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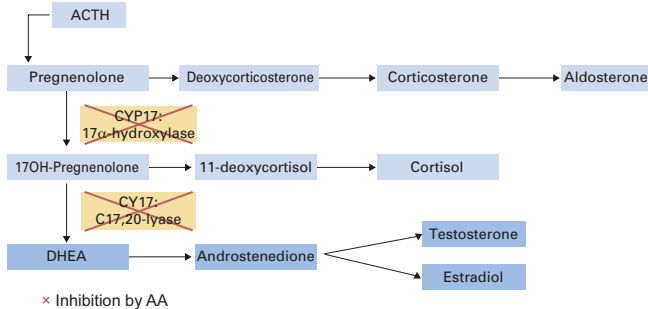
THE ONCOLOGY E-NEWSLETTER FROM SMARTANALYST

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INTELLIGENT INSIGHTS. SMART RESULTS.



In the Spotlight:

Abiraterone Acetate Shows Promise in Prostate Cancer

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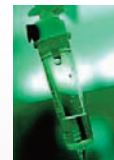
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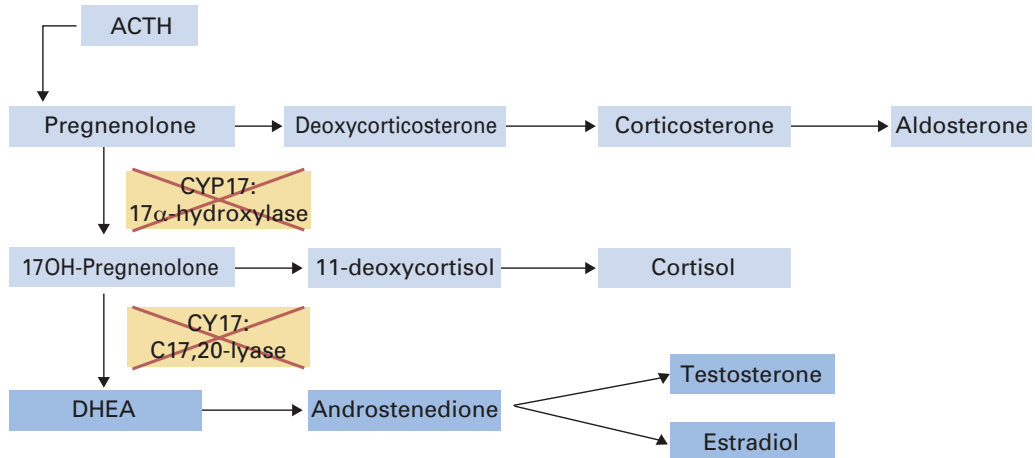
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Spotlight Report

Abiraterone Acetate Shows Promise in Prostate cancer

Blockade of Androgenic Steroid Synthesis for Treating Prostate Cancer



× Inhibition by AA

JCO, 21 July, 2008

Prostate cancer is the second-leading cancer killer of men after lung cancer. This year, an estimated 186,000 men in the U.S. will be diagnosed with prostate cancer and about 28,000 will die from the disease. Testosterone produced in the testes and adrenals stimulates the growth of prostate cancer cells. Abiraterone acetate (AA) (CB7630) is an orally administered inhibitor of the steroidal enzyme 17 α -hydroxylase and C17, 20 lyase, a cytochrome p450 complex that is involved in testosterone production. This drug was discovered at London's Royal Marsden Academy by a team headed by Ian Judson and tested by Dr. Johann de Bono in males with progressing prostate cancers. It is being developed by Cougar Biotechnology.

The prostate cancer foundation (PCF) therapeutic clinical investigation consortium conducted clinical testing of this new agent in Phase II clinical trials at five leading prostate cancer centers that are all members of the PCF consortium: Dana-Farber Cancer Institute at Harvard Medical Center, Johns Hopkins Cancer Center, MD Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, and the University of California at San Francisco.

In a Phase II study, AA plus prednisone was studied in patients with metastatic castration-resistant prostate cancer (CRPC) who had progressed on docetaxel based chemotherapy. At 3 months, 14 of 35 pts (40%) achieved a decline in PSA >50% from baseline showing that AA plus prednisone is well tolerated and active in progressive CRPC post-chemotherapy. Another Phase II study demonstrated that AA is well tolerated and produces encouraging anti-tumor activity in CRPC supporting that CRPC frequently remains hormone driven despite progression following ADT and docetaxel-based chemotherapy.

Another Phase I study demonstrated that AA exhibits anti-tumor activity in CRPC even in patients experiencing disease progression on ketoconazole. Despite overlapping mechanisms of action, responses to AA occur in patients with ketoconazole refractory disease. In a study published in recent issue of *JCO*, declines in prostate-specific antigen (PSA) 30%, 50%, and 90% were observed in 14 (66%), 12 (57%), and 6 (29%) patients, respectively, and lasted between 69 to 578 days.

"There is a general sense in the prostate cancer community that this agent is extremely promising and is very likely to have an important role in the management of prostate cancer patients," said Dr. Howard M. Sandler, a radiation oncologist at the University of Michigan. In April, 2008, Cougar initiated a randomized, double-blind, placebo-controlled Phase III trial of CB7630 plus prednisone in patients with metastatic CRPC who have failed docetaxel-based chemotherapy. The trial will be conducted at approximately 150 sites in North America, Europe and Australia. The primary endpoint of the trial will be overall survival.

Source: [ASCO, Cougar Biotechnology, JCO](#)

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Business

Roche Offers \$43.7 Billion to Acquire Remaining Shares of Genentech

Roche has proposed to acquire the outstanding publicly held interest in Genentech, for \$89.00 per share in cash, or a total payment of \$43.7 billion to equity holders of Genentech other than Roche. It currently owns 55.9% of all outstanding shares in Genentech. "The combined entity will be the seventh largest US pharmaceutical company in terms of market share and Genentech will operate as an independent research and early development center within Roche from its existing campus in South San Francisco, retaining its talent and approach to discover new molecules," Roche said in a statement from its Basel headquarters. "Our long and successful participation in Genentech has provided great benefits to both of our companies and shareholders. It has resulted in one of the biggest success stories in the healthcare industry," said Franz Humer, Roche board chairman. Genentech expects that a special committee of its Board of Directors will be convened soon to determine what action to take with respect to the proposal.

Roche also acquired an antibody screening company Arius Research for about \$189.2 million and a gene therapy company Mirus Bio Corp. for \$125 million. Arius is the developer of a proprietary antibody platform called Function FIRST, which will allow Roche to further strengthen its developmental portfolio in the areas of oncology.

Source: [Roche, Genentech](#)

MacroGenics Acquires Raven Biotechnologies

MacroGenics announced the acquisition of Raven Biotechnologies, a privately held biotechnology company in California, focused on the discovery and development of monoclonal antibody therapeutics for oncology through its cancer stem cell program. Using its proprietary technology platform, Raven has generated more than 1,300 monoclonal antibodies, including many that target cancer stem cells of the lung, colon, pancreas, prostate, breast and ovary. "Raven's discovery platform in cancer stem cell biology is highly complementary to MacroGenics' proprietary Fc-optimization and next-generation antibody platforms," said Scott Koenig, CEO of MacroGenics. MacroGenics will issue shares of its stock to purchase Raven. Other terms of the transaction were not disclosed.

Source: [MacroGenics](#)

Daiichi Sankyo Buys Anti-Cancer Technology from Seattle Genetics

Daiichi Sankyo has bought anti-cancer technology, developed by Washington-based Seattle Genetics that combines cancer-fighting compounds with antibody drugs to boost the effectiveness of treatments. Daiichi made a lump-sum payment of \$4 million to Seattle Genetics for the technology. Additional payments in the deal will be included when Daiichi files for approval of drugs developed using the technology and when those drugs hit the market. Daiichi Sankyo will send antibodies and compounds to Seattle Genetics to be combined, then have them shipped back to Japan for research and development. Daiichi will eventually handle the entire process on its own. Daiichi Sankyo, which is strong in developing drugs for lifestyle-related illnesses, plans to make cancer-fighting treatments using antibodies as one of its main businesses and had also acquired a German biotechnology start-up in June.

Source: [Seattle Genetics](#)



Business (cont'd)

Access Expands Pipeline with MacroChem Merger

Access Pharmaceuticals and MacroChem Corporation signed a definitive merger agreement enabling Access to acquire MacroChem through the issuance of 2.5 million shares of Access Pharmaceuticals' common stock. MacroChem's product portfolio includes two clinical stage oncology products, 4-thio Ara-C, which is a next generation nucleoside analogue and sodium phenylbutyrate. MacroChem's portfolio of late stage clinical drug candidates includes Pexiganan- topical anti-infective for the diabetic foot, EcoNail for onychomycosis, and dermatology assets- SEPA[®] and MacroDerm. The acquisition is expected to close in Q3'08.

"The oncology assets are highly synergistic with the oncology development efforts ongoing at Access, and we look forward to the opportunity to move them along and monetize those assets through additional partnering activities," said Jeffrey B. Davis, CEO of Access Pharmaceuticals.

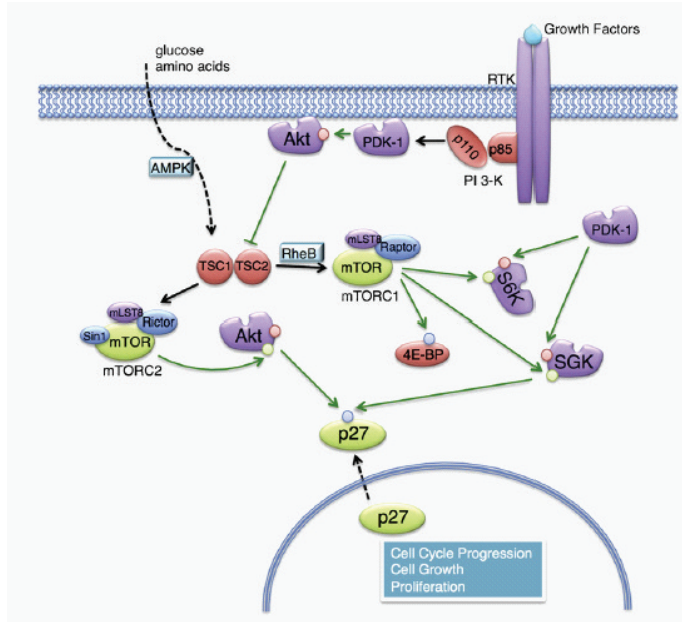
Source: [Access Pharmaceuticals](#)



Research Highlights

SGK and Akt Mediate mTOR Signaling

mTOR Signaling to Akt and SGK Converge to Regulate p27 Localization



Molecular Cell, 31, June 11, 2008

The serum and glucocorticoid-inducible kinase (SGK) and Akt kinases are downstream effectors of PI-3 kinase. SGK and Akt share many substrates and exhibit high homology (55%) in the catalytic domains. SGK and Akt kinases are key components of the mTOR (mammalian target of rapamycin) signaling pathway that regulates cell cycle progression and cell survival. p27 is a Cdk (cyclin-dependent kinase) inhibitor that blocks cyclin-E and Cdk2 activity during G0 to G1 phase of the cell cycle. Loss of the Cdk inhibitory function of p27 confers an advantage during cancer progression. p27 inhibitory activity is regulated to a large extent through localization in the cytoplasm via nuclear exclusion and allowing CDKs to promote cell cycle progression. Previous studies had shown that Akt phosphorylates p27 at Thr 157 and Thr 198, leading to impaired nuclear transport and maintaining

active cyclinE/Cdk2 complexes. Since Akt and SGK share many similarities and substrates, it was of interest to understand the role of SGK in p27 regulation.

mTOR is activated by nutrient and growth factor signaling. mTOR exists in two distinct complexes - 1) mTORC1 which includes mTOR and raptor (regulatory associated protein of mTOR) which is inhibited by rapamycin and 2) mTORC2 which is rapamycin insensitive and includes rictor (rapamycin-insensitive companion of mTOR) and mTOR. mTORC2 complex was shown to regulate Akt kinase activity through phosphorylation of Ser473 in the hydrophobic domain. Because of similarities between SGK and Akt kinases, it was logical to ask - is mTOR also the SGK hydrophobic motif kinase? Studies by Hong and colleagues published in *Molecular Cell* have shown that mTORC1 complex (rapamycin sensitive) phosphorylates SGK, thereby distinguishing it from Akt phosphorylation which is rapamycin insensitive. Down regulation of SGK by shRNA or rapamycin treatment was shown to reduce p27 phosphorylation at T157 leading to inhibition of nuclear localization. Thus it appears that two related and yet distinct kinases phosphorylate the same site on p27 with presumably similar consequences, suggesting that SGK is the mediator of mTORC1-dependent mechanisms whereas Akt mediates mTORC2-dependent mechanisms. These results show that SGK is a key enzyme in the mTOR signaling pathway modulating signaling mechanisms that have been attributed exclusively to Akt and drugs that block both SGK and Akt may be useful in treating cancers.

Source: [Molecular Cell](#)



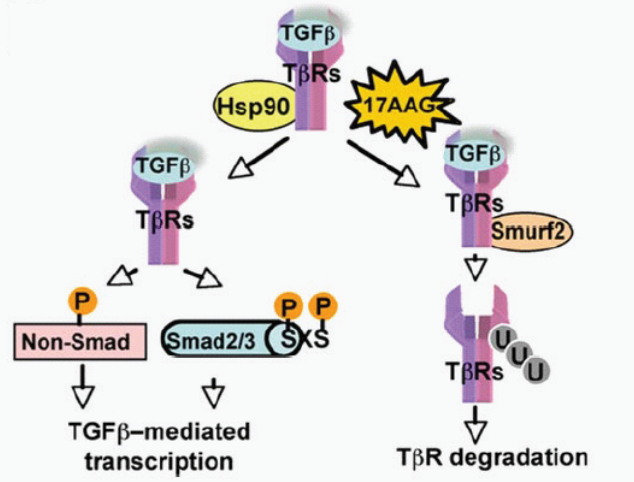
Research Highlights (cont'd)

Regulation of TGFβ by Hsp90

Transforming growth factor β (TGFβ) has dual and opposing roles in cancer, acting as both a tumor suppressor and a significant stimulator of tumor progression, invasion, and metastasis. TGFβ signals through TGFβ type I and type II receptors. Aberrant TGFβ responses are frequent in many cancers. Hsp90 is an abundant molecular chaperone that functions by facilitating protein folding and stabilization of a variety of proteins involved in cancer such as protein kinases and other proteins. Hsp90 inhibitors such as Geldanamycin and 17-AAG, a synthetic analogue of geldanamycin are in clinical trials for various cancers. While studying the anticancer properties of Hsp90 inhibitors, Katherine Wrighton and colleagues stumbled on a finding that Hsp90 inhibitors blocked antiproliferative effects of TGFβ. The authors of this study published in *PNAS*, have shown that TGFβ receptors are Hsp90-interacting proteins and stabilize TGFβ receptors. This study has demonstrated that TGFβ signaling is regulated by Hsp90 and that inhibition of Hsp90 by 17 AAG blocked TGFβ -mediated transcriptional responses by enhancing TGFβ receptor ubiquitination and degradation. Small molecule inhibitors of Hsp90 could turn off beneficial TGFβ -induced anti-proliferative effects in normal and early stage cancers despite the beneficial effect of these inhibitors in inhibiting unfavorable TGFβ -induced invasive and metastatic responses in late stage cancer. Thus small molecule inhibitors of Hsp90 may be useful in treating certain TGFβ -related cancers.

Source: *PNAS*

Working Model for the Regulation of TGF Signaling by Hsp90



PNAS, 105, July 8, 2008

Clinical and Biological Significance of TG2 in Ovarian Carcinoma

Overexpression of tissue type transglutaminase (TG2), a unique multifunctional protein, has been noted in several cancers where it contributes to the development of chemoresistance by exploiting integrin-mediated cell survival signaling pathways. In addition, TG2 overexpression results in cancer cell adhesion and invasion. Based on these features, TG2 seems to be an attractive therapeutic target. In a recent study published in *Cancer Research*, Sood et al. have evaluated the clinical and biological significance of TG2 for ovarian cancer patients.

In univariate as well as multivariate analysis, TG2 overexpression was associated with significantly worse patient survival. Transfection of TG2 into SKOV3ip1 cells promoted attachment and spreading on fibronectin-coated surfaces and increased the *in vitro* invasive potential of these cells. These results suggest that the TG2-dependent interaction between ovarian cancer cells and fibronectin is critical for inducing cell growth and survival. On the other hand, TG2 silencing with small interfering RNA (siRNA) in HeyA8 cells significantly decreased the invasive potential of the cells and also increased docetaxel-induced cell death. *In vivo* therapy experiments using chemotherapy-sensitive (HeyA8) and chemotherapy-resistant (HeyA8-MDR and RMG2) models showed that the combination therapy of TG2 siRNA-1,2-dioleoyl-sn-glycero-3-phosphatidylcholine (DOPC) with docetaxel was more effective than control siRNA-DOPC plus docetaxel or TG2 siRNA-DOPC alone. This antitumor activity was related to decreased proliferation and angiogenesis and increased tumor cell apoptosis *in vivo*. Given the clinical relationship between TG2 and ovarian cancer prognosis, the findings raise the possibility that TG2 silencing in combination with docetaxel chemotherapy could be a novel therapeutic option against advanced ovarian carcinoma.

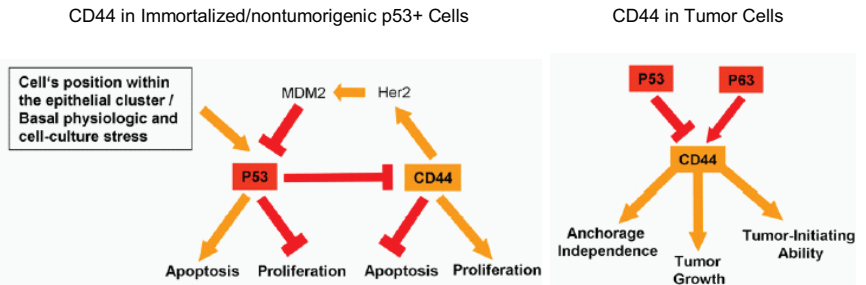
Source: *Cancer Research*



Research Highlights (cont'd)

Tumor-Suppressive Functions of p53 depend on its Repression of CD44 Expression

CD44, a transmembrane protein, has been found to support anchorage-independent growth *in vitro* and tumor growth and metastasis in experimental models of solid cancers. The tumor-promoting functions of CD44 are probably due to its ability to costimulate growth factor receptor signaling. Immunohistochemical analyses of



Cell, 134, 11, 2008

clinical samples of hepatocellular and renal carcinomas had demonstrated that CD44 protein is expressed at high levels together with elevated levels of p53, a key mediator of cellular responses to various stresses. In a study published in *Cell*, Robert Weinberg and colleagues examined the relationship between p53 and CD44 in human mammary epithelial cells.

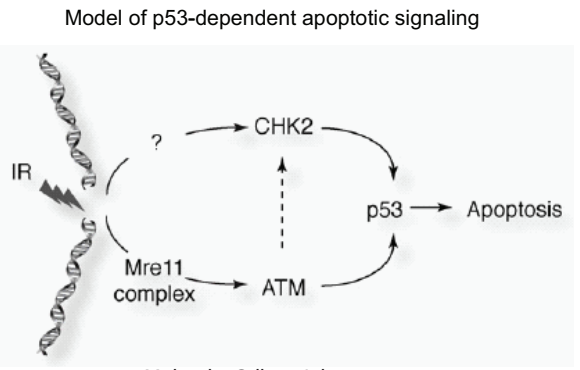
These investigators showed that under conditions of minimal stress *in vitro* and *in vivo*, the basal levels of p53 are sufficient to repress expression of CD44 mRNA. This interaction enables an untransformed cell to respond to stress-induced, p53-dependent cytostatic and apoptotic signals that would otherwise be blocked by the actions of CD44. Thus, CD44 is an effector of enhanced tumor growth in tumor cells with low p53 expression. In both tumorigenic and nontumorigenic cells, p63, a paralogue of p53, acts on the CD44 protein in a manner opposite to that of p53 by stimulating CD44 expression. These findings suggest that the derepression of CD44 resulting from inactivation of p53 can potentially assist the survival of immortalized, premalignant cells.

Source: *Cell*

Chk2 Suppresses the Oncogenic Potential of DNA Replication-Associated DNA Damage

The Mre11 complex (Mre11, Rad50, and Nbs1) and Chk2 play a central role in cellular response to DNA damage. This complex is required for repair and checkpoint activation in S phase by modulating the activity of the kinases Ataxia-telangiectasia mutated (ATM) and ATM and RAD3 related (ATR). Chk2 governs apoptosis. In a study published in *Molecular Cell*, Travis et al. examined the relationship between the Mre11 complex and Chk2 in the DNA-damage response via the establishment of *Nbs1^{ΔB/ΔB} Chk2^{-/-}* and *Mre11^{ATLD1/ATLD1} Chk2^{-/-}* mice and examined several phenotypic outcomes in cell cultures derived from them. The data demonstrated that Chk2 has substantial effects on apoptosis that are independent of the Mre 11 complex and ATM, as double mutants exhibited apoptotic defects that far exceeded those of the single mutants. The study further showed that double-strand breaks (DSBs) induced in G1 lymphocytes did not trigger Chk2-dependent apoptosis. These data clearly suggest a global role for Chk2 in responding to DNA replication-associated DNA damage, thus influencing apoptosis as well as tumor suppression.

Source: *Molecular Cell*



Molecular Cell, 31, July 11, 2008



Clinical Development

Biovest's BiovaxID Improves Survival in Phase III NHL Trial

BiovaxID is a personalized, patient-specific therapeutic vaccine designed to stimulate the patient's own immune system to recognize and destroy cancerous B-cells that may remain in the body or may arise after the patient has been treated with chemotherapy. Biovest International announced clinically and statistically significant unblinded data from its randomized controlled pivotal Phase III clinical trial of BiovaxID[®] vaccine for the treatment of non-hodgkins lymphoma (NHL). Biovest reported on two clinically relevant data points: First, for vaccinated patients followed up to 80 months, the overall results showed that BiovaxID improved median disease-free-survival by more than one year. The control arm showed a median time to relapse from first vaccination of 21.2 months, as compared to the BiovaxID arm which had a median time to relapse of 33.8 months. For these same patients measured at 36 months from vaccination, BiovaxID improved median disease-free-survival by approximately 100% - a statistically significant improvement as compared to the control group. Biovest intends to seek accelerated and/or conditional approvals immediately in the US and Europe, respectively, based on the current unblinded data.

Source: [BioVest International](#)

Cephalon's TREANDA plus Rituximab in Relapsed NHL

Cephalon announced the results of its Phase II study, enrolling 66 patients with relapsed, indolent B-cell or mantle cell lymphoma without documented resistance to prior rituximab therapy, in online edition of *JCO*. Patients received rituximab 375 mg/m² intravenously on day one and TREANDA (bendamustine hydrochloride) 90 mg/m² intravenously on days two and three of a 28-day cycle for up to six cycles. An additional dose of rituximab was given one week before the first cycle and four weeks after the last cycle. Overall response rate of 92% with a complete response rate of 41% was reported. These responses were durable, with a median duration of 21 months overall (19 months for the mantle cell population). Additionally, the combination of TREANDA and rituximab was associated with progression-free survival of 23 months overall. This combination study is one of three studies in patients with NHL that Cephalon submitted to the FDA in December 2007 requesting approval of TREANDA for the treatment of patients with indolent NHL who have progressed during or following treatment with rituximab or a rituximab-containing regimen. TREANDA was approved by the FDA in March 2008 for the treatment of patients with CLL and is not currently approved for use in NHL.

Source: [Cephalon](#)



Clinical Development (cont'd)

Positive Results for Denosumab in the Treatment of Bone Loss in Prostate Cancer

Denosumab is a fully human monoclonal antibody that specifically targets RANK Ligand- the essential regulator of osteoclasts (the cells that break down bone). Amgen is studying denosumab in numerous tumor types across the spectrum of cancer induced bone diseases. Amgen announced findings from a three-year pivotal Phase III placebo-controlled trial evaluating denosumab in the treatment of bone loss in men undergoing androgen deprivation therapy (ADT) for non-metastatic prostate cancer. In this study of more than 1,400 men, denosumab treatment produced statistically significantly greater increases in bone mineral density (BMD) at the lumbar spine (primary endpoint) and non-vertebral sites compared with placebo at multiple time points. During the 36-month evaluation period, men receiving denosumab experienced less than half the incidence of new vertebral fractures (a secondary endpoint) compared with those receiving placebo, a statistically significant finding. Also, in the denosumab arm there were fewer non-vertebral fractures over the 36-month period. The most common adverse events across both treatment arms were arthralgia, back pain, constipation, and pain in extremity.

Source: [Amgen](#)

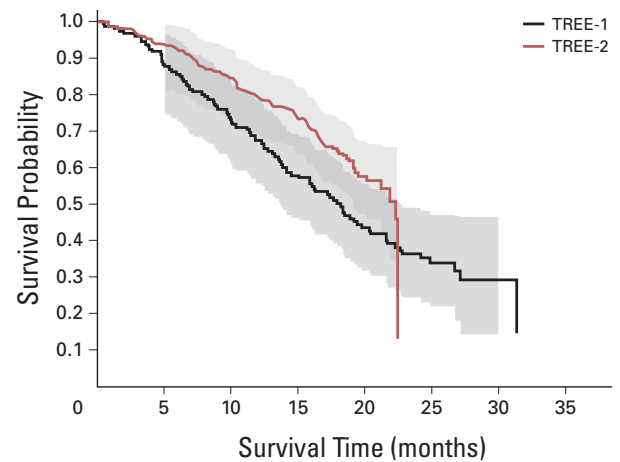
Efficacy of Oxaliplatin and Fluoropyrimidine as First-Line Treatment of mCRC

Oxaliplatin-based therapy is standard first-line treatment for advanced or metastatic colorectal cancer (mCRC). In a study published in *JCO*, Howard et al evaluated the safety and efficacy of three oxaliplatin and fluoropyrimidine regimens, with or without bevacizumab, as first-line treatment for mCRC. Patients with mCRC and no prior treatment for advanced disease were randomly assigned to mFOLFOX6 (bolus and infusion fluorouracil [FU] and leucovorin [LV] with oxaliplatin), bFOL (bolus FU and low-dose LV with oxaliplatin), or CapeOx (capecitabine with oxaliplatin) [TREE-1]. The study was modified such that subsequent patients were randomized to the same regimens plus bevacizumab (TREE-2).

A total of 150 and 223 patients were randomly assigned in the TREE-1 and TREE-2 cohorts, respectively. Incidence of grade 3/4 treatment-related adverse events during the first 12 weeks of treatment were 59%, 36%, and 67% for mFOLFOX6, bFOL, and CapeOx, respectively, (TREE-1) and 59%, 51%, and 56% for the corresponding treatments plus bevacizumab (TREE-2; primary end point). Capecitabine dose reduction to 1,700 mg/m²/d in TREE-2 resulted in improved tolerance. Overall response rates were 41%, 20%, and 27% (TREE-1) and 52%, 39%, and 46% (TREE-2); median overall survival (OS) was 19.2, 17.9, and 17.2 months (TREE-1) and 26.1, 20.4, and 24.6 months (TREE-2). The study concluded that the addition of bevacizumab to oxaliplatin and fluoropyrimidine regimens is well tolerated as first-line treatment of mCRC and does not markedly change overall toxicity.

Source: [JCO](#)

Kaplan-Meier plots of overall survival



JCO, 26, July 20, 2008



Biomarkers

GeneNews Launches World's First Blood Test for Colorectal Cancer Screening

GeneNews, a company focused on developing blood-based biomarker tests, announced the launch of ColonSentry™, the world's first blood-based molecular test for colorectal cancer (CRC) screening, in Canada. ColonSentry™ is a blood test that assesses a patient's current risk of having CRC allowing for a more targeted application of colonoscopy which could increase the detection rate of CRC by as much as 3 fold in an asymptomatic general population. The mRNA expression of a panel of seven specific genes is measured at the molecular level by quantitative RT-PCR thus assessing patient's current risk. ColonSentry™ will be performed at the Company's laboratory facilities in Richmond Hill, Canada and is the first in a series of blood-based molecular tests based on the company's platform technology, the award-winning Sentinel Principle™. "A patient-friendly blood test like ColonSentry™ is welcomed and will facilitate earlier detection and treatment of the disease, resulting in improved outcomes for patients with colorectal cancer," said Barry D. Stein, President of the Colorectal Cancer Association of Canada.

Source: [GeneNews](#)

Gene Expression–Based Survival Prediction in Lung Adenocarcinoma

Lung cancer represents the leading cause of cancer-related death in US with 5-year overall survival rate of only 15% due to detection at advanced stages requiring an urgent need to establish new diagnostic paradigms for detection of stage I–II patients likely to benefit from adjuvant chemotherapy.

Several studies of primary lung adenocarcinoma have reported the ability to generate expression signatures capable of grouping subjects according to their survival outcomes. However, their performance and general applicability has not been easy to establish because of small numbers of subjects, no uniform criteria for sample inclusion, annotation, sample processing and data analyses. To address these concerns, Kerby et al conducted a large, multi-site, blinded validation study to characterize the performance of several prognostic models based on gene expression for 442 lung adenocarcinomas. The study examined whether microarray measurements of gene expression either alone or combined with basic clinical covariates (stage, age, sex) could be used to predict overall survival in lung cancer subjects. Most methods performed better with clinical data, supporting the combined use of clinical and molecular information when building prognostic models for early-stage lung cancer.

Several classifiers were developed from the training data and tested on the independent data sets. The classifiers varied in their success in stratifying subjects according to risk. Researchers observed that clinical covariates improved upon gene expression alone as a mechanism for stratifying tumor samples. This study provides the largest available set of microarray data with extensive pathological and clinical annotation for lung adenocarcinomas.

Source: [Nature Medicine](#)



Biomarkers (cont'd)

EGFR FISH for Selection of Patients for EGFR-targeted Therapies

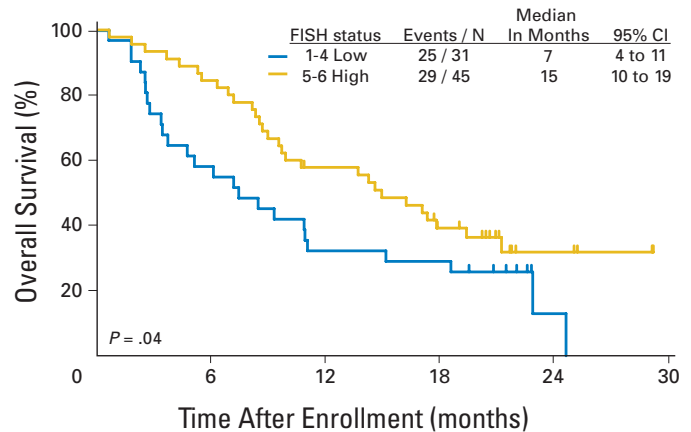
Epidermal growth factor receptor (*EGFR*) gene copy number detected by fluorescent in situ hybridization (FISH) is a reliable marker for prediction of clinical outcome after treatment with EGFR tyrosine kinase inhibitors. In the study published in *JCO*, Hirsch et al evaluated EGFR FISH as a predictive marker in NSCLC patients receiving the EGFR monoclonal antibody inhibitor, cetuximab plus chemotherapy.

The present Phase II selection (S0342) trial, enrolled 229 chemotherapy-naive patients with advanced-stage NSCLC for evaluating sequential or concurrent chemotherapy (paclitaxel plus carboplatin) with cetuximab. EGFR FISH was assessable in 76 patients with available tumor tissue.

Increased EGFR gene copy number (FISH positive) was present in 45 patient specimens (59.2%), whereas 31 specimens (40.7%) were FISH negative. Twenty-five (62.5%) of 40 patients in the concurrent treatment arm, and 20 (55.5%) of 36 patients in the sequential treatment arm were FISH positive respectively. The results showed that FISH-positive patients achieved a remarkable overall survival time when compared with the FISH-negative group (median, 15 vs. 7 months, respectively). In FISH-positive patients, the median PFS time was 6 months compared to 3 months for the FISH-negative patients. The objective response rate was numerically higher in FISH positive patients (45%) versus FISH-negative patients (26%). Moreover, survival favored FISH-positive patients receiving concurrent therapy. The findings demonstrated improved response, PFS, and overall survival in FISH-positive patients with advanced NSCLC receiving cetuximab-chemotherapy. These findings support the hypothesis that EGFR FISH may be broadly applicable for selection of patients for EGFR-targeted therapies.

Source: *JCO*

Overall Survival according to FISH status



JCO, 26, July 10, 2008



Regulatory

Genentech Warns of Anemia in Avastin Combo Trial

Genentech Inc. warned healthcare professionals about several cases of microangiopathic hemolytic anemia (MAHA) seen in patients treated with the company's blockbuster cancer drug Avastin in combination with Pfizer Inc's Sutent in a clinical trial. 25 patients were enrolled in a Phase I dose-escalation study combining Avastin and sunitinib malate. Five of 12 patients at the highest sunitinib dose level exhibited MAHA. Two of these cases were considered severe with evidence of thrombocytopenia, anemia, reticulocytosis, modest increases in serum creatinine levels, and severe hypertension, reversible posterior leukoencephalopathy syndrome, and proteinuria. The findings in these two cases were reversible within three weeks upon discontinuation of both drugs without additional interventions. This information led to the closure of a Phase II trial of sunitinib at 50 mg +/- Avastin. In a letter posted on the FDA's website MedWatch section, doctors were asked to report cases of MAHA or any serious adverse events suspected to be associated with the use of Avastin.

Source: [FDA](#)

FDA Approves AMDL-ELISA DR-70® (FDP) Blood Test for Monitoring CRC

AMDL, a leading bio-pharmaceutical company with operations in China and the US, announced that the US FDA has issued a letter of substantial equivalence to an existing predicate device and granted marketing approval to the AMDL-ELISA DR-70® (FDP) as a safe and effective blood test for monitoring patients who have been previously diagnosed with colorectal cancer (CRC). The FDA clearance was based upon data from study enrolling 180 patients, showing that DR-70 (FDP) is superior to carcino embryonic antigen(CEA) in the detection of patients with CRC. The AMDL-ELISA DR-70 (FDP) test showed strong clinical performance with a sensitivity of 91% and a specificity of 93% in testing conducted on patients with hepatocellular, cholangiocellular, pancreatic, colorectal, stomach and oesophagus cancers. The approval marks the first clearance to market that the FDA has granted for any monitoring product for CRC since January 14, 1982 when CEA was approved.

Source: [AMDL](#)



Regulatory (cont'd)

EU Approves Broader Use of Erbitux in mCRC as First-Line Treatment

Merck KGaA announced that European Commission has granted a broad approval for Erbitux® (cetuximab) to update its license for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer (mCRC) in combination with chemotherapy, and as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapies and who are intolerant to irinotecan.

The approval was granted following review of data from randomized, controlled Phase III (CRYSTALa) and Phase II (OPUSb) trials that demonstrated the superior efficacy of Erbitux in combination with standard chemotherapy in the first-line treatment of patients with mCRC compared to chemotherapy alone. Further analyses of these trials, found that patients with KRAS wild-type tumors experienced substantially increased efficacy with Erbitux and had statistically significant higher response rates and decreased risk of progression than patients receiving chemotherapy alone.

Marketing authorization has also been granted in Japan for the use of Erbitux® (cetuximab) in treating patients with epidermal growth factor receptor (EGFR)-positive, curatively unresectable metastatic colorectal cancer (mCRC) in combination with irinotecan. The Japanese approval was based on data from six different studies.

Source: [Merck KGaA](#)

US FDA, CDC Back Merck's Gardasil Shot as Safe

FDA and CDC closely monitor the safety of all vaccines through the Vaccine Adverse Event Reporting System (VAERS). Till now, there have been 9,749 VAERS reports of adverse events following Gardasil vaccination. Of these, 94% were classified as reports of non-serious events, and 6% as serious events. Concerns have been raised by consumers, parents, health care professionals about reports of deaths occurring in individuals after receiving Gardasil. Till June 30, 2008, 20 deaths had been reported to VAERS. There was not a common pattern to the deaths that would suggest they were caused by the vaccine. In cases where autopsy, death certificate and medical records were available, the cause of death was explained by factors other than the vaccine. Guillain-Barre Syndrome (GBS) has also been reported in individuals following vaccination with Gardasil. FDA and CDC have reviewed the reports of GBS and found that there is no evidence that Gardasil has increased the rate of GBS above that expected in the population. Based on the review of available information by FDA and CDC, Gardasil continues to be safe and effective, and its benefits continue to outweigh its risks.

Source: [FDA](#)