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POSTER ABSTRACTS

627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Treatment of Relapsed/Refractory Hgbcl and Bukitt's Lymphoma with c-Myc Rearrangement: A Multi-Center, Open-Label, Phase 2 Study of PC-002 (SepB), a First-in-Class Deubiquitinase Inhibitor Inducing Myc Degradation

Sung-Soo Yoon, MDPhD[1], *Zhiming Li*[2], *Keshu Zhou, MD*[3], *Xiaoxi Zhou, MD*[4], *Ye Guo, MD*[5], *Huilai Zhang, MD*[6], *Ki-Seong Eom*[7], *Seok Jin Kim, MD PhD*[8], *Sung Yong Oh, MD*[9], *Sung-Nam Lim, MD*[10], *Hagop Youssoufian, MD*[11], *Vernon Jiang, PhD*[12], *Zhanchun Huang*[11], *Georgina Kilfoil*[11], *Xin Wang*[11], *Zhixiang Cao*[11], *Xiang LI*[13], *Yihai Lin*[11], *Alexander Wu, PhD*[11], *Yiyou Chen, PhD*[11], *Yuqin Song, MD*[14]

[1] Seoul National University Hospital, Seoul, South Korea
[2] Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China
[3] Department of Hematology, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China
[4] Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[5] State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences&Peking Union Medical College, Tianjin, China
[6] Tianjin Medical Univ. Cancer Institute & Hospital, CHN, Tianjin, CHN
[7] Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of (South)
[8] Samsung Med. Ctr., Seoul, Korea, Republic of (South)
[9] Dong-A University Hospital, Busan, Korea, Republic of (South)
[10] Department of Hematology-Oncology, Inje University Haeundae Paik Hospital, Busan, Korea, Republic of (South)
[11] Cothera Bioscience, San Mateo„ CA
[12] Cothera Bioscience, San Mateo, CA
[13] Cothera Bioscience, BEIJING, China
[14] Department of Lymphoma, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, BEIJING, China

Background:
Burkitt lymphoma (BL) is one of the most aggressive B cell malignancies that is a high unmet need and characterized classically by *c-Myc* rearrangement. However, c-Myc is considered "undruggable" due to its structure and a lack of kinase activity. Degradation of c-Myc is mediated through the ubiquitin-proteasome system. Therefore, modulation of deubiquitination catalysis process may reduce the stability of c-Myc. PC-002 (also known as Sepantronium Bromide, or SepB) is a small molecule previously identified as a survivin suppressant with antitumor activity against a range of tumor types. More recently, we discovered that PC-002 has another novel mechanism of targeting cancers with *Myc* gene amplification by inhibiting the deubiquitinase activity of ubiquitin-specific proteases (USPs), which leads to Myc protein degradation. Preclinically, PC-002 shortens the half-life of c-Myc protein, induces rapid apoptosis of cells with *c-Myc* rearrangement, and demonstrates rapid tumor regression in *c-Myc*-rearranged BL and high grade B cell lymphoma (HGBCL) murine xenograft models. This discovery prompted us to initiate a Phase 2 proof-of-concept clinical trial in patients with relapsed/refractory *c-Myc* rearranged HGBCL, including Burkitt Lymphoma (*https://clinicaltrials.gov/ ct2/show/NCT05263583*).

Aims:
The aim of this trial (*https://clinicaltrials.gov/ct2/show/NCT05263583*) is to study safety and efficacy of PC-002 as monotherapy for *c-Myc* rearranged HGBCL, including Burkitt Lymphoma.

Methods:
NCT05263583 is a multicenter, open-label, Phase 2 dose-finding study of PC- 002 (Sepantronium Bromide, or SepB) in patients with relapsed/refractory HGBCL and Burkitt's lymphoma with *c-Myc* rearrangement. Patients will be treated with escalating

doses (3.6 and 4.8 mg/m ^{2}/day) of single-agent PC-002 administered by continuous intravenous infusion for 168 hours in 21-day cycles at two dose levels. The primary objective is to determine the safety, tolerability and recommended Phase 2 dose of PC-002. Cohorts of three patients will be enrolled at each dose level for PC-002 with expansion to six patients, if necessary, to assess toxicity. An additional 6 patients will be enrolled at the RP2D. Secondary objectives are Objective Response Rate (ORR), Duration of Response (DoR), Clinical Benefit Rate (CBR), Overall Survival (OS) and Progression-Free Survival (PFS). Exploratory objectives are aimed to measure PC-002 exposure and its relationship to clinical outcome and to assess the relationship between biomarkers and PC-002 efficacy.

Results:

As of 28 July 28, 2023, 3 patients of cohort 1 (3.6 mg/m ^{2}/day) with a median age of 33 years (range 19-67 years) had received $\geq$ 2 cycles of dosing (A cycle is defined as 7 days of treatment plus 14 days of rest). Two of the patients (2 males) have Burkitt Lymphoma and one (female) has HGBCL (DLBCL-TH). Adverse events deemed related to PC-002 included anemia and neutropenia. No dose-limiting toxicities have been reported. Preliminary assessment by image analysis and Lugano criteria showed partial response (PR) in 2 heavily pre-treated patients with relapsed/refractory BL after receiving 2 cycles of treatment. The duration of response in these two patients was 3 months and patients received at least 4 cycles of treatment. ORR of the 3 patients in Cohort 1 is 66.7% at 3.6 mg/m ^{2}/day dose. To date, 3 patients with a median age of 58 years (range 25-60 years) had been enrolled of cohort 2 (4.8 mg/m ^{2}/day) and completed at least one cycle of treatment.

Summary/Conclusion:

At the time of abstract submission, the 1 st cohort (3.6 mg/m ^{2}/day) of 3 patients have completed at least four cycles of treatment. PC-002 is generally well-tolerated at 3.6 mg/m ^{2}/day and progression to Cohort 2 at a dose of 4.8 mg/m ^{2}/ day was approved by the Safety Review Committee. Two patients with relapsed/refractory Burkitt Lymphoma at the starting dose of 3.6 mg/m ^{2}/day achieved a confirmed PR. ORR of the 3 patients in Cohort 1 is 66.7% after 2 cycles of 3.6 mg/m ^{2}/day (2 PRs). Three patients have been enrolled in Cohort 2 (4.8 mg/m ^{2}/day) and completed at least one cycle of treatment to date.

Disclosures No relevant conflicts of interest to declare.

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