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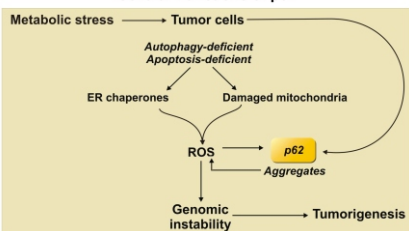
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INTELLIGENT INSIGHTS. SMART RESULT

Cellular Functions of p62



Cell, 137, June 12, 2009

In the Spotlight:

Autophagy Suppresses Tumorigenesis through Elimination of p62

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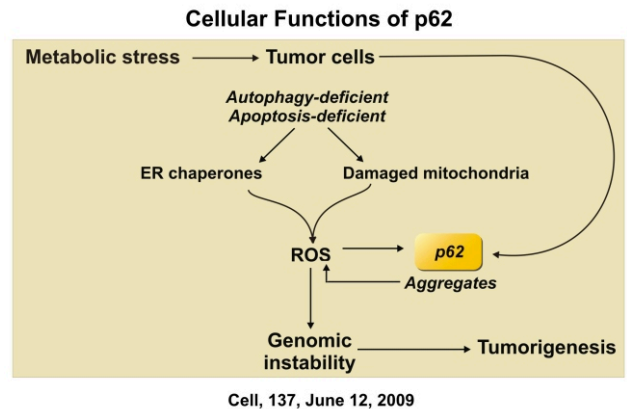
Spotlight Report

Autophagy Suppresses Tumorigenesis through Elimination of p62

Autophagy is generally considered a survival pathway in cells undergoing nutrient deprivation; however, allelic loss of the essential autophagy gene beclin1 occurs in human tumors and favors carcinogenesis in mice suggesting that autophagy is a tumor-suppression mechanism. In a study published in *Cell*, Mathew et al. provide evidence that impaired autophagy leads to p62 accumulation, thereby promoting tumorigenesis. In autophagy deficient and apoptosis-incompetent tumor cells, metabolic stress leads to the accumulation of p62, elevated expression of endoplasmic reticulum (ER) chaperones, damaged mitochondria, and reactive oxygen species (ROS). This increase in p62 levels is critical for tumorigenesis, as overexpression of p62 in the cell model leads to increased tumor volume in mouse xenograft experiments.

Investigators show that when cells with impairment in both apoptosis and autophagy are metabolically stressed, the accumulation of p62 leads to enhanced tumorigenicity through an undefined mechanism involving increased aneuploidy. These observations place p62 as the missing link between deficient autophagy and increased tumorigenesis through the control of genome instability. The increased ROS production in these cells might be responsible, at least in part, for the induction of p62 expression. p62 overexpression then contributes to additional ROS production as part of an amplifying loop, thereby promoting genome instability. Sustained p62 expression resulting from autophagy defects was sufficient to alter NF- κ B regulation and gene expression and to promote tumorigenesis. These findings place p62 at critical decision points that control cell death and survival and suggest that inducing clearance of p62 by promoting autophagy may be strategy for cancer prevention.

Source: *Cell*





Business News

Calando Enters into License Agreement with Cerulean

Arrowhead Research Corporation announced that its subsidiary, Calando Pharmaceuticals, has entered into a worldwide license agreement with Cerulean Pharma for Calando's drug delivery platform, Cyclosert, and associated clinical stage anti-cancer drug, IT-101, a DNA topoisomerase I inhibitors. Under the terms of the agreement, Cerulean made an upfront payment of \$2.4 million to Calando and will make development milestone payments of up to \$2.75 million if IT-101 progresses through clinical trials and receives marketing approval. If approved, Calando is also entitled to receive up to an additional \$30 million in sales milestone payments, plus royalties on net sales.

As a platform delivery system, Cyclosert may be utilized to generate a large number of new drugs in addition to IT-101. For each new drug candidate that Cerulean is able to bring to market utilizing the Cyclosert system, Calando will be entitled to \$3 million in development milestone payments. Once these products reach the market, Calando could potentially receive an additional \$15 million in sales milestone payments, plus royalties on net sales.

Source: Arrowhead Research Corporation

Morphotek Announces a Research Collaboration Agreement with Synageva

Morphotek, a subsidiary of Eisai Corporation of North America, announced a research collaboration agreement with Synageva BioPharma to express and develop therapeutic monoclonal antibodies for the potential treatment of various forms of cancer and infectious diseases. Under the terms of the agreement, Synageva will use its proprietary Synageva Expression Platform (SEP) technology and its expertise to produce and develop a therapeutic monoclonal antibody. SEP is an integrated platform of proprietary systems for protein production, processing and purification.

"We have a rich pipeline of antibody products such as MORAb-003, or farletuzumab, for ovarian cancer in Phase III, MORAb-009 for pancreatic cancer in Phase II and MORAb-004 that is pan-cancer specific in Phase I. We are always exploring new ways that may enhance the manufacturing process for our antibody products as a means to fulfill Eisai's human health care mission," stated Philip M. Sass, Chief Operating Officer, Morphotek.

Source: Morphotek

Bioniche Life Sciences and Endo Sign Licensing Agreement for Urocidin

Bioniche Life Sciences and Endo Pharmaceuticals jointly announced that Endo has licensed from Bioniche the exclusive rights to develop and market Urocidin in the US with an option for global rights. Urocidin is a patented formulation of Mycobacterial Cell Wall-DNA Complex developed by Bioniche for the treatment of non-muscle-invasive bladder cancer that is currently undergoing Phase III clinical testing. Under the agreement signed by both companies, Endo will pay Bioniche an up-front cash payment of \$20 million and the potential for up to \$110 million in additional payments linked to the achievement of future clinical, regulatory, and commercial milestones. In addition, Bioniche will manufacture the product and receive a transfer price for supply.

The first of two Phase III FDA-approved and Fast Track designated registration trials with Urocidin is nearing complete enrolment. In this trial, patients with non-muscle-invasive bladder cancer whose cancer is specifically refractory to current therapy are receiving Urocidin in an open label trial. Recruitment of 105 evaluable patients was completed in March, 2009. Data from the full cohort of evaluable patients from this trial, coupled with additional safety information to be collected from a second registration trial, will be used to support regulatory submissions under the FDA's Accelerated Approval program.

Source: Bioniche Life Sciences



**Business
News**
(Cont'd)

Debiopharm and Moffitt Sign Development and Commercialization Agreement

Debiopharm Group, a Swiss-based global biopharmaceutical group of companies, and Moffitt Cancer Center (Moffitt), announced the signing of an exclusive license agreement for the development and commercialization of Debio 0928, a small molecule in early preclinical development that inhibits the protein-protein interaction between Raf-1 and retinoblastoma protein (Rb). Rb acts as a barrier to cell division and proliferation. When Raf-1 physically interacts with Rb, it triggers a cascade of signals that eventually overcomes this barrier, thus inducing cellular proliferation. By preventing the interaction between Raf-1 and Rb and blocking the cell cycle, Debio 0928 creates a new strategy in the fight against cancer and is thus a potentially promising novel anti-tumor drug. Under the terms of the agreement, Debiopharm shall pay Moffitt an up-front fee, as well as predefined advanced milestone payments during the development of Debio 0928.

Source: Debiopharm



Research Highlight

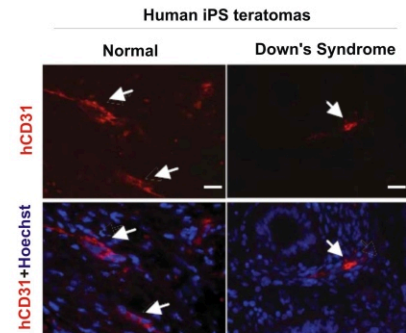
Role of DSCR1 in Down's Syndrome Suppression of Tumor Growth

For decades, scientists have known that people with Down's syndrome get certain types of cancer at dramatically lower rates than normal. In a recent report in *Nature*, Ryeom et al. have identified that having an extra copy of Down's syndrome candidate region 1 (*DSCR1*), a chromosome 21 gene present in triplicate in individuals with DS, is sufficient to slow cancer cell growth by preventing the tumor from developing its own blood supply.

The authors confirmed that Down's syndrome in mice limits tumor growth using transplantable tumor models - Lewis lung carcinoma and melanoma. Notably, growth suppression correlated with lower microvessel density and lesser VEGF-mediated proliferation of endothelial cells. To extend these studies to human cells, induced pluripotent stem cells (iPS) were generated from individuals with and without Down's syndrome, and these cells were allowed to form teratomas in mice. Less tumor cell growth and lower blood microvessel density were evident in the tumors derived from iPS from individuals with Down's syndrome. The researchers also showed that *DSCR1* expression is increased in Down's syndrome tissues and mouse model (Ts65Dn). Furthermore, the modest increase in expression by a single extra transgenic copy of *DSCR1* is sufficient to confer significant suppression of tumor growth in mice, and that such resistance is a consequence of calcineurin-mediated suppression of tumor angiogenesis. The data implicates VEGF-calcineurin-NFAT (nuclear factor of activated T cells) as a critical signaling axis in endothelial cells and suggests that maximal suppression of calcineurin requires increased expression of *DSCR1*, along with another chromosome 21 gene *Dyrk1a*, to markedly diminish angiogenesis. The findings define a mechanism for the protective function of chromosome 21 in solid tumor growth, and also identify two new potential targets (*DSCR1* and *DYRK1A*) for therapeutic intervention in solid tumors.

Source: *Nature*

Reduced Angiogenesis in Tumors from Down's Syndrome as seen by Human Anti - CD31 Immunofluorescence



Nature, 459, June 25, 2009

GOLPH3 Modulates mTOR Signaling

A hallmark feature of human cancer is its highly rearranged genome, manifesting as numerous copy-number amplifications and deletions detectable by genome-wide array-based comparative genome hybridization (array-CGH) profiling. A recent report in *Nature* by Scott et al, combined integrative genomics with clinicopathological and functional validation to identify a Golgi-localizing protein, GOLPH3, as a new oncoprotein targeted for gene amplification at 5p13 in several solid tumor types, including lung (56%), ovarian (38%), breast (32%), prostate (37%) and melanoma (32%).

Gain- and loss-of-function studies in vitro and in vivo validated *GOLPH3* as a bonafide oncogene with potent transforming activity. Knockdown of *GOLPH3* by siRNA resulted in considerable loss of anchorage-independent growth in three human cancer cell lines with 5p13 amplification and high expression level. Physically, *GOLPH3* localizes to the trans-Golgi network and interacts with components of the retromer complex, which in yeast has been linked to target of rapamycin (TOR) signaling. Most notable among the *GOLPH3*-interacting proteins was VPS35, a highly conserved member of the cargo-recognition complex of the retromer. This data raise the possibility that *GOLPH3* might function with VPS35 and the retromer to regulate receptor recycling of key molecules, thereby influencing downstream signaling through mTOR. It was also shown that enhanced activation of mTOR signaling was the molecular basis for the oncogenic activity of *GOLPH3*, which regulated cell size, and altered the response to an mTOR inhibitor in vivo. The data in yeast and humans establishes *GOLPH3* as a new oncogene that is commonly targeted for amplification in human cancer, and confers increased sensitivity to rapamycin. Although the predictive value of *GOLPH3* as a biomarker remains to be demonstrated, there is a possibility that *GOLPH3* expression level or gene copy-number status may predict sensitivity to mTOR inhibitors.

Source: *Nature*



Research Highlight (Cont'd)

AGTR1 Overexpression Confers Sensitivity to Losartan in Breast Cancer

A central aim in cancer research is to identify genetic alterations directly involved in tumorigenesis and develop therapies to target them. Arul Chinnaiyan and colleagues combined computational/experimental approach to identify novel biomarkers for targeted therapy by searching genes with marked overexpression across a panel of breast cancer profiling studies comprising 3,200 microarray experiments. In addition to ERBB2, the most significant meta-outlier, they found AGTR1 (angiotensin II receptor type I) to be markedly overexpressed in 1020% of breast cancer cases across multiple patient cohorts.

Validation experiments including cancer outlier profile analysis and meta-analysis confirmed that AGTR1 is highly overexpressed, in several cases more than 100-fold. AGTR1 overexpression was restricted to estrogen receptor positive tumors and was mutually exclusive with ERBB2 overexpression. To determine the function of AGTR1 in breast cancer, Rhodes et al. used an adenovirus construct to overexpress AGTR1 in H16N2 and HME human mammary epithelial cell. It was found that overexpression of AGTR1 alone or on stimulation did not have effect on proliferation, where as overexpression of AGTR1 combined with angiotensin II stimulation significantly promoted cell invasion in both cell lines. This highly invasive phenotype was attenuated by losartan, an AGTR1 blocker that is approved for treating hypertension. Losartan also reduced tumor growth by 30% in AGTR1-positive breast cancer xenografts, suggesting that AGTR1 sensitizes tumors to growth inhibition on treatment with losartan. Taken together, these observations indicate that marked AGTR1 overexpression defines a subpopulation of ER-positive and ERBB2-negative breast cancers that may benefit from targeted therapy with AGTR1 antagonists. The study provides a rationale for a clinical trial that includes losartan in the treatment of breast cancer patients with AGTR1 positive tumors.

Source: PNAS

Hedgehog Signaling is Dispensable for Adult HSC Function

The role of hedgehog signaling as a driver of certain solid tumors is well established and receiving considerable translational development. Hedgehog signaling might also be important for the development of leukemia, potentially identifying additional patients that would benefit from anti-hedgehog therapy. Its role as an important regulator of hematopoietic homeostasis, however, raises concerns about toxicities from systemic administration of anti-hedgehog drugs. Two papers in *Cell Stem Cell* now alleviate these concerns, showing that hedgehog signaling is not critical for adult hematopoietic homeostasis or for the development of leukemias.

Hofmann et al. showed that loss of Hh signaling through conditional deletion of Smoothened (*Smo*) in the adult hematopoietic compartment had no effect on hematopoiesis including bone marrow cellularity, peripheral blood counts or stress response to serial 5-fluorouracil treatment, alleviating concerns about hematological toxicity from systemic inhibition of Hh signaling. Furthermore, pharmacologic inhibition of Hh signaling with a potent and selective small molecule antagonist had no substantive effect on hematopoiesis in the mouse. In addition, Hh signaling was not required for the development of MLL-AF9-mediated acute myeloid leukemia (AML). Gao et al. corroborated their results by showing conditional *Smo* deletion/overactivation had no significant effects on adult hematopoietic stem cell (HSC) self-renewal and function. Moreover, there was a lack of synergism between the Notch and Hh pathways in HSC function. Detailed genome-wide transcriptome analysis revealed that silencing of Hh signaling does not significantly alter the HSC-specific gene expression signature. Together, these data indicate that hedgehog signaling is not required for adult hematopoiesis or for the development of some types of leukemia suggesting that systemic administration of hedgehog antagonists is unlikely to result in hematological toxicity. Further, the Hh pathway may not be a compelling target in hematopoietic malignancies.

Source: Cell Stem Cell^{1,2}



Clinical Development

Phase III Trial of Sutent in Metastatic Colorectal Cancer Discontinued

Pfizer announced the discontinuation of the SUN 1122 Phase III trial that evaluated Sutent (sunitinib malate), an oral multi-kinase inhibitor, plus FOLFIRI (irinotecan plus infusional 5-fluorouracil and leucovorin) versus FOLFIRI alone for the first-line treatment of metastatic colorectal cancer (CRC). The independent Data Monitoring Committee (DMC) found that the addition of sunitinib to the chemotherapy regimen FOLFIRI would be unable to demonstrate a statistically significant improvement in the primary endpoint of progression-free survival (PFS) compared to FOLFIRI alone, in this study. No new safety issues were identified.

Pfizer has notified clinical trial investigators involved in the study and regulatory agencies of these findings. However, Pfizer Oncology is continuing to study the potential role of sunitinib in the treatment of various solid tumors including advanced NSCLC, advanced breast cancer, advanced hepatocellular carcinoma and advanced hormone-refractory prostate cancer, in Phase III trials. Sunitinib is currently approved for both gastrointestinal stromal tumors (GIST) after disease progression or intolerance to imatinib mesylate, and advanced / metastatic renal cell carcinoma (RCC) based on efficacy and safety data from large, randomized Phase III clinical trials.

Source: Pfizer

Cephalon Provides Clinical Update on Lestaurtinib in Relapsed AML

Cephalon, announced results from a pivotal clinical trial of lestaurtinib (CEP-701), a potent inhibitor of several tyrosine kinases including FLT3 and a Janus kinase (JAK2), in patients with relapsed acute myelogenous leukemia (AML) expressing FLT3 activating mutations. The study was designed to show the benefit of lestaurtinib in this patient population when given in sequence with standard induction chemotherapy compared to those treated with standard induction chemotherapy alone. An analysis of the study showed that patients who were treated with lestaurtinib showed similar rates of complete response and no increased benefit in overall survival, compared to those who received induction chemotherapy alone.

"We are disappointed that this study with lestaurtinib did not demonstrate a benefit for this patient population but we remain committed to oncology clinical research and developing innovative therapies for life-threatening diseases," said Dr. Lesley Russell, Executive Vice President and Chief Medical Officer at Cephalon.

Source: Cephalon

Phase II Study of Aflibercept in Ovarian Cancer Patients with Recurrent SMA

Sanofi-aventis and Regeneron Pharmaceuticals announced that advanced ovarian cancer patients with recurrent symptomatic malignant ascites (SMA) receiving aflibercept (VEGF Trap) in a randomized, placebo-controlled Phase II study experienced a statistically significant improvement in the primary study endpoint, mean time to first repeat paracentesis (removal of fluid from the abdominal cavity), versus placebo control. The study enrolled 55 patients with SMA, related to advanced ovarian cancer, who had failed a prior platinum-based chemotherapy regimen and who had also received chemotherapy treatment with either liposomal doxorubicin or topotecan.

Mean time to first repeat paracentesis following a baseline procedure was 55 days with aflibercept as compared to 23 days for patients receiving placebo. Time to first repeat paracentesis was defined as the number of days between study randomization and the first post-randomization paracentesis or, in cases where there was no repeat paracentesis, study withdrawal, death, or 6 months from randomization. The types and frequencies of adverse events reported with aflibercept in this study were generally consistent with those reported in clinical studies with other anti-VEGF therapies in advanced ovarian cancer patients.

Source: Sanofi-aventis



Clinical Development (Cont'd)

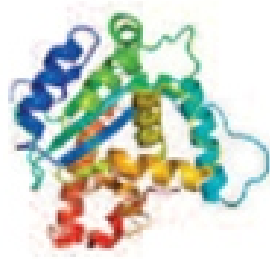
Progress Update for Pivotal Phase II Clinical Trial with Tamibarotene

CytRx Corporation provided a favorable progress update for its ongoing Phase II STAR-1 registration clinical trial evaluating the efficacy and safety of orally administered tamibarotene, as a third-line treatment for acute promyelocytic leukemia (APL). Tamibarotene is a synthetic retinoid compound specifically developed to overcome resistance to all-trans-retinoic acid (ATRA) therapy. The primary endpoint of the trial is to determine the rate of durable complete response for tamibarotene therapy when administered as a single agent to adult patients following treatment failure with all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO).

Of the 11 patients enrolled in the STAR-1 trial to date, 2 patients have achieved durable complete response and one has achieved morphologic leukemia-free state (MLFS), but withdrew from the trial to receive a bone marrow transplant before the durable complete response could be confirmed. One patient achieved a complete response, but did not maintain MLFS for the required 28 days to be considered a durable complete response. Another patient achieved a durable MLFS, but did not have the necessary increases in blood cells to be considered a durable complete response. "We are highly encouraged by the trial patients' response to tamibarotene, with five of the 11 APL patients, or 45%, achieving MLFS after failing on two other drug therapies," said Steven A. Kriegsman, CytRx President and CEO.

The FDA has granted Orphan Drug and Fast Track Designation for the use of tamibarotene in patients with relapsed or refractory APL. In addition, CytRx expects tamibarotene to be granted European orphan medicinal product designation for treatment of APL in the coming weeks. Tamibarotene is approved in Japan for use in relapsed or refractory APL.

Source: CytRx



Biomarkers

Exosome and DxS Partner to Develop Blood-based Cancer Tests

Exosome Diagnostics and DxS announced that they will collaborate on the development of blood based companion diagnostics for key cancer gene mutations, such as KRAS, BRAF and EGFR. The collaboration will use DxS' industry leading Scorpions real-time PCR Mutation Test Kits in conjunction with ExosomeDX's xOS technology which harvests high-quality nucleic acids from blood exosomes. Exosomes are small microvesicles shed by all solid tumors into blood. They contain virtually the entire cancer tumor transcriptome. In studies, ExosomeDX has identified most mRNA and miRNA in circulating tumor derived exosomes, all protected in the exosome lipid bi-layer from any blood-based RNase.

The collaboration will initially focus on developing blood-based measurement of KRAS, BRAF, EGFR and other key mutations for predicting patient response to targeted therapies. Blood based mutation measurement is particularly valuable in circumstances where tissue bioavailability is limited such as in lung, pancreatic and ovarian cancers. "Combining the ability to pull high-quality mutations from a simple blood draw with the unparalleled sensitivity and specificity of our Scorpion assays will provide our pharmaceutical and research customers with an ideal solution in personalized medicine," said Dr. Stephen Little, CEO Officer of DxS.

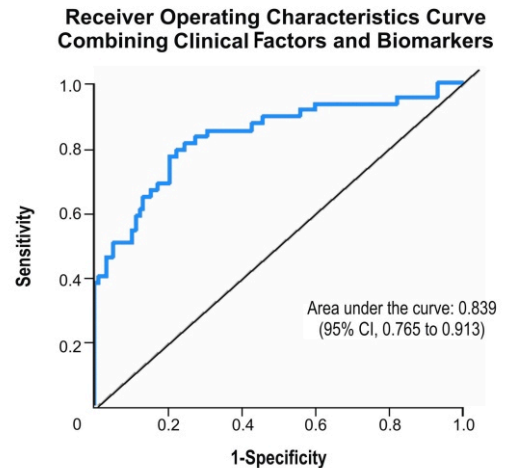
Source: Exosome Diagnostics

CTAP III: A Novel Blood Biomarker for Early Lung Cancer Detection (Fig 3)

Early detection and treatment of lung cancer is a promising strategy to reduce lung cancer mortality. However, there have been major hurdles in the discovery and validation of biomarkers for detection of preclinical lung cancer. In a study published in *JCO*, Yee and colleagues describe a novel approach to biomarker discovery that used the same subject as his/her own control to identify elevated proteins in the pulmonary venous effluent draining the tumor vascular bed compared to matched systemic arterial blood.

Initially, investigators paired pulmonary venous-radial arterial blood samples from 16 lung cancer patients and identified two candidate biomarkers, connective tissue-activating peptide III/neutrophil activating protein-2 (CTAP III/NAP-2) and haptoglobin. Both were higher in venous versus arterial blood. They verified their initial findings in 64-paired venous-arterial blood samples by immunoassay. In subsequent validation studies, elevated levels of CTAP III/NAP-2 and haptoglobin were confirmed in 28 pre- and postsurgical resection peripheral blood samples, two blinded sets of plasma from 149 participants in a lung cancer screening study (49 lung cancers and 100 controls), and in 266 participants from the National Heart, Lung, and Blood Institute Lung Health Study (45 lung cancers and 221 matched controls). CTAP III/NAP-2 levels decreased after tumor resection. Addition of age, smoking status, and forced expiratory volume in one second (FEV₁) to haptoglobin and CTAP III/ NAP-2 was found to improve the test performance to detect lung cancer in a high risk population not known to have lung cancer at the time of blood sampling (area under the curve, 0.84). Thus, the study underscores the importance of applying blood biomarkers not as a stand-alone test but as part of a multimodal lung cancer risk prediction model.

Source: *JCO*



JCO, 27, June 10, 2009



Biomarkers (Cont'd)

DEAR1: A Predictive Biomarker for Early-Onset Breast Cancer

Breast cancer in young women is more aggressive with higher rates of recurrence than breast cancers detected later in life. Little is known about the genetic pathways that underlie early-onset breast cancer. In a study published in *PLoS Medicine*, Lott et al. report the discovery of *DEAR1* (ductal epithelium associated RING Chromosome 1), a novel gene encoding a member of the TRIM (tripartite motif) subfamily of RING finger proteins such as BRCA1 and BRCA2, which have been implicated in early cancer development.

Graphical Representation of DEAR1 Exonic and Protein Structure



PLoS Medicine, 6, May 2009

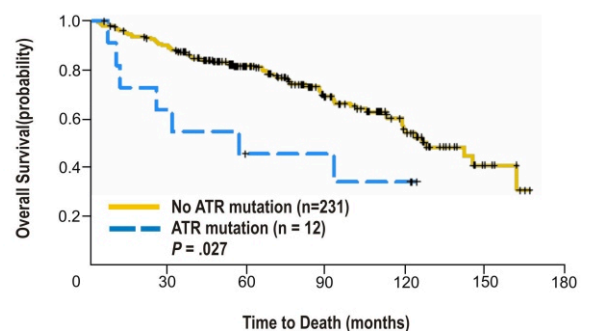
The researchers used "suppression subtractive hybridization" to identify *DEAR1* in human Chromosome 1 where loss of heterozygosity (LOH) frequently occurs. *DEAR1* expression was reduced or lost in several ductal carcinomas in situ and advanced breast cancers. Furthermore, many breast tumors carried *DEAR1* missense mutations or had lost both copies of *DEAR1*. To determine the function of *DEAR1*, the researchers replaced a normal copy of *DEAR1* into a breast cancer cell having mutated *DEAR1* and examined their growth in special 3-D cultures. The breast cancer cells without *DEAR1* grew rapidly without an organized structure while the cancer cells containing the copy of *DEAR1* formed structures that resembled normal breast acini. The researchers also silenced *DEAR1* expression in normal human mammary cells, and showed that without *DEAR1*, normal cells lost their ability to form proper acini. Finally, the researchers report that *DEAR1* expression (detected "immunohistochemically") was frequently lost in women having early-onset breast cancer and that this loss correlated with reduced local recurrence-free survival, strong family history of breast cancer and with poor outcome. Together, these observations identify *DEAR1* as an excellent predictive biomarker for early onset breast cancers.

Source: *PLoS Medicine*

ATR Mutation as a Biomarker in Endometrioid Endometrial Cancer

To date, the clinical utility of various clinical, surgical, and pathologic risk assessment models for patients with endometrial cancer remains suboptimal. Therefore, attention is being focused at identifying molecular signatures that could predict clinical outcomes and potentially guide the development of targeted therapies. Mutations in the DNA damage response gene *ATR* (exon 10 A10 mononucleotide repeat) have been previously described in endometrial and other cancers with defective DNA mismatch repair. In a recent report in *JCO*, Zigelboim et al., examine a series of 141 MSI-positive (microsatellite instability) endometrioid endometrial cancers for mutations in exon 10 of the *ATR* gene, given its importance in the activation of cell cycle checkpoints (Chk1 and Chk2) in response to DNA damage and its potential increased susceptibility to somatic mutations in the setting of defective mismatch repair.

Kaplan - Meier Curves for OS by ATR Mutation Status



JCO, 27, July 1, 2009

ATR mutations were identified in 12 cases (4.8%; three cases with insertions and nine cases with deletions). Mutations occurred exclusively in MSI-positive tumors, with an overall mutation rate of 8.5%. Mutation was not associated with age, race, surgical stage, International Federation of Gynecology and Obstetrics grade, or adjuvant treatment. Multivariate analyses revealed a significant association with reduced overall survival and disease-free survival. The study showed that truncating *ATR* mutations in endometrial cancers are associated with biologic aggressiveness as evidenced by reduced disease-free and overall survival. Knowledge of *ATR* mutation status may hold promise for individualized treatment and targeted therapies in patients with endometrial cancer.

Source: *JCO*



Regulatory



FDA Approval for ALIMTA as Maintenance Therapy for NSCLC

Eli Lilly announced that it received a fourth approval from the FDA for ALIMTA (pemetrexed for injection). The latest approval is for ALIMTA as maintenance therapy for locally advanced or metastatic non squamous NSCLC patients, whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy.

The FDA approval is based on the results from a global, multicenter, double-blind Phase III trial which was presented as an oral presentation at the ASCO annual meeting 2009. The trial compared efficacy with respect to overall survival (OS) of ALIMTA plus best supportive care vs placebo plus best supportive care in 663 patients with stage IIIB/IV NSCLC whose disease had not progressed after 4 cycles of platinum-based induction chemotherapy. In the overall study population, ALIMTA was statistically superior to placebo in terms OS (median 13.4 months vs 10.6 months,) and PFS (median 4.0 months vs 2.0 months). For the population of patients with non-squamous NSCLC, ALIMTA was superior to placebo for OS (median 15.5 months vs 10.3 months) and PFS (median 4.4 months vs 1.8 months).

ALIMTA is approved by the FDA for the following indications.

- In combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic non-squamous NSCLC. ALIMTA is not indicated for treatment of patients with squamous cell NSCLC.
- As a single agent for the treatment of patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy. ALIMTA is not indicated for treatment of patients with squamous cell NSCLC.
- In combination with cisplatin for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

Source: Eli Lilly

Positive CHMP Opinion for JAVLOR

Laboratoires Pierre Fabre announced that the Committee for Medicinal Products for Human Use (CHMP), the scientific advisory committee of the European Medicines Agency (EMA), has issued a positive opinion supporting approval and is recommending to grant marketing authorization for JAVLOR (vinflunine), a microtubule inhibitor, as monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

CHMP has issued a positive opinion based on two Phase II study results and on the only Phase III randomized study ever conducted in the indication of metastatic treatment of bladder cancer after failure of a prior platinum-containing regimen. Phase III trial randomized 370 patients. The planned multivariate analysis adjusting for prognostic factors showed statistically significant effect of vinflunine on OS; vinflunine plus best supportive care reduced the death risk by 23% vs best supportive care. OS was significantly longer for vinflunine plus best supportive care: 6.9 vs 4.3 months. ORR, disease control, PFS were all statistically significant favoring vinflunine plus best supportive care.

Source: Laboratoires Pierre Fabre