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INTELLIGENT INSIGHTS. SMART RESULTS

Spotlight-1:

New Prognostic Markers in Chronic Lymphocytic Leukemia: Implications on Treatment

Presented by Nicholas Chiorazzi at ASH 2012

Over the past decade, several prognostic markers based on genetic, phenotypic, or molecular characteristics of chronic lymphocytic leukemia (CLL) B cells have been brought forth. The clinical utility of these newer prognostic indicators, alone or in combination with each other and the clinical prognostic systems, is still being analyzed. A possible difference between the 'old' prognostic markers such as staging systems and the 'new' prognostic markers such as *IGHV* mutation status, FISH cytogenetics, and CD38 and ZAP-70 expression is an underlying biological connection to the disease that these new molecular markers reflect.

The author attempts to define biologic and molecular underpinnings of 3 sets of prognostic indicators: (1) genetic abnormalities quantified by FISH and/or defined by exploratory and more sensitive molecular techniques; (2) expression of specific proteins in or on CLL cells (i.e., CD38, CD49d, and ZAP-70); and (3) the *IGHV* mutation status of a CLL clone. Although, it has not yet been demonstrated conclusively, each of these is thought to be a reflection of the biologic properties of individual CLL patients, either directly, indicating a specific property of the CLL cell itself, or indirectly, representing influences of the host's microenvironment on the CLL cell. The new tyrosine kinase inhibitors currently in clinical trials support this interpretation. These and other biology-based indicators of patient clinical course and outcome can be used as starting points to understand and treat CLL.

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Spotlight-2:

Personalizing Therapy in AML and Predicting Prognosis: Role of Novel Molecular Genetic Markers

Presented by Jay P. Patel and Ross L. Levine at ASH 2012

Acute myeloid leukemia (AML) is the most common acute leukemia diagnosed in adults, with ~14K patients diagnosed each year in the US.[1,2] Most patients with AML die from relapsed disease. Although many studies over the past 4 decades have identified disease alleles in AML, recent genome-wide and candidate gene studies have identified additional recurrent somatic mutations in AML patients with biologic, clinical, and therapeutic importance. Patel and Levine have reviewed the prognostic relevance of novel AML disease alleles and discussed how genetic data can be used to inform outcome and therapy in AML. They have also reviewed the current challenges in translating genomic studies to the clinical setting, which remains a significant challenge and an urgent priority.

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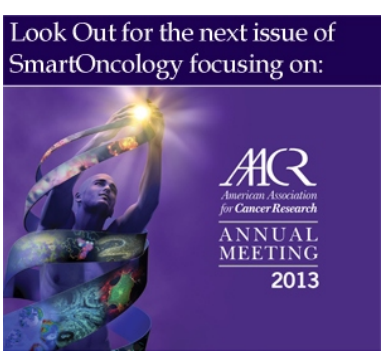

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Spotlight Report

SPOTLIGHT-1

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Over the past decade, several prognostic markers based on genetic, phenotypic, or molecular characteristics of chronic lymphocytic leukemia (CLL) B cells have been brought forth. The clinical utility of these newer prognostic indicators, alone or in combination with each other and the clinical prognostic systems, is still being analyzed. A possible difference between the 'old' prognostic markers such as staging systems and the 'new' prognostic markers such as *IGHV* mutation status, FISH cytogenetics, and CD38 and ZAP-70 expression is an underlying biological connection to the disease that these new molecular markers reflect.

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A set of specific, defined chromosomal abnormalities has predictive value for patient course and outcome. Listed in order of increasing disease severity, these include del(13q), tri12, del(11q), and del(17p). The 13q14 deletion is the most common genetic abnormality in CLL, found more often in patients with mutated *IGHV* genes (M-CLL), a subset with a more favorable clinical outcome than those with unmutated *IGHV genes* (U-CLL). CLL patients with trisomy 12 (tri12; approximately 15% of CLL patients) have shorter survival than those with a normal FISH panel analysis. There appears to be an association between tri12 and the presence of mutations in the *NOTCH1* gene, which extend the half-life of the protein. Furthermore, patients with a *NOTCH1* mutation have a shorter time to therapy and overall survival, whereas those with combined tri12 and *NOTCH1* mutation fare worse. CLL patients with the 11q22-23 deletion (~15% of CLL patients) often exhibit bulky adenopathy and experience an aggressive clinical course with shorter survival. Furthermore, these patients are often U-CLL, which is consistent with their poor clinical outcome. Nevertheless, these patients may respond to treatment with chemoimmunotherapy, although they inevitably relapse. CLL patients with the 17p deletion [del(17p); ~7% of CLL patients] almost invariably have aggressive clinical courses, most likely due to loss of *TP53*. Furthermore, mutations of *TP53* on the other allele occur in ~80% patients and lead to dire outcome. This deletion is a prime facilitator of clonal evolution to a more aggressive disease, and the number of leukemic cells with del(17p) often increase in patients who do not respond to therapy or who relapse after therapy.

Table 1: Established prognostic markers

Favorable	Unfavorable
Sole del(13q) abnormality – longest median survival (133 months)	del(11q)–extensive lymphadenopathy, disease progression, shorter survival (79 months) – therapy preferred: FC (Fludarabine-cyclophosphamide)
IGHV mutation >2%	del(17p) – short treatment-free interval, short median survival (32 months), and poor response to chemotherapy
CD38 mutation <30%	
Zap 70 mutation <20%	

Source: NCCN Guidelines version 1.2013 accessed on March 26, 2013

Although FISH analyses of these and other chromosomal aberrations have been extremely helpful in predicting clinical course and indicating ongoing evolution of the leukemic clone, the FISH approach is limited by the fact that it can only detect lesions already defined in other patients. For this reason, new and more sensitive techniques that define abnormalities so far unrecognized in CLL, have great potential and have begun to yield valuable information. Three such techniques are comparative genomic hybridization (CGH), genome-wide analyses of single nucleotide polymorphisms (SNPs), and[3] whole-exome or whole-genome sequencing ('next-generation sequencing' [NGS] or 'deep sequencing'). Although promising, such techniques are still investigational, and their application and integration into clinical practice will require a meticulous process of validation.

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Expression of CD38 and CD49d on CLL cells and ZAP-70 in CLL cells has proven valuable in predicting outcome in CLL. Unlike the aberrations defined by FISH that generally indicate abnormalities intrinsic to CLL leukemic B cells, these markers reflect the ability of CLL cells to respond to signals from the microenvironment.

Cell-surface CD38 has a pivotal role in initiating and modulating a series of input signals from the microenvironment. The percentage of cells within a CLL clone that display CD38 is an indicator of the potential and actual degree of cellular activation of the clone: those with higher numbers (than a defined percentage) are more responsive to activation signals or are activated and are therefore very often more aggressive. CD38 expression is a measure of cell division and a reflection of growth *in vivo*. The aggressiveness of $CD38^+$ cells appears to be compounded by their ability to migrate and take advantage of interactions with the microenvironment; ZAP-70 also appears to be involved in this action. The greater proliferative potential of $CD38^+$ clones and cells increases the likelihood that new genomic abnormalities will occur at the time of DNA replication. This is consistent with finding more cells with 11q and 17p deletions and clonal evolution in $CD38^+$ clones and in explaining the poor prognosis of patients with clones with higher numbers of $CD38^+$ cells. The percentage of $CD49d^+$ cells, like $CD38^+$ cells, is an independent indicator of prognosis in CLL, with higher levels (> 30%) being correlated with shorter survival times. Intracellular expression of ZAP-70 protein above a certain threshold of cells by immunofluorescence and flow cytometry (> 20%) has proven to be an important indicator of time-to-treatment and survival in CLL. Although the numbers of CLL cells expressing this protein are correlated with *IGHV* mutation status and CD38 expression, ZAP-70 levels are an independent marker of clinical outcome.

The clinical utility of *IGHV* mutation status has been well established in multiple clinical trials, with a high correlation between unmutated *IGHV* status and poor survival and, correspondingly, better prognosis in cases with mutations in *IGHV*. The biologic correlates of the prognostic utility of *IGHV* mutations in CLL have been linked to BCR structure, with the key findings being the differences in the presence or absence of significant numbers of *IGHV* mutations; the use of specific *IGHV* genes, which is in general, but not always, linked to *IGHV* mutation status; and the presence of stereotyped BCR structures.

Simplistically, CD38, CD49d, and ZAP-70 can be viewed as dynamic markers the prognostic value of which is a sign of level of aggressiveness at the time of sampling, whereas *IGHV* mutation status is a static marker (at the clonal level) that is indicative of the origin and maturational events of a B cell before transformation. Absence or presence of *IGHV* mutations reflects the type of Ag binding that the BCR accomplishes (e.g., polyreactive vs. oligo/monoreactive, respectively). Ag binding specificity is correlated with outcome because it indicates the breadth of antigenic epitopes that a BCR can engage, the affinity of these interactions, and the likelihood that survival/proliferation signals are delivered to a CLL cell.

The genetic abnormalities that occur in CLL are more difficult to classify in this manner, although their ability to predict clinical course and outcome are probably more akin to CD38, CD49d, and ZAP-70, because sub clones bearing such lesions can increase over time and lead to clinical deterioration (clonal evolution). It is likely that, like CD38, CD49d, and ZAP-70, chromosomal abnormalities are dynamic markers that are correlated with disease progression. This may not have been apparent at first but now it appears that chromosomal and genetic abnormalities are less numerous in the early stages of the disease and accumulate progressively in the disease, and this is likely the case for certain gene mutations identified recently by sensitive screening techniques.

It is tempting to try to link the biologic underpinnings of each of the above prognostic markers into a set of common interactions. This is feasible if the signaling nodes are expanded beyond those immediately identified by the specific markers to other known signaling molecules. This may be especially relevant because of the considerable therapeutic efficacy that the tyrosine kinase inhibitors are showing in the clinic, although in studies that are still relatively short (~30 months). For example, although Btk and PI3Kδ inhibition dampens BCR signaling, it also alters the consequences of CXCR4 stimulation. Similarly, PI3Kδ is a key player in CD38-mediated signal transduction that affects cell trafficking and survival. Furthermore, Btk is likely to influence the CD38 pathway in humans, because mice with a genetic defect in Btk are unresponsive to CD38 ligation, and this unresponsiveness extends to a series of NF-κB proteins. These findings illustrate not only the enormity of signaling network connections, but also the difficulty in pinpointing a single interaction as the crucial event in CLL cell biology or prognostication. This becomes even more complex for the broad effects introduced by genetic abnormalities that occur in CLL; in particular, miR changes can have widespread actions on cell survival and growth.

Finally, prognostication in patients with CLL should not only address disease progression and overall survival, but also response to therapy. Therefore,

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there are important conceptual differences between prognostic factors, which are typically evaluated at the time of diagnosis, and an ongoing evaluation that could lead to more accurate 'response predictors' capable of assessing the risks, e.g., of targeted therapy.

In conclusion, it appears that at least the 3 sets of markers discussed herein, and probably others (e.g., lymphocyte doubling time, serum levels of β_2-microglobulin, and thymidine kinase), reflect direct and indirect influences on the initiation, perpetuation, and accumulation of CLL clones, and it is these effects that translate into prognostic value. Viewed in this manner, the identification of biology-based prognostic indicators are starting points from which to understand CLL and modulate its clinical course and outcome.

SPOTLIGHT-2

Personalizing Therapy in AML and Predicting Prognosis: Role of Novel Molecular Genetic Markers

Presented by Jay P. Patel and Ross L. Levine at ASH 2012

Acute myeloid leukemia (AML) is the most common acute leukemia diagnosed in adults, with ~14K patients diagnosed each year in the US.[1,2] Most patients with AML die from relapsed disease. Although many studies over the past 4 decades have identified disease alleles in AML, recent genome-wide and candidate gene studies have identified additional recurrent somatic mutations in AML patients with biologic, clinical, and therapeutic importance. Patel and Levine have reviewed the prognostic relevance of novel AML disease alleles and discussed how genetic data can be used to inform outcome and therapy in AML. They have also reviewed the current challenges in translating genomic studies to the clinical setting, which remains a significant challenge and an urgent priority.

Currently, few genetic abnormalities are used to predict outcome and to direct therapy in AML (Table 1).[3]

Table 1: Common genetic abnormalities in AML in clinical use and their value

Mutations	Clinical value
CBF translocations: • t(8;21)(q22;q22) – fusion gene AML1/ETO – occurs in 5% to 12% of cases of AML[4] • inv(16)(p13q22)– fusion gene CBFbeta/MYH11 – occurs in 10-12% of all AML cases[4]	CBF AML is associated with favorable outcome with induction/consolidation with high dose cytarabine (complete remission and long-term disease-free survival)
Translocations associated with acute promyelocytic leukemia – t(15; 17)(q22; q12) – PML/RARα gene fusion, occurs in 5-8% of AML cases[4]	Sensitivity to all-trans retinoic acid and arsenic trioxide

Recently, Schlenk RF, *et al.*[5] showed that mutational analysis of *FLT3* in combination with *NPM1* or *CEBPA* mutations can be used to predict risk of relapse/ death or patients likely to achieve complete remission in normal karyotype AML and to identify patients who will benefit from allogeneic stem cell transplantation.[5] However, a large number of AML patients lack any of these abnormalities and there remains significant heterogeneity in clinical outcome within currently classified prognostic groups. These observations suggest there are additional biomarkers that can predict outcome in AML. Recent genetic studies have identified an increasing number of recurrent somatic mutations in AML patients, including mutations in *TET2*, *ASXL1*, *IDH1* and *IDH2*, *DNMT3A*, and *PHF6*. Several of these mutations have been shown to have prognostic importance in AML (Table 2).

Table 2: Revised risk stratification based on novel markers

Cytogenetic classification	Mutations		Clinical value
Normal karyotype or intermediate-risk cytogenetic lesions	*FLT3*-ITD-negative	Mutant *NMP1* and *IDH1* or *IDH2*	Favorable-risk AML (improved overall survival when treated with high-dose daunorubicin- 3-yr OS was 44% in E1900 trial)
	FLT3-ITD-negative	Wild-type *ASXL1*, *TET2*, *PHF6*, and *MLL*-PTD	Intermediate risk AML
	FLT3- ITD-negative or positive	Mutant CEBPA	
	FLT3- ITD-positive	Wild-type *TET2*, *MLL*-PTD, and *DNMT3A* and trisomy 8-negative	
	FLT3-ITD-negative	Mutant *ASXL1*, *TET2*, *PHF6*, or *MLL*-PTD	Unfavorable risk AML
	FLT3- ITD-positive	Mutant *TET2*, *MLL*-PTD, *DNMT3A* or trisomy 8 without mutant *CEBPA*	

It is important to translate these novel genetic findings to the clinic. With the discovery of novel genes associated with AML pathogenesis continuing at a high speed, the challenge is to integrate this knowledge into the current clinical understanding of AML. Profiling each AML patient for clinically relevant and actionable lesions is the first step in this process. Although whole-genome and whole-exome sequencing have been critical technologies in cancer discovery efforts, their applicability today presents several challenges in the wider clinical setting. Although costs of sequencing are plummeting, the bioinformatics infrastructure and expertise needed to rapidly analyze sequencing data remain limiting in most settings. In addition, most of the mutational data in exome/genome studies represent passenger mutations and/or mutations without clinical or therapeutic relevance.

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In contrast, the use of capture technologies followed by next generation sequencing may represent the best option for clinical use of molecular genetic information in the near term. In this process, the relevant genes are 'captured' by either PCR reactions performed in microdroplets or hybridized to oligonucleotide baits and then sequenced using next-generation sequencing. As newer "bench-top" sequencers are developed and optimized, their faster sequencing turnaround (1-3 days) will allow for high-throughput, albeit focused, mutational studies in the clinical setting so that these data can be used to inform induction and post-remission therapies in AML.

In conclusion, with the discovery of new, recurrently mutated genes in AML, the first step should be to interrogate the clinical relevance of the specific mutation in homogeneously treated clinical cohorts in the context of all other known AML disease alleles. This will allow the AML field to evaluate the relevance of specific biomarkers rapidly and to develop tests that allow for cost-effective, rapid molecular profiling in the clinical setting. Whereas functional studies of novel disease alleles will likely result in the identification of novel therapeutic targets and lead to a greater understanding of AML pathogenesis, the incorporation of novel biomarkers into the clinical setting is the most important short-term goal facing AML patients and clinicians today.

Business News

Abbott to Collaborate with Janssen and Pharmacyclics on Development of Companion Test for Investigational Leukemia Therapy

Abbott announced on February 21, 2013 that it will collaborate with Janssen Biotech and Pharmacyclics to explore the benefits of Abbott's proprietary FISH (fluorescence in situ hybridization) technology for use in developing a molecular companion diagnostic test to identify patients with a genetic subtype of chronic lymphocytic leukemia (CLL), the most common form of adult leukemia.

Under the agreement, Abbott will develop a FISH-based test to identify high-risk CLL patients who have a deletion within a specific chromosome [chromosome 17p (del17p)] and may respond to ibrutinib, an oral, small molecule inhibitor of Bruton tyrosine kinase (BTK). Ibrutinib is currently in development by Janssen and Pharmacyclics for several B-cell malignancies, including chronic leukemia and lymphoma. Patients harboring a deletion within chromosome 17p are poor responders to chemoimmunotherapy and have limited treatment options. Having a test that is able to accurately detect the 17p deletion identifies a specific patient population with a high unmet medical need.

In 2011, Abbott received US FDA clearance for its Vysis CLL FISH Probe Kit. The kit targets multiple genes, including TP53 (tumor protein p53 gene, located on chromosome 17p) within the del17p region, and is used as an aid for determining prognosis for patients with CLL. Abbott's Vysis CLL FISH Probe Kit will be used for investigational use only to determine genetic marker status as part of the co-development efforts between Janssen, Pharmacyclics and Abbott.

Source: Abbott

Ablynx and Spirogen Enter Into a Research Collaboration to Evaluate the Potential of Novel Toxin-Nanobody Drug Conjugates in Cancer

Ablynx and Spirogen have announced a research collaboration to evaluate the potential of a novel anti-cancer drug conjugate combining Spirogen's proprietary cytotoxic drugs, pyrrolobenzodiazepines (PBD), and associated linker technology, with Nanobodies generated using Ablynx's proprietary technology platform.

Under the terms of the collaboration, Ablynx will provide access to novel Nanobodies against a specific, undisclosed cancer target and Spirogen will provide access to its proprietary cytotoxic warheads (PBDs) and conjugation technologies. Both companies will contribute their resources towards the collaboration, which is expected to last up to a year initially. Following this feasibility phase, Ablynx will have the option to either in-license Spirogen's technology or, in collaboration with Spirogen, move development forward with a third party. No further terms have been disclosed.

Source: Ablynx

Leica Biosystems and Synthon Biopharmaceuticals Partner to Develop a Companion Diagnostic Program for Targeted Cancer Therapies

Leica Biosystems and Synthon Biopharmaceuticals have announced an agreement to collaborate on the development and commercialization of a companion diagnostic test using the Leica BOND system, paired with one of Synthon Biopharmaceutical's antibody-drug conjugates (ADCs), to enhance the treatment of solid tumors.

Synthon strengthens its innovative drug pipeline with the development of a companion diagnostic test. This agreement provides framework for further collaboration projects.

Source: Leica Biosystems

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Clinical Development

Phase III Trial of Cilengitide did not meet Primary Endpoint in Patients with Newly Diagnosed Glioblastoma

Merck Serono has announced that the Phase III CENTRIC trial of the investigational integrin inhibitor cilengitide did not meet its primary endpoint of significantly increasing overall survival (OS) when added to the current standard chemoradiotherapy regimen. CENTRIC is a randomized, controlled, multicenter, open-label Phase III trial. The trial evaluated the efficacy and safety of cilengitide in combination with temozolomide and radiotherapy in more than 500 patients from 23 countries with newly diagnosed glioblastoma and methylated MGMT gene promoter status. The trial was planned and is being conducted in partnership with the European Organisation for Research and Treatment of Cancer (EORTC).

Patient safety in CENTRIC was monitored frequently by an independent data monitoring committee and no new or unexpected safety concerns were noted. In prior clinical studies, the most frequently reported adverse events the investigators considered to be attributed to cilengitide included nausea and fatigue. Detailed trial results will be presented at the American Society of Clinical Oncology (ASCO) 2013 Annual Meeting (to be held from May 31 to June 4, 2013)

Source: Merck Serono

Belinostat BELIEF Trial Meets Primary Endpoint with Encouraging Response Rate

Final top-line data confirm that the primary endpoint was met for the belinostat pivotal trial for patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) with an encouraging objective response rate. Top-line data show an objective response rate (ORR) in the efficacy analysis set which is above the protocol criterion for a positive outcome of the trial. Belinostat thus has an ORR that is on par with the accelerated approved drugs. A Special Protocol Assessment agreement with the US Food and Drug Administration (FDA) required the CLN-19 BELIEF trial to reach an ORR of at least 20%. The FDA has granted belinostat Orphan Drug and Fast Track designation for the treatment of PTCL. All patients who received at least one dose of belinostat and had a confirmed PTCL diagnosis by the central pathology review were included in the efficacy analysis set. The responses have been confirmed by central independent radiology review. Detailed trial results will be presented at the American Society of Clinical Oncology (ASCO) 2013 Annual Meeting (to be held from May 31 to June 4, 2013).

Belinostat is currently being developed jointly by Topotarget and Spectrum Pharmaceuticals. Spectrum possesses the commercial rights to market belinostat in North America and India. A New Drug Application (NDA) for belinostat in PTCL is expected to be filed with the FDA by Spectrum in mid-2013.

Source: Topotarget

Aeterna Zentaris to Discontinue Phase III Trial in Multiple Myeloma with Perifosine Following Data Safety Monitoring Board Recommendation

Aeterna Zentaris announced that an independent Data Safety Monitoring Board (DSMB) has recommended discontinuing the ongoing Phase III study comparing the efficacy and safety of perifosine to placebo when combined with bortezomib (Velcade) and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma.

Based on the outcome of its pre-planned interim analysis of efficacy and safety, the DSMB recommended that patient enrollment be stopped and the study discontinued. The DSMB reported that it was highly unlikely the study would achieve a significant difference in its primary endpoint, progression free survival (PFS); no safety concerns were raised.

Source: Aeterna Zentaris

Amgen Announces Top-line Results of Phase III Talimogene Laherparepvec Trial in Melanoma

Amgen has announced top-line results from the Phase III trial in melanoma, which evaluated the efficacy and safety of talimogene laherparepvec for the treatment of unresected stage IIIB, IIIC, or IV melanoma compared to treatment with subcutaneous granulocyte-macrophage colony-stimulating factor (GM-CSF).

The study met its primary endpoint of durable response rate (DRR), defined as the rate of complete or partial response lasting continuously for at least six months. A statistically significant difference was observed in DRR: 16% in the talimogene laherparepvec arm versus 2% in the GM-CSF arm. The analysis of overall survival (OS), a key secondary endpoint of the study, is event driven. A pre-planned interim analysis conducted with the analysis of DRR has shown an OS trend in favor of talimogene laherparepvec as compared to GM-CSF. The OS data is expected to mature in late 2013 in line with previous guidance. The most frequent adverse events observed in this trial were fatigue, chills, and pyrexia. The most common serious adverse events include disease progression, cellulitis, and pyrexia.

Talimogene laherparepvec is an investigational oncolytic immunotherapy designed to work in two important and complementary ways – to cause local lytic destruction of tumors while also stimulating a systemic anti-tumor immune response.

Source: Amgen

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Regulatory

FDA Approves Roche's Kadcyla (Trastuzumab emtansine), the First Antibody-Drug Conjugate for Treating HER2-positive Metastatic Breast Cancer

The Food and Drug Administration has approved a first-of-a-kind breast cancer medication that targets tumor cells while sparing healthy ones. The drug Kadcyla from Roche is an antibody-drug conjugate and is made up of the antibody, trastuzumab, and the chemotherapy, DM1, joined together using a stable linker. Like Herceptin, Kadcyla binds to HER2-positive cells and blocks the signaling pathways. Once Kadcyla is taken up by those cells, it is designed to destroy them by releasing the DM1 inside the cells.

Cancer researchers say the drug may offer a clear advantage over older drugs because it delivers more medication with fewer side effects. The FDA approved the new treatment for about 20% of breast cancer patients with HER2-positive metastatic breast cancer (mBC) who have received prior treatment with Herceptin (trastuzumab) and a taxane chemotherapy. It was approved based on Phase III, randomised, open-label study comparing Kadcyla alone to lapatinib in combination with Xeloda (capecitabine) in 991 people. People who received Kadcyla lived a median of 5.8 months longer than those who received the combination of lapatinib and Xeloda, the standard of care in this setting (median overall survival: 30.9 months vs. 25.1 months). Median progression free survival was 9.6 months with Kadcyla vs. 6.4 months in those who received lapatinib plus Xeloda (HR=0.65, P<0.0001).

Kadcyla will cost $9,800 per month, compared to $4,500 per month for regular Herceptin. The company estimates a full course of Kadcyla, about nine months of medicine, will cost $94,000.

Source: Roche; Forbes

FDA Approves Stivarga for Advanced GIST

The US Food and Drug Administration on February 25, 2013, expanded the approved use of Stivarga (regorafenib) to treat patients with advanced gastrointestinal stromal tumors (GIST) that cannot be surgically removed and no longer respond to other FDA-approved treatments for this disease. Stivarga, a multi-kinase inhibitor, blocks several enzymes that promote cancer growth. Stivarga is already approved for patients with metastatic colorectal cancer who have received at least two lines of chemotherapy. With this new approval, Stivarga is intended to be used in patients whose GIST cancer cannot be removed by surgery or has spread to other parts of the body (metastatic) and is no longer responding to Gleevec (imatinib) and Sutent (sunitinib), two other FDA-approved drugs to treat GIST. Stivarga was reviewed under the FDA's priority review program, which provides an expedited six-month review for drugs that may provide safe and effective therapy when no satisfactory alternative therapy exists, or offer significant improvement compared to marketed products.

The safety and effectiveness of Stivarga for this use was evaluated in a clinical study of 199 patients with GIST that could not be surgically removed and had progressed after treatment with imatinib or sunitinib. Patients were randomly assigned to receive either Stivarga or a placebo till tumor progression or unacceptable side effects. Results showed patients who took Stivarga had a delay in tumor growth (PFS) that was, on average, 3.9 months later than patients who were given placebo (mPFS was 4.8 months in the regorafenib arm versus 0.9 months in the placebo arm; HR 0.27; P<0.0001). Most common side effects reported in patients treated with Stivarga were weakness and fatigue, hand-foot syndrome, diarrhea, loss of appetite, hypertension, mucositis, infection, pain, dysphonia, weight loss, rash, fever, and nausea. Serious adverse events, which occurred in less than 1% of patients, were hepatotoxicity, hemorrhage, and gastrointestinal perforation.

Source: Bayer

Roche Obtains EU Approval for Perjeta, a New Personalized Treatment for Aggressive Type of Breast Cancer

The European Medicines Agency (EMA) has approved Perjeta (pertuzumab) for patients with previously untreated HER2-positive metastatic breast cancer (mBC). Perjeta is approved in combination with Herceptin (trastuzumab) and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

The European approval comes after the Phase III CLEOPATRA trial, which showed that the combination of Perjeta, Herceptin, and chemotherapy provided patients with a median of 6.1 months longer without their disease worsening or death (PFS) from 12.4 months for people who received Herceptin and chemotherapy to 18.5 months for those who received Perjeta, Herceptin and chemotherapy. There was a 34% reduction in the risk of death (OS) in Perjeta arm compared to Herceptin and chemotherapy alone (mOS was not reached in Perjeta arm vs. 37.6 months with Herceptin and chemotherapy; HR=0.66; P=0.0008).

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Perjeta is an example of Roche's Personalised Healthcare Approach as it targets the HER2 receptor, a protein found in high quantities on the outside of HER2-positive breast cancer cells. Perjeta is believed to work in a way that is complementary to Herceptin, as the two medicines target different regions on the HER2 receptor.

Source: Roche

FDA Approves Lymphoseek to Help Locate Lymph Nodes in Patients with Certain Cancers

The US Food and Drug Administration has approved Lymphoseek (technetium Tc 99m tilmanocept) injection, a radioactive diagnostic imaging agent that helps doctors locate lymph nodes in patients with breast cancer or melanoma who are undergoing surgery to remove tumor-draining lymph nodes. Lymph nodes filter lymphatic fluid that flows from the body's tissues. This fluid may contain cancer cells, especially if the fluid drains a part of the body containing a tumor. By surgically removing and examining the lymph nodes that drain a tumor, doctors can sometimes determine if a cancer has spread.

Lymphoseek is the first new drug used for lymph node mapping to be approved in more than 30 years. Other FDA-approved drugs used for lymph node mapping include sulfur colloid (1974) and isosulfan blue (1981).

Lymphoseek's safety and effectiveness were established in two clinical trials of 332 patients with melanoma or breast cancer. All patients were injected with Lymphoseek and blue dye, another drug used to help locate lymph nodes. Surgeons subsequently removed suspected lymph nodes for pathologic examination. Confirmed lymph nodes were examined for their content of blue dye and/or Lymphoseek. Results showed Lymphoseek and blue dye had localized most lymph nodes, although a notable number of nodes were localized only by Lymphoseek (average 97% for Lymphoseek [range 94-100%]). The most common side effects identified in clinical trials was pain or irritation at the injection site (<1%).

Source: Navidea Biopharmaceuticals

FDA Awards Breakthrough Therapy Designation to LDK378 for ALK+ Non-Small Cell Lung Cancer

Novartis's selective ALK inhibitor LDK378 was awarded Breakthrough Therapy designation by the US Food and Drug Administration (FDA) for the treatment of patients with anaplastic lymphoma kinase positive (ALK+) metastatic non-small cell lung cancer (NSCLC) who had progressed during treatment with, or were intolerant to, crizotinib. There are limited treatment options for patients with ALK+ NSCLC, who tend to be non-smokers and younger than NSCLC patients without an ALK translocation. Breakthrough Therapy designation is based on 80% response rate seen in patients with ALK+ NSCLC who have been previously treated with crizotinib, in a Phase I trial.

Breakthrough Therapy designation is intended to expedite the development and review of drugs that treat serious or life-threatening condition. It is granted if the therapy has demonstrated substantial improvement over an available therapy on at least one clinically significant endpoint.

Novartis has initiated two Phase II clinical trials to further evaluate LDK378 with plans to initiate several Phase III clinical trials in later half of 2013. First regulatory filing is anticipated by early 2014.

Source: Novartis

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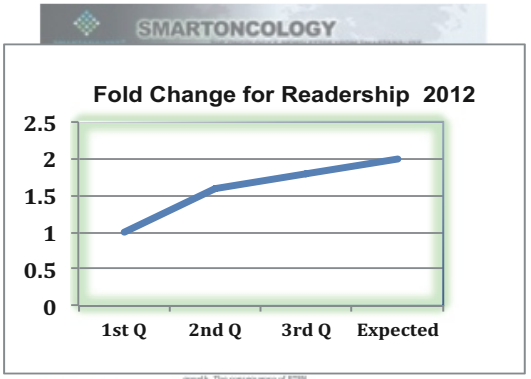

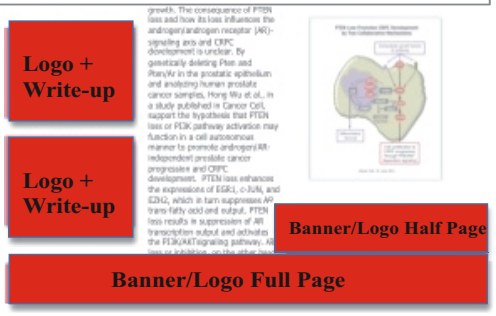

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