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**Tumor Suppressor Par-4 Activates an Extrinsic Pathway for Apoptosis**

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Spotlight Report

Tumor Suppressor Par-4 Activates an Extrinsic Pathway for Apoptosis

The protein, prostate apoptosis response-4 (Par-4), acts in the cytoplasm to trigger cell death signaling via caspase activation and the mitochondrial release of cytochrome c. In a study published in Cell, Burikhanov et al. provide evidence that Par-4 can also promote apoptosis from outside the cell, after its secretion in response to endoplasmic reticulum (ER) stress. Investigators identified a secreted form of Par-4 in the culture medium of both normal and malignant prostate cells (BPH-1 and PC-3 cells, respectively) and in Par-4 transgenic mice in vivo.

Secretion of Par-4 occurred by a brefeldin A-sensitive pathway, and was not dependent on apoptosis of the cells. The authors then found a link between the ER stress response and Par-4 secretion. ER stress resulted in an overall decrease in protein translation and the activation of the glucose-regulated ER stress chaperone protein, GRP78, expressed at the surface of cancer cells. The interaction of extracellular Par-4 and cell surface GRP78 led to apoptosis via ER stress. Moreover, extracellular Par-4 activated caspase-8 and caspase-3 in a FADD (Fas-associated protein with death domain)-dependent manner. Earlier studies have established that similar to Par-4, TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) selectively induces apoptosis in cancer cells only. The current study reveals that TRAIL causes secretion of Par-4, and secreted Par-4 regulates apoptosis by TRAIL. Consequently, inhibition of either extracellular Par-4 or cell surface GRP78 impedes apoptosis by TRAIL. Thus, Par-4 activates an extrinsic pathway involving cell surface GRP78 receptor for induction of apoptosis. The identification of an extracellular role for Par-4 significantly broadens its therapeutic potential for primary and metastatic tumors.

Source: Cell
Business News

**BMS to Acquire Medarex**

Bristol-Myers Squibb (BMS) and Medarex announced that the companies have signed a definitive merger agreement providing for the acquisition of Medarex by BMS, for $16 per share in cash. The transaction, with an aggregate purchase price of approximately $2.4 billion, has been unanimously approved by the board of directors of both companies.

BMS gains the following as a result of the acquisition:

- Medarex's UltiMAb Human Antibody Development System, which produces high affinity, fully human antibodies for use in a broad range of therapeutic areas, including immunology and oncology.
- Medarex's next-generation Antibody-Drug Conjugate technology, which is a novel and proprietary platform that could open new fields in oncology drug development.
- Rights to 7 antibodies in clinical trials under Medarex's sole sponsorship and 3 other antibodies being co-developed with other partners. Rights to pre-clinical assets in various stages of development by Medarex - in particular, monoclonal antibodies focused in oncology and immunology.
- Full ownership and rights to ipilimumab, a novel immunotherapy, which, if approved, could be an important contributor to BMS's future growth. The companies have collaborated on the development of ipilimumab, currently in Phase III development for the treatment of metastatic melanoma. The companies also have an ongoing Phase II study in lung cancer as well as Phase III studies in adjuvant melanoma and hormone-refractory prostate cancer.

*Source: BMS*

**Debiopharm Signs Business Deals for Debio 0929 and HSP90 Inhibitor, CUDC-305**

Debiopharm and MSM Protein Technologies (MSM) have signed an exclusive agreement for the development and commercialization of Debio 0929, an antibody targeting a G protein-coupled receptor (GPCR), to be developed into a new oncology therapeutic drug. Under the terms of the agreement, Debiopharm and MSM have formed a partnership to select antibodies against the GPCR. Upon completion of the discovery phase, MSM will grant Debiopharm a worldwide exclusive license for the development and commercialization of the antibody. MSM will retain marketing rights for Russia, Ukraine and several other countries in Eastern Europe and Asia. MSM will receive milestone payments from Debiopharm during the development of the product, as well as a share of royalties on net sales.

In another deal, Debiopharm and Curis entered into a worldwide, exclusive license agreement for Curis' Heat Shock Protein (Hsp90) technology, including CUDC-305, the company's lead Hsp90 inhibitor candidate. Under the terms of the agreement, Debiopharm will assume all future development responsibility and incur all future costs related to the licensed Hsp90 technology, including CUDC-305. Curis currently expects that Debiopharm will file an application with health authorities to begin Phase I clinical testing for CUDC-305 in Fall 2009.

*Source: Debiopharm*
Peregrine Licenses Anti-VEGF Antibodies to Affitech

Peregrine Pharmaceuticals and Affitech announced that they have entered into a licensing agreement for antibody therapeutic rights under Peregrine's preclinical anti-VEGF antibody program. Under the terms of the agreement, Affitech will license exclusive worldwide rights to develop and commercialize products under Peregrine's selective anti-VEGF intellectual property portfolio, including the fully human antibody r84, which was discovered by Affitech and jointly developed by the companies under an ongoing collaboration. Under the license agreement, Affitech will be responsible for future preclinical and clinical development and potential product commercialization. Peregrine will receive an upfront payment, research fees, future milestone payments and royalties on any future sales, and a share of sublicensing revenues.

The fully human and selective anti-VEGF monoclonal antibody, r84, which is the most advanced candidate in Peregrine's anti-VEGF antibody program, targets the cancer-promoting growth factor VEGF. Data has shown that r84 was as effective as Avastin (bevacizumab) in inhibiting tumor growth in a number of models of human cancers, including a mouse model of human breast cancer.

Source: Peregrine Pharmaceuticals

Vernalis and GSK Enter into an Agreement over a Novel Oncology Programme

Vernalis has entered into an exclusive collaboration and license agreement with GSK relating to a Vernalis research programme against an undisclosed oncology target. During the research phase, Vernalis will continue to apply its expertise in Structure Based Drug Design (SBDD) technologies to progress novel development candidates against the target. The deal is structured as a risk-sharing agreement, with Vernalis responsible for drug discovery activities and GSK for pre-clinical development. Upon IND filing, GSK will have the option to license all collaboration compounds and if this is exercised, it will then be responsible for all future development and commercialization activities.

Under the terms of the deal, Vernalis will receive $6 million upon signing and is eligible to earn up-front and potential milestone payments. Further milestones and royalties could be earned if products against the target are developed for indications other then oncology.

Source: Vernalis

Ambrilia and Kotinos Enters into an Agreement for PCK3145

Ambrilia and Kotinos Pharmaceuticals have entered into a Patent and Technology Purchase Agreement whereby Kotinos will acquire Ambrilia's prostate cancer therapeutic PCK3145, an angiogenesis inhibitor, and related assets. Under the agreement, Ambrilia is eligible to receive up to $15 million in development and sales milestones, including an upfront payment of $200,000 and double-digit royalties on product net sales.

A Phase I/II study conducted by Ambrilia has shown that PCK3145 had clinical activity in metastatic prostate cancer patients. PCK3145 was found to be safe and well tolerated, and was shown to increase prostate specific antigen doubling time and down-regulate matrix metalloprotease (MMP)-9 enzyme which has been implicated in cancer metastases. Disease stabilization as assessed by time to radiographic progression was also observed in several patients.

Source: Ambrilia
Research Highlight

Sequential Treatment of Drug-resistant Tumors with Targeted Minicells

The ability to specifically target therapeutic agents to the tumor and avoid exposure of normal tissues should substantially reduce cancer therapy-associated side effects. In a recent paper published in *Nature Biotechnology*, MacDiarmid et al. describe the use of tumor-targeted minicells (400 nm particles derived from bacteria) as effective siRNA vectors using bispecific antibodies in which one arm is bound to the outer membrane of the minicell and the other specific for a tumor antigen. The workers demonstrated that siRNAs passively accumulated in minicells, plasmids containing short hairpin RNAs (shRNAs) could be transfected into minicells. In *vitro*, epidermal growth factor receptor (EGFR)-bispecific antibodies coated minicells were taken up by EGFR-expressing human tumor cells through receptor-mediated endocytosis.

Degradation of the minicell through the lysosomal pathway resulted in the release of active siRNAs that targeted the cell cycle genes polo-like kinase 1 or cyclin-dependent kinase 1 resulting in cell death *in vitro*. Further, using EGFR-targeted minicells containing shRNAs to *MDR1*, the researchers demonstrated the suppression of expression of multidrug resistance protein (MDR1) in a variant of human colon cancer Caco-2 cells that express MDR1 (and EGFR). Subsequent administration of targeted minicells containing cytotoxic drugs eliminated the formerly drug-resistant tumors. The two waves of treatment, involving minicells loaded with both types of payload, enabled complete survival without toxicity in mice with tumor xenografts, while involving several thousand-fold less drug, siRNA and antibody than needed for conventional systemic administration of cancer therapies. This study reveals that targeting siRNA to tumors can be achieved using tumor-targeted minicells and that the sequential deployment of siRNA and then chemotherapy might prove effective for overcoming MDR1-related drug resistance while substantially reducing the amount of drug needed to elicit a cytotoxic response in the tumor cells.

Source: *Nature Biotechnology*

AKT-Independent Signaling Downstream of Oncogenic PIK3CA Mutations

Genetic alterations targeting the phosphatidylinositol 3-kinase (PI3K) pathway, leading to aberrant PI3K signaling, are highly prevalent in many human cancers. Gain-of-function mutations in PIK3CA, which encodes a key enzymatic subunit of PI3K, occur frequently in several tumors. PTEN tumor suppressor or PIK3CA oncogene mutations both direct PI3K-dependent tumorigenesis largely through activation of the AKT/PKB kinase. Downstream activation of the AKT kinase is regarded as the dominant tumor-promoting mechanism enacted by PI3K signaling.

Recent work by Vasudevan et al. published in *Cancer Cell*, however, demonstrates that AKT signaling is markedly diminished in many cancer cell lines and human breast tumors harboring PIK3CA mutations. Using phosphoprotein profiling and functional genomic studies, the researchers offer a modified conceptual framework for oncogenic PI3K signaling. In the setting of PTEN deficiency, excess upstream activation, or defective feedback regulation, PIK3CA mutant cancers are able to recruit both AKT and 3-Phosphoinositide-dependent kinase 1 (PDK1) to the plasma membrane and exhibit a robust AKT-dependent signal. On the other hand, if PTEN function remains intact and upstream or feedback pathways are not fully dysregulated, PIK3CA mutations may transduce an AKT-independent signal that engages PDK1 and serum/glucocorticoid regulated kinase 3 (SGK3). They, thus, exhibit only minimal AKT activation and a diminished reliance on AKT for anchorage-independent growth. Instead, the cells elaborate a signaling pathway involving the PI3K effector PDK1 and its downstream substrate SGK3. The cells retain robust PDK1 activation and membrane localization and exhibit dependency on SGK3, which undergoes PI3K- and PDK1-dependent activation. This study provides evidence that PIK3CA mutations may contribute to tumorigenicity through both AKT-dependent and AKT-independent mechanisms. It also implicates both PDK1 and SGK3 as key oncogenic effectors downstream of activating PIK3CA mutations. As several PI3K pathway inhibitors enter clinical trials, the knowledge of differential PI3K/PDK1 signaling may have important implications for rational therapeutics against this key cancer pathway.

Source: *Cancer Cell*
Modulation of MicroRNA Processing by p53

A widespread decrease in mature miRNAs is often observed in various human malignancies. In addition to genomic and epigenetic alterations, the deregulation might be attributable to the impairment of miRNA-processing steps. In a study published in *Nature*, Suzuki *et al.* postulate a direct connection between tumor suppressor networks and miRNA biogenesis machineries. To identify miRNAs potentially regulated by tumor suppressor p53, investigators measured the expression levels of a selected group of miRNAs after treatment with the DNA-damaging agent doxorubicin, a potent p53 inducer, in the p53 wild-type HCT116 human colon cancer cell line. It was observed that exposure to doxorubicin increased not only a known p53 target, miR-34a, but also a set of mature miRNAs such as miR-15a, miR-16-1, miR-23a, miR-26a, miR-103, miR-143, miR-145, miR-203 and miR-206.

In HCT116 cells and human diploid fibroblasts, p53 interacted with the Drosha processing complex through the association with DEAD-box RNA helicase p68 (also known as DDX5) and facilitated the processing of primary miRNAs to precursor miRNAs. The Drosha complex comprises Drosha, the DiGeorge syndrome critical region gene 8 (DGCR8) and multiple RNA-associated proteins including the DEAD box RNA helicases p68 and p72. Investigators also found that transcriptionally inactive p53 mutants interfere with a functional assembly between Drosha complex and p68, leading to attenuation of miRNA processing activity. These findings suggest that transcription-independent modulation of miRNA biogenesis is intrinsically embedded in a tumor suppressive program governed by p53. The present study offers an insight into a new approach to cancer treatment by modulating the p53 and miRNA pathways.

Source: *Nature*
Clinical Development

Tarceva Shows an OS Benefit in the First-Line Maintenance NSCLC Setting

OSI Pharmaceuticals announced overall survival (OS) data from the Phase III SATURN study at the 13th World Conference on Lung Cancer held in San Francisco from July 31-August 4, 2009. The study results showed that Tarceva (erlotinib) extended the survival of patients with advanced NSCLC when used as single agent, maintenance therapy in patients who did not progress following first-line treatment with platinum-based chemotherapy. Patients with NSCLC treated with Tarceva had a 23% improvement in OS, a key secondary endpoint of the study, compared with patients who received placebo. The median survival for patients receiving Tarceva was 12 months vs 11 months for patients receiving placebo. Specific analysis of EGFR "wild-type" patients showed that this group experienced a 30% improvement in survival. The study met its primary endpoint earlier and showed patients with advanced NSCLC who received Tarceva as a first-line maintenance treatment had a 41% improvement PFS compared to placebo.

The OS data will be submitted to the FDA and EMEA to support the earlier sNDA submitted in March 2009, for use of Tarceva as a first-line maintenance treatment for patients with advanced NSCLC.

Source: OSI Pharmaceuticals

Efficacy of Sorafenib in Advanced Breast Cancer and RCC

Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals announced that their first cooperative group-sponsored randomized Phase II trial in advanced metastatic breast cancer met its primary endpoint of PFS. The study evaluated Nexavar (sorafenib) tablets in combination with the oral chemotherapeutic, capecitabine, in 229 patients with locally advanced or metastatic HER-2 negative breast cancer. The study findings demonstrated that the median PFS was extended in patients treated with Nexavar and capecitabine compared to patients receiving capecitabine and placebo. In this trial, the safety and tolerability of the combination was as expected and did not show any new or unexpected toxicities. A complete data analysis from this study is expected to be presented at an upcoming scientific meeting.

In another trial, a Phase III TARGET study (Treatment Approaches in Renal Cancer Global Evaluation Trial) which enrolled 903 previously treated patients who were randomly assigned to receive sorafenib vs placebo. On demonstration of PFS benefit with sorafenib, patients assigned to placebo were offered sorafenib. OS was determined at two planned interim analyses and one final analysis, with a secondary OS analysis conducted by censoring placebo patients who crossed over to sorafenib. Final OS of patients receiving sorafenib was comparable with that of patients receiving placebo (17.8 vs 15.2 months, respectively); however, when postcross-over placebo survival data were censored, the difference became significant (17.8 vs 14.3 months, respectively). The results of TARGET establish the efficacy and safety of sorafenib in advanced RCC.

Source: Onyx Pharmaceuticals¹, JCO'

Vectibix in Combination with Chemotherapy Improves PFS in 1st Line mCRC

Amgen announced the results from a Phase III PRIME (Panitumumab Randomized trial in combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy) trial. The study results showed that vectibix (panitumumab), administered in combination with FOLFOX (an oxaliplatin-based chemotherapy), significantly prolonged PFS compared with FOLFOX alone in the first-line treatment of patients with KRAS wild-type metastatic colorectal cancer (mCRC).

Overall, the adverse event profile was as anticipated for an anti-EGFR antibody in combination with oxaliplatin-based chemotherapy. Originally designed to compare the treatment effect in the overall population, the study was amended to analyze outcomes with respect to the presence or absence of activating mutations in KRAS in the tumor itself. Tumor KRAS status was ascertained in more than 90% of the 1,183 patients enrolled in the trial. Significantly in patients with tumors harboring activating KRAS mutations, PFS was significantly inferior in the Vectibix arm. "These are the first prospective Phase III data to demonstrate the utility of KRAS mutational analysis as a predictive biomarker," said Roger M. Perlmutter, M.D., Ph.D., executive vice president of Research and Development at Amgen.

Source: Amgen
Positive Results for Denosumab in Bone Metastases Compared to Zometa

Amgen announced positive top-line results from a pivotal Phase III head-to-head trial evaluating denosumab, a RANKL (receptor activator of NF-κB ligand) inhibitor, administered subcutaneously vs Zometa (zoledronic acid) administered as an intravenous infusion in the treatment of bone metastases. The study enrolled 1,776 advanced cancer patients with solid tumors (not including breast and prostate cancer) or multiple myeloma. For the primary endpoint, patients treated with denosumab experienced a similar time to first skeletal-related event (SRE) compared with those receiving Zometa, which is statistically significant for non-inferiority ($p<0.0007$). The secondary endpoints, the delay in the time to first SRE associated with denosumab treatment and the time to first-and-subsequent SRE, although numerically greater were not statistically superior compared to Zometa. Overall, the incidence of adverse events and serious adverse events was consistent with what has been reported previously for these two agents. "We are very encouraged by the overall strength of the data, which we will present in a scientific forum later this year. We are also looking forward to reviewing the results of a final SRE study, in patients with advanced prostate cancer, next year," said Roger M. Perlmutter, M.D., Ph.D., executive vice president of Research and Development at Amgen.

Source: Amgen

A Potential Effect of Metformin in Human Breast Cancer

Clinical and epidemiologic evidence has linked hyperinsulinemia, insulin resistance, and diabetes to poor breast cancer outcomes. This has been coupled with enhanced understanding of molecular effects of metformin and its potential role in malignancy. It has been revealed that metformin may influence cancer cells through indirect (insulin-mediated) effects, or it may directly affect cell proliferation and apoptosis of cancer cells. In a study published in JCO, Jiralerspong et al. report the first evidence of a potential effect of metformin in human breast cancer.

The study identified 2,529 patients who received neoadjuvant chemotherapy for early-stage breast cancer. Patients were compared by groups: 68 diabetic patients taking metformin, 87 diabetic patients not taking metformin, and 2,374 nondiabetic patients. Diabetic patients treated with metformin experienced a pathologic complete response (pCR) rate of 24%, which was significantly greater than the pCR rate in diabetic women not treated with metformin (8%) and numerically (but not statistically) greater than the pCR rate in women without diabetes (16%). In multivariate models adjusting for body mass index, stage, tumor grade, hormone receptor and human epidermal growth factor receptor 2 status, age, presence of diabetes, and use of neoadjuvant taxanes, metformin use remained an independent predictor of pCR. The study concluded that diabetic patients with breast cancer receiving metformin and neoadjuvant chemotherapy have a higher pCR rate compared to diabetics not receiving metformin. Additional studies to evaluate the potential of metformin as an antitumor agent are warranted.

Source: JCO
CD47 is an Independent Indicator of Poor Prognosis for Patients with AML

CD47, an immunoglobulin-like membrane protein, interacts with a specific macrophage receptor, SIRPα, to downregulate the phagocytic potential of macrophages. Its expression allows some normal cells to avoid phagocytosis by macrophages. In a study published in *Cell*, Majeti et al. show that elevated CD47 expression by leukemic stem cells (LSCs) inhibits macrophage activity and is an independent indicator of poor prognosis for patients with acute myeloid leukemia. Investigators demonstrated that high levels of CD47 on LSCs isolated from patients with AML are predictive of leukemia resistance to therapy.

In clinical presentations of AML where the disease was refractory to or relapsed shortly after remission induction chemotherapy, high expression of CD47 result in the increased “escape” of LSC populations from macrophage-mediated surveillance, possibly reflecting the ability of LSCs to avoid macrophage-mediated control. This effect can be reversed by the presence of antibodies directed against CD47 or SIRPα. The group also found that AML patients can be stratified into distinct groups based on CD47 expression, and survival (both disease-free and overall) is markedly longer in patients expressing low levels of CD47. This experimental evidence, thus, provides the first glimpse of how a prosurvival signal for LSCs may be clinically subverted as a potential therapeutic target for leukemia using anti-CD47 monoclonal antibodies as monotherapy or a combination strategy that results in a synergistic stimulus for phagocytosis and specific elimination of AML LSC. These findings will lead to application of new therapies that will enhance the clearance of LSCs in vivo, ultimately leading to improved patient outcomes in AML.

*Source: Cell*
Cyfip1 is a Putative Invasion Suppressor in Epithelial Cancers

Identification of bona fide tumor suppressors is often challenging because of the large number of genetic alterations present in most human cancers. In a recent study published in *Cell*, Silva *et al.* evaluated human cancers and cancer cell lines for recurrent chromosomal focal deletions. The researchers analyzed the impact of silencing the genes located within chromosomal regions recurrently deleted in human cancers using a combination of high-resolution genomic analysis with a two-stage genetic study employing RNA interference (RNAi). By coupling genomic and genetic analysis, they identified that *CYFIP1*, a subunit of the WAVE complex which regulates invasive behaviour, as a potential tumor suppressor which is commonly deleted in human epithelial cancers. Furthermore, *CYFIP1* was frequently found in larger deletions and its loss of expression correlated with tumor progression and a poor clinical outcome, suggesting that *CYFIP1* might be a tumor suppressor.

Investigators found that silencing of *CYFIP1* disturbed normal epithelial morphogenesis in vitro (generated abnormal acini structures) and cooperated with oncogenic Ras to produce invasive carcinomas in vivo. The workers propose a model wherein depletion of WAVE components directly perturb actin dynamics, which in turn reduces epithelial adhesion leading to disorderization of tissue architecture. This disruption of tissue architecture by transformed cells causes the tumor to become invasive. To a growing list of genes that encode molecules regulating tissue architecture (e.g., E-cadherin, a6- and b4-Integrins, Podoplanin, or Scribble) and modify the invasive phenotype, this study adds *CYFIP1* since its suppression can promote the development of invasive carcinomas in models that would normally yield benign, noninvasive lesions. These findings demonstrate that alterations in either the *Cyfip1* locus or its expression contribute to the loss of epithelial cell architecture and promote tumor progression, marking this locus a strong candidate for a bona fide human invasion suppressor.

Source: *Cell*

Predictors of Primary Imatinib Resistance in CML

Therapeutic resistance to tyrosine kinase inhibitor (TKI), imatinib, is seen in 10-15% of patients and can be classified as primary or secondary. Primary imatinib resistance is distinguished from secondary resistance which re-emerges after attainment of cytogenetic remission. A major factor mediating secondary resistance is the emergence of acquired point mutations in the ABL kinase domain (KD) and *BCR-ABL1* gene amplification. However, the factors contributing to primary resistance are less well characterized. In a study published in *JCO*, Zhang *et al.* evaluated the utility of a clinical-grade limited gene expression panel for predicting response to imatinib in newly diagnosed CML, and assessing the mechanisms of secondary imatinib resistance when ABL1 kinase domain mutations were absent.

The study results showed that 15 genes in the panel distinguished blast phase from chronic phase disease, and 12 genes distinguished newly diagnosed CML from TKI-resistant CML without ABL1 kinase domain mutations. In newly diagnosed CML, investigators identified a strong differentially increased expression of a single gene, prostaglandin-endoperoxide synthase 1 (*PTGS1*) in imatinib-resistant patients. This finding that was confirmed in a second test set of 68 newly diagnosed, imatinib-treated CML patients. On the other hand, in a multivariate model, up to 11 different genes were identified which optimally discriminated secondary imatinib resistance lacking ABL1 kinase domain mutation from imatinib-responsive cases, likely related to the more complex pathogenesis of secondary resistance. The study findings indicated that gene expression profiling of CML at diagnosis for *PTGS1* may be useful in predicting imatinib response and in selecting alternate therapy.

Source: *JCO*
Expression of ER-α36 and Resistance to Tamoxifen in Breast Cancer

Estrogen receptor α (also known as ER-α66) is one of the most important determinants of susceptibility to endocrine therapy in breast cancer. However, approximately 40% of ER-α66 positive tumors fail to respond to tamoxifen therapy at diagnosis. Recently, Shi et al. have identified and cloned a 36-kDa variant of estrogen receptor α, ER-α36. To study the function of this new variant, investigators assessed ER-α36 protein expression in tumors from 896 women with operable primary breast cancer.

The study results showed that patients with ER-α66 positive breast tumors that also express high levels of ER-α36 are less likely to benefit from tamoxifen treatment than patients who do not. In patients with ER-α66 positive breast tumors who received adjuvant tamoxifen treatment, ER-α36 expression was associated with poorer survival and remained as an independent unfavorable factor of disease-free survival (DFS) and disease-specific survival (DSS) in multivariate analyses. However, in patients with ER-α66 positive tumor who received chemotherapy alone, high levels of ER-α36 seemed to be a favorable factor for survival in a multivariate analysis, indicating that patients with both ER-α66 and ER-α36 positive tumors may be less likely to benefit from tamoxifen treatment but may benefit from chemotherapy. Therefore, early identification of patients with ER-α66 positive breast cancer who may be resistant to tamoxifen treatment is extremely important in a clinical setting, because these patients may select an alternative endocrine therapy or other types of therapy from the diagnosis.

Source: JCO

DxS Collaborate with AstraZeneca to Provide a Companion Diagnostic for IRESSA

DxS has announced it is working closely with AstraZeneca to make available a companion diagnostic for use with IRESSA (gefitinib), AstraZeneca’s treatment for NSCLC. DxS’ clinical diagnostic, the TheraScreen: EGFR29 Mutation Kit will be used to test the mutation status of a patient’s EGFR oncogene to identify their eligibility for treatment with IRESSA. The TheraScreen: EGFR29 Mutation Kit, is the only CE-marked kit currently available and is based on DxS’ real-time PCR technology, ARMS and Scorpions. This technology allows for a highly sensitive and selective test which can detect low levels of mutant in a background of wild type genomic DNA in a tumour with time to result in less than three hours.

The collaboration follows the granting of marketing authorization for IRESSA in the EU for the treatment of adults with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK across all lines of therapy. Dr Stephen Little, CEO of DxS said, "We are very pleased to be working with AstraZeneca to provide a diagnostic for use with IRESSA. The results from the IPASS trial show just how important the development of a companion diagnostic is for use with IRESSA in ensuring that patients most likely to benefit receive the therapy. We hope that through the better understanding of the relationship between EGFR mutation status and response to anti-EGFR therapies such as IRESSA, patients receive the best possible cancer treatment."

Source: DxS
Regulatory

FDA Approves Avastin for Metastatic RCC
Genentech, a wholly-owned member of the Roche Group, announced that the FDA approved Avastin (bevacizumab) plus interferon-alfa for patients with metastatic renal cell carcinoma (RCC).

This FDA approval is based on data from a global, randomized, double-blind, placebo-controlled Phase III study (AVOREN) of 649 patients with previously untreated metastatic RCC. The study showed patients who received Avastin plus interferon-alfa had a 67% increase in the PFS compared to those who received interferon-alfa alone. In AVOREN, median PFS was 10.2 months for patients who received Avastin plus interferon-alfa compared to 5.4 months for patients who received interferon-alfa alone, corresponding to an 89% improvement in median PFS.

Source: Genentech

MabThera Receives Positive Opinion in Europe for Relapsed/Refractory CLL
Roche announced that the European Union’s Committee on Human Medicinal Products (CHMP) has issued a positive recommendation for the use of MabThera (rituximab) in patients with relapsed or refractory chronic lymphocytic leukaemia (CLL). This recommendation is based on the results from REACH, the largest randomized clinical trial ever reported in previously treated CLL. The study included included 552 patients with relapsed or refractory CLL. The results showed that patients with relapsed or refractory CLL who received MabThera in combination with chemotherapy lived an average 10 months longer without their disease progressing compared to those receiving chemotherapy alone (30.6 months vs. 20.6 months).

MabThera is already indicated for previously untreated patients with CLL in combination with chemotherapy in addition to other indications

Source: Roche

FDA Revises Prescribing Information for ERBITUX and Vectibix
ImClone Systems-BMS and Amgen announced that the FDA has approved revisions to the prescribing information for ERBITUX (cetuximab) and Vectibix (panitumumab) respectively concerning the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer (mCRC). The labeling revisions include a modification to the indication, which now includes a statement that retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for ERBITUX and Vectibix in patients whose tumors had K-ras mutations in codon 12 or 13 and that the use of ERBITUX and Vectibix is not recommended for the treatment of colorectal cancer with these mutations. Revisions concerning the use of ERBITUX and Vectibix in colorectal cancer tumors with K-ras mutations were also made to the clinical studies and clinical pharmacology sections of the products’ prescribing information.

These revisions are based on retrospective analyses across 7 randomized clinical trials that suggest anti-EGFR mAbs are not effective for the treatment of patients with mCRC containing K-ras mutations. In these trials, patients received standard of care (i.e., BSC or chemotherapy) and were randomized to receive an anti-EGFR antibody (cetuximab or panitumumab) or no additional therapy. In all studies, investigational tests were used to detect K-ras mutations in codon 12 or 13. The percentage of study populations for which K-ras status was assessed ranged from 23% to 92%.

Source: Imclone, Amgen
European Commission Approves Genzyme’s Mozobil

Genzyme announced that the European Commission has granted marketing authorization for Mozobil (plerixafor injection), providing a significant new option for patients with the blood cancers (lymphoma and multiple Myeloma) who require an autologous stem cell transplant.

Mozobil was evaluated in two randomized, double-blind, placebo controlled, Phase III studies in patients with non-Hodgkin's lymphoma and multiple myeloma. Patients were given Mozobil plus G-CSF or placebo plus G-CSF. The studies found that Mozobil in combination with G-CSF increased the number of patients achieving both the minimum and target stem cell levels in fewer apheresis sessions; allowed more patients to proceed to transplant; and increased the predictability of apheresis stem cell yield and timing. Year-long follow-up data also showed that the graft durability rates were comparable in the Mozobil plus G-CSF and placebo plus G-CSF trial arms. Mozobil was approved in the US in December 2008 where it is indicated for use in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the bloodstream for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma.

Source: Genzyme Corporation