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INTELLIGENT INSIGHTS. SMART RESULTS

In the Spotlight:

EGF Receptor is Required for KRAS-Induced Pancreatic Tumorigenesis

In the pancreas, acute or chronic inflammation or KRAS activation leads to replacement of damaged acini with duct-like cells, referred to as acinar-to-ductal metaplasia (ADM). This is an early step in pancreatic cancer progression and the relationship between ADM and pancreatic ductal adenocarcinoma (PDA) progression has been studied extensively. Oncogenic KRAS mutation promotes the focal development of ADM in the absence of exogenous inducers of inflammation. Mutant KRAS-expressing metaplastic ducts progress into ductal precursor lesions known as pancreatic intraepithelial neoplasias (PanINs), which gradually acquire additional genetic changes and evolve into PDA.

Recent work by Ardito and colleagues and Navas *et al.* demonstrate that ADM- and KRAS-driven pancreatic cancer require EGFR signalling; revealing a mechanism for developmental reprogramming that primes tumorigenesis. Researchers employed genetic and pharmacological inactivation of EGFR in KRAS driven mouse models to directly determine the contribution of endogenous EGFR pathway signaling to the development of ADM and PDA. They found that EGFR expression is upregulated in ADM and PanIN lesions. Knockout of EGFR in the pancreas or treatment of mice with pharmacological EGFR inhibitors suppressed ADM provoked by activated KRAS or the cholecystokinin analog, cerulein. Moreover, acute EGFR inhibition resulted in apoptosis in established ADM and PanIN lesions.

Read more

Tumor of the Month: Small Cell Lung Cancer

Lung cancers, the second most commonly diagnosed cancer in the US, constitute 14% of newly diagnosed cancers.[1] They are broadly divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The American Cancer Society predicted that 226,160 new cases of lung cancer will be diagnosed in 2012, and ~28, 270 of the new cases will be SCLC.[2] The lifetime risk of lung cancer (any form) is 1 in 18 for men and 1 in 16 for women. African-American men have highest risk of lung cancer.[3] Overall, 80% of lung cancer deaths are due to smoking, which plays a greater role in SCLC.[3] A decrease in lung cancer risk has been observed in both men and women in recent years. SCLC is particularly aggressive; median survival of patients with SCLC after diagnosis is 2 to 4 months if the patient is not treated.[4] As a whole, 5-year survival in patients with SCLC is 5-10%, but only 10% of SCLC patients survive the first two years after diagnosis.[4]

The staging of SCLC is simple compared to other types of cancers. SCLC staging is divided into Limited stage disease (LD) and Extensive-stage disease (ED). Limited stage disease refers to tumors confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes.[4] Although 30% of SCLCs are diagnosed at this stage, SCLCs disseminate very early in tumorigenesis making the disease difficult to treat and prone to relapse. Extensive-stage disease refers to tumors that have spread beyond the supraventricular area.

Read more

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Spotlight Report

EGF Receptor Required for KRAS-Induced Pancreatic Tumorigenesis

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Navas *et al.* found that EGFR knockout completely prevented PDA development in their KRAS model even in the context of deletion of CDKN2A, whereas both groups found that EGFR deletion delayed but did not eliminate PDA formation in KRAS-TP53 mutant models. These results established that EGFR is required for both the initiation and survival of ADM (and PanIN) lesions and showed that its ablation restricts the development of PDA. Rather than playing a generic function in KRAS-mediated transformation, EGFR has specific roles in PDA initiation, acting to facilitate the developmental reprogramming of pancreatic acinar cells. Ardito *et al.* showed that acute EGFR inhibition reduced levels of phospho-ERK1/2 and GTP-bound active RAS in ADM lesions in KRAS mice and acinar explants, respectively. However, Navas *et al.* did not observe changes in ERK1/2 activity in their model. Differences between the mouse models used in these two studies may account for some of these discrepancies.

Since inherited predisposition to chronic pancreatitis greatly increases PDA risk and precursor lesions harboring KRAS mutations are common in otherwise normal pancreatic tissue of elderly individuals, there may be a benefit in the development of preventive strategies that eradicate ADM and PanIN lesions. The present studies support the potential of targeting TGF alpha-ADAM17-EGFR axis as an approach to PDA prevention.

Source: Cancer Cell. 2012 Sep 11;22(3):304-17; Cancer Cell. 2012 Sep 11; 22(3):318-30.

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The current standard of care is a combination of cisplatin and etoposide.[5] Roughly 60-70% of patients

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respond to 1st line etoposide-cisplatin therapy. Patients with LD show median survival of 18-30 months, while patients with ED show median survival of 8-12 months. Incorporating thoracic radiation early in the chemotherapy cycle and hyperfractionation with twice-daily radiotherapy increases patient survival. Prophylactic cranial irradiation seems to add survival benefit to patients who respond well to chemotherapy.[5]

Response to 2nd line therapy correlates with the tumor's initial response to 1st line chemo and to the length of the progression-free interval after 1st line therapy is completed.[5] Topotecan has emerged as the best 2nd line therapy for SCLC, but only about 25% of patients respond to this drug.[5] At the 2011 ASCO meeting, Dr. Jotte's group presented evidence that amrubicin, a 3rd generation anthracycline and potent topoisomerase II inhibitor, showed a better RR, PFS, and safety than topotecan.[6] However, amrubicin did not show a statistically significant increase in overall survival.

A review by Stovold and colleagues identified pro-GRP (pro-gastrin related peptide) as a sensitive and specific marker of SCLC.[7] The authors also discuss another study that demonstrated that neuron specific enolase is a better prognostic marker for SCLC, while pro-GRP is a better diagnostic marker. Pro-GRP showed greater sensitivity than neuron specific enolase in LD-SCLC and greater specificity in detecting SCLC compared to NSCLC.

The RASTEN study, (NCT00717938) sponsored by Lund University Hospital (Sweden) and Sanofi-Aventis, will investigate whether the addition of enoxaparin - a low molecular weight heparin, will increase the overall survival in patients with SCLC. This randomized study will enroll about 390 SCLC patients who have not received previous systemic therapy. Patients will receive platinum therapy and a topoisomerase inhibitor every three weeks for 4-6 cycles. Patients in the experimental arm will also receive daily injections of enoxaparin. The primary endpoint is a significant increase in overall survival. The study will also assess toxicity during treatment.

The COMBAT Trial (NCT00826644) is comparing the efficacy of the Topoisomerase I inhibitor, belotecan, to etoposide in the treatment of chemotherapy naïve SCLC patients.This randomized, prospective, multi-center trial will enroll 150 ED SCLC patients. Patients will receive cisplatin (60 mg/m^2/day on day 1) plus belotecan (0.5 mg/m^2/day) on days 1 to 4 or etoposide (100 mg/m^2/day) on days 1-3. The 2nd cycle will begin on day 22. The trial is being sponsored by Chonnam National University Hospital (Korea) in collaboration with Chong Kun Dang Pharmaceuticals. The primary outcome will be response rate, while secondary measures will be overall response duration, time to progression, and overall survival.

ZIOPHARM Oncology (Charlestown, MA) is testing the alkylating agent, palifosfamide-tris, in the MATISSE Study (NCT01555710). The open-label, adaptive study will address the efficacy of palifosfamide-tris in combination with carboplatin and etoposide in patients with treatment naïve extensive disease SCLC (see Table 1). Overall survival is the primary outcome. Secondary outcomes are PFS, quality of life, objective response rate, response duration, and safety parameters. The study, which began in May 2012, will enroll 548 patients. ZIOPHARM notes that palifosfamide-tris exhibits promise in cancers with high ALDH, an enzyme associated with cancer stem cell-like activity and, therefore, resistance to chemotherapy.[8]

Table 1. MATISSE Study

Drug	Arm A	Arm B
Etoposide	100 mg/m^2/day 3 days every 21 days, maximum of 6 cycles	100 mg/m^2/day 3 days every 21 days, maximum of 6 cycles
Carboplatin	AUC 4 mg/ml/min 1 day every 21 days, maximum of 6 cycles	AUC 5 mg/ml/min 1 day every 21 days, maximum of 6 cycles
Palifosfamide-tris	130 mg/m^2/day 3 days every 21 days, maximum of 6 cycles	

Reck and colleagues recently published a randomized, double-blind, multicenter Phase II trial in which they added ipilumumab (an anti-CTLA4 monoclonal antibody) to paclitaxel and carboplatin for patients with ED-SCLC who had not been previously treated.[9] The study was randomized 1:1:1 (see Table 2).

Table 2. Reck *et al.* study cohorts

Drug	Concurrent ipilimumab regimen	Phased ipilimumab regimen	Control regimen
Treatment	Four doses paclitaxel/ carboplatin/ipilimumab, then 2 doses placebo/ paclitaxel/carboplatin	Two doses of placebo/ paclitaxel/ carboplatin, then four doses of ipilimumab/paclitaxel/ carboplatin	Up to six doses of placebo/ paclitaxel/ carboplatin
Paclitaxel	175mg/m^2	175mg/m^2	175mg/m^2
Carboplatin	AUC=6	AUC=6	AUC=6
Ipilimumab	10 mg/kg	10 mg/kg	Placebo

Patients without progression who continued to tolerate treatment received either ipilimumab (phased- and concurrent-ipilimumab arms) or placebo (control arm) once every 12 weeks as maintenance until progression, death, or intolerance. In the control arm, 44 patients were treated, while each of the experimental arms treated 42 patients. Patients in the phased ipilimumab arm showed increased median survival (6.44 months, 5.29-7.75) compared to control (5.26 months, 4.67-5.72) and concurrent ipilimumab (5.68 months, 5.19-6.87). Patients in the phased ipilimumab arm also showed improved immune-related PFS (irPFS) compared to the control arm [HR=0.64; P=0.03]. Although no

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improvement was seen in PFS or OS, the median OS was increased from 9.9 months for the control arm to 12.9 months for the phased cohort. The concurrent cohort saw a slight decrease in the median OS to 9.1 months. The authors were optimistic that ipilimumab warrants further investigation for the treatment of SCLC.

In the September 2012 issue of *Cancer Discovery*, Byers and colleagues profile 34 SCLC and 74 NSCLC by reverse phase protein arrays (RPPA) and gene expression arrays.[10] The authors began with RPPAs, which are able to identify changes in total protein levels as well as changes in post-translational modifications. The authors specifically looked at total protein levels and phosphorylation status of 193 proteins. The pathways dysregulated in SCLC were interesting. Rb was previously shown to be lost in some SCLCs. Byers and colleagues demonstrated that other components of the Rb pathway were also dysregulated. Specifically, E2F1, cyclin D1, p16, p21, EZH2, thymidylate synthase, and cyclin E1 were all significantly upregulated. Apoptotic proteins and DNA repair proteins were also dysregulated. The authors focused on the apoptotic protein, PARP-1, which was dramatically upregulated in SCLCs. They demonstrated that PAR levels were decreased when SCLC cell lines were treated with PARP inhibitors. Interestingly, the decrease in PAR levels were not enough to predict sensitivity to the PARP inhibitors as one cell line showed a dramatic decrease in PAR levels after drug treatment, but the line was still resistant to the drug. Combining a PARP inhibitor with etoposide, paclitaxel or irinotecan decreased cell survival. Addition of a PARP inhibitor to cells treated with paclitaxel and etoposide did not significantly increase the percentage of cells killed compared to the cells treated with paclitaxel and etoposide.

A search of clinicaltrials.gov shows that Sloan-Kettering is currently enrolling patients in a Phase II trial that will compare the PARP inhibitor, veliparib, in conjunction with temozolomide to temozolomide alone in relapsed or refractory SCLC (NCT01638546). PFS is the primary outcome measure. Secondary outcomes are ORR, OS, safety and tolerability.

Two papers in the advance online publication section of *Nature Genetics* use genomic techniques to identify mutations in SCLCs. These studies should also add to the list of potential new targets for SCLC.[11,12]

Business News

Symphogen Grants Exclusive Worldwide License of Oncology Drug Sym004 to Merck KGaA

Symphogen announced an exclusive worldwide license agreement with Merck KGaA, for Sym004, a recombinant immunoglobulin G1 (IgG1) comprising two anti-epidermal growth factor receptor (EGFR) monoclonal antibodies which target different non-overlapping EGFR epitopes. Sym004 is currently evaluated in a Phase I/II trial for the treatment of patients with advanced KRAS wild-type metastatic colorectal cancer (mCRC) who have previously progressed on treatment with standard chemotherapy and a marketed anti-EGFR monoclonal antibody. In addition, single-arm, open-label Phase II trial in patients with squamous cell carcinoma of the head and neck (SCCHN) who have failed anti-EGFR-based therapy is currently ongoing.

Under the agreement, Symphogen will receive €20 million from Merck. Symphogen is also eligible to receive up to €225 million for clinical development and regulatory milestones, €250 million for potential combined sales performance milestones and royalties on net worldwide sales. In exchange, Merck will gain exclusive worldwide rights to develop and commercialize Sym004.

Source: Symphogen

ImmuNext to Partner with Janssen for Development of Novel Immunotherapies for the Treatment of Cancer

ImmuNext announced that it has entered into an agreement with Janssen Biotech to develop novel therapeutics that modulate the immune system for the treatment of cancer. Under the terms of the agreement, ImmuNext will grant Janssen a worldwide, exclusive license to develop and commercialize therapeutics that antagonize the V-region immunoglobulin-containing suppressor of T-cell activation (VISTA, a newly identified negative checkpoint regulator) signaling pathway, while ImmuNext would receive an upfront payment, plus payments for reaching certain development and commercial-based milestones, which could total more than $150 million. ImmuNext is also eligible to receive royalties on sales of products and sponsored research support. Janssen will be responsible for clinical development and commercialization of all products.

Source: ImmuNext

SFJ Pharmaceuticals Enters into an Agreement with Pfizer to Co-Develop Dacomitinib

SFJ Pharmaceuticals Group (SFJ) announced that it has entered into a collaborative development agreement with Pfizer to conduct a Phase III clinical trial of Pfizer's investigational pan-HER (pan-human

Business News
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epidermal growth factor receptor) inhibitor, dacomitinib (PF-00299804). The trial, which will be conducted across multiple sites in Asia and Europe, will evaluate dacomitinib as a 1st line treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR.

Under the terms of the agreement, SFJ will provide the funding and clinical development supervision to generate the clinical data necessary to support a registration dossier on dacomitinib for marketing authorization by regulatory authorities for 1st line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations. If approved for this indication, SFJ will be eligible to receive milestone payments and earn-out payments.

Source: SFJ Pharmaceuticals

BioLineRx In-Licenses BL-8040, a Phase II Drug to Biokine for the Treatment of Hematological Cancers

BioLineRx announced that it has signed an exclusive, worldwide license agreement with Biokine Therapeutics for the development and commercialization of BL-8040 (formerly BKT-140), a Phase II drug candidate for the treatment of acute myeloid leukemia (AML), as well as other types of hematological cancer. BL-8040 is a short peptide that functions as a high-affinity antagonist for CXCR4, a chemokine receptor that is directly involved in tumor progression, angiogenesis, metastasis and cell survival.

There are no upfront payments due pursuant to the agreement. BioLineRx is obligated to pay a monthly development fee ranging from $50K to $100K for certain development services that Biokine has committed to provide under the agreement. If the agreed-upon clinical development plan is completed within certain defined timelines, BioLineRx is obligated to pay Biokine a milestone payment of $250K. The agreement does not contain any other milestone payments.

Source: BioLineRx

Genmab Enters Worldwide Agreement with Janssen for Daratumumab

Genmab announced a global license and development agreement for daratumumab (HuMax-CD38), a human CD38 monoclonal antibody with Janssen Biotech. Daratumumab is currently in development for multiple myeloma and may have potential in other cancer indications such as acute myeloid leukemia. Under the terms of the agreement, Genmab will grant Janssen an exclusive worldwide license to develop and commercialize daratumumab.

According to the agreement, Genmab will receive an upfront license fee of $55 million. Genmab could also be entitled to up to $1 billion in development, regulatory and sales milestones, in addition to tiered double digit royalties. Janssen will be fully responsible for all costs associated with developing and commercializing daratumumab, including the costs of ongoing Phase I/II studies.

Source: Genmab

Research Highlights

Recurrent R-spondin Fusions in colon cancer

Colorectal cancer (CRC) is the fourth most prevalent cancer in the US. ~15% of CRCs have microsatellite instability (MSI) arising from defects in the DNA mismatch-repair (MMR) system, whereas the other, 85% of microsatellite-stable (MSS) CRCs are the result of chromosomal instability. Genomic studies have identified mutations in genes, chromosomal structural variants and pathway alterations that probably contribute to CRC development. Identifying and understanding changes in cancer genomes is essential for the development of targeted therapeutics.

Seshagiri *et al.* in a study published in *Nature*, systematically analyzed more than 70 pairs of primary human colon tumors by applying next-generation sequencing to characterize their exomes, transcriptomes and copy-number alterations. They identified 36,303 protein-altering somatic changes that include several new recurrent mutations in the Wnt pathway gene *TCF7L2*, chromatin-remodelling genes such as *TET2* and *TET3* and receptor tyrosine kinases including *ERBB3*. An analysis for significantly mutated cancer genes identified 23 candidates, including the cell cycle checkpoint kinase *ATM*. Copy-number and RNA-seq data analysis identified amplifications and corresponding overexpression of *IGF2* in a subset of colon tumors and also using RNA-seq data the workers identified multiple fusion transcripts including recurrent gene fusions involving

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R-spondin family members *RSPO2* and *RSPO3* that together occur in 10% of colon tumors. The *RSPO* fusions were mutually exclusive with *APC* mutations, indicating that they probably have a role in the activation of Wnt signalling and tumorigenesis, consistently showing that the *RSPO* fusion proteins were capable of potentiating Wnt signalling.

The study findings indicate that the R-spondins probably function as drivers in human CRCs. Although further studies will be required to fully understand the role of R-spondin fusions in CRC development, they represent attractive targets for antibody-based therapy in CRC patients positive for R-spondin fusions. Other therapeutic strategies that target downstream components of the Wnt signaling cascade will probably be effective against tumors positive for R-spondin fusions.

Source: Nature. 2012 Aug 30; 488(7413):660-4.

Heterodimeric JAK-STAT Activation as a Mechanism of Persistence to JAK2 Inhibitor Therapy

The development of targeted therapies has improved outcomes for patients with kinase-mutant malignancies; but acquired resistance due to mutations in the target kinase or in other pathways that render cancer cells insensitive to kinase inhibitor therapy remain important clinical concerns. Although JAK inhibitors are now used to treat patients with myeloproliferative neoplasm (MPN), so far JAK inhibitor treatment has not been associated with significant decreases in disease burden in most patients with MPN. To understand mechanisms by which MPN cells survive despite chronic JAK kinase inhibition, Koppikar *et al.* performed saturation mutagenesis19 and next-generation sequencing in cells exposed to two structurally different JAK2 inhibitors, INCB18424 and JAK Inhibitor I.

Investigators observed that JAK2 inhibitor persistence is associated with reactivation of JAK–STAT signalling and with heterodimerization between activated JAK2 and JAK1 or TYK2, consistent with activation of JAK2 *in trans* by other JAK kinases. Moreover, this phenomenon is reversible: JAK2 inhibitor withdrawal is associated with resensitization to JAK2 kinase inhibitors and with reversible changes in JAK2 expression. RNA interference and pharmacological studies showed that JAK2-inhibitor-persistent cells remain dependent on JAK2 protein expression. These results suggest that kinase inhibitor persistence can occur through reversible changes in JAK2 expression and transphosphorylation. Persistent JAK2 activation in the setting of exposure to JAK inhibitor allows cells to survive without decreasing dependence on JAK2 expression.Consequently, treatments that lead to JAK2 degradation (Hsp90 inhibitors or histone deacetylase inhibitors) or that retain the ability to inhibit JAK2 in persistent cells have the potential to improve therapeutic efficacy in patients with MPN.

Source:Nature. 2012 Sep 6;489(7414):155-9.

Passenger Deletions Generate Therapeutic Vulnerabilities in Cancer

Targeted treatments directed against amplified or mutant-activated key driver on coproteins have provided encouraging clinical progress, whereas exploiting loss-of-function mutations or gene deletions has received considerably less attention and has not been as successful so far. In a study published in Nature, Muller *et al.* proposed that the homozygous deletion of redundant essential housekeeping genes could create cancer-specific vulnerabilities, in which pharmacological inactivation of the second, non-deleted homologue would result in the complete loss of activity in tumor cells carrying the deletion, without compromising the health of normal cells, in which both genes are intact and expressed. The glycolytic gene enolase 1 (ENO1) in the 1p36 locus is deleted in glioblastoma (GBM), which is tolerated by the expression of ENO2.

Investigators have shown that short-hairpin-RNA-mediated silencing of ENO2 selectively inhibits growth, survival and the tumorigenic potential of ENO1-deleted GBM cells, and that the enolase inhibitor phosphonoacetohydroxamate is selectively toxic to ENO1-deleted GBM cells relative to ENO1-intact GBM cells or normal astrocytes. Given the large number of homozygous deletions across many different cancer types spanning many hundreds of genes, the model described here for GBM should be applicable to the development of personalized treatments for many other cancer types.

Source: Nature. 2012 Aug 16;488(7411):337-42.

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Clinical Development

T-DM1 Significantly Improved Survival of People with HER2+ve mBC

Genentech announced updated results from the Phase III EMILIA study, which showed that trastuzumab emtansine (T-DM1), a HER2 antibody-drug conjugate, significantly improved overall survival (OS) of people with HER2-positive metastatic breast cancer (mBC) compared to the combination of lapatinib and Xeloda (capecitabine). The EMILIA study, in 991 subjects with HER2-positive mBC who had previously received Herceptin (trastuzumab) and taxane chemotherapy, has now met both co-primary efficacy endpoints of significant improvements in OS and progression-free survival (PFS). This data will be presented at an upcoming medical meeting. Genentech has submitted a Biologics License Application (BLA) for trastuzumab emtansine to the FDA, and Roche will shortly be submitting a Marketing Authorization Application to the European Medicines Agency (EMA).

Based on these updated results, people in the lapatinib and Xeloda arm of EMILIA will be offered the option to receive trastuzumab emtansine. Genentech is also planning to open an Expanded Access Program (EAP) in the US to provide under certain circumstances, people with HER2-positive mBC access to trastuzumab emtansine while the company seeks regulatory approval.

Source: Genentech

Temporary Suspension of Patient Enrollment for Phase III Study of ARQ 197 in NSCLC

Kyowa Hakko Kirin Co. announced the temporary suspension of patient enrollment in an international Phase III (ATTENTION - Asian Trial of Tivantinib plus Erlotinib vs. Erlotinib for NSCLC without EGFR Mutation) study evaluating the combination of ARQ 197 (tivantinib) and erlotinib in patients with advanced or metastatic NSCLC in Asia (Japan, Korea, and Taiwan), according to the recommendations by Safety Review Committee. This study is a randomized, double-blinded trial comparing ARQ197, a proto oncogene protein c met inhibitor, and erlotinib to placebo and erlotinib. Patient enrollment has been suspended based on the higher frequency of interstitial lung disease cases in the study as one of drug-related adverse reactions.

Kyowa Hakko Kirin signed a license agreement with ArQule for the exclusive rights to the development and sales of ARQ 197 in Japan and some parts of Asia (China, Korea, and Taiwan) on April 27th, 2007.

Source: Kyowa Hakko Kirin

POINTBREAK Phase III Study Did Not Meet Primary Endpoint in Patients with Non-squamous NSCLC

Eli Lilly and Company announced that the Phase III POINTBREAK trial did not meet its primary endpoint of improved OS for patients with non-squamous NSCLC who were randomized to receive a combination of ALIMTA (pemetrexed for injection) with bevacizumab (AVASTIN) and carboplatin induction followed by ALIMTA plus bevacizumab maintenance, the ALIMTA arm, compared to the combination of paclitaxel with bevacizumab and carboplatin followed by bevacizumab maintenance, the paclitaxel arm. The study did meet one of its secondary endpoints of improved PFS for the ALIMTA arm.

Patients with previously untreated stage IIIB/IV non-squamous NSCLC and a performance status of 0-1 (n=939) were randomized to receive ALIMTA + carboplatin + bevacizumab, along with dexamethasone and folic acid and vitamin B12 supplementation (n=472) or paclitaxel + carboplatin + bevacizumab, with dexamethasone (n=467). Patients whose disease did not progress following 1st line treatment received either maintenance of ALIMTA plus bevacizumab (n=292) on the ALIMTA arm, while those on the paclitaxel arm received bevacizumab as a single agent (n=298). Patients randomized to the ALIMTA arm achieved a mOS of 12.6 months vs. 13.4 months for patients on the paclitaxel arm (HR 1.00; p=0.949). POINTBREAK showed a statistically significant improvement in PFS (6.0 months versus 5.6 months [HR 0.83; p=0.012]) in the ALIMTA arm. Secondary objectives also included overall response rate (34.1% versus 33.0%) and disease control rate (65.9% versus 69.8%), which did not show a difference between the two arms. A pre-specified non-comparative survival analysis for a subgroup of patients treated with maintenance therapy showed a median survival of 17.7 months for the ALIMTA arm and 15.7 months for the paclitaxel arm and PFS of 8.6 months and 6.9 months. Significantly, ($p \leq 0.025$) more drug-related grade 3/4 anemia (14.5% versus 2.7%), thrombocytopenia (23.3% versus 5.6%) and fatigue (10.9% versus 5.0%) were seen on the ALIMTA arm.

Source: Eli Lilly

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Resminostat Achieves mOS of 8.0 Months in 2nd line Advanced HCC Patients

4SC AG announced the publication of convincing OS data from a Phase II study with its lead anti-cancer drug Resminostat, a histone deacetylases inhibitor, as a novel combination therapy approach with sorafenib in 2nd line advanced HCC at the 2012 annual meeting of the International Liver Cancer Association in Berlin, Germany, on 16 September 2012.

The international, open-label, two-arm SHELTER study enrolled patients with advanced HCC who had shown proven radiological tumor progression under 1st line treatment with the cancer drug sorafenib. The study investigated safety and efficacy of resminostat as a monotherapy and in combination with sorafenib in this patient group with currently no approved treatment option. Final median OS of 8.0 months was determined in the resminostat/sorafenib combination 'intend-to-treat' (ITT) population (n=26). In the resminostat monotherapy group (ITT population, n=19), the final median OS value has been determined as 4.1 months. In both study arms, resminostat has proven to be safe and well tolerated.

Resminostat progression-free survival (PFS) efficacy data of the SHELTER study have been presented earlier this year at the Annual Meeting of the American Society of Clinical Oncology (ASCO) on 4 June 2012 in Chicago (USA). The data for the resminostat/sorafenib combination therapy showed a progression-free survival rate (PFSR) after 12 weeks of treatment of 70.0% and a median PFS of 4.7 months. For the resminostat monotherapy group, the final PFSR at 12 weeks was 35.3% and the median PFS was 2.2 months. As previously reported, the primary study endpoint PFSR at 12 weeks had been achieved ahead of schedule in both the combination and the monotherapy group. Pivotal Phase III trial of resmonostat is planned by mid-2013 in 2nd line HCC patients preferably with a partner.

Source: 4SC

Positive Clinical Data from Phase II Trial of JX594 in Sorafenib-Refractory HCC Patients

Jennerex presented Phase II clinical data of JX594 delivered first intravenously and subsequently through intra-tumoral route demonstrating safety as well as disease control and tumor responses in patients with HCC at the International Liver Cancer Association (ILCA) Annual Meeting in Berlin, Germany, by Mong Cho, M.D., from Pusan National University Yangsan Hospital, South Korea.

Twenty five Asian patients with advanced HCC, 20 of whom were refractory to sorafenib, were treated with an initial intravenous dose of JX594, and the majority of patients then received sequential intra-tumoral doses of JX594 at week one and three. The majority of patients subsequently received treatment with sorafenib. Following treatment with JX594 alone at four weeks, 62% of patients had disease control as measured by modified RECIST. Tumor biopsies of four patients following intravenous infusion showed four of four patients had local infection of JX594 in tumor tissue while normal liver tissue was not affected, providing further evidence of JX-594's tumor selectivity and the ability to administer JX594 intravenously. Also after six or 12 weeks, 59% of patients had disease control as measured by modified RECIST and 75% of patients had objective responses by Choi criteria. 85% of patients had disease control by mRECIST and /or Choi response.

Source: Jennerex

Peregrine Announces Major Discrepancies in its Bavituximab Phase II 2nd line NSCLC Trial

Peregrine Pharmaceuticals announced that during the course of preparing for an end-of-Phase II meeting with regulatory authorities and following recent data announcements from its randomized, double-blind placebo-controlled Phase II trial of bavituximab in 2nd line NSCLC, it discovered major discrepancies between some patient sample test results and patient treatment code assignments. Due to the double-blind nature of the trial, Peregrine was not permitted to have access to either patient group assignments or related product coding information. As part of the trial's execution, Peregrine contracted with independent third-party contractors to execute treatment group assignments and oversee clinical trial material coding and distribution according to established procedures. A subsequent review of information has determined that the source of these discrepancies appear to have been associated with the independent third-party contracted to code and distribute investigational drug product. Peregrine intends to communicate further as soon as it is able to determine the impact of this issue. In the meantime, company has asked its investors not to rely on clinical data that the company disclosed on or before September 7, 2012 from its Phase II bavituximab trial in patients with 2nd line NSCLC or any presentations or other documents related to this Phase II trial.

Peregrine Pharmaceuticals, presented interim results of this Phase II trial at the 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology. The trial enrolled 121 patients (117 evaluable per the study protocol) with 2nd line non-squamous NSCLC following one prior chemotherapy regimen. Patients

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were equally randomized to 1 of the 3 treatment arms, docetaxel plus either placebo (control arm), 1 mg/kg bavituximab, or 3 mg/kg bavituximab until disease progression. The interim data showed a statistically significant improvement in OS (Hazard Ratio 0.524, p-value .0154) and a doubling of mOS in the bavituximab-containing arms compared to the control arm. The interim results from the study showed no significant safety differences between the three treatment arms as determined by the trial's independent data monitoring committee.

Source: Peregrine Pharmaceuticals[1,2]

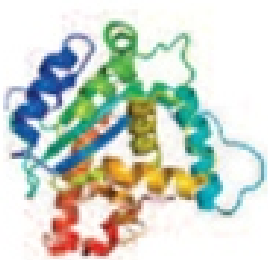
Geron Provides Update on Imetelstat Clinical Development Program

Geron Corporation announced that, on the basis of an unplanned interim analysis, it is discontinuing its randomized Phase II study of imetelstat, a telomerase inhibitor, in metastatic HER2-negative breast cancer because mPFS in the imetelstat arm was shorter than in the comparator arm. The Company also announced that it is continuing its randomized Phase II study of imetelstat in advanced NSCLC. Although a separate interim analysis of the NSCLC study suggested a modest trend of efficacy in favor of the imetelstat arm, the pre-specified success criteria in this trial are unlikely to be met, and therefore it is doubtful that Geron will take imetelstat forward into Phase III development for NSCLC.

The study in metastatic HER2-negative breast cancer was a randomized, controlled trial of 166 patients in which imetelstat was evaluated in combination with paclitaxel, compared to paclitaxel alone. The primary efficacy endpoint was an estimate of PFS. In this trial, a scheduled periodic review conducted by Geron's Internal Safety Monitoring Committee reported a greater number of deaths and number of patients discontinuing paclitaxel in the imetelstat arm compared to the control arm. Based on these observations, an unplanned interim analysis of efficacy was performed that showed a median PFS of 6.2 months for patients receiving treatment with imetelstat in combination with paclitaxel, compared to 8.0 months for patients receiving paclitaxel alone (hazard ratio = 1.62; p = 0.028). Although the absolute number of deaths was higher in the imetelstat arm (16 vs. 10), there was no statistically significant difference in OS. Based on these findings, Geron has discontinued this trial.

Geron's plans for further development of imetelstat in hematologic malignancies have not been adversely impacted by these results. The Company is evaluating imetelstat in two hematologic malignancies: essential thrombocythemia (ET) and multiple myeloma. Geron continues to expect to release top-line results from these studies in the fourth quarter of this year.

Source: Geron



Biomarkers

RUNX1 Mutations are Associated with Poor Outcome in Patients with Cytogenetically Normal AML

Cytogenetically normal AML (CN-AML) is the largest cytogenetic group among patients with AML and several recurring mutations with prognostic significance in genes such as *FLT3, NPM1, CEBPA, WT1, MLL, IDH1, IDH2,* and *TET2* have been identified. The runt-related transcription factor 1 (*RUNX1*) gene encodes a transcription factor required for definitive hematopoiesis. Acquired *RUNX1* mutations have been associated with poor clinical outcome in younger patients with CN-AML; however, these mutations were not found to impact outcome in older patients with CN-AML.

Mendler *et al.* in a study published in *JCO*, investigated the association of *RUNX1* mutations with therapeutic outcome in younger and older patients with primary CN-AML and with gene/microRNA expression signatures. Investigators found that *RUNX1* mutations occur in a substantial proportion of patients with primary CN-AML with wild-type *NPM1* and *CEBPA*. They are twice as common in older than younger patients with CN-AML and negatively impact outcome in both age groups. The mutations were associated with *ASXL1* mutations and inversely associated with *NPM1* and *CEBPA* mutations. *RUNX1*-mutated patients had lower complete remission rates and shorter disease-free survival, overall survival, and event-free survival than *RUNX1* wild-type patients. Because *RUNX1* mutations were more common in older patients and almost never coexisted with *NPM1* mutations, *RUNX1* mutation–associated expression signatures were derived in older, *NPM1* wild-type patients and featured upregulation of genes normally expressed in primitive hematopoietic cells and B-cell progenitors, including *DNTT, BAALC, BLNK, CD109, RBPMS*, and *FLT3*, and downregulation of promoters of myelopoiesis, including *CEBPA* and *miR-223*.

Thus, patients harboring *RUNX1* mutations warrant strong consideration of up-front novel therapies

Biomarkers (Cont'd)

and/or early allogeneic stem-cell transplantation. *RUNX1* mutation–associated expression signatures are characteristic of primitive hematopoietic and lymphoid progenitors and provide candidate molecules to guide development of novel therapeutic approaches.

Source: J Clin Oncol. 2012 Sep 1;30(25):3109-18.

MicroRNAs in the p53 Network: Micro-management of Tumor Suppression

In recent years, MicroRNAs (miRNAs) have been identified as mediators of tumor suppression and stress responses exerted by the p53 tumor suppressor. p53 is one of the most commonly mutated tumor suppressors and is a transcription factor that is thought to function mainly by regulating the expression of target genes. HeikoHermeking, in an article in *Nature Reviews Cancer*, describes the intricate interplay between p53 and miRNAs, which indicates that various miRNAs regulate, and are regulated by, p53 activity.

p53 regulates the processing of precursor miRNAs, either directly by binding to DROSHA or indirectly, as mutant p53 binds to and inactivates p63 and thereby downregulates the expression of DICER1. Also, p53 may affect miRNA target gene selection by regulating mRNA-binding proteins, such as RNA-binding-motif protein 38 (RBM38). p53 regulated miRNAs mediate tumor suppression and stress responses by regulating multiple key processes, such as cell cycle progression, migration, epithelial–mesenchymal transition, stemness, metabolism, differentiation and cell survival. miRNAs achieve this by directly targeting the translation and mRNA stability of central components of these processes. In response to stress, such as oncogene activation and DNA damage, p53 regulated miRNAs are engaged in diverse types of feed forward and feedback loops that mediate amplification, robustness, fine-tuning and buffering of signals, and collectively contribute to appropriate cellular reactions. Accordingly, the expression and activity of p53 itself is also under the control of miRNAs. Genes encoding p53 regulated miRNAs are often targets for inactivation by genetic and epigenetic mechanisms in human tumors, indicating that they are tumor suppressor genes. These findings suggest that detection of the inactivation of p53 induced miRNAs in biopsy samples or body fluids may have diagnostic and/or prognostic value and knowledge about the p53–miRNA network may be exploited for diagnostic and therapeutic approaches in cancer prevention and treatment.

Source: Nature Reviews Cancer.2012 Sep; 12: 613-626.

Transforming Fusions of FGFR and TACC Genes in Human Glioblastoma

Glioblastoma multiforme (GBM) is among the most lethal forms of human cancer. Chromosomal translocations leading to production of oncogenic fusion proteins are critical events in the pathogenesis of human cancer. In a study published in *Science*, Singh *et. al*, examined whether such alterations are present in the GBM. Investigators used massively parallel, paired-end sequencing of expressed transcripts (RNA-seq) to detect gene fusions in short-term cultures of glioma stem like cells (GSCs) freshly isolated from nine patients with primary GBMs.The study showed that a small subset of GBMs (3.1%; 3 of 97 tumors examined) harbors oncogenic chromosomal translocations that fuse in-frame the tyrosine kinase coding domains of fibroblast growth factor receptor (FGFR) genes (FGFR1 or FGFR3) to the transforming acidic coiled-coil (TACC) coding domains of TACC1 or TACC3, respectively. The functional characterization of the FGFR-TACC fusion genes found in a small subset of GBM patients indicates that the constitutively active FGFR-TK and the TACC domain are both essential for oncogenesis. The FGFR-TACC fusion protein displays oncogenic activity when introduced into astrocytes or stereotactically transduced in the mouse brain. The fusion protein, which localizes to mitotic spindle poles, has constitutive kinase activity and induces mitotic and chromosomal segregation defects and triggers aneuploidy.

Inhibition of FGFR kinase corrects the aneuploidy, and oral administration of an FGFR inhibitor prolongs survival of mice harboring intracranial FGFR3-TACC3–initiated glioma. The antitumor effects in mouse models and the correction of a neuploidy precipitated by FGFR-TK inhibition of glioma cells driven by FGFR-TACC fusions provide a strong rationale for clinical investigation of FGFR inhibitors in GBM patients whose tumors exhibit FGFR-TACC rearrangements.

Source: Science. 2012 Sep 7;337(6099):1231-5.

Regulatory

FDA Approves Enzalutamide for Patients with Metastatic CRPC Previously Treated with Docetaxel

Astellas Pharma announced that the FDA has granted approval to XTANDI (enzalutamide) capsules for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have previously received docetaxel. XTANDI is an oral, once-daily androgen receptor inhibitor. The FDA accepted the XTANDI New Drug Application (NDA) on July 23, 2012, and granted the filing Priority Review Designation with a Prescription Drug User Fee Act (PDUFA) action date of November 22, 2012. Separately, a Marketing Authorization Application for XTANDI has been accepted for review by the European Medicines Agency (EMA).

The efficacy and safety of XTANDI were assessed in a randomized, placebo-controlled, multicentre phase III clinical trial. A total of 1,199 patients with mCRPC who had previously received docetaxel were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily(N = 800) or placebo (N = 399). XTANDI-treated patients had a statistically-significant improvement in mOS compared to the placebo group: 18.4 months in the XTANDI group vs. 13.6 months in the placebo group (P<0.0001). XTANDI provided a 37% reduction in risk of death compared to placebo (hazard ratio = 0.631).

Source: Astellas Pharma

Merck Withdraws European Filing for Erbitux in NSCLC

Merck announced the strategic decision to voluntarily withdraw the marketing authorization application (MAA) to the EMA of a label extension for Erbitux (cetuximab) in combination with standard 1st platinum-based chemotherapy in patients with advanced or metastatic NSCLC with high EGFR expression. The decision to withdraw the application was based on feedback from European regulatory authorities, indicating that further data would be required. The decision does not alter the proven utility of Erbitux in its already approved indications in metastatic colorectal cancer (mCRC) and squamous cell carcinoma of the head and neck (SCCHN).

Source: Merck

FDA Approves Bosutinib for Patients with Previously Treated Philadelphia Chromosome-Positive CML

Pfizer announced that FDA has approved BOSULIF (bosutinib), an Abl and Src kinase inhibitor, for the treatment of adult patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance, or intolerance to prior therapy. Patients in the registrational trial included patients who were previously treated with imatinib or imatinib plus at least one 2nd generation tyrosine kinase inhibitor (TKI). Once daily BOSULIF represents the only therapy approved with pivotal trial data that included CML patients treated with imatinib followed by a 2nd generation TKI.

Registrational trial, Study 200 was a global, single-arm, open-label, multi-cohort, Phase I/II study of more than 500 patients with imatinib-resistant or –intolerant Ph+ CML with separate cohorts for chronic, accelerated and blast phase disease previously treated with one prior TKI (imatinib) or more than one TKI (imatinib followed by dasatinib and/or nilotinib).The major cytogenetic response (MCyR) at 24 weeks for patients with chronic phase CML who had been previously treated with imatinib only (n=266) was 33.8%. With a minimum follow-up of 23 months, 53.4% of patients achieved a MCyR.

Source: Pfizer

Pfizer Receives EU Marketing Authorization for Axitinib

Pfizer announced that the European Commission (EC) has granted marketing authorization for INLYTA (axitinib) for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine. INLYTA, a kinase inhibitor, is an oral therapy that was designed to selectively inhibit vascular endothelial growth factor (VEGF) receptors 1, 2 and 3.

The approval is based on data from the Phase III AXIS trial, which demonstrated that INLYTA significantly extended PFS (P<0.0001) with a median PFS of 6.8 months compared with 4.7 months for those treated with sorafenib, a current 2nd line standard of care for this patient population, representing a 45% improvement in median PFS compared to sorafenib. In January 2012, INLYTA was approved by the FDA for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

Source: Pfizer

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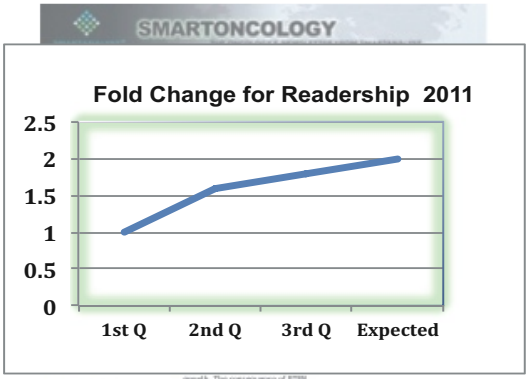

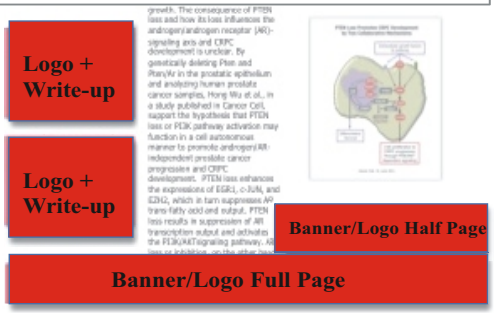

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