

THE CLINICAL CANCER LETTER

Cancer research news for clinicians

Leukemia

GA101 Associated with Better PFS In Phase III Trial Versus Rituximab in CLL

An interim analysis found that a phase III study met its primary endpoint, demonstrating that obinutuzumab (GA101) plus chlorambucil increased progression-free survival compared to Rituxan (rituximab) plus chlorambucil in patients with previously untreated chronic lymphocytic leukemia.

These data were reached well ahead of the target completion date in 2014 as a result of the magnitude of difference seen between the two study arms.

GA101 is the first type II anti-CD20 medicine that is glycoengineered, where specific sugar molecules in GA101 were modified to change its

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Lymphoma

Two Phase II Ibrutinib Studies Presented to EHA Demonstrate Efficacy as a Monotherapy

Two separate phase II studies demonstrated that ibrutinib, an investigational Bruton's tyrosine kinase inhibitor, showed efficacy as a monotherapy: one in patients with relapsed or refractory mantle cell lymphoma, and the other in diffuse large B-cell lymphoma.

In mantle cell lymphoma, patients taking ibrutinib demonstrated an overall response rate of 68 percent, with a complete response rate of 21 percent. The estimated median duration of response in all responding patients was 17.5 months. The median progression-free survival was 13.9 months, and while the median overall survival has not yet been reached, it is estimated to be 58 percent at 18 months.

In the study, 111 patients with relapsed or refractory mantle cell lymphoma were treated with ibrutinib. Patients were divided into two cohorts based on prior bortezomib exposure—either bortezomib-naïve (n=63) or bortezomib-exposed (n=48). Both groups received 560 mg of ibrutinib

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FDA News

FDA Approves Gilotrif Tablets in NSCLC, Boehringer Ingelheim's First Approved Cancer Drug

FDA approved Gilotrif (afatinib) tablets as a first-line treatment for patients with metastatic non-small cell lung cancer whose tumors have epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

The safety and efficacy of afatinib have not been established in patients whose tumors have other EGFR mutations.

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Phase III Trial Meets Endpoint In PFS With GA101 in CLL

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interaction with the body's immune cells. This modification creates a unique antibody that is designed to act as an immunotherapy. In addition, GA101 binds to CD20 with the aim of inducing direct cell death.

The data from the study, CLL11, will be submitted for consideration to the annual meeting of the American Society of Hematology in New Orleans, Dec. 7-10. GA101 is sponsored by Genentech.

CLL11 is a randomized three-arm study investigating the efficacy and safety profile of either GA101 plus chlorambucil or Rituxan plus chlorambucil compared to chlorambucil alone in 781 previously untreated people with CLL and co-existing medical conditions who are in need of therapy. The study included two stages of analysis.

Stage One included 589 patients and compared GA101 plus chlorambucil to chlorambucil alone and Rituxan plus chlorambucil to chlorambucil alone. Stage 1 results were reported earlier this year and showed that GA101 plus chlorambucil doubled the time people lived without their disease worsening compared to chlorambucil alone (23 months compared to 10.9 months, HR=0.14, 95% CI 0.09-0.21, $p<.0001$).

Stage Two enrolled an additional 192 patients to enable the final direct comparison of GA101 versus Rituxan, both in combination with chlorambucil.

Based on the stage one analysis of the study, marketing applications for GA101 were submitted to

FDA and the European Medicines Agency in April 2013. FDA granted the GA101 application both Breakthrough Therapy Designation and Priority Review.

No new safety signals for GA101 or Rituxan were identified in this analysis, and adverse events were similar to those observed in the first stage of the study which was previously reported earlier this year.

GA101 is currently being investigated in multiple head-to-head phase III studies versus Rituxan in indolent non-Hodgkin's lymphoma and diffuse large B-cell lymphoma.

Waldenstrom's Macroglobulinemia Study: Ibrutinib Lowers IgM, Bone Marrow Disease Burden

A phase II study examining ibrutinib in 35 patients with relapsed/refractory Waldenstrom's macroglobulinemia demonstrated an overall response rate of 83 percent.

In WM the malignant B-cells produce large amounts of immunoglobulin M. IgM causes the blood to thicken and causes many of the symptoms of the disease.

In the study, which consisted of six treatment cycles of four weeks per cycle, levels of IgM were reduced from 3,190 mg/dL at baseline to 1,232 mg/dL (six cycles best response; $p=5.1 \times 10^{-9}$) and bone marrow disease burden decreased from 70 percent down to 40 percent ($p=0.0004$).

Red blood cell production improved with levels of hematocrit increasing from 30.8 to 39.7 percent (six cycles best response; $p=1.1 \times 10^{-11}$). The study data were presented at the International Conference on Malignant Lymphoma in Switzerland.

The safety profile observed in patients with WM was similar to the established safety profile in other B-cell malignancies. Grade 3 and higher adverse events associated with the treatment of ibrutinib were infrequent with thrombocytopenia and neutropenia seen in 8.6 percent, and single cases of stomatitis and atrial fibrillation. None of these events led to ibrutinib discontinuation.

As of June 3, 91.4 percent of patients remain on the study with a minimum of 6 cycles of follow up. The study was extended by an additional 28 patients to further evaluate the safety and efficacy of ibrutinib in WM and a total of 63 patients are now enrolled.

Ibrutinib is an investigational agent designed to target and inhibit Bruton's tyrosine kinase. Janssen Biotech Inc. and Pharmacyclics Inc. are co-developing ibrutinib.

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Lymphoma

Two Phase II Ibrutinib Studies Demonstrate Efficacy

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orally, once a day until disease progression or no longer tolerated by the patient.

In the diffuse large B-cell lymphoma study, investigators examined whether ibrutinib would be more active in the Activated B-cell-like subtype of DLBCL compared to the Germinal Center B-cell-like subtype. The ABC subtype of DLBCL is dependent on the B-cell antigen receptor pathway, of which BTK is a key element.

Patients with the ABC subtype showed a preferential response to ibrutinib monotherapy compared to those with the GCB subtype, with an overall response rate of 41 percent compared to 5 percent, respectively ($p=0.007$). Median overall survival was 9.7 months for the ABC subtype compared to 3.35 months for the GCB subtype.

Within the ABC subtype group, only patients who had a CD79B mutation responded to treatment; patients with only an MYD88 mutation did not respond to treatment, suggesting a MYD88-dependent but BCR-independent pathogenesis for some DLBCL tumors, according to Janssen Research & Development, which is jointly developing ibrutinib with Pharmacyclics Inc.

The two studies were presented at the European Hematology Association's annual congress June 13-16. The findings expanded on the results reported by investigators at the American Society of Hematology Congress in December 2012.

Breast Cancer

ASCO Recommends Discussing Pharmacological Prevention

The American Society of Clinical Oncology issued an updated clinical practice guideline on pharmacological prevention interventions for premenopausal and postmenopausal women who are at increased risk for breast cancer.

Compared to the previous version of the guideline, this third update strongly recommends discussing the use of tamoxifen with premenopausal women, and tamoxifen and raloxifene with postmenopausal women at increased risk.

There is also a recommendation for discussing the option of exemestane as an alternative option for postmenopausal women.

The updated guideline, "Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: American Society of Clinical Oncology Clinical Practice Guideline," was published in the *Journal of Clinical Oncology*. The original guideline was published in 1999 and was updated in 2002 and 2009.

The key recommendations of the guideline are as follows:

- Tamoxifen (20 mg per day orally for five years) should be discussed as an option to reduce the risk of invasive, estrogen receptor-positive breast cancer in premenopausal or postmenopausal women.

- Raloxifene (60 mg per day orally for five years) should also be discussed as an option to reduce the risk of invasive, ER-positive breast cancer. Its use is limited to postmenopausal women.

- Exemestane (25 mg per day orally for five years) should be discussed as an alternative to reduce the risk of invasive, ER-positive breast cancer in postmenopausal women.

While exemestane is approved for the treatment of breast cancer, the FDA has not yet approved its use in breast cancer prevention.

According to ASCO, this recommendation is based on data from a single clinical trial that showed up to a 70 percent reduction in overall and ER-positive invasive breast cancer incidence with exemestane compared to placebo over a three year period.

All three agents should be discussed with women aged 35 years of older without a personal history of breast cancer who are at increased risk of developing invasive breast cancer, based on risk factors such as the woman's age, race, and medical and reproductive history, according to ASCO.

"Not every woman should use these preventive agents, but we believe women who are at increased risk for breast cancer should be given the option, because in some cases the magnitude of the risk reduction is large. For some women, these therapies can reduce the risk of breast cancer by up to 50 percent," said Kala Visvanathan, co-chair of the guideline panel and associate professor of epidemiology and oncology at the Johns Hopkins Bloomberg School of Public Health and the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center.

More information on the guideline can be found at <http://www.asco.org/guidelines/bcrr>.

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Liver Cancer

Elderly and Younger Patients Have Similar Outcomes Following Radioembolization

A study demonstrated similar long-term treatment outcomes following radioembolization in both elderly and younger patients with primary liver cancer.

“Our findings suggest that age alone should not be a discriminating factor for the management of HCC patients. This is important because there is a trend towards increased age in patients diagnosed with HCC, particularly in developed countries,” said the article’s lead author, Rita Golfieri, professor of radiology in the Department of Digestive Diseases and Internal Medicine of The University of Bologna.

The analysis found essentially identical long-term treatment outcomes following radioembolization using SIR-Spheres in 128 patients aged 70 years or older, compared with 197 younger patients with otherwise similar demographics.

Researchers also performed an additional sub-analysis of 49 very elderly patients ranging from 75-87 years, with a median age of 78. The study was published online in the *Journal of Hepatology*, the official journal of the European Association for the Study of the Liver.

The elderly and younger age groups had similar baseline characteristics, with many having multinodular, advanced-stage HCC which was present in both lobes of the liver and had reasonably-well compensated (Child-Pugh class A) underlying cirrhosis.

Radioembolization with SIR-Spheres was equally well-tolerated in both age groups.

Elderly patients had a significantly lower tumor burden, smaller liver volume—both overall and the amount targeted by radioembolization—and were less likely to have had hepatitis B viral infection.

Overall survival of patients in the study was not statistically significant between elderly and younger patients, a median 14.5 compared to 12.8 months, respectively.

There was also no significant difference in survival between patients 75 years or older and those under that age, with a median 14.9 vs. 12.8 months.

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Kidney Cancer

Cancer Genome Atlas Researchers Link Cell Metabolism Pathways To Disease Aggressiveness

Investigators in The Cancer Genome Atlas Research Network uncovered a connection between how tumor cells use energy from metabolic processes and the aggressiveness of clear cell renal cell carcinoma.

Their findings showed that normal metabolism is altered in ccRCC tumor cells, and involves a shift from using one metabolic pathway to another. This metabolic shift correlates with tumor stage and severity in some cases. The researchers also found mutations in a pathway that may cause increased aggressiveness in this cancer.

Taken together, the findings may offer new insight into underlying disease mechanisms and potential treatments as well as an understanding of how some cancer cells can shift from using normal metabolic pathways to alternative pathways, thereby providing a growth advantage to tumor cells.

In general, changes in metabolic enzymes that promote growth of the tumor are associated with worse patient outcomes in this disease. The results of this study were published online in *Nature*.

“Because of TCGA’s comprehensive characterization of kidney tumors and correlating that with patient survival data, researchers now can begin applying this knowledge to validating prognostic biomarkers and identifying new therapeutic strategies for this disease,” said NIH Director Francis Collins.

Researchers examined nearly 450 ccRCC tumors and matched each with a normal sample from the same patient. When they looked at the amounts of specific proteins expressed in cancer cells, they found that low levels of one protein essential to cell metabolism, AMPK, and high levels of acetyl-CoA carboxylase were associated with worse patient outcomes.

Additional, researchers discovered that, in some cases, the metabolic shift may be caused by changes in the PI3K cellular pathway, which helps regulate cell metabolism. The investigators observed a number of changes in PI3K pathway genes and its regulators in tumor cells, including DNA mutations in protein-coding areas, as well as other changes affecting gene expression. They found such alterations in the PI3K pathway—or its partner pathways, AKT and mTOR—in 29 percent of tumor samples.

Myelodysplastic Syndromes

Statistical Models Determine Stem-Cell Transplant Effectiveness

A new study set the first statistically-based guidelines for determining whether a stem cell transplant is appropriate for older patients with myelodysplastic syndromes.

Researchers at the Dana-Farber Cancer Institute used mathematical models to analyze hundreds of international MDS cases, and found that reduced intensity transplants of donor stem cells are advisable for patients aged 60-70 who have higher-risk forms of MDS that are likely to turn into leukemia in the near future.

The model indicates that, for patients with lower-risk MDS, non-transplant treatments are preferable. The research published online in the *Journal of Clinical Oncology*.

Researchers collected data on 514 patients, aged 60-70, who were newly diagnosed with MDS. For both lower- and higher-risk groups, they built separate mathematical models to compare treatment outcomes in patients who received reduced-intensity donor stem cell transplants with outcomes in patients who received non-transplant therapies. They analyzed length of survival and the quality of life in those groups.

Patients in the lower-risk groups who underwent transplant lived an average of 38 months after treatment, less than the 77 months for those who were treated without transplant. For patients in the higher-risk groups, by contrast, average life expectancy was 36 months for those receiving transplants, better than the 28 months for those receiving non-transplant therapies. Adjusting for patients' quality of life did not change the conclusions regarding the relative merits of the treatments.

"Our study helps inform older MDS patients and their doctors whether a stem cell transplant is preferred or whether it makes more sense to pursue other options," said lead author John Koreth, medical oncologist in the Division of Hematologic Malignancies at Dana-Farber.

"The clear result is that, on balance, reduced-intensity stem cell transplantation offers a survival benefit for patients with higher-risk MDS, but not for those with lower-risk disease."

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Multiple Myeloma

Phase II Elotuzumab Study Demonstrates 33 Months PFS

A phase II study evaluated two doses of elotuzumab in combination with lenalidomide and low-dose dexamethasone in patients with previously-treated multiple myeloma.

In the 10 mg/kg arm, the dosage currently used in ongoing phase III trials, median progression-free survival was 33 months after a median followup of 20.8 months (95% CI: 14.9-NA). The objective response rate was 92 percent.

In the 20 mg/kg arm, median PFS was 18 months after a median follow-up of 17.1 months (95% CI: 12.912-32.361), with an ORR of 76 percent.

Elotuzumab is a humanized monoclonal antibody that targets the cell-surface protein CS1, which is highly expressed on multiple myeloma cells. The updated data were presented at the annual congress of the European Hematology Association.

Safety data were consistent with previously-reported results for elotuzumab from this trial. Most treatment-emergent adverse events occurred within 18 months of initiating therapy. The most common grade 3/4 adverse events were lymphopenia, neutropenia, thrombocytopenia, anemia, leukopenia, hyperglycemia, pneumonia, diarrhea, fatigue, and hypokalemia.

Studies of elotuzumab in combination with lenalidomide and low-dose dexamethasone at a dose of 10 mg/kg are ongoing. ELOQUENT-1, a phase III trial in first-line multiple myeloma trial is currently enrolling patients and a second phase III trial, ELOQUENT-2, of patients with relapsed/refractory multiple myeloma is fully enrolled. Elotuzumab is sponsored by Bristol Meyers Squibb and AbbVie.

Leukemia

Ibrutinib Demonstrates 71% ORR In Phase Ib/II CLL and SLL Study

Results from a phase Ib/II study show that ibrutinib is well tolerated and produced durable responses at both dose levels studied in patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma.

Promising results were seen in patients with advanced disease and in patients with high-risk disease

as defined by clinical or genetic features, such as deletion of part of chromosome 17, which generally corresponds with a poor response to chemotherapy.

Overall response rates were 71 percent for patients in each treatment arm, split based on dosage—patients received 420 mg (n=51) or 840 mg (n=34) of ibrutinib monotherapy orally, once daily. Study patients with del17p had an overall response rate of 68 percent.

After an estimated median follow-up period of 26 months, 75 percent of all patients were progression free and 83 percent of patients were still alive. The study data were published online in the *New England Journal of Medicine*.

Ibrutinib is an investigational, oral Bruton's tyrosine kinase inhibitor being developed jointly by Janssen Research & Development and Pharmacyclics Inc.

Ibrutinib has been granted three breakthrough therapy designations by the FDA as a monotherapy for the treatment of patients with CLL or SLL with del17p; patients with relapsed/refractory MCL who have received prior therapy, and in patients with Waldenstrom's macroglobulinemia.

Prostate Cancer

Biomarker Test Outperforms PSA and Gleason Score in Study

Study data demonstrated that the Decipher test, developed by GenomeDx Biosciences, outperformed existing risk assessment tools for predicting metastatic prostate cancer in patients following prostate surgery. The test more accurately classified prostate cancer patients compared to conventional clinical variables such as Gleason score and PSA.

In the study, the test identified a high-risk patient group that was four times more likely to have metastatic cancer. Conversely, Decipher reclassified 60 percent of clinically high-risk patients as low risk, who were 2.5 times less likely to have metastatic cancer.

The test measures 22 genomic biomarkers associated with metastatic cancer to generate a result that indicates the likelihood of metastasis. The result is completely independent of PSA and other existing clinical variables. The study was published online in the *Journal of Urology*.

The study enrolled 1,010 men at elevated risk of recurrence following prostate surgery, finding that the overall incidence of metastatic disease was 6 percent after five years, with 20 percent of patients with a high

Decipher result having a 22.5 percent incidence of metastasis after five years.

GenomeDx expects to make the test more widely available to U.S. patients in the third quarter of this year.

NCI CTEP Approved Trials For the Month of July

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month. For further information, contact the principal investigator listed.

Phase I

9342: A Phase 1 Trial of MLN8237 Plus Romidepsin for Relapsed/Refractory Aggressive B-Cell and T-Cell Lymphomas. MD Anderson Cancer Center; Fanale, Michelle Anne. (713) 792-2860

9467: A Phase 1 Study of Brentuximab Vedotin in Combination with Temsirolimus in Relapsed and Refractory Hodgkin Lymphoma. Memorial Sloan Kettering Cancer Center; Moskowitz, Alison J. (212) 639-4839

9493: A Phase I Study of Autologous Activated NK Cells ± rhIL15 in Children and Young Adults with Refractory Solid Tumors. National Institutes of Health; Merchant, Melinda Sue. (301) 443-7955

E4412: A Phase I Study with an Expansion Cohort of the Combination of Ipilimumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma. Eastern Cooperative Oncology Group; Diefenbach, Catherine S. Magid. (212) 731-5670

Phase I/II

S1221: Phase I/II Study of the Safety and Efficacy of the AKT Inhibitor GSK2141795 in Combination with the BRAF Inhibitor Dabrafenib in Patients with BRAF Mutant Cancer. Southwest Oncology Group Ribas, Antoni (310) 206-3928

Phase II

RTOG-1201: A Phase II Randomized Trial of High Versus Standard Intensity Local or Systemic Therapy for Unresectable Pancreatic Cancer. Radiation Therapy Oncology Group; Ben-Josef, Edgar. (215) 615-3558

URCC12048: Feasibility, Acceptability and Mechanisms of Brief Behavioral Therapy (BBT) for Sleep Problems During Chemotherapy: A Phase II Randomized Controlled Trial. University of Rochester; Palesh, Oxana. (650) 725-7011

Phase III

A041202: A Randomized Phase III Study of Bendamustine Plus Rituximab Versus Ibrutinib Plus Rituximab Versus Ibrutinib Alone in Untreated Older Patients (≥ 65 Years of Age) with Chronic Lymphocytic Leukemia (CLL). Cancer and Leukemia Group B; Woyach, Jennifer Ann. (614) 293-8330

Pilot Phase

9431: Genome-Wide Methylation and Gene Re-Expression Analysis of Resectable Lung Tumor Tissue Pairs Obtained Pre- and Post-Treatment with 5-Azacytidine and Entinostat. University of New Mexico; Shaheen, Montaser. (812) 230-1521

Other Phases

A151220: Evaluating PTEN Expression and Mutations in PIK3CA, BRAF, NRAS, and KRAS as Predictors of Efficacy in Cetuximab- or Bevacizumab-Treated Colorectal Cancer Patients. Cancer and Leukemia Group B; Venook, Alan Paul. (415) 353-7065

AALL13B4-Q: Chromatin Structure in ETP Leukemias MerTK as a Target in ETP Leukemia. Children's Oncology Group; Hunger, Stephen P. (720) 777-8855

AAML13B2-Q: Molecular Analysis of DS-AML. Children's Oncology Group; Weiss, Mitchell J. (215) 590-0565

AHOD13B2-Q: The Role of MGMT in Pediatric Hodgkin Lymphoma and Chemotherapy Induced Toxicities. Children's Oncology Group; Harrison, Douglas J. (401) 444-5171

AMC-S006: Improving Participation in AMC Clinical Trials (IMPACTS). AIDS-Associated Malignancies Clinical Trials Consortium; Burkhalter, Jack Eryn. (646) 888-0040

ANBL13B4-Q: Evaluation of Vesicular

Monoamine Transporter Protein Expression as a Predictor of MIBG Uptake in High-Risk Neuroblastoma. Children's Oncology Group; DuBois, Steven G. (415) 476-3831

ARST13B2-Q: Prognostic Significance of Fusion Status for Low Risk and Metastatic Alveolar Rhabdomyosarcoma (ARMS). Children's Oncology Group; Rudzinski, Erin Renee. (206) 987-0375

ECOG-E2197E-E1199D-ECOG-ICSC: Prognostic Value of Tumor-Infiltrating Lymphocytes (TILs) in Two Phase III Randomized Adjuvant Breast Cancer Trials: ECOG 2197 and ECOG 1199. Eastern Cooperative Oncology Group; Adams, Sylvia. (212) 263-6485

NSABP-C08-DS1: Analysis of Molecular Profiling Data for Discovery of Models for Predicting Bevacizumab Benefit of Stage II and III Colon Cancer. National Surgical Adjuvant Breast and Bowel Project; Pogue-Geile, Katherine. (412) 359-8774

S9400-S0333-A: Genetic Analysis of Adult B-Cell Acute Lymphoblastic Leukemia (ALL). Southwest Oncology Group; Radich, Jerald Patrick. (206) 667-4118

SWOG-S8814B-SWOG-ICSC: Molecular Predictors of Outcome on CAF Plus Tamoxifen Versus Tamoxifen Alone in Postmenopausal Women with Node-Positive, Receptor-Positive Breast Cancer - A Transcriptome Expression Analysis of SWOG S8814. Southwest Oncology Group; Albain, Kathy S. (708) 216-5005

FDA News

FDA Approves Gilotrif Tablets In Non-Small Cell Lung Cancer

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Among patients diagnosed with NSCLC, it is estimated that between 10 and 15 percent of Caucasians and approximately 40 percent of Asians have EGFR mutations. Two of the EGFR mutations for which Gilotrif is indicated occur in 90 percent of these cases.

The drug, which was discovered and developed by Boehringer Ingelheim Pharmaceuticals, is the first FDA-approved oncology product from the company.

BI collaborated with Qiagen on the development of a companion diagnostic for Gilotrif. Qiagen's

Therascreen EGFR RGQ PCR Kit for detection of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations was reviewed and approved by the FDA in parallel to Gilotrif, and will be used to identify patients who may be eligible for treatment.

The approval of afatinib was based on the demonstration of improved progression-free survival in an international, open-label, randomized trial.

This trial enrolled 345 patients with metastatic NSCLC whose tumors tested positive for EGFR mutations. Patients were randomized to receive afatinib 40 mg orally once daily (n=230) or pemetrexed/cisplatin (n=115).

Randomization was stratified according to EGFR mutation status—exon 19 deletion vs. exon 21 (L858R) vs. ‘other’—and by Asian vs. non-Asian. The major efficacy outcome was progression-free survival as assessed by an independent review committee.

Of 345 patients enrolled, 65 percent were female, the median age was 61 years, 26 percent were Caucasian, and 72 percent were Asian.

The majority of patients had a tumor sample with an EGFR mutation categorized as either exon 19 deletion (49 percent) or exon 21 (L858R) substitution (40 percent), while the remaining 11 percent had ‘other’ mutations.

A statistically significant prolongation of PFS determined by the IRC was demonstrated for patients assigned to the afatinib treatment arm [HR 0.58 (95% CI: 0.43, 0.78); $p < 0.001$, stratified log-rank test].

The median PFS was 11.1 months in the afatinib arm and 6.9 months in the chemotherapy arm. Objective response rates were 50.4 and 19.1 percent in the afatinib and chemotherapy arms, respectively. No statistically significant difference in overall survival between the two arms was demonstrated.

In patients whose tumors have exon 19 deletions or exon 21 (L858R) substitution mutations, the median PFS was 13.6 months in the afatinib arm and 6.9 months in the chemotherapy arm.

The most frequent adverse reactions from afatinib were diarrhea, rash/dermatitis acneiform, stomatitis, paronychia, dry skin, decreased appetite and pruritus.

Serious adverse reactions were reported in 29 percent of patients treated with afatinib. The most frequent serious adverse reactions were diarrhea, vomiting; and dyspnea, fatigue, and hypokalemia. Fatal adverse reactions in afatinib-treated patients included pulmonary toxicity/ interstitial lung disease-like adverse reactions, sepsis, and pneumonia.

The company must now seek for second-line marketing authorization, said Brooke Baker, an analyst with research and consulting firm GlobalData.

Baker, who covers oncology and hematology, said the drug has significant challenges in the NSCLC market: “There are concerns regarding Gilotrif’s toxicity among some in the NSCLC space, and indeed Gilotrif’s FDA prescribing information carries a warning against severe diarrhea.”

“We believe these safety concerns, combined with a lack of head-to-head data against entrenched anti-EGFR therapies such as Tarceva, could limit Gilotrif’s uptake in the U.S. NSCLC market starting from 2013.”

Following entry into the U.S. market, BI expects to launch Gilotrif in the E.U. and Japan later this year. However, once launched in these markets, Gilotrif will have to contend with established drugs such as Iressa and Tarceva.

“Based on expected positive results from the LUX-Lung 5 phase III trial investigating Gilotrif as a second-line therapy in NSCLC patients failing other first-line treatments, the second-line setting could present a great opportunity for BI’s drug to gain patient and market share,” Baker said.

“Iressa and Tarceva both face patent expiration by the end of the decade, and Gilotrif is well positioned to become the leading branded EGFR-targeted therapy after that occurs; but until that time, we believe that BI will need to push hard for second-line marketing authorization in the U.S. and E.U. in order to fully realize Gilotrif’s sales potential.”

Regulatory News **FDA Approves Implant For Breast Reconstruction**

FDA approved the MemoryShape Breast Implant to rebuild breast tissue in women of any age and to increase breast size for use in women at least 22 years old.

The approval was based on six years of data from 955 women demonstrating that there is a reasonable assurance of safety and effectiveness for this implant.

FDA requires that Mentor Worldwide, the implant’s manufacturer, conduct a series of post-approval studies to assess long-term safety and effectiveness outcomes and the risks of rare disease and continue to follow women who received the implant as part of a pre-market study.

FDA granted clearance to a new version of the xTAG CYP2D6 kit developed by Luminex Corporation.

Cytochrome P450 2D6 (CYP2D6) is a clinically important gene that encodes a phase one drug metabolizing enzyme. CYP2D6 metabolizes greater than 25 percent of the drugs in use today including cardiovascular drugs, antipsychotics, antidepressants, pain medications, b-blockers, antiemetics, antiarrhythmics and anticancer drugs.

Variations in the CYP2D6 gene can result in distinct drug metabolizing phenotypes leading to sub-optimal drug responses, such as drug toxicity, adverse drug reactions, or inadequate therapeutic effects.

The IVD assay is run on the Luminex 100/200 instrument. This new version of the kit optimizes performance on the *17 allele and features an updated software algorithm that detects all 17 genotypes that the assay is cleared for, including deletion and duplication genotypes.

The European Medicines Agency granted orphan drug designation for Zybrestat (fosbretabulin tromethamine) for the treatment of ovarian cancer. A disease is defined as rare in the EU if it affects fewer than five in 10,000 people.

A phase II trial of Zybrestat and Avastin (bevacizumab) is being conducted by the Gynecologic Oncology Group, in collaboration with Genentech, the manufacturer of Avastin. A total of 107 patients with advanced, platinum-sensitive and resistant ovarian cancer have been enrolled in this trial at over 80 clinical sites in the U.S. Data is expected to be available in early 2014. Zybrestat is sponsored by OXiGENE Inc.

The Japanese Ministry of Health, Labor and Welfare approved Avastin (bevacizumab) for the treatment of malignant glioma, including newly diagnosed glioblastoma, in combination with radiotherapy and temozolomide chemotherapy, and as monotherapy for treatment of recurrent GBM and certain other types of high grade glioma following prior therapy.

The approval was based on data from three clinical studies in GBM: the phase II BRAIN study, a Japanese phase II study (JO22506), and the phase III AVAglio study, which demonstrated an increase in progression-free survival but no significant increase in overall survival. Avastin is sponsored by Roche.

The European Medicines Agency's Committee for Medicinal Products for Human Use granted a positive opinion to the subcutaneous formulation of Herceptin (trastuzumab), which uses a recombinant human hyaluronidase (rHuPH20), for the treatment of patients with HER2-positive breast cancer in Europe.

A phase III study, HannaH, demonstrated that Herceptin SC may help decrease the time patients spend receiving treatment at a hospital or physician's practice, by reducing the administration time. The SC dose can be administered in two to five minutes.

Study results showed that the safety and efficacy of the subcutaneous formulation of Herceptin is comparable to treatment with Herceptin administered intravenously.

Herceptin is sponsored by Roche. The recombinant human hyaluronidase was developed by Halozyme Therapeutics Inc.

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