



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Treatment of Relapsed/Refractory Hgbcl and Burkitt'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, MDPhD¹, Zhiming Li², Keshu Zhou, MD³, Xiaoxi Zhou, MD⁴, Ye Guo, MD⁵, Huilai Zhang, MD⁶, Ki-Seong Eom⁷, Seok Jin Kim, MD PhD⁸, Sung Yong Oh, MD⁹, Sung-Nam Lim, MD¹⁰, Hagop Youssoufian, MD¹¹, Vernon Jiang, PhD¹², Zhanchun Huang¹¹, Georgina Kilfoil¹¹, Xin Wang¹¹, Zhixiang Cao¹¹, Xiang Li¹³, Yihai Lin¹¹, Alexander Wu, PhD¹¹, Yiyu Chen, PhD¹¹, Yuqin Song, MD¹⁴

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/m²/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 2023, 3 patients of cohort 1 (3.6 mg/m²/day) with a median age of 33 years (range 19-67 years) had received ≥ 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/m²/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/m²/day) and completed at least one cycle of treatment.

Summary/Conclusion:

At the time of abstract submission, the 1st cohort (3.6 mg/m²/day) of 3 patients have completed at least four cycles of treatment. PC-002 is generally well-tolerated at 3.6 mg/m²/day and progression to Cohort 2 at a dose of 4.8 mg/m²/day was approved by the Safety Review Committee. Two patients with relapsed/refractory Burkitt Lymphoma at the starting dose of 3.6 mg/m²/day achieved a confirmed PR. ORR of the 3 patients in Cohort 1 is 66.7% after 2 cycles of 3.6 mg/m²/day (2 PRs). Three patients have been enrolled in Cohort 2 (4.8 mg/m²/day) and completed at least one cycle of treatment to date.

Disclosures No relevant conflicts of interest to declare.

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