19, 58%), and MYC (5, 15%). Twenty four (72%) of cases harbored ≥1 actionable GA; most commonly, KRAS (11, 33%), BRAF (7, 21%), PIK3CA (5, 15%), and FBXW7 (3, 9%). Actionable GAs characterized by gene amplifications were detected in FGFR1 (2, 6%), EGFR (1, 3%), and MET (1, 3%). An activating ERBB2 point mutation not detectable by IHC or FISH, potentially targetable with anti-HER2 therapies was identified in 1 pt (3%). KRAS, BRAF, ERBB2, MET, and EGFR were the only actionable GAs that were mutually exclusive. Four pts identified as KRAS WT by hotspot analysis were KRAS mutants by the more comprehensive NGS assay.

Conclusions: For metastatic CRC, comprehensive genomic profiling can identify actionable GAs not currently tested for in routine practice. Results point to the potential of MTOR, BRAF, ERBB2 and EGFR targeted therapies for a significant subset of pts.
HEPATOCELLULAR CARINOMA (HCC)

Next-generation sequencing of serum microRNA (miRNA) in hepatocellular carcinoma (HCC) patients on targeted therapy.
Abstract #4096

Author(s): Robin Kate Kelley, Aaron N. Chang, Esperanza Anguiano, Jimmy Hwang, Hubert J. Stoppler, Ryan M. McWhirter, Anna L. Parks, Bilal Hameed, Oren K. Fix, Elizabeth M. Wayne, Halla Sayed Nimeiri, Pamela N. Munster, Alan P. Venook, Andrei Goga; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Baylor Institute for Immunology Research, Dallas, TX; USCF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; School of Medicine, University of California, San Francisco, CA; University of California, San Francisco, San Francisco, CA; Feinberg School of Medicine, Northwestern University, Chicago, IL

Background: Circulating biomarkers are urgently needed in HCC. miRNA are noncoding RNA that regulate mRNA expression and are detectable in tumor tissue and extracellular compartments. This pilot study explored the feasibility of using next-generation RNA sequencing to characterize miRNA abundance in serum from HCC patients at baseline and on targeted therapy.

Methods: Banked serum samples (400µL) were obtained from HCC patients enrolled on a phase I clinical trial of sorafenib plus the mTOR inhibitor, temsirolimus. Control sera were obtained from patients with non-malignant liver diseases (NMLD). Total RNA was purified using Trizol-LS and miRNeasy kit. Mature miRNA were size-selected by gel electrophoresis. Samples were sequenced by Illumina HiSeq 2500, 5M reads per sample. Raw reads were mapped using Novoalign, quantified, and normalized to total reads and exogenous spike-in miRNA recovery. Comparisons between HCC vs. NMLD and baseline vs. on treatment cohorts were performed using one-way ANOVA and false discovery rate (FDR) correction. Candidate signature miRNA were derived by fold change, p-value, and abundance cutoffs and cross-referenced to literature.

Results: Cohorts: HCC baseline (n=23) and paired on treatment (n=20 cases, 30 samples), NMLD (n=12). HCC cohort: HBV+/dual 40%, HCV+ 32%. NMLD cohort: HCV+ 83%. 38 of 65 (58%) total samples qualified. Candidate miRNA were identified which showed up-regulation in HCC vs. NMLD (non-significant) and in elevated vs. normal alpha-fetoprotein (AFP) (FDR p<0.05). Multiple miRNA families showed a trend toward down-regulation on treatment with temsirolimus plus sorafenib including Let-7 and miR-17/92 family members. Serum signatures for HCC vs. NMLD and elevated AFP overlapped with miRNA expression in a published dataset of HCC tumors.

Conclusions: Serum miRNA in HCC patients can be characterized by next-generation sequencing. Differences in miRNA abundance were observed between HCC cases and NMLD controls, and within HCC cases according to clinical covariates including treatment status and AFP. Serum miRNA warrant further study as novel biomarkers in HCC.
LYNCH SYNDROME

Myriad Genetics
Multigene panel testing in patients suspected to have Lynch syndrome.
Abstract #1509

Author(s): Matthew B. Yurgelun, Brian Allen, Rajesh R. Kaldate, Karla Bowles, Benjamin Roa, Richard J. Wenstrup, Anne-Renee Hartman, Sapna Syngal; Dana-Farber Cancer Institute, Boston, MA; Myriad Genetic Laboratories, Inc., Salt Lake City, UT

Background: Multigene panels are increasingly used for assessing hereditary cancer risk due to their ability to analyze numerous cancer susceptibility genes in parallel. Our aim was to study the outcomes of multi-gene panel testing in patients undergoing clinical testing for Lynch syndrome (LS).

Methods: The study cohort was 1,260 consecutive patients with a history of LS-associated cancer and/or polyps who had undergone clinical genetic testing for LS in a commercial laboratory. Genomic DNA mutations were identified using a 25-gene hereditary cancer panel based on emulsion PCR and next generation sequencing. Germline sequence variations and large rearrangements were classified for pathogenicity. Patients’ personal/family histories of cancer were obtained from test request forms submitted with clinical LS testing.

Results: Panel testing found ≥1 pathogenic mutation in 160/1,260 (13%) patients and ≥1 variant of uncertain significance in 552/1,260 (44%) patients. Of the 160 mutation carriers, 116 (73%) had a mutation in one of the 5 LS genes, whereas 48 (30%) had a mutation in one of the 20 non-LS genes tested including 4 (3%) with both LS and non-LS mutations. Of the 48 non-LS mutations, 15 (31%) were in \( \text{BRCA1/2} \), 10 (21%) were in genes underlying other hereditary colorectal cancer syndromes (\( \text{APC} \), biallelic \( \text{MUTYH} \), \( \text{PTEN} \), and \( \text{STK11} \)), and the remaining 23 (48%) were in other cancer susceptibility genes (\( \text{ATM} \), \( \text{BARD1} \), \( \text{BRIP1} \), \( \text{CHEK2} \), \( \text{NBN} \), \( \text{PALB2} \), and \( \text{RAD51C} \)). Based on their personal/family histories, a large majority of patients met NCCN criteria for LS testing but not hereditary breast/ovarian cancer (HBOC) testing (Table).

Conclusions: In this large cohort of patients suspected to have LS, 30% of mutation carriers identified by panel testing had non-LS cancer susceptibility gene mutations. With more comprehensive genetic testing approaches, many unexpected mutations will be found in patients who do not fulfill classic clinical criteria for their syndrome.

<table>
<thead>
<tr>
<th></th>
<th>Met NCCN LS criteria</th>
<th>Met NCCN HBOC criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td>1112/1,260 (88%)</td>
<td>312/1,260 (25%)</td>
</tr>
<tr>
<td>All mutation carriers</td>
<td>150/160 (94%)</td>
<td>30/160 (19%)</td>
</tr>
<tr>
<td>LS carriers</td>
<td>111/116 (96%)</td>
<td>20/116 (17%)</td>
</tr>
<tr>
<td>All non-LS carriers</td>
<td>43/48 (90%)</td>
<td>11/48 (23%)</td>
</tr>
<tr>
<td>( \text{BRCA1/2} ) carriers</td>
<td>14/15 (93%)</td>
<td>5/15 (33%)</td>
</tr>
</tbody>
</table>

Rows/columns are not mutually exclusive.
**MELANOMA**

**MK-3475, Merck (MRK)**

Clinical efficacy and correlation with tumor PD-L1 expression in patients (pts) with melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475.

Abstract #3005

Author(s): Richard Kefford, Antoni Ribas, Omid Hamid, Caroline Robert, Adil Daud, Jedd D. Wolchok, Anthony M. Joshua, F. Stephen Hodi, Tara C. Gangadhar, Peter Hersey, Jeffrey S. Weber, Roxana Stefania Dronca, Amita Patnaik, Hassane M. Zarour, Marisa Dolled-Filhart, Jared Luceford, Kenneth Emanuel, Scot Ebbinghaus, Soonmo Peter Kang, Wen-Jen Hwu; Westmead Hospital and Melanoma Institute Australia, University of Sydney, Westmead, Australia; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; The Angeles Clinic and Research Institute, Los Angeles, CA; Institut Gustave Roussy, Villejuif, France; University of California, San Francisco, San Francisco, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Princess Margaret Cancer Centre, Toronto, ON, Canada; Dana-Farber Cancer Institute, Boston, MA; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; University of Sydney, Sydney, Australia; Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL; Mayo Clinic, Department of Medical Oncology, Rochester, MN; South Texas Accelerated Research Therapeutics (START) Center for Cancer Care, San Antonio, TX; University of Pittsburgh Cancer Institute, Pittsburgh, PA; Merck & Co., Inc., Whitehouse Station, NJ; Merck & Co, Inc, North Wales, PA; Merck & Co, Inc, Rahway, NJ; The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** MK-3475 demonstrated antitumor activity and acceptable safety in a phase I MEL cohort. We provide updated efficacy data and correlation with tumor PD-L1 expression.

**Methods:** 135 pts received MK-3475 10 mg/kg Q2W (n = 57), 10 mg/kg Q3W (n = 56), or 2 mg/kg Q3W (n = 22). Response was assessed every 12 wk by RECIST 1.1 by independent central review and by immune-related response criteria (irRC) by investigator. Biopsy was required in the 60 d before MK-3475. Tumor PD-L1 expression was assessed by IHC. A preliminary cutoff of 1% of stained tumor cells defined PD-L1 positivity.

**Results:** As of 10/18/2013, all pts had ≥13 mo follow-up. Median time on treatment was 23 wk (range, 1 dose to 97 wk). In pts with measurable disease, ORR was 41% by RECIST (Table). Objective responses were observed as late as 64 wk, with some conversions to CR seen as late as 72 wk. Median response duration was not reached; responses were ongoing for 87% of responders. Median PFS was 31 wk. Median OS was not reached, and OS rate at 1 y was 81%. Tumor PD-L1 expression was evaluable in 71 pts with measurable disease and ≥1 tumor evaluation (77% PD-L1+). Of these pts, PD-L1 expression was associated with improved ORR by RECIST (51% vs 6%, P = .0012 [Fisher’s exact]) and PFS (median 12 vs 3 mo, HR 0.31, 95% CI 0.16-0.61, P = .0004 [log-rank]). 1-y OS rate was 84% in PD-L1+ and 69% in PD-L1− pts (P = .2146 [log-rank]). There were no treatment-related deaths; 14% of pts experienced drug-related grade 3/4 AEs.

**Conclusions:** MK-3475 induces durable responses and favorable 1-y OS with acceptable safety in MEL. Although tumor PD-L1 positivity was associated with improved ORR and PFS, antitumor activity was also observed in pts with low baseline PD-L1 expression. These preliminary data require confirmation.

Clinical trial information: NCT01295827.

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NON-HODGKIN’S LYMPHOMA

**Urelumab, Bristol-Myers Squibb (BMY)**

Biomarker characterization using mass cytometry in a phase 1 trial of urelumab (BMS-663513) in subjects with advanced solid tumors and relapsed/refractory B-cell non-Hodgkin lymphoma.

Abstract #3017

Author(s): Cariad Chester, Serena Chang, John F. Kurland, Idit Sagiv-Barfi, Debra Czerwinski, Amanda Rajapaksa, Erin Waller, Mohith Sadaram, Lori Richards, Lewis J. Cohen, Christoph Matthias Ahlers, Maria Jure-Kunkel, Holden Maecker, Ronald Levy, Holbrook Edwin Kohrt; Department of Medicine, Division of Oncology, Stanford University, Stanford, CA; Institute for Immunity, Transplantation and Infection, Stanford School of Medicine, Stanford, CA; Bristol-Myers Squibb, Princeton, NJ

**Background:** Anti-CD137 antibody was shown in both murine cancer models and in a first-in-human, phase I trial (Sznol et al., 2008) to increase peripheral activated CD8 T cells and IFN-inducible genes, thereby facilitating a cytolytic, antitumor, Th1 response. A multiparametric immune pharmacodynamic assessment of the effects of anti-CD137 therapy has not been previously performed.

**Methods:** We employed the novel technology of mass cytometry time of flight (CyTOF) to investigate the patient’s global immune status prior to and during a phase 1 study (NCT01471210) of Urelumab, a fully human anti-CD137 antibody, administered once per 3-week cycle in patients with solid tumors and B-cell non-Hodgkin’s lymphoma. Peripheral blood was obtained at 4 time points throughout treatment (baseline, 24-hrs after 1st dose of cycle 1, immediately before cycle 2, and post cycle 3 at response evaluation, C3R). PBMCs were isolated and stimulated for 4 hours with PMA/ionomycin. Immune cell characterization and function were analyzed in FlowJo and SPADE from mass cytometry results.

**Results:** Preliminary findings from 4 patients show an increase in CD8 T cells up to 40.6% (SEM+/-13%) and NK cells up to 61.7% (SEM+/-20%) with a decrease in CD4 T cells up to 23.2% (SEM+/-6.5%) and regulatory CD4 T cells up to 17.8% (SEM+/-15%) comparing C3R to baseline. CyTOF cytokine analysis, revealed increases in GMCSF and IFN-gamma by C3R. CyTOF cytokine analysis, revealed increases in GMCSF and IFN-gamma by C3R.

**Conclusions:** These preliminary data are consistent with anti-CD137 agonism and generate hypotheses of putative biomarkers of clinical activity now being investigated and to be reported from the ongoing clinical trial. Clinical trial information: NCT01471210.
NON-SMALL CELL LUNG CANCER (NSCLC)

Abstract #e14000

Author(s): Keerti Munnalal Khandelwal, Carlos Prevegliano,, Runhua Shi, Guillermo Sangster, Eduardo Toledo Gonzalez, Syed Hasan Raza Jafri; Louisiana State University Health Sciences Center, Shreveport, LA; Division of Oncology, The University of Texas Health and Science Center at Houston, Houston, TX

Background: Most patients with lung cancer at the time of diagnosis have stage IV or metastatic disease. Various prognostic markers like performance are associated with worse outcome. We wanted to study if sarcopenia is a marker of poor outcome in stage IV NSCLC patients.

Methods: Patients with metastatic NSCLC at diagnosis managed at Feist weiller cancer center between Jan 1, 2000 to June 30, 2011 were retrospectively studied. Abdominal CT scan done within one month of diagnosis was reviewed to determine the skeletal muscle area (SMA) using MIPAV (Medical Image Processing, Analysis, and Visualization) software. SMA was calculated at L1-L2 level by two investigators who were blinded to patient outcome. Skeletal muscle index (SMI) was calculated as (SMA/height (m²)). Kaplan-Meier method was used to estimate progression free survival and overall survival. Log-rank test were used to compare the survivals among various factors. Multivariate Cox regression was used to perform survival analysis in order to estimate the hazards ratio for various factors.

Results: 112 patient CT scans were included in the analysis. Range of SMI was 23 to 77. Using receiver operating characteristics (ROC) analysis SMI value of 40 was selected to divide the group into sarcopenic (SMI ≤40) and non-sarcopenic ( >40). There was no difference in race, sex, performance status, histology and number of metastatic sites between the two groups. Sarcopenic patients were less likely to have any response to chemotherapy. Using multivariate analysis adjusting for age, sex, race and histology sarcopenic patients were found to have adverse progression free survival (HR= 1.69,95% CI (1.12-2.58), p value =0.013 ) and overall survival (HR=1.58,95% CI (1.04-2.41), p value= 0.032).

Conclusions: Sarcopenia (SMI ≤40) is a marker of poor outcome and response to chemotherapy in patients with stage IV NSCLC. This should be validated in a prospective study.

PD1-Efficacy Biomarker Signature

Association of epithelial-mesenchymal transition status with PD1/PDL1 expression and a distinct immunophenotype in non-small cell lung cancer: Implications for immunotherapy biomarkers.
Abstract #3018

Author(s): Yanyan Lou, Lixia Diao, Lauren Averett Byers, Don Lynn Gibbons, Warren Denning, Jing Wang, Vassiliki Papadimitrakopoulou, Ignacio Ivan Wistuba, Sangeeta Goswami, Maria Angelica Cortez, James Welsh, Jonathan M. Kurie, John Heymach; MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Programmed cell death 1 (PD-1) and its ligand PD-L1 have emerged as a critical inhibitory pathway that maintains immune suppression in the tumor microenvironment. Patients with non-small-
cell lung cancer (NSCLC) have responded to PD-1/PD-L1 blockade, indicating the crucial role of immune suppression in NSCLC. It is imperative to understand the immune features of NSCLC and identify biomarkers to select which patients may benefit from checkpoint blockade. Epithelial-mesenchymal transition (EMT) is a key process driving metastasis. Our previous study developed a robust EMT gene signature predicting resistance to EGFR and PI3K/Akt inhibitors, highlighting differential patterns of drug responsiveness for epithelial and mesenchymal cells.

**Methods:** We used this EMT gene signature and gene expression profiles in adenocarcinoma from The Cancer Genome Atlas (TCGA) and the PROSPECT database at MD Anderson Cancer Center (tumors collected in 240 patients undergoing surgical resection with curative intent) to study the tumor microenvironment immune profile. Tumor samples were first classified by our validated EMT signature as epithelial (low EMT scores defined by EMT scores ≤ lowest 1/3) or mesenchymal (high EMT scores defined by EMT scores ≥ highest 1/3). Gene expression profiles of immune related genes in each tumor were then analyzed.

**Results:** Mesenchymal NSCLC is highly associated with a distinct immune phenotype in the tumor microenvironment as compared to epithelial NSCLC. Overexpression of genes for immune inhibitory molecules including PD-L1 ($P = 1.6 \times 10^{-13}$), PD-1 ($P = 9.5 \times 10^{-5}$), CTLA-4, TIM3, BTLA, IL-10, IL-6, and TGF-b ($P<0.0001$ for all others) are associated with mesenchymal NSCLC in both the TCGA and PROSPECT databases.

**Conclusions:** This study demonstrates mesenchymal NSCLC (high EMT scores) is associated with distinct immune phenotypes with increased expression of immune inhibitory molecules. This study provides a potential mechanism for EMT associated immunosuppression. It suggests EMT may be a biomarker for checkpoint inhibitors and potentially other immunotherapy agents.

**MetMab, Roche**

Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial. Abstract #8000

Author(s): David R. Spigel, Martin J. Edelman, Kenneth O’Byrne, Luis Paz-Ares, David S. Shames, Wei Yu, Virginia E. Paton, Tony Mok; Sarah Cannon Research Institute, Nashville, TN; University of New Mexico Cancer Center, Albuquerque, NM; Queensland University of Technology, Brisbane, Australia; University Hospital Virgen del Rocío, Seville, Spain; Genentech, South San Francisco, CA; The Chinese University of Hong Kong, Hong Kong, China

**Background:** A placebo-controlled, phase II trial of erlotinib + onartuzumab, a humanized monovalent antibody to the MET receptor, demonstrated a benefit in progression-free survival (PFS) when compared with erlotinib in patients with MET-positive NSCLC (JCO 2013;31;4105). The aim of the METLung trial was to confirm the efficacy and safety of onartuzumab + erlotinib in MET-positive NSCLC.

**Methods:** This prospective, randomized, double-blind, placebo-controlled trial enrolled patients with previously treated MET-positive stage IIIb/IV NSCLC. MET diagnostic status was determined by an immunohistochemistry (IHC) assay using the CONFIRM anti-total MET SP44 monoclonal antibody (Ventana). Eligibility criteria included: ECOG PS 0–1, 1–2 prior lines of chemotherapy, and normal organ function. Stratification factors: EGFR mutation status (activating mutation vs negative; cobas® EGFR
assay), MET IHC (2+ vs 3+), number of prior treatments (1 vs 2), and histology (squamous vs non-squamous). Patients were randomized (1:1) to receive erlotinib 150mg PO daily + placebo or onartuzumab 15mg/kg IV every 21 days. Tumor assessments occurred every 6 weeks. The primary endpoint was overall survival (OS). The sample size (n=490) was based on the assumption that adding onartuzumab to erlotinib would improve OS by 41% with 90% power (one-sided alpha 0.025). An interim analysis was planned when 67% (244 events) of the final events were reached.

Results: 499 patients were enrolled between Jan 2012 and Aug 2013. An independent data review committee recommended to stop the trial for futility, as the addition of onartuzumab to erlotinib did not improve OS (HR 1.27, p=0.068; median OS 6.8 mos vs 9.1 mos), PFS (HR 0.99, p=0.92; median PFS 2.7 mos vs 2.6 mos), or overall response rate (8.4% vs 9.6%; p=0.63). The most frequent adverse events that were higher in the combination arm were peripheral edema, hypoalbuminemia, back pain, dyspnea, nausea, acneiform dermatitis, and rash.

Conclusions: The phase III study did not confirm the efficacy results observed in the phase II study. Exploratory analyses based on molecular subgroups are pending. Clinical trial information: NCT01456325.

**Xalkori, Pfizer (PFE)**

**Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC).**

Abstract #8001

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Background: c-Met-amplified NSCLC defines a subset of NSCLC that may be sensitive to the small-molecule tyrosine kinase inhibitor crizotinib, approved multinationally for the treatment of advanced ALK-positive NSCLC. Efficacy and safety data are presented for crizotinib in patients with advanced c-Met-amplified NSCLC within 3 categories of amplification MET/CEP7 ratio >1.8-≤2.2 (Low), >2.2-≤5 (Intermediate) and >5 (High).

Methods: c-MET amplification status was determined by FISH, with 10-12 patients to be enrolled into each amplification category. If 2 or more objective responses occur in a category, 19 additional patients are to be enrolled. This study is part of an ongoing phase 1 crizotinib study (NCT00585195). Patients received crizotinib 250 mg BID. Responses were assessed using RECIST v1.0.

Results: At data cut-off, 16 patients were enrolled; 3 were subsequently determined not to have an amplification meeting MET/CEP7 criteria. 13 patients with c-MET-amplified NSCLC [Low (n=1), Intermediate (n=6) and High (n=6)] enrolled and received crizotinib, with 12 evaluable for response.
Median age was 63 years (range 42-79), 92% of patients were ECOG 0 or 1 and 77% were ex-smokers. To date 4 PRs (33%; 95% CI: 10.65) have been observed (Low (n=0), Intermediate (n=1; 20%) and High (3; 50%). Median duration of response was 35 weeks [95% CI: 16,112]. Median treatment duration was 15.7 weeks (range 4 -188), and 6 patients were on treatment at the data cut-off; 5 patients have died (all disease-related). 75% of the 16 patients enrolled had treatment-related adverse events (AEs): most commonly diarrhea (50%), nausea (31%), vomiting (31%), peripheral edema (n=25%) and visual impairment (25%). Most AEs were grade 1 in severity. There were no treatment-related serious AEs or treatment-related permanent discontinuations. Accrual of patients with c-Met-amplified NSCLC is ongoing.

**Conclusions:** Crizotinib appears to have antitumor activity in patients with c-Met-amplified NSCLC and a generally tolerable and manageable AE profile. These findings warrant further study of crizotinib in advanced c-MET-amplified NSCLC and ongoing exploration of the MET/CEP7 ratio associated with clinical benefit. Clinical trial information: NCT00585195.

**OVARIAN CANCER**

**Olaparib, AstraZeneca (AZN)**

**Characterization of ovarian cancer long-term responders on olaparib.**

Abstract #5534

Author(s): Stephanie Lheureux, Jonathan A. Ledermann, Stanley B. Kaye, Charlie Gourley, Michael Friedlander, David Bowtell, Jacques De Greve, Anna deFazio, Ronnie Shapira-Frommer, Johann Sebastian De Bono, M. William Audeh, Elise C. Kohn, Kathryn Alsop, Clare L. Scott, Ursula Matulonis, Bella Kaufman, Brent Burger, Jane D Robertson, Tony Ho, Amit M. Oza; Princess Margaret Cancer Centre, Toronto, ON, Canada; University College London Cancer Institute, London, United Kingdom; Drug Development Unit at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK, London, United Kingdom; Edinburgh Cancer Research UK Centre, Edinburgh, United Kingdom; Prince of Wales Hospital, Sydney, Australia; Peter MacCallum Cancer Centre, Melbourne, Australia; Familial Cancer Clinic and Medical Oncology, University Hospital Brussels, UZ Brussel, Brussels, Belgium; Westmead Institute for Cancer Research, University of Sydney at Westmead Millennium Institute, Sydney, Australia; Ella Institute for Research and Treatment of Melanoma, Sheba Medical Center, Affiliated to Sackler Faculty of Medicine Tel Aviv University, Tel Hashomer, Israel; The Royal Marsden NHS Foundation Trust, Surrey, United Kingdom; Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA; National Cancer Institute, National Institutes of Health, Bethesda, MD; Royal Melbourne Hospital, Victoria, Australia; Dana-Farber Cancer Institute, Boston, MA; The Breast Cancer Unit, Institute of Oncology, Sheba Medical Center, Tel Hashomer, Israel; AstraZeneca, Macclesfield, United Kingdom; AstraZeneca, Wilmington, DE; Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada

**Background:** BRCA1/2 mutations (BRCAm) appear to predict benefit from PARP inhibition. However, non-mutation carriers also benefit and not all patients (pts) with BRCAm respond to PARP inhibitors. The objective of this study was to identify and clinically characterize pts remaining on durable olaparib therapy for further molecular analyses to determine the features underlying long-term response.
Methods: A retrospective meta-analysis comprised pts with recurrent ovarian cancer (OC) from trials in the olaparib clinical program. Long- and short-term benefits were defined as olaparib treatment for > 2 years and < 6 months respectively, segregated by monotherapy or maintenance.

Results: 372 OC pts, 323 with BRCAm have been already treated with olaparib 400 mg bid capsule as monotherapy at time of relapse (Studies D0810C000001-02-09-12-20-24-42). In these trials, 197 pts (53%) were treated < 6 months from which 169 pts (52.3%) had BRCAm. Conversely, there were pts with long-term benefit from olaparib, such as 6 pts in the D0810C000020 study, treated for > 4 years. The table shows the OC pts treated with maintenance olaparib (n=136) and also with olaparib in combination with chemotherapy followed by maintenance (n=81), separating out the pts with BRCAm.

Conclusions: Although many long-term responders to olaparib have BRCAm, there are several with no known BRCAm. Response durability may be related to a number of factors including germline and somatic BRCAmutations. The clinical and molecular characterization of these pts and comparison with short- or median-term disease control will improve understanding of response and resistance to PARP inhibitors.

<table>
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<tr>
<th>Treatment duration</th>
<th>D0810C000019: Olaparib maintenance 400 mg bid capsule monotherapy*</th>
<th>D0810C000041: Combination with carboplatin/paclitaxel followed by maintenance 400 mg bid capsule monotherapy*</th>
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<tr>
<td>Pts</td>
<td>All (n=136)</td>
<td>BRCAm (n=74)</td>
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<tr>
<td>&lt; 6 months</td>
<td>49 (36%)</td>
<td>21 (28.4%)</td>
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<tr>
<td>&gt; 24 months</td>
<td>32 (23.5%)</td>
<td>21 (28.4%)</td>
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</tbody>
</table>

Abbreviations: wt, wild type; vus, variant unknown significance. *Data cut off: November 2012.

Vintafolide, Merck (MRK)


Abstract #5533

Author(s): Wael A. Harb, Siu-Long Yao, Binh Nguyen, Robin Mogg; Horizon Oncology Center, Lafayette, IN; Merck Sharp & Dohme, North Wales, PA; Endocyte, Inc., West Lafayette, IN; Merck Research Laboratories, West Point, PA

Background: In treating cancer, companion diagnostics are most useful when they can identify patients who cannot benefit from treatment. However, existing tests suffer from inaccuracy due to dependence on single specimens of a multifocal tumor or dependence on historically obtained specimens that may not represent the current tumor state. This analysis evaluates the performance characteristics of etarfolatide (EC20), a technetium-folate imaging diagnostic designed to provide real-time information on all patient tumor lesions that may respond to treatment with vintafolide (desacetylvinblastine-folate conjugate, EC145).
Methods: 209 baseline lesions from 44 patients were evaluated in a phase 2 open-label, multicenter study of vintafolide in advanced ovarian cancer (EC-FV-02, NCT00507741). Data from 9 patients (52 lesions) without follow-up were excluded. 21 lesions were categorized as not evaluable, and 6 lesions were categorized as not imaged. 8 lesions that did not meet minimal size criteria were also excluded. The final analysis set included 107 lesions from 33 patients.

Results: Etarfolatide correctly identified 24 of 26 lesions whose tumor size numerically decreased following vintafolide treatment (sensitivity for numerical decrease=92%). The corresponding negative predictive value (NPV=percent of EC20– lesions that did not numerically decrease) was 86% with a specificity of 15% and a positive predictive value (PPV=percent of EC20+ lesions that numerically decreased) of 26%. Among the etarfolatide negative lesions, 0 decreased by at least 30%. Among the etarfolatide positive lesions, 5 decreased by at least 30%. Therefore, among the 5 lesions that decreased by at least 30%, 5 were etarfolatide positive (sensitivity=100%). Among 102 lesions that did not decrease by at least 30%, 14 were etarfolatide negative (specificity=14%), corresponding to PPV and NPV of 5% and 100%, respectively.

Conclusions: Etarfolatide identified nearly all tumor lesions that responded to vintafolide treatment in a phase 2 ovarian cancer study. Lesions that do not demonstrate etarfolatide uptake will not demonstrate major shrinkage (>30%) following vintafolide treatment. Clinical trial information: NCT00507741.

PANCREATIC CANCER

Next-generation sequencing in pancreatic cancer: Novel mutations and potential targets for therapy. Abstract #e15228

Author(s): Andrea S. Teague, Benjamin R. Tan, Joel Picus, Albert C. Lockhart, Steven Sorscher, Rama Suresh, Steven M. Strasberg, William G. Hawkins, Ryan C. Fields, David Linehan, Andrew Bredemeyer, Catherine E Cottrell, Andrea Wang-Gillam; Washington University School of Medicine in St. Louis, St. Louis, MO; Division of Oncology, Washington University in St. Louis, St. Louis, MO; Washington University in St. Louis, St. Louis, MO; Department of Surgery, Washington University School of Medicine, St. Louis, MO; Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO

Background: Pancreatic adenocarcinoma (PA) has one of the worst prognoses of all malignancies prompting the search for oncogenic mutations that might be targets for therapy.

Methods: We conducted a retrospective analysis of patients with PA who had next-generation sequencing (NGS). Key genes included were APC, ATM, BRAF, BRCA1, BRCA2, FLT3, NOTCH1, MET, FGFR4, MAPK1, MAP2K2, IDH1, IDH2, RET, JAK2, Kras, NRAS, PTEN, EGFR, PIK3CA, PDGFRα, RUNX1, KIT, ALK, and TP53. Fluorescence in-situ hybridization (FISH) for EGFR gene amplification and MLL and ALK gene rearrangement was performed in a subset of patients. Variants were annotated with data incorporated from dbSNP, ClinVar and COSMIC. In-silico predictions were performed where applicable using PROVEAN (Protein Variation Effect Analyzer) and SIFT, and/or Polyphen (Polymorphism Phenotyping v2).
**Results:** Among 45 patients with NGS, 31 patients (68.9%) had KRAS mutations and 14 patients (31.1%) were wild-type for KRAS. Of 29 patients whose tumors underwent FISH, 3 patients had EGFR gene amplification, 1 patient had both EGFR gene amplification and ALK gene rearrangement, and 1 patient was positive for the MLL gene rearrangement. There were novel mutations not previously described in the COSMIC database, and at least 8 were predicted to be deleterious or damaging. There was a novel missense variant observed in BRCA1 and several missense variants of unknown significance in BRCA2. A novel variant was found in RET, predicted by Polyphen as probably damaging and by Provean as neutral. A novel variant in PIK3CA was predicted to be deleterious by Provean/SIFT. Possible targetable alterations include mutations in NOTCH1, JAK2, ATM, FLT3, PTEN and EGFR, among others. Of the 31 patients with mutant KRAS, 21 had resectable PA with known follow-up, with a median overall survival of 21.5 months (8.4-58.9). In the wild-type KRAS patients, 9 of the 14 patients had resectable PA with known follow-up, with a median overall survival of 17.3 months (6.2-91.6).

**Conclusions:** NGS of PA confirmed common mutations and also revealed genomic alterations that may be potentially responsive to available targeted agents. The discovery of novel mutations PA warrants further investigation.

**RNA-seq and KRAS mutational status in ascitic pancreatic cancer cells: Novel results and distinct subsets.**  
Abstract #e15214

Author(s): Talia Golan, S. Gail Eckhardt, Chani Stossel, Dikla Atias, Guoliang Wang, Todd M. Pitts, Dara Aisner, Colin D. Weekes, Raanan Berger, Aik-Choon Tan; Chaim Sheba Medical Center, Ramat Gan, Israel; University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO; Sheba Medical Center, Ramat Gan, Israel; University of Colorado Comprehensive Cancer Center, Denver, CO; University of Colorado Denver, Aurora, CO; University of Colorado Cancer Center, Aurora, CO; Uro-oncologist, Tel Hashomer, Tel Hashomer, Israel

**Background:** Approximately 90% of pancreatic ductal-adenocarcinoma (PDAC) tumors harbor an activating mutation in the KRAS oncogene, driving proliferative and survival signals. However, this information has largely been obtained from primary tumor tissue while the prevalence of KRAS mutations in metastatic lesions is poorly studied. Since approximately 15-20% of advanced PDAC patients develop ascites, we developed a novel model system of viable ascites-derived PDAC (ad-PDAC) cells that can then be characterized and used for therapeutic studies.

**Methods:** The KRAS oncogene was analyzed in ad-PDAC cells obtained from 19 patients by targeted next-generation or direct sequencing methods.

**Results:** Surprisingly, 17/19 samples were WT, while the two remaining specimens harbored the p.G12R mutation. None of the ad-PDAC cells exhibited the most common p.G12D mutation. Concordance of KRAS status was observed between the ad-PDAC cells and primary tumor in only 4/7 available pairs (3 WT and 1 p.G12R). The 3 discordant primary samples harbored p.G12D (2) and p.G12V (1) with KRAS WT in the ad-PDAC cells. Additionally we analyzed another 28 ad-PDAC samples by RNA-seq. We performed unsupervised clustering on 31 transcriptomes and observed that patients clustered into two groups identified by high or low KRAS expression. The median overall survival was 8.8 and 18.2 months for the high or low KRAS expression groups, respectively (p = 0.0013). Gene set enrichment analysis of the two groups revealed that the high KRAS expression cluster was enriched with RAS/RAF/MEK, PI3K, adherens
junctions and TGF signaling pathways, whereas the low KRAS expression cluster was enriched with ribosome, oxidative phosphorylation and proteasome pathways.

**Conclusions:** These hypothesis-generating data demonstrate discordant KRAS mutational status from what would be expected, with 90% of ad-PDAC cells exhibiting a WT KRAS genotype. Furthermore, the variability noted between the primary/ad-PDAC pairs as well as the clustering analysis, if confirmed in larger data sets, suggests that there may be ways to exploit distinct therapeutic targets in groups of pancreatic cancer patients with ascites, based on their KRAS expression profile.

**PANCREATIC DUCTAL ADENOCARCINOMA**

**c-MET mRNA Expression Assay, Response Genetics (RGDX)**

c-MET mRNA expression in pancreatic ductal adenocarcinoma and stromal tissue: Prognostic and therapeutic implications.

Abstract #e15199

Author(s): Martin K. H. Maus, Craig Stephens, Dirk Waldschmidt, Anika Roll, Stephanie H. Astrow, Hans-Michael Steffen, Jack Hsiang, Gary Zeger, Arnulf H Hölscher, Peter Philipp Griminger; Department of General, Visceral, and Tumor Surgery, University of Cologne, Cologne, Germany; Response Genetics, Inc., Los Angeles, CA; Department of Gastroenterology and Hepatology, University of Cologne, Cologne, Germany; University of Cologne, Department of Gastroenterology and Hepatology, Cologne, Germany; Keck School of Medicine, Department of Pathology, University of Southern California, Los Angeles, CA; Department of General, Visceral, and Cancer Surgery, University of Cologne, Cologne, Germany

**Background:** Pancreatic ductal adenocarcinoma is one of the most aggressive solid malignancies. The c-MET oncogene plays a crucial role in mediating local invasion, systemic dissemination and resistance in this cancer. The genetic makeup of surrounding stromal tissue has shown to be relevant for drug delivery in pancreatic cancer as exemplified by nab-paclitaxel binding to the stromal protein SPARK. In this study we investigated c-MET mRNA expression patterns in pancreatic ductal adenocarcinoma and stromal tissue in patients with clinical outcome information.

**Methods:** FFPE tumor specimens from patients with resectable pancreatic cancer that underwent surgery and adjuvant chemotherapy with gemcitabine were evaluated. c-MET mRNA expression results could be obtained for 25 cases in tumor and 19 cases in stromal tissue as not all samples were sufficient in quality and quantity for microdissection and mRNA analysis. Specifically designed primers and probes were used to detect mRNA c-MET expression levels by quantitative RT-PCR in reference to beta-actin.

**Results:** c-MET mRNA expression was significantly divergent between pancreatic stromal (median 1.0, range 0.37-5.05) and tumor (median 3.8, range 0.78-12.27) tissue (p<0.0001). When statistically evaluated for the best cut-off, patients with high (>5.00) c-MET expression in the tumor tissue had a worse overall survival. (p<0.003). c-MET mRNA expression in stromal tissue did not correlate with outcome.

**Conclusions:** According to this data high c-MET expression is a negative prognostic indicator for pancreatic cancer. Further studies have to evaluate if c-MET expression may predict response to new c-
MET inhibitors like cabozantinib. The role of c-MET expression in pancreatic stromal tissue needs further investigation.

**PROGESTERONE RECEPTER (PR)-EXPRESSING CANCERS**

**Onapristone, Arno (ARNID)**

* A randomized, parallel-dose phase 1 study of onapristone (ONA) in patients (pts) with progesterone receptor (PR)-expressing cancers.

**Abstract #TPS2643**

**Author(s):** Paul H. Cottu, Andrea Varga, Sylvie Giaachetti, Eric Leblanc, Marc Espie, Anas Gazzah, Veronique Dieras, Catherine Lhomme, Francois Marc Lokie, Keyvan Rezai, Alice Susannah Bexon, Erard M. Gilles, Joseph Bisaha, Alexander Zukiwski, Jacques Bonneterre; Institut Curie, Paris, France; DITEP, Drug Development Department, Institut Gustave Roussy, Villejuif, France; INSERM U776, Paris, France; Centre Oscar Lambret, Lille, France; Hospital Saint-Louis, Paris, France; Drug Development Department (DITEP), Gustave Roussy Institute, Villejuif, France; Département d’Oncologie Médicale, Institut Curie - Hôpital Claudius Régnaud, Paris, France; Department of Medicine, Gustave Roussy, Villejuif, France; Centre Rene Huguenin, Saint-Cloud, France; Institut Curie-Hôpital René Huguenin, Saint-Cloud, France; Bexon Clinical Consulting LLC, Montclair, NJ; Invivis Pharmaceuticals, Bridgewater, NJ; Arno Therapeutics, Flemington, NJ; Centre Oscar Lambret, Université Lille Nord de France, Lille, France

**Background:** ONA is a type I PR antagonist, which prevents PR-induced DNA transcription. Presence of transcriptionally activated PR (APR), could indicate potential for ONA anticancer activity and could be used as a predictive biomarker. Development of an IHC companion diagnostic which identifies distinct subnuclear PR distribution patterns is ongoing, and could help select patients with PR-positive cancers most likely to respond to ONA, including endometrial and breast cancers. ONA anti-cancer activity has been documented in multiple preclinical models. Prior ONA clinical studies led to objective responses in pts with hormone therapy-naïve or tamoxifen-resistant breast cancer. ONA appeared well tolerated with the exception of LFT abnormalities, which would not preclude development in oncology. An extended-release (ER) tablet formulation of ONA was designed to address the LFT elevations seen with immediate-release (IR) ONA, by reducing the C$_{max}$.

**Methods:** This is a multi-center, open-label, randomized, parallel-group, 2-stage phase 1 study with an expansion component (total n ~60). Female pts ≥18 years with tumors expressing PR are eligible. Tumor tissue is required to determine PR (both A and B isotypes) and APR status. The primary endpoint is determination of the recommended phase 2 dose (RP2D) of ER ONA, with a 57-day period for observation of dose-limiting toxicity (DLT). Secondary endpoints include safety/tolerability, efficacy, and real-time PK. Tissue specimens will be used to determine relationship of APR to preliminary efficacy. Six pts per cohort are receiving ONA ER tablets 10, 20, 30, 40 or 50 mg BID, or ONA IR tablets 100 mg QD until progressive disease or intolerable safety Stage 1: Six dose cohorts are randomized in parallel. A data review committee (DRC) monitors/reviews safety signals and all DLTs. Stage 2: when sufficient pts have been treated for 8 weeks, the DRC will review all safety, PK and efficacy data to determine the RP2D. The RP2D dose cohort will be expanded by enrolling 24 additional pts to confirm the safety profile and provide a preliminary assessment of anti-tumor activity. Stage 1 is open for accrual. Clinical trial information: NCT02052128.
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<td>Exelixis, Inc. (EXEL)</td>
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<td>Trial Data - Updated Results</td>
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<td>EGFR (Epidermal Growth Factor Receptor), Angiopoietin Receptors (TE-1 and TIE-2), FMS-like tyrosine kinase 3 (FLT3), Hepatocyte growth factor receptor (-cMet), KIT/CD123, RET, VEGF Receptor (vEGF/R)</td>
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<td>Gilead Sciences, Inc. (GILD)</td>
<td>GS-9733 Chronic Lymphocytic Leukemia (CLL)/Small Cell Lymphocytic Lymphoma (SLL) - NHL</td>
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<td>IMGN929 Non-Hodgkin's Lymphoma (NHL)</td>
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<td>Incyte Corporation (INCY)</td>
<td>INCB24360 Melanoma</td>
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<td>Inovio Pharmaceuticals, Inc. (INO)</td>
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<td>Dencizumab Non-Small Cell Lung Cancer (NSCLC)</td>
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<td>PF-05082696 Non-Hodgkin's Lymphoma (NHL)</td>
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<td>Pharmacycics, Inc. (PCYC)</td>
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<td>Bruton's Tyrosine Kinase (BTK), Interleukin-2-inducible T-cell kinase (ITK)</td>
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<td>PV-10 Melanoma</td>
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<td>Puma Biotechnology, Inc. (PBYI)</td>
<td>Neratinib Brain Cancer (secondary; metastases)</td>
<td>Trial Data - Top-Line Results</td>
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<td>EGFR (Epidermal Growth Factor Receptor), ErbB4/HER4, HER5/HER6 or ErbB-2</td>
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<td>Antibody-drug Conjugate (ADC), CD20b, Microtubules (Tubulin)</td>
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<td>Mitogen-activated ERK kinase (MEK, MAPK, MAP2K)</td>
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<td>Programmed death-1 receptor (PD-1)/Programmed death ligands (PD-L1 and PD-L2)</td>
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<td>Seattle Genetics, Inc. (SGEN)</td>
<td>SGN-CD19A Non-Hodgkin's Lymphoma (NHL)</td>
<td>Trial Data - Top-Line Results</td>
<td>I</td>
<td>Antibody-drug Conjugate (ADC)</td>
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Other BioMedTracker reports that may be of interest:

**Breast and Gynecological Cancer Report**
*May 2014*

This report describes current treatment paradigms for breast and gynecological cancers, then highlights drugs and mechanisms of action that show promise.

Included are details about the following topics:

- Potential FDA approval timelines for breast and ovarian cancer drug candidates.
- A summary of the competitive landscape and how new drug candidates may fit into existing treatment paradigms.
- An analysis of drug characteristics and likelihood of approval (LOA) for drugs in development.
- Discussion of drug targets and promising experimental agents in development.

Learn more about [BioMedTracker’s 2014 Breast and Gynecological Cancer Report](#).

**Cancer Immunotherapies**
*May 2014*

This report focuses on the promising new classes of therapies that have driven a renewed interest in the field, including:

- Programmed-death (anti-PD-1 drugs) and other immune checkpoint inhibitors
- Dendritic cell (DC) therapies
- T-cell therapies (CAR-T)
- Cancer vaccines

Download a complimentary copy of BioMedTracker’s report on [Cancer Immunotherapies](#).

**Breast Cancer KOL Insight Interview**
*May 2014*

Key Opinion Interview (KOL) with a medical oncologist in the New York metropolitan area regarding breast cancer treatments.

For the free highlights and information on purchasing the full transcript, visit [BioMedTracker’s Breast Cancer KOL Insight Interview](#) online.