

INTELLIGENT INSIGHTS. SMART RESULTS

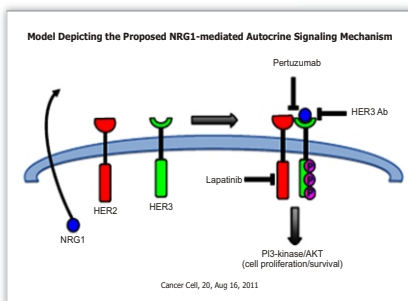


**SMARTConference First Insights Report**  
 Insight from U.S. KOLs and payers into the impact of data presented at ESMO September 23 - 27, 2011 Conference in Stockholm  
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## In the Spotlight:

### Neuregulin-1-mediated Tumors May Benefit from HER2:HER3-targeted Therapies

Several mutationally activated kinases are clinically validated cancer drug targets. Consequently, there is rapidly growing interest in tumor genotyping to prospectively identify patients most likely to benefit from these agents. However, genomic testing may not capture all patients who might derive benefit from such medicines because oncogenic kinase-mediated pathways do not necessarily require mutational activation.



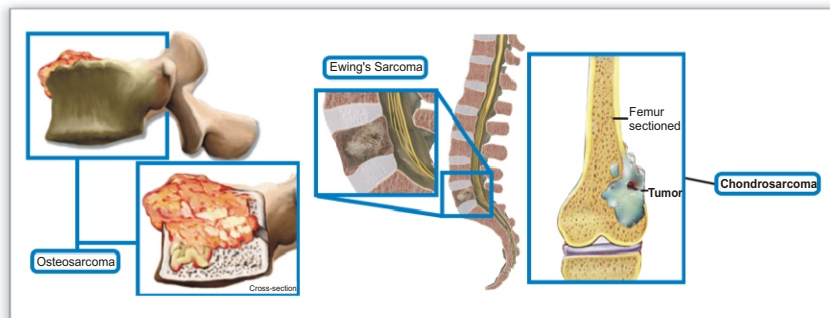
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### Tumor of the Month - Bone Cancer

August is the bone cancer awareness month. Primary bone cancer is rare, accounting for less than 1% of all cancers, with only about 2300 new cases reported in the US each year. Bone comprises different tissues, including osteoid (compact bone), cartilaginous, fibrous tissue, and marrow. Bone cancer classification correlates to the tissue type from which it originated. Secondary bone tumors can also result from a cancer whose primary origin was another organ in the body, such as lung, prostate, or breast, and had metastasized to the bone.

Common types of primary bone cancers include osteosarcoma, Ewing's sarcoma, and chondrosarcoma. Osteosarcoma is predominantly found in children and adolescents 10-19 years of age.

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### Business News

Array Announces New Oncology Agreement with Genentech

[Read More...](#)

### Research Highlights

Compromised CDK1 Activity Sensitizes BRCA-proficient Cancers to PARP Inhibition

[Read More...](#)

### Clinical Development

Top-line Phase II Results for Ofatumumab in 2<sup>nd</sup> Line Aggressive Lymphoma

[Read More...](#)

### Biomarkers

Secondary Somatic Mutations Restoring BRCA1/2 Predict Chemotherapy Resistance

[Read More...](#)

### Regulatory

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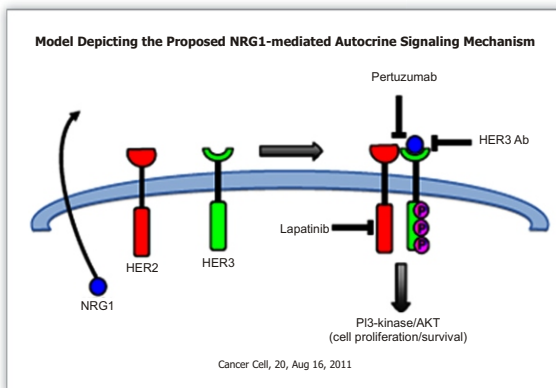
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## Spotlight Report

### Neuregulin-1-mediated Tumors May Benefit from HER2:HER3-targeted Therapies



Several mutationally activated kinases are clinically validated cancer drug targets. Consequently, there is rapidly growing interest in tumor genotyping to prospectively identify patients most likely to benefit from these agents. However, genomic testing may not capture all patients who might derive benefit from such medicines because oncogenic kinase-mediated pathways do not necessarily require mutational activation.

By profiling nearly 700 human cancer cell lines, Wilson *et al.* have identified a subset of non-HER2-amplified

cancer cells with sensitivity to HER2 kinase inhibition - particularly from head and neck tumors. These cells were found to depend on a neuregulin-1 (NRG1)-mediated autocrine loop driving HER3 activation, resulting in its heterodimerization with HER2. HER2 subsequently phosphorylates HER3, resulting in the activation of the PI3K/Akt pathway promoting cell survival and proliferation. This pathway can be inhibited at multiple steps: first, by preventing NRG1 from binding HER3 using HER3-targeted antibodies; second, by preventing HER2:HER3 heterodimerization using a heterodimer-blocking antibody such as pertuzumab; and finally, by inhibiting HER2 kinase activity, using an HER2 TKI such as lapatinib. Elevated NRG1 expression and activated HER3 are strongly associated with lapatinib sensitivity *in vitro*, and these biomarkers were enriched in a subset of primary head and neck cancer samples. The findings suggest that patients with NRG1-driven tumors lacking HER2 amplification may derive significant clinical benefit from HER2:HER3-directed therapies. These observations also highlight the potential importance of identifying non-mutationally driven receptor tyrosine kinase (RTK) dependencies in human tumors to inform biomarker strategies for clinical development of selective kinase inhibitors.

Source: *Cancer Cell*. 2011 Aug; 20(2):158-172.

## Tumor of the Month - Bone Cancer

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Common types of primary bone cancers include **osteosarcoma**, Ewing's sarcoma, and chondrosarcoma. Osteosarcoma is predominantly found in children and adolescents 10-19 years of age. Although the exact cause is unknown, osteosarcoma may result from previous exposure to high-dose external radiation therapy or anti-cancer drugs. It is also speculated that the rapid bone growth seen during adolescence may be related to its development. This

type of bone cancer originates in the osteoid compact tissue and often occurs in the knee and upper arm. **Chondrosarcoma** occurs mainly in the cartilaginous tissue found in the pelvis, upper leg, and shoulder. Chondrosarcoma patients are usually over 40 years old and the risk increases with age. **Ewing's sarcoma** predominantly affects adolescent boys under 19 years of age. It can arise in the soft tissue, but usually originates in the bone along the backbone, legs, arms, and pelvis. Only a small percentage of bone cancers are related to heredity. Other types of bone tumors also include chordomas and giant cell tumor of the bone. **Chordomas** are speculated to arise from pieces of notochord that failed to properly break down. In most cases, the cause is sporadic, although inherited gene mutations have also been linked to its development. Chordomas can occur in the skull, causing headache or impaired vision, in the spine or tailbone, resulting in pain and numbness. **Giant cell bone tumors** occur spontaneously, and in rare cases may be linked with



## Tumor of the Month (Cont'd)

hyperparathyroidism and Paget's disease. Patients with giant cell tumor have pain in the area of the tumor, along with fluid accumulation in the nearby joint. There is also an increased risk of bone breakage in the affected area.

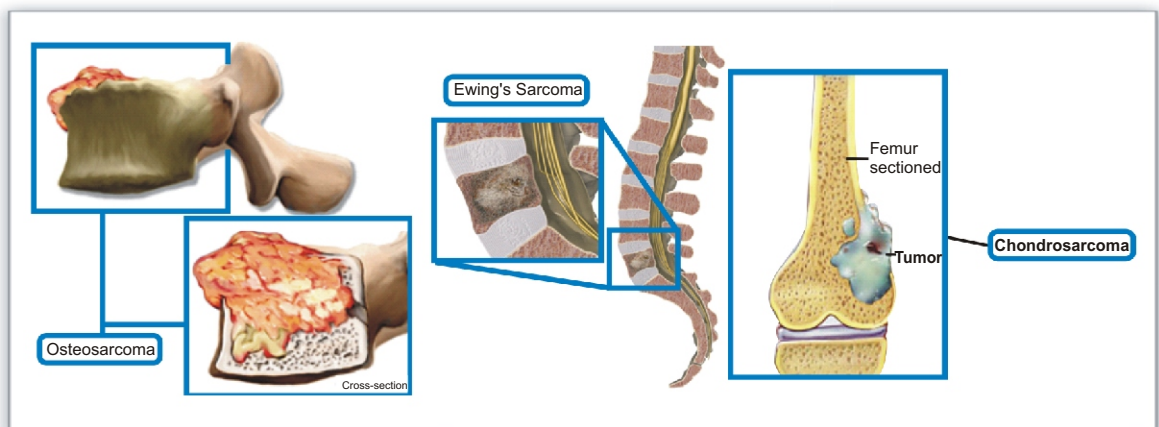
Bone cancer usually manifests with persistent pain and/or unusual swelling in or near the bone. Bones may also be weakened and susceptible to breaks and fractures. More systemic, nonspecific symptoms that may also manifest include fatigue, fever, weight loss, and anemia. Symptoms can vary, depending on the size and location of the tumor. Bone cancers are detected through X-ray, bone scan, CT scan, MRI, or PET, accompanied by a biopsy and blood test measuring levels of alkaline phosphatase, although high levels of ALP are normally present in growing children. Treatment for bone cancer depends on the size, location, and stage of the cancer, as well as a patient's performance status. Treatment options include surgery, chemotherapy, radiation therapy, and cryosurgery, with surgery being the most common.

Recent advancements and improvements have been achieved in the surgical removal of bone tumors, in order to spare limbs and maximize limb function. Surgery may involve a bone graft (auto- or allograft), rotationplasty, or prosthetic implant. Cryosurgery may be used as an alternative to surgery. Radiation therapy is often used to treat chondrosarcoma and Ewing's sarcoma. Chemotherapy is normally administered as combination regimens and may also be combined with radiation therapy. **Chondrosarcoma** is classified by location and histology and hence, is the basis for its treatment. There is currently no standard chemotherapy regimen for conventional chondrosarcoma (grades 1-3). Mesenchymal chondrosarcoma treatment follows guidelines for the treatment of Ewing's sarcoma, and treatment of dedifferentiated chondrosarcoma follows that of osteosarcoma. Patients with **Ewing's sarcoma** may

receive 1<sup>st</sup> line therapy chemotherapy regimen combinations VAC/IE (vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide), VAI (vincristine, doxorubicin, ifosfamide), or VIDE (vincristine, ifosfamide, doxorubicin, etoposide). Relapsed and refractory patients may receive combinations containing cyclophosphamide, topotecan, temozolomide, irinotecan, ifosfamide, etoposide, carboplatin, docetaxel, and/or gemcitabine as 2<sup>nd</sup> line therapy. **Osteosarcoma** patients may be administered 1<sup>st</sup> line combinations containing cisplatin, doxorubicin, high-dose methotrexate, ifosfamide, etoposide, and/or epirubicin. Relapsed and refractory patients may be administered 2<sup>nd</sup> line therapy containing docetaxel, gemcitabine, cyclophosphamide, etoposide, topotecan, ifosfamide, and/or carboplatin.

There are currently several agents undergoing clinical trials for the treatment of bone tumors, including ridaforolimus, bevacizumab, imatinib, dasatinib, and cixutumumab. Ridaforolimus, an mTOR inhibitor, is currently in Phase III testing as a maintenance therapy for patients with metastatic soft tissue sarcoma or bone sarcoma. Bevacizumab is undergoing Phase III testing in combination with chemotherapy as a 1<sup>st</sup> line therapy for patients with osteosarcoma. Cixutumumab, a monoclonal antibody targeting the insulin growth factor receptor IGF-1R, is being tested in Phase III trials for patients with previously treated, advanced Ewing's sarcoma. Imatinib and dasatinib, agents currently used for the treatment of chronic myelogenous leukemia, are being studied in Phase II trials for the treatment of chordomas, chondrosarcoma, and giant cell bone tumors.

Source: [www.cancer.gov](http://www.cancer.gov); NCCN guidelines Version 2.2011 Bone Cancer; [www.macmillian.org.uk](http://www.macmillian.org.uk); [www.clinicaltrials.gov](http://www.clinicaltrials.gov); [www.cancerindex.org](http://www.cancerindex.org); [www.webmd.com](http://www.webmd.com); [www.health.uab.edu/13975](http://www.health.uab.edu/13975); [www.cancer.org](http://www.cancer.org); [www.mayoclinic.org](http://www.mayoclinic.org)





## Business News

### Array Announces New Oncology Agreement with Genentech

Array BioPharma announced an oncology agreement with Genentech, a member of the Roche Group, for the development of each company's small-molecule, Checkpoint kinase 1 (ChK-1) program. ChK-1 is a protein kinase that regulates the tumor cell's response to DNA damage often caused by treatment with chemotherapy. The programs include Genentech's compound GDC-0425 (RG7602), currently in Phase I, and Array's compound ARRY-575, which is being prepared for an investigational new drug application to initiate a Phase I trial in cancer patients.

Under the terms of the agreement, Genentech is responsible for all clinical development and commercialization activities. Array will receive an upfront payment of \$28 million and is eligible to receive clinical and commercial milestone payments of up to \$685, million and up to double-digit royalties on sales of any resulting drugs. Full financial terms have not been disclosed.

Source: Array BioPharma

### Roche Acquires mtm Laboratories AG, Expanding Offering in Cervical Cancer Testing

Roche announced that it has signed an agreement, under which it will acquire 100% of mtm laboratories AG (mtm), a privately held company based in Heidelberg, Germany. mtm is a global leader in developing *in vitro* diagnostics, with a focus on early detection and diagnosis of cervical cancer. mtm will become a part of Roche's Tissue Diagnostics (Ventana Medical Systems, Inc.) business unit. Under the terms of the agreement, Roche will pay mtm shareholders an upfront payment of nearly €130 million, as well as up to €60 million upon achieving performance-related milestones.

mtm's proprietary test solutions are based on the p16 biomarker and have been developed for the identification and diagnosis of pre-cancerous cervical lesions. p16, a gene involved in tumor suppression in the cell, is an established marker of the early oncogenic process leading to cancer. The level of p16 protein becomes markedly increased after persistent HPV infection leads to oncogenic transformation of cells in the cervix. In addition to p16's benefit to cervical cancer testing, p16 has been reported to have emerging clinical utility in other cancers, including anogenital cancers, head and neck cancer, lung cancer, and breast cancer.

Source: Roche



## Research Highlights

### Compromised CDK1 Activity Sensitizes BRCA-proficient Cancers to PARP Inhibition

Cyclin-dependent kinase 1 (Cdk1) is a core component of the cell cycle machinery and participates upstream in DNA damage response pathways. Its function in S phase checkpoint control is compromised in Cdk1-depleted cells; consequently, cancer cells are sensitized to a range of DNA-damaging agents. Cdk1 phosphorylates breast cancer-associated 1 (BRCA1) and this phosphorylation is necessary for BRCA1 to efficiently form foci at sites of DNA damage and to facilitate checkpoint activation. BRCA1 is also crucial for DNA repair by homologous recombination. When poly (ADP-ribose) polymerase (PARP) is inhibited, single-strand breaks (SSBs) degenerate to more lethal double-strand breaks (DSBs) that require repair by homologous recombination. Cells that are deficient in homologous recombination, such as those that lack functional BRCA1 or BRCA2, are hypersensitive to inhibition of PARP. However, BRCA-deficient tumors represent only a small fraction of adult cancers, which might restrict the therapeutic utility of PARP inhibitor monotherapy.

In a study published in *Nature Medicine*, Johnson *et al.* showed that Cdk1 is necessary not only for BRCA1-mediated S phase checkpoint activation, but also for homologous recombination. Consequently, depletion or inhibition of Cdk1 compromises the ability of cells to repair DNA by homologous recombination and sensitizes them to PARP inhibition both *in vitro* and *in vivo*. Furthermore, non-transformed cells or tissues do not become sensitized to treatment with a PARP inhibitor. Combined inhibition of Cdk1 and PARP in BRCA-wild-type cancer cells results in reduced colony formation, delayed growth of human tumor xenografts, and tumor regression with prolonged survival in a mouse model of lung adenocarcinoma. Inhibition of Cdk1 does not sensitize non-transformed cells or tissues to inhibition of PARP. Because reduced Cdk1 activity impairs BRCA1 function and consequently, repair by homologous recombination, depletion or inhibition of Cdk1 creates a state of "BRCAness" in transformed cells and represents a plausible strategy for expanding the utility of PARP inhibitors to BRCA-proficient cancers.

Source: *Nature Medicine*. 2011 Jun 26;17(7):875-82.



## Research Highlights (Cont'd)

### **Pim-2, a Serine/Threonine Kinase, a Novel Anti-apoptotic Mediator in Myeloma Cells**

Multiple myeloma (MM) cells enhance osteoclast (OC) formation and suppress osteoblast (OB) differentiation of bone marrow stromal cells (BMSCs). This not only creates destructive bone lesions, but also provides a cellular microenvironment to protect MM cells from various apoptotic insults. IL-6 and TNF family cytokines TNF- $\alpha$ , BAFF, and APRIL are among the predominant anti-apoptotic factors for MM cells elaborated by the bone marrow microenvironment surrounding MM. IL-6 is mainly produced by BMSCs, whereas OCs are a major producer of BAFF and APRIL in the MM bone marrow microenvironment. The serine/threonine kinase Pim-2 has been demonstrated to be transcriptionally up-regulated to promote survival of hematopoietic cells in response to ambient growth factors and cytokines.

In a study published in *Leukemia*, Asano *et al.* demonstrated that Pim-2 is up-regulated in MM cells by BMSCs and OCs, and acts as an important pro-survival mediator. IL-6 and TNF family cytokines (TNF- $\alpha$ , BAFF and APRIL, but not IGF-1) cooperatively enhance the expression of Pim-2 in MM cells. The MM bone marrow microenvironment up-regulates Pim-2 expression in MM cells through activation of the JAK2/STAT3 pathway for IL-6 and the NF- $\kappa$ B pathway for TNF family cytokines to promote MM cell survival. Pim-2 short interfering RNA reduces MM cell viability in co-cultures with BMSCs or OCs. Thus, up-regulation of Pim-2 appears to be a novel anti-apoptotic mechanism for MM cell survival. Therefore, Pim-2 overexpressed in MM cells in the MM bone marrow microenvironment appears to be an important therapeutic target. IGF-1 is another critical microenvironment-derived survival factor for MM cells, and inhibition of the IGF-1/PI3K/Akt pathway by Akt or mammalian target of rapamycin inhibitors has drawn considerable attention as a new therapeutic modality against MM. Because Pim-2 up-regulation is largely independent of the PI3K/Akt pathway, and

because inhibition of Pim-2 and PI3K/Akt pathways cooperatively reduces MM cell survival, Pim-2 should be targeted to improve anti-MM efficacy together with PI3K/Akt pathway inhibitors. A therapeutic impact of Pim-2 inhibition on MM survival would be further warranted when potent specific inhibitors for Pim-2 become available.

*Source: Leukemia. 2011 Jul;25(7):1182-8.*

### **PHLPP1 Acts as Tumor Suppressor Gene in Prostate Cancer**

Hyperactivation of the PI3-kinase/Akt pathway is a driving force of many cancers. Recent genetic studies in mice have shown that neoplasia and cancer in PTEN-deficient prostate depend on Akt activation. Because PHLPP1/2 are the two known phosphatases to specifically revert this activation, Chen *et al.* determined the relevance of PHLPP1 as a tumor suppressor by combining GEM (genetically engineered mice) modeling with patient whole genome analysis.

Results demonstrated that PHLPP1 loss causes neoplasia and partial Pten-loss causes carcinoma in mouse prostate. This genetic setting initially triggers a growth-suppressive response via p53 and the PHLPP2 ortholog, and reveals spontaneous TP53 inactivation as a condition for disease progression. These findings were further validated in 218 human prostate cancer samples. The co-deletion of PTEN and PHLPP1 in patient samples is highly restricted to metastatic disease and tightly correlated to deletion of p53 and PHLPP2. These data establish a conceptual framework for progression of PTEN-mutant prostate cancer to life-threatening disease. The study concluded that PHLPP1 is a tumor suppressor in human prostate cancer, and strong activation of Akt signaling through loss of PTEN and PHLPP1 is associated with the loss of TP53. The coincidence of these three deletion events is frequent in metastatic prostate cancer, but absent from primary tumors.

*Source: Cancer Cell. 2011 Aug; 20(2):173-186.*

## Clinical Development

### **Top-line Phase II Results for Ofatumumab in 2<sup>nd</sup> Line Aggressive Lymphoma**

Genmab announced top-line results from a Phase II study of ofatumumab, a human monoclonal antibody in combination with salvage chemotherapy to treat relapsed or refractory aggressive lymphoma, including diffuse large B-cell lymphoma (DLBCL).

A total of 61 patients with aggressive lymphoma, who had persistent or progressive disease after 1<sup>st</sup> treatment with rituximab combined with chemotherapy, were treated in the study. The primary

objective of the study was to evaluate the overall response rate of patients to ofatumumab in combination with ICE (ifosfamide-carboplatin-etoposide) or DHAP (cytosine arabinoside-cisplatin-dexamethasone) chemotherapy, according to the criteria, Revised Response Criteria for Malignant Lymphoma, recognized by regulatory authorities. The overall response rate (ORR) was 61%. There were no unexpected safety findings. The most common grade 3 or higher adverse events were thrombocytopenia (59% patients), anemia (36%), neutropenia (26%),



## Clinical Development (Cont'd)

lymphopenia (23%), leukopenia (18%), febrile neutropenia (13%), and hypokalemia (13%).

These data will be submitted for presentation at the December 2011 Annual Meeting of the American Society of Hematology (ASH) in San Diego, US. In the US, ofatumumab is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

Source: *Genmab*

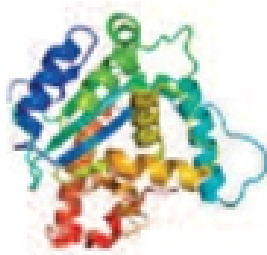
### Positive Interim Results from a Phase III Trial in Ovarian Cancer with Paclical

Oasmia has completed an interim analysis of the ongoing Phase III study in ovarian cancer. The interim analysis, based on data from nearly 400 patients, showed the expected efficacy of Paclical compared to the comparator Taxol. The results pointed toward a favorable efficacy for Paclical. Oasmia has developed a new approach for evaluation of a cancer drug that involves a biomarker, CA125. CA125 (cancer antigen 125) is a protein, often elevated in women with ovarian cancer. It is a blood test and the analysis of CA125 is used in clinical practice to evaluate the

treatment of ovarian cancer. An increased value in a woman previously diagnosed with ovarian cancer is usually an indication of progression. This has not previously been used to evaluate the efficacy of a Phase III study. The design of the study is in accordance with the scientific advice received by the European Medicines Agency (EMA), in 2008. The interim analysis was performed by calculating the levels of CA125 using a method developed in collaboration with experts in the field and in accordance with the scientific advice received by the EMA in 2008.

Results from the interim analysis show that Paclical reduces CA125 to the same level as Taxol. The results will provide the basis for submission for marketing authorization. The filing process will start immediately. The ongoing clinical study will continue as planned to collect additional data on, e.g., PFS and OS. Based on these results, Oasmia will apply for marketing authorization for Paclical in the EU and some countries within the emerging markets, for ovarian cancer.

Source: *Oasmia*



## Biomarkers

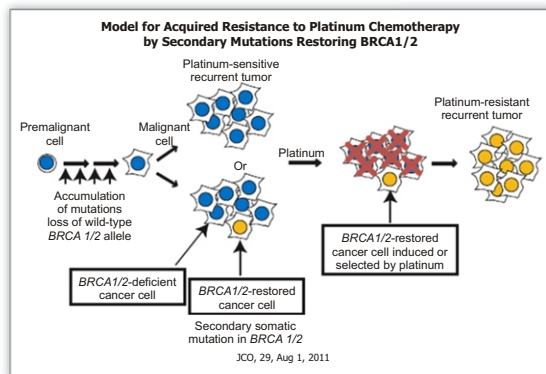
### Secondary Somatic Mutations Restoring BRCA1/2 Predict Chemotherapy Resistance

Nearly 15% of ovarian carcinomas occur in women with heterozygous germline mutations in *BRCA1* and *BRCA2* (*BRCA1/2*), with most having deletions of the wild-type *BRCA1/2* allele, leading to a neoplasm deficient in the *BRCA1/2* protein. Majority of women with *BRCA1/2*-mutated ovarian carcinomas ultimately develop recurrent disease that is resistant to platinum agents.

A recent retrospective study published in *JCO* by Norquist *et al.* adds to the current understanding of *BRCA1/2* carcinogenesis, and reveals that the presence of secondary somatic mutations that restore *BRCA1/2* in recurrent carcinomas is significantly correlated with resistance to both cisplatin and PARP inhibitors. Loss of heterozygosity in *BRCA1/2* leads to a carcinoma deficient in the *BRCA1/2* protein. This carcinoma with decreased ability to repair DNA then becomes highly sensitive to DNA cross-linking agents such as platinum drugs. Secondary mutations restoring the DNA repair function of *BRCA1/2* can occur within the carcinoma, likely as a consequence of prior chemotherapy or perhaps from genomic instability and spontaneous mutation. This restoration of DNA repair can then lead to acquired resistance to platinum and likely resistance to PARP inhibition. The researchers also found that the presence of a secondary mutation restoring *BRCA1/2* is a better predictor of platinum resistance than interval since last treatment. Additionally, secondary mutations are significantly more common in recurrent carcinomas

sampled after more than one chemotherapy regimen than those sampled after a single chemotherapy regimen. There was a marked association between prior history of breast carcinoma and secondary mutations in either primary or recurrent ovarian carcinomas, with breast carcinoma often preceding ovarian carcinoma by many years. The ability to predict the response to platinum chemotherapy is clinically valuable, as it would allow the avoidance of unnecessary toxicity and earlier use of alternate agents. Although this work supports the clinical utility of testing for secondary mutations in *BRCA1/2*-mutated ovarian carcinomas to predict platinum resistance, clinical implementation may be challenging because this is a technically demanding test requiring careful microdissection and allelic identification.

Source: *J Clin Oncol.* 2011 Aug 1;29(22):3008-15.





## Biomarkers (Cont'd)

### Prognostic Influence of *DNMT3A* Mutations in Acute Myeloid Leukemia

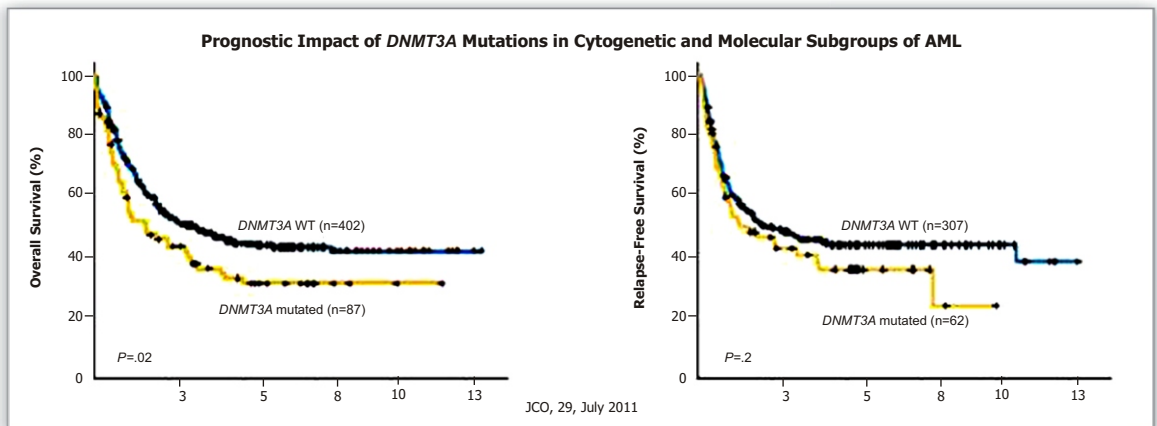
Acute myeloid leukemia (AML) is a complex disease caused by mutations, deregulated gene expression, and epigenetic modifications of genes, leading to increased proliferation and decreased differentiation of hematopoietic progenitor cells. Molecular markers in AML have helped to better characterize patients, improve risk stratification, especially in patients with cytogenetically normal AML (CN-AML). Some of these markers have clinical implications for transplant indications and the use of targeted therapy. Important examples are mutations in Nucleophosmin 1 (*NPM1*) and CCAAT/enhancer-binding protein alpha (*CEBPA*), both of which are associated with a favorable outcome and lack of a transplant benefit. In contrast, FMS-like tyrosine kinase 3 (*FLT3*) mutations are associated with adverse outcomes. Mutations in the DNA methyltransferase 3A (*DNMT3A*) gene have been associated with a negative impact on overall survival (OS), but the prognostic impact of *DNMT3A* mutations in terms of impact on remission rate and relapse-free survival (RFS) is still missing.

In a study published in *JCO*, Thol *et al.* investigated the frequency and prognostic influence of *DNMT3A* mutations in AML. Their results show that *DNMT3A* mutations are one of the most frequent molecular aberrations currently observed in AML. Mutations in *DNMT3A* are independently associated with a negative prognosis, especially in patients with CN-AML belonging to the *NPM1/FLT3*-ITD high-risk group.

*DNMT3A* mutations were associated with a higher platelet count and bone marrow blast count. Additionally, such patients were more likely to have mutations in *NPM1* and *IDH1*, with a trend toward a higher *FLT3* mutation rate. Survival analysis showed a significant negative prognostic effect of *DNMT3A* mutations for OS, specifically seen in patients with CN-AML. It also conferred a negative prognosis in patients with wild-type *FLT3* and wild-type *NPM1*. Interestingly, *DNMT3A* mutations had no prognostic effect in patients with mutated *NPM1*. These findings suggest that *DNMT3A* mutations have a stronger effect on disease proliferation and treatment resistance in AML cells that are more immature than more mature AML. The workers also evaluated the effect of *DNMT3A* mutation status on transplantation outcome and found no significant difference in OS among *DNMT3A*-mutated patients with a related donor, compared with patients without a related donor.

These prognostic findings suggest that *DNMT3A* sequencing in patients at the time of diagnosis adds valuable information for risk stratification, but may be limited to patients with CN-AML. Additionally, *DNMT3A* mutations should be analyzed in treatment trials with novel drugs to identify agents with a specific effect in patients with *DNMT3A* mutation. Hypomethylating agents and histone deacetylase inhibitors are the most obvious candidate drugs for evaluation.

Source: *J Clin Oncol.* 2011 Jul 20;29(21):2889-96.



## Regulatory

### FDA Approves Vemurafenib and Companion Diagnostic for BRAF Mutation Positive Metastatic Melanoma

US FDA approved Roche's Zelboraf (vemurafenib) for the treatment of BRAF V600E mutation-positive, inoperable or metastatic melanoma, as determined by an FDA-approved test. The FDA also approved the cobas 4800 BRAF V600 Mutation Test, a diagnostic

test developed by Roche to identify patients eligible for treatment. Zelboraf is the 1<sup>st</sup> and only FDA-approved personalized medicine shown to improve survival in people with BRAF V600E mutation-positive metastatic melanoma, demonstrating the benefits of Roche's personalized healthcare approach. It is designed to target and inhibit some mutated forms of the BRAF protein found in about half of all cases of



## Regulatory (Cont'd)

melanoma, the deadliest and most aggressive form of skin cancer.

The FDA approval of Zelboraf is based on results from two clinical studies (BRIM3 and BRIM2) in people with BRAF V600E mutation-positive, inoperable or metastatic melanoma as determined by the cobas BRAF Mutation Test. Zelboraf should be used only in people whose inoperable or metastatic melanoma carries a BRAF V600E mutation, which can be determined by the FDA-approved cobas BRAF Mutation Test. The cobas BRAF Mutation Test has improved sensitivity, accuracy and speed compared to other commonly used, unapproved detection methods. Zelboraf will be available in the US within two weeks of approval. Roche has also submitted NDAs for Zelboraf in the EU, Switzerland, Australia, New Zealand, Brazil, India, Mexico and Canada.

*Source: Roche*

### **Merck Submitted an MAA for Ridaforolimus in EU**

ARIAD Pharmaceuticals announced that its ridaforolimus partner Merck has submitted a marketing authorization application (MAA) for ridaforolimus with the European Medicines Agency (EMA). The application was submitted on July 29, 2011 and marks the start of Merck's global submission strategy for ridaforolimus, which includes Europe, US, Canada, Asia-Pacific and Latin America, and other key markets around the world.

ARIAD expects Merck to submit a new drug application (NDA) in the US shortly. If approved, the oral ridaforolimus, an investigational mTOR inhibitor, would be the first molecularly targeted drug for the treatment of patients with metastatic sarcomas and the first sarcoma drug to be approved for use in the maintenance setting. Following completion of the administrative validation process for the MAA by the EMA, which is targeted for mid-August, the application will have been accepted and the scientific review will begin. Acceptance of the MAA will trigger a \$25 million milestone payment by Merck to ARIAD. Approval of ridaforolimus in the US will secure a \$25 million milestone payment by Merck to ARIAD, and approval to sell ridaforolimus, including pricing approval, in the EU will secure a \$10 million milestone payment.

*Source: ARIAD Pharmaceuticals*

### **Talon Files Marqibo NDA in ALL**

Talon Therapeutics submitted its new drug application (NDA) for Marqibo to the US FDA, seeking accelerated approval of Marqibo in adult Ph-ALL (acute

lymphoblastic leukemia) in second or greater relapse or that has progressed following two or more prior lines of anti-leukemia therapy. Marqibo is a novel, targeted Optisome-encapsulated formulation product candidate of the FDA-approved anticancer drug vincristine.

There is a significant unmet medical need in this rare hematologic malignancy where Marqibo may provide significant benefit. Marqibo's pivotal study in this advanced and heavily pre-treated population, including those requiring 3<sup>rd</sup> through 7<sup>th</sup> line therapy and with an ECOG performance status of 0-3, resulted in an overall remission rate of 20% with side effects that were predictable and manageable with no unexpected toxicities. Currently available 3<sup>rd</sup> line, single-agent therapies induce few responses ( $\leq 4\%$ ) and are highly toxic.

*Source: Talon Therapeutics*

### **FDA Accepted Eisai's sNDA for Dacogen in AML**

The US FDA has accepted Eisai's supplemental new drug application (sNDA) for review, seeking approval of Dacogen (decitabine) for injection in the treatment of acute myeloid leukemia (AML). Dacogen has been marketed by Eisai in the US since 2006 as a treatment for myelodysplastic syndromes (MDS). AML is a life-threatening cancer of the blood for which there are few treatment options. Acceptance of the sNDA indicates that the FDA has found the company's submission to be sufficiently complete for review. The sNDA was submitted on May 6, 2011 to the FDA.

The application is based on a Phase III randomized open-label, multicenter trial (DACO-016) comparing Dacogen versus patient's choice with physician's advice of either supportive care or low-dose cytarabine in patients 65 years and older with newly diagnosed *de novo* or secondary AML and with poor- or intermediate-risk cytogenetics. Of the 485 patients, 242 were randomized to Dacogen and 243 to patient's choice of supportive care or low-dose cytarabine. Dacogen was administered at 20 mg/m<sup>2</sup> for one hour by intravenous infusion once daily for five consecutive days, repeated every four weeks, continued as long as the patient derived benefit. Patients treated with cytarabine received 20 mg/m<sup>2</sup> subcutaneously once daily for 10 consecutive days, every four weeks. The median duration of treatment for patients on Dacogen was 4.4 months, compared to 2.4 months in the cytarabine group.

*Source: Eisai*




## SMARTConference First Insights Report

Insight from U.S. KOLs and payers into the impact of data presented at ESMO September 23 - 27, 2011 Conference in Stockholm

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**First Insights Report goes beyond the surface. It provides timely competitive intelligence from key clinical and reimbursement decision makers**

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PDF slide format and complementary live or Web presentation of the results

Rapid insight from  
**25 US and EU KOLs and 25 payers** on the implications of key data presented at the covered conference.  
Results compiled into an Executive Summary

- ◆ Understand the impact on treatment choice and reimbursement
- ◆ Gain intelligence on competitive pipeline and inline products
- ◆ Determine optimal pathways for pipeline clinical development programs
- ◆ Identify acquisition opportunities

### Cancer Types and Therapeutic Agents Covered:

<b>Lung Cancer</b>	<ul style="list-style-type: none"> <li>• Vorinostat</li> <li>• Iniparib</li> <li>• Afatinib</li> </ul>
<b>Ovarian Cancer</b>	<ul style="list-style-type: none"> <li>• Bevacizumab</li> </ul>
<b>Melanoma</b>	<ul style="list-style-type: none"> <li>• Veliparib</li> <li>• Vemurafenib</li> </ul>
<b>Breast Cancer</b>	<ul style="list-style-type: none"> <li>• Everolimus</li> <li>• Trastuzumab emtansine</li> <li>• Sorafenib</li> </ul>
<b>Colorectal Cancer</b>	<ul style="list-style-type: none"> <li>• Afibercept</li> <li>• Cetuximab</li> </ul>
<b>Prostate Cancer</b>	<ul style="list-style-type: none"> <li>• Alpharadin</li> <li>• Abiraterone acetate</li> <li>• Denosumab</li> </ul>



- **A SMART Synopsis of Today's Oncology Headlines. We find the stories that matter most, so you don't have to.**

- **An E-Newsletter that both educates and informs.**

- **SmartAnalyst is a strategic consulting firm that has supported multiple pharma client engagements over a ten-year history. Oncology has been a core indication of analytical focus.**

- **SMARTOncology is a reflection of SmartAnalyst's Oncology experience and expertise. We inform our readers about headlining news that matters most, while also educating our audience with "Tumor of The Month" articles and supplementing issues with our own Key Insights.**

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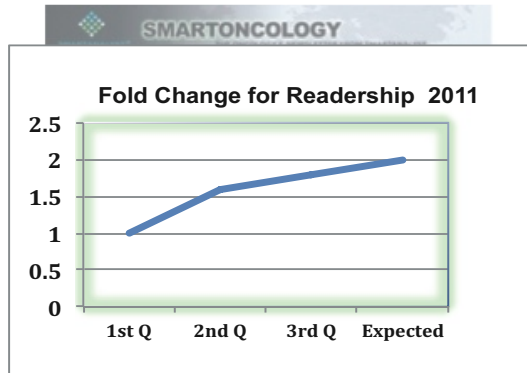
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