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POSTER ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

A Phase 1 Trial of OPB-111077 in Combination with Bendamustine (B) and Rituximab (R) in Patients with Relapsed or Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Preliminary Results of Dose-Escalation Stage

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Background
OPB-111077, a first-in-class small molecule, is an orally available antitumor agent with an inhibitory effect on mitochondrial oxidative phosphorylation (OXPHOS). OPB-111077 inhibits mitochondrial respiratory chain complex I, which leads to inhibition of energy production and activation of the AMPK-mTOR energy stress sensor pathway, as well as inhibition of the signal transducer and activator of transcription (STAT) 3 pathway. In non-clinical studies using cultured cells and murine xenograft models, OPB-111077 showed antitumor effects in a variety of tumor cell lines, including hematological and solid tumors, and OPB-111077 in combination with an alkylating agent has a potential synergistic antitumor effect for malignant lymphoma. Here we report the preliminary results from the dose-escalation (DE) stage of an ongoing phase 1 trial (NCT04049825) of OPB-111077 in combination with bendamustine (B) and rituximab (R) in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).
Method
This trial is composed of 2 stages. OPB-111077 is administered in combination with B in a DE stage and with B and R in a dose-expansion (EX) stage. The DE stage uses a 3+3 design. The objectives of the DE stage are to evaluate the tolerability and safety of OPB-111077 in combination with B and to determine the recommended dose for the EX stage based on dose-limiting toxicity (DLT). A secondary objective is to evaluate efficacy. Response assessment is based on IWG Lugano response criteria for non-Hodgkin lymphoma (NHL) (2014). Key eligibility criteria include age 20 to 80 years (inclusive), at least initial standard treatment, measurable lesions, and Eastern Cooperative Oncology Group performance status score of 0 or 1. OPB-111077 is orally administered once daily on Days 3 to 6, Days 10 to 13, and Days 17 to 20 of each cycle. The duration of each cycle is 21 days, except for Cycle 1, which is 23 days. The dose in the first cohort is 200 mg/day, increasing as appropriate to 400 mg/day in Cohort 2 and then to 600 mg/day in Cohort 3. B is administered intravenously at 120 (or 90) mg/m ^{2} once daily on Days 1 and 2 of each cycle for up to 6 cycles.
Results
As of 31 Jan 2023, 16 patients had been treated with OPB-111077 + B (120 mg/m ^{2}) at OPB-111077 doses of 200 mg (Cohort 1, n = 3), 400 mg (Cohort 2, n = 6), and 600 mg (Cohort 3, n = 7). Patients had received 1 to 6 prior lines of chemotherapy, median age was 70.0 (range 54 - 79) years, and 56.3% were male. Median treatment duration was 69.0 days. No DLT was observed in Cohort 1 or in the first 3 patients in Cohort 2. In Cohort 3, 2 patients experienced DLTs of neutropenia (grade

4) and neutropenia (grade 3, dose interruption of ≥21 consecutive days), respectively. As the Efficacy and Safety Evaluation Committee (ESEC) judged the OPB-111077 600-mg dose to be intolerable, in accordance with the scheme for the DE stage, new 3 patients were added to Cohort 2. One of the 6 patients in Cohort 2 experienced DLTs of anorexia (grade 3) and neutropenia (grade 4, dose interruption of ≥21 consecutive days). Based on the ESEC's recommendation, the recommended dose for the EX stage was set at OPB-111077 400 mg + B 120 mg/m ^{2}. The most common (≥90%) treatment-related adverse events of any grade were lymphopenia (93.8%, grade 3: ≥93.8%), leukopenia (93.8%, grade 3: ≥81.3%), and nausea (93.8%, grade 3: ≥18.8%). The overall response rate [complete response (CR) + partial response (PR)] and CR rate were respectively 62.5% and 43.8%. Median progression-free survival was 257.0 days.

Conclusion

OPB-111077 400 mg + B 120 mg/m ^{2} combination treatment showed a tolerable safety profile. The preliminary data are encouraging, especially regarding the efficacy of OPB-111077 combination treatment, including CR in patients with DLBCL. The DE stage of the trial is still ongoing and the EX stage, which will evaluate the safety and efficacy of OPB-111077 in combination with B + R, is now recruiting.

Disclosures Toubai: *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Abbvie, Kyowa Kirin Co., Ltd., Chugai Pharmaceutical Co, Meiji-Seika Pharma, Takeda Pharmaceuticals, Sanofi, Astellas Pharma Inc, Otsuka Pharmaceutical Co,.Ltd., Janssen Pharmaceuticals, Amgen Inc., Ono Pharmaceutical Co., Ltd., Nippon Shinyaku Co., Ltd.:* Honoraria. **Kuroda:** *Bristol Myeres Squibb, Kyowa Kirin, Chugai, Japan Blood Product Organization, Daiichi Sankyo, Mochida, Ono, Sanofi, Eisai, Taiho, Sumitomo, Asahikasei, Otsuka, Takeda, Shionogi Janssen, Novartis, Abbvie, Pfizer, Nippion Shinyaku, Astellas:* Consultancy, Honoraria, Research Funding. **Suehiro:** *Amgen:* Research Funding; *Genmab:* Honoraria, Research Funding; *Otsuka:* Research Funding; *Incyte:* Research Funding; *Nippon Shinyaku:* Honoraria; *Pfizer:* Honoraria; *Janssen:* Honoraria; *Meiji Pharma:* Honoraria; *Kyowa Kirin:* Research Funding; *Nippon Kayaku:* Honoraria, Research Funding; *Teijin:* Research Funding; *Abbvie:* Honoraria, Research Funding; *BMS:* Honoraria; *Sanofi:* Honoraria; *Chugai:* Honoraria, Research Funding. **Mishima:** *Chugai Pharmaceutical Inc, Roche:* Ended employment in the past 24 months; *Bristol Myers Squibb:* Research Funding; *Eizai:* Research Funding; *Kyowa-Kirin:* Research Funding; *Taiho:* Research Funding; *Takeda:* Research Funding; *Janssen:* Honoraria. **Sunami:** *Chugai Pharma:* Research Funding; *Abbvie, Incyte, GlaxoSmithKline, Novartis, Pfizer, BeiGene, Kyowa Kirin, Ono, Otsuka and Chugai:* Research Funding; *Sanofi, BMS and Janssen:* Honoraria, Research Funding. **Kato:** *Bristol-Myers Squibb, Celgene, Dainippon-Sumitomo, Janssen, Kyowa Kirin, MSD, Mundi, Ono:* Honoraria; *AbbVie, AstraZeneca, Celgene, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Janssen, Novartis:* Consultancy; *AbbVie, Bristol-Myers Squibb, Celgene, Chugai, Daiichi Sankyo, Eisai, Janssen, Kyowa Kirin, Novartis, Ono:* Research Funding. **Ota:** *Otsuka Pharmaceutical Co.,Ltd.:* Current Employment. **Mitsuki:** *Otsuka Pharmaceutical Co.,Ltd.:* Current Employment. **Yokota:** *Otsuka Pharmaceutical Co.,Ltd.:* Current Employment. **Sano:** *Astex Pharmaceuticals, Inc.:* Current Employment. **Terui:** *Bristl Myers Squibb:* Speakers Bureau; *Eizai:* Speakers Bureau; *Symbio Pharmaceutical:* Speakers Bureau; *Chugai Pharmaceutical Inc, Roche:* Speakers Bureau; *Ono:* Speakers Bureau.

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