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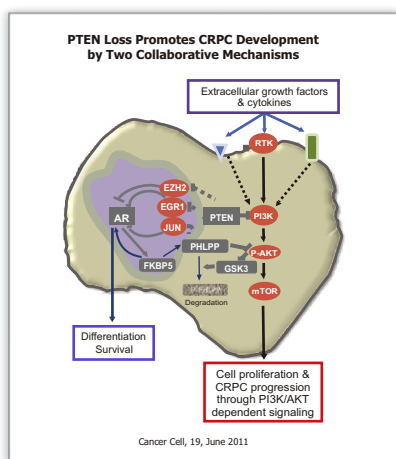


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## In the Spotlight:

### Cell Autonomous Role of PTEN in Regulating CRPC Growth

Resistance to androgen deprivation therapy is the major hurdle for managing patients with advanced prostate cancer. Therefore, understanding the molecular mechanisms underlying castrate-resistant prostate cancer (CRPC) is required for designing therapeutic strategies to overcome resistance. Studies have shown that PTEN loss or activation of the PI3K/AKT pathway leads to enhanced cell proliferation, survival, and migration as well as castration-resistant growth.



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### Tumor of the Month - Bladder Cancer

July is Bladder Cancer awareness month. According to the American Cancer Society, in 2010, there were approximately 70,530 new cases of and 14,680 deaths resulting from bladder cancer in the US alone. This cancer is more common in men than women and 90% of all bladder cancer cases are present in people over the age of 55 (a large portion of those numbers being Caucasian individuals).

Bladder Cancer Treatment Options				
<b>Stage 0</b> <ul style="list-style-type: none"> <li>TUR w/fulguration</li> <li>Segmental cystectomy</li> <li>Radical cystectomy</li> <li>Clinical trial</li> </ul>	<b>Stage I</b> <ul style="list-style-type: none"> <li>TUR w/fulguration</li> <li>Segmental cystectomy</li> <li>Radical cystectomy</li> <li>Radiation implants w/ or w/o external RT</li> <li>Clinical trial</li> </ul>	<b>Stage II</b> <ul style="list-style-type: none"> <li>TUR</li> <li>Segmental cystectomy</li> <li>Radical cystectomy w/ or w/o surgery to remove pelvic Lns</li> <li>Combination chemo</li> <li>External RT w/chemo or radiation implants</li> </ul>	<b>Stage III</b> <ul style="list-style-type: none"> <li>Segmental cystectomy</li> <li>Radical cystectomy w/ surgery to remove LN</li> <li>Combination chemo + radical cystectomy</li> <li>External RT w/chemo or radiation implants</li> </ul>	<b>Stage IV</b> <ul style="list-style-type: none"> <li>Cystectomy</li> <li>Radical cystectomy w/ surgery to remove LN</li> <li>Chemotherapy</li> <li>External RT</li> <li>Urinary diversion</li> <li>Clinical trial</li> <li>Palliative care</li> </ul>

Based on NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer V.2.2011  
TUR = transurethral resection; RT = radiation therapy; LN = lymph node

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### Business News

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[Read More...](#)

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[Read More...](#)

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[Read More...](#)

### Regulatory

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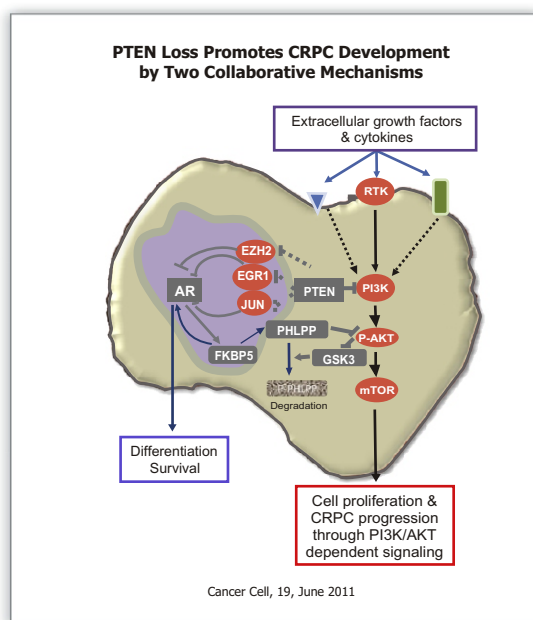
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## Spotlight Report

### Cell Autonomous Role of PTEN in Regulating CRPC Growth



Resistance to androgen deprivation therapy is the major hurdle for managing patients with advanced prostate cancer. Therefore, understanding the molecular mechanisms underlying castrate-resistant prostate cancer (CRPC) is required for designing therapeutic strategies to overcome resistance. Studies have shown that PTEN loss or activation of the

PI3K/AKT pathway leads to enhanced cell proliferation, survival, and migration as well as castration-resistant growth. The consequence of PTEN loss and how its loss influences the androgen/androgen receptor (AR)-signaling axis and CRPC development is unclear. By genetically deleting *Pten* and *Pten/Ar* in the prostatic epithelium and analyzing human prostate cancer samples, Hong Wu *et al.*, in a study published in *Cancer Cell*, support the hypothesis that PTEN loss or PI3K pathway activation may function in a cell autonomous manner to promote androgen/AR-independent prostate cancer progression and CRPC development.

PTEN loss enhances the expressions of EGR1, c-JUN, and EZH2, which in turn suppresses AR *trans*-fatty acid and output. PTEN loss results in suppression of AR transcription output and activates the PI3K/AKT signaling pathway. AR loss or inhibition, on the other hand, can further activate AKT activity via downregulation of the FKBP5 scaffold protein and PHLPP phosphatase, leading to androgen/AR-independent prostate epithelial proliferation. The study identifies PI3K and AR pathway crosstalk as a mechanism of CRPC development, with potentially important implications for prostate cancer etiology and therapy. Thus, more effective blockade of the androgen/AR axis with new generation inhibitors such as abiraterone and MDV3100 in combination with mTOR or PI3K/mTOR dual inhibitors may prove to be further advantageous in treating CRPC cases initiated by alterations of PTEN/PI3K pathway.

Source: *Cancer Cell*. 2011;19(6):792-804.

## Tumor of the Month - Bladder Cancer

July is Bladder Cancer awareness month. According to the American Cancer Society, in 2010, there were approximately 70,530 new cases of and 14,680 deaths resulting from bladder cancer in the US alone. This cancer is more common in men than women and 90% of all bladder cancer cases are present in people over the age of 55 (a large portion of those numbers being Caucasian individuals). Over 80% of cases are associated with environmental factors, with smoking being the most common. Other risk factors include occupations that expose employees to high levels of carcinogens (e.g., truck drivers, painters, textile, etc), certain chemotherapeutic agents, pelvic radiation, and arsenic exposure. There may also be a possible genetic link to bladder cancer due to an increased risk in individuals who have a family history of bladder cancer.

There are several types of bladder cancer - classification is related to the cell type from which it originated. Transitional cell carcinoma (or urothelial carcinoma) is the most common. Squamous cell carcinoma and adenocarcinoma, which originates in glandular cells, are less common. Patients with bladder cancer have an increased chance of developing tumors in other parts of the urinary system, such as the lining of kidneys, ureters, or urethra.

Bladder cancer is normally staged on a scale from 0 to IV. A patient with stage 0 presents abnormal cells in lining of bladder. This stage can also be divided into substages 0a (papillary carcinoma) or 0is (carcinoma in situ) depending on the morphology of the tumor. Stage I patients present abnormal cells that have transformed into malignant cells and spread to tissue under inner lining of bladder. In stage II, malignant



## Tumor of the Month (Cont'd)

cells spread to muscle wall of bladder, and in stage III, spread to fatty tissue surrounding bladder and possibly reproductive organs. Patients with stage IV have tumor cells that spread to wall of abdomen or pelvis, and possibly to distal lymph nodes and other parts of the body. 70-80% of patients are diagnosed with stage 0a, 0is, or 1, and have superficial, noninvasive tumors that can often be cured. Prognosis of bladder cancer depends greatly on the depth of invasion into the bladder wall and the degree of tumor differentiation. Patients with deeply invasive tumors that are less differentiated and have lymph node involvement have only a 30-50% 5yr OS following radical cystectomy. Patients with progressive or recurrent invasive bladder cancer have a poor prognosis. If a patients present with late stage cancer that has invaded the pelvic viscera or metastasized to distant sites, 5yr OS is uncommon and these patients are treated mainly with symptomatic palliative care.

There are four main types of standard treatment for bladder cancer: surgery, radiation therapy, chemotherapy, or biologic (immuno-) therapy. Patients who have surgery can undergo transurethral resection with fulguration (burning of the tumor with high-energy electricity), radical cystectomy (removal of bladder and any affected lymph nodes or organs), segmental cystectomy (removal of part of the bladder, in the case of a localized tumor), or urinary diversion. Adjuvant therapy may also be given after surgery. Radiation therapy may be administered before or after surgery or in individuals who cannot undergo surgery. External beam radiation is delivered from a source outside of the body and internal radiation therapy involves surgical implantation of radioactive material in or near the tumor.

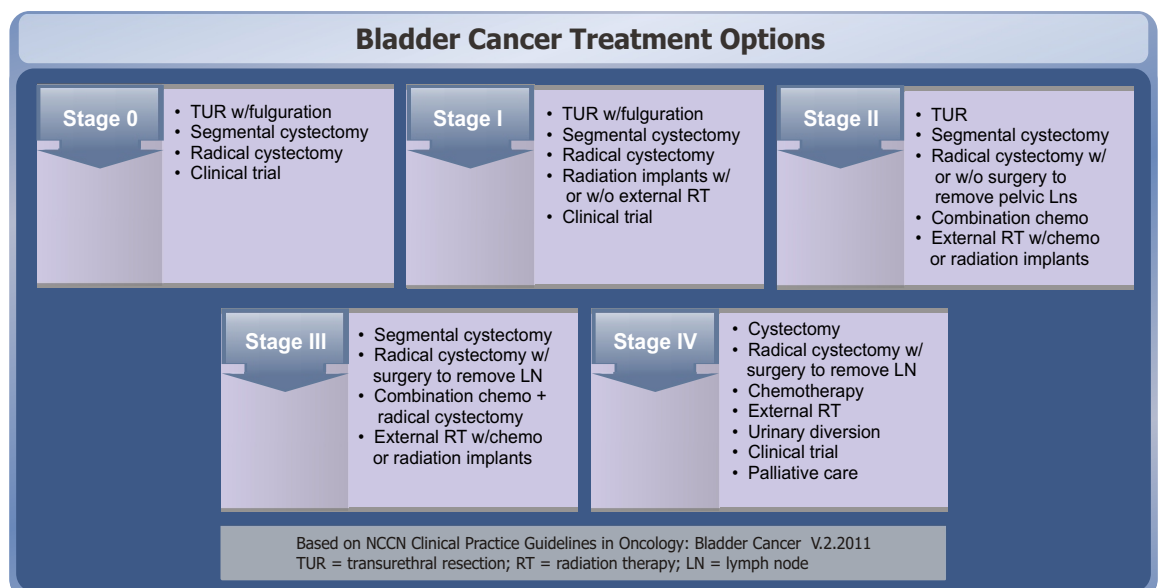
Chemotherapy is administered orally, intravenously, or intravesically (inserted into the bladder through a urinary catheter). Chemotherapeutic agents that are administered i.v. include M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin), gemcitabine,

doxorubicin, epirubicin, valrubicin, paclitaxel or carboplatin. Gemcitabine-cisplatin combination is the current standard of care in first-line. Mitomycin may be given intravesically. Bacillus Calmette-Guerin (BCG), also given intravesically, is a bacterium used in tuberculosis vaccines. This immunotherapy utilizes the immune system to attack tumor cells in the bladder wall. Interferon alpha is sometimes used in combination with BCG. Immunotherapy can be administered after TURBT to reduce the risk that cancer will recur.

Both the type and stage of bladder cancer influence treatment option(s). (See figure). Treatment of recurrent bladder cancer depends on prior therapy and the sites of recurrence. Clinical trials are usually recommended. There are several agents currently undergoing phase III clinical testing for bladder cancer, including urocidin, eflornithine and apaziquone. Urocidin (Endo Pharmaceuticals) has a unique dual mechanism of action that acts as an immune stimulator while also having direct anti-cancer activity. Eflornithine (Genzyme) is currently used to treat African sleeping sickness and apaziquone (Spectrum Pharmaceuticals) is a chemical analog of mitomycin C that induces apoptosis.

Recent laboratory research is also focusing on prognostic and predictive biomarkers for bladder cancer. Scientists at the UC Davis Cancer Center, found a particular microRNA expressed in bladder cancer cell lines. When this miRNA, miR-34a, was activated in bladder cancer cells in vitro, it was found to result in an increase in cells being killed by cisplatin. It was concluded that miR-34a may be used to predict chemosensitivity.

Source: R.L. Vinall, et al. *International Journal of Cancer*, 2011; DOI: 10.1002/ijc.26256; *Clinicaltrials.gov*; SEER; NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer V.2.2011; Reidl, K. et al. *J. Anal. Toxicol.* 2006 30(3): 187-95, 3; Cheng, J. *Cancer Res* 2003 63; 179; *webmd.com*; *mayoclinic.com*; [www.bladdercancersupport.org](http://www.bladdercancersupport.org); [cancer.gov](http://cancer.gov); [cancer.org](http://cancer.org)





## Business News

### **Micromet Announces Solid Tumor BiTE Antibody Collaboration with Amgen**

Micromet announced that it has entered into a collaboration agreement with Amgen for the research of BiTE antibodies against three undisclosed solid tumor targets. BiTE antibodies are designed to direct the body's cytotoxic, or cell-destroying, T cells against tumor cells and represent a new therapeutic approach to cancer therapy. Amgen will have the right to pursue development and commercialization of BiTE antibodies against up to two of these targets, to be selected by Amgen. Under the terms of the agreement, Amgen is expected to pay €10 million upon deal execution. If milestones in multiple indications and tumor types are achieved, Micromet is eligible to receive up to €342 million in clinical and commercial milestone payments. Micromet is also eligible to receive up to double-digit royalties on worldwide net sales.

For the second BiTE program, Micromet is eligible to receive an additional cash payment upon initiation of the program, milestones, royalties, and development funding comparable to the first program. Micromet will be primarily responsible for the discovery and pre-clinical development of the BiTE antibodies. Amgen will lead the clinical development, manufacturing, and commercialization of any products resulting from the collaboration.

*Source: Micromet*

### **BMS and Innate Pharma Collaborate for an Investigational Immuno-Oncology Biologic**

Bristol-Myers Squibb (BMS) and Innate Pharma announced a global agreement for the development and commercialization of IPH2102, a novel antibody in Phase I development for the treatment of cancer. Under the terms of the agreement, Innate Pharma will grant to BMS exclusive worldwide rights to develop, manufacture, and commercialize IPH2102 and related compounds blocking KIR receptors. Innate Pharma will continue to develop IPH2102 in acute myeloid leukemia (AML) through to the end of Phase II. Innate Pharma will also provide pre-clinical support for the development of IPH2102. BMS will fund the development of IPH2102, make an upfront payment of \$35 million and additional payments of up to \$430 million, depending on the achievement of prespecified milestones during the development and commercialization period, as well as prespecified tiered double-digit royalty payments on worldwide net sales.

*Source: Innate Pharma*

### **Onconova and SymBio to Collaborate for Rigosertib, a Multi-TKI**

Onconova Therapeutics and SymBio Pharmaceuticals Limited announced that they will collaborate to develop and commercialize rigosertib in Japan and Korea. Onconova is conducting late-stage clinical trials with rigosertib in the US, Europe, and India for the treatment of myelodysplastic syndrome (MDS) and solid tumors. A pivotal trial in the refractory/relapsed MDS clinical program is under way in the US and Europe. The US FDA has granted orphan drug designation for the use of rigosertib in MDS and has agreed to a special protocol assessment (SPA) for the Phase III trial design. The clinical program in solid tumors is also advancing with the initiation of a Phase II/III combination trial in pancreatic cancer and Phase II single agent trial in ovarian cancer.

Under the terms of the agreement, SymBio has an exclusive license for Japan and Korea and will develop and commercialize rigosertib in these countries. Onconova will receive an upfront payment and development milestones tied to the progress of rigosertib, as well as sales milestone payments plus royalties on net sales. The two companies will enter into an agreement for the supply of development stage and commercial product.

*Source: Onconova*

### **Evotec and Roche to Jointly Develop Biomarkers in Oncology**

Evotec and Roche announced collaboration in novel protein activity-based biomarkers for Roche's oncology drugs under development. Evotec will employ its PhosphoScout platform to discover protein phosphorylations that predict favorable dosage and efficacy of targeted cancer drugs in patients. Roche will be responsible for conducting clinical trials and assessing the development of companion diagnostics for patient stratification. Under the initial 3-year term, Evotec and Roche will conduct multiple biomarker programs for therapeutic antibodies or small molecule inhibitors. Evotec will receive undisclosed upfront and success-based payments for each program.

Evotec's PhosphoScout platform employs high-end mass spectrometry to identify and quantify thousands of cellular phosphorylation events on a global scale. Unlike immunoassays, PhosphoScout allows truly unbiased systems-wide profiling of signaling pathways. Monitoring changes in the cellular phosphoproteome in response to drug treatment not only supports mechanistic understanding of targeted drugs but also enables the discovery of predictive biomarkers.

*Source: Evotec*



## Research Highlights

### **CCL2 Recruits Inflammatory Monocytes to Facilitate Breast Tumor Metastasis**

Macrophages, which are abundant in the tumor microenvironment, have diverse roles in tumor progression. At metastatic sites, a distinct population of metastasis-associated macrophages promotes the extravasation, seeding, and persistent growth of tumor cells. Distinct chemokine signals recruit inflammatory and resident monocytes, with inflammatory monocytes responding to CCL2. To understand the origin of macrophages in primary tumors and their metastatic sites, Qian *et al.*, in a study published in *Nature*, measured monocyte trafficking by identifying subpopulations and sorting them into inflammatory monocytes expressing Gr1 and Ly6c and resident monocytes that lacked these markers.

Investigators defined the origin of these macrophages by showing that Gr1-positive inflammatory monocytes are preferentially recruited to pulmonary metastases but not to primary mammary tumors in mice. This process also occurs for human inflammatory monocytes in pulmonary metastases of human breast cancer cells. The recruitment of these inflammatory monocytes, which express CCR2 (the receptor for chemokine CCL2), as well as the subsequent recruitment of metastasis-associated macrophages and their interaction with metastasizing tumor cells, is dependent on CCL2 synthesized by both the tumor and the stroma. Inhibition of CCL2-CCR2 signaling blocks the recruitment of inflammatory monocytes, inhibits metastasis *in vivo* and prolongs the survival of tumor-bearing mice. Depletion of tumor cell-derived CCL2 also inhibits metastatic seeding. Inflammatory monocytes promote the extravasation of tumor cells in a process that requires monocyte-derived vascular endothelial growth factor. These experiments indicate that CCL2 synthesized by metastatic tumor cells and by the target-site tissue stroma is critical for the recruitment of a subpopulation of CCR2-expressing monocytes that enhance the subsequent extravasation of the tumor cells. Mechanistically, this occurs at least in part through targeted delivery of molecules such as VEGFA that promote extravasation. Inflammatory monocytes are continually recruited by a CCL2-dependent mechanism and differentiate into macrophages that promote the subsequent growth of metastatic cells. These data, together with the clinical association of CCL2 overexpression in human cancers with poor prognosis, strongly argue for therapeutic approaches targeted against monocyte recruitment and function for treating metastatic breast cancer.

Source: *Nature*. 2011;475(7355):222-225.

### **BCL6 Enables Ph<sup>+</sup> ALL Cells to Survive BCR-ABL1 Kinase Inhibition**

The *BCR-ABL1* fusion gene is found in nearly all chronic myeloid leukemias (CMLs) and in ~25% of acute lymphoblastic leukemias (ALLs); the resultant oncogenic protein can be targeted by tyrosine kinase inhibitors such as imatinib. Targeted therapies that are toxic only to cells with specific oncogenic lesions can be highly effective until resistance mechanisms emerge. On the basis that the acute cellular response to treatment could reveal protective feedback signaling and hence potential resistance mechanisms, Duy *et al.*, in a study published in *Nature Medicine*, analyzed gene expression changes following imatinib treatment of human *BCR-ABL1* ALL and CML cell lines. They discovered that BCL-6, a transcriptional repressor previously found to be subjected to oncogenic translocations in lymphomas, was highly upregulated. This upregulation appears to be due to reduced signaling through known downstream mediators of BCR-ABL1 signaling.

To investigate whether BCL-6 was cytoprotective through transcriptional repression of known tumor suppressor genes, the authors showed that imatinib treatment causes a modest recruitment of BCL-6 to the promoters of the genes encoding p53, p21, and p27. As evidence that BCL-6 is functionally involved in the repression of tumor suppressor pathways, the authors found that ALL cells deficient for BCL-6 displayed upregulation of p53 and ARF, slower cell cycle progression, impaired colony-forming ability, and enhanced senescence induction. In addition, loss of BCL-6 reduced the *in vivo* transplantation efficiency of ALL cells, indicating a defective stem cell function. As proof that the BCL-6 expression level directly influences the response to imatinib (rather than merely being a readout of BCR-ABL1 inhibition), the authors found that loss or overexpression of BCL-6 had the expected effects on the *in vitro* sensitivity of ALL cells to imatinib. Treatment with retro-inverso BCL-6 peptide inhibitor sensitized leukemias to an alternative BCR-ABL1 inhibitor, nilotinib, and increased the survival of the mice. This suggests that BCL-6 inhibition may hold promise for overcoming clinical resistance to BCR-ABL1 inhibition. This report reinforces the view that the status of signaling pathways downstream of BCR-ABL1 can be an important determinant of the therapeutic response to inhibition and that targeted inhibition of BCL6 can lead to eradication of drug-resistant and leukemia-initiating subclones.

Source: *Nature*. 2011;473(7347):384-388.



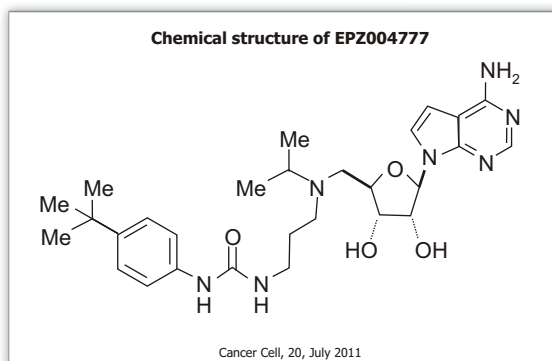
## Research Highlights (Cont'd)

### Selective Killing of MLL Cells by a Potent Small Molecule DOT1L Inhibitor

Mixed lineage leukemia (MLL) is a genetically distinct form of acute leukemia that constitutes more than 70% of infant leukemias and ~10% of adult acute myeloid leukemias (AMLs). MLL represents a particularly aggressive form of leukemia. Patients with this disease generally have poor prognoses and often suffer from early relapse after treatment with current therapies. There is, thus, a great need for new treatment modalities for patients suffering with MLL.

In MLL, chromosomal translocations of the MLL gene result in recruitment of DOT1L to aberrant gene locations. This causes ectopic histone H3, lysine 79 (H3K79) methylation, and increased expression of genes involved in leukemogenesis. DOT1L has thus been proposed as a potential therapeutic target in MLL. In a recent study published in *Cancer Cell*, Pollock *et al.* reported the development of EPZ004777, a potent, selective inhibitor of DOT1L. They designed and characterized EPZ004777 as a starting point toward the development of personalized medicines for the treatment of patients suffering from MLL. The compound blocks cellular H3K79 methylation, inhibits

leukemogenic gene expression, and selectively kills cultured cells bearing MLL translocations. In addition, it was also observed that EPZ004777 has antitumor activity in a mouse MLL xenograft model. The poor pharmacokinetic properties of EPZ004777 preclude its clinical development; however, the researchers are currently developing related inhibitors with improved potency and drug-like properties for this purpose. This work demonstrates the utility of DOT1L inhibition as an approach to targeted therapy for MLL patients.



Source: *Cancer Cell*. 2011;20(1):53-65.

## Clinical Development

### Afinitor Met Primary Endpoint in a Phase III Study in Women with Advanced BC

Novartis announced that an interim analysis of a pivotal Phase III, BOLERO-2 (Breast cancer trials of Oral Everolimus-2) study, which showed that Afinitor (everolimus) tablets in combination with exemestane significantly extended progression-free survival (PFS), compared with placebo plus exemestane in women with advanced breast cancer.

The BOLERO-2 study enrolled more than 700 postmenopausal women with estrogen receptor-positive locally advanced or metastatic breast cancer, whose disease has progressed, despite treatment with the nonsteroidal aromatase inhibitors letrozole or anastrozole. The primary endpoint was PFS. Secondary endpoints included overall survival, overall response rate, incidence of adverse events, patient-reported outcomes, and clinical benefit rate. The trial was stopped early after interim results showed the primary endpoint of PFS was met. Results will be presented at an upcoming medical conference, and worldwide regulatory submissions are being planned by the end of 2011.

Source: *Novartis*

### Pertuzumab Meets Primary Endpoint in HER2-positive Metastatic Breast Cancer

Roche announced that CLEOPATRA (Clinical

Evaluation Of Pertuzumab And TRastuzumab), a pivotal Phase III study, met its primary endpoint in HER2-positive metastatic breast cancer (mBC) patients. The two-arm study enrolled 808 people with previously untreated HER2-positive mBC from 19 countries worldwide. The primary study endpoint was progression-free survival as assessed by an independent review. Secondary endpoints were overall survival, safety profile, overall response rate, duration of remission, quality of life, and correlation of biomarkers with clinical outcomes.

The study showed that people with HER2-positive mBC who received the combination of two targeted medicines, pertuzumab and Herceptin (trastuzumab), plus docetaxel chemotherapy lived significantly longer without their disease getting worse (progression-free survival) than did people who received only Herceptin and docetaxel. No new safety signals were observed, and adverse events were consistent with those seen in previous studies of pertuzumab and Herceptin, either in combination or alone. Pertuzumab is a monoclonal antibody being studied in early-stage HER2-positive mBC. It is an investigational HER2-targeted medicine called a HER2 dimerization inhibitor (HDI). Roche is planning to submit the study results for global regulatory approval this year.

Source: *Roche*



## Clinical Development (Cont'd)

### Phase II Trial of Ganetespib Shows Activity in Advanced NSCLC

Synta Pharmaceuticals presented results at the International Association for the Study of Lung Cancer (IASLC) 14<sup>th</sup> World Conference, held from July 3 to 7 in Amsterdam, the Netherlands, from a Phase II single-agent clinical trial of ganetespib in advanced non-small cell lung cancer (NSCLC) that showed promising clinical activity in patients with progressive disease. Ganetespib is a potent inhibitor of heat shock protein 90 (Hsp90) currently being studied in a broad range of clinical trials.

Of the 23 patients in the Phase II trial tested for ALK translocation or rearrangement (ALK+), eight patients were ALK+ in at least one assay. Six of these eight patients (75%) showed tumor shrinkage in target lesions, one patient showed no change in tumor size, and one patient achieved stable disease (tumor growth < 20%). The disease control rate in this population was 7/8 (88%), and the objective response rate (CR + PR) was 4/8 (50%). At the IASLC meeting, an additional case study was presented demonstrating that the combination of ganetespib and docetaxel is active in a patient whose disease has progressed after ganetespib single-agent treatment.

Source: *Synta Pharmaceuticals*

### Positive Phase II Results of Vismodegib in Advanced BCC

Genentech announced that a pivotal Phase II study with vismodegib, a hedgehog cell-signaling pathway inhibitor, showed positive results in people with advanced basal cell carcinoma (BCC) for whom surgery is considered inappropriate. ERIVANCE BCC, an international, single-arm, multicenter, two-cohort, open-label, Phase II study enrolled 104 patients with advanced BCC. Study participants received 150 mg vismodegib orally, once daily until disease progression or intolerable toxicity. The primary endpoint of the trial showed an overall response rate (ORR) of 43% in the locally advanced BCC cohort, and 30% in metastatic BCC, as assessed by independent review. Study investigators assessed the ORR for locally advanced BCC and metastatic BCC at 60% and 46%, respectively (secondary endpoint). The median duration of PFS by independent review for both metastatic and locally advanced BCC patients was 9.5 months. In addition, the clinical benefit rate showed vismodegib shrank tumors or healed visible lesions, or prevented them from growing any further in 75% of patients, as assessed by independent review. The most common drug-related adverse events were muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite, and diarrhea.

Genentech is developing vismodegib in collaboration with Curis. In order to provide patients with advanced BCC who are appropriate candidates access to vismodegib while Genentech discusses next steps

with FDA, the company is conducting an expanded patient access study in the US.

Source: *Genentech*

### Promising OS Data of Baviximab from Phase II Trial in NSCLC

Peregrine Pharmaceuticals reported promising median overall survival (OS) of 12.4 months from a Phase II clinical trial evaluating baviximab, a first-in-class phosphatidylserine-targeting monoclonal antibody, plus carboplatin and paclitaxel in patients with previously untreated, locally advanced or metastatic NSCLC. This survival is 20% longer than the 10.3 month median OS from a separate historic control trial using carboplatin and paclitaxel alone in a similar patient population. This new median OS data point is consistent with encouraging earlier data from this trial, including ORR of 43% and median PFS of 6.1 months, versus historic control data of 15% ORR and 4.5 months PFS.

"A two month extension in patient survival is significant in this aggressive form of cancer and we are excited to have another therapy in later-stage clinical development to meet this urgent medical need," commented Raghunadharao Digumarti, MD, principal investigator of this trial.

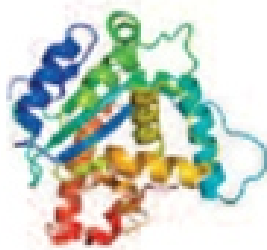
Source: *Peregrine Pharmaceuticals*

### Phase II Results of MLN8237 in B-cell and T-cell NHL

Millennium: The Takeda Oncology Company announced the presentation of results from an ongoing Phase II study of MLN8237, an investigational Aurora A kinase inhibitor, in patients with relapsed/refractory aggressive B-cell and T-cell non-Hodgkin's lymphoma (NHL). These data were reported in an oral presentation at the 11<sup>th</sup> International Congress on Malignant Lymphoma, held from June 15 to 18 in Lugano, Switzerland. Results from the ongoing multicenter Phase II study were reported in 48 patients with relapsed/refractory aggressive B-cell or T-cell NHL. Out of total patients enrolled, 83% (n = 40) of patients had B-cell NHL, and 17% (n = 8) had T-cell NHL. Patients had received a median of three prior therapies. The results from 41 evaluable patients showed the following:

- ORR was 32% (n = 13).
- CR rate was 12% (n = 5).
- ORR was 57% (n = 4) among T-cell NHL patients and 26% (n = 9) among B-cell NHL patients.
- The most common grade 3 or higher adverse events were neutropenia, thrombocytopenia, stomatitis, and fatigue.
- The most common nonhematologic adverse events were fatigue, diarrhea, alopecia, and somnolence.

Source: *Millennium: The Takeda Oncology Company*



## Biomarkers

### Elevated Expression of CUEDC2 Protein Confers Endocrine Resistance in Breast Cancer

Resistance to endocrine therapies is one of the major barriers to the successful treatment of breast cancer. Estrogen receptor- $\alpha$  (ER- $\alpha$ ) expression is currently the main biomarker of response to endocrine therapy. Although reduced expression of ER- $\alpha$  is a known contributing factor to endocrine resistance, the mechanism of ER- $\alpha$  downregulation in endocrine resistance is still not fully understood. Elucidating the regulation of ER- $\alpha$  expression may provide new therapeutic targets for overcoming endocrine resistance. The CUE domains are small, moderately conserved ubiquitin-binding domains of ~40 amino acids found in a variety of eukaryotic proteins. These proteins are involved in the recognition of monoubiquitin and polyubiquitin as well as in facilitating intramolecular monoubiquitination. The function of CUE domain-containing protein-2 (CUEDC2) remains largely undefined.

In a study published in *Nature Medicine*, Pan *et al.* investigated the possible role of CUEDC2 protein in controlling ER- $\alpha$  expression and found that CUEDC2 downregulates ER- $\alpha$  stability through the ubiquitin-proteasome pathway. The expression of CUEDC2 was increased in breast cancers and was inversely correlated with ER- $\alpha$  expression. People with tumors that highly expressed CUEDC2 had a weaker response to tamoxifen treatment and relapsed early. Moreover, ectopic expression of CUEDC2 rendered breast cancer cells resistant to tamoxifen, raising the possibility that CUEDC2 acts as a determinant of endocrine resistance in breast cancers. Several lines of evidence suggest that re-expressing ER- $\alpha$  in ER- $\alpha$ -negative breast cancer cells can restore tamoxifen sensitivity. Therefore, restoring ER- $\alpha$  expression by inhibiting CUEDC2 provides a potential new strategy for restoring tamoxifen sensitivity. Thus, CUEDC2 is potentially a new predictive marker of endocrine resistance and might be a therapeutic target for tamoxifen resistance in breast cancers.

Source: *Nature Medicine*. 2011;17(6):708-714.

### Alternatively Spliced NKp30 Isoforms Affect the Prognosis of Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) result from the aberrant signaling from oncogenic tyrosine kinase

receptors, usually the one encoded by KIT. The malignancy expresses NKp30 ligands and is treated with natural killer (NK)-stimulatory KIT tyrosine kinase inhibitors. Delahaye *et al.*, in a study published in *Nature Medicine*, showed that the therapeutic off-target effect of tyrosine kinase inhibitors is mediated by NK cells and dendritic cells (DCs). By inhibiting KIT in DCs, the drugs can promote DC-to-NK crosstalk that ultimately stimulates NK cells to produce interferon- $\gamma$  (IFN- $\gamma$ ). The drug-induced IFN- $\gamma$  production by NK cells represents an independent predictor of long-term survival in advanced GIST treated with these agents. Researchers demonstrated that alternative splicing of the *NCR3* gene has a profound impact on its functions and that the distinct NKp30 isoforms can relay opposed signals that are either immunostimulatory or immunosuppressive. On analyzing GIST-associated NK cell phenotypes, they detected a predominant downregulation of one particular type of stimulatory NK cell receptors, NKp30 (but not NKp46 or NKG2D). NKp30 is involved in the recognition of tumor and DCs. They described the influence of three NKp30 splice variants on the prognosis of GIST.

Healthy individuals and those with GIST show distinct patterns of transcription of functionally different NKp30 isoforms. In a retrospective analysis of 80 individuals with GIST, predominant expression of the immunosuppressive NKp30c isoform (over the immunostimulatory NKp30a and NKp30b isoforms) was associated with reduced survival of subjects, decreased NKp30-dependent tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and CD107a release, and defective IFN- $\gamma$  and interleukin-12 (IL-12) secretion in the NK-DC crosstalk that could be restored by blocking of IL-10. Preferential NKp30c expression resulted partly from a single-nucleotide polymorphism at position 3790 in the 3' untranslated region of the gene encoding NKp30. The genetically determined NKp30 status predicts the clinical outcomes of individuals with GIST independently from *KIT* mutation. Subclassifying metastatic GIST on the basis of the NKp30 profile might help in designing innovative clinical trials. Thus, beyond its utility as a biomarker, the mutational status of the NKp30 locus and its expression profile could guide a new type of NK-centered, GIST-specific immunotherapy.

Source: *Nature Medicine*. 2011;17(6):700-707.

## Regulatory

### Ipilimumab Approved for the Treatment of Previously Treated Advanced Melanoma in the EU

Bristol-Myers Squibb announced that the European Commission has approved YERVOY (ipilimumab), a

cytotoxic T-lymphocyte antigen 4 inhibitor, for the treatment of adult patients with previously treated advanced melanoma.

The approval is based on a Phase III, double-blind





## Regulatory (Cont'd)

study that randomized 676 patients with unresectable or metastatic melanoma who were previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Patients were randomized in a 3:1:1 ratio to receive YERVOY (3 mg/kg) in combination with the investigational peptide vaccine gp100 (n = 403), YERVOY alone (3 mg/kg; n = 137), or gp100 alone (n = 136). Kaplan-Meier estimated survival rate at 1 year was 46% in the YERVOY arm versus 25% in the gp100 arm. The estimated survival rate at 2 years was 24% in the YERVOY arm versus 14% in the gp100 arm. Patients treated with YERVOY had a 34% reduction in the risk of death over the gp100 control arm. Patients treated with YERVOY (ipilimumab) plus gp100 had a 32% reduction in the risk of death over the gp100 control arm. Median overall survival was 10, 10, and 6 months for the YERVOY alone, YERVOY + gp100 arm, and gp100 alone arms, respectively.

On March 25, 2011, the FDA approved YERVOY 3 mg/kg for the treatment of patients with unresectable (inoperable) or metastatic melanoma in the US.

*Source: Bristol-Myers Squibb*

### Positive CHMP Opinion for Vectibix in Combination with Chemotherapy

Amgen announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion recommending that Vectibix (panitumumab) be approved for use in the EU in 1<sup>st</sup> line in combination with FOLFOX and in 2<sup>nd</sup> in combination with FOLFIRI in patients who have received 1<sup>st</sup> fluoropyrimidine-based chemotherapy (excluding irinotecan) for patients with wild-type KRAS metastatic colorectal cancer (mCRC), following a successful re-examination procedure by Amgen. Data from studies 20050203 (PRIME) and 20050181 ('181) showed that adding Vectibix to either FOLFOX or FOLFIRI chemotherapy improved PFS versus chemotherapy alone for patients with wild-type KRAS mCRC. In addition, the overall response rate of Vectibix plus chemotherapy was higher than chemotherapy alone. Although numerically greater, the improvement in median overall survival did not achieve statistical significance in the Vectibix arm of either trial.

Vectibix is already approved and established in 40 countries as a monotherapy treatment for patients with wild-type KRAS mCRC, when standard chemotherapy is no longer effective. In the US, Vectibix received accelerated approval in September 2006 as a monotherapy for the treatment of patients with EGFR-expressing mCRC after disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

*Source: Amgen*

### FDA Grants Accelerated Approval of ISTODAX in PTCL

Celgene Corporation announced that the US FDA has granted accelerated approval for its supplemental new drug application (sNDA) for an additional indication for ISTODAX (romidepsin), a histone deacetylase inhibitor, for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. ISTODAX is also approved for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. These indications are based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated. PTCL approval was based on a priority (6 month) review by the FDA.

The ISTODAX sNDA approval is based on results from two studies, a Phase II, multicenter, international, open-label, single-arm study of ISTODAX in patients with PTCL who had failed at least one prior systemic therapy, which was presented at the 2010 American Society of Hematology annual meeting; and a single-arm clinical study of ISTODAX in patients with PTCL who had failed prior therapy.

*Source: Celgene*

### Genentech Provides Update from FDA Hearing on Avastin for Metastatic BC

Genentech announced that during an FDA hearing, the FDA's Oncologic Drugs Advisory Committee (ODAC) recommended that the FDA withdraw its approval of Avastin (bevacizumab) in combination with paclitaxel chemotherapy for previously untreated (1<sup>st</sup> line) HER2-negative metastatic breast cancer (BC). The committee's recommendation is not the final decision, and Avastin plus paclitaxel is still FDA-approved for women with HER2-negative metastatic BC. The FDA Commissioner will make the final decision on whether Avastin should remain approved for metastatic BC.

"We are very disappointed by the committee's recommendation and hope the Commissioner does not decide to remove this important medicine for women with an incurable disease who already have too few treatment options," said Hal Barron, MD, chief medical officer and head, Global Product Development.

*Source: Genentech*



### What is in the Report?

SmartAnalyst will survey 50 U.S./E.U. KOLs and payers on the implications of key data presented at the covered conference and captures general market trend information. The ASCO 2011 report will focus on 23 assets across six cancer types. The results will be compiled into an Executive Summary.

Prostate	<ul style="list-style-type: none"> <li>• J&amp;J (COU-AA-301)</li> <li>• Exelixis (Cabozantinib)- Ph II</li> <li>• Takeda (TAK-700)</li> </ul>
Breast	<ul style="list-style-type: none"> <li>• Novartis (Dovitinib)- Ph II</li> <li>• Celgene (nab-paclitaxel)</li> </ul>
Ovarian	<ul style="list-style-type: none"> <li>• Celgene (nab-paclitaxel)</li> <li>• Roche (Bevacizumab)</li> <li>• AstraZeneca (Olaparib)</li> <li>• Sanofi (Iniparib)- Ph II</li> </ul>
Melanoma	<ul style="list-style-type: none"> <li>• GSK (MAGE-A3)</li> <li>• BMS (Ipilimumab)</li> <li>• Roche/Genentech (Vemurafenib)</li> <li>• Celgene (nab-paclitaxel)</li> </ul>
Lung	<ul style="list-style-type: none"> <li>• Roche/Genentech (Erlotinib)</li> <li>• Sanofi (Iniparib)</li> <li>• Genentech/Roche (MetMAB)</li> <li>• Synta (Ganetespib)</li> </ul>
Hematological	<ul style="list-style-type: none"> <li>• Clavis Pharma (Elacystarabine)</li> <li>• Eli Lilly (Ezastaurin)</li> <li>• Pfizer (Inotumumab)</li> </ul>
mRCC	<ul style="list-style-type: none"> <li>• AVEO Pharmaceuticals (Tivozanib [AV-951])</li> <li>• Pfizer (Axitinib)</li> <li>• Novartis (Everolimus)</li> </ul>

Contact your SmartAnalyst Business Development Director, email a request for order form to [mtuli@smartanalyst.com](mailto:mtuli@smartanalyst.com), or call (212) 331-0010.

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