BLINCYTO® (blinatumomab) Significantly Improved Overall Survival In Patients With B-Cell Precursor Acute Lymphoblastic Leukemia Compared To Chemotherapy

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BLINCYTO Almost Doubled Median Overall Survival in High-Risk Patients With B-Cell Precursor Acute Lymphoblastic Leukemia Compared to Standard of Care Chemotherapy

BLINCYTO is the First-and-Only Bispecific CD19-Directed CD3 T Cell Engager (BiTE®) Immunotherapy to Demonstrate Overall Survival Benefit in Patients With Philadelphia Chromosome-Negative Relapsed or Refractory Acute Lymphoblastic Leukemia

Results Published in The New England Journal of Medicine

THOUSAND OAKS, Calif., March 1, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced the *New England Journal of Medicine* published results from the Phase 3 TOWER study evaluating the efficacy of BLINCYTO® (blinatumomab) versus standard of care (SOC) chemotherapy in high-risk adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), one of the most aggressive B-cell malignancies. Results from the analysis showed that median overall survival (OS) was 7.7 months (95 percent CI: 5.6, 9.6) for BLINCYTO versus four months (95 percent CI: 2.9, 5.3) for SOC (hazard ratio [HR] for death=0.71; *p*=0.012). The TOWER study is the confirmatory study for the Phase 2 trial that supported the U.S. Food and Drug Administration's (FDA) accelerated approval designation for BLINCYTO in 2014.

BLINCYTO is a bispecific CD19-directed CD3 T cell engager (BiTE®) antibody construct. It is the first bispecific antibody construct from Amgen's BiTE® platform, which helps the body's immune system target cancer cells and represents an entirely new area of oncology research. BiTE® antibody constructs are currently being investigated for their potential to treat a wide variety of cancers.

"Historically, patients with relapsed or refractory ALL have a poor prognosis, with an overall survival of just four months on standard of care chemotherapy," said Max S. Topp, M.D., professor and head of Hematology, University Hospital of Wuerzburg, Germany. "Findings from this head-to-head study showed that BLINCYTO almost doubled the median overall survival from four to 7.7 months, offering these high-risk patients a much needed alternative to chemotherapy that is both innovative and effective."

The survival benefit for BLINCYTO was independent of allogeneic stem cell transplant (alloSCT), as the median OS, censored at the time of alloSCT, was 6.9 months for BLINCYTO versus 3.9 months for SOC. Improvement in OS was generally consistent regardless of age, prior salvage therapy or prior alloSCT. The magnitude of this benefit appeared greatest in earlier lines of salvage. Neutropenia and infection greater than or equal to Grade 3 appeared less frequently with BLINCYTO compared to SOC, while neurological events appeared at a similar rate between arms.

"Adults with Ph- relapsed or refractory B-cell precursor ALL are in critical need of new treatment options," said Hagop M. Kantarjian, M.D., professor and chair of the Department of Leukemia at The University of Texas MD Anderson Cancer Center, Houston. "Results from the TOWER study reinforce the potential of this single agent bispecific T cell engager immunotherapy, which helped a higher percentage of patients achieve minimal residual disease response versus standard of care chemotherapy, highlighting the depth and quality of remissions achieved."

Evaluation of key secondary endpoints showed that remission rates were also higher for BLINCYTO versus SOC. In the BLINCYTO group, 34 percent of patients achieved complete remission versus 16 percent in the SOC group. Patients receiving BLINCYTO also had a higher rate of combined complete remission or complete remission with partial or incomplete hematologic recovery (44 percent versus 25 percent).

Among patients with complete remission or complete remission with partial or incomplete hematologic recovery, 76 percent in the BLINCYTO group versus 48 percent in the SOC group achieved minimal residual disease (MRD) negative status, a measure of eradication of residual disease at the molecular level. Also among these patients, the median duration of remission was 7.3 months in the BLINCYTO group versus 4.6 months in the SOC group. For the key secondary efficacy endpoint of event-free survival, six month estimates in the BLINCYTO and chemotherapy groups were 30.7 percent and 12.5 percent, and the HR was 0.55 (95 percent CI: 0.43, 0.71), favoring BLINCYTO.

"As the first study of an immunotherapy to demonstrate overall survival benefit in adult patients with Ph- relapsed or refractory B-cell precursor ALL, TOWER represents an important advance in the understanding of this aggressive, ultra-orphan disease," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "As demonstrated by the data published today in the *New England Journal of Medicine*, BLINCYTO has proven to improve overall survival, extend remission rates and reduce minimal residual disease in these high-risk patients who previously have had limited effective options."

Safety results among subjects who received BLINCYTO were comparable to those seen in the Phase 2 studies in adult patients with Ph- relapsed or refractory B-cell precursor ALL. For the most common adverse events (greater than or equal to 10 percent incidence rate) in the BLINCYTO arm, only three events (cough, pyrexia, cytokine release syndrome) occurred at an incidence rate that was at least 5 percent higher for BLINCYTO compared to SOC chemotherapy.

ALL is a rare and rapidly progressing cancer of the blood and bone marrow.[1,2] Adult patients diagnosed with Ph- B-cell precursor ALL are often young, with a median age at diagnosis of 34-39.[3,4] Currently, there is no broadly accepted standard treatment regimen for adult patients with relapsed or refractory ALL beyond chemotherapy.[5] Adults with relapsed or refractory ALL typically have a very poor prognosis, with a median OS of three to five months.[6]

About the TOWER Study

The TOWER study was a Phase 3, randomized, open-label study investigating the efficacy of BLINCYTO versus SOC chemotherapy in 405 adult patients with Ph- relapsed or refractory B-cell precursor ALL. Patients were randomized in a 2:1 ratio to receive BLINCYTO (n=271) or treatment with

investigator choice of one of four protocol-defined SOC chemotherapy regimens (n=134). The primary endpoint was OS. Key secondary endpoints included complete remission within 12 weeks, the combined endpoint of complete remission plus complete remission with partial or incomplete hematologic recovery and event-free survival. Other secondary endpoints included remission duration, MRD remission ($<10^{-4}$), alloSCT rate and adverse event rates.

The TOWER study is the confirmatory trial for BLINCYTO. Click here to read about the trial on ClinicalTrials.gov.

About Adult ALL

In the United States (U.S.), the incidence of adult ALL is approximately 0.9 per 100,000 persons per year.[7] The incidence of adult ALL in European countries is generally between 0.6 to 0.9 per 100,000 persons per year.[7] In adult ALL, approximately 75 percent is B-cell precursor ALL, of which 75-80 percent is Ph- and roughly half will be refractory to treatment or experience relapse.[7] In the U.S., the incidence of adult Ph- relapsed or refractory B-cell precursor ALL was approximately 650 patients in 2015 and in the European Union (EU), the estimated incidence is approximately 1,200 patients per year.[7,8]

About BLINCYTO® (blinatumomab)

BLINCYTO is a bispecific CD19-directed CD3 T cell engager (BiTE®) antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells.

BLINCYTO was granted breakthrough therapy and priority review designations by the FDA, and is now approved in the U.S. for the treatment of Ph- relapsed or refractory B-cell precursor ALL. This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials.

In November 2015, BLINCYTO was granted conditional marketing authorization in the EU for the treatment of adults with Ph- relapsed or refractory B-cell precursor ALL.

About BiTE® Technology

Bispecific T cell engager (BiTE®) antibody constructs are a type of immunotherapy being investigated for fighting cancer by helping the body's immune system to detect and target malignant cells. The modified antibodies are designed to engage two different targets simultaneously, thereby juxtaposing T cells (a type of white blood cell capable of killing other cells perceived as threats) to cancer cells. BiTE® antibody constructs help place the T cells within reach of the targeted cell, with the intent of allowing T cells to inject toxins and trigger the cancer cell to die (apoptosis). BiTE® antibody constructs are currently being investigated for their potential to treat a wide variety of cancers. For more information, visit www.biteantibodies.com.

BLINCYTO® U.S. Product Safety Information

Important Safety Information Regarding BLINCYTO® (blinatumomab) U.S. Indication

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® as recommended.**
- **Neurological toxicities, which may be severe, life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® as recommended.**

Contraindications

BLINCYTO® is contraindicated in patients with a known hypersensitivity to blinatumomab or to any component of the product formulation.

Warnings and Precautions

- Cytokine Release Syndrome (CRS): CRS, which may be life-threatening or fatal, occurred in patients receiving BLINCYTO®. Infusion reactions have occurred and may be clinically indistinguishable from manifestations of CRS. Closely monitor patients for signs and symptoms of serious events such as pyrexia, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin (TBILI), disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). Interrupt or discontinue BLINCYTO® as outlined in the Prescribing Information (PI).
- Neurological Toxicities: Approximately 64% of patients receiving BLINCYTO® in clinical trials experienced neurological toxicities. The median time to onset of any neurological toxicity was 4 days. The most common (≥ 10%) manifestations of neurological toxicity were headache, tremor, dizziness, and altered state of consciousness. Severe, life-threatening, or fatal neurological toxicities occurred in approximately 17% of patients, including encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The neurological toxicity profile varied by age group. Monitor patients for signs or symptoms and interrupt or discontinue BLINCYTO® as outlined in the PI.
- Infections: Approximately 25% of patients receiving BLINCYTO® experienced serious infections, some of which were life-threatening or fatal. Administer prophylactic antibiotics and employ surveillance testing as appropriate during treatment. Monitor patients for signs or symptoms of infection and treat appropriately, including interruption or discontinuation of BLINCYTO® as needed.

- Tumor Lysis Syndrome (TLS): TLS, which may be life-threatening or fatal, has been observed. Preventive measures, including pretreatment nontoxic cytoreduction and on-treatment hydration, should be used during BLINCYTO® treatment. Monitor patients for signs and symptoms of TLS and interrupt or discontinue BLINCYTO® as needed to manage these events.
- Neutropenia and Febrile Neutropenia, including life-threatening cases, have been observed. Monitor appropriate laboratory parameters during BLINCYTO® infusion and interrupt BLINCYTO® if prolonged neutropenia occurs.
- Effects on Ability to Drive and Use Machines: Due to the possibility of neurological events, including seizures, patients receiving BLINCYTO® are at risk for loss of consciousness, and should be advised against driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO® is being administered.
- Elevated Liver Enzymes: Transient elevations in liver enzymes have been associated with BLINCYTO® treatment with a median time to onset of 3 days. In patients receiving BLINCYTO®, although the majority of these events were observed in the setting of CRS, some cases of elevated liver enzymes were observed outside the setting of CRS, with a median time to onset of 15 days. Grade 3 or greater elevations in liver enzymes occurred in 6% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients. Monitor ALT, AST, gamma-glutamyl transferase (GGT), and TBILI prior to the start of and during BLINCYTO® treatment. BLINCYTO® treatment should be interrupted if transaminases rise to > 5 times the upper limit of normal (ULN) or if TBILI rises to > 3 times ULN.
- Pancreatitis: Fatal pancreatitis has been reported in patients receiving BLINCYTO® in combination with dexamethasone in clinical trials and the post-marketing setting. Evaluate patients who develop signs and symptoms of pancreatitis and interrupt or discontinue BLINCYTO® and dexamethasone as needed.
- Leukoencephalopathy: Although the clinical significance is unknown, cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO®, especially in patients previously treated with cranial irradiation and antileukemic chemotherapy.
- Preparation and administration errors have occurred with BLINCYTO® treatment. Follow instructions for preparation (including admixing) and administration in the PI strictly to minimize medication errors (including underdose and overdose).
- Immunization: Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of BLINCYTO® treatment, during treatment, and until immune recovery following last cycle of BLINCYTO®.

Adverse Reactions

- The most common adverse reactions (≥ 20%) in the safety population studied in clinical trials were pyrexia (66%), headache (34%), nausea (27%), edema (26%), hypokalemia (26%), anemia (25%), febrile neutropenia (24%), neutropenia (22%), thrombocytopenia (20%), and abdominal pain (20%). The safety population included 225 patients weighing 45 kg or more and 57 patients weighing less than 45 kg. For some adverse reactions, there were differences in the incidence rates by age subgroup.
- In patients weighing greater than or equal to 45 kg, serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia (9%), pyrexia (6%), sepsis (5%), pneumonia (5%), device-related infection (4%), neutropenia (3%), tremor (3%), overdose (3%), encephalopathy (3%), infection (2%), confusion (3%) and headache (2%).
- In patients weighing less than 45 kg, serious adverse reactions were reported in 51% of patients. The most common serious adverse reactions (≥ 2%) included pyrexia (12%), febrile neutropenia (9%), cytokine release syndrome (4%), convulsion (4%), device-related infection (4%), hypoxia (4%), sepsis (4%), and overdose (4%).

U.S. Dosage and Administration Guidelines

- BLINCYTO® is administered as a continuous intravenous infusion at a constant flow rate using an infusion pump which should be programmable, lockable, non-elastomeric, and have an alarm.
- It is very important that the instructions for preparation (including admixing) and administration provided in the full Prescribing Information are strictly followed to minimize medication errors (including underdose and overdose).

Please see full Prescribing Information, including **Boxed WARNINGS** and Medication Guide, for BLINCYTO® at www.BLINCYTO.com.

Important EU Product Safety Information

This product is subject to additional monitoring in the EU and EEA. All suspected adverse reactions should be reported in accordance with the national reporting system.

The adverse reactions described in this section were identified in the pivotal clinical study (N=189).The most serious adverse reactions that may occur during blinatumomab treatment include: infections (31.7%), neurologic events (16.4%), neutropenia/febrile neutropenia (15.3%) cytokine release syndrome (0.5%), and tumor lysis syndrome (0.5%). The most common adverse reactions were: infusion-related reactions (67.2%), infections (63.0%), pyrexia (59.8%), headache (34.4%), febrile neutropenia (28%), peripheral edema (25.9%), nausea (24.3%), hypokalaemia (23.8%), constipation (20.6%), anaemia (20.1%), cough (18.5%), diarrhea (18.0%), tremor (17.5%), neutropenia (17.5%), abdominal pain (16.9%), insomnia

(15.3%), fatigue (15.3%), and chills (15.3%).

Please refer to the Summary of Product Characteristics for full European prescribing information.

About Amgen's Commitment to Oncology
Amgen Oncology is committed to helping patients take on some of the toughest cancers, such as those that have been resistant to drugs, those that progress rapidly through the body and those where limited treatment options exist. Amgen's supportive care treatments help patients combat certain side effects of strong chemotherapy, and our targeted medicines and immunotherapies focus on more than a dozen different malignancies, ranging from blood cancers to solid tumors. With decades of experience providing therapies for cancer patients, Amgen continues to grow its portfolio of innovative and biosimilar oncology medicines.

About Amgen
Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/amgen.

Forward-Looking Statements
This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. We or others could identify safety, side effects or manufacturing problems with our products after they are on the market. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Discovery or identification of new product candidates cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate will be successful and become a commercial product. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations. Our efforts to acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all. We are increasingly dependent on information technology systems, infrastructure and data security. Our stock price is volatile and may be affected by a number of events. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock.

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References:

1. Cancer Research UK. Acute lymphoblastic leukaemia risks and causes. http://www.cancerresearchuk.org/about-cancer/type/all/about/acute-lymphoblastic-leukaemia-risks-and-causes. Accessed Dec. 13, 2016
2. Mayo Clinic. Acute lymphocytic leukemia. http://www.mayoclinic.org/diseases-conditions/acute-lymphocytic-leukemia/basics/definition/con-20042915. Accessed Dec. 13, 2016.
3. Kenderian SS, Al-Kali A, Gangat N, et al. Monosomal karyotype in Philadelphia chromosome-negative acute lymphoblastic leukemia. *Blood Cancer J*. 2013;3e122.

4. Faderl S, Kantarjian HM, Thomas DA, et al. Outcome of Philadelphia chromosome-positive adult lymphoblastic leukemia. *Leuk Lymphoma*. 2000;36(3-4):263-73.
5. Davis T, Farag SS. Treating relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia: liposome-encapsulated vincristine. *Int J Nanomedicine*. 2013:8:3479-88.
6. Advani AS. New immune strategies for the treatment of acute lymphoblastic leukemia: Antibodies and chimeric antigen receptors. *Hematology Am Soc Hematol Educ Program*. 2013;131-7.
7. Katz AJ, Chia VM, Schoonen M, et al. Acute lymphoblastic leukemia: an assessment of international incidence, survival, and disease burden. *Cancer Causes Control*. 2015;26(11):1627-42.
8. Amgen Data on File.