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INTELLIGENT INSIGHTS. SMART RESULTS

In the Spotlight:

2012 ASCO GI Cancers Symposium Highlights

Positive Phase III Results of Regorafenib in mCRC Patients Who have Progressed after Standard Therapies

Regorafenib (BAY 73-4506) is an oral multikinase inhibitor of a broad range of angiogenic, oncogenic, and stromal kinases. The Phase III CORRECT trial was conducted to evaluate efficacy and safety of regorafenib in patients with mCRC who had progressed after treatment with all approved standard therapies. Patients were randomized 2:1 to receive regorafenib (160 mg OD PO, 3 weeks on/1 week off) plus BSC (best supportive care), or placebo (PL) plus BSC. From May 2010 to March 2011, 760 patients were randomized (regorafenib: 505; PL: 255).

The estimated hazard ratio (HR) for overall survival (OS) was 0.773 (95% CI: 0.635–0.941; 1-sided P = 0.0051). Median OS was 6.4 months for regorafenib and 5.0 months for PL. The estimated HR for PFS was 0.493 (95% CI: 0.4180.581; 1-sided P < 0.000001). Median PFS was 1.9 months for regorafenib and 1.7 months for PL. ORR was 1.6% for regorafenib and 0.4% for PL. DCR was 44% for regorafenib and 15% for PL (P < 0.000001).

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Tumor of the Month - Ovarian Cancer

Despite comprising a mere 3% of cancer cases in women, ovarian cancer is the fifth leading cause of cancer deaths in women in the US. According to the National Cancer Institute, there will be 22,280 new cases and 15,500 deaths from ovarian cancer in 2012 in the US. The relative 5-year survival rate is 46% but decreases to 28% if diagnosed after the disease has spread to distant organs and lymph nodes. Little progress has been made in diagnosing or treating this disease: in 1975, the relative survival was 34.8%. The lack of progress is due in part to the constellation of symptoms that are also found in a variety of other common conditions; the lack of simple, accurate diagnostics; the persistence of dormant cancer cells; and the lack of anatomical barriers to prevent ovarian cancer cells from disseminating to the peritoneal cavity.

More than 90% of ovarian cancers are epithelial cancers (EOC), which arise from cells that cover the surface of the ovaries or those that line the inclusion cysts. The tumors have a great deal of heterogeneity. Germ cell ovarian cancers compose roughly 5% of cases and stromal ovarian tumors make up another 5% of cases. Primary peritoneal cancer looks like and is treated like ovarian cancer but derives from the peritoneum.

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The E-newsletter team: Dr. Shirish Kumar, Sarika Manchanda, Dr. Vinamrata Bhatia, Kimberly Tully, Courtenay Veenis, Monica Tuli.

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2012 ASCO GI Cancers Symposium Highlights

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Source: 2012 ASCO GI Cancers Symposium, Abstract No: LBA385

Phase III Results of Everolimus in Previously Treated Patients with Advanced Gastric Cancer

Prognosis for patients with advanced gastric cancer (AGC) after failure of first-line chemotherapy is poor. Currently, there is no level 1 evidence established for second-line treatment. In a randomized Phase III study, patients aged ≥18 years with confirmed AGC and disease progression after one or two lines of systemic chemotherapy were randomized 2:1 to oral everolimus (EVE) 10 mg/d plus BSC or placebo (PL) plus BSC. Randomization was stratified by region (Asia vs. rest of world) and previous lines of chemotherapy (one vs. two).

A total of 656 patients from 23 countries were enrolled from July 2009 to December 2010; 439 were randomized to EVE and 217 to PL. Median OS was 5.39 months with EVE vs. 4.34 months with PL (HR: 0.90; 95% CI: 0.75–1.08; P = 0.1244). Median PFS per local investigator assessment was 1.68 months with EVE vs. 1.41 months with PL (HR: 0.66; 95% CI: 0.56–0.78; P < 0.0001). Six-month PFS estimates were 12.0% with EVE and 4.3% with PL. OS and PFS results were consistent across the various subgroups. ORR (95% CI) was 4.5% (2.6%–7.1%) with EVE vs. 2.1% (0.6%–5.3%) with PL. The most common grade 3/4 adverse events were anemia (16.0% with EVE vs. 12.6% with PL), decreased appetite (11.0% vs. 5.6%), and fatigue (7.8% vs. 5.1%).

Source: 2012 ASCO GI Cancers Symposium, Abstract No: LBA3

Negative Phase III Results of Cetuximab plus Brivanib in Patients with Chemo-refractory *KRAS* WT mCRC

Addition of brivanib, a tyrosine kinase inhibitor targeting VEGFR/FGFR, to cetuximab has shown encouraging activity in an early-phase clinical trial. Patients with mCRC previously treated with combination chemotherapy were randomized 1:1 to receive cetuximab 400 mg/m^2 IV loading dose followed by weekly maintenance of 250 mg/m^2 plus either brivanib 800 mg PO daily (Arm A) or placebo (Arm B). Patients may have had one prior anti-VEGF, but no prior anti-EGFR therapy.

A total of 750 patients were randomized (376 in Arm A and 374 in Arm B). Median OS in the intent-to-treat population was 8.8 months in Arm A and 8.1 months in Arm B (HR: 0.88; 95% CI: 0.74–1.03; P = 0.12). Median PFS was 5.0 months in Arm A and 3.4 months in Arm B (HR: 0.72; 95% CI: 0.62–0.84; P < 0.0001). Both partial responses (13.6% vs. 7.2%, P = 0.004) and stable disease (50% vs. 44%) were higher in Arm A. Incidence of any ≥grade 3 AEs was 78% in Arm A and 53% in Arm B. Most frequent ≥grade 3 AEs were fatigue (25%), hypertension (11%), and rash (10%) in Arm A vs. fatigue (11%), rash (5%), and dyspnea (5%) in Arm B. Time to deterioration of physical function was shorter and global quality-of-life scores

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were lower in Arm A than in Arm B. Despite positive effects on PFS and OR, the combination of cetuximab plus brivanib did not significantly improve OS in patients with chemotherapy-refractory, *KRAS* WT mCRC.

Source: 2012 ASCO GI Cancers Symposium, Abstract No: 386

Results of Two Phase III Trials of Panitumumab for First- and Second-line mCRC

In the primary analysis of Study 181, panitumumab + FOLFIRI significantly improved PFS vs. FOLFIRI as second-line therapy in patients with *KRAS* WT mCRC. Patients were randomized 1:1 to panitumumab (6.0 mg/kg Q2W) + FOLFIRI (Arm 1) vs. FOLFIRI alone (Arm 2). Patients had one prior fluoropyrimidine-based chemotherapy regimen for mCRC. A total of 1,186 patients received treatment: 591 in Arm 1 and 595 in Arm 2. Of the 1,186 patients, 1,083 (91%) had *KRAS* results. In Arm 1, PFS (6.7 months in Arm 1 vs. 4.9 months in Arm 2; HR: 0.82; P = 0.023) and ORR (36% in Arm 1 vs. 10% in Arm 2) were improved, and there was a trend toward improved OS (14.5 months in Arm 1 vs. 12.5 months in Arm 2; HR: 0.92; P = 0.366) in patients with *KRAS* WT mCRC. In patients with MT *KRAS*, there was no difference in efficacy.

Final PRIME results showed that panitumumab + chemotherapy significantly improved PFS and ORR vs. chemotherapy alone for first-line *KRAS* WT mCRC. Patients had no prior chemotherapy for mCRC. Out of 1,183 patients with WT or MT *KRAS* mCRC, 1,057 met the criteria for inclusion in the skin toxicity (ST) analysis. mPFS was 11.3 months in panitumumab Gr 2-4 ST arm vs. 6.1 months in panitumumab Gr 0-1 ST arm vs. 8.7 months in chemotherapy-alone arm in *KRAS* WT mCRC patients. mOS were 27.7 months in panitumumab Gr 2-4 ST arm vs. 11.5 months in panitumumab Gr 0-1 ST arm vs. 19.7 months in chemotherapy-alone *KRAS* WT mCRC patients. The overall safety profile was broadly comparable across ST groups and treatment arms. It was concluded that patients with *KRAS* WT mCRC receiving panitumumab with ST Gr 2-4 had longer PFS and OS than patients receiving chemotherapy alone.

Source: 2012 ASCO GI Cancers Symposium, Abstract No: 387; 2012 ASCO GI Cancers Symposium, Abstract No: 531

Significant Phase III Results of Bevacizumab plus FOLFOX4 in Previously Treated Advanced CRC Patients

VEGF-A gene is alternatively spliced into two families by alternative splice site usage in exon 8. The pro-angiogenic (e.g., VEGF165) isoforms are generated by proximal splice site selection and the anti-angiogenic (e.g., $VEGF_{165}b$) by distal splice site selection. The relative levels of the isoforms vary in CRC. $VEGF_{165}b$ overexpression in mice inhibits bevacizumab treatment.

To determine whether survival was better in patients with low $VEGF_{165}b$ when treated with FOLFOX4 + bevacizumab (Arm A) than FOLFOX4 + placebo (Arm B), 108 coded patient samples from the E3200 trial of FOLFOX4 ± bevacizumab were successfully stained for VEGF-$A_{165}b$ and scored in well-differentiated tissue relative to normal tissue blind to outcome. Adjusted Cox binary analysis of $VEGF_{165}b$/normal comparing staining ratio in bevacizumab- vs. placebo-treated patients demonstrated significantly better survival for the less than median ratios (HR: 0.28; P = 0.0031; mPFS: 8.4 months vs. 5.1 months in placebo), whereas in the higher than median $VEGF_{165}b$/normal group, there was no effect of bevacizumab (HR: 0.96, mPFS: 11.9 months vs. 11.0 months in placebo). These results indicate that low $VEGF_{165}b$ levels in well-differentiated tumors may predict response to bevacizumab.

Source: 2012 ASCO GI Cancers Symposium, Abstract No: 545

Preliminary Safety Data of Phase II/III Trial with MGN1703 in Patients with Advanced CRC

The synthetic DNA–based immunomodulator MGN1703 acts as an agonist of toll-like receptor 9. A Phase II/III study (IMPACT) was initiated in patients with advanced CRC having disease control after first-line therapy. The efficacy and safety of the study treatment will be evaluated based on extensive immunological tests, radiological assessment, safety laboratory results, and assessments of the quality of life.

Preliminary safety data were presented at the 2012 ASCO GI cancer symposium. The majority of adverse events were assessed as not drug-related by the investigator. The remaining AEs were mild night sweat (not assessable), mild fever (at three occasions, possible related), and mild arthralgia (certain related) in one patient each. Three SAEs have been reported so far, of which one was assessed as probably drug-related – atypical pneumonia. Local reactions such as mild redness and swelling at injection site were reported only in one patient. No laboratory or clinical signs of autoimmunity or dose-limiting toxicities have been reported so far. With these preliminary safety results of the ongoing clinical study in patients with advanced CRC, it could be shown that treatment with MGN1703 at the dosage of 60 mg is well tolerated and safe.

Source: 2012 ASCO GI Cancers Symposium, Abstract No: 633

Prolongation of Doxifluridine and Addition of Cisplatin to Mitomycin C did not Improve Treatment Outcome in Advanced Gastric Cancer Patients

To improve adjuvant MF (mitomycin C and fluoropyrimidine) chemotherapy, researchers

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prolonged the administration of oral fluoropyrimidine (F), added cisplatin (P) to MF (MFP), and performed a Phase III randomized trial to determine whether this strategy could improve the 3-year relapse-free survival (3yRFS) in curatively resected advanced gastric cancer (AGC) patients.

For MFP group, the administration of doxifluridine was extended for 12 months, and 6 shots of monthly 60 mg/m^2 of cisplatin were added to MF. Between February 2002 and August 2006, a 871 patients were randomized (435 in MF and 436 in MFP). With a median follow-up of 6.6 years in April 2011, a total of 353 events (relapse or death) have been observed. There was no difference in RFS between the two groups (HR: 1.10; 95% CI: 0.89–1.35; P = 0.3918; 5yRFS 61.1% in MF and 57.9% in MFP). Difference in OS was also insignificant (HR: 1.11; 95% CI: 0.89–1.39; P = 0.3349; 5yOS 66.5% in MF and 65.0% in MFP).

Source: 2012 ASCO GI Cancers Symposium, Abstract No: 76

Tumor of the Month - Ovarian Cancer

Despite comprising a mere 3% of cancer cases in women, ovarian cancer is the fifth leading cause of cancer deaths in women in the US. According to the National Cancer Institute, there will be 22,280 new cases and 15,500 deaths from ovarian cancer in 2012 in the US. The relative 5-year survival rate is 46% but decreases to 28% if diagnosed after the disease has spread to distant organs and lymph nodes. Little progress has been made in diagnosing or treating this disease: in 1975, the relative survival was 34.8%. The lack of progress is due in part to the constellation of symptoms that are also found in a variety of other common conditions; the lack of simple, accurate diagnostics; the persistence of dormant cancer cells; and the lack of anatomical barriers to prevent ovarian cancer cells from disseminating to the peritoneal cavity.

More than 90% of ovarian cancers are epithelial cancers (EOC), which arise from cells that cover the surface of the ovaries or those that line the inclusion cysts. The tumors have a great deal of heterogeneity. Germ cell ovarian cancers compose roughly 5% of cases and stromal ovarian tumors make up another 5% of cases. Primary peritoneal cancer looks like and is treated like ovarian cancer but derives from the peritoneum.

Patients diagnosed with stage 1 cancer (disease confined to the ovaries) have a 90% cure rate. Unfortunately, only 20% of patients are diagnosed so early in the disease. Stages 2–4 describe disease that has metastasized to the pelvic organs (stage 2), abdomen (stage 3), or beyond the peritoneal cavity (stage 4).

Although CA125 (cancer antigen 125) levels are tested to diagnose ovarian cancer or to determine how well therapy is working, its usefulness is limited. CA125 levels can increase due to other conditions (i.e., endometrial, peritoneal, or fallopian tube cancer) and can be released by some normal cells. Furthermore, non-epithelial ovarian cancers do not show an increase in CA125 levels. A recent study tried to increase sensitivity by combining CA125 screening with screening for seven markers derived from proteomic analysis, but the added markers failed to improve the sensitivity of pre-clinical diagnosis of ovarian cancer.

In the January 25, 2012, issue of *JAMA*, Paul Pharoah's group published results showing that patients with a mutation in the BRCA2 gene were more likely to survive to 5 years after diagnosis (52%) than patients with a mutation in BRCA1 (44%). Both groups had a survival advantage over patients who had wild-type copies of the genes (36%).

Tumor debulking is used even in patients for whom complete resection is impossible. For patients with advanced ovarian cancer, it becomes difficult for surgeons to extract all of the cancerous tissue; therefore, most patients (except those with stage 1A grade 1 or stage 1B grade 1 tumors) receive chemotherapy. Currently, first-line chemotherapy consists of paclitaxel plus cisplatin or carboplatin. Unfortunately, most patients become resistant to therapy and most patients are encouraged to enroll in clinical trials.

BioNumerik Pharmaceuticals is conducting a Phase III trial on patients with stage III or IV platinum-/taxane-resistant EOC. Its drug, Karenitecin, is a novel compound of the camptothecin class but with fewer side effects, improved efficacy, less susceptibility to drug resistance mechanisms, and an improved safety profile. Its trial pits Karenitecin against topotecan in terms of safety and efficacy, PFS, OS, and severity and incidence of hematological toxicities.

The folate receptor is expressed at high levels on 90%–95% of ovarian cancers but not on normal tissues. Morphotek is targeting the folate receptor with its monoclonal antibody MORAb-003 (farletuzumab) in the FAR131 Phase III trial. The trial is enrolling patients with EOC that relapsed 6–24 months after first-line platinum-containing therapy. The trial will assess the safety and efficacy of treating patients with MORAb-003 in combination with carboplatin and taxane.

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Endocyte is also targeting the folate receptor. Its drug EC145 conjugates folate to a super potent vinca alkaloid. The Phase III trial, "study for women with platinum resistant ovarian cancer evaluating EC145 in combination with Doxil (PROCEED)," is enrolling platinum-resistant patients to assess PFS in patients treated with pegylated liposomal doxorubicin (PLD) + placebo compared with patients treated with PLD + EC145. Endocyte has a companion imaging diagnostic, EC20, which also targets the folate receptor.

The anti-angiogenic peptide, AMG-386 (Amgen), inhibits the interaction between the Tie receptor and its ligands – angiopoietins 1 and 2. The drug is being tested in the TRINOVA-1 study to determine whether AMG-386 + paclitaxel shows superiority to placebo + paclitaxel in partial platinum-sensitive or platinum-resistant cancers. The TRINOVA-2 study will assess whether AMG-386 + PLD is superior to placebo + PLD in partial platinum-sensitive or platinum-resistant cancers. The results of this study should be interesting as a Phase I/II trial testing pazopanib, an oral angiogenesis inhibitor that targets VEGFRs, PDGRs, and c-kit, was discontinued due to disappointing results. The results were published in the *British Journal of Cancer*, in which pazopanib was tested in combination with carboplatin and paclitaxel. Overall, 10 of 12 patients discontinued treatment and 67% experienced serious treatment-related adverse events.

PARP inhibitors took the cancer world by storm several years ago when it was shown that cancer cells carrying a mutant BRCA1 or BRCA2, which are components of the homologous recombination pathway, were susceptible to drugs that inhibited poly (ADP-ribose) polymerase (PARP), a gene important in an alternative DNA repair pathway. Stan Kaye and colleagues published the results of a Phase II trial comparing the safety and efficacy of two different doses of olaparib with PLD in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. Patients were assigned in a 1:1:1 ratio to olaparib 200 mg twice per day or 400 mg twice per day continuously or PLD 50 mg/m^2 IV every 28 days. ORRs were not significantly different: 25% for olaparib 200 mg, 31% for olaparib 400 mg, and 18% for PLD. Median PFS was not statistically significant for either dose of olaparib when compared with PLD (6.5 months for 200 mg, 8.8 months for 400 mg, and 7.1 months for PLD). Interestingly, a lower percentage of patients developed new lesions in the olaparib 200 mg and olaparib 400 mg groups (28.1% and 34.4%, respectively) than in the PLD group (45.5%). The authors noted that 8 of 25 patients in the study who have crossed over from PLD have continued on treatment with olaparib, indicating the potential for continued benefit in patients with BRCA1/2-mutated ovarian cancer and suggesting that future trials in PLD-treated patients would be of interest.

In December 2011, the European Commission approved bevacizumab in combination with standard chemotherapy (carboplatin and paclitaxel) as a frontline (first line following surgery) therapy for advanced ovarian cancer. Roche submitted the related marketing authorization on the basis of results from the GOG 0218 and ICON7 clinical trials. Genentech filed for approval in the US for this indication in mid-2011.

Source: Cancer.gov; Ovariancancer.org; Oncolink.org; emedicine; Bast RC, Jr., Hennessy B, Mills GB. The biology of ovarian cancer: New opportunities for translation. Nat Rev Cancer (2009) 9:415-28; Moore LE, Pfeiffer RM, Zhang Z, et al. Proteomic biomarkers in combination with CA 125 for detection of epithelial ovarian cancer using prediagnostic serum samples from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. Cancer. 2012;118:91-100; Bolton KL, Chenevix- Trench G, Goh C, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA. 2012;307:382-9; Bionumerik; Morphotek; Endocyte; du Bois A, Vergote I, Wimberger P, et al. Open-label feasibility study of pazopanib, carboplatin, and paclitaxel in women with newly diagnosed, untreated, gynaecologic tumours: A phase I/II trial of the AGO study group. Br J Cancer. Advance online publication January 12, 2012; Kaye SB, Lubinski K, Matulonis U, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol.

Business News

Collaborative Development and Worldwide License Agreement for PCI-32765 between Janssen Biotech and Pharmacyclics

Janssen Biotech announced that it has executed an agreement with Pharmacyclics to jointly develop and market the anti-cancer compound PCI-32765. This compound is an orally active, small molecule inhibitor of Bruton's tyrosine kinase (Btk), an essential element of the B-cell antigen receptor (BCR) signaling pathway. BCR signaling is a critical pathway required for tumor expansion and proliferation, and PCI-32765 exerts its anti-tumor function by blocking BCR

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signaling and thereby inducing cell death. A number of Phase I and II studies with PCI-32765 are ongoing across a panel of B-cell malignancy disorders, including CLL, MCL, and DLBCL.

According to the terms of the agreement, the companies have entered into a worldwide 50/50 profit–loss agreement, sharing development and commercialization activities. Janssen has made an upfront payment of $150 M, which will be recorded in the fourth quarter, and will make additional payments on the basis of the achievement of certain development and regulatory milestones. This transaction is expected to have a dilutive impact to Johnson & Johnson's 2011 earnings per share of ~$0.04–$0.05.

Source: Pharmacyclics

Exelixis Licenses PI3K-Delta Program to Merck

Exelixis announced that it has granted to Merck, known as MSD outside of the US and Canada, an exclusive worldwide license to its PI3K-delta research and development program, including XL499, the company's most advanced pre-clinical PI3K-delta inhibitor and other related compounds. PI3K-delta is a member of the class 1 family of phosphoinositide-3 kinases and is predominantly expressed in cells of the immune system. Selectively targeting PI3K-delta has shown potential in the treatment of certain lymphomas.

Under the terms of the agreement, Merck will have a worldwide exclusive license and sole responsibility to research, develop, and commercialize compounds originating from the program. Merck will make an upfront payment of $12 M to Exelixis, and Exelixis will be eligible for potential development and regulatory milestone payments for multiple indications of up to $239 M. Exelixis will also be eligible for potential combined sales performance milestones and royalties on net sales of products emerging from the agreement. Milestones and royalties are payable on compounds emerging from Exelixis' PI3K-delta program or from certain compounds that arise from Merck's internal discovery efforts targeting PI3K-delta during a certain duration.

Source: Exelixis

Aeterna Zentaris Announces Collaboration with Ventana Medical Systems to Develop Companion Diagnostic in Cancer for AEZS-108

Aeterna Zentaris announced that it has entered into a collaboration agreement with Ventana Medical Systems, a member of the Roche Group, to develop a companion diagnostic for the immunohistochemical determination of luteinizing hormone–releasing hormone (LHRH) receptor expression, for the company's doxorubicin LHRH-targeted conjugate compound AEZS-108.

AEZS-108 represents a new targeting concept in oncology: using a hybrid molecule composed of a synthetic peptide carrier and a well-known chemotherapy agent, doxorubicin. AEZS-108 is the first intravenous drug in a clinical study that directs a chemotherapy agent specifically to LHRH receptor–expressing tumors, resulting in more targeted treatment with less damage to healthy tissues. The product has successfully completed Phase II studies for the treatment of endometrial and ovarian cancers and is also in Phase II trials in prostate and bladder cancers.

Source: Aeterna Zentaris

SFJ Pharma Announces Agreement with Pfizer to Develop Axitinib for Adjuvant Treatment of RCC

SFJ Pharma announced that it has entered into a collaborative development agreement with Pfizer to conduct a Phase III clinical trial in Asia of Pfizer's investigational agent axitinib for the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy. Axitinib is an oral, selective inhibitor of VEGF receptors 1, 2, and 3, which can influence tumor growth, vascular angiogenesis, and progression of cancer. Axitinib is currently under review by the US FDA, the EMA, the Japanese Ministry of Health, Labor and Welfare, and several other regulatory agencies worldwide as a treatment for advanced RCC.

Under the terms of the agreement, SFJ will provide the funding and clinical development supervision to generate clinical data necessary to submit axitinib for review by regulatory authorities for the adjuvant treatment of patients at high risk of recurrent RCC following nephrectomy. SFJ will be eligible to receive milestone payments under the agreement. In addition, if approved, Pfizer intends to commercialize axitinib for this indication, and SFJ will receive earn-out payments under the agreement. Axitinib is also being investigated in a randomized Phase III clinical trial in patients with treatment-naive as well as previously treated advanced RCC.

Source: SFJ Pharma

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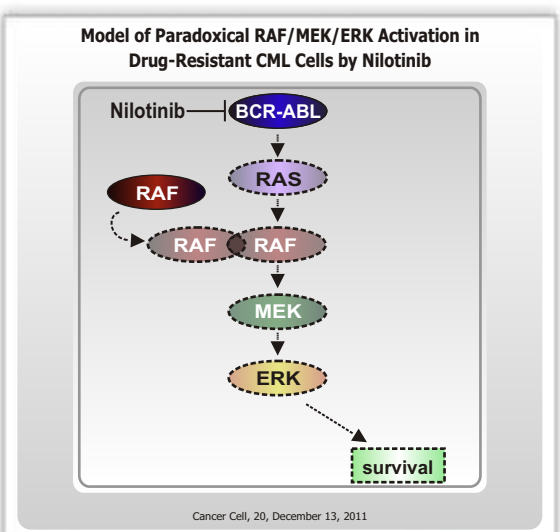
Research Highlights

Nilotinib and MEK Inhibitors Induce Synthetic Lethality through Paradoxical Activation of RAF in Drug-resistant CML

Chronic myeloid leukemia (CML) is characterized by the presence of the Philadelphia chromosome, a chromosome 9/chromosome 22 translocation that fuses BCR (encoding breakpoint cluster region) to ABL, which encodes the Abelson tyrosine kinase. The RAS/RAF/MEK/ERK pathway promotes CML cell survival. Under some circumstances, RAF inhibitors drive paradoxical activation of BRAF and CRAF to accelerate tumorigenesis by hyperactivating MEK and ERK. Acquired drug resistance through BCR–ABL–dependent and BCR–ABL–independent mechanisms is thus a persistent problem for the treatment of CML.

In a recent study published in *Cancer Cell*, Packer *et al.* investigated whether other kinase inhibitors can also drive paradoxical activation of RAF, MEK, and ERK and investigated the underlying mechanisms and potential clinical consequences. They showed that some frontline CML drugs such as imatinib, nilotinib, and dasatinib possess weak off-target activity against RAF and, therefore, drive paradoxical activation of BRAF and CRAF in a RAS-dependent manner. Critically, because RAS is activated by BCR–ABL, in drug-resistant CML cells, RAS activity persists in the presence of these drugs, driving paradoxical activation of BRAF, CRAF, MEK, and ERK and leading to an unexpected dependency on the pathway. Consequently, nilotinib synergizes with MEK inhibitors to kill drug-resistant CML cells *in vitro* and block tumor growth in mice.



This study showed that paradoxical activation of BRAF and CRAF can drive unexpected biological responses in CML and has uncovered a synthetic lethal interaction that can be used to kill drug-resistant CML cells *in vitro* and *in vivo*. This provides an intriguing strategy that may prevent the emergence of drug-resistant clones in patients with CML.

Source: Cancer Cell. 2011;20:715–727

SB1518, a Novel Macrocyclic Pyrimidine-based JAK2 Inhibitor, for the Treatment of Myeloid and Lymphoid Malignancies

The Janus kinase (JAK) family of tyrosine kinases has important roles in the cellular signaling pathways that control proliferation, differentiation, and cell death. FLT3 (FMS-like tyrosine kinase-3) belongs to a family of class III receptor tyrosine kinases, and it is the most frequently mutated gene in acute myeloid leukemia, leading to poor prognosis in some patients. JAK2 and FLT3 offer hope as novel targets for the development of innovative therapies. Macrocyclic organic compounds in general constitute a structural class that possesses immense potential for pharmacological applications, but their utility has not been fully exploited because of the synthetic challenges and concerns over apparent lack of "druglikeness."

Hart *et al.* recently reported in *Leukemia* the structure and pharmacological profile of SB1518, a novel pyrimidine-based, low-molecular-weight macrocycle with selective potent inhibitory activities against JAK2 and FLT3. SB1518 exhibits favorable pharmaceutical properties and shows efficacy in cellular and animal models of hematological malignancies as well as primary cells derived from patients with myeloproliferative disease. The agent shows potent effects on cellular JAK–STAT pathways, inhibiting tyrosine phosphorylation on JAK2 (Y221) and downstream STATs. As a consequence, SB1518 has potent anti-proliferative effects on myeloid and lymphoid cell lines driven by mutant or WT JAK2 or FLT3, resulting from cell cycle arrest and induction of apoptosis. SB1518 inhibits intra-tumor JAK2/STAT5 signaling in a dose-dependent manner, leading to tumor growth inhibition in a subcutaneous model generated with SET-2 cells derived from a JAK2V617F patient with megakaryoblastic leukemia. Moreover, SB1518 is active against primary erythroid progenitor cells sampled from patients with myeloproliferative disease.

This study reveals a novel chemical entity selective for JAK2 over JAK1 and JAK3 with additional activity

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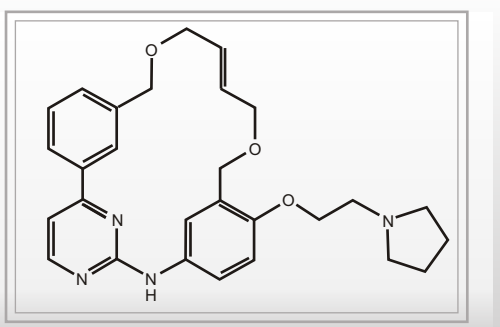
against FLT3. It is efficacious against cell lines dependent on constitutively active or ligand-activated JAK2 and FLT3 signaling and effectively blocks STAT signaling in these cells. SB1518's favorable pharmaceutical and pharmacological properties provide a rationale for clinical development in multiple myeloid and lymphoid disease indications.

***In vitro* kinase spectrum of SB1518**



Leukemia, 25, Nov, 2011

Source: Leukemia. 2011;25(11):1751–1759

SF3B1 and Other Novel Cancer Genes in Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is an incurable disease characterized by extensive clinical heterogeneity despite a common diagnostic immunophenotype (surface expression of CD19+, CD20+dim, CD5+, CD23+, and sIgMdim). The ability to predict a more aggressive disease course has improved with the use of tests for biologic markers (degree of somatic hypermutation in the variable region of the immunoglobulin heavy chain [IGHV] gene and expression of ZAP70) and the detection of cytogenetic abnormalities (deletions in chromosomes 11q, 13q, or 17p and trisomy 12). Despite these advances, prediction of the disease course is not highly reliable.

In a recent study published in *NEJM*, Wang *et al.* obtained DNA samples from leukemia cells in 91 patients with CLL and performed massively parallel sequencing of 88 whole exomes and whole genomes, together with sequencing of matched germline DNA, to characterize the spectrum of somatic mutations in this disease. Nine genes mutated at significant frequencies were identified, including four with established roles in CLL (TP53 in 15% of patients, ATM in 9%, MYD88 in 10%, and NOTCH1 in 4%) and five with unestablished roles (SF3B1, ZMYM3, MAPK1, FBXW7, and DDX3X). SF3B1, which functions at the catalytic core of the spliceosome, was the second most frequently mutated gene (with mutations occurring in 15% of patients). SF3B1 mutations occurred primarily in tumors with deletions in chromosome 11q, which are associated with a poor prognosis in patients with CLL.

Research findings regarding SF3B1 mutations and identification of coding mutations in CLL can lead to the development of mechanistic hypotheses, novel prognostic markers, and potential therapeutic

Source: N Engl J Med. 2011;365(26):2497–2506

Clinical Development

AstraZeneca Discontinues Olaparib Development Programme in Ovarian Cancer

AstraZeneca announced that its investigational compound olaparib will not progress into Phase III development for the maintenance treatment of serous ovarian cancer. Olaparib is an oral PARP inhibitor that exploits DNA repair pathways to preferentially kill cancer cells.

The decision to discontinue olaparib's development in serous ovarian cancer was made following a review of an interim analysis of a Phase II study (Study 19), which indicated that the previously reported PFS benefit is unlikely to translate into an OS benefit, the definitive measure of patient benefit in ovarian cancer. In addition, attempts to identify a suitable tablet dose for use in Phase III studies have not been successful. No new safety concerns were identified for patients.

Source: AstraZeneca

Phase III BRISK-PS Study with Brivanib did not Meet Primary Endpoint in HCC Patients

BMS reported that the Phase III BRISK-PS (Brivanib Study in HCC Patients at Risk Post Sorafenib) clinical trial in patients with hepatocellular carcinoma (HCC) who failed or are intolerant to sorafenib did not meet the primary endpoint of improving OS vs. placebo. Brivanib inhibits vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor (FGFR).

BRISK-PS is a multicenter, double-blind, randomized study of the investigational agent brivanib plus BSC vs. placebo plus BSC in HCC patients who have progressed on sorafenib. The BRISK-PS study is one of four Phase III clinical trials evaluating brivanib in different HCC patient populations. These ongoing Phase III studies continue as planned.

Source: BMS

Tivozanib Successfully Demonstrated PFS Superiority over Sorafenib in RCC Patients in Phase III TIVO-1 Trial

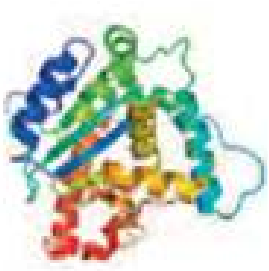
Aveo and Astellas Pharma announced that tivozanib demonstrated superiority over sorafenib in the primary endpoint of PFS in TIVO-1, a global,

Clinical Development
(Cont'd)

randomized, Phase III clinical trial evaluating the efficacy and safety of investigational drug tivozanib compared with sorafenib in 517 patients with advanced renal cell carcinoma (RCC). TIVO-1 is the first registration study in first-line RCC that is comparing an investigational agent against an approved VEGF therapy. All patients in TIVO-1 had clear cell RCC, had undergone a prior nephrectomy, and had not previously been treated with either a VEGF or an mTOR therapy.

Based on the topline analysis of events in TIVO-1, determined by a blinded, independent review committee, tivozanib demonstrated a statistically significant improvement in PFS with a median PFS of 11.9 months compared with a median PFS of 9.1 months for sorafenib in the overall study population. Tivozanib demonstrated a statistically significant improvement in PFS with a median PFS of 12.7 months compared with a median PFS of 9.1 months for sorafenib in the pre-specified subpopulation of patients who were treatment-naive (no prior systemic anti-cancer therapy); this subpopulation was ~70% of the total study population. Tivozanib demonstrated a well-tolerated safety profile consistent with the Phase II experience; the most commonly reported side effect was hypertension, a well-established on-target and manageable effect of VEGFR inhibitors.

Source: Aveo



Biomarkers

Targeting of Tumor Suppressor GRHL3 by a miR-21–dependent Proto-oncogenic Network Results in PTEN Loss and Tumorigenesis

Despite its prevalence, the molecular basis of squamous cell carcinoma (SCC) remains poorly understood. Evidence exists that activation of Ras signaling, in concert with inhibition of NF-kB function, is sufficient for malignant transformation of keratinocytes. Activated Ras stimulates multiple effectors including the RAF/MEK/ERK pathway, the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway, and the guanine nucleotide exchange factors. An alternate mechanism for activation of PI3K/AKT/mTOR signaling in SCC is through loss of expression of the phosphatase and tensin homolog (PTEN) tumor suppressor gene. PTEN acts as the most important negative regulator of the PI3K pathway, and its inactivation leads to increased activity of the serine/threonine kinases, PDK1, and AKT. Despite this, somatic mutations, gene deletions, and promoter hypermethylation of PTEN have not been detected in human SCC, suggesting that other mechanisms of inactivating the gene may be involved in SCC pathogenesis.

Earlier studies have shown that mice lacking the Grainyhead-like 3 *(GRHL3)* gene exhibit multiple epidermal abnormalities. *GRHL3* is a member of a highly conserved family of transcription factors critical for epidermal development and homeostasis. In a recent study published in *Cancer Cell*, Darido *et al.* investigated the role of this developmental transcription factor in adult skin homeostasis and skin cancer development.

Researchers identified GRHL3 as a potent tumor suppressor in SCC in both humans and mice and demonstrated that targeting of GRHL3 by a miR-21–dependent proto-oncogenic network underpins SCC in humans. They defined PTEN as the critical downstream effector of GRHL3 tumor suppressor activity, providing the elusive explanation for the low levels of PTEN expression in SCC that occur in the absence of genetic or epigenetic alterations to the gene. In humans, a miR-21 proto-oncogenic network synchronously targets both tumor suppressors GRHL3 and PTEN, leading to amplification of PI3K/AKT/mTOR signaling and induction of SCC of both skin, and head and neck origins. Reduced levels of GRHL3 and PTEN were evident in human skin, and head and neck SCC, associated with increased expression of miR-21. Deletion of GRHL3 in adult epidermis evoked loss of expression of PTEN, a direct GRHL3 target, resulting in aggressive SCC induced by activation of PI3K/AKT/mTOR signaling. Restoration of PTEN expression completely abrogated SCC formation. This study defines the GRHL3–PTEN axis as a critical tumor suppressor pathway in SCC and demonstrates that GRHL3/PTEN–deficient SCC displays an oncogene addiction to the PI3K/AKT–signaling pathway, with profound downregulation of the MAPK/ERK pathway. Emerging from this work is an increased rationale for the use of direct inhibitors of PI3K/AKT/mTORC1 signaling and/or antagonists of miR-21 in the treatment of SCC.

Source: Cancer Cell. 2011;20(5):635–648

The NOD-like Receptor NLRP12 Attenuates Colon Inflammation and Tumorigenesis

Patients with inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis are at increased risk for the development of colorectal cancer. Although the precise molecular mechanism of IBD-related colorectal tumor formation is incompletely understood, it is widely viewed that chronic inflammation shapes the tumorigenic micro-environment in the gut by inducing cytokines, chemokines, and other factors through NF-kB, ERK, and STAT3 signaling. Innate immune receptors such as Toll-like receptors (TLR) at the surface of epithelial cells and immune cells initiate this inflammatory

Biomarkers (Cont'd)

process by activating the downstream transcription factor NF-kB, which is a central mediator of proinflammatory cytokine and chemokine production. In addition to TLRs, the immune system uses pattern recognition receptors (PRRs) to induce the production of inflammatory cytokines in response to microbial components that include C-type lectin receptors (CLRs), RIG-I-like receptors (RLRs), HIN-200 proteins and nucleotide binding, and oligomerization domain-like receptors belonging to the NOD-like receptor (NLR) family.

NLRP12 is a member of the intracellular NLR family, which has been suggested to downregulate the production of inflammatory cytokines, but its physiological role in regulating inflammation has not been characterized. Zaki *et al.*, in a study published in *Cancer Cell*, analyzed mice deficient in NLRP12 to study its role in inflammatory diseases such as colitis and colorectal tumorigenesis. They showed that NLRP12-deficient mice are highly susceptible to colon inflammation and tumorigenesis, which is associated with increased production of inflammatory cytokines, chemokines, and tumorigenic factors. Enhanced colon inflammation and colorectal tumor development in NLRP12-deficient mice are due to a failure to dampen NF-kB and ERK activation in macrophages.

This study demonstrates a regulatory mechanism of intestinal inflammation and tumorigenesis by PRRs and paves the way to further understanding the role of NLR proteins in gastrointestinal disorders. This may help identify new therapeutic approaches to control inflammatory bowel diseases.

Source: Cancer Cell. 2011;20(5):649–660

Genetic Activation of the *MET* Pathway and Prognosis of Patients with High-risk, Radically Resected Gastric Cancer

Activation of the MET/HGF pathway promotes proliferative and anti-apoptotic activities that are common to many growth factors, but specifically, MET activation demonstrated stimulation of cell–cell detachment, migration, and invasiveness. This pathway has been found frequently expressed in gastric carcinomas and is associated with a more aggressive phenotype.

This background prompted Graziano *et al.* to verify the hypothesis that MET activation by gene copy number gain (CNG) alone or in combination with the HGF DATE (deoxyadenosine tract element)–activating truncation may promote a more aggressive gastric cancer phenotype and poor prognosis. MET CNG of five or more copies and homozygous HGF-truncated DATE occurred in 10% and 13% patients, respectively. Patients with MET CNG of five or more copies (MET-positive) showed significantly worse prognosis with multivariate hazard ratio (HR) of 3.02 (95% CI: 1.71–5.33; $P < 0.001$) for DFS and multivariate HR of 2.91 (95% CI: 1.65–5.11; $P < 0.001$) for OS. HGF-truncated DATE did not show relevant prognostic effect. The findings contribute to the hypothesis that novel anti-MET therapies could induce clinically relevant anticancer effects in the subgroup of patients with gastric cancer whose tumors are MET positive (CNG of five copies), or less likely, with HGF homozygous DATE truncation and normal MET CNG status. This information may lead to the optimal development of these compounds.

Source: J Clin Oncol. 2011;29(36):4789–4795

TFAP2E–DKK4 and Chemoresistance in CRC

Genomic and epigenetic alterations of the gene encoding transcription factor AP-2 epsilon (TFAP2E) are common in human cancers. The gene encoding dickkopf homolog 4 protein (DKK4) is a potential downstream target of TFAP2E and has been implicated in chemotherapy resistance. Ebert *et al.* evaluated the role of TFAP2E and DKK4 as predictors of the response of CRC (colorectal cancer) to chemotherapy and published the findings in a recent issue of *NEJM.*

The expression, methylation, and function of TFAP2E in CRC cell lines *in vitro* and in CRC patients were analyzed. TFAP2E was hypermethylated in 51% patients in the initial cohort. Hypermethylation was associated with decreased expression of TFAP2E in primary and mCRC specimens and cell lines. DKK4 overexpression led to increased fluorouracil chemoresistance in CRC cell lines, whereas the introduction of TFAP2E was associated with increased sensitivity to fluorouracil treatment. Data indicate that fluorouracil-based chemotherapy is largely ineffective in patients with CRC with TFAP2E hypermethylation.

Specific targeting of DKK4 in these individuals may, therefore, be an option for overcoming TFAP2E-mediated chemoresistance.

Source: N Engl J Med. 2012;366(1):44–53

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Regulatory

Roche's Avastin Receives EU Approval for the Treatment of Women with Newly Diagnosed Advanced Ovarian Cancer

European Commission has approved Avastin (bevacizumab) in combination with standard chemotherapy as a frontline (first line following surgery) treatment for women with advanced ovarian cancer.

Avastin has demonstrated a significant improvement in the time women with ovarian cancer live without the disease getting worse (PFS) in three large Phase III studies (GOG 0218 and ICON7 in the frontline setting and OCEANS in the recurrent, platinum-sensitive setting). This approval will enable the use of Avastin in combination with carboplatin and paclitaxel for the frontline treatment of advanced (FIGO stages IIIB, IIIC, and IV) epithelial ovarian, primary peritoneal, or fallopian tube cancer for women in Europe. Avastin is administered in addition to chemotherapy for up to six cycles of treatment followed by continued use of Avastin as a single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.

Source: Roche

US FDA Approves Pfizer's Axitinib for Patients with Previously Treated Advanced RCC

Pfizer announced that the US FDA has approved Inlyta (axitinib), a kinase inhibitor, for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy. The approval is based on data from the Phase III AXIS trial, which demonstrated that Inlyta significantly extended (PFS) [HR=0.67, 0.54-0.81, P<0.0001] with a median PFS of 6.7 months (95% CI: 6.3, 8.6) compared with 4.7 months (95% CI: 4.6, 5.6) for those treated with sorafenib, a current standard of care (SOC) for this patient population, representing a 43% improvement in median PFS compared to sorafenib.

Inlyta, a kinase inhibitor, is an oral therapy that was designed to selectively inhibit vascular endothelial growth factor (VEGF) receptors 1, 2 and 3,which are receptors that can influence tumor growth, vascular angiogenesis and progression of cancer (the spread of tumors). Axitinib is also being investigated in a randomized clinical trial in patients with treatment-naïve as well as previously treated advanced RCC. Additionally, under a collaborative development agreement between Pfizer and SFJ Pharma, SFJ will conduct a Phase III clinical trial in Asia studying axitinib for adjuvant treatment of patients at high risk of recurrent RCC following nephrectomy.

Source: Pfizer

FDA Approves BTG's Drug Voraxaze for Cancer Toxicity

US health regulators gave the nod to a drug from British specialty drugmaker BTG Plc that helps cancer patients get rid of toxic levels of a chemotherapy treatment. The drug – called Voraxaze – helps eliminate methotrexate in patients whose kidney function has been compromised by treatment with high doses of the chemotherapy agent. Methotrexate is used to treat breast, bone, and lung cancers as well as leukemia. It is normally eliminated from the body by the kidneys, but prolonged high doses of the drug can result in kidney failure.

BTG's injectable treatment can quickly break down the chemotherapy medicine and allow the body to expel it. The FDA granted Voraxaze orphan drug status, meant for rare diseases or conditions that affect a very small portion of the population. As incentive for companies to develop such drugs, the orphan designation comes with 7 years of marketing exclusivity before a rival medicine can be approved.

In a clinical trial of 22 patients, Voraxaze eliminated 95% of methotrexate from blood. For 10 of the patients, methotrexate decreased to a low level within 15 minutes and stayed that way for 8 days. Common side effects were low blood pressure, headaches, nausea, and vomiting.

Source: BTG Plc

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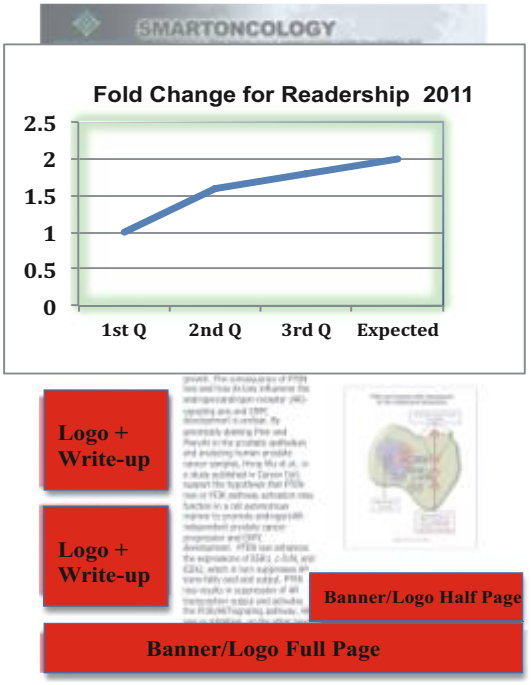

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