BeiGene Announces Results of Phase 3 ASPEN Trial of Zanubrutinib Compared to Ibrutinib for the Treatment of Patients with Waldenström’s Macroglobulinemia

- **Primary Endpoint of Statistical Superiority Related to Deep Response (VGPR or Better) Was Not Met; However, Zanubrutinib Demonstrated More Frequent VGPRs (28.4% vs.19.2% in Overall Population)**

- **Zanubrutinib Demonstrated Advantages in Safety and Tolerability Compared to Ibrutinib**

- **ASPEN is the Largest Phase 3 Trial in Waldenström’s Macroglobulinemia and the First Comparative Trial Readout for BTK Inhibitors**

- **Company to Hold Investor Conference Call and Webcast Today at 8:30 AM ET**

CAMBRIDGE, Mass. and BEIJING, China, December 16, 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 results from the Phase 3 ASPEN trial comparing its BTK inhibitor BRUKINSA™ (zanubrutinib) to ibrutinib for the treatment of Waldenström’s macroglobulinemia (WM). While the trial did not achieve statistical significance on its primary endpoint of superiority in complete response (CR) and very good partial response (VGPR) rates for zanubrutinib compared to ibrutinib, zanubrutinib demonstrated a higher VGPR rate as well as improvements in safety and tolerability in this first randomized comparative trial to read out within the BTK inhibitor class.

The ASPEN trial is a randomized Phase 3 trial in 229 patients with WM conducted in 61 centers in Europe, Australia, and the United States. The study includes two cohorts, a randomized cohort (cohort 1) consisting of 201 patients with a MYD88 mutation and a non-randomized cohort (cohort 2) in which 28 patients with MYD88 wild-type (MYD88WT) received zanubrutinib because they have historically responded poorly to ibrutinib therapy.

The randomized cohort 1 enrolled 102 patients (including 83 relapsed or refractory (R/R) patients and 19 treatment-naïve (TN) patients) in the zanubrutinib arm and 99 patients (including 81 R/R patients and 18 TN patients) in the ibrutinib arm. Patients in the zanubrutinib arm were assigned to receive zanubrutinib 160 mg twice daily (BID) and patients in the ibrutinib arm received 420 mg of ibrutinib once daily (QD).
Results from cohort 1 in the Phase 3 ASPEN trial, as of the data cutoff date of August 31, 2019 with a median follow-up of 19.4 months, include:

- In R/R patients, the VGPR rate as assessed by independent review committee (IRC) was 28.9% in the zanubrutinib arm and 19.8% in the ibrutinib arm (no patients achieved a CR in either arm). The difference was not statistically significant (2-sided p=0.1160);

- In the overall patient population, the VGPR rate as assessed by IRC was 28.4% in the zanubrutinib arm and 19.2% in the ibrutinib arm (no patients achieved a CR in either arm). The difference was not statistically significant (2-sided descriptive p=0.0921);

- In the R/R patient population, the major response rate (MRR), which is the rate of partial response (PR) or better, as assessed by IRC was 78.3% in the zanubrutinib arm and 80.2% in the ibrutinib arm; in the overall patient population, the MRR was 77.5% in the zanubrutinib arm and 77.8% in the ibrutinib arm;

- While the trial was not powered to detect a statistically significant improvement in progression free survival (PFS), and follow-up data for PFS is still short, early PFS and overall survival (OS) data for zanubrutinib were directionally consistent with the higher VGPR rates in the zanubrutinib arm:
  - The 12-month PFS rate was 92.4% (83.8-96.5) in R/R patients and 89.7% (81.7-94.3) in all patients in the zanubrutinib arm, compared to 85.9% (75.9-91.9) in R/R patients and 87.2% (78.6-92.5) in all patients in the ibrutinib arm; and
  - The 12-month OS rate was 98.8% (91.6-99.8) for R/R patients and 97.0% (90.9-99.0) for all patients in the zanubrutinib arm, compared to 92.5% (84.1-96.6) in R/R patients and 93.9% (86.8-97.2) in all patients in the ibrutinib arm;

- Grade ≥3 adverse events (AEs) were 58.4% in the zanubrutinib arm and 63.3% in the ibrutinib arm. In the zanubrutinib arm, four (4.0%) patients discontinued treatment due to AEs and there was one (1.0%) fatal adverse event; in the ibrutinib arm, nine patients (9.2%) discontinued due to AEs and there were four (4.1%) fatal adverse events;

- For AEs of special interest for BTK inhibitors, atrial fibrillation/flutter of any grade was 2.0% in the zanubrutinib arm and 15.3% in the ibrutinib arm; minor bleeding
was 48.5% for zanubrutinib and 59.2% for ibrutinib; major hemorrhage was 5.9% for zanubrutinib and 9.2% for ibrutinib; and diarrhea was 20.8% for zanubrutinib and 31.6% for ibrutinib; and

- The rate of neutropenia was higher in the zanubrutinib arm (29.7%) as compared to the ibrutinib arm (13.3%).

Summary Tables:

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<tr>
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<th><strong>Zanubrutinib</strong> (N = 83)</th>
<th><strong>Ibrutinib</strong> (N = 81)</th>
<th><strong>Zanubrutinib</strong> (N = 102)</th>
<th><strong>Ibrutinib</strong> (N = 99)</th>
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<tbody>
<tr>
<td><strong>Efficacy</strong></td>
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<tr>
<td>VGPR + CR Rate</td>
<td>28.9%</td>
<td>19.8%</td>
<td>28.4%</td>
<td>19.2%</td>
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<td>PFS (12 month) (CI)</td>
<td>92.4% (88.9 – 98.8)</td>
<td>85.9% (75.9 – 91.9)</td>
<td>89.7% (81.7 – 94.3)</td>
<td>87.2% (78.6 – 92.5)</td>
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<tr>
<td>OS (12 month) (CI)</td>
<td>98.8% (91.6 – 99.8)</td>
<td>92.5% (84.1 – 96.6)</td>
<td>97.0% (90.9 – 99.0)</td>
<td>93.9% (86.8 – 97.2)</td>
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<tr>
<td><strong>Safety</strong></td>
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<tr>
<td>Grade ≥3 AEs</td>
<td>58.4%</td>
<td>63.3%</td>
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<tr>
<td>Treatment discontinuation due to AEs</td>
<td>4 (4.0%)</td>
<td>9 (9.2%)</td>
<td>4 (4.0%)</td>
<td>9 (9.2%)</td>
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<tr>
<td>Fatal AEs</td>
<td>1 (1.0%)</td>
<td>4 (4.1%)</td>
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<tr>
<td>Atrial fibrillation / flutter of any grade</td>
<td>2.0%</td>
<td>15.3%</td>
<td>2.0%</td>
<td>15.3%</td>
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<tr>
<td>Minor bleeding</td>
<td>48.5%</td>
<td>59.2%</td>
<td>48.5%</td>
<td>59.2%</td>
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<td>Major hemorrhage</td>
<td>5.9%</td>
<td>9.2%</td>
<td>5.9%</td>
<td>9.2%</td>
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<tr>
<td>Diarrhea</td>
<td>20.8%</td>
<td>31.6%</td>
<td>20.8%</td>
<td>31.6%</td>
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<tr>
<td>Neutropenia</td>
<td>29.7%</td>
<td>13.3%</td>
<td>29.7%</td>
<td>13.3%</td>
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“Our researchers sought to design a BTK inhibitor that would improve efficacy and decrease side effects in patients by maximizing BTK inhibition and minimizing off-target binding. We took a bold approach to our clinical development plan by evaluating zanubrutinib directly against ibrutinib in patients with WM and are encouraged by the improvements in VGPR rates and safety,” said Jane Huang, M.D., Chief Medical
Officer, Hematology at BeiGene. “The ASPEN trial, which was the largest prospective trial for patients with WM ever run, showed consistent safety advantages for patients treated with zanubrutinib compared to ibrutinib. While falling short of a statistically significant improvement in CR and VGPR, we believe the trial demonstrated that zanubrutinib is a highly potent BTK inhibitor that has clinical benefit and trends toward increased response quality.”

Dr. Huang continued, “Today’s results are consistent with what we know about zanubrutinib from our broad clinical development program – that it is a more selective BTK inhibitor with beneficial pharmacokinetics designed to provide deep, meaningful responses for many patients. We plan to discuss our findings with regulatory authorities in the U.S. and Europe and plan to submit these data for presentation, with additional analysis, to an upcoming medical meeting. In addition, we will continue to evaluate zanubrutinib compared to ibrutinib in our ongoing Phase 3 ALPINE trial in patients with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).”

“WM is a devastating and incurable disease with significant morbidity. These meaningful results help us advance the understanding of the role of BTK specificity and off-target effects during treatment,” 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, and a member of the steering committee and principal investigator for the ASPEN trial. “Despite not reaching the primary endpoint, 28.4% of zanubrutinib patients achieved VGPR as compared to 19.2% in the ibrutinib arm, and zanubrutinib had a more favorable safety profile, suggesting improved clinical benefit for zanubrutinib over standard BTKi therapy in the treatment of patients with WM.”

About the ASPEN trial

The Phase 3 randomized, open-label, multicenter ASPEN clinical trial (NCT03053440) evaluated BRUKINSA versus ibrutinib in people with relapsed/refractory (R/R) or treatment-naïve (TN) Waldenström’s macroglobulinemia. The primary objective was to establish superiority of BRUKINSA compared to ibrutinib as demonstrated by the proportion of people achieving complete response (CR) or very good partial response (VGPR). Secondary endpoints included major response rate, duration of response and progression-free survival, and safety, measured by incidence, timing and severity of treatment-emergent adverse events. The pre-specified analysis populations for the trial included the overall population (n=201) and R/R patients (n=164).
Results of cohort 2 were previously presented at the 24th Congress of European Hematology Association (EHA) and showed an overall response rate (ORR) of 80.8%, a major response rate (MRR; partial response or better) of 53.8% and a VGPR rate of 23.1%.

The data from the study were masked and the results were first available for analysis this past week. The Company plans to submit the full ASPEN results for presentation to an upcoming medical congress.

**BeiGene Conference Call and Webcast Information**

Investors and analysts are invited to join the conference call on Monday, December 16 at 8:30 a.m. ET using the following dial-in information:

U.S. Toll-Free: +1 (844) 461-9930
Hong Kong: +852 5819-4851
China: +86 400-682-8609
Conference ID: 2885995

A live webcast of the conference call and the slides from the presentation can be accessed from the investors section of BeiGene’s website at http://ir.beigene.com or http://hkexir.beigene.com. An archived replay will be available two hours after the event for 90 days.

**About the Zanubrutinib Clinical Trial Program**

Clinical trials of zanubrutinib include:

- Fully-enrolled Phase 3 ASPEN clinical trial in patients with Waldenström’s 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 BRUKINSA™ (zanubrutinib)

BRUKINSA 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 approved by the U.S. FDA to treat adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy on November 14, 2019. This indication was 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.

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 Waldenström's macroglobulinemia.

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.


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 Logistics Sarl, a Bristol-Myers Squibb company.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 clinical data for patients from the ASPEN trial and advantages compared to ibrutinib; plans for regulatory discussions and submission of data from the ASPEN trial; BeiGene's further advancement of, and anticipated clinical development, regulatory milestones and commercialization of its drug candidates; and continuing and further development and commercialization efforts and transactions with third parties. 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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