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INTELLIGENT INSIGHTS. SMART RESULTS

In the Spotlight:

Comprehensive Genomic Characterization of Squamous Cell Lung Cancers

Lung squamous cell carcinoma (SQCC) is a common type of lung cancer, causing ~400,000 deaths per year worldwide. Genomic alterations in squamous cell lung cancers have not been comprehensively characterized, and molecularly targeted agents have not been specifically developed for its treatment. Meyerson *et al.* conducted a comprehensive study of lung SQCCs from a large cohort of patients as a part of The Cancer Genome Atlas (TCGA) project. They profiled 178 lung squamous cell carcinomas to provide a comprehensive landscape of genomic and epigenomic alterations. This tumor type displayed a large number and variety of DNA alterations with a mean of 360 exonic mutations, 323 altered copy number segments, and 165 genomic rearrangements per tumor.

At the level of whole chromosome arm SCNAs (somatic copy number alterations), lung SQCCs exhibit many similarities to 205 cases of lung adenocarcinoma as analyzed by TCGA. The most notable difference between these cancers is selective amplification of chromosome 3q in lung SQCC. There were 50 peaks of significant amplification or deletion, several of which included SCNAs that were previously seen in lung SQCCs including SOX2, PDGFRA and/or KIT, EGFR, FGFR1 and/orWHSC1L1, CCND1, and CDKN2A. Other peaks that defined regions of SCNA included amplifications of chromosomal segments containing NFE2L2, MYC, CDK6, MDM2, BCL2L1, and EYS and deletions of FOXP1, PTEN, and NF1.

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Tumor of the Month: Neuroblastoma

While childhood cancer has been on the rise since 1975,[1] the incidence of neuroblastoma (NB), which accounts for 7% of childhood cancers, has remained constant. Approximately 650 children are diagnosed with neuroblastoma each year in the US and ~2/3 of these patients will have metastatic disease at the time of diagnosis. It is the most common cancer in children under the age of one. The average age of a patient diagnosed with NB is 1-2 years old; 90% of all cases are seen in children under the age of 5 and is seen rarely in children over the age of 10.

Neuroblastomas perplexed the medical community, as the tumors are known to spontaneously regress in some cases. This may be due to the biology of the disease. Neuroblastomas begin in the early nerve cells of the sympathetic nervous system: One third of the tumors begin in the adrenal glands, one third begin in the sympathetic nerve ganglion of the abdomen, and most of the remaining tumors begin in the sympathetic ganglia near the spine in the cheek, neck or pelvis.[1] The immature nerves that form the tumor may differentiate into mature neurons, resulting in a benign ganglioneuroma, or may die. Currently, tumors that spontaneously regress show close to a triploid number of chromosomes. These tumors do not show MYCN amplification or loss of chromosome 1p or telomerase expression, but do seem to express Ha-ras and TrkA. Ganglioneuroblastomas are stroma-rich, localized tumors.[2] The stroma seems to secrete factors that inhibit growth and metastasis of the tumor cells.

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Spotlight Report

Comprehensive Genomic Characterization of Squamous Cell Lung Cancers

Lung squamous cell carcinoma (SQCC) is a common type of lung cancer, causing ~400,000 deaths per year worldwide. Genomic alterations in squamous cell lung cancers have not been comprehensively characterized, and molecularly targeted agents have not been specifically developed for its treatment. Meyerson *et al.* conducted a comprehensive study of lung SQCCs from a large cohort of patients as a part of The Cancer Genome Atlas (TCGA) project. They profiled 178 lung squamous cell carcinomas to provide a comprehensive landscape of genomic and epigenomic alterations. This tumor type displayed a large number and variety of DNA alterations with a mean of 360 exonic mutations, 323 altered copy number segments, and 165 genomic rearrangements per tumor.

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Lung SQCC gene expression sub-type signatures were applied to both of the expression platforms, yielding four sub-types designated as classical (36%), basal (25%), secretory (24%), and primitive (15%). The classical sub-type was characterized by alterations in KEAP1, NFE2L2, and PTEN as well as pronounced hypermethylation and chromosomal instability. The 3q26 amplicon was present in all of the sub-types, but it was most characteristic of the classical sub-type, which also showed the greatest overexpression of three known oncogenes on 3q: SOX2, TP63, and PIK3CA. The primitive expression sub-type more commonly exhibited RB1 and PTEN alterations, and the basal expression sub-type showed NF1 alterations. Amplification of FGFR1 and WHSC1L1 was anti-correlated with the classical sub-type and specifically with NFE2L2 or KEAP1 mutated samples. Although CDKN2A alterations are common in lung SQCCs, they are not associated with any particular expression sub-type.

The current study has identified a potentially targetable gene or pathway alteration in most lung SQCC samples studied. This data can help to organize efforts to analyze lung SQCC clinical tumor specimens for a panel of specific, actionable mutations to select patients for appropriately targeted clinical trials. It could thereby help to facilitate effective personalized therapy for this deadly disease.

Source: Nature. 2012 Sep 27;489(7417):519-25

Tumor of the Month - Neuroblastoma

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benign ganglioneuroma, or may die. Currently, tumors that spontaneously regress show close to a triploid number of chromosomes. These tumors do not show MYCN amplification or loss of chromosome 1p or telomerase expression, but do seem to express Ha-ras and TrkA. Ganglioneuroblastomas are stroma-rich, localized tumors.[2] The stroma seems to secrete factors that inhibit growth and metastasis of the tumor cells.

When comparing patients diagnosed between 1974 and 1989 to patients diagnosed between 1999 and 2005, the 5-year overall survival increased from 46% to 71%.[3] The NCI is careful to note that this statistic can be misleading due to heterogeneity in NBs. Age is a key determinant in the prognosis for 5-year survival; patients younger than 1 year at the time of diagnosis have a 90% survival rate. This decreases dramatically as the age of diagnosis increases: 68% for 1 to 4 years, 52% for 5 to 9 years, 66% for 10 to 14 years. In children over the age of 18 months, the survival rate for stage IV disease is 30-50% even with aggressive therapy. Patients are divided into low, intermediate, and high-risk patients. Other characteristics that affect prognosis include clinical stage of the disease, site of the primary tumor, tumor histology, and regional lymph node involvement (for patients older than 1 year).[3]

The NCI identifies three distinct types of Neuroblastoma.[3] Type 1 NB, which has the best prognosis and often spontaneously regresses, expresses the Trk A neurotropin receptor, and is hyperdiploid. Type 2 NB expresses both the TrkB neurotropin receptor and its ligand. Patients with Type 2 NB have genomically unstable tumors that gain chromosome 17q and show loss of heterozygosity at chromosomes 14q or 11q. Finally, Type 3 NB shows amplification of the MYCN gene, gain of 17q, and loss of 1p. Types 2 and 3 have poor prognoses.

Currently, the types of NB are not used to determine treatment. MYCN amplification and activation of Myc-dependent gene expression predict poor outcome, but many aggressive tumors do not express MYCN.[2] High expression of MRP1 and acquisition of an additional copy of 17q are both independent indicators of poor prognosis. Poor survival is predicted by low expression of GABA receptor-associated protein (GABARAP) and GABA (A) alpha2 receptor subunit,[4] consistent with the undifferentiated phenotype of the neurons. Genome wide association studies identified SNPs on chromosome 6p22 that correlate with aggressive tumors.[5]

Although only 1-2% of neuroblastoma is inherited, most patients with inherited disease are diagnosed before they are a year old. Mutations in the ALK gene are associated with familial neuroblastoma. ALK mutations are also seen in 8-12% of spontaneous neuroblastomas.[3] ALK is one target of the small molecular inhibitor, crizotinib, which is currently being tested in clinical trials for NB.

In patients with localized disease, the standard of care is surgical resection. The disease should be accurately staged by dissecting nearby lymph nodes and tissue should be obtained for biological studies.[3] Patients in the low-risk category also undergo surgical resection. If their disease is symptomatic, particularly if there is spinal compression, chemotherapy is used. Standard chemotherapy for NB patients includes a cocktail of carboplatin, cyclophosphamide, doxorubicin, and etoposide. In order to minimize long-term side effects, the lowest effective cumulative doses possible are used. Intermediate-risk patients are treated with 12-24 weeks of the above chemotherapy regimen following surgery. The same regimen is used at high doses in patients with high-risk disease. They may also receive high doses of ifosfamide and cisplatin. After a response is seen, the patients undergo surgery followed by myeloablative chemotherapy, autologous stem cell transplantation (ASCT), and possibly irradiation of the residual tumor. They then receive six months of oral 13-cis-retinoic acid.[3]

Limited Phase III clinical trials are ongoing for neuroblastoma; one of those is addressing abnormal muscle movement in NB patients (NCT00033293) and one looks at the use of sodium thiosulfate to prevent hearing loss in patients being treated with cisplatin (NCT00716976).

The GD2 antigen, which is found in neuroblastomas are targeted by the human-mouse chimeric monoclonal antibody, ch14.18, in two Phase III trials (NCT00026312 and NCT00030719). NCT00026312 is currently in its second phase, which begins on day 56 after ASCT. Patients will receive GM-CSF (IV or SC, sargramostim) on days 0-13 of courses 1, 3, and 5 and ch14.18 (IV) on days 3-6 of courses 1 through 5. During courses 2 and 4, patients will receive IL-2 infusion on days 0-3 and 7-10. In the absence of disease progression or unacceptable toxicity, this therapy will be repeated every 28 days for 5 courses. Beginning on day 11 of immunotherapy, patients will also receive isotretinoin (oral) twice daily for 14 days, which will be repeated every 28 days for 6 courses. Primary outcome is EFS. Multiple secondary outcomes will be addressed.

The official title of NCT00030719 is "Combination Chemotherapy With or Without Filgrastim Before Surgery, High-Dose Chemotherapy, and Radiation Therapy Followed by Isotretinoin With or Without Monoclonal Antibody in Treating Patients With Neuroblastoma." The trial sponsor is University Hospitals of Leicester NHS Trust. Patients will be randomized to one of eight arms.

Dr. Giselle Sholler at the Van Andel Research Institute is running a Phase I/II trial to test the efficacy of

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adding TPI287, a synthetic, third-generation taxane, to a regimen of temozolomide and irinotecan (NCT0150508). One hundred thirty-two patients will be randomized to the comparator or experimental arms. Both arms have 28-day cycles. Patients in the comparator arm will receive temozolomide (100 mg/m^2) on days 1-5 and irinotecan (I.V., 10 mg/m^2) on days 1-5 and 8-12. If these patients progress prior to completion of the sixth cycle, they will be allowed to cross-over to the experimental arm. Patients in the experimental arm will have TPI287 (125 mg/m^2) on days 1, 8, and 15 of each cycle, in addition to the drugs given to those patients in the comparator arm. Primary outcome measures are adverse events as a measure of safety and tolerability and ORR. Secondary outcome measures include ORR, PR, quality of life, PK, PFS, median OS, and assessment of pain.

Memorial Sloan Kettering has several protocols testing the monoclonal antibody, 3F8, which targets the GD2 antigen expressed on some neuroblastomas and has been used since 1987.[6,7] They are also testing a bivalent vaccine in conjunction with β-glucan in NCT00911560. The vaccine covalently links the antigens GD2L and GD3L to keyhole limpet hemocyanin. The trial will include oral β-glucan, which augments neutrophil cytotoxicity as well as OPT-821, which serves as an immunoadjuvant.[8] In this dose escalation study, patients will receive seven subcutaneous injections at weeks 1, 2, 3, 8, 30, 32, and 52. The two weeks on, two weeks off cycle for β-glucan (40 mg/kg/day) will begin six or seven weeks after the vaccinations begin and may extend up to one cycle after the last vaccination. Primary outcomes include the maximum tolerated dose of OPT-821, EFS in patients having a second (or later) complete/very good partial response, and assessment of anti-NB activity via molecular assessment of the bone marrow. Secondary outcomes include determination of whether the vaccine produces an immune response against the target antigens, determination of anti-neuroblastoma activity of the vaccine plus β-glucan, determination of the immune response against the target antigens, assessment of gene polymorphisms in FcRIIa, FcRIIIa, CR3, and CD18 for possible association with outcome.

The Children's Oncology Group (COG) is testing the Aurora A kinase inhibitor, MLN8237 (alisertib), in 228 patients with recurrent or refractory solid tumors (including neuroblastoma) or leukemia (NCT01154816). Overall response rate (ORR) will be the primary outcome measure; toxicity and PK are secondary outcome measures. Patients will be stratified according to the type of tumor. In each 21-day cycle, patients will receive oral alisertib once daily on days 1 to 7 for up to 35 courses. Unacceptable toxicity or disease progression will stop treatment. Patients will be followed for up to five years after completing the regimen.

COG is also testing crizotinib, the oral, small molecule inhibitor of ALK and c-Met, in patients with relapsed or refractory solid tumors (including neuroblastoma) or anaplastic large cell lymphoma (NCT00939770). In this open-label, Phase I/II study, 196 patients will receive crizotinib twice daily for 28 days. In the absence of unacceptable toxicity or disease progression, the cycle will repeat every 28 days. Primary outcomes are maximum tolerated dose, toxicities of the dosing schedule, and pharmacokinetics.

Bevacizumab is tested in two Phase II trials for neuroblastoma. In one, NCT01114555, patients with relapsed or refractory NB will be given bevacizumab in combination with irinotecan and temozolomide. On days 1 and 15, patients will receive bevacizumab (IV, 15 mg/kg/dose). On day 4, they will receive concurrent doses of irinotecan (IV, 50 mg/m^2/day x 5) and temozolomide (PO, 150 mg/m^2/day x 5 days). Tumor response to the combination of drugs is the primary outcome. Secondary outcome measures include toxicity of the combination, evaluation of angiogenic markers, and time to progression.

In NCT01492673, bevacizumab will be tested in conjunction with cyclophosphamide and topotecan in relapsed/refractory Ewing's sarcoma, and neuroblastoma. This open-label, single group trial consists of 21-day treatment cycles. On day-3, patients will receive bevacizumab. On days 0-4 of every cycle, patients will receive cyclophosphamide (IV, 250 mg/m^2/day) over 30 minutes followed by topotecan (IV, 0.75 mg/m^2/day) over 30 minutes. Bevacizumab is the only drug whose dose will be modified. Primary outcomes include efficacy as measured by ORR after two treatment cycles and duration of response. Safety is the secondary outcome measured.

Business News

VentiRx Collaborates with Celgene for Development of TLR8 Agonist VTX-2337

VentiRx Pharmaceuticals announced the formation of an exclusive, world-wide collaboration with Celgene Corporation for the development of VTX-2337, a highly potent and selective TLR8 agonist for the treatment of cancer. VentiRx has advanced VTX-2337 into clinical trials designed to evaluate the compound in multiple oncology indications in combination with a variety of anti-cancer agents, including chemotherapy and monoclonal antibody therapy.

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Under terms of the agreement, Celgene will provide a $35 million upfront payment to fund further research and development of VTX-2337 through pre-defined clinical endpoints. During the option period, VentiRx will be eligible to receive additional funding, including a potential equity investment by Celgene.

Source: VentiRx Pharmaceuticals

MacroGenics and Servier Enter Strategic Alliance to Develop and Commercialize Anti-cancer DART Products

MacroGenics and Servier announced that they have entered into an option agreement for the development and commercialization of Dual-Affinity Re-Targeting (DART) products directed at three undisclosed tumor targets. MacroGenics' DART technology is a proprietary, bi-specific antibody platform in which a single recombinant molecule is able to target two different antigens. These DART proteins can be used to redirect the body's cell-destroying, immune effector cells against tumor cells.

Under the terms of the agreement, MacroGenics will receive a $20 million upfront payment. MacroGenics retains full development and commercialization rights to the three pre-clinical DART programs in the US, Canada, Mexico, Japan, Korea, and India, while Servier has the option to obtain an exclusive license covering the rest of the world for each of the programs. Servier may exercise its option for one of the programs prior to IND submission, and for each of the other two programs upon completion of an initial Phase 1 clinical trial. If Servier exercises such options, MacroGenics will receive option exercise fees, which, when combined with preclinical milestones, would total an additional $80 million. MacroGenics could also receive up to an additional $1 billion in clinical, regulatory, and commercialization milestone payments for the three programs. Both parties will share the clinical development costs for each program following the exercise of such option. Finally, MacroGenics may receive tiered, double-digit royalties on future net sales.

Source: MacroGenics

Quest PharmaTech Acquires Immunoglobulin E Technology from Advanced Immune Therapeutics for the Treatment of Cancer

Quest PharmaTech has signed a technology purchase agreement with Advanced Immune Therapeutics to acquire all of the assets related to their AllergoOncology technology, a new technology based on tumor associated Immunoglobulin E (IgE) antibody for the treatment of cancer.

The AllergoOncology technology is both novel and attractive since there is increasing evidence of an inverse correlation between levels of IgE and the incidences of several cancers, which strongly suggests a potential role of IgE in modulating cancer biology and cancer immunotherapy.The acquired technology platform includes two pending US patent applications and potential product candidates for breast and prostate cancer treatment. Under the purchase agreement, Advanced Immune Therapeutics will receive 500,000 common shares of Quest. The deal also provides single-digit royalty payments on future revenues.

Source: Quest PharmaTech

Sanofi and Massachusetts General Hospital Launch Oncology Research Collaboration

Sanofi announced a 2-year agreement with Massachusetts General Hospital (MGH) aimed at furthering translational medicine research to develop new treatments for various types of hematological malignancies and solid tumors. The project-based collaboration unites scientists from MGH and Sanofi, with the goal of maximizing the strengths of both academic and industry cross-organizational expertise, and will include both pre-clinical and clinical translational research to elucidate questions from proof-of-concept to tolerability, efficacy, and effectiveness.

Sanofi has incorporated a translational and experimental medicine (T&EM) approach to drug discovery and clinical development, combining an expertise in biological science with a deep understanding of the needs of patients with complex diseases. The company has fully integrated T&EM into the drug discovery and development processes, with a dedicated team of basic research and T&EM experts delivering scientific tools and designs around predictive biomarkers, molecular/mechanistic proof-of-concept (mPOC), identification of rational combinations, and interpretation of resistance mechanisms to identify patients most likely to respond to a given therapy. The initial agreement is two years with the option to extend for a longer term at the discretion of both partners. Financial details of the collaboration were not disclosed.

Source: Sanofi

LLS and Celgene Corporation Announce Partnership to Accelerate Blood Cancer Therapies

The Leukemia & Lymphoma Society (LLS) and Celgene Corporation announced a partnership to identify and fund promising blood cancer research projects. The collaboration will leverage LLS's infrastructure for the identification and acceleration of innovative research at academic centers in priority research areas with significant unmet medical need. These projects will rapidly advance the scientific and

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medical understanding of the haematological malignances. Celgene and LLS will also work together through LLS's Therapy Acceleration Program (TAP) to partner with biotechnology companies to speed the development of novel blood cancer treatments.

The Celgene partnership is the first for LLS's new "Targets, Leads & Candidates Program" a novel approach to venture philanthropy partnerships with the pharmaceutical industry. These partnerships are critical for patients as they have the potential to bring together the most innovative academic science and transform it more quickly with pharmaceutical company resources into critically needed therapies.

Source: Leukemia & Lymphoma Society (LLS)

Medimmune Collaborates with Leading Cancer Organizations to Advance Novel Immunotherapy Research

The Cancer Research Institute (CRI), the Ludwig Institute for Cancer Research, and MedImmune have signed an agreement to advance the research of immunotherapy in cancer. The research will focus on clinical trials to test novel combinations of immunotherapies, including three investigational monoclonal antibodies from MedImmune's pipeline. These monoclonal antibodies include the CTLA-4 blocking antibody (tremelimumab), an OX40 receptor agonist antibody, and a B7 homolog 1 (or Programmed Death-1 Ligand 1) blocking antibody.

The Ludwig Institute and CRI will conduct trials of cancer immunotherapy combinations using three investigational monoclonal antibodies that MedImmune will provide to CRI and the Ludwig Institute from its product pipeline, combined with other priority agents available to the CRI/Ludwig portfolio or potentially accessed through additional partnerships. In addition to the combination trials, MedImmune will continue its original development plan for the three agents, which are currently being studied in pre-clinical and clinical studies. The clinical trials will be conducted by CRI and the Ludwig Institute through their jointly coordinated global Cancer Vaccine Collaborative (CVC) network of clinical immunologists and oncologists with extensive knowledge and focus on immunotherapy programs.

Source: MedImmune

Research Highlights

LIFR is a Breast Cancer Metastasis Suppressor Upstream of the Hippo-YAP Pathway and a Prognostic Marker

Breast cancer begins as a local disease and can metastasize to the lymph nodes and other organs. Surgery, chemotherapy, and radiation therapy can control many localized tumors, but the overall utility of these treatment methods in restricting the development of metastasis and treating metastatic disease is limited. New technologies have led to the identification of molecules that contribute to the development of metastasis. In this study, Ma *et al.* investigated E-cadherin–independent functions of miR-9 and identified LIFR (leukemia inhibitory factor receptor) as a miR-9 target in E-cadherin–negative tumor cells and a new metastasis suppressor.

LIFR is highly relevant in human tumors: Although 94% of normal breast tissues have high LIFR expression, this protein is down regulated or lost in a significant fraction of patients with DCIS or invasive breast cancer, and is inversely associated with lymph node metastasis in patients with invasive breast carcinoma. Significantly, tumors with loss of LIFR correlated with poor prognosis in ~1,000 women with non-metastatic stage I–III breast cancer. It was found that LIFR functions through the Hippo-YAP pathway to suppress metastasis. Whereas a conserved Hippo kinase cascade has been established in *Drosophila* and mammals, the cell membrane receptors that activate Hippo signaling remain elusive. LIFR alters Scribble localization and activates the MST-LATS-YAP phosphorylation cascade. Taken together with previous findings, miR-9 can target two alternative metastasis suppressors, LIFR and E-cadherin; whereas E-cadherin maintains adherens junctions and sequesters β-catenin at the cytoplasmic membrane, LIFR promotes localization of Scribble to the cell membrane, which in turn activates Hippo signaling, leading to the phosphorylation and functional inactivation of the transcriptional co-activator YAP.

Breast cancer data from The Cancer Genome Atlas (TCGA), suggests that both mir-9-1 and mir-9-2 have a moderate but significant inverse correlation with *LIFR*, indicating that LIFR can be suppressed by miR-9, as well as other mechanisms. The expression levels of *LIFR* and *IL6ST* (encoding the co-receptor gp130) were positively correlated in human breast tumors. Also, knockdown of gp130 reversed LIFR-induced YAP

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phosphorylation, whereas LIF stimulation recapitulated the effect of LIFR on YAP phosphorylation in breast cancer cells. Results suggest that the co-receptor (gp130) and the ligand (LIF) may be involved in LIFR-induced cell-membrane localization of Scribble and subsequent activation of the Hippo phosphorylation cascade. It is envisioned that therapeutic intervention centered on restoring LIFR expression or function could be useful for blocking breast cancer metastasis.

Source: Nat Med. 2012 Sep 23;18(10):1511-7

Oncogenic NRAS Signaling Differentially Regulates Survival and Proliferation in Melanoma

The RAS proto-oncogene is activated across a diverse range of human cancers, including 15–20% of the melanomas that harbor activating *NRAS* mutations. Agents that block mitogen-activated protein kinase (MAPK) signaling components downstream of RAS, including the serine/threonine protein kinases BRAF, MEK, and extracellular-signal–related kinase (ERK), have notably positive pre-clinical and clinical effects in several cancer types, particularly *BRAF*-mutant melanoma. Clinically, single-agent MEK inhibition has limited efficacy against neuroblastoma RAS homolog (*NRAS*)-mutant melanoma, and BRAF inhibitors not shown to be beneficial in *RAS*-mutant cancers. Currently, potent inhibitors of the BRAF proto-oncogene have revolutionized therapy for melanoma harboring mutations in *BRAF*, yet *NRAS*-mutant melanoma remains without an effective therapy. Efforts to target oncogenic RAS mutants directly have thus far been unsuccessful.

As direct pharmacological inhibition of the RAS proto-oncogene has so far been unsuccessful, Kwong *et al.* explored systems biology approaches to identify synergistic drug combination(s) that can mimic RAS inhibition. They showed evidence for a model in which the signaling output downstream of NRAS-MEK-ERK is gated, resulting in the decoupling of two major cancer biological phenotypes, proliferation and survival, which in turn provides the molecular basis for coextinction of MEK and CDK4 to approximate NRAS inhibition. Leveraging an inducible mouse model of *NRAS*-mutant melanoma, they demonstrated that pharmacological inhibition of MEK activates apoptosis but not cell-cycle arrest, which is in contrast to complete genetic NRAS extinction that triggers both of these effects. Network modeling pinpointed cyclin-dependent kinase 4 (CDK4) as a key driver of this differential phenotype. Accordingly, combined pharmacological inhibition of MEK and CDK4 *in vivo* led to substantial synergy in therapeutic efficacy.

The researchers suggest a gradient model of oncogenic NRAS signaling in which the output is gated, resulting in the decoupling of discrete downstream biological phenotypes as a result of incomplete inhibition. Such a gated signaling model offers a new framework to identify non-obvious coextinction target(s) for combined pharmacological inhibition in *NRAS*-mutant melanomas which is also a key complement to the knowledge-based approach of designing combination strategies based on existing pathway models.

Source: Nat Med. 2012 Sep 16;18(10):1503-10

STAT3-Driven Up-regulation of TLR2 Promotes Gastric Tumorigenesis Independent of Tumor Inflammation

Gastric cancer (GC) is the second most lethal cancer worldwide and it represents a growing number of cancers that are associated with inflammation. Although the molecular mechanisms underlying the pathogenesis of these cancers remain unclear, a causal correlation is established between inflammation triggered by microbes and gastrointestinal cancers, as evidenced by chronic gastritis caused by infection with the Gram-negative pathogen, *Helicobacter pylori* being a major risk factor for human GC. The involvement of pathogenic microbes in gastrointestinal inflammation and carcinogenesis has implicated Toll-like receptors (TLRs), a key family of microbial sensors of the host innate and adaptive immune systems in mediating chronic inflammatory responses that promote tumorigenesis. TLR2 and TLR4 gene expression is elevated in *H. pylori*-positive gastritis patients, and TLR2 and TLR4 gene polymorphisms are associated with an increased GC risk. However, expression status of these TLRs in human GC is unclear.

Hyperactivation of the signal transducer and activator of transcription (STAT) 3 oncogene is a hallmark of many epithelial tumors, including gastric cancer, however, the full spectrum of actions by which STAT3 elicits its oncogenicity remains ill-defined. This oncogenicity is attributed mainly to its direct transcriptional upregulation of genes, which promote angiogenesis, cell cycle progression, and cell survival. The complex role of STAT3 in cancer is evidenced by the fact STAT3 can promote both a protumorigenic, chronic inflammatory microenvironment and conversely, suppress antitumor innate and adaptive immune responses. Emerging evidence invokes

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functional overlap between STAT3 and nuclear factor-kB (NF-kB) oncogenic and inflammatory signaling pathways in driving inflammation-associated cancers.

Tye *et al.* investigated whether crosstalk between STAT3 and TLR signaling contributes to the molecular pathogenesis of GC. Using a GC mouse model driven by hyperactivation of the STAT3 oncogene, the researchers show that STAT3 directly upregulates the epithelial expression of the innate immune pathogen recognition receptor TLR2 in gastric tumors. While gastric tumorigenesis is associated with inflammation, the workers unexpectedly revealed that TLR2 promoted gastric epithelial cell survival and proliferation rather than tumor inflammation. Genetic and therapeutic targeting of TLR2 inhibited gastric tumorigenesis, but not inflammation, characterized by reduced proliferation and increased apoptosis of the gastric epithelium. Increased STAT3 pathway activation and TLR2 expression were also associated with poor GC patient survival. This study reveals an unexpected role for TLR2 in the oncogenic function of STAT3. Given the emergence of TLR signaling cascades as key oncogenic drivers in various tumors also characterized by STAT3 hyperactivation, these findings suggest that selective blockade of TLR2 may provide a therapeutic approach to suppress tumorigenesis.

Source: Cancer Cell. 2012 Oct 16;22(4):466-78

Therapeutic Targeting of the Cyclin D3:CDK4/6 Complex in T Cell Leukemia

D-type cyclins (D1, D2, and D3) bind cyclin-dependent kinases 4 and 6 (CDK4/6), and the activity of cyclin D:CDK4/6 complexes promotes entry into the cell cycle. Cyclin D:CDK4/6 complexes are believed to promote cell cycle progression through at least two functions: By interacting with cell cycle inhibitors, such as p21Cip1 and p27Kip1, and by phosphorylating the retinoblastoma tumor suppressor (Rb). Deregulated expression of all D-type cyclins is frequently observed in hematopoietic malignancies. Induction of T cell acute lymphoblastic leukemia (T-ALL), a disease caused by transformation of lymphocyte progenitors, requires cyclin D3. Specific cyclin D overexpression is associated with distinct T-ALL subsets. Early thymocyte progenitor-ALL is characterized by cyclin D2 overexpression, whereas more mature forms of T-ALL are associated with D3 overexpression. Notch signaling directly regulates cyclin D3 expression, and blocking cyclin D3 expression by γ-secretase inhibition of the oncogenic intracellular domain of Notch1 (ICN1) in Ccnd3-/- bone marrow progenitors prevents initiation of the disease. These data suggest that deciphering the functions of cyclin D is critical for the development of strategies to prevent an oncogenic cell cycle and D-type cyclins and/or their downstream interacting partners could be attractive therapeutic targets in this type of disease.

Sawai *et al.* demonstrate that the cyclin D3:CDK4/6 complex has unique functions in the expansion of normally developing T cell progenitors and induction of T cell leukemia. They also show that cyclin D2, a D-type cyclin also expressed in developing T cell progenitors, cannot replace cyclin D3. The authors present genetic evidence that combined deletion of p27Kip1 and Rb, which regulate progression through the G1 phase of the cell cycle, rescue the defect in early T cell (Ccnd3-/- thymocytes) development by the deletion of cyclin D3. Also, inhibition of the kinase function of cyclin D:CDK4/6 activity abrogates both cell cycle entry in T-ALL and disease progression in animal models of T-ALL. These studies identify unique functions for cyclin D3:CDK4/6 complexes and suggest potential therapeutic protocols for this devastating blood tumor.

Source: Cancer Cell. 2012 Oct 16;22(4):452-65

Clinical Development

Axitinib did not Meet Primary Endpoint in Phase III Trial of Treatment-Naïve Patients with Advanced RCC

Pfizer announced that a Phase III study of INLYTA (axitinib) did not meet its primary endpoint of demonstrating statistically significantly longer progression-free survival (PFS) versus sorafenib in treatment-naïve patients with advanced renal cell carcinoma (RCC).

AGILE 1051, a Phase III trial of more than 280 treatment-naïve patients with advanced RCC, was powered to show a 78% improvement in PFS benefit with INLYTA over sorafenib. The primary endpoint of the study was PFS. The secondary endpoints of the study included overall survival, response rate, and safety. Pre-specified subgroups were also analyzed and included patients with either good Performance Status (ECOG PS 0) or intermediate Performance Status (ECOG PS 1). A preliminary review of the data showed that overall the median PFS for INLYTA exceeded the median PFS for sorafenib, but did not meet statistical significance. In a pre-specified subgroup of patients classified as good Performance

Clinical Development
(Cont'd)

Status (ECOG PS 0), the median PFS for INLYTA exceeded the median PFS for sorafenib. In another pre-specified subgroup of patients classified as intermediate Performance Status (ECOG PS 1), there was no difference between INLYTA and sorafenib. Adverse events for INLYTA were generally consistent with previous findings in INLYTA patients with advanced RCC who had been treated with a prior systemic therapy. Earlier this year, INLYTA was approved for patients with previously treated advanced RCC in the US, EU, Japan, Switzerland, Canada, Korea, and Australia.

Source: Pfizer

Lilly Announces Positive Results for Ramucirumab in Phase III Gastric Cancer Trial

Eli Lilly and Company announced that the REGARD trial, a Phase III study of ramucirumab, a vascular endothelial growth factor receptor-2 antagonist, in patients with metastatic gastric cancer, met its primary endpoint of improved OS and also showed prolonged PFS. This trial is the first Phase III data read-out for ramucirumab.

The REGARD trial is a Phase III randomized, double-blinded study of ramucirumab and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on 1st line platinum- or fluoropyrimidine-containing combination therapy. The primary endpoint of the REGARD trial was OS and secondary endpoints included: PFS; proportion of participants who are progression-free at week 12; proportion of participants with objective response, or objective response rate; duration of response; and safety. The most frequent adverse reaction (any grade) occurring at a higher rate on the ramucirumab arm was hypertension (12%). Other adverse reactions (> 5%) occurring at a higher rate on the ramucirumab arm compared to the placebo arm were diarrhea and headache.

REGARD is one of two ramucirumab Phase III studies in gastric cancer. RAINBOW, a Phase III trial of ramucirumab in combination with paclitaxel, completed patient enrollment last month. Lilly plans to present data from the REGARD trial at an upcoming scientific meeting and will discuss submission plans with regulatory authorities.

Source: Eli Lilly

ABRAXANE Meets Primary Endpoint of PFS in Phase III Chemotherapy-Naïve Metastatic Melanoma Study

Celgene International Sàrl, a subsidiary of Celgene Corporation announced results of its Phase III, randomized, international study (CA033) of ABRAXANE (paclitaxel protein-bound particles for injectable suspension (albumin-bound)) in chemotherapy-naïve patients with metastatic melanoma. In the study, the primary endpoint was met with patients receiving ABRAXANE demonstrating a statistically significant improvement in PFS compared to patients receiving dacarbazine (DTIC) chemotherapy.

The CA033 study is a Celgene-sponsored, open-label, controlled, and randomized study comparing ABRAXANE to standard chemotherapy, DTIC, in patients with metastatic melanoma. In the study, 529 chemotherapy-naïve patients were randomized to receive either ABRAXANE or DTIC. The primary study endpoint was independently-assessed PFS. Secondary endpoints included OS, overall response rate and disease control, safety, and tolerability. The safety profile of ABRAXANE observed in the CA033 study was consistent with other ABRAXANE pivotal clinical trials. Data from this study will be presented at the Society for Melanoma Research (SMR) Congress 2012 in Los Angeles in November. Future regulatory and clinical strategies are being reviewed in light of these results.

Source: Celgene

Sapacitabine Nearly Doubles Expected Survival of Elderly Patients with MDS after Front-Line Therapy Failure

Cyclacel Pharmaceuticals presented updated data from an ongoing, multicenter, Phase II randomized trial of sapacitabine, a DNA polymerase inhibitors, in older patients with intermediate-2 or high-risk myelodysplastic syndromes (MDS) after treatment failure of front-line hypomethylating agents, such as azacitidine and/or decitabine at the Eighth Annual Hematologic Malignancies 2012 Conference, held on October 10-14, 2012, in Houston, Texas.

This open-label, multi-center, Phase II study randomized 63 patients aged 60 years or older with MDS of intermediate-2 (n=52) or high-risk (n=11) classification by the International Prognostic Scoring System (IPSS) at study entry to receive sapacitabine every 4 weeks on one of 3 dosing schedules: 200 mg twice daily for 7 days (Arm G), 300 mg once daily for 7 days (Arm H), or 100 mg once daily for 5 days per week for 2 weeks (Arm I). The primary efficacy endpoint of the study was 1-year survival with the objective of identifying a dosing schedule that produces a better 1-year survival rate in the event that all three dosing schedules are active. All patients in the study progressed after receiving azacitidine, decitabine, or both agents. The updated median survival for all three arms was 252 days (~8 months).

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The median survival for each arm was 291 days (~10 months) for Arm G, 274 days (~9 months) for Arm H, and 227 days (~8 months) for Arm I. Twenty-two percent of patients are still alive and longer follow-up is needed to assess 1-year survival and OS of each arm.

Source: Cyclacel

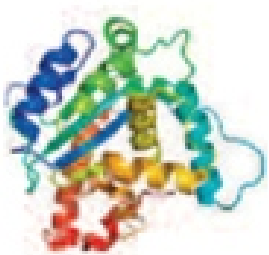
Oxford BioMedica Announces Update on TroVax Development Strategy

Oxford BioMedica announced plans to close the Phase II study in the US to assess the activity of TroVax® (MVA-5T4), an immunostimulant, in patients with progressive hormone refractory prostate cancer (HRPC). However, TroVax continues to have an active Phase II development programme in other indications led by academic collaborators in the UK.

Oxford BioMedica initiated a randomized, open-label Phase II study in patients with metastatic HRPC in September 2010. Since then, the prostate cancer treatment landscape in the US has changed with new products available and other clinical trials targeting the same indication. Competition for suitable patients with HRPC has been high and recruitment into the study has been much slower than originally anticipated with 26 patients recruited to date. While early data from this study are encouraging; the Board has made a strategic decision to close the US trial in order to focus on investigator-led Phase II studies currently in the UK.

In July 2012, Oxford BioMedica's partners at Cardiff University, Wales (UK) initiated a Phase II trial to assess the safety and immunological activity of TroVax in patients with inoperable metastatic colorectal cancer. The Company expects two further investigator-led Phase II studies in mesothelioma and ovarian cancer to be initiated in the UK by academic collaborators in Q4 2012. Securing a development or financial partner for TroVax's future late-stage development remains a key strategic priority for the Company and discussions with interested parties are ongoing.

Source: Oxford BioMedica



Biomarkers

Immuno-histochemical Double-hit Score is a Strong Predictor of Outcome in DLBCL Patients Treated with R-CHOP

Diffuse large B-cell lymphoma (DLBCL) is a clinically and biologically heterogeneous disease. A general improvement in survival rates has been achieved since rituximab (R) was added to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) approximately a decade ago, and R-CHOP has now become the standard treatment. Still, ~40% of patients with DLBCL suffer relapses within a short time frame and eventually die as a result of the disease. Roughly 5% of DLBCLs are double-hit lymphomas (DHLs) with translocations of both MYC and BCL2. DHLs are characterized by poor outcome.

Marie *et al.* tested whether DLBCLs with high expression of MYC protein and BCL2 protein share the clinical features and poor prognosis of DHLs. On the basis of immunohistochemical MYC and BCL2 expression, a double-hitscore (DHS) was assigned to all patients with DLBCL. The DHS-2 group, defined by high expression of both MYC and BCL2 protein, comprised 29% of the patients. DHS 2 was significantly associated with lower complete response rate, shorter OS, and shorter progression-free survival (PFS). DHS was validated in an independent cohort of 116 patients who were treated with R-CHOP. Similar results were presented by Gascoyne *et al.*, who investigated whether expression of MYC protein, with or without BCL2 protein expression, could risk-stratify patients at diagnosis. MYC protein is correlated with presence of high MYC mRNA and MYC translocation, but the latter was less frequent. MYC protein expression was only associated with inferior overall and progression-free survival when BCL2 protein was co-expressed.

The data suggest that the DHS can be readily used on routinely processed tumor samples to identify patients with DLBCL who have a high likelihood of demonstrating an unsatisfactory response to standard treatment and who could be candidates for novel therapeutic strategies. MYC and BCL2 represent relevant biomarkers that should be tested in the context of clinical trials such that more effective therapies can be offered to these high-risk patients.

Source: J Clin Oncol. 2012 Oct 1;30(28):3460-7; J Clin Oncol. 2012 Oct 1;30(28):3452-9; Blood. 2011 Feb 24;117(8):2319-31

Association of *KRAS* G13D Tumor Mutations with Outcome in mCRC Patients Treated with 1st Line Chemotherapy with or Without Cetuximab

Epidermal growth factor receptor (EGFR) monoclonal antibodies are used for treatment of EGFR-expressing metastatic colorectal cancer (mCRC). Recent mCRC trials have consistently reported that patients with *KRAS*-mutated tumors do not benefit from treatment with the EGFR monoclonal antibodies cetuximab and

Biomarkers (Cont'd)

currently, patients with *KRAS* codon 12– or 13–mutated mCRC are not treated with these agents. Several studies have shown that a minority of patients with *KRAS*-mutated CRC respond to EGFR-targeted therapy and that *KRAS* codon 13–mutated tumors are over-represented in this group compared with other *KRAS* mutations.

Tejpar *et al.* analyzed pooled individual patient data from two randomized trials that investigated first-line chemotherapy with or without cetuximab to validate previously reported finding of improved clinical outcome for patients with *KRAS* G13D–mutant tumors receiving cetuximab for chemorefractory mCRC. Patients with *KRAS*-mutant tumors were divided into those with *KRAS* G13D mutations, G12V mutations, and other *KRAS* mutations. *KRAS* G12V–mutant tumors were considered separately to explore their potential association with poor prognosis.

Significant heterogeneous treatment effects were observed in patients with different tumor *KRAS* mutation subgroups. Patients with *KRAS* G13D tumor mutations seemed to respond differently from those with other *KRAS* mutations when receiving cetuximab. Patients with tumors harboring *KRAS* G13D mutations fared worse in the control arm but better in the cetuximab-containing arm. Patients with tumors harboring *KRAS* G12V and other mutations were associated with worse outcome when receiving chemotherapy plus cetuximab, compared with chemotherapy alone, whereas those with *KRAS* G13D–mutant tumors benefited from this combination, further highlighting the potential differences in tumor biology of different *KRAS* mutations when treated with EGFR-targeted agents in combination with standard chemotherapy regimens. No marked associations were found between patients with tumor *KRAS* G12V mutations and worse outcome compared with patients with tumors containing other *KRAS* mutations.

Findings generally support the increasing body of evidence from CRC and other diseases that not all *KRAS* mutations have the same effects on tumor biology and patient outcome. The data suggest that *KRAS* G13D mutations are associated with improved clinical outcome when cetuximab is added to first-line chemotherapy. Meanwhile, pre-clinical efforts are ongoing to improve understanding of the mechanisms underlying differential responses. Currently, the value of *KRAS* testing is unprecedented, with tumor *KRAS* status as the only clinically validated biomarker for the efficacy of treatment with cetuximab.

Source: J Clin Oncol. 2012 Oct 10;30(29):3570-7

Relative Mitochondrial Priming of Myeloblasts and Normal HSCs Determines Chemotherapeutic Success in AML

Acute Myeloid Leukemia (AML) is a malignancy, primarily of adults, in which a malignant myeloid clone in the bone marrow is arrested in development and proliferates abnormally. A highly successful, empirically derived treatment scheme combining cytarabine with an anthracycline has yielded a 70% remission rate, greater overall survival, and even cures for what is otherwise a fatal disease. The only curative option for patients who are resistant to or relapse after this induction regimen is allogeneic bone marrow or stem cell transplantation (Allo-SCT), which consists of an intensive preparatory chemotherapeutic regimen followed by introduction of donor hematopoietic stem cells (HSCs).

Mitochondrial priming is controlled by the BCL-2 family of proteins. This family consists of proapoptotic and antiapoptotic members. If proapoptotic members overwhelm the antiapoptotic members, the threshold of death is crossed and the cell dies. The BCL-2 family consists of four groups of proteins containing at least one of four homology domains called the BH domains (BH1–BH4). Letai *et al.* defined priming functionally as the magnitude of response of mitochondria to proapoptotic peptides derived from the BH3 domains of BH3-only proteins. In practice, this is measured as the release of cytochrome c or the loss of mitochondrial transmembrane potential caused by standardized doses of BH3 peptides in an assay called BH3 profiling. The greater the loss of mitochondrial transmembrane potential caused by the BH3-only peptides, the more cells are primed for death. Loss of potential caused by BH3 peptides like BIM, which promiscuously inhibits all the antiapoptotic members, provides a measure of overall priming. Sensitizer BH3 peptides such as BAD, NOXA, and HRK inhibit only specific antiapoptotic members and thus provide a measurement of dependence on the antiapoptotic proteins they inhibit. For instance, mitochondrial response to the NOXA BH3 peptide is an indication of dependence on MCL-1, whereas mitochondrial response to BAD BH3 peptide is an indication of dependence on BCL-2, BCL-w, or BCL-XL.

In the case of AML, researchers found that in a preliminary series of 15 patients, achieving remission was related to the degree of mitochondrial priming. They expand upon those results to explain a wide range of clinical phenomena associated with AML that have previously lacked a clear biological mechanism. It was found that differential priming determines not only the initial response rate but also risk of relapse. Using AML cell lines, they demonstrate that increasing

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mitochondrial priming enhances chemo sensitivity. It was determined that the source of a therapeutic index in AML depends upon AML cells being more primed than normal hematopoietic stem cells (HSC). It was found that low priming identifies a subset of patients with a very high risk of relapse for whom allogeneic stem cell transplantation is likely to be required for cure. Finally, they use BH3 profiling to identify dependence on BCL-2 present even in chemo-refractory myeloblasts but not in normal HSC, suggesting another potential avenue to rescue low-primed AML cases. The results demonstrate that the functional information about mitochondrial apoptotic priming provided by BH3 profiling not only is useful in defining biological mechanisms in AML but also can be potentially exploited as a clinical predictive biomarker in AML.

Source: Cell. 2012 Oct 12;151(2):344-55

Regulatory

FDA Approves ABRAXANE for the 1st Line Treatment of Advanced NSCLC

Celgene Corporation announced that the FDA has approved Abraxane (paclitaxel protein-bound particles for injectable suspension (albumin-bound)) for the 1st line treatment of locally advanced or metastatic NSCLC, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

The Abraxane sNDA approval is based upon the results of CA-031, a Phase III, multi-center, randomized, open-label study where patients with advanced NSCLC received either Abraxane weekly plus carboplatin every three weeks (n=521) or paclitaxel every three weeks plus carboplatin (n=531). The study met its primary end-point demonstrating a statistically significant higher overall response rate for patients in the Abraxane arm compared to those in the paclitaxel arm (33% vs. 25%). Abraxane demonstrated a higher overall response rate as compared to paclitaxel for squamous cell carcinoma (41% vs. 24%) and large cell carcinoma (33% vs. 15%). Abraxane achieved a similar overall response rate to paclitaxel in patients with carcinoma/adenocarcinoma (26% vs. 27%).

Additional regulatory submissions have been filed in Japan, Australia, and New Zealand with anticipated decisions in 2013.

Source: Celgene

FDA Approves ALIMTA in the Continuation Maintenance Setting for Advanced Non-squamous NSCLC

Eli Lilly and Company announced that patients may receive Alimta (pemetrexed for injection) as a maintenance therapy following 1st line Alimta plus cisplatin for locally advanced or metastatic non-squamous (NS) NSCLC. The FDA approved the label inclusion of Phase III data that demonstrated PFS and OS advantages in the continuation maintenance setting for these patients.

In October 2011, the European Commission granted approval for the use of Alimta as a single agent for continuation maintenance in patients with advanced NS NSCLC based on PFS and preliminary OS. On September 21, 2012, the Committee for Medicinal Products for Human Use (CHMP) in the European Union (EU) issued a positive opinion for a label update for Alimta in the continuation maintenance setting for certain patients with advanced non-squamous NSCLC after initial treatment with Alimta plus cisplatin.

The FDA and European Commission approvals were based on results from PARAMOUNT, a global, multicenter, double-blind Phase III trial, the final results of which were presented at the American Society of Clinical Oncology (ASCO) annual meeting in Chicago, Ill. on June 4, 2012. PARAMOUNT was the first study to evaluate the 1st line use of Alimta plus cisplatin therapy followed immediately by the use of Alimta as a single-agent in the continuation maintenance setting. A total of 939 patients with advanced non-squamous NSCLC were enrolled in the study and received ALIMTA in combination with cisplatin induction therapy. Patients whose disease had not progressed during the ALIMTA plus cisplatin induction and who had an ECOG performance status of 0-1 (n=539) were randomized two-to-one to receive Alimta maintenance plus best supportive care (n=359) or placebo plus best supportive care (n=180) until disease progression. Final results of the PARAMOUNT trial demonstrated a statistically significant 22% reduction in the risk of death (HR=0.78; P=0.02) with Alimta, compared to placebo. This reduction in the risk of death resulted in an improved median OS from the time patients were randomized of 13.9 months median for patients receiving Alimta, compared to 11.0 months median for patients on the placebo arm. Median PFS measured from randomization was 4.1 months on the Alimta arm as compared to 2.8 months on the placebo arm with a hazard ratio of 0.62.

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Alimta is already indicated for locally advanced or metastatic non-squamous NSCLC in the following settings:

- Initial treatment in combination with cisplatin
- Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based 1st line chemotherapy
- After prior chemotherapy as a single-agent

Source: Eli Lilly; FDA label

DACOGEN Approved in the EU for the Treatment of AML

Astex Pharmaceuticals announced that the European Commission has approved the marketing authorization for Dacogen (decitabine), a DNA hypomethylating agent for the treatment of adult patients (age 65 years and above) with newly diagnosed de novo or secondary acute myeloid leukemia (AML) according to the World Health Organization (WHO) classification, who are not candidates for standard induction chemotherapy.

The data in support of the marketing authorization is based on the Phase III DACO-016 trial that compared decitabine to patients' choice with physician advice of either supportive care or low-dose cytarabine in the treatment of older patients with AML. The analysis of the protocol-specified results demonstrated an increase of 54% in median OS in patients taking decitabine (7.7 months for decitabine patients, compared to 5.0 months for patients in the comparator arm; HR=0.85, P=0.108). An updated analysis of mature survival data confirmed this strong trend for improved OS and provided clinically significant evidence of the efficacy of decitabine (HR=0.82; nominal P=0.037).

Source: Astex Pharmaceuticals

Bayer's Stivarga Approved by FDA for the Treatment of mCRC

Bayer HealthCare announced that the FDA approved Stivarga (regorafenib), an oral multi-kinase inhibitor for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with currently available therapies (including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and if KRAS wild type, an anti-EGFR therapy).

The approval of Stivarga is based on results from the pivotal Phase III study (CORRECT) that demonstrated a statistically significant improvement in OS and PFS compared to placebo in patients with mCRC whose disease had progressed after approved standard therapies. In the Phase III CORRECT (Colorectal cancer treated with regorafenib or placebo after failure of standard therapy) trial, regorafenib plus best supportive care (BSC) significantly improved OS (HR=0.77, 2-sided P= 0.0102) and PFS (HR=0.49, 2-sided P <0.0001) compared to placebo plus BSC. Median OS was 6.4 months with regorafenib versus 5.0 months with placebo; median PFS was 2.0 months with regorafenib versus 1.7 months with placebo. The data also showed a survival benefit (OS and PFS) in the regorafenib arm across nearly all subgroups analyzed. No difference in overall response rate was observed. Five patients (1%) in the regorafenib arm and one patient (0.4%) in the placebo arm experienced partial responses. History of KRAS evaluation was reported for 729 (96%) patients; 430 (59%) of these patients were reported to have KRAS mutation.

Regorafenib is also under investigation in metastatic and/or unresectable gastrointestinal stromal tumors (GIST) for patients whose disease had progressed despite prior treatment with imatinib and sunitinib. Bayer has submitted a New Drug Application to the FDA for regorafenib in GIST in August 2012.

Source: Bayer HealthCare

Avastin Receives Positive Opinion from EU Authority for the Treatment of Recurrent, Platinum-sensitive Ovarian Cancer

Roche announced that the CHMP has supported the use of Avastin in combination with carboplatin and gemcitabine for the treatment of adult patients with the first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor targeted agents. Avastin is administered in combination with carboplatin and gemcitabine chemotherapy for 6 cycles and up to 10 cycles followed by continued use of Avastin as single agent until disease progression. The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

In platinum-sensitive ovarian cancer, a Phase III study (OCEANS) of Avastin demonstrated that those women who received the combination of Avastin and chemotherapy and then continued Avastin alone lived significantly longer without their disease getting worse (progression-free survival) compared to those who received chemotherapy only.

Source: Roche

Xalkori Receives Conditional Marketing Authorization in the Europe for the Treatment of Adults with Previously Treated ALK-positive Advanced Non-Small Cell Lung Cancer

Pfizer announced that the European Commission has

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given conditional marketing authorization for Xalkori (crizotinib) in the EU for the treatment of adults with previously-treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). A conditional marketing authorization is renewable annually. Pfizer will be required to submit data to the European Medicines Agency (EMA) from the recently completed PROFILE 1007 study, which was presented in September at the ESMO 2012 Congress in Vienna, Austria. The study met its primary endpoint of increasing PFS in previously treated ALK-positive advanced NSCLC patients (mean PFS was 7.7 months with crizotinib compared to 3 months with standard chemotherapy). Following review of the 1007 results by the EMA's Committee for Medicinal Products for Human Use (CHMP), the European Commission will consider converting the conditional marketing authorization to a normal marketing authorization.

Xalkori is an oral, anaplastic lymphoma kinase (ALK) inhibitor indicated only for patients testing positive for ALK as tested by an accurate and validated ALK assay in laboratories.

Source: Pfizer

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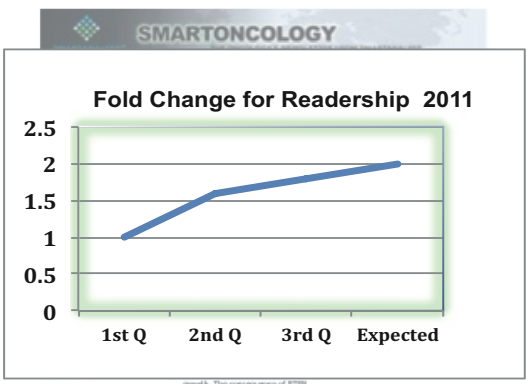

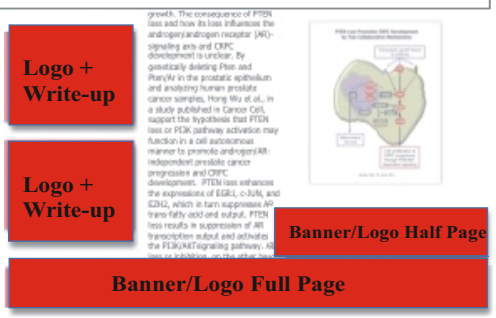

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