PR01 Acquisition of resistance to anti-EGFR therapy drives genomic heterogeneity and lesion-specific responses in colorectal cancer. Giulia Siravegna1, Mariangela Russo1, Lawrence S. Blaszkowsky2, Giorgio Corti3, Giovanni Crisafulli1, Leanne G. Ahronian2, Benedetta Mussolin5, Eunice L. Kwak2, Michela Buscarino3, Luca Lazzari1, Emanuele Valtorta4, Mauro Truini4, Nicholas A. Jessop5, Hayley E. Robinson2, Theodore S. Hong6, Mari Mino-Kenudson2, Federica Di Nicolantonio1, Ashraf Thabet2, Andrea Sartore-Bianchi4, Salvatore Siena5, John Iafrate2, Ryan B. Corcoran2, Alberto Bardelli1. 1University of Torino - IRCCS Candiolo, Candiolo, Italy; 2Massachusetts General Hospital, Boston, MA; 3Candiolo Cancer Institute, Candiolo, Italy; 4Niguarda Cancer Center, Ospedale Niguarda Ca’ Granda, Milano, Italy.

How genomic heterogeneity associated with acquired resistance to targeted agents affects response to subsequent lines of therapy is unknown. Exposure to therapy may result in selection of sub-clonal cell populations, capable of growing under drug pressures. Therefore, a single-lesion biopsy at disease progression may vastly underrepresent the molecular heterogeneity of resistant tumor clones in an individual patient and may fail to detect the existence of distinct but important resistance mechanisms that could impact clinical response. To this aim, we identified a colorectal cancer (CRC) patient in whom multiple tumor biopsies were obtained at resistance following prolonged response to with the anti-EGFR antibody cetuximab and irinotecan therapy. Full-exome sequencing of 1000 cancer genes of both primary tumor and progression biopsy revealed a TP53 mutation in all samples and a novel MAP2K1 p.K57T mutation in one of the progressing liver biopsy. Interestingly, a mutation at the same MAP2K1 codon was identified in the cetuximab-resistant HCA46 CRC cell line. Biochemical analysis of preclinical model showed constitutive activation of MEK and ERK despite cetuximab treatment. Exogenous expression of the same mutant MEK1, but not wild-type MEK1, in an independent RAS-WT CRC cell line, LIM1215, conferred resistance to cetuximab or panitumumab. However, the combination of the MEK inhibitor trametinib with either cetuximab or panitumumab restored sensitivity, suggesting a potential therapeutic strategy to overcome resistance to EGFR blockade caused by this mutation.

Accordingly, the patient was treated with the combination of panitumumab and trametinib. After 3 months, imaging demonstrated a reduction in size of the biopsied liver metastasis harboring the MAP2K1 mutation, but revealed that some other lesions had progressed. Plasma for circulating DNA (ctDNA) analysis was longitudinally collected during combinatorial treatment. Pre-treatment plasma was analyzed using next-generation sequencing (NGS), confirming the presence of both TP53 and MAP2K1 variants, but surprisingly unveiling an additional KRAS mutation. ddPCR analysis of longitudinal timepoints of ctDNA unveiled that TP53 mutant levels dropped after initiation of therapy, but rose later during treatment with concomitantly/in parallel to CEA ones. However, MAP2K1 mutant levels declined, while KRAS mutant ones rose markedly during therapy, indicating outgrowth of a resistant KRAS-mutant clone. Biopsy of a different liver metastasis’ segment that progressed despite panitumumab and trametinib revealed the same KRAS mutation identified in ctDNA.

In summary these findings illustrate how individual metastatic lesions can develop distinct resistance mechanisms to targeted agents, leading to striking differences in lesion-specific response to subsequent targeted therapies. As more trials evaluating targeted therapy strategies designed to overcome specific acquired resistance mechanisms enter the clinic, genomic results from single-tumor biopsies should be interpreted with caution. By contrast, liquid biopsy approaches have the potential to detect the presence of simultaneous resistance mechanisms residing in separate metastases in a single patient and to monitor the effects of subsequent targeted therapies.
PR02  Identification of a potent and selective chemical probe for exploring the role of CDK8/19 in cancer biology.  Paul A. Clarke1, Trevor Dale2, Christina Esdar3, Dennis Waalboer1, Olajumoke Adenijipopoola1, Maria-Jesus Ortiz-Ruiz1, Aurelie Mallinger2, Ken Ewan2, Robert te Poele1, Sharon Gowan1, Paul Workman1, Kai Schiemann3, Suzanne A. Eccles1, Dirk Wienke3, Julian Blagg1. 1Cancer Research UK Unit, The Institute of Cancer Research, London, United Kingdom; 2School of Bioscience, Cardiff University, Cardiff, United Kingdom; 3Merck KGaA, Merck Serono, Darmstadt, Germany.

The discovery of chemical probes by testing libraries of small molecules against cellular pathway screens has re-emerged as a hit discovery strategy. We previously reported a series of 3,4,5-trisubstituted pyridines identified from a high-throughput cell-based reporter assay of WNT pathway signaling. We were able to optimize this series and identified CCT251545 as a chemical tool that potently inhibits readouts of WNT signaling pathway activity with evidence for in vivo activity. A series of cell-based assays activating WNT signaling at distinct loci identified the TCF locale as the likely target. CCT251545 was not a general inhibitor of the transcription machinery and did not affect expression of TCFs. Regulation of beta-catenin/TCF transcription involves recruitment or loss of DNA binding proteins, histone modification and also interaction with additional protein networks. Given the potential complexity of these multiple networked interactions, we employed an unbiased chemical proteomics strategy to identify molecular targets of CCT251545. Knowledge of the structure-activity-relationships of the series allowed us to identify derivatives that retained cellular potency and were suitable for linker coupling to generate an affinity matrix. SILAC-based quantitative mass spectrometry identified target proteins captured by incubation of the immobilized compound with lysates from cells grown in media with different forms of isotopically-labeled amino acids. Competition experiments with unconjugated analogues allowed us to identify affinities of proteins bound to the immobilized probe. These experiments identified Mediator complex-associated protein kinases CDK8 and CDK19 as targets of the 3,4,5-trisubstituted pyridine series. We show that CCT251545 is a selective and potent ATP competitive chemical probe for these two kinases, with >100-fold selectivity over 291 other kinases. X-ray crystallography demonstrates a Type 1 binding mode involving insertion of the CDK8 C-terminus into the ligand-binding site. In contrast to Type II-like CDK8/19 ligands, CCT251545 displays potent cell-based activity. We demonstrate that CCT251545 not only alters WNT-pathway regulated gene expression, but also other CDK8/19 targets including genes regulated by STAT1. Consistent with this we find that phosphorylation of STAT1SER727 is a biomarker of CDK8 kinase activity in vitro and in vivo. Finally, we show in vivo activity of CCT251545 in WNT-dependent tumors. The potential role for CDK8, and by implication CDK19, as an oncoprotein further highlights the need for an active and specific probe compound that can be used as a complementary reagent to RNAi tools. Here we demonstrate that the small molecule CCT251545 fulfils this requirement as a potent, selective, cell-active chemical probe that can be used with confidence to explore the consequences of CDK8/19 kinase function in cellular and in vivo animal models.


Anaplastic lymphoma kinase (ALK) rearrangement, which was first identified in non-small cell lung cancer (NSCLC) in 2007, is observed in 3%-5% of non-small-cell lung cancer (NSCLC) patients. For the treatment of ALK-rearranged non-small-cell lung cancer (NSCLC) patient, crizotinib, cMET/ALK/ROS1-TKI was tested and has shown remarkable tumor shrinkage in clinical trials for the treatment of advanced ALK-rearranged NSCLC patients. However, these tumors inevitably develop resistance to crizotinib due to various secondary mutations, ALK fusion gene amplification, or bypass pathway activation mediated by other receptor tyrosine kinases. To overcome crizotinib resistance, multiple ALK-TKIs have been developed. Ceritinib, a next-generation ALK-TKI, showed great efficacy in crizotinib-refractory, ALK-rearranged NSCLC patients in a clinical trial. However, the emergence of resistance to ALK-TKI is a major limitation for the effective therapy.
Although various secondary mutations or bypass pathway activation-mediated resistance have been identified, large part of the resistance mechanism is still unknown.

In this study, we explored ceritinib-resistant mechanisms using ceritinib-resistant, echinoderm microtubule-associated protein-like 4-ALK-positive H3122 cells and ceritinib-resistant patient-derived cells. Genetic alteration was examined by sequencing of cancer related genes. Protein expression related to ceritinib was examined by receptor-tyrosine kinase (RTK) array, immunoblotting and IHC. To overcome the identified resistance, single or combination treatment of the kinase inhibitors was tested in vitro and in vivo.

We identified three novel ceritinib resistance mechanisms: a resistance mutation (L1198F), fibroblast growth factor receptor 3 (FGFR3) activation, and cMET gene amplification. L1198F-mutated ALK was the most sensitive to crizotinib. Molecular dynamic structure simulation successfully predicted the affinity of ceritinib or crizotinib to wild type and L1198F-mutated ALK. The patient-derived cMET-amplified ceritinib-resistant cells were sensitive to crizotinib, and the FGFR3-upregulated, ceritinib-resistant H3122 cells were re-sensitized to ALK-TKIs by FGFR inhibitor co-treatment.

Our study revealed multiple ceritinib resistance mechanisms and suggest that some of the ceritinib resistance can be overcome by crizotinib.

Concurrent Session 4: Therapeutic Vaccines
Friday, November 6, 4:15 p.m.-6:15 p.m.
Ballroom C

PR04 Comprehensive analyses of tumor immunity with implications to cancer immunotherapies.
Bo Li. Dana-Farber Cancer Institute, Brookline, MA.

Recent breakthrough in checkpoint blockade drugs achieved remarkable success in treating late stage tumors, although a substantial fraction of patients failed to respond. Despite growing efforts, the clinical and molecular prognostic predictors of immunotherapy response remain elusive. We developed a novel computational method to deconvolute six tumor-infiltrating immune cells from the molecular profiles of over 10,000 samples across 23 cancer types, and validated the estimates using simulations, orthogonal estimates, and pathology. Correlating the computationally-inferred immune infiltrates with patient clinical features, viral infection status, and cancer genetic alterations, we discovered associations not only extensively supported by previous studies, but also novel ones such as B cell infiltration with better outcome in glioblastoma. Analysis of cancer/testis antigen expression and CD8 T-cell abundance suggested that MAGEA3 is potentially effective in melanoma but not in NSCLC, and implicated CALR3 and SPAG5 as alternative cancer vaccine targets. We also observed PD-1 and CTLA4 expression to be associated with CD8 T-cell abundance in most cancers, supporting combined use of checkpoint blockade drugs. Finally, we found that melanomas expressing high levels of CTLA4 showed two distinct levels of CD8 T-cell infiltration, which may influence clinical responses to anti-CTLA4 agents. Taken together, our systematic analyses of tumor immunity have the potential to inform effective cancer vaccines and checkpoint blockade therapies.
Genomic assessment of exceptional responders is a promising approach to identify predictors of response to antibody therapy directed against the immune checkpoint programmed death 1 (PD-1) receptor, which has been shown to yield prolonged and deep responses in multiple types of human cancer. We identified a patient with endometrial cancer who experienced an exceptional response to pembrolizumab, an antibody to programmed death 1 (PD-1) receptor. The primary endometrial cancer specimen and the biopsy from the recurrent supraclavicular lymph node (LN) metastasis obtained prior to treatment were analyzed by hybrid-capture based genomic profiling at a commercial CLIA-certified laboratory, Foundation Medicine, targeting all exons of 315 cancer-related genes. In the patient’s pre-treatment endometrial cancer specimens we identified a mutation in DNA polymerase epsilon gene (POLE), which is associated with disruption of the exonuclease activity required for proofreading function and results in a high mutation burden or “ultramutator” phenotype. This tumor did harbor a large number of mutations: 32 likely pathogenic sequence variants and 116 variants of unknown significance (VUS). We next reviewed genomic alterations in 252 deidentified endometrioid endometrial cancers that underwent genomic profiling with the FoundationOne assay and determined that 23 (9.1%) had sequence variants in POLE. The cancers with POLE sequence variants had a mean of 21.2 +/-4.1 mutations identified as likely pathogenic and 82.2 +/-25 variants identified as VUS, compared with a mean of 7.5+/-.0.5 likely pathogenic variants and 12.8 +/- 2.6 VUS in POLE wt cases (mean +/- S.E.; p<0.005 and P=0.015 , respectively). This is consistent with TCGA data showing that POLE mutant cancers typically harbor an extremely high mutational burden. To determine if POLE mutant cancers were associated with an immune signature, analysis of RNA sequencing data from endometrioid endometrial cancers in TCGA was performed. POLE mutant cancers have higher expression of several genes encoding for immune checkpoint-related proteins, including PD-L1 and PD-L2, than either MSI or MSS endometrioid cancers. POLE mutant cancers also showed higher expression of T-cell markers such as CD8A, CD3G, PD-1 and CTLA-4, suggesting the presence of a pre-existing T-cell infiltrate. Analysis of histologic image data from TCGA confirmed that POLE mutant cancers had presence of a robust lymphocytic infiltrate. These data suggest that endometrial cancers harboring POLE mutations are associated with expression of immune checkpoint genes and evidence of lymphocytic infiltration. Thus, these tumors may be exceptionally vulnerable to treatment with immune checkpoint inhibitor therapy. We propose further clinical investigation with immunotherapy in endometrial and other cancers with POLE mutations.

**PR06 Phase 1b dose-escalation study of trametinib (MEKi) plus palbociclib (CDK4/6i) in patients with advanced solid tumors.**

Ryan J. Sullivan, Rodabe N. Amaria, Donald P. Lawrence, John Brennan, Cathie Leister, Rajendra Singh, Jeff Legos, Holger Thurm, Li Yan, Keith T. Flaherty, Michael A. Davies, Jeffrey Sosman. Massachusetts General Hospital Cancer Center, Boston, MA; MD Anderson Cancer Center, Houston, TX; GlaxoSmithKline, Collegeville, PA; Independent, Philadelphia, PA; Novartis, East Hanover, NJ; Pfizer, La Jolla, CA; GlaxoSmithKline, Philadelphia, PA; Vanderbilt University, Nashville, TN.

Background: Combined inhibition of the MAPK pathway and CDK4/6 is an emerging treatment strategy for cancer. Dual inhibition of MEK, a key mediator of the MAPK pathway, and CDK4/6 showed synergy in cellular growth and survival assays in preclinical models, particularly in the setting of activating Ras
mutations. Trametinib (Tram) is a reversible, highly selective, allosteric inhibitor of MEK1 and MEK2 that is non-competitive towards adenosine triphosphate (ATP) and inhibits both MEK activation and kinase activity. Palbociclib (Palbo) is a highly selective reversible oral inhibitor of CDK4/6. This phase Ia study (NCT02065063) evaluated trametinib once daily combined with palbociclib 21 days-on / 7 days-off (21/7) in patients (pts) with advanced solid malignancies. Methods: The primary objectives were to determine the safety, tolerability, recommended combination regimen (RCR). Secondary objectives were to characterize the pharmacokinetics (PK) and describe anti-cancer activity. Pts were accrued to dose escalating cohorts and treated with Tram at 1.5 or 2.0 mg once daily (QD) co-administered with Palbo at 75, 100, or 125 mg 21/7 in 28-day cycles. Results: As of 24 August 2015, 28 pts were enrolled [18 M, 10 F; median age 59 yr (range 31 to 77)]. Systemic exposure to trametinib or palbociclib in combination was similar to that observed with single agents. The RCRs were determined to be Tram 2.0 mg QD plus Palbo 75 mg 21/7 (RCR1) and Tram 1.5 mg QD plus Palbo 100 mg 21/7 (RCR2). DLTs were observed in 1 (Gr 3 mucocitis) out of 7 (14.3%) and 1 (Gr 3 left ventricular ejection fraction decrease) out of 6 (16.7%) evaluable pts at RCR1 and RCR2, respectively. Two higher dose levels above RCR1 and RCR2 were deemed intolerable with DLTs observed in 2 out of 7 evaluable pts at Tram 2.0 mg QD plus Palbo 100 mg 21/7 (Gr 3 fatigue, and Gr 3 LVEF decrease); and in 2 out of 4 evaluable pts at Tram 1.5 mg QD and Palbo 125 mg 21/7 (Gr 3 hypertension and vitreous hemorrhage, and Gr 4 thrombocytopenia, respectively). Common adverse events (AEs), regardless of study drug relationship, were diarrhea (67.9%), acneiform rash (64.3%), and fatigue (53.6%). Grade 3 AEs and Grade 4 AEs occurred in 21 (75%) and 6 (21.4%) individual patients, respectively. Two patients with melanoma and CRC treated at RCR1 experienced partial responses that are ongoing, with duration of drug exposure of 13.6 and 10.8 months respectively at time of data cut-off. The patient with melanoma does not have any known BRAF or RAS mutations, while the patient with CRC has a known NRAS mutation Q61K 181C->A but no known BRAF mutation. Conclusions: Two RCRs for trametinib and palbociclib combination were determined together with the preliminary safety and PK/PD profile, as well as clinical activity. (This study is funded by GlaxoSmithKline and Pfizer, Inc.)

PR07 AZD9291 activity in patients with leptomeningeal disease from non-small cell lung cancer: A phase I study. Dae Ho Lee1, Dong-Wan Kim2, Myung-Ju Ahn3, Byoung Chul Cho4, Jong Seok Lee5, Xin Ye6, Pamela Yang7, Haiyi Jiang8, James Chih-Hsin Yang9, Asan Medical Center, Seoul, Korea; 2Seoul National University Hospital, Seoul, Korea; 3Samsung Medical Center, Seoul, Korea; 4Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea; 5Seoul National University, Bundang Hospital, Seongnam, Korea; 6AstraZeneca, Shanghai, China; 7National Taiwan University Hospital, Taipei, Taiwan.

This abstract has been withheld from publication due to its inclusion in the AACR-NCI-EORTC Molecular Targets Conference 2015 Official Press Program. It will be posted online at the time of its presentation in a press conference or in a session.

Concurrent Session 6: Advances in Targeting the Hormone Axis
Saturday, November 7, 4:30 p.m.-6:30 p.m.
Ballroom C

PR08 ARV-330: An androgen receptor PROTAC degrader for prostate cancer. James D. Winkler1, Meizhong Jin1, Andy P. Crew1, AnnMarie K. Rossi1, Ryan R. Willard1, Hanqing Dong1, Kam Siu1, Jing Wang1, Deborah A. Gordon1, Xin Chen1, Caterina Ferraro1, Craig M. Crews1, Kevin Coleman1, Taavi K. Neklesa1. 1Arvinas, Inc., New Haven, CT; 2Yale University, New Haven, CT.

Patients with prostate cancer who progress on therapy often have enhanced Androgen Receptor (AR) signaling due to several mechanisms: increased androgen production, increased AR expression, and/or specific AR mutations that render current therapies ineffective. A novel approach to block AR signaling is to specifically target AR for degradation. To do this, we have created AR PROTACs (PROtein-TArgeting
Chimeras), bi-functional molecules that have an AR binding moiety on one end and an E3 ligase-recruiting element on the other end, which leads to AR ubiquitination and degradation. We have applied this technology to determine whether it could address mechanisms of resistance to current therapy in prostate cancer models.

Our lead AR PROTAC, ARV-330, degrades AR in LNCaP and VCaP cells with 50% degradation concentrations (DC50s) < 1nM. AR degradation had functional consequences in cells, suppressing the AR target gene PSA, inhibiting proliferation, and potently inducing apoptosis in VCaP cells, with maximal apoptosis observed around 20 nM, versus 1 uM for enzalutamide. While both ARV-330 and enzalutamide block proliferation of VCaP cells in response to 0.1 nM of the AR agonist R1881, enzalutamide lost antiproliferative potency with increasing R1881 concentrations, whereas ARV-330 maintained antiproliferative effects. In cells containing the ARF876L mutation, enzalutamide was ineffective; however, ARV-330 maintained complete effectiveness. In mice, ARV-330 exhibited good pharmacokinetic properties, with t1/2 values of several hours and bioavailability of >80% after sc injection. Treatment of mice with ARV-330, at doses ranging from 0.3 to 10 mg/kg, resulted in reduction of AR protein levels and prostate involution in normal mice and, in mice implanted with VCaP tumors, reduction in plasma PSA and blockade of tumor growth.

In summary, the AR PROTAC ARV-330 removes AR from prostate cancer cells in a potent manner and produces therapeutic effects as a result. This cellular efficacy has translated into biomarker activity and efficacy in animal models, and ARV-330 is now in preclinical development. Thus, targeted degradation of AR may provide a novel mechanism for providing efficacious therapy for patients with prostate cancer for whom current therapies have failed.


Background: Inhibitors of androgen receptor (AR) signaling axis, such as enzalutamide and abiraterone, represent important advances in the management of castration-resistant prostate cancer (CRPC). However, resistance to these drugs is still occurring. Recent reports suggest that there are several mechanisms of resistance. Ligand independent AR activation such as induction of AR splice variants or c-Myc expression is a major emerging mechanism of CRPC progression. There is an urgent need for developing a novel therapy to address these unresolved issues.

Methods: For assay of androgen-independent AR transactivation, prostate cancer cells were transiently transfected with androgen-responsive reporter gene construct. The transfected cells were treated with growth factor and cytokine in steroid-depleted media, and luciferase activity was measured. To evaluate the effect of TAS3681 on AR and c-Myc protein expression, prostate cancer cells were treated with TAS3681 in steroid-depleted media. AR and c-Myc protein levels were determined by Western blot. Real-time PCR was used to analyze the mRNA levels of c-Myc and c-Myc target gene. Chromatin immunoprecipitation was performed to determine the enrichment of AR at the element.

Results: TAS3681 dose-dependently reduced AR protein levels in prostate cancer cells. In contrast to enzalutamide, TAS3681 suppressed androgen-independent AR transactivation by growth factor and cytokine. In prostate cancer cells which express full-length AR and splice variant AR-v7, TAS3681 suppressed AR-v7 target gene expression through downregulation of AR-v7 occupancy at the enhancer. Moreover, TAS3681 reduced expression of c-Myc, critical driver of androgen-independent mechanisms of prostate cancer progression, via AR downregulation activity. In addition, real-time PCR assay showed the suppression of c-Myc and c-Myc target gene mRNA levels by TAS3681 but not by enzalutamide.
Conclusion: Our findings suggest that TAS3681, a new type AR antagonist with AR downregulation activity, has a potential to overcome ligand-independent AR activation and could be a candidate of breakthrough therapy for resistance to current AR pathway target drugs.

PR10  RAD1901, an orally available selective estrogen receptor downregulator, has potent antitumor activity in in vitro and in vivo models of ER+ breast cancer.  Teeru Bihani1, Jeffrey Brown2, Gary Hattersley1, Fiona Garner1. 1Radius Health, Waltham, MA; 2Pharmagellan, Milton, MA.

Breast cancer is the most frequent type of cancer diagnosed in women, with over 200,000 new cases diagnosed in the US each year. Treatment strategies are typically based on the tumors receptor status; that is, whether a tumor expresses estrogen receptor (ER), progesterone receptor (PR), or Her2. Estrogen receptor positive (ER+) breast cancers comprise approximately two-thirds of all breast cancers. For decades the approach to treat ER+ disease revolved around altering the ligand interactions with the receptor; either by preventing estrogen binding (e.g., tamoxifen) or preventing estrogen biosynthesis (aromatase inhibitors). While patients typically respond well to these agents, estrogen-independent ER activity and recurrent ER mutations are increasingly being reported as contributing factors to endocrine resistance and continue to be a clinical hurdle. Given this growing unmet medical need, selective estrogen receptor downregulators, or SERDs, have gained widespread attention as new therapeutic treatment strategies for ER + disease. Indeed, fulvestrant has been shown to downregulate ER and cause tumor growth inhibition in many ER+ breast cancer models. However, in the clinic fulvestrant appears to be limited by PK exposure properties and this, combined with its intramuscular route of administration, underscores the need for novel orally available SERDs. Here, we describe RAD1901, an orally administered SERD that binds ER and targets it for degradation in a dose-dependent manner. Biochemical affinity binding studies and cocrystallization experiments revealed insights into RAD1901 complexes with both wild-type and mutant forms of ER. In addition, RAD1901 treatment resulted in decreased cell proliferation in in vitro breast cancer cell lines and had profound single agent tumor growth inhibition in in vivo xenograft models. Consistent with these findings, RAD1901 treatment resulted in decreased expression levels of ER target genes. Interestingly, the extent of tumor growth inhibition induced by RAD1901 in vivo was dependent on ER expression levels, demonstrating the specificity of RAD1901 and predicting its activity in ER-driven cancers. Importantly, RAD1901 was also able to induce significant tumor growth inhibition in clinically relevant and representative patient-derived xenograft models, at a level similar to or greater than fulvestrant. In conclusion, our preclinical data demonstrate that RAD1901 is an orally available SERD, with potent single agent antitumor activity. RAD1901 is currently under clinical investigation in post-menopausal women with advanced ER+ disease.

Spotlight on Proffered Papers: Session 3

Sunday, November 8, 3:45 p.m.-4:25 p.m.
Veterans Memorial Auditorium

PR11  Phase I study of a novel PARP1/2 selective inhibitor, BGB-290.  Jason Lickliter1, Hui Gan2, Tarek Meniawy3, Jason Yang1, Lai Wang4, Michael Millward1. 1Nucleaus Network, Melbourne, Australia; 2Austin Health Hospital, Melbourne, Australia; 3Linear Clinical Research/Sir Charles Gairdner Hospital, Nedlands, Australia; 4BeiGene (Beijing), Co., Ltd, Beijing, China.

This abstract has been withheld from publication due to its inclusion in the AACR-NCI-EORTC Molecular Targets Conference 2015 Official Press Program. It will be posted online at the time of its presentation in a press conference or in a session.
PR12  Discovery and preclinical evaluation of cEt-modified KRAS antisense oligonucleotide inhibitors.  
Alexey S. Revenko1, Sarah J. Ross2, Lyndsey L. Hanson3, Rebecca Ellston1, Chris May1, Sanjay K. Pandey1,  
Linda K. Buckett3, Stephanie K. Klein3, Mitchell Revill3, Kevin Hudson3, Brett P. Monia1, David C. Blakey3, Paul  
Lyne4, Allan R. MacLeod1. 1Isis Pharmaceuticals, Carlsbad, CA; 2AstraZeneca, Cambridge, United Kingdom;  
3AstraZeneca, Macclesfield, United Kingdom; 4AstraZeneca, Waltham, MA.

KRAS is one of the most frequently mutated genes in cancer and its activation is thought to underlie the  
pathogenesis of up to 30% of all human tumors. However, to date KRAS has proven difficult to target with  
traditional pharmacologic approaches. Antisense technology is particularly attractive for such difficult drug  
targets as antisense oligonucleotide (ASO) inhibitors can be designed based on a target’s RNA sequence  
alone.

cEt ASOs have been recently described and demonstrated to have significantly increased potency over  
previous generation ASO chemistries. Moreover, STAT3Rx/AZD9150, a cEt modified ASO targeting STAT3  
mRNA was recently shown to produce robust STAT3 depletion in a broad range of xenograft models (AACR  
2013) and importantly has also demonstrated promising single-agent antitumor activity in patients with  
advanced treatment-refractory cancers in phase I studies (ASCO 2013, EORTC 2014).

Here, we describe the preclinical evaluation of potent and selective cEt ASOs targeted to human or mouse  
KRAS mRNA. A human-specific KRAS cEt ASO which potently and selectively down-regulated KRAS  
demonstrated anti-proliferative effects and the expected down-stream pathway inhibition in a panel of  
KRAS mutant NSCLC, CRC and PDAC cells. The KRAS ASO was differentiated from MAPK pathway inhibitors  
selectively inhibiting the proliferation of KRAS mutant not KRAS wild type cells and not causing feedback  
reactivation of the MAPK or PI3K pathways. Systemic delivery of the KRAS ASO to mice bearing KRAS  
mutant NSCLC or CRC xenografts resulted in significant inhibition of KRAS tumor expression and antitumor  
activity. Importantly, the KRAS ASO also showed significant target knockdown and antitumor effects in  
KRAS mutant NSCLC patient-derived xenografts (PDX).

Finally, potent and selective murine-specific KRAS ASO produced robust target knockdown in a broad set of  
tissues without detectable tolerability signals associated with ASO-mediated systemic KRAS inhibition.

Taken together these data suggest that KRAS ASOs are an attractive therapeutic approach to target KRAS  
for the treatment of human cancers.

PR13  Clinical safety and activity from a phase 1 study of LOXO-101, a selective TRKA/B/C inhibitor, in  
solid-tumor patients with NTRK gene fusions.  David S. Hong1, Marcia S. Brose2, Robert C. Doebele3, Alice  
T. Shaw4, Afshin Dowlati5, Todd M. Bauer6, Anna F. Farago4, Adriana Estrada-Bernal5, Anh T. Lee3, Michael C.  
Cox7, Nisha Nanda1, Jennifer A. Low1, Howard A. Burris, III6. 1MD Anderson Cancer Center, Houston, TX;  
2University of Pennsylvania, Philadelphia, PA; 3University of Colorado, Aurora, CO; 4Massachusetts General  
Hospital, Boston, MA; 5University Hospitals Case Medical Center, Cleveland, OH; 6Sarah Cannon Research  
Institute / Tennessee Oncology, PLLC, Nashville, TN; 7Loxo Oncology, South San Francisco, CA.

This abstract has been withheld from publication due to its inclusion in the AACR-NCI-EORTC Molecular  
Targets Conference 2015 Official Press Program. It will be posted online at the time of its presentation in a  
press conference or in a session.