BeiGene Announces Clinical Data on BRUKINSA™ (Zanubrutinib) at the 61st American Society of Hematology (ASH) Annual Meeting

Oral presentations on data from two clinical trials in chronic lymphocytic leukemia or small lymphocytic lymphoma

Poster presentation on data from clinical trial of BRUKINSA combined with tislelizumab in B-cell malignancies

CAMBRIDGE, Mass. and BEIJING, China, December 8, 2019 (GLOBE NEWSWIRE) -- BeiGene, Ltd. (NASDAQ: BGNE; HKEX: 06160), a commercial-stage biopharmaceutical company focused on developing and commercializing innovative molecularly-targeted and immuno-oncology drugs for the treatment of cancer, today announced clinical data from three trials of its BTK inhibitor BRUKINSA™ (zanubrutinib) were presented at the 61st American Society of Hematology (ASH) Annual Meeting in Orlando, FL. In two oral presentations of BRUKINSA in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), the drug candidate demonstrated consistent safety and a high overall response rate (ORR); in the poster presentation of BRUKINSA combined with BeiGene’s investigational anti-PD-1 antibody tislelizumab in patients with previously treated B-cell malignancies, the combination treatment showed preliminary efficacy and was generally well tolerated.

“The data presented today showing clinical activity and tolerability of BRUKINSA in patients with CLL or SLL are promising for its potential use in patients living with these cancers,” said Constantine S. Tam, M.D., Disease Group Lead for Low Grade Lymphoma and Chronic Lymphocytic Leukemia at the Peter MacCallum Cancer Center and Director of Hematology at St. Vincent’s Hospital, Australia. “BTK inhibitors have become an important standard of care for B-cell malignancies, offering the potential for durable responses with manageable safety profiles. It’s encouraging to have more evidence that zanubrutinib can be effective in treating CLL or SLL, including in patients with del(17p) who typically have a worse prognosis and few treatment options.”

“The results presented today on BRUKINSA, a BTK inhibitor designed to maximize target occupancy and minimize off-target binding, demonstrated robust clinical activity and a safety profile consistent with what we’ve observed to date in our clinical trials, including safety data that supported the recent U.S. FDA accelerated approval in patients with previously treated mantle cell lymphoma,” said Jane Huang, M.D., Chief Medical Officer, hematology at BeiGene. “CLL or SLL is the most common type of leukemia in adults, and despite the advancements of BTK inhibitor therapy for these
cancers, there remains a need for highly selective BTK inhibitors capable of promoting long-term responses, and with a safety profile that is tolerable over time. The results presented here today further demonstrate the potential for BRUKINSA to help people living with these persistent, life-threatening cancers.”

Initial Results from SEQUOIA Trial Arm C in Treatment-Naïve (TN) CLL or SLL Patients with Del(17p)

Presentation 499

Initial results from Arm C in the open-label, Phase 3 SEQUOIA trial (NCT03336333) of BRUKINSA as a monotherapy demonstrated a high ORR in patients with TN CLL or SLL whose tumor exhibits the deletion of chromosome 17p13.1 [del(17p)]. The safety profile was consistent with that observed in previous clinical trials of BRUKINSA in B-cell malignancies. At the data cutoff of August 7, 2019, with a median follow-up of 10 months, initial results included:

- The ORR was 92.7% (101/109); the partial response (PR) rate was 78.9% (86/109); the PR rate with lymphocytosis was 11.9% (13/109); and the complete response (CR) rate was 1.9% (2/109); only four cases of disease progression occurred;

- 36.7% of patients (40/109) experienced at least one grade ≥3 adverse event (AE) and only one patient discontinued treatment due to AEs;

- The most common grade ≥3 AEs, occurring in more than two patients, were neutropenia (10.1%), pneumonia (3.7%) and hypertension (2.8%);

- 23.9% of patients (26/109) experienced at least one serious AE; and

- One patient experienced a fatal AE, pneumonia leading to sepsis and death, which was considered related to treatment drug by the study investigator.

Updated Results from a Phase 1/2 Trial in Patients with CLL or SLL

Presentation 500

Updated results from the open-label, dose-escalation, single-arm, global Phase 1/2 trial (NCT02343120) showed that BRUKINSA was generally well-tolerated and active in patients with relapsed/refractory (R/R) or TN CLL/SLL, irrespective of del(17p) status
At the data cutoff of May 8, 2019, with a median follow-up of 29.5 months, results included:

- The ORR was 95.9% (118/123); the PR rate was 73.2% (90/123); the PR rate with lymphocytosis was 6.5% (8/123); the CR rate was 16.3% (20/123), including one patient who achieved a CR with incomplete bone marrow recovery;

- The median duration of treatment was 25.8 months and 80% of patients (98/123) remained on study treatment; two-year progression-free survival (PFS) was 91% in R/R patients and 95% in TN patients;

- 61.8% of patients (76/123) experienced at least one grade ≥3 AE and only five patients discontinued treatment due to AEs;

- The most common AEs (≥20%) were contusion (47.2%), upper respiratory tract infection (42.3%), diarrhea (31.7%), cough (29.3%), headache (23.6%), and fatigue (20.3%);

- 47.2% of patients (58/123) experienced at least one serious AE; and

- One patient experienced a fatal AE, neoplasm-malignant recurrent squamous cell carcinoma, considered unrelated to treatment drug by the study investigator.

BRUKINSA in Combination with PD-1 Inhibitor Tislelizumab in Patients with Previously Treated B-Cell Lymphoid Malignancies

Presentation 1594

Preliminary findings from the open-label, multicenter, Phase 1b trial (NCT02795182) showed that BRUKINSA in combination with the investigational anti-PD-1 antibody tislelizumab demonstrated a generally manageable toxicity profile in patients with R/R B-cell malignancies. A total of 70 patients enrolled in the trial, including 54 patients with aggressive non-Hodgkin’s lymphomas (NHLs) which consist of diffuse large B-cell lymphoma, transformed follicular lymphoma, Richter’s transformation, and central nervous system (CNS) lymphoma. At the data cutoff of August 31, 2019, with a median follow-up of 8.1 months, preliminary findings included:

- Of the 54 patients with aggressive NHLs, the ORR was 37.0% (20/54); the PR rate was 20.4% (11/54); the CR rate was 16.7% (9/54); stable disease (SD) rate was 9.3% (5/54);
• 71.4% of patients (50/70) experienced at least one grade ≥3 AE and 14.3% of patients (10/70) discontinued BRUKINSA and/or tislelizumab treatment due to AEs;
• The most common grade ≥3 AEs were neutropenia (12.9%), anemia (10.0%), thrombocytopenia (7.1%), pneumonia (5.7%), neutrophil count decreased (5.7%), tumor lysis syndrome (4.3%), sepsis (4.3%), immune-mediated enterocolitis (4.3%), hypertension (4.3%), lymphocyte count decreased (2.9%), hemolytic transfusion reaction (2.9%), febrile neutropenia (2.9%), back pain (2.9%), acute kidney injury (2.9%), abscess limb (2.9%), and abdominal pain (2.9%);
• Grade ≥3 immune-related AEs (irAEs) were reported in 15.7% of patients (11/70) with immune-mediated enterocolitis (4.3%), and pneumonitis (2.9%) occurring in more than one patient; and
• Five patients experienced fatal AEs, four of which in the setting of progressive disease were considered unrelated to treatment including multi-organ dysfunction, septic shock and pneumonia, respiratory failure, and aspiration pneumonia, and one of toxic epidermal necrolysis which was considered related to treatment by the study investigator.

About BRUKINSA™ (zanubrutinib)

BRUKINSA (zanubrutinib) is a small molecule inhibitor of Bruton’s tyrosine kinase (BTK) discovered by BeiGene scientists that is currently being evaluated globally in a broad pivotal clinical program as a monotherapy and in combination with other therapies to treat various B-cell malignancies. BRUKINSA was granted accelerated approval by the U.S. FDA to treat adult patients with MCL who have received at least one prior therapy in November 2019. This accelerated approval is based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

New Drug Applications (NDAs) in China for relapsed refractory (R/R) MCL and R/R chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) have been accepted by the China National Medical Products Administration (NMPA) and granted priority review and are pending approval.
BRUKINSA is not approved for use outside the United States. BRUKINSA is not approved for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma.

IMPORTANT SAFETY INFORMATION FOR BRUKINSA (ZANUBRUTINIB)

Warnings and Precautions

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

**Second Primary Malignancies**

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

**Cardiac Arrhythmias**

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

**Embryo-Fetal Toxicity**

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

**Adverse Reactions**

The most common adverse reactions in > 10% of patients who received BRUKINSA were neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory tract infection (38%), white blood cell count decreased (30%), hemoglobin decreased (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%),
musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%). The most frequent serious adverse reactions were pneumonia (11%) and hemorrhage (5%).

Drug Interactions

**CYP3A Inhibitors:** When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

**CYP3A Inducers:** Avoid coadministration with moderate or strong CYP3A inducers.

Specific Populations

**Hepatic Impairment:** The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

**INDICATION**

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Please see full Prescribing Information at beigene.com/PDF/BRUKINSAUSPI.pdf and Patient Information at beigene.com/PDF/BRUKINSAUSPPI.pdf

About the Zanubrutinib Clinical Trial Program

Clinical trials of zanubrutinib include:

- Fully-enrolled Phase 3 ASPEN clinical trial in patients with Waldenström macroglobulinemia (WM) comparing zanubrutinib to ibrutinib (NCT03053440), currently the only approved BTK inhibitor for WM;

- Phase 3 SEQUOIA trial comparing zanubrutinib with bendamustine plus rituximab in patients with treatment-naive (TN) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) (NCT03336333);
• Phase 3 ALPINE trial comparing zanubrutinib to ibrutinib in patients with relapsed/refractory (R/R) CLL/SLL (NCT03734016);

• Phase 2 trial in combination with GAZYVA® (obinutuzumab) in patients with R/R follicular lymphoma (FL) (NCT03332017);

• Phase 3 trial comparing zanubrutinib and rituximab to bendamustine and rituximab in patients with untreated MCL (NCT04002297);

• Phase 2 MAGNOLIA trial in patients with R/R marginal zone lymphoma (MZL) (NCT03846427);

• Phase 2 ROSEWOOD trial (NCT03332017) in China comparing obinutuzumab and zanubrutinib vs obinutuzumab alone in treating patients with R/R FL;

• Completed Phase 2 trials in patients with R/R MCL (NCT03206970) and R/R CLL/SLL (NCT03206918); and

• Completed enrollment in Phase 2 clinical trial in patients with WM (NCT03332173).

About Tislelizumab

Tislelizumab (BGB-A317) is an investigational humanized IgG4 anti–PD-1 monoclonal antibody specifically designed to minimize binding to FcγR on macrophages. In pre-clinical studies, binding to FcγR on macrophages has been shown to compromise the anti-tumor activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T effector cells. Tislelizumab is the first drug candidate produced from BeiGene’s immuno-oncology biologics program and is being developed as a monotherapy and in combination with other therapies for the treatment of a broad array of both solid tumor and hematologic cancers.

Select ongoing clinical trials of tislelizumab include a Phase 3 clinical trial in patients with second-line or third-line non-small cell lung cancer (NSCLC); a Phase 3 clinical trial in first-line patients with hepatocellular carcinoma (HCC); a Phase 3 clinical trial in second-line patients with esophageal squamous carcinoma (ESCC); a Phase 3 clinical trial in first-line patients with gastric cancer (GC); a Phase 3 clinical trial in first-line patients with ESCC; and a Phase 2 clinical trial in second- or third-line patients with HCC. The aforementioned trials are enrolling patients in multiple countries, including the United States, Europe, and China.
In addition to a pivotal Phase 2 clinical trial in patients with relapsed or refractory (R/R) classical Hodgkin’s lymphoma (cHL) and a pivotal Phase 2 clinical trial in patients with locally advanced or metastatic urothelial cancer, BeiGene is conducting a Phase 3 clinical trial in first-line patients with non-squamous NSCLC; a Phase 3 clinical trial in first-line patients with squamous NSCLC; a Phase 3 clinical trial in patients with first-line nasopharyngeal cancer (NPC); a Phase 3 clinical trial in first-line patients with urothelial carcinoma (UC); a Phase 3 clinical trial in patients with localized ESCC; and a Phase 2 trial in patients with MSI-H or dMMR solid tumors. These studies have been enrolling patients primarily in China.

New drug applications (NDA) for tislelizumab in patients with R/R cHL and in patients with previously treated locally advanced or metastatic UC have been accepted and granted priority review by the China National Medical Products Administration (NMPA, formerly known as CFDA). BeiGene has full development and commercial rights to tislelizumab worldwide.

About BeiGene

BeiGene is a global, commercial-stage, research-based biotechnology company focused on molecularly-targeted and immuno-oncology cancer therapeutics. With a team of over 3,000 employees in the United States, China, Australia, and Europe; BeiGene is advancing a pipeline consisting of novel oral small molecules and monoclonal antibodies for cancer. BeiGene is also working to create combination solutions aimed to have both a meaningful and lasting impact on cancer patients. In the United States, BeiGene markets and distributes BRUKINSA™ (zanubrutinib) and in China, the Company markets ABRAXANE® (nanoparticle albumin–bound paclitaxel), REVLIMID® (lenalidomide), and VIDAZA® (azacitidine) under a license from Celgene Corporation.1

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws, including statements regarding promising clinical results from trials of BRUKINSA (zanubrutinib) and tislelizumab and BeiGene’s further advancement of, and anticipated clinical development, regulatory milestones and commercialization of BRUKINSA (zanubrutinib) and tislelizumab. Actual results may differ materially from those indicated in the forward-looking statements as a result of various important factors, including BeiGene’s ability to demonstrate the efficacy and safety of its drug candidates; the
clinical results for its drug candidates, which may not support further development or marketing approval; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials and marketing approval; BeiGene's ability to achieve commercial success for its marketed products and drug candidates, if approved; BeiGene's ability to obtain and maintain protection of intellectual property for its technology and drugs; BeiGene's reliance on third parties to conduct drug development, manufacturing and other services; BeiGene's limited operating history and BeiGene's ability to obtain additional funding for operations and to complete the development and commercialization of its drug candidates, as well as those risks more fully discussed in the section entitled “Risk Factors” in BeiGene's most recent quarterly report on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in BeiGene's subsequent filings with the U.S. Securities and Exchange Commission. All information in this press release is as of the date of this press release, and BeiGene undertakes no duty to update such information unless required by law.

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