BeiGene Presents Clinical Data on Zanubrutinib and Tislelizumab at the 25th European Hematology Association (EHA) Virtual Congress

CAMBRIDGE, Mass. and BEIJING, China, June 12, 2020 (GLOBE NEWSWIRE) -- BeiGene, Ltd. (NASDAQ: BGNE; HKEX: 06160), a commercial-stage biotechnology company focused on developing and commercializing innovative molecularly-targeted and immuno-oncology drugs for the treatment of cancer, today announced that data on its BTK inhibitor zanubrutinib in relapsed/refractory (R/R) marginal zone lymphoma (MZL) and other B-cell malignancies and its anti-PD-1 antibody tislelizumab in R/R NK/T-cell lymphomas were presented at the 25th European Hematology Association (EHA) Virtual Congress, taking place on June 11-14.

“We’re pleased to share clinical results from several trials in our broad hematology development program at this year’s EHA. Zanubrutinib demonstrated encouraging efficacy and safety in multiple indications, including R/R MZL, which expands on data presented previously,” said Jane Huang, M.D., Chief Medical Officer, Hematology at BeiGene. “We look forward to receiving data from the potentially registration-enabling Phase 2 trial of zanubrutinib in R/R MZL, which has completed enrollment.”

Phase 1/2 Study of Zanubrutinib in R/R MZL

Abstract: EP1165

Data presented at EHA were from the MZL cohort of an open-label, multicenter Phase 1/2 trial of zanubrutinib in patients with B-cell malignancies (NCT02343120). Twenty patients with R/R MZL were enrolled in this cohort, including nine with extranodal disease, five with nodal disease, and six with splenic disease.

“The high response rate observed in this study is encouraging, and zanubrutinib achieved durable responses across all subtypes. In addition, it was well tolerated among patients with R/R MZL,” commented Alessandra Tedeschi, M.D., Niguarda Cancer Center, Italy.

At the data cutoff of January 29, 2020, with a median follow-up of 27.1 months (8.3 – 51.1), 12 patients remained on study treatment. Results included:

- The overall response rate (ORR) assessed by investigator was 80% (95% confidence interval [CI]: 56.3, 94.3), with a complete response (CR) rate of 15% and a partial response (PR) rate of 65%:
  - In patients with extranodal MZL, the ORR was 77.8% (95% CI: 40.0, 97.2), including one CR and six PRs;
  - In patients with nodal MZL, the ORR was 100% (95% CI: 47.8, 100.0), including two CRs and three PRs; and
  - In patients with splenic MZL, the ORR was 66.7% (95% CI: 22.3, 95.7), including four PRs;
• The median time to response (TTR) was 2.8 months (2.6-39.6);
• At 18 months, 66.2% of responders remained in response (95% CI: 32.4, 86);
• The progression-free survival (PFS) rate at 24 months was 59.4% (95% CI: 33, 79);
• The overall survival (OS) rate at 24 months was 83.2% (95% CI: 56, 94);
• Zanubrutinib was well tolerated in patients with R/R MZL:
  - All patients experienced at least one adverse event (AE), which were primarily grade 1 or 2 in severity. The most frequently reported AEs of any grade (≥20%) include diarrhea (35%), contusion (35%), rash (35%), upper respiratory tract infection (30%), neutropenia (25%), pyrexia (25%), nasopharyngitis (20%), sinusitis (20%), nausea (20%), and fatigue (20%);
  - The most common grade ≥3 AEs (≥10%) were neutropenia (15%), anemia (10%), and pyrexia (10%);
  - Serious AEs were reported in 45% of patients (9/20); and
  - One patient discontinued treatment due to an AE and there were no deaths reported.

Biomarker Identification in R/R Non-Germinal Center B-Cell-Like (Non-GCB) Diffuse Large B-Cell Lymphoma (DLBCL) Treated with Zanubrutinib

Abstract: EP1246

Data presented at EHA were from four clinical trials evaluating efficacy and biomarker identification of zanubrutinib in patients with R/R non-GCB DLBCL, including two trials of zanubrutinib as a monotherapy (study 1: NCT04170283; study 2: NCT03145064) and two trials of zanubrutinib in combination with an anti-CD20 antibody (study 3: NCT02569476; study 4: NCT03520920). A total of 121 patients were included in the analysis, with 79 from the monotherapy trials and 42 from the combination trials. At the data cutoff of September 9, 2019 for study 1, August 31, 2019 for study 2 and 3, and May 31, 2019 for study 4, the results included:

• Across all four trials, the unadjusted ORR in patients with non-GCB DLBCL was similar, with an average of 29.8% (22.7-35.0); the median PFS ranged from 2.8 to 4.9 months, and the median OS ranged from 8.4 to 11.8 months;
• In the 49 patients with GEP-confirmed activated B-cell (ABC) DLBCL classification, the ORR tended to be higher (42.9%) than non-GCB DLBCL and was comparable for monotherapy (42.1%) and combination therapy (45.5%);
• In the 56 non-GCB patients with HTG gene expression profiles, PAX5 expression was higher in monotherapy responders than non-responders, and PIM1, BCL2, and FOXP1 expression was higher in combination therapy responders than non-responders;
Patients with double expressions of MYC and BCL2 tended to have higher ORRs (61% vs. 29%, p=0.12) and longer PFS (5.2 months vs. 3.6 months, p=0.16) and OS (10 months vs. 7 months, p = 0.21);

In the 77 patients with NGS panel data, those with CD79B mutations showed significantly higher ORR than the ones without (60% vs. 26.9%, p=0.005); and

All three patients with NOTCH1 mutations responded to zanubrutinib monotherapy.

Zanubrutinib in Combination with Rituximab in R/R Non-Hodgkin's Lymphoma (NHL)

Abstract: EP1271

Data presented at EHA were from a single-arm, multicenter Phase 2 trial of zanubrutinib in combination with rituximab in patients with R/R NHL (NCT03520920). A total of 41 patients were enrolled in this trial, including 20 with non-GCB DLBCL who previously received standard anthracycline ± rituximab-based treatment, 16 with follicular lymphoma (FL) who received at least one prior therapy, and five with MZL who received at least one prior therapy. At the data cutoff of August 31, 2019, with a median follow-up of 10.28 months (0.8-19.8), 14 patients remained on study treatment and the results included:

- In patients with R/R non-GCB DLBCL,
  - The ORR as assessed by investigator per Lugano criteria 2014 was 35.0% (95% CI: 15.4, 59.2), including one (5%) CR and six (30%) PRs;
  - Median duration of response (DoR) was 8.79 months (95% CI: 0.72, 14.78);
  - Median PFS was 3.38 months (95% CI: 2.69, 5.49);
  - 12-month PFS event free rate was 17.4% (95% CI: 4.3, 37.7);
  - At the time of data cutoff, two patients remained on the study treatment;

- In patients with R/R FL,
  - The ORR as assessed by investigator per Lugano criteria 2014 was 56.3% (95% CI: 29.9, 80.2), including three (19%) CRs and six (38%) PRs;
  - Median DoR was not reached;
  - Median PFS was not estimable (NE; 95% CI: 5.49, NE);
  - 12-month PFS event free rate was 66.0% (95% CI: 36.5, 84.3);
  - At the time of data cutoff, nine patients remained on the study treatment;

- In patients with R/R MZL,
  - The ORR as assessed by investigator per Lugano criteria 2014 was 60.0% (95% CI: 14.7, 94.7), including one (20%) CR and two (40%) PRs;
  - Median DoR was not reached;
  - Median PFS was NE (95% CI: 11.01, NE);
12-month PFS event free rate was 75.0% (95% CI: 12.8, 96.1);
At the time of data cutoff, three patients remained on the study treatment;

- The safety profile demonstrated in this trial for the four cohorts was consistent with previous results of zanubrutinib, including:
  - 97.6% of patients experienced at least one AE, with the most common (≥10%) of any grade being decreased neutrophil count, decreased white blood cell count, anemia, upper abdominal pain, increased alanine aminotransferase, pyrexia, upper respiratory tract infection, decreased platelet count, increased aspartate aminotransferase, and purpura;
  - Grade ≥3 AEs were reported in 46.3% of patients, with the most common (≥10%) being decreased neutrophil count and decreased white blood cell count, and serious AEs were reported in 19.5% of patients;
  - Grade ≥3 infection events were reported in 9.8% of patients, and no grade ≥3 hemorrhage events were reported; and
  - Three patients with non-GCB DLBCL experienced a fatal AE, but none were reported in the FL and MZL cohorts.

Preliminary Results of Tislelizumab in R/R Extranodal NK/T-Cell Lymphoma

Abstract: EP1268

Preliminary efficacy and safety data presented at EHA were from the R/R extranodal NK/T-cell lymphoma cohort of the Phase 2 trial of tislelizumab in patients with R/R NK/T-cell neoplasms (NCT03493451). Twenty-two patients with R/R extranodal NK/T-cell lymphoma who received at least one prior systemic therapy were enrolled in this cohort and received tislelizumab (200 mg every three weeks) until disease progression, unacceptable toxicity, or end of study. At the data cutoff of October 11, 2019, six patients remained on study treatment and the results included:

- The ORR assessed by investigator per Lugano criteria with LYRIC modification for immunomodulatory drugs (Cheson et al 2016) was 31.8% (95% CI: 13.9, 54.9), with a CR rate of 18.2% and a PR rate of 13.6%;
- The median DoR had not been reached and the median TTR was 5.75 months (2.14-14.29);
- The median PFS was 2.7 months (95%CI: 1.45, 5.32) and the median PFS follow-up duration was 11.3 months;
- Tislelizumab was generally well-tolerated, including:
  - The most frequently reported (≥15%) treatment-emergent adverse events (TEAEs) were anemia and pyrexia (27.3%, each) and hypoalbuminemia, hyperglycemia, and hypokalemia (18.2%, each);
  - Grade ≥3 TEAEs were reported in 11 (50%) patients; anemia and neutrophil count decrease were reported in at least two patients;
Serious TEAEs were reported in eight (36.4%) patients, with four patients determined to be possibly related to tislelizumab;

Immune-related (ir) TEAEs were reported in seven (31.8%) patients;

One patient experienced a TEAE of grade 5 respiratory failure leading to treatment discontinuation, which was not related to tislelizumab as assessed by investigator; and

One patient experienced a fatal TEAE.

Preliminary Results of Tislelizumab in R/R Peripheral T-Cell Lymphomas (PTCL)

Abstract: EP1235

Preliminary efficacy and safety data presented at EHA were from the R/R PTCL cohort of the Phase 2 trial of tislelizumab in patients with R/R NK/T-cell neoplasms (NCT03493451). Forty-four patients with R/R PTCL who received at least one prior combination therapy enrolled in this cohort, including 21 patients with PTCL-not otherwise specified (PTCL-NOS), 11 patients of angioimmunoblastic T-cell lymphoma (AITL), and 12 patients with anaplastic large-cell lymphoma (ALCL). Patients received tislelizumab (200 mg every three weeks) until disease progression, unacceptable toxicity, or end of study. At the data cutoff of October 11, 2019, six patients remained on the study treatment and the results included:

- Across all PTCL subtypes, the ORR as assessed by investigator per Lugano criteria (2014) with LYRIC modification for immunomodulatory drugs (Cheson et al 2016) was 20.5% (95% CI: 9.8, 35.3);
  - In patients with R/R PTCL-NOS, the ORR was 23.8% (95% CI: 8.2, 47.2), including three CRs and two PRs;
  - In patients with R/R AITL, the ORR was 18.2% (95% CI: 2.3, 51.8), including two PRs;
  - In patients with R/R ALCL, the ORR was 16.7% (95% CI: 2.1, 48.4), including two PRs;

- Across all PTCL subtypes, the median DoR was 8.2 months (95% CI: 2.7, NE);
  - In patients with R/R PTCL-NOS, the median DoR was NE (95% CI: 2.7, NE);
  - In patients with R/R AITL, the median DoR was 3.2 months (95% CI: NE, NE);
  - In patients with R/R ALCL, the median DoR was 8.3 months (95% CI: 8.2, 8.4);

- Across all PTCL subtypes, the median TTR was 2.9 months (95% CI: 22.1, 5.8);
  - In patients with R/R PTCL-NOS, the median TTR was 4.6 (95% CI: 2.8, 5.8);
  - In patients with R/R AITL, the median TTR was 2.5 months (95% CI: 2.1, 2.9);
  - In patients with R/R ALCL, the median TTR was 2.7 months (95% CI: 2.7, 2.7);

- Across all PTCL subtypes, the median PFS was 2.7 months (95% CI: 2.6, 4.8);
In patients with R/R PTCL-NOS, the median PFS was 2.7 (95% CI: 2.2, 5.4);
In patients with R/R AITL, the median PFS was 3.4 months (95% CI: 1.6, 5.3);
In patients with R/R ALCL, the median PFS was 2.7 months (95% CI: 1.0, 10.9);

- Tislelizumab was generally well-tolerated and the safety profile was similar to that of other anti-PD-1 antibodies, including:
  - The most frequently reported (≥10%) TEAEs were pyrexia (34.1%), asthenia and anemia (18.2%), arthralgia, cough, and thrombocytopenia (15.9%), pruritus (13.6%), and erythema, hypothyroidism, neutropenia, and upper respiratory tract infection (11.4%);
  - Grade ≥3 TEAEs were reported in 23 (52.3%) patients; neutropenia, anemia, thrombocytopenia, general physical health deterioration, pneumonia and pyrexia were reported in at least two patients;
  - Serious TEAEs were reported in 21 (47.7%) patients;
  - irTEAEs were reported in 18 (40.9%) patients, with all being Grade 1 or 2 except one event of Grade 3 erythema; and
  - Nine (23.7%) patients discontinued treatment due to TEAEs; and three (6.8%) patients experienced a fatal TEAE, all of which were assessed to be likely related to disease progression.

To learn more about BeiGene’s pipeline and data presented at the 25th EHA Virtual Congress, visit our virtual booth at https://beigenemedical.eu/.

**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.

BRUKINSA was approved in China for the treatment of MCL in adult patients who have received at least one prior therapy and CLL or SLL in adult patients who have received at least one prior therapy in June 2020.

BRUKINSA is not approved for use outside the United States and China.

**IMPORTANT U.S. 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%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Drug Interactions

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

CYP3A Inducers: Avoid co-administration 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 Tislelizumab**

Tislelizumab (BGB-A317) is a 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 from BeiGene’s immuno-oncology biologics program and is being developed internationally as a monotherapy and in combination with other therapies for the treatment of a broad array of both solid tumor and hematologic cancers.

Tislelizumab is approved by the China National Medical Products Administration as a treatment for patients with classical Hodgkin’s lymphoma who received at least two prior therapies and for patients with locally advanced or metastatic urothelial carcinoma (UC) with PD-L1 high expression whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Additionally, the Center for Drug Evaluation (CDE) of the China National Medical Products Administration (NMPA) has accepted a supplemental new drug application (sNDA) of BeiGene’s anti-PD-1 antibody tislelizumab in combination with two chemotherapy regimens for first-line treatment of patients with advanced squamous non-small cell lung cancer (NSCLC).

Currently, 15 potentially registration-enabling clinical trials are being conducted in China and globally, including 11 Phase 3 trials and four pivotal Phase 2 trials.

Tislelizumab is not approved for use outside of China.

**About BeiGene**

BeiGene is a global, commercial-stage biotechnology company focused on discovering, developing, manufacturing, and commercializing innovative medicines to improve treatment
outcomes and access for patients worldwide. Our 3,800+ employees in China, the United States, Australia, and Europe are committed to expediting the development of a diverse pipeline of novel therapeutics for cancer. We currently market or plan to market two internally-discovered oncology products: BTK inhibitor BRUKINSA® (zanubrutinib) in the United States and China, and anti-PD-1 antibody tislelizumab in China. We also market or plan to market in China additional oncology products licensed from Amgen Inc., Celgene Logistics Sàrl, a Bristol Myers Squibb (BMS) company, and EUSA Pharma. To learn more about BeiGene, please visit www.beigene.com and follow us on Twitter at @BeiGeneUSA.

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 from ongoing clinical trials of zanubrutinib and tislelizumab; 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; the impact of the COVID-19 pandemic on the Company's clinical development, commercial and other operations, 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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