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INTELLIGENT INSIGHTS. SMART RESULTS.

A new look:

With this issue of the *Oncology Newsletter*, **SMARTANALYST** is taking the first step towards improving all communications materials. In the coming issues, you'll notice more upgrades in look, delivery and interactivity.



Business News

Takeda to Acquire Millennium

Roche Acquires Piramed

Celera Grants License to Merck

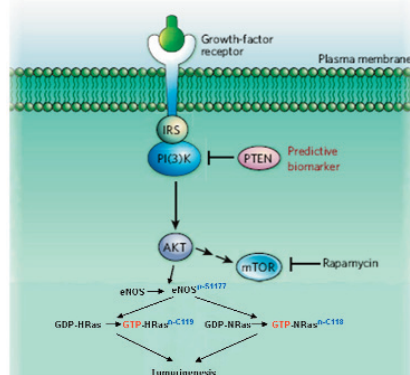
Antisoma Licenses Rights to Develop AMPK Activators

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At **SMARTANALYST**, we support the decision-making process for licensing, business development, new product planning, and R&D groups within pharmaceutical and biotech companies.

We currently work with leading pharmaceutical and biotech firms globally.



In the Spotlight:

eNOS Activation Fosters Cancer Cell Growth via Ras

RAS family members, HRas, NRas and KRas, are mutated to remain in the active GTP-bound oncogenic state in many cancers. Activation of the PI3Kinase/AKT signaling pathway by oncogenic Ras is required for maintenance of tumor growth. [Read more...](#)



Research Highlights

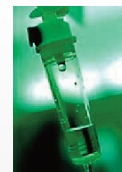
Efficacy of JAK2 Inhibitor in Animal Models of MPD

Angiogenesis Suppression by si RNAs

SGX393 Inhibits Mutant Bcr-Abl^{T315I} in CML

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Biomarkers

A Susceptibility Locus for Lung Cancer

Variations in Bleomycin Hydrolase Gene in Testicular Cancer

Noninvasive Imaging Surrogates For Brain Tumor

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Regulatory

European Approval for ALIMTA[®]

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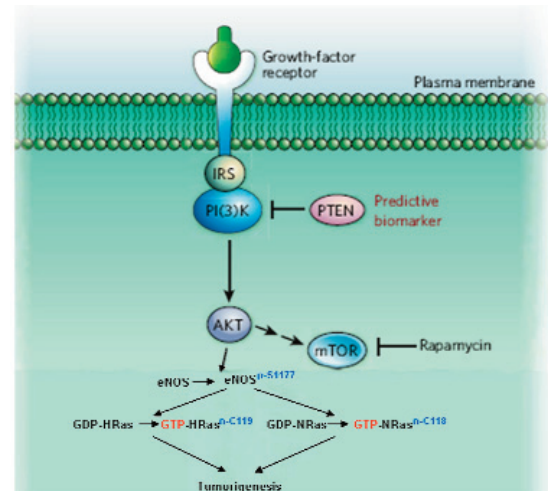
Spotlight Report

eNOS Activation Fosters Cancer Cell Growth via RAS

RAS family members, HRas, NRas and KRas, are mutated to remain in the active GTP-bound oncogenic state in many cancers. Activation of the PI3Kinase/AKT signaling pathway by oncogenic Ras is required for maintenance of tumor growth. AKT kinase phosphorylates a number of substrates including endothelial nitric oxide synthase (eNOS), BAD, TSC2 etc. eNOS catalyses the synthesis of nitric oxide and this can facilitate S-nitrosylation of the thiol group of cysteines such as that of C₁₁₈ of HRas which increases GTP-bound form of HRas.

Lim and his colleagues have shown, in a report published in *Nature*, that blocking phosphorylation of eNOS by AKT inhibited tumor initiation and maintenance. The authors have demonstrated that the need for PI3K-AKT signaling during initiation and maintenance of oncogenic Ras-driven tumor growth is due, in part, to activation of eNOS through phosphorylation of S₁₁₇₇. This, in turn leads to nitrosylation of C₁₁₈ of Ras family members. Thus, oncogenic KRas driven pancreatic cancer tumor growth was mediated by eNOS nitrosylation of endogenous wild-type HRas and NRas. In a chemical carcinogen-induced Ras-driven cancer model there was a three fold drop in the number of tumors in eNOS^{-/-} mice compared to eNOS^{+/+} mice. Delivery of a peptide fragment of the protein cavtratin, which can inhibit eNOS, displayed anti-tumor activity in animal models. These results suggest a key role for tumor-expressed eNOS and that inhibition of eNOS may have therapeutic value in the treatment of Ras-driven human cancers such as pancreatic cancers.

Source: [Nature](#)



Nature, 452, April 3, 2008



Business

Takeda to Acquire Millennium for Offer Valued at \$8.8 Billion

Takeda Pharmaceutical Company Ltd. and Millennium Pharmaceuticals, Inc. entered into a definitive agreement following which Takeda will acquire Millennium for \$8.8 billion through a cash tender offer of \$25.00 per share. Millennium markets Velcade® (bortezomib) for Injection—a novel, market-leading oncology product approved in more than 85 countries. Millennium also has novel product candidates in oncology and inflammation. The acquisition of Millennium will help Takeda in becoming a global leader in oncology with critical mass in the areas of oncology discovery, development, regulatory affairs and commercialization.

Source: [Takeda](#)



Business
(cont'd)

Roche Fully Acquires Biotech Company Piramed

Roche announced the acquisition of Piramed Ltd., a privately-owned UK company focusing on therapeutics targeting PI3-kinase (PI3-K). Through this acquisition, Piramed's two major research programs targeting PI3-K- alpha in oncology and PI3K-delta in inflammatory disease will strengthen Roche's pipeline. The PI3-K-alpha program has a compound in Phase I and is currently being developed in collaboration with Genentech, in whom Roche has a majority ownership interest. Under the terms of the agreement, Roche will acquire 100% of Piramed's shares for USD 160 million, plus a milestone payment of USD 15 million, which will be due upon commencement of Phase II clinical trials for the company's oncology program.

Source: Roche

Celera Grants License to Merck for Cancer Targets

Celera, an Applera Corporation business, announced a two year exclusive license agreement with Merck & Co., Inc., providing Merck with access up to ten cancer targets for the development of RNA interference (RNAi) based therapeutics. These therapeutic targets are over-expressed on the surface of several different tumor cell types and were identified using Celera's proteomics discovery platform.

"This new agreement combines the strength of our novel proteomics target discovery and validation capability with Merck's expertise in developing RNAi based therapeutics," said Steve Ruben, vice president of proteomic research at Celera. Under the terms of the agreement, Merck will pay Celera a license fee for exclusive access to the ten targets, in addition to the payment of development and commercial milestones plus royalties on selected targets that it advances successfully. Merck also has the option to extend the exclusivity period or add additional targets. Financial terms of the agreement were not disclosed.

Source: Celera

Antisoma Licenses Rights to Develop Betagenon's AMPK Activators

Antisoma and Betagenon announced that Antisoma has licensed rights to develop and commercialize Betagenon's AMP activated protein kinase (AMPK) activators in cancer indications. Betagenon has shown that besides diabetes, AMPK activators also have significant potential in cancer treatment. Activation of AMPK by Betagenon's agonists down regulates mammalian target of rapamycin and elongation factor-2 and suppresses lipid synthesis in tumor cells. This has been associated with significant cancer cell-killing activity in vitro and anti-tumor activity in animal models. Antisoma plans to continue the preclinical evaluation of AMPK activators from Betagenon's pipeline. The two companies have also formed a collaboration to further explore the potential of AMPK-based approaches to cancer treatment.

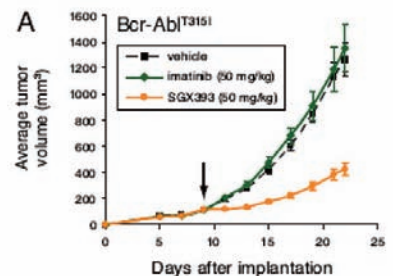
Source: Antisoma



Research Highlights

SGX393 Inhibits Mutant Bcr-Abl^{T315I} in CML

Bcr-Abl, the deregulated tyrosine kinase that causes chronic myeloid leukemia (CML) is inhibited by imatinib which is the first line therapy for the disease. The second line inhibitors, nilotinib and dasatinib are effective against most imatinib-resistant Bcr-Abl mutants except Bcr-Abl^{T315I} which is emerging as a common mechanism of salvage therapy failure. Thus, an inhibitor of Bcr-Abl^{T315I} is required to overcome the resistance to Abl kinase inhibitor therapy.



PNAS, 105, April 8, 2008



Research Highlights (cont'd)

In the recent study published in *PNAS*, Thomas O'Hare and colleagues reported that Bcr-Abl inhibitor, SGX393 blocks the growth of BaF3 cells expressing native or mutant Bcr-Abl, including Bcr-Abl^{T315I} with minimum toxicity against Bcr-Abl-negative cell lines. Similar results were observed with SGX393 in primary hematopoietic cells expressing Bcr-Abl^{T315I}. A screen for Bcr-Abl mutants emerging in the presence of SGX393 demonstrated concentration-dependent reduction in the number and range of mutations. Furthermore, SGX393 inhibited Bcr-Abl^{T315I} kinase activity in primary CML and Philadelphia chromosome-positive leukemia. As SGX393 is active against native Bcr-Abl and the Bcr-Abl^{T315I} mutant, monotherapy with an inhibitor of this type might be sufficient to induce responses in patients harboring only Bcr-Abl^{T315I}. Combining SGX393 with nilotinib and dasatinib completely suppressed outgrowth of resistant clones, including Bcr-Abl^{T315I} *in vitro*. Thus, this combination treatment may be useful for reducing the incidence of Bcr-Abl mutants in CML patients and possibly eliminate Bcr-Abl-dependent resistance.

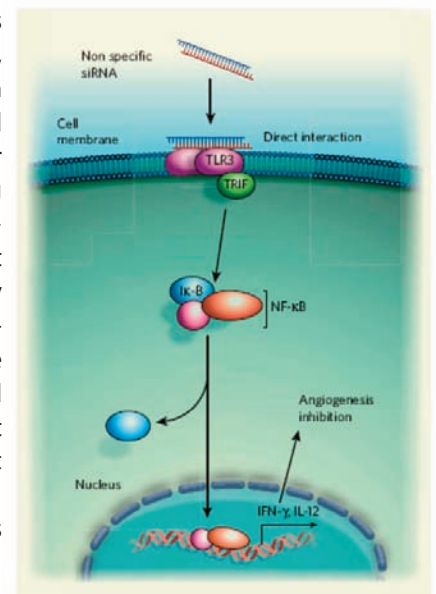
Source: *PNAS*

Angiogenesis Suppression by si RNAs

Sequence specific gene silencing by small interfering RNAs (siRNAs) has attracted several therapeutic applications for various diseases. Angiogenesis, the process by which new blood vessels are formed, is required for the growth of cancers, and also occurs as choroidal neovascularization (CNV) associated with age-related macular degeneration. siRNAs targeting VEGF or its receptor are undergoing clinical trials for CNV, based on the premise of blocking VEGF-mediated angiogenesis pathway by means of intracellular RNA interference. However Kleinman et al. show, in a study published in *Nature*, that anti-angiogenesis effect in CNV is a siRNA-class effect and can be induced by siRNAs in a non-specific manner. Further, the authors found that all non-specific and VEGF specific siRNAs bind to Toll-like receptor (TLR) 3, an immune system regulator present on the surface of many cells. siRNA-mediated inhibition of CNV in mouse models was observed in VEGF1-deficient mice but not in TLR3-deficient mice. Soluble TLR3 protein reversed the inhibitory effect of siRNAs. To have anti-angiogenesis effects, siRNAs had to be at least 21 nucleotides in length. These studies clearly imply that siRNAs of 21 nucleotides or more can have side effects unrelated to their gene silencing potential.

Source: *Nature*

Angiogenesis suppression by siRNAs

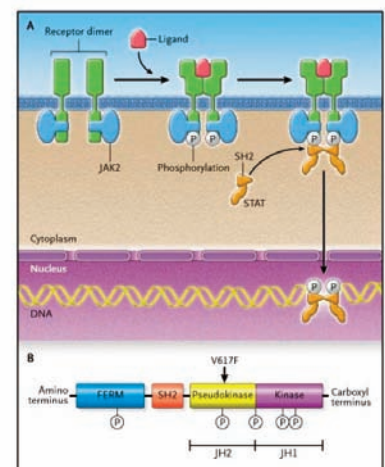


Nature, 452, April 3, 2008

Efficacy of JAK2 Inhibitor in Animal Models of MPD

The myeloproliferative disorders (MPDs) polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are clonal malignancies of multipotent haematopoietic progenitors. MPDs are characterized by overproduction of mature, functional blood cells. The recent discovery of the JAK2 mutation in patients with MPDs has ignited major activity in the science and treatment of these diseases. The JAK2V617F mutation, observed in ~99% of PV and ~50% of ET and PMF patients, represents an attractive target for targeted therapy.

In a study published in *Cancer Cell*, Werning and colleagues have used a selective small molecule inhibitor of JAK2 to demonstrate therapeutic efficacy in a murine model of MPD induced by JAK2617F. TG101348 is a small molecule ATP competitive inhibitor designed to inhibit JAK2 wild type and mutant V617F with an IC₅₀ of 3 nM and is highly selective against other kinases. The authors used a murine bone marrow transplant assay of



NEJM, 352, April 28, 2005

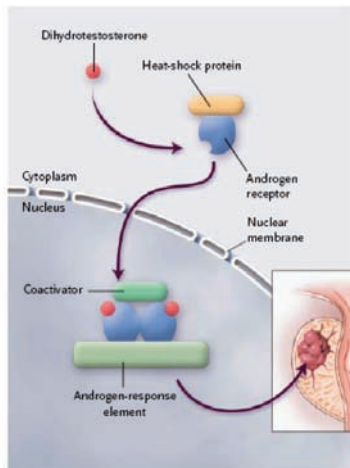


Research Highlights (cont'd)

established PV that recapitulates many of the features of the human disease. In this animal model the disease was fully established prior to the initiation of therapy and a dose dependent response to therapy was demonstrated. Responses were correlated with surrogate end points such as reduction of JAK2 mutant allele by quantitative PCR and inhibition of phospho-STAT5 protein level in tumors. These studies demonstrate that TGI101348 was safe and effective in the treatment of MPDs and also identify surrogate end points for response that may be of value in clinical trials in humans.

Source: *Cancer cell*

Androgen Receptor Cofactor p44 in the Regulation of Prostate Cancer Cell Proliferation



NEJM, October 2004

Androgen receptors (ARs) play an important role in prostate cancer development, including progression into androgen independent cancer. In association with its coactivators, AR activates transcription of AR target genes. Alterations in the cellular concentrations of AR cofactors might influence selective expression of AR target genes, thereby mediating the switch between proliferation and growth inhibition.

Yi Peng and colleagues identified p44/MEP50 as an AR coactivator and showed that it is expressed as a nuclear protein in benign prostate and as a cytoplasmic protein in prostate cancer cells. In addition, transgenic mice lacking one allele for p44 (p44^{+/-}) exhibited excessive epithelial cell proliferation that resulted in a precancerous lesion termed high-grade prostatic intraepithelial neoplasia. In the present study published in *PNAS*, investigators showed that preferential expression of p44 in the nucleus inhibits proliferation of LNCaP cells in an AR-dependent manner, while preferential expression of p44 in the cytoplasm enhances cell proliferation. These effects are influenced by distinct S phase cell-cycle regulatory genes which include p21 that is up-regulated by nuclear p44 and cyclin D2 and CDK6, which are up-regulated

by cytoplasmic p44. The study also showed that high levels of both cytoplasmic and nuclear p44 are associated with androgen-independent prostate cancer. These results enhance the understanding of mechanisms by which AR regulates prostate cancer cell proliferation and growth suppression.

Source: *PNAS*



Clinical Development

Hedgehog Antagonist GDC-0449 Shows Promise in Advanced Basal Cell Carcinoma

Basal cell carcinoma affects about one million people a year and currently there are no treatments available that can slow the tumor growth in advanced patients. A latest research presented at the 2008 Annual Meeting of the American Association for Cancer Research revealed that GDC-0449, a systemic Hedgehog pathway antagonist, shrinks tumors in patients with advanced basal cell carcinoma with limited side effects. Abnormal activation of Hedgehog signaling pathway because of mutations in cell surface receptors, PTCH and SMO, is the cause of most basal cell carcinomas. This first-in-human Phase I trial enrolled nine patients with advanced basal cell carcinoma. Patients received oral doses of GDC-0449 once a day continuously. Of the nine patients treated six had shrinkage of the tumor and two patients had prolonged periods without tumor growth. One patient had a clinical improvement for over 438 days. Investigators examined the skin cells sampled from participants for the presence of GLI1, a genetic marker of Hedgehog pathway activity. Among all patients tested to date, there was a reduction in this marker, indicating that the drug was affecting the Hedgehog pathway. The drug was extremely well tolerated.

Source: *AACR*



Clinical Development (cont'd)

Phase II Study of Sunitinib in Metastatic Breast Cancer

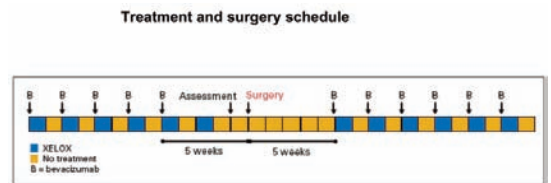
Sunitinib malate, an oral tyrosine kinase inhibitor, targets several receptor tyrosine kinases and colony-stimulating factor-1 receptor. Single-agent sunitinib has demonstrated antitumor activity in several preclinical breast cancer models, both alone and in combination with chemotherapy. In the present Phase II, open-label, multicenter study published in *JCO*, Burstein et al. evaluated the efficacy and safety of sunitinib treatment in patients with metastatic breast cancer (MBC). The study enrolled sixty-four patients, previously treated with an anthracycline and a taxane, who received sunitinib 50 mg/d in 6-week cycles (4 weeks on, then 2 weeks off treatment). The clinical benefit rate with sunitinib treatment was 16%, with 11% of patients achieving a partial response. Clinical activity was seen irrespective of HER2 and ER status. Response rates of 15% in cases of triple-negative tumors, and 25% in trastuzumab-treated, HER2-positive tumors constitute important findings, given the limited treatment options available for such patients. Median time to progression and overall survival was 10 and 38 weeks, respectively. Most adverse events were of mild-to-moderate severity and manageable with supportive treatment and/or dose modification. The study concluded that sunitinib is active in patients with heavily pretreated MBC.

Source: *JCO*

Perioperative Bevacizumab for Hepatectomy in Metastatic Colorectal Cancer

Patients with colorectal cancer (CRC) and liver metastases have a poor prognosis, but can benefit from perioperative chemotherapy and disease resection. A Phase II study reported in *JCO* was conducted to know the impact of perioperative bevacizumab on surgical complications and hepatic regeneration after liver resection. Study included 56 patients with metastatic CRC with liver metastases, potentially curable by resection. Patients received biweekly bevacizumab plus capecitabine and oxaliplatin for six cycles. The sixth cycle of therapy did not include bevacizumab, resulting in 5 weeks between the last administration of bevacizumab and surgery. Objective response to neoadjuvant chemotherapy was achieved in 41 patients (73%). No increased intraoperative bleeding events or wound-healing complications were observed in 52 patients who underwent liver resection and only three patients (6%) required perioperative blood transfusions. Postoperative liver function and regeneration were normal in all but one patient. This study confirmed that bevacizumab plus standard chemotherapy is a feasible, safe, and effective neoadjuvant regimen in patients with metastatic CRC.

Source: *JCO*



JCO, 26, April 10, 2008

EndoTAG™-1 Shows Survival Benefit Compared with Gemcitabine in Pancreatic Cancer

MediGene AG presented the efficacy data of the company's drug candidate EndoTAG™-1 for the treatment of pancreatic carcinoma. Results from a controlled clinical Phase II trial demonstrate clear survival advantage of EndoTAG™-1 compared with the approved standard drug gemcitabine. The mode of action of EndoTAG™-1 was revealed for the first time which is targeted at "starving out" tumors by selective destruction of tumor blood vessels. EndoTAG™-1 is a positively charged lipid complex which attaches itself specifically to negatively charged endothelial cells of tumor blood vessels.

During the controlled Phase II trial, 200 patients suffering from pancreatic carcinoma received gemcitabine (control group), or gemcitabine in combination with EndoTAG™-1 in three different dosages (11, 22, and 44 mg/m²). The median survival time of the patients treated with gemcitabine was 7.2 months whereas the combination therapy with gemcitabine and EndoTAG™-1 resulted in a dose-dependent increase in the median survival time to 8.1 months, 8.8 months, and 9.4 months, respectively, in the three EndoTAG™ groups. The six-month survival rate also increased dose-dependently, i.e. from 63.3 % in the group treated with gemcitabine, to 66.1 %, 72.4 %, and 80.7 %, respectively in the three EndoTAG™ groups. The positive safety profile of EndoTAG™-1 known from earlier trials was also confirmed in this Phase II trial.

Source: MediGene



Biomarkers

A Susceptibility Locus for Lung Cancer Maps to Nicotinic Receptor Genes on 15q25

Lung cancer is the most common cause of cancer death worldwide, caused mainly by tobacco smoking. It has an important heritable component and identifying genes that are associated with the risk for lung cancer may suggest chemoprevention targets. Three papers – two published in *Nature* and one in *Nature Genetics* - have identified variations in the same region of long arm of chromosome 15 as associated with lung cancer. This locus contains several genes, including three that encode nicotinic acetylcholine receptor subunits (CHRNA5, CHRNA3 and CHRNB4) which have an affinity for nicotine. However, the three studies disagree on whether the connection is direct or mediated via smoking behavior. Previous studies had identified the genes encoding subunits of nicotinic acetylcholine receptors as strongly associated with smoking behavior. These results provide strong evidence of a locus at 15q25 predisposing to lung cancer, and reconfirmed nicotinic acetylcholine receptors as potential chemopreventative targets.

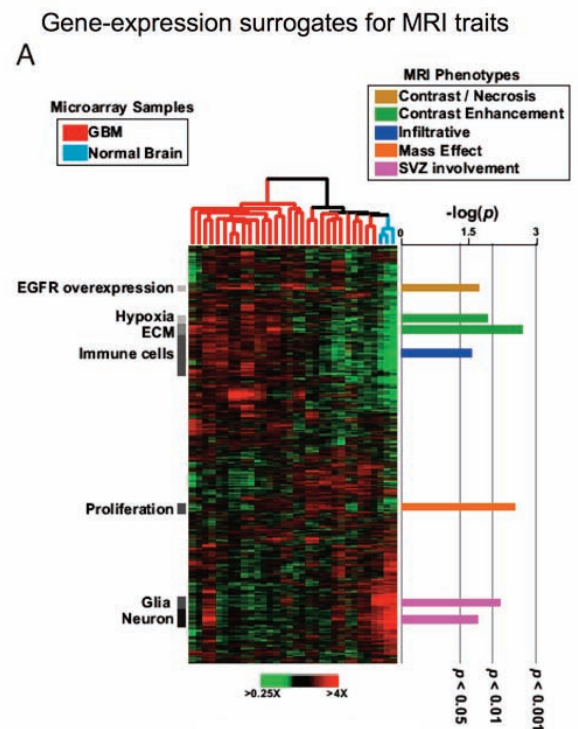
Source: *Nature*

Noninvasive Imaging Surrogates for Brain Tumor

There has been an exponential growth in the power and clinical utility of imaging modalities. Simultaneously, the development of functional genomic tools such as DNA microarrays has provided powerful methods for analyzing the molecular basis of disease on a genome-wide level. But one of the limitations with the microarray-based studies is the interpretation of molecular findings into clinically useful interventions.

In a recent study published in *PNAS*, Maximilian Diehn and colleagues combined functional genomic datasets and medical imaging to develop a multidimensional map of gene-expression patterns in glioblastoma multiforme (GBM) which provided insights into tumor biology. Using this information, investigators were able to identify potential imaging biomarkers for different classes of anti-GBM therapeutic agents, including antiangiogenesis and EGFR-based therapies. Tumor contrast enhancement (CE) predicted activation of specific hypoxia. Particularly, an "infiltrative" imaging phenotype was identified that predicted patient outcome. Patients with this imaging phenotype had a greater tendency toward having multiple tumor foci and demonstrated significantly shorter survival than their counterparts. The study results showed that the fusion of imaging and functional genomic datasets offers the potential for noninvasively selecting patients and providing rapid clinical translation.

Source: *PNAS*



PNAS, 105, April 1, 2008



Biomarkers (cont'd)

Variations in Bleomycin Hydrolase Gene in Testicular Cancer

Testicular germ-cell cancer (TC) is the most common malignancy among young adult men. Bleomycin has been the most intensively studied in patients with germ cell cancer in combination with platinum-based chemotherapy regimens. However, the use of bleomycin is limited due to associated complications. Response to chemotherapy may be determined by gene polymorphisms involved in metabolism of cytotoxic drugs. In a study published in *JCO*, Esther and colleagues have demonstrated that variations in the bleomycin hydrolase (BLMH) gene are associated with reduced survival in patients with germ cell testicular cancer. Data were collected on survival and BLMH genotype of 304 patients treated with bleomycin-containing chemotherapy at the University Medical Center Groningen, the Netherlands, between 1977 and 2003. Results showed that presence of the G/G genotype (homozygous variant) is associated with decreased overall survival, compared with the A/G (heterozygous variant) and A/A (wild-type variant) genotypes. G/G genotype proves to be an unfavorable prognostic factor. This association may be of value for risk classification and selection for alternative treatment strategies in patients with disseminated TC. Thus in patients with the presence of SNP resulting in GG allelic change, treatment with cisplatin, etoposide and ifosfamide may be preferred over cisplatin, etoposide and bleomycin.

Source: *JCO*



Regulatory

European Approval for ALIMTA® in NSCLC

Eli Lilly and Company announced that European health authorities have approved the use of Alimta® (pemetrexed for injection) for a histologically-based use in the first-line treatment of advanced NSCLC in combination with cisplatin with other than predominantly squamous cell histology. The approval was based on a Phase III randomized study that evaluated pemetrexed plus cisplatin versus Gemzar® (gemcitabine HCl for injection) plus cisplatin. This 1,725-patient study, in a pre-planned histological analysis, found that patients with either adenocarcinoma or large-cell carcinoma had a clinically relevant improvement in overall survival when treated with the pemetrexed regimen in the first-line setting in comparison to patients with squamous cell histology. This regulatory approval applies to all 27 countries of the EU, as well as Norway, Iceland, and Liechtenstein. Pemetrexed is already approved as a second-line, single agent for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy.

Source: Eli Lilly

Oncophage® Approved in Russia for Kidney Cancer

Antigenics Inc. announced that the Russian Ministry of Public Health has approved the use of Oncophage (vitespen) in the treatment of kidney cancer patients at intermediate risk for disease recurrence. The company expects to launch Oncophage in Russia in the second half of 2008. This registration was based on results of randomized, Phase III kidney cancer trial of 604 patients who were without renal cell carcinoma at baseline which showed that patients receiving Oncophage in the intermediate-risk population (stages I/II high-grade, III T1/2/3a low-grade) who were without disease at baseline (n = 362) demonstrated a clinically significant improvement in recurrence-free survival of approximately 45% over patients in the observation arm. Oncophage is not approved outside of Russia. Oncophage has received fast track and orphan drug designations from the FDA for both kidney cancer and metastatic melanoma.

Source: Antigenics

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