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INTELLIGENT INSIGHTS. SMARTRESULTS.

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# Spotlight Report

## Genitourinary Cancers Symposium Highlights

2009 ASCO Genitourinary Cancers Symposium  
February 26-28, 2009, Orlando, Florida

### Safety and Overall Survival Data from SPARC Trial

Results of the pre-specified exploratory analyses of Phase III, SPARC trial (Satraplatin and Prednisone Against Refractory Cancer) presented at Genitourinary Cancers Symposium showed an improvement in overall survival in a subset of patients refractory to docetaxel. The SPARC trial evaluated satraplatin, a member of the platinum family of compounds, plus prednisone vs placebo plus prednisone in 950 patients with androgen-independent or castrate-refractory prostate cancer (CRPC) who had progressed after initial chemotherapy. Of the 950 patients in the SPARC trial, 488 received first-line docetaxel. As there is no universally accepted definition of docetaxel-refractory CRPC patients, two definitions were adopted based on the literature: R1) disease progression while on docetaxel or within 100 days of the last docetaxel dose; and R2) disease progression while on docetaxel or within 50 days of the last docetaxel dose.

When stratified and adjusted for the three pre-specified prognostic factors (lactate dehydrogenase, hemoglobin and alkaline phosphatase) which showed statistically significant imbalances between the two treatment arms, there was a positive trend toward better overall survival for the patients treated with satraplatin. The observed trend in the following 3 groups was: 1) patients who had progressed after receiving docetaxel - hazard ratio 0.78; 2) R1 group - hazard ratio 0.65 and 3) R2 group - hazard ratio 0.69. Safety findings in the SPARC trial were consistent with previous clinical studies involving satraplatin. "I am encouraged by the positive trends in overall survival observed in patients refractory to docetaxel when adjusted for significant prognostic factors, along with the treatment's safety profile," said Daniel Petrylak, one of the principal investigators of the SPARC trial.

*Source: GPC Biotech AG*

### Positive Abiraterone Phase II Data in CRPC

Cougar Biotechnology presented the results from ongoing Phase II clinical trials of CB7630 (abiraterone acetate), at the ASCO Genitourinary Cancers Symposium. In the poster presentation of Phase II clinical trial of CB7630 (COU-AA-002) in combination with prednisone, Dr. Ryan, the lead investigator of the study, presented data on the 31 evaluable patients treated in the trial. In this trial, CB7630 in combination with prednisone was administered once daily to chemotherapy-naïve, ketoconazole-naïve patients with CRPC, who had progressive disease despite treatment with LHRH analogues and other hormonal therapies. Of the 31 evaluable patients, 77% experienced a decline in prostate specific antigen (PSA) levels of greater than 30%, 71% experienced a PSA decline of greater than 50% and 26% experienced PSA declines of greater than 90%. For the 31 evaluable patients, the median time to PSA progression has not yet been reached, with patients continuing to be treated for 10+ months.

Another Phase II trial (COU-AA-BMA) of CB7630 investigated associations between serum and microenvironment (bone marrow) androgen concentrations and response to CB7630. In this trial, CB7630 in combination with prednisone was administered orally, once daily, to patients with CRPC, who had progressive disease despite treatment with LHRH analogues and multiple other therapies. In the poster presentation, Dr. Eleni Efstathiou presented data on the 50 evaluable patients treated in the trial. Of these evaluable patients, 48% experienced a confirmed decline in PSA levels of greater than 50%. In addition, 12% experienced PSA declines of greater than 90%. For the 50 evaluable patients, the median duration of treatment was 41 weeks (10.3 months). A decline in both serum and bone marrow testosterone levels to below detectable levels (<10ng/ml) was seen in all patients in the trial. Also, patients with depleted baseline bone marrow testosterone levels (<10ng/ml) appeared to progress earlier when treated with CB7630, compared to patients with measurable baseline bone marrow testosterone levels.

*Source: Cougar Biotechnology*



## Spotlight Report (cont'd.)

### Efficacy and Safety Data from a Phase II Picoplatin Trial in CRPC

Poniard Pharmaceuticals announced the presentation of new efficacy and safety data from its ongoing Phase II clinical trial of picoplatin in combination with docetaxel and prednisone as first-line therapy for metastatic CRPC. The trial enrolled 30 patients with metastatic CRPC who had not received prior chemotherapy. The latest trial findings demonstrate reduction of PSA levels of at least 50% in 21 of 27 (78%) evaluable patients. To date, the median time to PSA progression is 8.5 months. Radiologic responses evaluated using RECIST (Response Evaluation Criteria in Solid Tumors) showed an overall response rate of 8% and a 54% disease control rate. This data indicates that picoplatin can be safely administered with full-dose docetaxel. Neutropenia was the main hematologic toxicity. Thrombocytopenia was less severe and less frequent with picoplatin, administered in combination with docetaxel compared with picoplatin administered alone.

In addition to the Phase II clinical trial in metastatic CRPC, Poniard is evaluating intravenous picoplatin in an ongoing pivotal Phase III trial, known as SPEAR (Study of Picoplatin Efficacy After Relapse), in small cell lung cancer. Picoplatin is also being evaluated in an ongoing Phase II clinical trial in patients with metastatic colorectal cancer.

*Source: Poniard Pharmaceuticals*

### AV-951 Shows Activity in Advanced Kidney Cancer

AVEO announced positive interim results from a Phase II clinical trial of AV-951, a novel, oral, triple VEGF receptor inhibitor, in patients with advanced renal cell carcinoma (RCC). As assessed by independent radiological review, patients with advanced RCC treated with AV-951 experienced a 91.7% disease control rate at 16 weeks. The data also demonstrated that AV-951 was well-tolerated.

The Phase II placebo-controlled, randomized discontinuation trial assessed the efficacy and safety of once-daily, oral AV-951 in 272 patients with locally advanced or metastatic RCC and no prior VEGF-targeted therapy. The study results showed that disease control rate at 16 weeks was 88.8% (89.4% in clear cell RCC) by investigator assessment and 91.7% (91.9% in clear cell RCC) by independent radiology assessment. Objective response rate at 16 weeks was 26.4% (29.6% in clear cell RCC) by investigator assessment and 20.1% (20.6% in clear cell RCC) by independent radiology assessment using standard RECIST criteria. Among patients with >25% tumor regression who continued uninterrupted treatment on AV-951, the median progression free survival (PFS) has not been reached during a follow-up duration of 12.6 months. AVEO has also initiated Phase Ib clinical trials of AV-951: in combination with temsirolimus in patients with mRCC; in combination with the FOLFOX6 chemotherapy regimen in patients with advanced colorectal cancer and other gastrointestinal cancers; and in combination with paclitaxel in patients with metastatic breast cancer.

*Source: AVEO Pharmaceuticals*

### Transcript-Based Six-Gene Test to Predict Survival of CRPC

Dana-Farber Cancer Institute and Source MDx announced that Source MDx's whole blood RNA transcript-based Precision Profiles™ diagnostic test predicted survival in men with CRPC. These results were presented at ASCO Genitourinary Cancers Symposium. In a study of 62 CRPC patients, the model separated patients into a high risk group (survival less than 2.2 years) and a low risk group (survival greater than 2.2 years).

The six-gene CRPC Precision Profile™ was 96% accurate in predicting low risk CRPC patients alive at study end and 93% accurate in predicting high risk CRPC patients who died prior to study completion, suggesting that the model may be a powerful tool for stratifying CRPC patients in clinical trials. This data also shows that individual differences in gene transcripts associated with cell-mediated and humoral immunity are associated with survival in CRPC patients. The Prostate Cancer Clinical Trials Consortium (PCCTC) will begin a prospective, multisite clinical trial to validate using Source MDx's six-gene CRPC Precision Profile™ to stratify aggressive vs. non-aggressive CRPC patients.

*Source: SourceMDx*



## Business News

### Merck and Schering-Plough to Merge

Merck and Schering-Plough announced that their Boards of Directors have unanimously approved a definitive merger agreement under which the two companies will combine, under the name Merck, in a stock and cash transaction. Under the terms of the agreement, Schering-Plough shareholders will receive 0.5767 shares and \$10.50 in cash for each share of Schering-Plough. Each Merck share will automatically become a share of the combined company. Merck Chairman, President and CEO Richard T. Clark will lead the combined company.

The combined company will have a more diverse portfolio across important therapeutic areas, including cardiovascular, respiratory, oncology, neuroscience, infectious disease, immunology and women's health. Schering-Plough's current oncology products will enable Merck to expand its presence in this area and provide the necessary foundation to take advantage of the combined company's promising pipeline.

*Source: Merck*

### Roche Completes Acquisition of Genentech

Roche and Genentech announced that Roche has completed its acquisition of Genentech pursuant to a short-form merger in which Genentech became a wholly-owned member of the Roche Group. Roche and Genentech earlier signed a merger agreement under which Roche would acquire the outstanding publicly held interest in Genentech for \$95.00 per share in cash, or a total payment of approximately \$46.8 billion to equity holders of Genentech other than Roche.

Under the terms of the agreement, research and early development will operate as an independent center within Roche from its existing campus in South San Francisco, retaining its talent and approach to discovering and progressing new molecules. Roche's Pharma commercial operations in the US will be moved from Nutley, New Jersey, to Genentech's site in South San Francisco. The combined company's US commercial operations in pharmaceuticals will operate under the Genentech name, leveraging the strong brand value of Genentech in the US market.

*Source: Roche*

### Bayer Enters Strategic Agreement with Genzyme

Bayer HealthCare announced that it has entered a new strategic agreement with Genzyme Corporation. Under the agreement, Bayer will transfer its hematological oncology portfolio to Genzyme, including the worldwide development and distribution rights for alemtuzumab currently marketed as MabCampath® or Campath®, and gives Genzyme exclusive worldwide licenses for Leukine® (sargramostim) and Fludara® (fludarabine phosphate) for all present and future indications. In return, Bayer will receive milestone payments and royalties, depending on sales achieved by Genzyme, amounting up to \$ 650 million from Genzyme. Bayer will then focus its resources in oncology on Nexavar® and additional development products.

Alemtuzumab, a recombinant DNA-derived humanized monoclonal antibody, is currently marketed as MabCampath® or Campath® for the treatment of B-cell chronic lymphocytic leukemia (B-CLL). Sargramostim, a granulocyte colony stimulating factor agonist, is indicated for use following induction chemotherapy in older adults with acute myelogenous leukemia (AML) to shorten the time to neutrophil recovery and reduce the incidence of severe and life-threatening infections. Intravenous (i.v.) formulation of fludarabine is indicated for the treatment of adult patients with B-cell CLL who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen.

*Source: Bayer*



## **Business** (cont'd.)

### **AVEO and Biogen Idec to Develop and Commercialize ErbB3-Targeted Antibodies**

AVEO Pharmaceuticals announced a definitive agreement with Biogen Idec for the development and commercialization of AVEO's novel discovery-stage ErbB3-targeted antibodies for the potential treatment of cancer and other diseases. ErbB3 is a type 1 tyrosine kinase receptor of the EFGR family that is widely expressed in human carcinomas, with demonstrated overexpression, and correlated with poor prognosis in several different tumor types, including breast, ovarian, prostate, colorectal, pancreatic, gastric and head & neck cancers.

Under the terms of the agreement, AVEO will receive an up-front payment and is eligible to receive milestone payments based upon the achievement of specified development goals. Biogen Idec will have an option exercisable at proof of concept to development and commercialization rights to ErbB3 binding antibodies for territories outside of North America. AVEO retains all North American commercialization rights, and is responsible for leading global development of the ErbB3 program.

*Source: AVEO*

### **Provenance Announces License Agreement with Merck Serono for Immunocytokine**

Provenance Biopharmaceuticals announced the execution of a license agreement with Merck Serono for DI-Leu16-IL2, a novel antibody-cytokine fusion protein targeting the B cell antigen. Under this agreement, Merck Serono has granted exclusive worldwide rights to Provenance to develop and commercialize DI-Leu16-IL2. This protein therapeutic is currently being tested in an investigator sponsored clinical trial in patients with Non-Hodgkin's lymphoma. Under the terms of the DI-Leu16-IL2 license agreement, Merck Serono will receive an upfront payment, several development and commercial milestones, and royalties on sales. Provenance will be responsible for the clinical development and commercialization.

*Source: Provenance Biopharmaceuticals*



# Research Highlights

## Silencing or Fueling Metastasis with VEGF Inhibitors

Angiogenesis inhibitors often do not prolong survival of cancer patients by more than a few months, as the tumors eventually develop resistance. In March issue of *Cancer Cell*, two papers from leading angiogenesis laboratories reported enhanced metastasis with these agents despite primary tumor inhibition. These perplexing findings not only explain resistance to VEGF inhibitors, but also challenge the prevailing dogma on the utility of antiangiogenesis as a cancer treatment strategy.

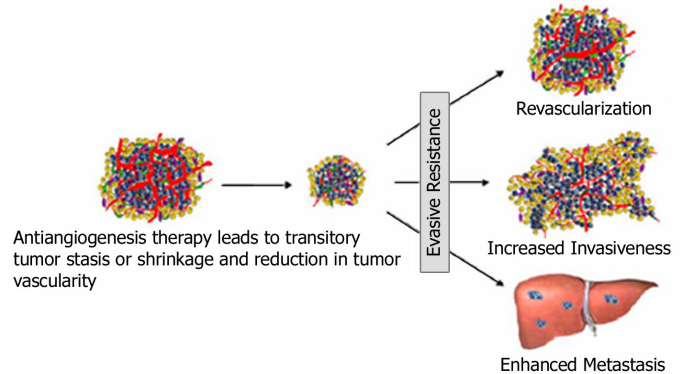
Ribes and colleagues report increased tumor invasion and metastasis after treatment with VEGF targeting agents.

<sup>1</sup>The study points to an adaptive or evasive response of tumor cells to disrupted vasculature. VEGF inhibitors induce a chronic "inflamed" state characterized by elevated cytokines that facilitate permeability and egress of tumor cells. While these drugs cause hypoxia, tumor cells are better equipped to cope with it. In addition, tumors recruit other vascular supply mechanisms not inhibited by VEGF-inhibitors, substantiated by VEGF-A gene ablation studies. Another report by Ebos and colleagues show accelerated tumor growth in mice receiving VEGF inhibitors, implicating a class effect of "metastatic conditioning" by such agents. <sup>2</sup>The study suggests that host responses to VEGF inhibition can result in increased tumor extravasation. Mice receiving short term sunitinib showed increased spontaneous metastatic burden associated with decreased survival.

It seems the effects of VEGF-targeted therapy may depend on multiple parameters such as VEGF levels, co-option, VEGF dependence, lymphatic versus hematogenous metastasis, tumor models, treatment duration, drug dosage, and single agent versus combination treatments. Emerging clinical evidence is consistent with some of these findings. Rapid tumor regrowth has been observed in some patients during 'drug holidays.' On the other hand, colorectal cancer and glioblastoma patients treated with VEGF antibody lived longer, despite higher incidence of distant recurrence in the latter. While reasons explaining these observations remain speculative, they raise questions on the utility of maintenance therapy with these drugs, among others. Another question is whether combination with other targeted agents might counteract the prometastatic behavior of these drugs. Distinct antivasculature strategies might emerge in future for optimal exploitation of these drugs.

Source: *Cancer Cell* <sup>1, 2</sup>

### Adaptive-Evasive Responses by Tumors to Antiangiogenic Therapies



Cancer Cell, 15, March 2009



## Research Highlights (cont'd.)

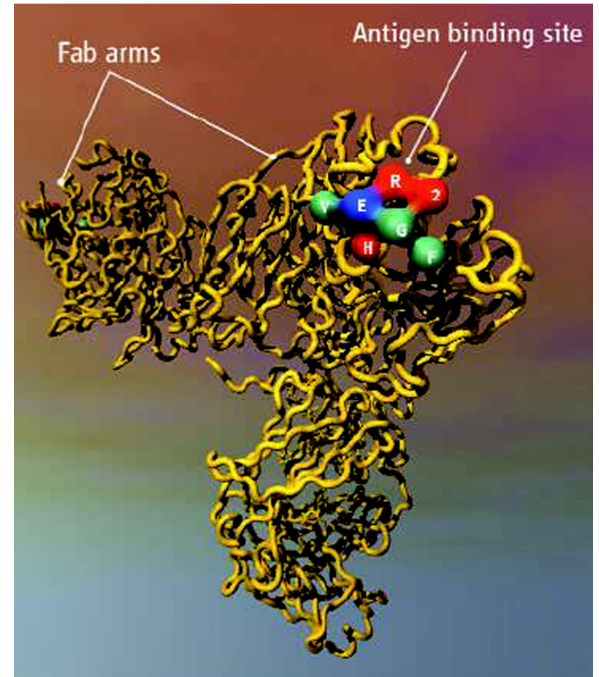
### Two-in-One Designer Antibodies

The binding of antibodies to specific single antigens has prompted their use for numerous targeted therapies. However, the concept of an antibody that recognizes more than one antigen is intriguing. In a recent issue of *Science*, Bostrom *et al.* describe a new "two-in-one" designer antibody concept in which the antibody with the same binding site is engineered to recognize two different antigens with high affinity. Investigators generated a library of Herceptin antibody variants with mutations in the light chain complementarity determining regions, and identified Fab arms that can bind a new protein antigen while maintaining human epidermal growth factor receptor 2 (HER2) binding. The two antigens studied were vascular endothelial growth factor (VEGF) and HER2, representing well-known tumor targets.

Crystallographic and mutagenesis studies demonstrated that the binding surface on the antibody for each antigen overlapped, but within the buried surface of each binding site, distinct amino acids contributed to the binding strength for each antigen. The antibody bH1 exhibited the highest dual affinity for the two completely different protein antigens, VEGF and HER2. VEGF binding was primarily mediated by light-chain residues and HER2 binding by heavy-chain residues. The overlapping binding areas indicated that each antibody binding site cannot bind both antigens simultaneously. An affinity-improved version of bH1 inhibited both HER2- and VEGF-mediated cell proliferation *in vitro* and tumor progression in mouse models. The potential for high-affinity antibody binding of more than one antigen is interesting and poses opportunities for future basic research, and perhaps clinical development of antibody combination therapy.

Source: *Science*

### Two-in-One Antibody



**Red:** Binding site interacting with HER2  
**Green:** Binding site interacting with VEGF  
**Blue:** Shared site

*Science*, 323, March 20, 2009



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

**Accelerated Metastasis through Immunosuppression during Snail-Induced EMT**

Epithelial–mesenchymal transition (EMT), mediated in part by the transcription factor snail (Snail), can increase cell invasion and metastasis. In a recent study in *Cancer Cell*, Kudo-Saito *et al.* demonstrated Snail-induced EMT accelerates cancer metastasis in murine and human melanoma cells by not only enhancing invasive ability but also by immunosuppression. Changes in the host immune system included multiple immunosuppression and immunoresistance via mechanisms that involved immunosuppressive cytokines, regulatory T cells, impaired dendritic cells, and cytotoxic T lymphocyte resistance, induced partly through thrombospondin-1 (TSP1) production.

Snail-transduced (Snail<sup>+</sup>) melanoma with typical EMT features induced severe immunosuppression both *in vitro* and *in vivo* with almost no infiltration of antitumor effector cells, and almost no induction of CD8<sup>+</sup> responses specific for tumor antigens. This led to enhanced tumor metastasis in various organs of the mice implanted with subcutaneous Snail<sup>+</sup> tumors. The researchers also observed that Snail-induced EMT

also renders melanoma cells resistant to cytotoxic T lymphocyte lysis as well as to chemotherapeutic agents like 5-fluorouracil, cyclophosphamide, and paclitaxel. These effects were possibly mediated by induction of regulatory T cells with high forkhead box protein P3 (Foxp3) expression and impaired dendritic cells with low co-stimulatory molecule expression but high expression of the immunosuppressive enzyme IDO (indoleamine 2,3-dioxygenase). Finally, the workers injected the tumors with snail-specific siRNA and anti-TSP1 monoclonal antibody and found that these significantly inhibited tumor growth and metastasis due to an increase in tumor-specific tumor-infiltrating lymphocytes and systemic immune responses. This study suggests that the use of *snail*-targeting therapy could simultaneously inhibit both cancer metastasis and multiple immunosuppressions in human cancers such as melanoma, pancreatic and colorectal carcinomas.

Source: *Cancer Cell*

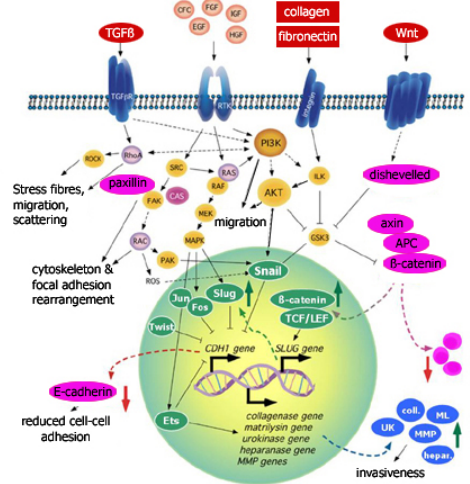
**Pin1, a Notch1 Target, Enhances Notch1 Activation in Cancer**

The Notch signaling pathway, a conserved intercellular signaling mechanism, is essential for cell-cell communication and stem cell renewal and differentiation in many post-natal tissues. Four different Notch receptors (NOTCH1 to NOTCH4) and five ligands (Jagged-1 and -2 and Delta-like 1, 2 and 4) have been characterized in mammalian cells. Ligand–receptor engagement results in two successive proteolytic cleavages in Notch, involving tumor necrosis factor- $\alpha$  converting enzyme and a multi-protein complex that has  $\gamma$ -secretase activity. This results in the release of Notch intra-cytoplasmic domain which acts as a transcriptional activator in the nucleus modulating the expression of target genes. Deregulated Notch signaling network has been linked to carcinogenesis and its alteration has been implicated in mammary tumorigenesis wherein it is causally involved in the oncogenic conversion of breast epithelial cells. The mechanisms underlying alteration in Notch activation in breast oncogenesis, specially the regulation of Notch1 processing and its downstream effects contributing to the neoplastic phenotype, remain obscure.

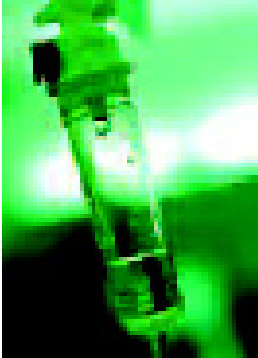
In a recent publication in *Nature Cell Biology*, Rustighi *et al.* have demonstrated the role of Pin1 as an activator of Notch1 through its prolyl-isomerase activity. Pin1 potentiates Notch1 cleavage by  $\gamma$ secretase, leading to an increased release of the active intracellular domain ultimately enhancing Notch1 transcriptional and tumorigenic activity, both *in vitro* and *in vivo*. Notch1 in turn directly up-regulates Pin1 by inducing transcription, thereby generating a positive loop that amplifies Notch1 signaling. Investigators found a strong correlation between Pin1 over-expression and deregulated high levels of activated Notch1 and Notch-1 target HES-1. Thus, the molecular circuitry established by Notch1 and Pin1 may have a key role in cancer and genetic or pharmacological manipulation of Notch signaling, and may provide a novel potential strategy for the treatment of human tumors.

Source: *Nature Cell Biology*

Schematic of the Signal Transduction Pathways Associated with EMT



Oncogene, 24, Nov 2005



# Clinical Development

## **Pfizer Discontinues One Sunitinib Phase III Trial in Advanced Breast Cancer**

Pfizer announced the discontinuation of one of its Phase III studies based on statistical assessment for futility: the SUN 1107 Phase III study of Sutent® (sunitinib malate) in advanced breast cancer. SUN 1107 evaluated single-agent sunitinib versus single-agent capecitabine for the treatment of a broad range of patients with advanced breast cancer after failure of standard treatment. An independent Data Monitoring Committee (DMC) found that even if the trial had been allowed to continue, treatment with single-agent sunitinib would be unable to demonstrate a statistically significant improvement in the primary endpoint of progression free survival (PFS) compared to single-agent capecitabine in the study population. Data from this trial are currently being analyzed.

“We are disappointed with these results given the previous findings that suggested sunitinib may provide benefit for patients with this difficult-to-treat cancer,” said Dr. Mace Rothenberg, senior vice president of Clinical Development and Medical Affairs for Pfizer’s Oncology Business Unit. “In ongoing studies, we remain committed to evaluating sunitinib in advanced breast cancer and are continuing to study sunitinib in different populations and with different regimens.” The company is continuing to evaluate sunitinib as a single-agent and in combination with standard-of-care chemotherapy in specific patient populations with advanced breast cancer through three additional Phase III and two Phase II trials.

*Source: Pfizer*

## **Positive Results of ProLindac™ Phase II Ovarian Cancer Trial**

Access Pharmaceuticals announced positive safety and efficacy results from its Phase II study of ProLindac™, a novel diaminocyclohexane (DACH) platinum prodrug, in late-stage, heavily pretreated ovarian cancer patients. The study enrolled 26 patients and explored 3 different dose levels and 2 dosing regimens of ProLindac as a monotherapy treatment for advanced ovarian cancer. Of patients eligible for evaluation according to standard RECIST criteria, clinically-meaningful disease stabilization was achieved in 42% of all patients, and 66% of all patients in the higher dose groups. Sustained and significant reductions in Ca-125, the established specific serum marker for ovarian cancer, were also observed in several patients. No patient in any dose group exhibited any signs of acute neurotoxicity, which is a major adverse side effect of the approved DACH platinum, Eloxatin, and ProLindac was well-tolerated overall. The maximum tolerated dose of ProLindac was established as well as the recommended dose levels for future combination studies.

“These data provide us with a strong incentive to continue the clinical development of ProLindac. As previously announced, we are currently planning a number of combination trials, looking at combining ProLindac with other cancer agents, such as taxol and gemcitabine, in multiple solid tumor indications including colorectal and ovarian,” stated Jeffrey B. Davis, President & CEO, Access.

*Source: Access Pharmaceuticals*



## **Clinical Development** (cont'd.)

### **Herceptin® Prolongs the Lives of HER2-Positive Gastric Cancer Patients**

Roche announced results from a major international study which show that adding Herceptin® (trastuzumab) to standard chemotherapy significantly prolongs lives of patients with HER2-positive gastric cancer. The results are from the ToGA, a large international Phase III trial, investigating the benefit of Herceptin as the first therapy for patients with advanced and inoperable gastric cancer. Full data will be presented at the upcoming medical meeting. Approximately 3,800 patients were tested for HER2-positive tumors and 594 patients with HER2-positive disease were enrolled into the study. Patients were randomized to receive one of the regimens as their first line of treatment: I) A fluoropyrimidine (Xeloda or 5-FU) and cisplatin every 3 weeks for 6 cycles II) Herceptin 6mg/kg every 3 weeks until progression in combination with a fluoropyrimidine and cisplatin for 6 cycles. The pre-planned interim analysis was triggered by the occurrence of 347 events. No new or unexpected side effects were observed.

“Based on the clear positive outcome from this clinical study, the addition of Herceptin to chemotherapy offers a new important option for patients with HER2-positive stomach cancer as Herceptin extends survival and will bring this group of patients a significant benefit,” said principal investigator Prof. Eric Van Cutsem, University Hospital Gasthuisberg in Leuven, Belgium.

*Source: Roche*

### **Sutent Increases PFS for Patients with Advanced Pancreatic Islet Cell Tumors**

Pfizer announced that a Phase III clinical trial of Sutent® (sunitinib malate) has been stopped early after the drug showed significant benefit in patients with advanced pancreatic islet cell tumors, also known as pancreatic neuroendocrine tumors. An independent Data Monitoring Committee (DMC) recommended halting the trial after concluding that Sutent demonstrated greater PFS compared to placebo, plus best supportive care in patients with pancreatic islet cell tumors.

“We are delighted by these findings which demonstrate that Sutent provides a benefit for patients with advanced, well-differentiated pancreatic islet cell tumors — a rare cancer with limited treatment options,” said Dr. Mace Rothenberg, senior vice president of medical development and clinical affairs for Pfizer’s Oncology Business Unit. The full data set from this trial is being analyzed and more details will be presented at an upcoming scientific meeting. Sutent is currently approved for both advanced renal cell carcinoma (RCC) and second-line gastrointestinal stromal tumor (GIST).

*Source: Pfizer*

### **Adjuvant Imatinib Therapy after Resection of Localized, Primary GIST**

Glivec® (imatinib mesylate), a Bcr-Abl protein tyrosine kinase inhibitor, is effective in first-line treatment of metastatic gastrointestinal stromal tumor (GIST). In a randomized Phase III, double-blind, placebo-controlled, multicentre trial published in *Lancet*, DeMatteo *et al.* postulated that adjuvant treatment with imatinib would improve recurrence-free survival compared with placebo after resection of localized, primary GIST. Patients enrolled in the study were randomly assigned to imatinib 400 mg (n=359) or to placebo (n=354) daily for 1 year after surgical resection. At median follow-up of 19•7 months, 8% patients in the imatinib group and 20% in the placebo group had tumor recurrence or had died. Imatinib significantly improved recurrence-free survival compared with placebo (98% vs 83% at 1 year). Adjuvant imatinib was well-tolerated.

Based on these study results, Novartis has received a positive opinion supporting European Union approval of Glivec® as a post-surgery treatment for patients at significant risk of relapse following removal of GIST.

*Source: Lancet, Novartis*



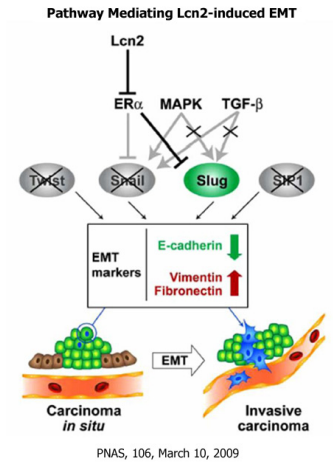
# Biomarkers



## Lipocalin 2 Promotes Breast Cancer Progression

The epithelial to mesenchymal transition (EMT) is one of the key processes involved in tumor progression and metastasis. In a study published in *PNAS*, Yanga *et al.* report that the overexpression of lipocalin 2 (Lcn2, also referred to as neurophil gelatinase-associated lipocalin) in human breast cancer cells induces EMT. Overexpression of Lcn2 in human breast cancer cells was found to up-regulate mesenchymal markers, including vimentin and fibronectin, down-regulate the epithelial marker E-cadherin, and significantly increase cell motility and invasiveness. These changes in marker expression and cell motility are hallmarks of EMT. On the other hand, Lcn2 silencing increased the levels of the epithelial marker E-cadherin and reduced the levels of mesenchymal markers vimentin and fibronectin.

Because of the importance of estrogen signaling in breast cancer, investigators examined the estrogen receptor  $\alpha$  (ER $\alpha$ ) status in the cell lines. The reduced expression of estrogen ER $\alpha$  and increased expression of the key EMT transcription factor, Slug were observed with Lcn2 expression. This data demonstrate that Lcn2 induces EMT via the ER $\alpha$ /Slug axis by first down-regulating ER $\alpha$ , which subsequently leads to induced Slug expression, decreased E-cadherin expression, and eventually the transition to the mesenchymal phenotype. Investigators also demonstrate, by using an orthotopic animal model, that Lcn2 induces a poorly differentiated phenotype and increases local invasion and lymph node metastasis. Additionally, both the tissue and urinary Lcn2 levels were associated with invasive and metastatic human breast cancer, providing *in vivo* support of the *in vitro* and animal studies. The study demonstrates that Lcn2 promotes breast cancer progression by inducing EMT through the ER $\alpha$ /Slug axis and may be a useful biomarker of breast cancer.



Source: *PNAS*

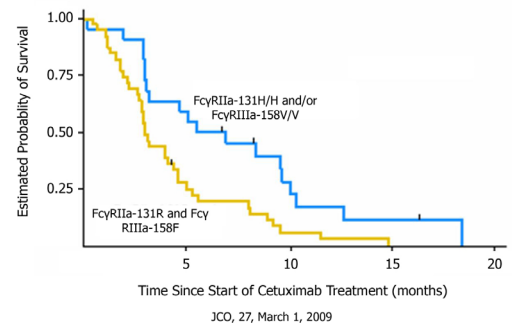
## Predictive and Prognostic Markers for Cetuximab Treated mCRC Patients

Cetuximab, a chimeric immunoglobulin 1 (IgG1) monoclonal antibody (mAb), has shown efficacy in irinotecan refractory patients with metastatic colorectal cancer (mCRC), mainly in wild-type *KRAS* tumors. Cetuximab may also exert antitumor effects through antibody-dependent cell-mediated cytotoxicity (ADCC) in which antibody Fc portion interacts with Fc receptors (FcγRs) expressed by immune cells. Clinical studies have shown that ADCC is influenced by FcγRIIa-H131R and FcγRIIIa-V158F polymorphisms. In a study published in *JCO*, Bibeau *et al.* evaluated the influence of FcγRIIa and FcγRIIIa polymorphisms and *KRAS* mutations on the outcome of 69 patients with irinotecan-resistant mCRC treated with cetuximab plus irinotecan.

The study results showed that *KRAS* mutations were associated with lower response rate (4% v 27% in nonmutated patient) and shorter PFS (3.0 vs 5.3 months). Patients with FcγRIIa-131H/H and/or FcγRIIIa-158V/V genotypes had a significantly longer median PFS than 131 R and 158F carriers (5.5 vs 3.0 months) whatever be the *KRAS* status. The study confirms that *KRAS* mutation in the tumors is highly predictive of non-response to a cetuximab-based therapy. Combined FcγRIIa and FcγRIIIa polymorphisms (131H/H and/or 158V/V genotypes) are prognostic factors for PFS in mCRC patients treated with cetuximab plus irinotecan. As these polymorphisms are also clinically relevant in mutated *KRAS* mCRC in which EGFR pathway is constitutively activated, an important role of ADCC in cetuximab efficacy can be presumed.

Source: *JCO*

PFS for Patients with mCRC according to the FcγR Polymorphisms Combination





## **Biomarkers** (cont'd.)

### **Transposon-Based Genetic Screen Identifies Genes Altered in Colorectal Cancer**

Transposons are mobile segments of DNA that can move around to different positions in the genome of a single cell leading to mutations or a change in the amount of DNA in the genome. Insertional mutagens, such as the Sleeping Beauty (SB) transposon, are increasingly being used because the inserted sequence serves as a molecular tag to facilitate identification of the affected gene. Genomic studies have revealed that human colorectal cancers undergo numerous genetic and epigenetic alterations. These changes occur in two types of genes- those that play a causal role in tumor formation and progression ("drivers") and others that have little or no functional effect on tumor growth ("passengers").

In a study published in *Science*, Starr *et al.* describe a transposon-based genetic screen in mice to help identify potential driver genes in colon carcinoma using a SB system to generate insertional mutations. Investigators first confined the transposition to the gastro-intestinal tract in mice and then crossed these mutagenic mice with mice expressing SB transposase in gastrointestinal tract epithelium. The resulting offspring had intestinal lesions that included intraepithelial neoplasia, adenomas and adenocarcinomas. The workers then analyzed more than 16,000 transposon insertions and identified 77 candidate colorectal cancer genes, 60 of which are mutated and/or dysregulated in human colorectal cancer and thus are most likely to drive tumorigenesis. The most commonly mutated gene identified was *Apc* which is seen in 70-80% cases. Others included *PTEN*, *SMAD4*, *Fbxw7*, *Bmpr1a*, etc. They were also able to identify 17 candidate genes that had not previously been implicated in the disease including *POLI*, *PTPRK*, and *RSPO2*.

*Source: Science*

### **Potential Role for Sarcosine in Prostate Cancer Progression**

A wide range of metabolites are known to help distinguish tumors from healthy tissue, identify tumor types, study tumor growth, and are now being used to profile systemic metabolism in tumor diagnosis and prognosis. These metabolomic approaches are also revealing tumorigenesis pathways and potentially new therapeutic targets. In a recent study published in *Nature*, Sreekumar *et al* have identified sarcosine (an N-methyl derivative of glycine) in urine as a metabolite whose levels are markedly raised in progressive and metastatic prostatic carcinoma. They profiled more than a thousand metabolites related to prostatic carcinoma in tissue, urine and blood specimens, and reported 91 metabolites whose levels were altered in metastatic samples. The metabolomic profiles of six metabolites (sarcosine, uracil, kynurenine, glycerol-3-phosphate, leucine and proline) were significantly increased on disease progression from benign to clinically localized to metastatic prostate cancer.

The researchers found an increase in amino acid metabolism, nitrogen breakdown pathways and methyltransferase activity (EZH2) during cancer progression to metastatic disease and focused on sarcosine, a differential metabolite that characterize these processes. While clinically localized cancer samples showed an increase in the levels of sarcosine, metastatic samples showed markedly elevated levels whereas no detectable levels of sarcosine were found in benign specimens. The addition of this metabolite or knockdown of the enzyme sarcosine dehydrogenase that leads to sarcosine degradation to non-invasive benign prostate epithelial cells imparted an invasive phenotype to the cell line. Finally, knockdown of histone methyltransferase EZH2 and glycine-N-methyl transferase (that converts glycine to sarcosine), resulted in significant reduction in cell invasion and a several-fold decrease in sarcosine levels. The sarcosine pathway is regulated by androgen receptor and the ERG gene fusion product. This study indicates the possible use of urinary sarcosine level in monitoring disease progression and aggressiveness in prostatic cancer.

*Source: Nature*



# Regulatory



## FDA Approves Afinitor® for Treatment of Advanced Kidney Cancer

Novartis announced that Afinitor® (everolimus) tablets has been approved by the FDA for patients with advanced RCC after failure of treatment with Sutent® (sunitinib) or Nexavar® (sorafenib). The approval is based on data from the RECORD-1 trial that showed Afinitor, mTOR inhibitor, when compared with placebo, more than doubled the time without tumor growth or death in patients with advanced kidney cancer (4.9 vs. 1.9 months) and reduced the risk of disease progression or death by 67%. Also, additional data show that after 10 months of treatment with Afinitor, approximately 25% of patients still had no tumor growth. Novartis has filed regulatory submissions in the EU, Switzerland and Japan, and with other regulatory agencies globally.

*Source: Novartis*

## MEPACT® Receives Approval in Europe for Osteosarcoma

IDM Pharma announced that the European Commission has granted a Centralized marketing authorization for MEPACT® (mifamurtide), a macrophage stimulant, for the treatment of patients with non-metastatic, resectable osteosarcoma. The Centralized marketing authorization allows MEPACT to be marketed in the 27 Member States of the EU, as well as in Iceland, Liechtenstein and Norway. The approval was based on the Phase III MEPACT trial (INT-0133), a National Cancer Institute funded cooperative group study conducted by the Children's Oncology Group (COG) and the largest study ever completed in osteosarcoma, enrolling approximately 800 patients. The study evaluated patient outcomes with the addition of MEPACT to three- or four-drug adjuvant chemotherapy (cisplatin, doxorubicin, and methotrexate with or without ifosfamide). Results demonstrated that the addition of MEPACT to chemotherapy resulted in approximately a 30% decrease in the risk of death with 78% of patients surviving after 6 years of follow-up after treatment with MEPACT.

In the US, the company continues to gather patient follow up data from the Phase III trial of mifamurtide and to respond to other questions in the non-approvable letter the company received from the FDA. The company plans to submit an amended New Drug Application for mifamurtide in mid-2009.

*Source: IDM Pharma*

## An Update for 1st Line SCCHN sBLA for ERBITUX® in US

ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, and BMS announced that the companies received a complete response letter from the FDA for the first-line squamous cell carcinoma of the head and neck (SCCHN) supplemental Biologics License Application (sBLA) for ERBITUX® (cetuximab). The sBLA was accepted for filing and granted a priority review status in October 2008. In its complete response letter, the FDA requested an additional pharmacokinetic study to confirm the comparability of ERBITUX used in the first-line head and neck submission as compared to ERBITUX currently marketed in the US. As previously announced, ImClone Systems and BMS recently withdrew the advanced NSCLC sBLA for ERBITUX because of the same matter. In both cases, the companies continue to work with the FDA to confirm pharmacokinetic comparability.

In head and neck cancer, ERBITUX is approved by the FDA to treat locally or regionally advanced SCCHN in combination with radiation therapy, and as a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed.

*Source: Lilly*



## Regulatory (cont'd.)

### **FDA Advisory Committee Recommends Accelerated Approval of Avastin® in Glioblastoma**

Genentech announced that the FDA Oncologic Drugs Advisory Committee voted unanimously that the response seen with Avastin® (bevacizumab) in people with previously treated glioblastoma (GBM) is of sufficient magnitude to be reasonably likely to predict clinical benefit. The FDA is expected to make a decision whether to grant accelerated approval of Avastin for use in this most aggressive form of brain cancer by May 5, 2009.

The application is based on positive, independently reviewed data from the non-comparative Phase II BRAIN study (AVF3708g) of 167 patients. In the 85 patients treated with Avastin alone, the trial showed that in 28% patients, tumors shrank to at least half their original size. In those whose tumors shrank, half experienced a response of at least 5.6 months. In addition, 43% lived 6 months without their disease getting worse. Avastin is currently approved for the first- and second-line treatment of metastatic colorectal cancer in combination with intravenous 5-FU-based chemotherapy and for the first-line treatment of unresectable, locally advanced, recurrent or metastatic NSCLC in combination with carboplatin and paclitaxel.

*Source: Genentech*

### **NICE Refuses Funding for Tyverb®**

NICE issued its final appraisal determination advising against NHS funding for Tyverb® (lapatinib), a treatment for an aggressive form of advanced breast cancer (ErbB2-positive). Lapatinib in combination with Xeloda® offers a new treatment option for women whose disease has returned despite treatment with standard chemotherapies and Herceptin® (trastuzumab). GSK will consider appealing against this decision.

During the lapatinib assessment, NICE proposed new advice for the assessment of treatments in small patient populations with a short life expectancy. GSK submitted a sub-group analysis that met the overall survival (OS) criterion of this new NICE advice. However NICE concluded that while the data analysis could be useful in guiding future research, as it stands it would not change their conclusions. NICE's decision reflects the difficulty in demonstrating significant survival benefits in patients at this advanced stage of disease.

*Source: GSK*