



SMARTANALYST

SMARTONCOLOGY

THE ONCOLOGY E-NEWSLETTER FROM SMARTANALYST

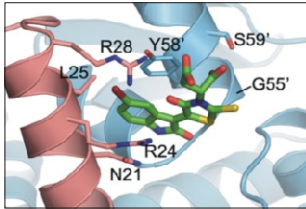
www.smartoncology.com

Volume 3, Issue 5

Monthly Oncology E-newsletter | May 20, 2010

INTELLIGENT INSIGHTS. SMART RESULTS

Molecular Interactions between 79-6 and the BCL6 BTB Domain



Cancer Cell, 17, April 13, 2010

In the Spotlight:

A Small-Molecule Inhibitor of BCL6 Kills DLBCL Cells *In Vitro* and *In Vivo*

Personalized cancer medicine offers the hope that by identifying cancer-causing mutations in critical regulatory genes, one can target these mutant proteins to cure cancer while limiting the side effects. As these proteins usually mediate their actions...

[Read more](#)



Business News

Astellas Pharma to Acquire OSI Pharmaceuticals

BI and Micromet Announce Global Collaboration for MM BiTE Antibody

Array BioPharma and Novartis Partner for Development of ARRY-162

Peregrine and Stason Enter into Agreement for Innovative TNT Technologies

[Click HERE to read more](#)



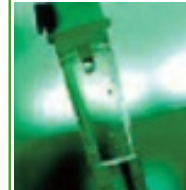
Research Highlights

Migrastatin Analogues Target Fascin to Block Tumor Metastasis

ERβ Impedes Prostate Cancer EMT: Implications for Gleason Grading

Chemoprevention of Colorectal Cancer by Targeting APC-deficient Cells for Apoptosis

[Click HERE to read more](#)



Clinical Development

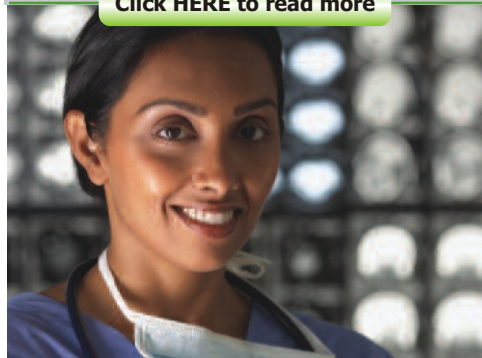
Pfizer Discontinues Phase III Trial of Sutent in Advanced Hepatocellular Carcinoma

Mesupron Confirms Impressive Increase in OS of Patients with Pancreatic Cancer

Celator Announces Positive Data from Phase II Study of CPX-351 in AML

Allovetin-7 Achieves Median Survival in Phase II Melanoma Trial

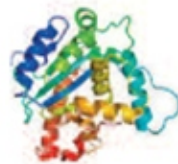
[Click HERE to read more](#)



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

We currently work with leading pharmaceutical and biotech firms globally

[CLICK HERE to visit SMARTANALYST](#)



Biomarkers

IGF1R Gene Copy Number is Associated with Survival in Operable NSCLC

Subtypes in HER2-Positive Breast Cancer Reveal a Prognostic Predictor

A Re-evaluation of KRAS Mutational "Hotspots"

VeriStrat Identifies Patients Likely to Respond to Erlotinib

[Click HERE to read more](#)



Regulatory

FDA Approves PROVENGE for the Treatment of Advanced Prostate Cancer

Tarceva Received Approval in EU for Maintenance Use in Advanced NSCLC

[Click HERE to read more](#)

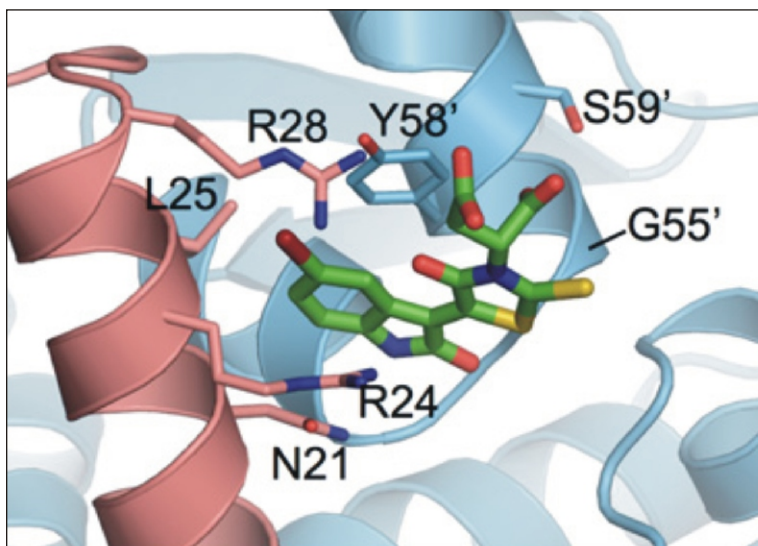


Spotlight Report

A Small-Molecule Inhibitor of BCL6 Kills DLBCL Cells *In Vitro* and *In Vivo*

Personalized cancer medicine offers the hope that by identifying cancer-causing mutations in critical regulatory genes, one can target these mutant proteins to cure cancer while limiting the side effects. As these proteins usually mediate their actions through extensive protein interaction surfaces, they have been considered non-amenable to targeting with small molecules. Over the last decade small-molecule inhibitors have been identified for an increasing number of protein-protein interactions and these transcriptional repressors usually mediate their effects on gene expression through recruitment of cofactors that either enzymatically modify the chromatin structure of target genes or serve as adaptors for such proteins. A major roadblock has been the inability to find specific, bioavailable small-molecule inhibitors of non-enzymatic proteins, especially oncogenic transcription factors.

Molecular Interactions between 79-6 and the BCL6 BTB Domain



Cancer Cell, 17, April 13, 2010

In a recent study published in *Cancer Cell*, Cerchetti *et al.* identified a small-molecule inhibitor of transcriptional repressor protein interactions for the most common form of diffuse large B cell lymphoma (DLBCL). BCL6, an oncogenic transcriptional repressor, is responsible for the majority (4070%) of this malignancy. Oncogenic over-expression of BCL6, whether via chromosomal translocation, promoter mutation, or gene amplification, permits continued B progenitor cell proliferation and acquisition of additional mutations, leading to the formation of an aggressive B cell lymphoma. Its depletion or blockade potently kills DLBCL cells, making BCL6 a critical therapeutic target.



**Spotlight
Report**
(Cont'd)

The researchers, using an integrated biochemical and computational structural analysis of BCL6, identified a pocket within the BTB repression domain that is required for recruitment of the SMRT co-repressor that links BCL6 to histone deacetylases to repress transcription. Computer modeling allowed the identification of a set of 1000 small molecules predicted to bind the target pocket and from among these, 100 compounds were then screened for their ability to block BCL6-mediated transcriptional repression. A lead compound, "79-6," was identified that reproducibly inhibited BCL6. 79-6 appears to selectively inhibit BCL6 because it did not affect transcription repression caused by several other BTB-containing proteins. The addition of 79-6 to DLBCL cell lines reactivated BCL6-regulated genes only in DLBCLs expressing BCL6, but had no effect on DLBCL lines that did not express BCL-6. This effect translated into 79-6 specifically inducing apoptosis in BCL6-dependent DLBCLs transplanted into SCID mice, but not in BCL6-independent tumors. Only minor toxicities (mild leucopenia) were identified in mice administered many rounds of the drug. This work represents one of the few true examples of transcriptional therapy, and this type of targeted transcriptional inhibition, via structures to fit small molecules into critical motifs, is a model for how other high-value cancer targets might be attacked.

Source: Cancer Cell



Business News

Astellas Pharma to Acquire OSI Pharmaceuticals

Astellas Pharma and OSI Pharmaceuticals, a biotechnology company primarily focused on the discovery, development and commercialization of molecular targeted therapies addressing medical needs in oncology, diabetes and obesity, announced that they have entered into a definitive merger agreement under which Astellas will acquire OSI. The Boards of Directors of both companies have unanimously approved the merger. The all-cash transaction is valued at \$4.0 billion. The combined company will create a world-class oncology platform supporting Astellas's stated growth strategy of becoming a global category leader in oncology. OSI commercializes Tarceva (erlotinib), a leading cancer medication.

Masafumi Nogimori, president and CEO of Astellas, said, "The merger with OSI provides Astellas with a top-tier oncology platform in the US and an expanded product portfolio and pipelines. In addition to Tarceva, we are pleased to add its oncology infrastructure, discovery platform, expanded pipelines and talent base to our existing businesses. We look forward to working together with our OSI colleagues to grow the combined business and realize our shared goal of improving the health of the people around the world every day."

Source: Astellas Pharma

BI and Micromet Announce Global Collaboration for MM BiTE Antibody

Boehringer Ingelheim (BI) and Micromet announced that they have entered into a collaboration agreement for the research, development, and commercialization of a new BiTE antibody for the treatment of multiple myeloma. BiTE antibodies are designed to direct the body's cytotoxic T cells against tumor cells, and represent a new therapeutic approach to cancer therapy.

Under the terms of the agreement, BI will pay Micromet an upfront cash payment of €5M. Micromet will be eligible to receive development and regulatory milestone payments of up to €50M and tiered low double-digit royalties on product sales outside the US. In the US, Micromet and BI will jointly co-promote the BiTE antibody with commercial terms commensurate with a profit split. Micromet will be responsible for the discovery of the BiTE antibody and will jointly conduct further pre-clinical studies with BI. BI will be responsible for all manufacturing activities, clinical development, and worldwide commercialization subject to Micromet's co-promotion right in the US.

Source: Boehringer Ingelheim



**Business
News**
(Cont'd)

Array BioPharma and Novartis Partner for Development of ARRY-162

Array BioPharma has entered into an agreement with Novartis for the worldwide development of a small-molecule MEK inhibitor, ARRY-162, which is currently in a Phase I trial designed to determine the maximum tolerated dose and evaluate safety, pharmacokinetics, and pharmacodynamics of ARRY-162 in advanced cancer patients with solid tumors. Array has initiated an expansion phase of this trial initially in biliary tract cancer patients.

Under the terms of the agreement, Array will initially receive \$45M consisting of an upfront and milestone payment and is eligible to receive an additional \$422M if certain clinical, regulatory, and commercial milestones are achieved. In addition, Array plans to co-develop ARRY-162 in one or more specific indications and fund a portion of development costs. The agreement provides Array with double-digit royalties on sales of approved drugs outside of the US, with a significantly higher royalty rate for US sales provided that the company meets its co-funding obligations.

Source: Array BioPharma

Peregrine and Stason Enter into Agreement for Innovative TNT Technologies

Peregrine Pharmaceuticals and Stason Pharmaceuticals announced agreements granting Stason certain exclusive development and commercialization rights to Peregrine's tumor necrosis therapy (TNT) technologies. TNT technologies use monoclonal antibodies to target intracellular tumor antigens in necrotic tissues. Peregrine's lead TNT product Cotara is a monoclonal antibody conjugated with a radioisotope Iodine-131. Cotara is currently being evaluated in a Phase II clinical trial in the US and India for the treatment of patients with glioblastoma multiforme.

Under the terms of the agreements, Stason is acquiring exclusive rights from Peregrine for its TNT technologies in certain Asia-Pacific Economic Cooperation (APEC) countries. Peregrine has retained exclusive rights to its TNT technologies in the US, EU, and other select countries internationally. The agreements also include certain nonexclusive licenses for Peregrine's proprietary radiolabeling technologies and its fully human NHS76 TNT antibody to enable and accelerate Stason's development of TNT products. Peregrine will receive upfront fees, annual fees, and milestone payments from Stason over the term of the agreements, as well as double-digit royalty payments on net sales. Upon successful commercialization of a product and payment of predetermined royalties to Peregrine within the first 7 years of this agreement, Stason will have a right to negotiate with Peregrine for further expansion worldwide. If commercialization is not achieved within the first 7 years, Stason will lose exclusivity to its APEC territories.

Source: Peregrine Pharmaceuticals

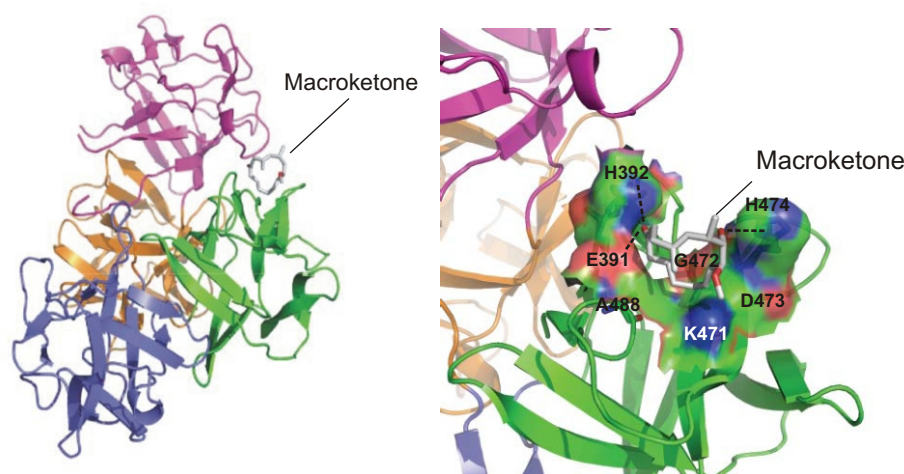


Research Highlight

Migrastatin Analogues Target Fascin to Block Tumor Metastasis

Tumor metastasis is the primary cause of death in cancer patients. Migrastatin is a natural product secreted by *Streptomyces*, and synthesized migrastatin analogs such as macroketone are potent inhibitors of metastatic tumor cell migration, invasion and metastasis. In a recent study reported in *Nature*, Lin Chen *et al.* elucidate the mechanism involved and show that these migrastatin analogues target and inhibit the activity of the actin bundling protein, fascin, which is critical to cell movement.

Overall Structure of Fascin and Macroketone Complex



Nature, 464, April 15, 2010

In order for a cancer cell to leave a primary tumor, fascin bundles actin filaments together like a thick finger and the front edge of this finger creeps forward and pulls along the rear of the cell. Migrastatin analogs bind to individual fascin, preventing the actin fibers from adhering to each other and forming the pushing leading edge. As individual actin fibers are too soft when they are not bundled together, the cell is unable to move. The agent did not stop the cancer cells implanted into the animals from forming tumors or from growing, but it completely prevented tumor cells from spreading, compared with control animals. Even when given after tumors are formed, most cancer spread was blocked. Fascin is overexpressed in metastatic tumor cells but is only expressed at a very low level in normal epithelial cells, thus a treatment that attacks fascin will have comparatively little effect on normal cells, unlike traditional chemotherapy that attacks all dividing cells. Another key finding reported by the workers was the X-ray crystal structures of fascin and of the complex of fascin and migrastatin analogs macroketone. The images showed precisely how macroketone snugly nestles into a pocket of fascin affecting the way it regulates actin filament bundling, and these molecular images provide an approach for rational drug design of other molecules inhibiting the function of fascin, the therapeutic target. These results suggest that actin cytoskeletal proteins, such as fascin, may present new molecular targets for cancer treatment in a manner similar to the microtubule protein tubulin.

Source: *Nature*

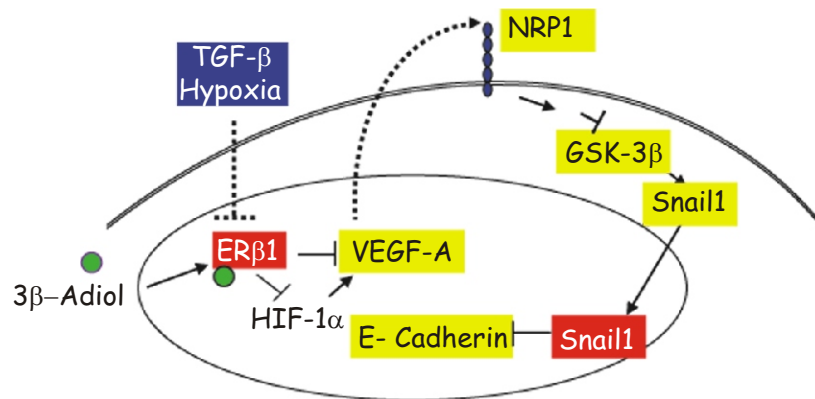


Research Highlight
(Cont'd)

ERβ Impedes Prostate Cancer EMT: Implications for Gleason Grading

The Gleason grading system for prostate cancer is based on the degree of histological differentiation, and it is valuable for assessing prognosis and choice of therapy. High Gleason grade prostate carcinomas are aggressive, poorly differentiated tumors that exhibit diminished estrogen receptor β (ERβ) expression. Mak *et al.* in *Cancer Cell* described a signaling pathway involving ERβ that determines whether prostate carcinoma cells maintain an epithelial phenotype or undergo epithelial-mesenchymal transition (EMT), suggesting that ERβ would have a prognostic or therapeutic value. They reported that loss of ERβ, which distinguishes high from low Gleason grade tumors, is associated with the expression of an EMT program of dedifferentiation that involves HIF-1 and VEGF/neuropilin signaling. A key function of ERβ and its specific ligand 5α -androstane-3β, 17β-diol (3β-adiol) is to maintain an epithelial phenotype and repress mesenchymal characteristics in prostate carcinoma. Stimuli (TGF-β and hypoxia) that induce an EMT diminish ERβ expression, and loss of ERβ is sufficient to promote an EMT. The mechanism involves ERβ-mediated destabilization of HIF-1α and transcriptional repression of VEGF-A. The VEGF-A receptor neuropilin-1 drives the EMT by promoting Snail1 nuclear localization. Importantly, this mechanism is manifested in high Gleason grade cancers, which exhibit significantly more HIF-1α and VEGF expression, and Snail1 nuclear localization compared to low Gleason grade cancers.

Regulation of EMT by ERβ



Cancer Cell, 17, April 13, 2010

This study raises the possibility that measurement of ERβ and EMT markers will help to subclassify patients with intermediate Gleason scores into groups with a high or low risk of progression, and hence, guide therapeutic decision making. It also suggests that drugs that modulate ERβ, or its downstream effectors such as HIF, VEGF, neuropilin-1, and AKT, could favorably alter the natural history of this disease. These findings should facilitate our understanding of the mechanisms responsible for the aggressive behavior exhibited by these high-grade cancers and the development of effective methods for their therapeutic intervention.

Source: *Cancer Cell*



**Research
Highlight**
(Cont'd)

Chemoprevention of Colorectal Cancer by Targeting APC-deficient Cells for Apoptosis

Cancer chemoprevention uses natural, synthetic, or biological substances to reverse, suppress, or prevent either the initial phase of carcinogenesis or the progression of neoplastic cells to cancer. However, the broad application of chemoprevention is compromised at present by limited effectiveness and potential toxicity. To overcome these challenges, Zhang *et al.* in a study published in *Nature* report a new chemoprevention approach that specifically targets premalignant tumor cells for apoptosis.

It is known that the membrane-bound tumor necrosis factor-related ligand TRAIL (also called TNFSF10 and Apo2L) induces apoptosis in cancer cells but not in normal cells. With a view to develop a way of specifically targeting premalignant tumor cells for apoptosis, the researchers report that in a C57BL/6J-ApcMin/J (ApcMin) mouse model, a combination of TRAIL and all-trans-retinyl acetate (RAc) causes premalignant intestinal polyp or adenoma cells lacking the APC (adenomatous polyposis coli) gene to undergo apoptosis. Normal cells appear unaffected by the treatment. A deficiency in the adenomatous polyposis coli (APC) gene and subsequent activation of β -catenin lead to the repression of cellular caspase-8 inhibitor c-FLIP (also known as CFLAR) expression through the activation of c-Myc. All-trans-retinyl acetate (RAc) independently upregulates tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) death receptors and suppresses decoy receptors. Thus, the combination of TRAIL and RAc induces apoptosis in APC-deficient premalignant cells without affecting normal cells *in vitro*. In addition, investigators showed that a short-term and noncontinuous TRAIL and RAc treatment induces apoptosis specifically in intestinal polyps, strongly inhibit tumor growth, and prolongs survival in multiple intestinal neoplasms mice. They also demonstrated that TRAIL and RAc induce significant cell death in human colon polyps, providing a potentially selective approach for colorectal cancer chemoprevention by targeting APC-deficient cells for apoptosis. The therapy has the advantage of requiring short, intermittent treatment cycles rather than long-term exposure, and it could prove useful in preventing human colon cancer.

Source: Nature



Clinical Development

Pfizer Discontinues Phase III Trial of Sutent in Advanced Hepatocellular Carcinoma

Pfizer has halted a Phase III drug trial, announcing that Sutent (Sunitinib) had failed because of a high rate of serious events in liver cancer patients taking doses of the medicine. Sutent, which recorded nearly \$1 billion in sales last year, has received the FDA approval for use in people with advanced kidney and stomach cancer, and Pfizer continues testing the drug on a variety of other cancers. In March 2010, Pfizer stopped two late-stage studies of Sutent, known generically as sunitinib malate, saying it did not help patients with advanced breast cancer.

The most recent Sutent trial stoppage occurred after an independent Data Monitoring Committee determined that the drug led to an increase in serious adverse events when compared to standard liver cancer therapy using Bayer's Nexavar treatment. In addition, Sutent did not demonstrate any significant difference in overall survival rates compared with Nexavar, according to a statement from Pfizer.

Source: Pfizer

Mesupron Confirm Impressive Increase in OS of Patients with Pancreatic Cancer

WILEX AG announced that a clinical Phase II combination trial with an oral drug candidate Mesupron, an urokinase-type plasminogen activator inhibitor, in pancreatic cancer patients has been completed successfully. Final analysis confirms preliminary data published in September 2009, which demonstrated an improvement in tumor response and increase in overall survival (OS). The results will be announced at the annual meeting of the American Society of Clinical Oncology (ASCO), which will take place from June 4 to 8, 2010, in Chicago, US.

In the completed Phase II trial, patients with locally advanced, inoperable, nonmetastatic pancreatic cancer were treated with Mesupron, together with the chemotherapeutic Gemcitabine. The aim of Mesupron is to inhibit the urokinase plasminogen activator enzyme system (uPA), which plays a key role in the growth and spread of different malignant tumors. Mesupron is the first uPA inhibitor worldwide in clinical development and has shown positive activity in cancer patients in a Phase II trial. As previously demonstrated in the eight completed Phase I trials, Mesupron proved to be safe and well tolerated.

Source: Willex

Celator Announces Positive Data from Phase II Study of CPX-351 in AML

Celator Pharmaceuticals announced positive results from its Phase II study of CPX-351, a DNA topoisomerase I inhibitor, in patients, 60-75 years of age, with untreated acute myeloid leukemia (AML). The primary endpoint of the study, the rate of patients achieving a complete remission (CR) with a CPX-351 (Cytarabine: Daunorubicin) liposome injection compared to a "7+3" regimen (7 days for cytarabine and 3 days for daunorubicin), achieved statistical significance. In addition, there was a reduction in the 30- and 60-day mortality with CPX-351 versus the "7+3" regimen.

CPX-351 represents a new approach to developing combinations of drugs in which drug molar ratios with synergistic anti-tumor activity are encapsulated in a drug delivery vehicle to maintain the desired ratio following administration. CPX-351 has been granted the orphan drug status by the FDA for the treatment of AML.

The multicenter, randomized, open-label trial enrolled 126 patients. The control arm, cytarabine plus daunorubicin, has been the SOC for treating patients with AML for more than 30 years. The primary endpoint of the study was a comparison of complete remission rates which include CR and CR with an incomplete recovery, to a specified level of neutrophils and/or platelets (CRi). Both CR and CRi result in patients becoming leukemia-free. The secondary endpoints of the study include duration of CR, event-free survival, 12-month survival, and the rate of patients going on to receive stem cell transplantation.

Source: Celator Pharmaceuticals



Clinical Development (Cont'd)

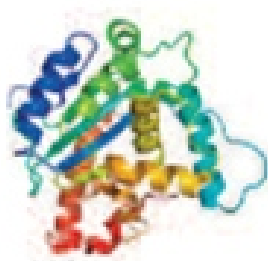
Allovetin-7 Achieves Median Survival in Phase II Melanoma Trial

Vical announced updated data from the company's Phase II trial of high-dose (2 mg) Allovetin-7 in patients with metastatic melanoma. The trial was a single-arm, open-label study in which 127 chemo-refractory or chemo-intolerant patients were treated with high-dose Allovetin-7. Allovetin-7 is a novel gene-based immunotherapeutic with a unique mechanism of action that is fundamentally different from currently approved treatments, and has the potential to be the first new primary treatment approved for metastatic melanoma in nearly 20 years.

The median age of patients enrolled in the study was 60 years, and patients as old as 98 years were treated with Allovetin-7, yet there were no treatment-related Grade 3 or 4 adverse events and no withdrawals from the trial for tolerability. The overall response rate (ORR) for the 127 patients receiving the high-dose treatment was 11.8%, with 4 complete responders and 11 partial responders. The median duration of response (MDR) was 13.8 months, ranging from a minimum of 6 months to a maximum of 66 months and still ongoing. Median survival was 18.8 months. These data compare favorably against historical controls from other studies in metastatic melanoma.

Findings from the Phase II trial were incorporated into the design of a Phase III pivotal trial through a Special Protocol Assessment agreement (SPA) with the FDA. The trial is evaluating Allovetin-7 as 1st line therapy in patients with Stage III or IV recurrent metastatic melanoma.

Source: Vical



Biomarkers

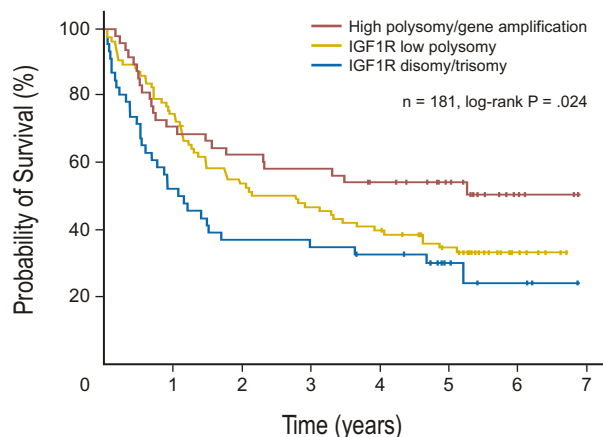
IGF1R Gene Copy Number is Associated with Survival in Operable NSCLC

Identification of biomarkers for selecting patients who are most likely to derive clinical benefit from insulin-like growth factor receptor 1 (IGF1R) inhibitors is needed. An important initial step in predictive marker discovery for IGF pathway inhibitors is a descriptive characterization of the IGF1R gene and protein aberrations in tumors from patients with NSCLC.

In a study published in *JCO*, Hirsch *et al.* studied 189 patients with NSCLC who underwent curative pulmonary resection. Investigators used large-core tissue microarray with sufficient amount of tumor tissue for adequate protein and gene copy number assessment. The expression of IGF1R was evaluated by immunohistochemistry (IHC) using two antibodies, the Ventana G11 antibody and the Novus anti-IGF1R antibody. The pattern of IHC staining differed between the two antibodies. Importantly, the results obtained with the Ventana G11 antibody correlated significantly with the mRNA expression whereas this correlation was not observed for the Novus antibody, suggesting that the former reagent provides a more accurate method for detection of the IGF1R protein. Lack of association between anti-IGF1R Novus antibody staining and IGF1R mRNA expression is an indirect indication of poor specificity of this antibody. The study further showed that IGF1R protein expression and mRNA expression were higher in squamous cell carcinomas than in other histologies. IGF1R protein and gene expression did not associate with survival, whereas a high IGF1R gene copy number was associated with better prognosis in surgically resected NSCLC. Patients with tumors harboring high IGF1R gene copy numbers (amplification and high polysomy) had higher 3-year survival compared with tumors with low polysomy and trisomy/disomy. Future studies would determine if any of these tests would predict sensitivity to IGF1R inhibitors and would elucidate the prognostic value of the IGF1R gene copy number in NSCLC.

Source: *JCO*

OS according to IGF1R Gene Copy Number



JCO, 28, May 1, 2010



Biomarkers (Cont'd)

Subtypes in HER2-positive Breast Cancer Reveal a Prognostic Predictor

HER2 has emerged as an important prognostic breast cancer biomarker, but HER2-positive disease remains a clinical challenge because of variations in prognosis and response to therapy. The molecular mechanisms connecting HER2 activity to aggressive disease remain elusive, and most prognostic gene expression signatures classify HER2-positive breast cancers uniformly as having poor outcome.

Aiming to further stratify HER2-positive breast cancers, Staff *et al.* used gene expression and genomic analysis to characterize a set of 58 HER-2 amplified tumors from patients who did not receive adjuvant trastuzumab. The results published in *JCO* explained that gene expression profiling identified three clusters of HER2-positive tumors with distinct biologic characteristics independent of conventional biomarkers such as ER, histologic grade, tumor size, and LN status. One cluster (cluster 2) had considerably worse clinical outcome than the other two, and based on the gene expression clustering, the researchers constructed a 158-gene prognostic predictor (HDPP) that separated these HER2-positive tumors into two groups with significantly different prognoses. HDPP was comprehensively validated for prognosis in HER2-overexpressing tumors from independent breast cancer data sets and identified a sizable subgroup with remarkably good OS and/or DMFS. HDPP was a strong and independent prognostic factor in HER2-overexpressing tumors, both overall and in subgroups based on stage, Histologic grade, and ER status. Notably, HDPP distinguished a large subgroup of ER-negative/HER2-positive tumors with remarkably good DMFS. This gene signature may become a tool for improved prognostication of outcome and selection of patients for new treatment regimens.

Source: JCO

A Re-evaluation of KRAS Mutational "Hotspots"

A KRAS mutational status is known to be both a prognostic and predictive biomarker in patients with colorectal cancer. Specifically, mutations in "hotspot" codons of the KRAS gene are associated with more aggressive disease in these individuals and with a poor response to EGFR inhibitors. However, recent work from Smith *et al.* published in *Br. J. Cancer* might increase the clinical utility of this biomarker, as the authors have identified additional KRAS mutations that they recommend for inclusion in routine screening of KRAS mutational status in these patients.

The researchers screened the KRAS gene in 106 colorectal tumors and identified four additional KRAS mutations (Leu19Phe, Lys117Asn, Ala146Thr, and Arg164Gln), which were verified to be tumor-specific as they were not detected in genomic DNA from matched blood samples. The investigators noted that the Lys117Asn and Ala146Thr mutations conferred similar phenotypes *in vitro* to those mediated by mutations in the "hotspot" codons 12, 13 and 61, indicating the potential ability of these additional mutations to alter the phenotype of patients with colorectal cancer, and therefore their response to chemotherapy. Furthermore, the Ala146Thr mutation was found in 6.5% of the tumors, none of which had additional KRAS mutations in the "hotspot" codons, and the authors stress that current screening protocols are therefore unable to detect all significant KRAS mutations. In recent times, personalized medicine is receiving increased interest and resources. Accordingly, future personalized patient treatments will be decided on the basis of both patient and tumor genotype and phenotype. The need to stratify the treatment of colorectal cancer with chemotherapy, based on whether or not KRAS mutations are present, exemplifies this.

Source: Br. J. Cancer



Biomarkers (Cont'd)

VeriStrat Identifies Patients Likely to Respond to Erlotinib

Results from the VeriStrat biomarker analysis of a multicenter Phase III trial showed that the VeriStrat test identified patients who were likely to have a survival benefit from treatment with erlotinib, a commonly prescribed oral therapy for advanced NSCLC. VeriStrat is a pretreatment, serum test for patients with advanced NSCLC. The study retrospectively applied the VeriStrat proteomic analysis to a subset of the patient population from a study BR.21, a Phase III, multicenter trial of erlotinib versus placebo in previously treated patients with NSCLC. The VeriStrat analysis involved 441 of the 729 patients from the BR.21 study and classified patients as either "VeriStrat Good" or "VeriStrat Poor" based on a proteomic profile. Following treatment with erlotinib, patients in the group classified as VeriStrat Good had a median survival of 10.5 months compared with 4.0 months in the group classified as VeriStrat Poor. VeriStrat Good patients also had a significantly higher tumor response rate than VeriStrat Poor patients (11.5% vs. 1.0%, $p = 0.002$).

The era of personalized medicine requires that we can have biomarkers to select therapy, that these can be easily obtained, and that the results are available in a short time frame. Analysis of a serum protein profile such as VeriStrat meets these criteria. Several therapies such as erlotinib, docetaxel or pemetrexed are approved in either the maintenance setting, the 2nd or 3rd line setting or both and it has been difficult to determine which of these therapies might be the best for an individual, especially an individual without an EGFR mutation. The data presented suggest that a positive VeriStrat test can pick those patients most likely to benefit from erlotinib.

Source: Biodesix



Regulatory



FDA Approves PROVENGE for the Treatment of Advanced Prostate Cancer

Dendreon Corporation announced that the FDA has approved PROVENGE (sipuleucel-T), an autologous cellular immunotherapy, for the treatment of asymptomatic or minimally symptomatic metastatic, castrate-resistant (hormone-refractory) prostate cancer (CRPC). PROVENGE is designed to induce an immune response against prostatic acid phosphatase (PAP), an antigen expressed in most prostate cancers, and is the first in a new therapeutic class known as autologous cellular immunotherapies.

Three Phase III studies involving 737 patients were submitted to the FDA to support licensure. The pivotal study was the Phase III IMPACT (IMmunotherapy for Prostate AdenoCarcinoma Treatment) trial (D9902B), a 512-patient, multicenter, randomized, double blinded, placebo-controlled study that evaluated men with asymptomatic or minimally symptomatic, metastatic CRPC. PROVENGE extended median survival beyond 2-years, demonstrating a median improvement of 4.1 months compared to the control group (25.8 months vs 21.7 months). Overall, PROVENGE reduced the risk of death by 22.5% compared to the control group. Results from a similarly designed Study D9901 in asymptomatic metastatic CRPC also demonstrated a survival advantage of similar clinical magnitude as the IMPACT study.

Source: Dendreon Corporation

Tarceva Received Approval in EU for Maintenance Use in Advanced NSCLC

OSI Pharmaceuticals announced that its international partner for Tarceva (erlotinib), Roche, received approval from the European Commission for Tarceva as a monotherapy maintenance treatment in patients with advanced NSCLC whose disease remains stable after a platinum-based initial chemotherapy.

The EU approval was based on data from the pivotal Phase III SATURN study. SATURN was an international, placebo-controlled, randomized, double-blinded study that enrolled 889 patients with advanced NSCLC. Patients were treated with 4 cycles of the standard 1st platinum-based chemotherapy and then randomized to Tarceva or placebo if the cancer did not progress. SATURN showed that Tarceva significantly extended OS and significantly improved progression-free survival in a broad patient population, including squamous and non-squamous histology, compared with placebo. On April 16, 2010, OSI announced that the FDA approved Tarceva as a maintenance treatment for patients with locally advanced or NSCLC whose disease has not progressed after 4 cycles of platinum-based 1st line chemotherapy.

Source: OSI Pharmaceuticals