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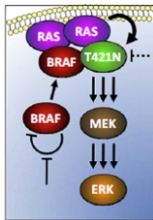
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INTELLIGENT INSIGHTS. SMART RESULTS

### A Model of Paradoxical CRAF Activation by BRAF



Cell, 140, Jan 22, 2010

## In the Spotlight:

### Kinase-Dead BRAF and Oncogenic RAS Drive Tumor Progression through CRAF

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Abbott and Pierre Fabre to Develop and Commercialize Pre-Clinical mAb

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BioMarin to Acquire LEAD Therapeutics

3SBio and Ascentage Pharma to Develop and Commercialize Cancer Therapeutics

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Survival Benefits with KRX-0401 in the Treatment of mCRC

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## Biomarkers

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## Regulatory

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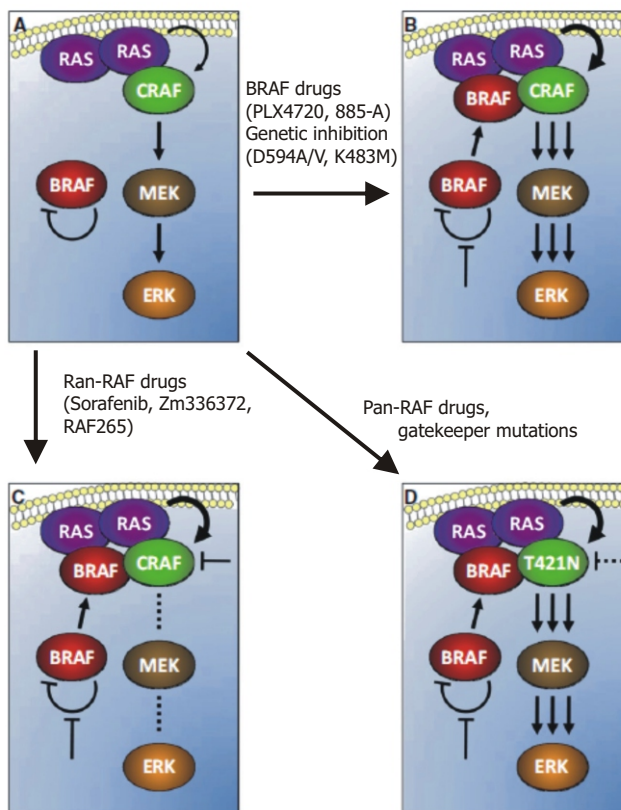


## Spotlight Report

### Kinase-Dead BRAF and Oncogenic RAS Drive Tumor Progression through CRAF

The RAS-ERK (extracellular signal-regulated protein kinase) MAPK (mitogen-activated protein kinase) signaling pathway regulates cell responses to environmental cues that include survival, proliferation, senescence, and differentiation. But, it also plays an important role in human cancer when the constitutive pathway activation favors proliferation and survival. In a recent article in *Cell*, Heidorn and colleagues provide important insight into the genetics of tumorigenesis mediated by kinase-dead BRAF in the presence of oncogenic RAS. Using a mouse model, the workers showed that the inhibition of BRAF by chemical or genetic means in the presence of oncogenic or growth factor-activated RAS induces BRAF binding to CRAF, leading to CRAF hyperactivation and consequently elevated MEK and ERK signaling. This does not occur when oncogenic BRAF is inhibited, demonstrating that BRAF inhibition *per se* does not drive pathway activation; it only occurs when BRAF is inhibited in the presence of oncogenic RAS. Kinase-dead BRAF mimics the effects of the BRAF-selective drugs and kinase-dead BRAF and oncogenic RAS cooperate to induce melanoma in mice. The authors postulate that in RAS-mutant cells, BRAF maintains itself in an inactive conformation through its own kinase activity, either through auto-phosphorylation or by phosphorylating a partner protein which then keeps it inactive. The results also suggest several potential mechanisms by which resistance to RAF-targeting drugs could develop in patients. BRAF-mutant tumors could become resistant to BRAF-selective drugs if they acquire a mutation in RAS or an upstream component that activates RAS, or if the drugs select a population of cells harboring pre-existing mutations in RAS.

#### A Model of Paradoxical CRAF Activation by BRAF



Cell, 140, Jan 22, 2010

The study provides a molecular basis for the design of clinical trials using BRAF drugs and highlights the importance of understanding signaling pathway in clinical practice. Genetic screening of patients prior to administering BRAF-selective drugs would be required not only to identify those who are likely to respond, but also to exclude those who could experience adverse effects, thereby ensuring successful implementation of personalized medicine.

Source: *Cell*



## Business News

### **Spectrum Pharmaceuticals Licenses Belinostat to TopoTarget**

Spectrum Pharmaceuticals has entered into a co-development and commercialization agreement with TopoTarget A/S for Belinostat, a novel histone deacetylase (HDAC) inhibitor. Belinostat is in a registrational trial, under a Special Protocol Assessment (SPA), as a monotherapy for relapsed or refractory Peripheral T-Cell Lymphoma (PTCL), an indication in which it has been granted Orphan Drug and Fast Track designations by the FDA. Belinostat is also under investigation in a randomized Phase II trial, as a combination therapy with carboplatin and paclitaxel, for the cancer of unknown primary (CUP).

Under the terms of the agreement, Spectrum licensed the rights to TopoTarget A/S for North America and India and gave an option for China, in exchange for an upfront cash payment of \$30 million, potential milestone payments of up to \$320 million, and 1 million shares of its common stock based on the successful achievement of certain development, regulatory, and commercial milestones, as well as double-digit royalties on net sales of Belinostat. Spectrum and TopoTarget will jointly fund development activities: 70% of the clinical trial costs will be borne by Spectrum and 30% by TopoTarget for new trials.

*Source: Spectrum*

### **Abbott and Pierre Fabre to Develop and Commercialize Pre-clinical mAb**

Abbott has signed an exclusive worldwide licensing agreement with Pierre Fabre SA to develop and commercialize h224G11, a pre-clinical monoclonal antibody (mAb) targeting the cMet receptor, for treatment of cancer. As part of the agreement, the companies will also collaborate on research to explore next-generation cMet antibodies. Under the terms of the agreement, Abbott will lead the development and commercialization of mAb. Pierre Fabre SA will receive an initial upfront payment of \$25 million and research funding for two years to support further discovery efforts.

*Source: Abbott*

### **Tenx Biopharma Licenses Zanolimumab from Genmab**

TenX Biopharma has signed a licensing agreement to acquire exclusive worldwide rights from Genmab to develop and commercialize zanolimumab (HuMax-CD4), a fully human monoclonal IgG1k antibody, for treatment of cutaneous and peripheral T cell lymphoma. Under the terms of the agreement, Genmab will receive an upfront license fee of \$4.5 million and will be entitled to milestones and royalties on sales of zanolimumab. TenX will be responsible for all the future costs of developing, manufacturing, and commercializing zanolimumab. "Zanolimumab has promise for treatment of patients with T cell cancers, and potential in other cancer types for which existing therapies are inadequate. We are building a pipeline of new medicines for high unmet need, with a focus on the patient through business efficiency," said Gardiner F.H. Smith, CEO of TenX Biopharma.

*Source: Tenx Biopharma*



**Business  
News**  
(Cont'd)

**BioMarin to Acquire LEAD Therapeutics**

BioMarin Pharmaceutical has entered into a stock purchase agreement to acquire LEAD Therapeutics (LEAD), with a key compound LT-673, an orally available poly (ADP-ribose) polymerase (PARP) inhibitor, for treatment of patients with rare, genetically defined cancers. Under the terms of the agreement, BioMarin will pay \$18 million upfront to LEAD's stockholders and an additional \$11 million upon the acceptance of the IND filing (filing expected by end of 2010), and up to \$68 million for development and launch milestones for LT-673. With this acquisition, BioMarin expects to incur operating expenses and acquisition-related charges of about \$11.0-13.0 million in 2010. Subject to customary closing conditions, the acquisition is expected to be completed by mid-February 2010.

*Source: BioMarin*

**3SBio and Ascentage Pharma to Develop, and Commercialize Cancer Therapeutics**

3SBio and Ascentage Pharma Group Corporation announced the formation of a strategic alliance to research, develop, and commercialize best-in-class targeted cancer therapeutics focusing on programmed cell death, or apoptosis. The alliance will leverage Ascentage Pharma's expertise in structure-based small molecule design, lead optimization, and preclinical development with 3SBio's proven drug development and commercialization capabilities in China. Under the terms of the agreement, 3SBio will make a \$3 million equity investment in Ascentage Pharma to fund R&D programs. 3SBio will have the exclusive rights to develop and commercialize cancer therapeutics, in China, which are discovered through Ascentage Pharma programs, while Ascentage Pharma will retain the rights for the rest of the world and receive future milestone and royalty payments from 3SBio's sales in China.

*Source: 3SBio*



## Research Highlight

### Phosphorylation by Cdk2 is Required for Myc to Repress Ras-induced Senescence

It has been known for over two decades that no more than two activated oncogenes, c-myc and H-ras, are sufficient to transform primary rodent cells into cancerous cells. KRas and Myc promote growth, but their expression can also induce apoptosis or cellular senescence. A recent paper by Hydbring *et al.* in *PNAS* provides a rationale for the cooperativity between Myc and Ras in malignant transformation. Their results suggest that Myc and Ras complement each other by repressing senescence and apoptosis, respectively, not necessary attributable to abnormal functions of these proteins. They present evidence for an important function of Myc in repressing Ras-induced senescence as well as senescence triggered by other activators of the MAPK pathway, including activated c-Raf, Mek, and TPA. Cyclin-dependent kinase 2 (Cdk2) suppresses the induction of senescence by Myc and phosphorylates Myc to bypass Ras-induced senescence, confirming its importance in averting oncogene-induced senescence. Over-expression of Myc can circumvent the induction of senescence by oncogenic Ras, and this activity is dependent on Cdk2-mediated phosphorylation of Myc at Ser-62. Furthermore, inhibition of Cdk2 following the activation of oncogenic Ras blocks Myc-mediated inhibition of senescence and attenuates the accumulation of activating and repressive MYC-containing complexes at anti-senescence and pro-senescence gene promoters, respectively.

Therefore, the results of this study indicate that Cdk2 should be re-evaluated as a target for cancer therapy. Cdk2-selective pharmacological inhibitors push Myc-transformed cells into senescence, suggesting that the inhibition of Cdk2, possibly in combination with Cdk1 inhibition, could potentially be a therapeutic principle for combating tumors with deregulated Myc or Ras. This emphasizes the urge to find drugs that can target Myc and/or Ras activity, but cooperativity between Myc and Ras remains unclear.

Source: *PNAS*<sup>1,2</sup>

### Proposed Model for the Regulation of Senescence by Myc



PNAS,107, Jan 5, 2010

### Preexistence and Clonal Selection of MET Amplification in EGFR Mutant NSCLC

Kinase inhibitors have emerged as effective clinical therapies for cancers that exhibit oncogene addiction to a particular kinase. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib are effective clinical therapies for patients with advanced non-small cell lung cancer (NSCLC) who have EGFR-activating mutations. A recent study by Turke *et al.* published in *Cancer Cell* modeled *in vitro* resistance to PF00299804, an irreversible EGFR inhibitor, in the TKI-sensitive EGFR-mutant NSCLC cell line, HCC827. Researchers evaluated the potency of the MET ligand, HGF, to promote resistance to EGFR TKIs. They observed that MET amplification is present in a small fraction of cells before drug exposure, and its development is dramatically accelerated by HGF. MET amplification activates ERBB3/PI3K/AKT signaling in EGFR-mutant lung cancers and causes resistance to EGFR kinase inhibitors. MET activation also induces drug resistance, but through GAB1 signaling. This activation of MET signaling (by amplification and HGF mediation) may, in fact, account for a larger fraction of gefitinib- or erlotinib-resistant tumors. The workers identified subpopulations of cells with MET amplification prior to drug exposure. Surprisingly, HGF accelerated the development of MET amplification both *in vitro* and *in vivo*. EGFR kinase inhibitor resistance either due to MET amplification or autocrine HGF production was cured *in vivo* by combined EGFR and MET inhibition.

These findings provide insight into the origin of drug resistance in EGFR-mutant cancers and into the future therapeutic strategies for the treatment of EGFR-mutant NSCLC. The results support the rationale for a combination of an irreversible EGFR inhibitor (effective against EGFR T790M) and a MET inhibitor as initial therapy, specifically in a molecularly defined cohort of patients with evidence of preexisting MET amplification. There is also potential to prospectively identify treatment-naive patients with EGFR-mutant lung cancer who are likely to develop MET amplification and may benefit from such initial combination therapy.

Source: *Cancer Cell*

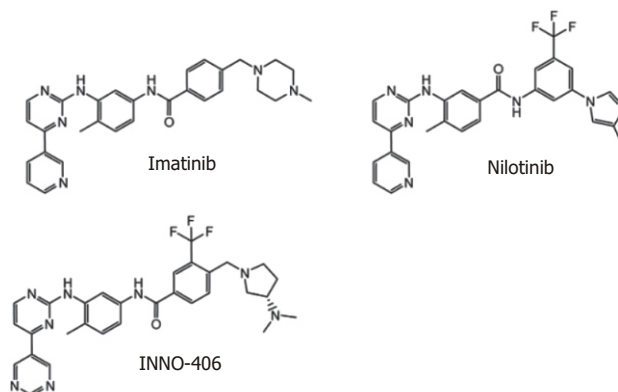


## Research Highlight (Cont'd)

### Chemical Proteomics Native Target Profiling of INNO-406 in CML Cells

Expression of the oncogenic fusion protein BCR-ABL is the hallmark of chronic myeloid leukemia (CML) and inhibition of its tyrosine kinase activity by imatinib has become the paradigm of targeted therapy. The newest of these drugs, the dual ABL/LYN inhibitor INNO-406 (NS-187, bafetinib), is a structural analog of imatinib and nilotinib, which exhibits a 25- to 55-fold increase over imatinib in *in vitro* activity against BCR-ABL. Rix *et al.* in *Leukemia* developed an unbiased chemical proteomics native target profile of INNO-406 in CML cells combined with functional assays using 272 recombinant kinases. By applying a two-tiered approach, they described the global target profile of INNO-406, which, together with the profiles of imatinib, nilotinib, dasatinib, and bosutinib, provides a basis for patient-specific use of such kinase inhibitors as single agents or in combination therapy against CML. The workers identified several new INNO-406 targets, including the kinases ZAK, DDR1/2, and various ephrin receptors. They also observed potent activity against PDGFR $\alpha$  V561D, but not the D842V mutant, both of which are frequently found in GIST. The oxidoreductase NQO2, inhibited by both imatinib and nilotinib, is not a relevant target of INNO-406.

#### Chemical Structures of Imatinib, Nilotinib and INNO-406



*Leukemia*, 24, 2010

Overall, INNO-406 has an improved activity over imatinib, but has a slightly broader target profile than that of imatinib and nilotinib. However, one of the most relevant differences of INNO-406 from other second generation BCR-ABL inhibitors lies in its distinct selectivity profile about the SFK and TEC family kinases, while retaining improved efficacy against imatinib-resistant CML cells through the inhibition of LYN. In contrast to dasatinib and bosutinib, INNO-406 does not inhibit all SRC kinases and most TEC family kinases and is therefore expected to elicit fewer immune-related side effects. Thus, given the improved efficacy against imatinib-resistant CML cells through its potent inhibition of LYN in addition to wild-type BCR-ABL and most of its clinically relevant mutants, INNO-406 represents an attractive additional component in the drug arsenal against CML.

Source: *Leukemia*

### Mutant p53 Drives Invasion by Promoting Integrin Recycling

p53 is a tumor suppressor protein whose function is frequently lost in cancers through missense mutations within the TP53 gene. This results in the expression of point-mutated p53 proteins that have both lost wild-type tumor suppressor activity and show gain of functions that contribute to transformation and metastasis. Muller *et al.* identified a key mechanism by which mutant p53 can promote invasive behavior of cells through a gain of function that contribute to transformation and metastasis. These activities of p53 reflect enhanced integrin and epidermal growth factor receptor (EGFR) trafficking, which depends on Rab-coupling protein (RCP).

The results published in *Cell* showed that the ability of mutant p53 proteins to contribute to the development of invasive and metastatic cancers *in vivo* was paralleled by their ability to enhance RCP-dependent recycling of integrin in H1299 lung cancer cells, thereby promoting trafficking and signaling of growth factor receptors. Mutant p53 was found to reflect an inhibition of TAp63, as illustrated by MCF 10A cells that exhibited enhanced cell invasion and transformation. These findings can drive both random migration and invasion through the enhancement of integrin recycling pathways. This new appreciation of mutant p53 function raises the possibility of the mutant protein being a target for the design of novel therapies aimed at inhibiting cancer dissemination, rather than the appearance of the primary tumor. These findings indicate a possibility that blocking alpha5/beta1-integrin and/or the EGF receptor will have therapeutic benefits in mutant p53-expressing cancers.

Source: *Cell*



## Clinical Development



### **Denosumab Superior to Zometa in Prostate Cancer Patients with Bone Metastases**

Amgen announced that a pivotal, Phase III, head-to-head trial evaluating denosumab (a monoclonal antibody targeting the receptor activator of NF- $\kappa$ B ligand (RANKL)) against Zometa (zoledronic acid) in the treatment of bone metastases in 1,901 men with advanced prostate cancer met its primary and secondary endpoints. Denosumab demonstrated superiority over Zometa for delaying the time to the first on-study skeletal-related event (SRE) (fracture, radiation to bone, surgery to bone, or spinal cord compression) and reducing the rate of multiple SREs. Both results were statistically significant. Overall rates of adverse events and serious adverse events, including infections, were generally similar between the two arms.

This study is the last of three pivotal trials conducted in over 5,700 advanced cancer patients, investigating the potential of denosumab to treat bone metastases. Results from the previous two trials were presented in September 2009. These three studies will form the basis of the clinical evidence package for denosumab in advanced cancer, which will be submitted to regulatory authorities later this year.

*Source: Amgen*

### **Phase II Trial of Picoplatin in mCRC Meets Primary Endpoint**

Poniard Pharmaceuticals presented final data from a randomized, controlled Phase II trial of picoplatin (a DNA synthesis inhibitor) in metastatic colorectal cancer (mCRC) patients, at the American Society of Clinical Oncology (ASCO) 2010 Gastrointestinal (GI) Cancers Symposium in Orlando, Florida, held on January 22-24, 2010. The trial evaluated picoplatin as a neuropathy-sparing alternative to oxaliplatin for the first-line treatment of mCRC in 101 patients who had not received prior chemotherapy. The primary objective of the trial was to measure the relative incidence and severity of neuropathy with picoplatin in combination with the 5-fluorouracil and leucovorin (FOLPI) regimen against oxaliplatin in combination with the 5-fluorouracil and leucovorin (FOLFOX) regimen.

The study met its primary objective, as the FOLPI regimen was associated with a statistically significant reduction in neurotoxicity, compared to the FOLFOX regimen. Regardless of grade, neuropathy was at 26% in FOLPI-treated patients and 62% in FOLFOX-treated patients. No grade 3/4 neuropathy was observed with FOLPI. The results also suggested that FOLPI had efficacy similar to that of FOLFOX. "We believe that these Phase 2 data confirm picoplatin's potential as an alternative to oxaliplatin in the first-line treatment of metastatic CRC and will support the design of a Phase 3 study. Our ultimate goal is to secure a strategic partnership to support further development of picoplatin in CRC and other solid tumor indications, including prostate and ovarian cancers," said Jerry McMahon, PhD, Chairman and CEO of Poniard.

*Source: Poniard*



## **Clinical Development** (Cont'd)

### **Phase III Trial of Sutent in Patients with Pancreatic NETs Meets Primary Endpoint**

Pfizer announced final results from a randomized Phase III trial of Sutent (sunitinib malate) in patients with advanced pancreatic neuroendocrine tumors (NETs), at the 2010 ASCO GI Cancers Symposium in Orlando, Florida. In this trial, patients were randomized to either the sunitinib (n = 86) plus best supportive care arm or the placebo plus best supportive care arm (n = 85). An independent Data Monitoring Committee (DMC) recommended to halt the trial in February 2009 because sunitinib demonstrated significant benefits and the primary endpoint (PFS) was met. Median PFS was 11.4 months in sunitinib-treated patients, compared to 5.5 months in placebo-treated patients. Sutent also prolonged OS, a secondary endpoint of the trial. These findings served as the basis for the recent filings of supplemental applications for sunitinib in the treatment of pancreatic NETs with regulatory authorities in the US, Europe, and Canada. Sutent is approved for the treatment of advanced/metastatic renal cell carcinoma and gastrointestinal stromal tumor after disease progression or intolerance to imatinib mesylate.

*Source: Pfizer*

### **Survival Benefits with KRX-0401 in mCRC Treatment**

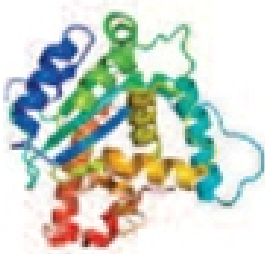
Keryx Biopharmaceuticals reported updated results from a Phase II trial of KRX-0401 (perifosine) (a PI3K/Akt pathway inhibitor of cancer) in combination with capecitabine as a treatment for advanced, metastatic colon cancer (mCRC), at the 2010 ASCO GI Cancers Symposium. In this randomized, double-blind, placebo-controlled study, heavily pre-treated patients with 2<sup>nd</sup> or 3<sup>rd</sup> line mCRC were randomized to receive capecitabine plus either perifosine or placebo. The study enrolled 38 patients, of which 34 were third-line or greater. The primary endpoint of the study was to measure time to progression (TTP). Overall response rate (ORR) and OS were measured as secondary endpoints. Perifosine + capecitabine more than doubled the TTP, compared to capecitabine + placebo (28 weeks vs. 11 weeks). 35 patients were evaluable for response. The ORR was 20% with capecitabine + perifosine vs. 7% with capecitabine + placebo, and the respective clinical benefit rates were 74% vs. 40%. Median OS was 18 months in the capecitabine + perifosine group vs. 11 months in the capecitabine + placebo group.

Keryx also reached an agreement with the FDA regarding a Special Protocol Assessment (SPA) on the design of a Phase III trial for perifosine in patients with refractory mCRC. The US-based Phase III trial X-PECT will evaluate the drug in combination with capecitabine. Nearly 430 patients will be recruited for the trial, which is due to start in Q2 2010. Study completion is due in H2 2011. Keryx in-licenses Perifosine from Aeterna Zentaris in the US, Canada, and Mexico.

*Source: Keryx*



# Biomarkers

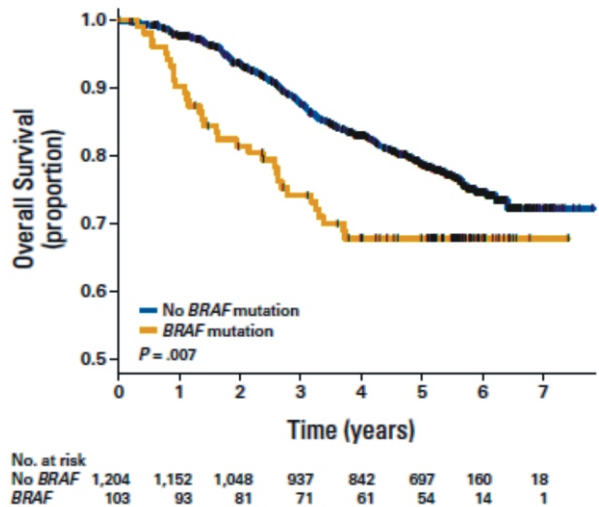


## Prognostic Role of KRAS and BRAF in Stage II and III Resected Colon Cancer

Mutations within the KRAS proto-oncogene have predictive value but are of uncertain prognostic value in the treatment of advanced colorectal cancer. The prognostic role of KRAS and BRAF in colon cancer was explained in the *Journal of Clinical Oncology* by Roth et al. Researchers took advantage of the PETACC-3 trial to evaluate the prognostic value of the above mutations in relation to relapse-free survival (RFS) and overall survival (OS). PETACC-3 is a large, randomized, Phase III trial assessing the role of irinotecan added to fluorouracil (FU)/leucovorin (FA) as adjuvant treatment for stage II and III colon cancer, in which 3,278 patients were accrued.

The BRAF gene encodes a serine/threonine protein kinase belonging to the RAS-RAF-MEK-ERK kinase pathway, regulated by KRAS protein activity and involved in CRC development. KRAS and BRAF mutations have been reported to be mutually exclusive events within tumors. The KRAS and BRAF mutation frequency was similar in stage II and III colon cancer. Survival analyses were based on univariate and multivariate proportional hazard regression models. In a multivariate analysis of the stage, tumor site, nodal status, sex, age, and grade and microsatellite instability (MSI) status, the KRAS mutation was associated with grade, while the BRAF mutation was significantly associated with females and highly significantly associated with right-sided tumors, old age, high grade, and MSI-high tumors. In univariate and multivariate analyses, KRAS mutations did not have a major prognostic value regarding RFS or OS. The BRAF mutation was not prognostic for RFS but was for OS, particularly in patients with MSI-low and MSI-stable tumors. Additional analysis of KRAS and BRAF mutations for molecular prognostic factors is underway and will be helpful in the evaluation of the weightage of these mutations in the evolution of this cancer.

### OS Curves Estimated by the method of Kaplan-Meier Comparing Cases with and without Mutations in BRAF



JCO, 28, Jan 20, 2010

Source: *J Clin Oncol*



## **Biomarkers** (Cont'd)

### **DNA Methylation Signatures Identify Biologically Distinct Subtypes in AML**

It has been appreciated in recent years that there are chemical codes in addition to the DNA sequence that control the behavior of normal and malignant cells. These additional codes are called "epi"genetic, as they are found outside of the DNA sequence. In a study published in *Cancer Cell*, Melnick et al. examined a specific epigenetic marker, DNA methylation, which plays a critical role in controlling gene expression. Investigators examined DNA methylation in 344 patients diagnosed with AML. Clustering of these patients by methylation data segregated them into 16 groups. This led to the identification of five methylation signatures with no other common morphologic or molecular features but with distinct clinical outcomes, suggesting that these are unique forms of AML with their own biological characteristics.

In addition, DNA methylation profiles segregated patients with CEBPA (CCAAT/enhancer-binding protein alpha) aberrations from other sub-types of leukemia, defined four epigenetically distinct forms of AML with NPM1 mutations, and showed that established AML1-ETO, CBF $\beta$ -MYH11, and PML-RARA leukemia entities are associated with specific methylation profiles. The study also identified a robust 15-gene methylation classifier that was predictive of overall survival in an independent patient cohort. Although epigenetic deregulation has been recognized as a hallmark of cancer for some time, the use of epigenomics to further improve an understanding of the biology of these diseases has only recently become feasible in the clinical context. The study showed that DNA methylation profiling is a powerful tool for the clinical stratification of AML and to further explore and define the biology of this disease.

*Source: Cancer Cell*

### **AstraZeneca and Dako to Develop Companion Diagnostics for Cancer Treatments**

AstraZeneca and Dako Denmark have entered into a collaboration agreement to develop companion diagnostic tests for multiple AstraZeneca oncology projects, including biologics and small molecules, in different stages of discovery and development. Under the terms of the agreement, the companies will work together to develop diagnostic tests to help physicians determine the most appropriate cancer treatment for patients. The financial terms of the deal were not disclosed. The collaboration will leverage Dako's position as a leader in cancer diagnostics and a strong partner in the development of diagnostic tests used in conjunction with drug therapies. AstraZeneca will bring its extensive experience in the development and commercialization of vital oncology products worldwide.

Ruth March, Personalized Healthcare Leader at AstraZeneca said, "For AstraZeneca, today's announcement marks the continuation of their commitment to Personalized Healthcare as demonstrated by the launch of IRESSA in the EU for patients with activating mutations of EGFR-TK (epidermal growth factor receptor-tyrosine kinase)." The agreement advances Dako's ongoing strategy to collaborate with strong partners in the pharmaceutical sector to enhance its offering of companion diagnostic assays.

*Source: Dako*



## Regulatory



### Herceptin Approved in EU for HER2-Positive Advanced Gastric Cancer

Roche announced that the European Commission has approved Herceptin (trastuzumab) in combination with chemotherapy for use in patients with HER2-positive metastatic gastric cancer. The approval is based on results from the international ToGA trial, which showed that treatment with Herceptin significantly prolongs the lives of patients with this aggressive cancer. The OS for patients with high levels of HER2 was 16 months vs. 11.8 months (on average) for those receiving chemotherapy alone.

"Herceptin is the first targeted biological therapy to show a survival benefit in advanced stomach cancer and represents a significant advance in the treatment of this devastating disease," said Pascal Soriot, Chief Operating Officer, Roche Pharmaceutical Division.

*Source: Roche*

### TYKERB Receives Accelerated Approval for 1<sup>st</sup> line Combination Treatment of HR+, HER2+/ErbB2+ Metastatic BC

GlaxoSmithKline announced that the FDA has granted accelerated approval for a new combination regimen using TYKERB (lapatinib) as a 1<sup>st</sup> line treatment for women with metastatic breast cancer (BC). TYKERB is now indicated in combination with letrozole for treatment of postmenopausal women with hormone receptor positive (HR+) metastatic BC that overexpresses the HER2 receptor, for which hormonal therapy is indicated. This accelerated approval was based on the results of a double-blind, placebo-controlled study that enrolled 219 women diagnosed with postmenopausal, HR+ and HER2+ metastatic BC. Women treated with lapatinib and letrozole experienced a 5.2-month increase in median PFS over those treated with letrozole alone. However, TYKERB in combination with an aromatase inhibitor has not been compared with a trastuzumab-containing chemotherapy regimen for the treatment of metastatic BC.

TYKERB is already indicated in combination with capecitabine for treatment of patients with advanced or metastatic BC whose tumors overexpress HER2 and have received prior therapy, including an anthracycline, a taxane, and trastuzumab.

*Source: GSK*

### FDA Approves Rituxan plus Chemotherapy for CD20-positive CLL

Genentech and Biogen Idec announced that the FDA has approved Rituxan (rituximab) in combination with fludarabine and cyclophosphamide (FC) for people with previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL).

The approval is based on data from two Phase III studies, CLL8 and REACH. Sponsored by Roche, CLL8 was a global, multi-center, randomized, open-label, Phase III study that enrolled 817 patients with previously untreated CD20-positive CLL. REACH was a global, multi-center, randomized, open-label, Phase III study sponsored by Genentech, Biogen Idec, and Roche, which enrolled 552 patients with previously treated CD20-positive CLL who had not previously received Rituxan (Rituxan-naive). Both studies evaluated Rituxan plus FC against FC alone. The primary endpoint for both studies was PFS and secondary endpoints included overall survival, event-free survival, duration of response, response rate, complete response, and toxicity.

In the CLL8 study, patients who received Rituxan plus FC had a PFS of 39.8, compared to 31.5 months for those who received FC alone. In the REACH study, previously treated patients who received Rituxan plus FC had a median PFS of 26.7 months, compared to 21.7 months for those who received FC alone. In both trials, PFS results were supported by a significant increase in overall and complete response rates.

*Source: Genentech*



## **Regulatory** (Cont'd)

### **Tasigna Receives FDA Priority Review for Newly Diagnosed Patients with Early-stage CLL**

Novartis announced that Tasigna (nilotinib), a Bcr-Abl-tyrosine-kinase-inhibitor, has been granted priority review by the FDA for treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase. In addition to the US, regulatory submissions have been filed in the EU and Japan. All filings are based on data demonstrating superior efficacy of Tasigna in the first head-to-head comparison with the standard of care Glivec® in newly diagnosed Ph+ CML patients.

The regulatory submissions are based on data from the Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients (ENESTnd) Phase III clinical trial. This randomized, open-label, multi-center trial compared the efficacy and safety of Tasigna with that of Glivec in adult patients with newly diagnosed Ph+ CML in chronic phase. Significantly fewer patients progressed to more advanced stages of the disease with Tasigna than the standard of care Glivec (imatinib) at 12 months. Tasigna also showed statistically significant improvement over Glivec in every other measure of efficacy, including major molecular response (MMR) and complete cytogenetic response (CCyR), at 12 months.

*Source: Novartis*