News Release

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Dainippon Sumitomo Pharma Co., Ltd.

Dainippon Sumitomo Pharma announces clinical data of anti-cancer drugs BBI608 and BBI503 were presented at the 2014 ASCO Annual Meeting

Osaka, Japan, June 2, 2014 – Dainippon Sumitomo Pharma Co., Ltd. (Head office: Osaka, Japan; President: Masayo Tada) ("DSP") announced that clinical study data of BBI608 and BBI503 were presented in poster sessions at the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting which began in Chicago on May 30, 2014. DSP issued a press release on the titles and highlights of these presentations on May 15, 2014.

1. A phase I extension study of BBI608, a first-in-class cancer stem cell (CSC) inhibitor, in patients with advanced solid tumors. (Abstract# 2546)

【Objectives of the study】

The Phase I/II dose escalation study of several formulations of BBI608 (BBI608-101 study) in patients with advanced solid tumors was conducted to determine the safety, tolerability, recommended dose, pharmacokinetics (PK) and preliminary anti-tumor activity of BBI608. Results of the BBI608 formulation designed to improve compliance and reduce side effects in pivotal trials were presented at the 2014 ASCO Annual Meeting, as announced in the DSP press release dated May 15, 2014.

【Highlights of the presentation】

Twenty-four patients with advanced solid tumors including colorectal cancer (CRC), ovarian cancer and anal squamous cancer received 500 mg of the original BBI608 formulation once on Day 1, then 500 mg of the new BBI608 formulation once a day either fasting or after meal on Days 4 and 8, followed by 500 mg of the new BBI608 formulation twice daily until disease progression or unacceptable toxicity.

Neither significant difference in plasma exposure between the two formulations nor significant food effect was observed. Further test on the dosing interval of the new formulation (twice daily 4 h apart vs. twice daily 12 h apart) showed that the administration cohort of 12 h apart had fewer gastrointestinal adverse events, while both cohorts had adverse events including diarrhea, abdominal pain, nausea, vomiting, anorexia and fatigue. The recommended dosing regimen for BBI608 to be used in pivotal trials was determined to be 500 mg twice daily 12 h apart.

Among 15 patients receiving the new formulation twice daily 12 h apart, prolonged stable disease was observed in 2 of 7 non-CRC patients (ovarian cancer-16 weeks and anal squamous cancer-32 weeks). Among the 8 CRC patients enrolled, disease control was observed in 67% evaluable for response (4/6), median progression free survival and overall survival responses were 17 weeks and 40 weeks, respectively.

2. A phase Ib study of the cancer stem cell inhibitor BBI608 administered with paclitaxel in patients with advanced malignancies. (Abstract # 2530)

【Objectives of the study】
This phase I study in patients with advanced cancer was conducted to determine safety, tolerability, recommended dose and preliminary anti-cancer activity of BBI608 plus paclitaxel (BBI608-201 study).
Based on the results of BBI608-201 study, phase III study (global clinical trial: BBI608-336 study) by combination therapy with paclitaxel in patients with gastric/GEJ adenocarcinoma was initiated in the U.S.

【Highlights of the presentation】
<The results of the clinical study (BBI608-201 study)>
BBI608 was administered in 3 escalating dose cohorts (200 mg twice daily, 400 mg twice daily, 500 mg twice daily) in combination with paclitaxel (80 mg/m^2, intravenous injection, once weekly, 3 of every 4 weeks) in 24 patients including gastric/GEJ adenocarcinoma, ovarian cancer, melanoma, bladder cancer and non-small cell lung cancer (NSCLC). The administration was continued until progression of disease, unacceptable toxicity or other discontinuation criteria was met.
The combination of BBI608 (500 mg twice daily) and paclitaxel was well tolerated. No new adverse events were observed. Most common adverse events observed were grade 1, 2 diarrhea, abdominal cramps, nausea, vomiting. Grade 3 events related to protocol therapy occurred in 4 patients and included diarrhea, dehydration, and weakness. No significant pharmacokinetic interactions were observed.
Disease control (CR+PR+SD) was observed in 10 of 15 (67%) evaluable patients. Of 5 patients with refractory gastric/GEJ adenocarcinoma enrolled, 3 showed tumor regression. Two patients who failed prior taxane had prolonged SD of more than 5 months. Tumor regression or SD of more than 16 weeks was also seen in patients with platinum-resistant ovarian cancer (1 of 2), melanoma (2 of 3), bladder cancer (1 of 3) and NSCLC (1 of 1).

<Background: *In vitro* and *in vivo* data of BBI608 in combination with paclitaxel>
In the *in vitro* sphere formation assay, suppression of sphere formation and a decrease of p-STAT3 and CD44 expression levels were observed in BBI608 alone and BBI608/paclitaxel combination groups, while paclitaxel alone did not show any effect. The anti-cancer activities of BBI608 and paclitaxel alone or in combination on tumor growth were examined in murine xenograft models of human cancer. The combined administration showed synergistic suppression of tumor growth in comparison with monotherapy of either BBI608 or paclitaxel. Expression levels of p-STAT3 and CD44 were suppressed in the BBI608 cohort and BBI608/paclitaxel combination cohort, but not in the paclitaxel monotherapy cohort.

3. A phase I dose escalation study of BBI503, a first-in-class cancer stemness kinase inhibitor in adult patients with advanced solid tumors. (Abstract# 2527)

【Objectives of the study】
A first-in-human phase I dose escalation study in patients with advanced solid tumors was conducted to determine safety, tolerability, recommended dose, pharmacokinetics and preliminary anti-tumor activity of BBI503 (BBI503-101 study).

【Highlights of the presentation】
<The results of the study (BBI503-101 study)>
Escalating doses from 10 mg to 450 mg once daily were administered orally (one cycle: 28 days) to 26 patients including heavily-pretreated for colorectal cancer, head and neck cancer, renal cell carcinoma and hepatocellular carcinoma. The administration was continued until disease progression, unacceptable toxicity or other discontinuation criteria were met.
MTD was not reached. BBI503 was well tolerated, with mild gastrointestinal adverse events, including grade 1, 2 diarrhea, abdominal cramping, nausea, anorexia as well as fatigue. Grade 3 diarrhea was observed in 2 patients at 450 mg, one of which represented DLT. No related hematological toxicity was observed. BBI503 showed increase of plasma concentration in dose-dependent manner up to 300 mg once daily. From these results, once daily recommended dose of BBI503 was determined to be 300 mg.
Of 20 evaluable patients, 11 (55%) showed SD with a median time to progression of 16 weeks. Of those patients with SD, prolonged SD of more than 16 weeks was observed in 9.

<Background: *In vivo* data of BBI503's action to cancer stem cells>
BBI503 was compared with an approved multi-kinase inhibitor in terms of action against self-renewal capacity of cancer stem cells using human tumor xenograft mouse models. The treatment of mice harboring xenograft tumors with BBI503 resulted in a 7-fold decrease in the number of cancer stem cells compared to untreated mice. Conversely, treatment with an approved multi-kinase inhibitor resulted in an increase in the cancer stem cell population.

Reference information (BBI608 and BBI503):
BBI608 and BBI503 are orally-administered first-in-class anti-cancer stem cells (CSCs) drugs created and currently under development by Boston Biomedical, Inc., a DSP subsidiary in the U.S. BBI608 and BBI503 are small-molecule compounds targeting cancer stem cell (cancer cell with stem cell-like properties) self-renewal and inducing cell death in CSC as well as other heterogeneous cancer cells. Targeting CSCs holds promise for fundamentally advancing cancer treatment by potentially reducing treatment resistance, metastasis and recurrence.
In preclinical studies, BBI608 has been shown to inhibit the STAT3, Nanog and β-catenin pathways in the preclinical study while BBI503 has been shown to inhibit multi-kinase.

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