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INTELLIGENT INSIGHTS. SMART RESULTS.

## In the Spotlight: ASCO Highlights



ASCO | Annual '09 Meeting  
Personalizing Cancer Care

May 29-June 2, 2009 in Orlando, FL



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AstraZeneca and Merck to Investigate Novel Combination Anticancer Regimen

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STK33 as a Target for Treatment of Mutant KRAS-driven Cancers

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### Clinical Development

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Neoadjuvant Everolimus Phase II study in ER-positive Breast Cancer

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### Biomarkers

FLEX Study: KRAS Status Fails to Predict Cetuximab Response in Lung Cancer  
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### Regulatory

FDA Grants Full Approval for Sprycel for CML  
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FDA Advisory Panel Makes Favorable Recommendation for ARZERRA  
NICE Recommends Erbitux for mCRC and Sutent for mRCC

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The E-newsletter team: Dr. Anuradha Dhingra, Ms.Meenu Grover, Ms. Sarika Manchanda.  
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## ASCO Highlights

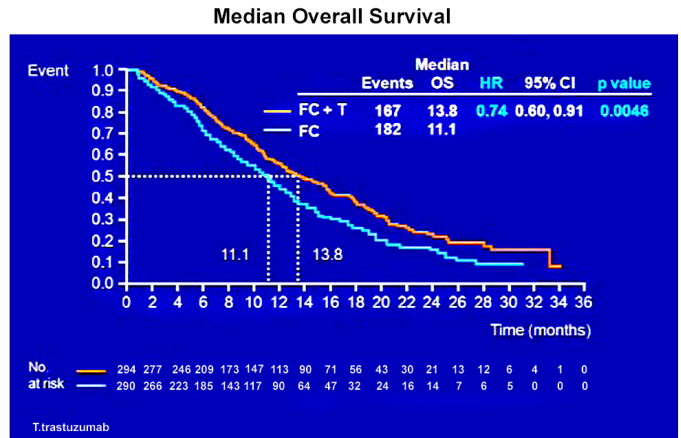
# Spotlight Report

## Trastuzumab is a New, Effective Treatment for HER2-positive Gastric Cancer

Dr. Eric Van Cutsem reported the results of a randomized Phase III ToGA trial, supported by Roche, at the ASCO 2009 meeting. The ToGA trial is an ongoing open-label, multicenter study evaluating the efficacy and safety of trastuzumab in combination with a fluoropyrimidine, either capecitabine or 5-FU plus cisplatin versus chemotherapy alone as first-line therapy in patients with HER2-positive advanced gastric cancer.

Tumors from 3,807 patients were centrally tested for HER2 status: 594 (22.1%) were found HER2 positive. These patients were randomized to receive herceptin (H)+CT (5-fluorouracil or capecitabine and cisplatin) or CT alone. H was given until disease progression. The primary end point was overall survival (OS). Median OS was prolonged by 3 months with H+CT compared to CT alone: 13.8 vs. 11.1 months, respectively. Overall response rate (ORR) was 47.3% in the H+CT arm and 34.5% in the CT arm. A safety analysis showed similar rates of grade 3 or 4 hematologic and nonhematologic events. Cardiotoxicity, which has been shown to be elevated with trastuzumab therapy in some patients, was similar between the two groups although asymptomatic left ventricular ejection fraction decreases were slightly higher among patients on trastuzumab (4.6% of pts in the H+CT arm and 1.1% in the CT arm)

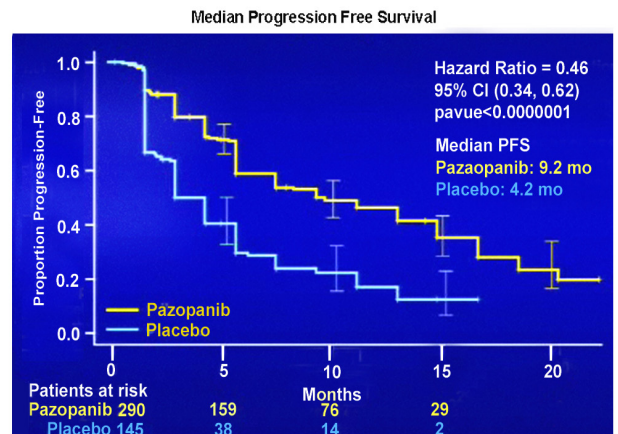
Source: ASCO Abstract No: LBA4509



## Pazopanib Shows Clinical Efficacy in Treatment Naïve Advanced RCC Patients

Dr. Cora Sternberg presented the results of a study (VEG105192) supported by GSK, evaluating the efficacy and safety of pazopanib compared with placebo in advanced renal cell carcinoma (RCC), at the ASCO 2009 meeting. Pazopanib is an angiogenesis inhibitor, targeting the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors and c-kit.

Patients (pts) with clear cell advanced RCC and measurable disease with no prior treatment (n= 233) or 1 prior cytokine-based treatment (n= 202), were stratified and randomized (2:1) to pazopanib. The primary endpoint was PFS. Secondary endpoints included OS, response rate (RR), and safety. PFS was significantly prolonged with pazopanib in the overall study population {9.2 vs. 4.2 months (mos)}, in treatment naïve pts (11.1 vs. 2.8 mos) and in cytokine-pretreated pts (7.4 vs. 4.2 mos). RR was 30% with pazopanib (vs. 3% with placebo) and median duration of response was 58.7 weeks. Pazopanib monotherapy was well tolerated. Final OS results are awaited, although an interim analysis showed survival to be 21.1 mos with pazopanib and 18.7 mos with placebo. Based on the trial data, GSK has applied for regulatory approvals of pazopanib for advanced RCC in the US and Europe.



Source: ASCO Abstract No: 5021^

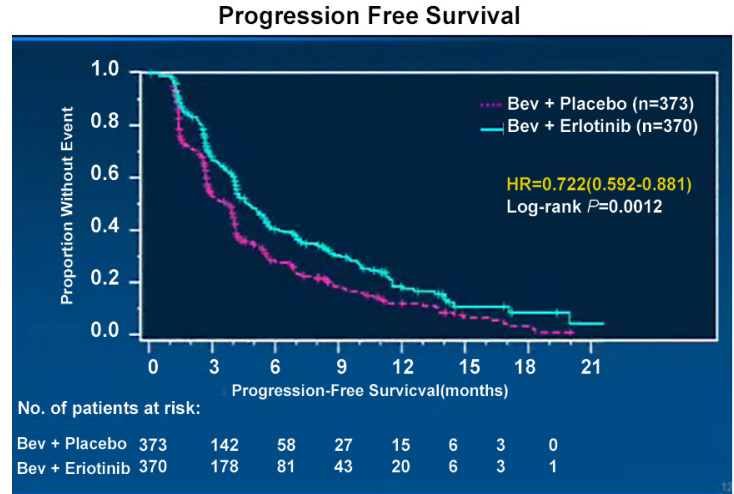
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## Spotlight Report (cont'd.)

### Adding Erlotinib to Bevacizumab Maintenance Improves PFS in NSCLC

A Phase IIIb ATLAS trial, sponsored by Genentech, demonstrated that adding erlotinib (E) to maintenance therapy with bevacizumab (B) delayed disease progression in advanced NSCLC patients. The ATLAS study was designed to evaluate B + E vs. B alone, following B + platin-containing doublet chemotherapy, in patients (pts) with stage IIIb/IV NSCLC. Pts who had not experienced disease progression (DP) or significant toxicity were then randomized to receive B + E or B + placebo (P). The primary objective of ATLAS was to compare PFS in pts receiving B + E versus B + placebo. 1,160 pts were enrolled and 768 randomized from May 2005 to May 2008. The median PFS was 4.8 mos for (B + E) vs. 3.7 mos for (B + P). The safety profile for B + E was consistent with known profiles for B and E. More patients receiving erlotinib were without disease progression at 3 mos (68% vs. 53% of the placebo group) and at 6 months (40% vs. 28%). Grade 3/4 events were reported in 44% of 367 patients in the erlotinib arm and in 30% of 368 in the placebo arm.



Source: ASCO Abstract No: LBA8002

### Positive Oncophage Interim Survival Data in Intermediate-Risk Kidney Cancer patients

Antigenics announced results of an interim analysis from the company's ongoing global patient survival registry, INSPIRE, at the ASCO 2009 meeting. The results demonstrated an approximately 46% lower risk of death when treated with Oncophage (vitespen) cancer vaccine compared with observation (n = 362) in patients with kidney cancer at intermediate risk of disease recurrence (stages I/II high-grade, III T1/2/3a low-grade). The total reported deaths in the intermediate-risk population were 18 (9.8%) in the Oncophage arm compared with 32 deaths (18%) in the observation arm. In addition, there was a promising trend for OS in patients treated with Oncophage in the total population eligible for the study, which included intermediate and high-risk patients (n = 604). As of the January 5, 2009 data cutoff, 18 additional deaths have been reported, with seven in the Oncophage arm and 11 in the observation arm. Christopher G. Wood, lead US investigator, presented these survival results at the 2009 meeting of the ASCO.

The interim analysis from the patient registry, INSPIRE, launched in 2007, reflects a median follow-up of 4.5 years from the largest, randomized Phase III kidney cancer trial ever completed to date in the adjuvant setting. Final results from INSPIRE, are expected by mid 2010.

Source: Antigenics Inc., ASCO Abstract No: 3009



## Spotlight Report (cont'd.)

### **Avastin plus Commonly Used Chemotherapies Improves PFS in Advanced Breast Cancer**

Genentech presented results of a Phase III study (RIBBON 1) that showed Avastin (bevacizumab) plus commonly used chemotherapies, capecitabine and anthracycline-based therapies, increased PFS compared to the chemotherapies alone. The safety profile of Avastin was consistent with previous experience, and no new safety signals for Avastin were observed in the study.

RIBBON 1 comprised two independently powered study groups. Group I evaluated capecitabine plus Avastin versus capecitabine plus placebo. Group II evaluated a taxane (paclitaxel/docetaxel) or anthracycline-based chemotherapy (doxorubicin/epirubicin) plus Avastin versus the chemotherapy plus placebo. Group I had a 45% improvement in the PFS compared to those who received the chemotherapy alone (31% risk reduction). Group II had a 55% improvement in the PFS compared to those who received chemotherapy alone (36% risk reduction).

In February 2008, Avastin received accelerated approval from the FDA for advanced breast cancer, in combination with paclitaxel, for the treatment of patients who have not received chemotherapy for advanced HER2-negative breast cancer. Avastin is not indicated for patients with breast cancer that has progressed following administration of anthracycline and taxane chemotherapy for metastatic disease. The FDA review of data from the positive RIBBON 1 and AVADO studies is required for the accelerated approval to be converted into a full approval.

*Source: ASCO Abstract No: 1005*

### **No Significant Improvement with Adjuvant Bevacizumab in Early-Stage Colorectal Cancer**

Dr. Norman Wolmark presented the results of a Phase III trial aiming to determine whether mFOLFOX6 plus bevacizumab (mFF6+B) would prolong disease-free survival (DFS) compared to mFOLFOX6 (mFF6) alone in early stage colorectal cancer, at ASCO 2009 meeting. The addition of bevacizumab to mFF6 did not result in an overall statistically significant prolongation in DFS.

Patients in respective arms (1,338 and 1,334) were randomized to receive either mFF6 alone or mFF6+B. After a median follow-up of 36 months, 77.4% of patients were disease-free if they had the targeted therapy added to a modified FOLFOX6 chemotherapy regimen, slightly better than the 75.5% disease-free survival rate in patients given FOLFOX6 alone. The patients treated with bevacizumab for a full year after surgery were 40% less likely to have new disease at 1 year. The DFS rate at 1 year was 94.4% with adjuvant chemotherapy plus bevacizumab vs. 90.7% with chemotherapy alone. "It was clear that there was a significant transient benefit during the 1 year that bevacizumab was given," Dr. Wolmark said, questioning whether the drug needs to be given longer to have an impact in the adjuvant setting. The investigators "strongly suggest" consideration of the use of adjuvant bevacizumab for longer than 1 year, he said.

*Source: ASCO Abstract No: LBA4*



## Spotlight Report (cont'd.)

### Maintenance with Pemetrexed Improves OS and PFS in Lung Cancer

Pemetrexed's efficacy, favorable tolerability profile, and ease of administration provided a strong rationale for evaluation as maintenance therapy in patients with advanced NSCLC. Dr. Chandra P. Belani presented the final analyses for all outcomes, including OS, from a Phase III study of Pemetrexed vs. Placebo in pts with stage IIIB/IV NSCLC who had not progressed on four cycles of platinum-based chemotherapy. Patients were randomized 2:1 to receive pemetrexed (Pem) + best supportive care (BSC) or Placebo + BSC in 21-day cycles until disease progression. In the 663 randomized pts (Pem 441: Placebo 222), Pem resulted in significantly better OS (13.4 vs. 10.6 mos), PFS (4.4 mos vs. 2.6 mos) and response (51.7% vs. 33.3%). The improvements in PFS and OS were observed primarily in patients with non-squamous histology. OS significantly improved from 10.3 months with placebo to 15.5 months with pemetrexed in this sub group. Drug-related grade 3/4 toxicities were higher for Pem (16% vs 4%); specifically, fatigue (5% vs 0.5%) and neutropenia (2.9% vs. 0%).

"I think that a demonstration of 5-month improvement in a subset of patients based on histology is significant," said Dr. Belani, deputy director of the Penn State Hershey Cancer Institute in Hershey, Pennsylvania. Pemetrexed is approved as a first-line treatment for advanced non-squamous NSCLC in combination with cisplatin, and as a single agent in patients with recurrent disease.

*Source: ASCO Abstract No: CRA8000*

### Nimotuzumab is as Efficacious as Other EGFR Drugs with Lesser Toxicities in SCCHN

YM BioSciences reported results from a randomized trial of nimotuzumab, an antibody targeting EGFR, assessing its safety and efficacy in combination with radiation therapy (RT) or chemoradiation therapy (CRT) in patients with inoperable (Stage III or IVa) squamous cell carcinoma of the head and neck (SCCHN) at the 2009 ASCO annual meeting.

A total of 92 were enrolled and randomly assigned to Group A: radical radiotherapy (RT) and Group B: chemoradiotherapy (CRT). Randomization within Group A: [RT] vs. [RT+ nimotuzumab] and within Group B: [CRT] vs.[CRT + nimotuzumab]. Out of total patients enrolled, 76 were considered evaluable. The addition of nimotuzumab to both the radiation and chemoradiation regimens improved the overall response rate, survival rate at 30 months, median PFS and median OS. Survival rate ITT: Group B: 69.5% vs. 21.7% (CRT), Group A: 39.1% vs. 21.7% (RT alone). PFS: RT alone – 3 mos vs. 8 mos, RT+CT – 5 mos vs. 13 mos. The study concluded that the concurrent use of nimotuzumab with chemoradiotherapy enhances long-term loco-regional control and survival. Adding biological agents to physically targeted modality improves long-term therapeutic outcome of SCCHN.

*Source: ASCO Abstract No: 6041*

### Positive Study Findings with BSI-201, a PARP1 inhibitor, in Metastatic TNBC

Sanofi-aventis reported results from a Phase II study of BSI-201, a poly(ADP-ribose) polymerase (PARP1) inhibitor, in combination with gemcitabine and carboplatin (GC) chemotherapy, in patients with metastatic triple-negative breast cancer (TNBC). TNBC is an aggressive breast cancer subtype that shares molecular and pathologic features with BRCA1-related breast cancers.

In the randomized study, 116 women with metastatic TNBC, were randomly assigned to receive GC in combination with the investigational agent BSI-201 or GC alone. The primary study endpoint was clinical benefit rate (CBR = CR + PR + SD  $\geq$  6 months). Secondary study endpoints included PFS, OS and safety. 62% of patients receiving BSI-201 + GC showed clinical benefit, compared with 21% in the group receiving chemotherapy alone. Tumor response (complete or partial response) was observed in 48% of patients who received BSI-201 combined with chemotherapy vs. 16% in GC alone group. Women who received BSI-201 had a median PFS of 6.9 months and OS of 9.2 months compared with 3.3 and 5.7 months, respectively, for women who received chemotherapy alone. BSI-201 did not add to the frequency or severity of adverse events associated with chemotherapy.

*Source: ASCO Abstract No: 3*



## Business News

### Exelixis and Sanofi-aventis Collaborate for Discovery of PI3K Inhibitors

Sanofi-aventis and Exelixis signed a global licensing and collaboration agreement for the discovery of inhibitors of phosphoinositide-3 kinase (PI3K) for the treatment of cancer. Sanofi-aventis will have a worldwide exclusive license to XL147, a PI3K inhibitor, and XL765, a PI3K/TORC1/TORC2 inhibitor, which are currently in Phase I and Phase Ib/II clinical trials respectively. The companies will combine efforts in establishing several pre-clinical PI3K programs and jointly share responsibility for research and preclinical activities. Sanofi-aventis will pay Exelixis aggregate upfront cash payments of \$140 million under the licensing and collaboration agreement. Exelixis will be eligible to receive development, regulatory and commercial milestones of over \$1 billion in the aggregate, as well as royalties on sales of any products commercialized under the license or collaboration.

George A. Scangos, president and CEO of Exelixis said, "Sanofi-aventis and Exelixis are committed to realizing the full potential of these compounds and other PI3K inhibitors to provide cancer patients with new treatment options." Clinical data from the Phase I trials of XL147 and XL765 were presented at the ASCO Annual Meeting 2009.

*Source: Exelixis*

### Acquisition of CuraGen Corporation by Celldex Therapeutics

Celldex Therapeutics announced that it has entered into a definitive agreement to acquire CuraGen Corporation. Celldex will acquire CuraGen in a tax-free, stock-for-stock transaction, which values CuraGen at approximately \$94.5 million. The acquisition will add a portfolio of oncology-focused, fully-owned antibodies to Celldex's Precision Targeted Immunotherapy Platform. CuraGen is expected to have a cash balance of at least \$54.5 million net of certain acquisition-related costs. Celldex's pipeline of immunotherapeutic consists of product candidates in varying stages of development with lead candidate, CDX-110, currently undergoing evaluation in a Phase II clinical trial in newly diagnosed glioblastoma multiforme. Another lead candidate, CDX-1307, is currently enrolling patients in a Phase I study with epithelial tumors. In addition, the Company recently completed the successful preclinical development of CDX-1401, a candidate for study in multiple solid tumors.

*Source: Curagen*

### Takeda to Acquire IDM Pharma

Takeda Pharmaceutical Company and IDM Pharma announced that Takeda America Holdings, a wholly-owned subsidiary of Takeda (Takeda America), and IDM Pharma have entered into an agreement for Takeda America to acquire IDM Pharma. Under the agreement, Takeda America will purchase IDM Pharma's all outstanding shares for \$2.64 per share in an all cash tender offer followed by a merger. Takeda's business unit responsible for global oncology strategy and development, will have global development responsibility for IDM Pharma's primary asset, MEPACT (mifamurtide). Takeda Pharmaceuticals Europe will be responsible for commercializing MEPACT in Europe. IDM Pharma received European marketing approval for MEPACT, a therapy indicated for the treatment of non-metastatic osteosarcoma (malignant bone cancer) following surgical removal of the tumor (resection) in children, adolescents and young adults.

*Source: IDM Pharma*

### AstraZeneca and Merck to Investigate Novel Combination Anticancer Regimen

AstraZeneca and Merck announced a collaboration to research a novel combination anticancer regimen composed of two investigational compounds, MK-2206, a potent, non-ATP allosteric Akt inhibitor, from Merck and AZD6244, a selective MEK inhibitor from AstraZeneca. This is the first time that two large pharmaceutical companies have collaborated to evaluate the potential for combining candidate molecules at such an early stage of development. Under the terms of the agreement, AstraZeneca and Merck will work together to evaluate co-administration of the compounds in a Phase I clinical trial for treatment of solid cancer tumors. All development costs will be shared. AZD6244 has completed Phase I evaluation, demonstrating proof of mechanism, and several Phase II monotherapy studies, which showed evidence of clinical activity. Phase I clinical data on MK-2206 were presented at the ASCO annual meeting. Preclinical evidence indicates that combined administration of these compounds could enhance their anticancer properties.

*Source: AstraZeneca*



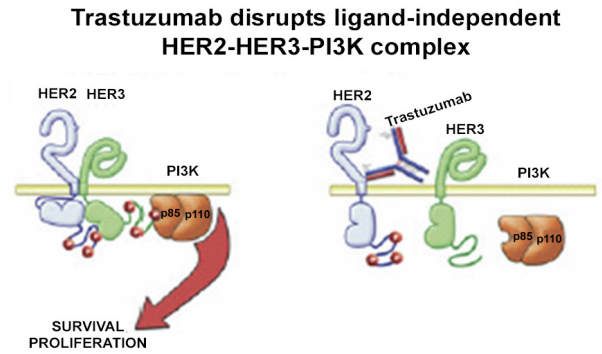
# Research Highlights

## Ligand-Independent HER2/HER3/PI3K Complex Disruption by Trastuzumab

Nearly 1/5th of breast tumors possess the 17q11-24 ErbB2-containing amplicon and show a dramatic overexpression of ErbB2. Trastuzumab, a humanized antibody targeting ErbB2, is useful as an adjuvant in patients whose tumors over-express ErbB2. However, a uniform response to this agent is not seen in all cases and gaps still exist in our understanding of trastuzumab's mechanism of action and ability to predict patient response.

In a recent study reported in *Cancer Cell*, Junttila *et al.* showed that trastuzumab causes destabilization of ligand-independent constitutive ErbB2/ErbB3 complexes, uncoupling of ErbB3 from ErbB2, and blockade of downstream PI3K/AKT signaling in ErbB2-overexpressing tumor cells. Even though, ErbB2-overexpressing tumor cells have high levels of P-Y ErbB3 and high PI3K/AKT activity, heregulins (HRG) treatment causes a further increase in both. Moreover, HRG prevents trastuzumab from disrupting ErbB2/ErbB3 complexes. ErbB2-overexpressing breast tumor lines with low PTEN or activating PIK3CA mutations do not respond to trastuzumab; AKT activity and tumor cell proliferation remain high. In all tumor cells, irrespective of the presence or absence of PI3K pathway mutations, trastuzumab disrupts ligand-independent ErbB2/ErbB3 complexes, leading to a loss of p85/p110a from ErbB3. However, in trastuzumab-treated cells with mutant PI3K or low PTEN, AKT activity remains high. These results suggest that despite uncoupling p85/p110a from the ErbB2/ErbB3 complex, mutant PI3K remains localized at the membrane, perhaps using its Ras-binding domain, where it continues to catalyze PIP3 formation, AKT activation, and tumor cell proliferation. Thus the combination of trastuzumab and the PI3K inhibitor GDC-0941, a selective and potent PI3K inhibitor, because of its high efficacy, warrants clinical evaluation in patients who have not been treated with a HER2-directed therapy in the metastatic setting. Moreover, patients who progress on trastuzumab or lapatinib (a HER2-directed tyrosine kinase inhibitor) may benefit from additional therapy that includes the PI3K inhibitor GDC-0941.

Source: *Cancer Cell*



Cancer Cell, 15, May 5, 2009



**Research Highlights**  
(cont'd.)

**Non-genetic Origins of Cell-to-cell Variability in TRAIL-induced Apoptosis**

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a type II transmembrane protein. In apoptosis mediated by it, the time between TRAIL exposure and caspase activation is highly variable. This cell-to-cell variation in the decision to undergo apoptosis is largely predetermined by differences in protein abundances at the time of stimulation, and is not due to genetic, epigenetic, cell-cycle differences or random molecular noise.

In a recent study reported in *Nature*, Spencer *et al.* imaged sister cells expressing reporters of caspase activation and mitochondrial outer membrane permeabilization after exposure to TRAIL. They demonstrated that naturally occurring differences in the levels or states of proteins regulating receptor-mediated apoptosis are the primary causes of cell-to-cell variability in the timing and probability of death in human cell lines (HeLa and MCF10A mammary epithelial cells). Protein state is transmitted from mother to daughter, giving rise to transient heritability in fate, but protein synthesis promotes rapid divergence in the sister cells. This suggests that TRAIL responsiveness is in fact encoded in the proteome; symmetric partitioning of the proteome between daughter cells ensures that recently divided daughter cells respond similarly. Random fluctuations in protein synthesis and degradation erode that symmetry over time, reducing the correlation in time variation. The study provides compelling evidence that variation in the cellular state does not result solely from a definable perturbation but may arise spontaneously in an isogenic cell population. This state is heritable, transient, and encoded by the proteome. One significant implication of this work pertains to the role of noise in the cell-death decision. The realization that there is little intrinsic noise in the cell-death decision may impact therapeutic design and has implications for understanding 'fractional killing' of tumor cells after exposure to chemotherapy.

Source: *Nature*

**Novel Strategies for Combating CRPC**

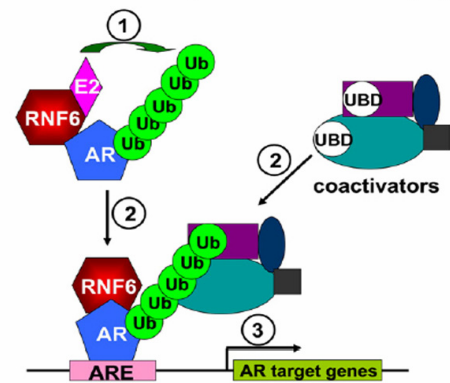
The androgen receptor (AR), a key transcription factor, is directly linked to numerous diseases, including prostate cancer. Tran *et al.* in a study published in *Science*, identified two compounds, RD162 and MDV3100, that maintain AR antagonism in the presence of high AR expression. These diarylthiohydantoin bind to the androgen receptor with greater relative affinity than the bicalutamide. In LNCaP human prostate cancer cells, both agents reduced AR nuclear translocation and DNA binding. RD162 and MDV3100 induced significant tumour regression in castration resistant prostate cancer (CRPC) mouse xenograft models using LNCaP or LAPC4 prostate cancer cells. MDV3100 is being tested in a Phase I and II clinical trial in 30 men with CRPC who have progressed on first-line anti-androgens.

Preliminary data showed that prostate-specific antigen (PSA) levels reduced by >50% in 13 patients.

In another study published in *Cancer Cell*, Xu *et al.* conducted a screen for proteins that bind AR and identified the E3 ubiquitin ligase RING finger protein 6 (RNF6). Although RNF6 induced polyubiquitylation of AR, it did not promote AR degradation. Rather, it seems to promote AR transcriptional activity, as *RNF6* knockdown by short hairpin RNA (shRNA) altered the recruitment of AR to some target genes and, hence, altered the gene expression profile in LNCaP cells. Ubiquitylation may affect AR transcriptional activity by influencing the recruitment of transcription cofactors containing the ubiquitin-interacting domain (or domains) to facilitate transcriptional regulation of AR target genes. RNF6 or other members of the ubiquitylation machinery could be valid therapeutic targets in prostate cancer. In a recent study in *PNAS*, Jones *et al.* identified two non-competitive inhibitors of AR, pyvinium pamoate and the natural product harmol hydrochloride. These agents inhibit transcription of *KLK3* (which encodes PSA) in LNCaP cells, suggesting distinct mechanisms of action. These early studies suggest promising new therapeutic strategies for combating CRPC.

Source: *Science*, *PNAS*, *Cancer Cell*

Postulated Model of Regulation of AR Activity by RNF6



Cancer Cell, 15, April 7, 2009



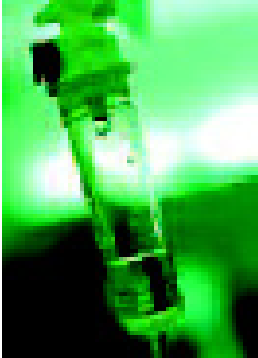
## Research Highlights (cont'd.)

### STK33 as a Target for Treatment of Mutant KRAS-driven Cancers

Efforts to develop drugs that inhibit oncogenes such as RAS proteins have been largely unsuccessful, even though *RAS* gene family members are mutated in approximately 30% of human tumors. As a result of an oncogenic mutation, cancer cells may also develop secondary dependencies on genes that are themselves not oncogenes. Perturbation of these genes may result in oncogene-specific “synthetic lethal” interactions that could provide new therapeutic opportunities and an alternative to therapeutic targeting of oncogenes.

In a study published in *Cell*, Claudia Scholl *et al.* identified synthetic lethal genetic interactions in the context of mutant *KRAS*. They used high-throughput RNAi screens in human cancer cell lines that were categorized according to the presence or absence of a transforming *KRAS* mutation, and identified and functionally validated a serine/threonine protein kinase, STK33, that is selectively required for the survival and proliferation of mutant *KRAS*-dependent cancer cells across a wide range of tissue contexts. The results show that cells that are dependent on mutant *KRAS*, exhibit selective sensitivity to suppression of STK33, irrespective of tissue origin and genetic context. STK33 thus emerges as a component of a signaling pathway that is aberrantly required due to adaptation to a functionally relevant *KRAS* mutation. STK33 promotes cancer cell viability in a kinase activity-dependent manner by regulating the suppression of mitochondrial apoptosis mediated through S6K1-induced inactivation of the death agonist BAD selectively in mutant *KRAS*-dependent cells. This study provides basis to envision STK33 inhibition as a strategy for therapeutic intervention in a broad spectrum of tumors associated with mutant *KRAS* and also demonstrate the potential of RNAi screens for discovering functional dependencies created by oncogenic mutations that may enable therapeutic intervention for cancers with “undruggable” genetic alterations.

*Source: Cell*



# Clinical Development

## Long-Term Durability of Ceplene in Sustaining Leukemia-Free Survival

EpiCept Corporation has released long-term data showing that the use of Ceplene when administered in conjunction with low-dose interleukin-2 (IL-2) provides durable protection from leukemia relapse in patients with Acute Myeloid Leukemia (AML), based on a minimum of six years of follow-up. These data was presented at the European Hematology Association's (EHA) 14th Congress in Berlin, Germany. Researchers analyzed follow-up data from patients enrolled in the Phase III pivotal trial of Ceplene. The primary endpoint assesses the durability of the benefit of Ceplene with IL-2 in achieving leukemia-free-survival (LFS), after a minimum of six years, in patients who have achieved first complete remission (CR1) and among the overall patient group. The study found that the Ceplene/IL-2 treatment group continued to show statistically significant differences in LFS in the overall treatment population and among the CR1 group.

Jack Talley, President and CEO of EpiCept, remarked "These data provide further demonstration of the positive and prolonged clinical benefits Ceplene can provide AML patients in preventing relapse of this deadly disease. We continue to be keenly focused on further expanding the extraordinary impact that Ceplene can have on AML patients through our regulatory advancement of the drug in North America."

*Source: EpiCept*

## Positive Phase II Data of OGX-011 in Advanced Prostate Cancer Trial

OncoGenex Pharmaceuticals announced the final results of a randomized Phase II trial presented during an oral presentation at the ASCO Annual Meeting. Analyses indicated a survival benefit in patients treated with OGX-011 in combination with docetaxel, compared to docetaxel alone. The median OS in patients with advanced metastatic prostate cancer who were treated with OGX-011 plus docetaxel was 23.8 months compared to 16.9 months for patients treated with docetaxel alone. Patients treated with OGX-011 had a rate of death 51% lower than patients treated with docetaxel alone. Additional exploratory analyses found that the lower rate of death was associated with the effect of OGX-011 treatment even when varying amounts of chemotherapy were administered.

Dr. Chi, principal investigator of the trial said, "A 6.9 month median OS difference would represent a significant improvement over the current standard docetaxel therapy. The consistent results in favor of the OGX-011 treatment arm in this trial are a clear indication that Phase III trials are warranted."

*Source: Oncogenex*

## Everolimus Phase II Positive Results in Lymphoma Patients

Results of Phase II trial of everolimus (Afinitor) presented at the 14th annual European Hematology Association Congress in Germany showed that 33% of patients with relapsed non-Hodgkin's lymphoma (NHL) and Hodgkin's disease treated with everolimus experienced a 50% or greater reduction in tumor size. The median time to disease progression for all 145 patients enrolled in the study was 4.3 months and the median duration of response for the 48 responders was 6.8 months.

Based on results from this study, Novartis has initiated PILLAR-2 (Pivotal Lymphoma trials of RAD001), a Phase III trial investigating adjuvant treatment with everolimus in poor-risk patients with diffuse large B-cell lymphoma (DLBCL) who achieved complete remission with first-line rituximab combined with chemotherapy. This worldwide study will evaluate the potential of everolimus to extend disease-free survival in patients with DLBCL.

*Source: Novartis*



## Clinical Development (cont'd.)

### Neoadjuvant Everolimus in ER-positive Breast Cancer Patients

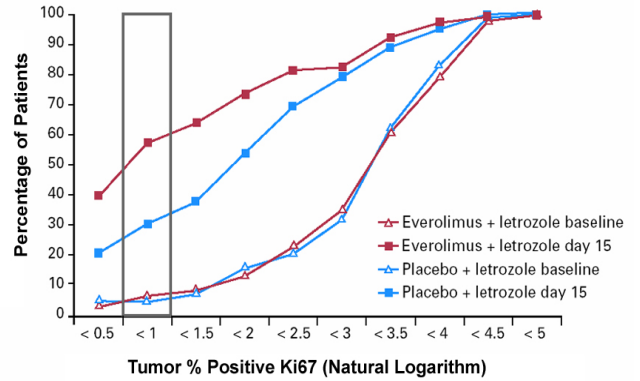
The mammalian target of rapamycin (mTOR), a kinase in the phosphoinositide-3-kinase (PI3K)/Akt signaling pathway, integrates growth factor stimulation with energy and nutrient signaling to control cell growth and proliferation.

In a recent study reported in *JCO*, Baselga *et al.* evaluated the benefit of combining everolimus and letrozole in the neoadjuvant treatment of postmenopausal women with ER-positive breast cancer. The study successfully met its primary endpoint by showing that the combination of everolimus and letrozole generated antitumor responses in a significantly higher proportion of patients compared to treatment with letrozole and placebo (68% v 59%). Ki67 expression correlates with cell proliferation, and high expression correlates with a poor prognosis.

An antiproliferative response in a significantly higher proportion of patients in the everolimus group was observed than in the placebo group. The extent of Ki67 reduction correlated with the clinical response, and thus the patients with progressive disease had high rates of proliferation. In addition, patients with mutations in the PIK3CA exon 9 helical domain, who have been shown to have a poor long-term outcome, showed a relatively small antiproliferative response to letrozole alone but a good response to everolimus plus letrozole. This finding supports an association between PI3K/Akt/mTOR signaling and insensitivity to endocrine therapies. In conclusion, the study showed that everolimus significantly increased the efficacy of letrozole in the treatment of newly diagnosed, ER-positive breast cancer in terms of both clinical and antiproliferative response; safety profile of the combination is acceptable.

Source: *JCO*

Antiproliferative Response at Day 15 Compared with Baseline



JCO, 27, June 1, 2009



# Biomarkers



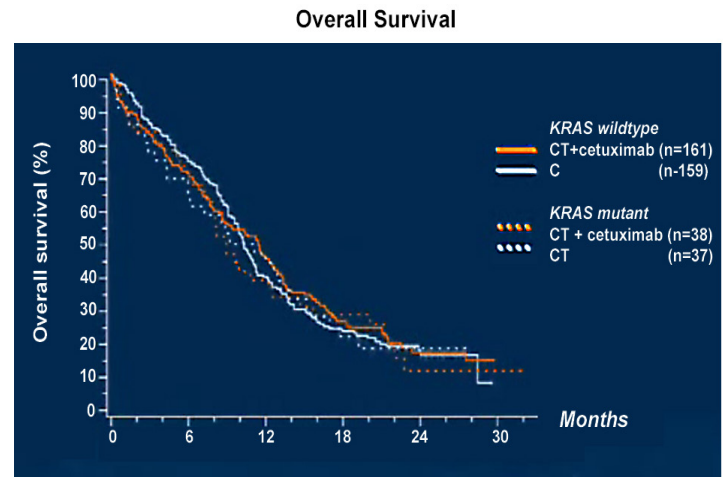
## FLEX Study: KRAS Status Fails to Predict Cetuximab Response in Lung Cancer

The multinational, randomized, Phase III FLEX study compared cisplatin/vinorelbine (CT) plus the EGFR-antibody, cetuximab (Erbix), with CT alone in the 1st-line treatment of patients (pts) with advanced EGFR-expressing NSCLC and demonstrated a statistically significant OS benefit for the cetuximab combination.

In a current study presented at ASCO 2009 meeting by O'Byrne *et al.* archived tumor samples from 35% of the 1,125 FLEX patients were evaluated, and a KRAS mutation was detected in 75 of 395 (19%) samples. There was no significant difference in OS by KRAS mutation status or by treatment type.

The finding is striking because KRAS mutation status has been shown to predict cetuximab benefit in colorectal cancer. Among patients with wild-type KRAS tumors, median OS was 11.4 months with chemotherapy plus cetuximab vs. 10.3 months with chemotherapy alone (hazard ratio, 0.96). In those with KRAS mutant tumors, median OS was 8.9 months in the cetuximab arm vs. 11.1 months in the control arm. Patients treated with cetuximab who developed early acne-like rash of any grade had a longer median OS than those without acne-like rash: 15.0 months vs 8.8 months. Also the PFS and response rates by FISH status failed to indicate response to cetuximab therapy. Thus, clinical data from the FLEX study do not support the hypothesis that KRAS mutation status is predictive for cetuximab efficacy when combined with 1st-line chemotherapy in advanced NSCLC, whereas early acne-like rash of any grade appears to be associated with better outcome in patients treated with platinum-based chemotherapy plus cetuximab in this setting.

Source: ASCO 2009



## Genomic Strategy in Modules of Oncogenic Pathway Signaling Networks

The phenotypic and molecular heterogeneity of human cancers is reflected by the variations in activity of cell-signaling pathways that control cell growth and determine cell fate. Studies describing gene mutations in a number of human cancers have emphasized the importance of placing such data in pathway-specific contexts. Signals from complex biological networks, such as those involved in cancer, reflect the activity of these functional networks assembled from modules that respond to input signals.

A recent study reported in *Molecular Cell* by Chang *et al.* describes an approach to dissect oncogenic signaling pathways into functional modules on the basis of gene expression signatures, which can then be used to analyse disease outcome and responses to therapeutics. Such pathway-specific interpretations are also important for understanding the functional relevance of gene alterations in human cancers. Using the Ras and E2F signaling pathways, the researchers defined a core set of genes for each pathway. They then utilized the NCI-60 data set, which comprises expression profiles of human cancer cell lines, to identify genes related to the core pathway that showed similar variation in their expression as the core genes. They were thus able to generate signatures (20 in the Ras pathway and 8 in the E2F pathway) that correspond to sets of genes that share expression patterns. The resulting signatures revealed the discrete modules of the cell-signaling pathways and became tools to provide a measure of the individual activities that foster pathway complexity pertaining to disease outcomes and response to pathway-specific therapeutics. This model of pathway structure constitutes a framework to study the processes by which information propagates through cellular networks and can help elucidate the relationships of cellular and clinical phenotypes.

Source: *Molecular Cell*



## Biomarkers (cont'd.)

### EGFR Mutations in Plasma Samples Predict Tumor Response in NSCLC Patients

Epidermal growth factor receptor (EGFR) is frequently over expressed in NSCLC and is a promising target for therapy. Tyrosine kinase inhibitors (TKIs) that target EGFR, such as gefitinib, have demonstrated effectiveness in patients with refractory NSCLC. EGFR mutations can be readily detected in primary tumors but are difficult to detect in refractory NSCLC, as tumor tissues are difficult to obtain.

In a study reported in *JCO*, Bai *et al.* have used plasma samples of patients with NSCLC as surrogate tumor tissues for detecting genetic alterations as they often contain circulating DNA derived from tumor tissues. In a single-center study, plasma samples of patients with stages IIIB to IV NSCLC were analyzed for EGFR mutations. Matched tumor tissues were used for reference. Eighty one EGFR exon 19 or 21 mutations in the plasma samples of 79 (34.3%) patients were detected, including 56 exon 19 deletion mutations and 25 exon 21 point mutations. Seventy nine mutations were detected in 77 (33.5%) of the matched primary tumors, including 53 in exon 19 and 26 in exon 21. In addition, patients with EGFR mutations had significantly longer PFS after gefitinib treatment than patients without these mutations, which suggest that these patients might have benefited from the treatment. The study concluded that EGFR mutations can be reliably detected in plasma DNA of patients with stages IIIB to IV NSCLC and can be used as a biomarker to predict tumor response to TKIs.

Source: *JCO*

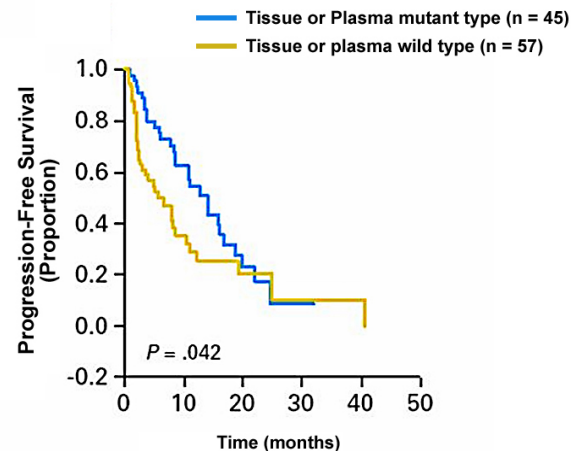
### Predictive Role of Genetic Variants on the Outcome of mCRC

*UGT1A1\*28* is considered the main pharmacogenetic predictor of the toxicity outcome of irinotecan-treated patients. *UGT1A1\*28*, located in the promoter region of *UGT1A1* gene, is known to be involved in irinotecan toxic metabolite 7-ethyl-10-hydroxycamptothecin (SN-38) detoxification and can influence the toxicity outcome of first-line advanced colorectal cancer (CRC) patients treated with FOLFIRI. There is a need to define the relative contribution of *UGT1A* polymorphisms other than *UGT1A1\*28* to predict the outcome of irinotecan therapy.

In a study reported in *JCO*, Cecchin *et al.* evaluated the effect of other *UGT1A* variants and haplotypes, involved in SN-38 glucuronidation, on severe toxicity and efficacy of FOLFIRI. It was found that *UGT1A1* variants (*\*60* and *\*93*), in addition to *\*28*, are associated with the hematologic effects in response to irinotecan and seem to confer different degrees of risk. In multivariate analysis, the presence of haplotype II (all the variant alleles but *UGT1A9\*22*) seems to be predictive of better response and time to progression (TTP) compared with the other haplotypes. The only significant predictor of severe hematologic toxicity after the first cycle of therapy is *UGT1A7\*3/\*3*. Haplotype I (all the reference sequence alleles but *UGT1A9\*22*) seems to be protective of severe hematologic toxicity, observed during the entire course of therapy, which is possibly the cumulative effect of all the polymorphisms. Hence, genotyping a few more markers in the *UGT1A* genes, instead of single *UGT1A1\*28*, can be a better prediction of outcome of FOLFIRI patients.

Source: *JCO*

### PFS curves for Patients Treated with Gefitinib





# Regulatory



## FDA Grants Full Approval for Sprycel for CML

Bristol-Myers Squibb announced that FDA has granted full approval for SPRYCEL (dasatinib) for the treatment of adults in all phases of chronic myeloid leukemia (CML) (chronic, accelerated, or myeloid or lymphoid blast phase) with resistance or intolerance to prior therapy, including Gleevec (imatinib mesylate).

SPRYCEL, an oral tyrosine kinase inhibitor, was originally approved under the accelerated approval regulations for serious or life-threatening illnesses of the Food, Drug and Cosmetic Act, based on its effectiveness on hematologic and cytogenetic response rates in CML. The full approval was based, in part, on results from a Phase III randomized, open-label dose-optimization study that enrolled 670 chronic phase CML patients with resistance or intolerance to Gleevec. Two-year follow-up data demonstrated 80% PFS rate in gleevec-resistant or intolerant patients with chronic phase CML.

*Source: BMS*

## Afinitor Recommended for Advanced RCC in EU

Novartis has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP), supporting European Union (EU) approval of Afinitor (everolimus) tablets for the treatment of patients with advanced renal cell carcinoma (RCC). Approval was based on data from RECORD-1 (REnal Cell cancer treatment with Oral RAD001 given Daily), the largest Phase III clinical trial. The study results showed that when compared with placebo, Afinitor more than doubled the time without tumor growth or death in patients with advanced kidney cancer (4.9 vs. 1.9 months) whose disease progressed following prior therapy. Additionally, the data showed Afinitor reduced the risk of disease progression or death by 67%. The decision of European Commission will apply to all 27 EU member states.

Afinitor is approved in the US as the first oral, daily therapy (5 mg and 10 mg tablets) to treat patients with advanced RCC after failure of treatment with sunitinib or sorafenib.

*Source: Novartis*

## FDA Advisory Panel Makes Favorable Recommendation for ARZERRA

GSK and Genmab announced that the FDA Oncologic Drugs Advisory Committee (ODAC) recommended that the ARZERRA (Ofatumumab) data are reasonably likely to predict clinical benefit for patients with chronic lymphocytic leukemia (CLL) whose disease is refractory to fludarabine and alemtuzumab. Ofatumumab is an investigational monoclonal antibody. The advisory committee made its decision based on an interim analysis of a pivotal trial that was presented at the American Society of Hematology 2008 annual meeting and ASCO 2009 annual meeting. Ofatumumab is being developed under collaboration between Genmab and the GSK Oncology and BioPharm R&D Units. Ofatumumab is not yet approved in any country.

"The committee's positive vote in support of ofatumumab is a potential milestone for patients with CLL. While current initial treatments for CLL can provide prolonged remissions, some patients will progress rapidly and relapse, which highlights the need for new therapies. We look forward to working with the FDA towards an approval for ofatumumab." said Debasish Roychowdhury, Senior Vice President and Head, Medicines Development, GlaxoSmithKline Oncology.

*Source: GSK*



## Regulatory (cont'd.)

### NICE Recommends Erbitux for mCRC and Sutent for mRCC

The National Institute for Health and Clinical Excellence (NICE) has published a Final Appraisal Determination (FAD) recommending the use of Erbitux (cetuximab) in combination with chemotherapy as a first-line treatment for patients with metastatic (advanced) colorectal cancer (mCRC). Erbitux is the only first-line targeted therapy for mCRC that is recommended by NICE. The treatment is recommended for patients in whom the cancer has spread only to the liver and who have normal or 'wild-type' KRAS tumors. The evidence supporting NICE's decision includes the CRYSTAL study, published in NEJM (April 2009), which demonstrated the efficacy of Erbitux in mCRC patients with KRAS wild-type tumors, representing up to 65% of patients.

NICE also recommended sunitinib as a first-line treatment option for patients with advanced and/or metastatic renal cell carcinoma (RCC) who are suitable for immunotherapy. The final guidance represents an about-face from a previous NICE statement, recommending against approval of sunitinib, as well as bevacizumab, sorafenib, and temsirolimus, for advanced and/or metastatic RCC, for use within the National Health System (NHS), based on cost-effectiveness grounds. According to a press release issued by NICE, the agency decided to split its appraisal of sunitinib from that of the other agents "in order to get guidance out to the NHS as quickly as possible." This decision came after Pfizer, the manufacturer of sunitinib, reached an agreement with NICE, whereby Pfizer would pay the bill for the first 6 weeks of treatment.

*Source: Merck Serono, NICE*