Clinical Activity of Cirmtuzumab, an Anti-ROR1 Antibody, in Combination with Ibrutinib; Interim Results of a Phase 1b/2 Study in Mantle Cell Lymphoma (MCL) or Chronic Lymphocytic Leukemia (CLL)

Hue Lee, MD, Michael Y. Choi, MD, Tanya Siddiqui, MD, William G. Wierda, MD, PhD, Jacqueline C. Barrientos, MD, MS, Nicole Lamanna, MD, Alec Goldenberg, MD, Iris Sull, MD, Joseph Tuscano, MD, Sukanthini Subbiah, MD, Elizabeth K. Weche, MD, Xen Iamopoulos, MD, PhD, James B. Breitnour, MD, MPH, Frank J. Hsu, MD, Michael Wang, MD, Calirona Jamieson, MD, PhD, and Thomas J. Kipps, MD, PhD

Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, Moores Cancer Center, University of California San Diego, La Jolla, CA, Department of Hematology, and Hemostasis, Cell Transplantation, City of Hope, Duarte, CA, Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, Karches Center for Oncology Research, The Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY, Weill Cornell Comprehensive Cancer Center, Columbia University Medical Center, New York, NY, Marikoinico Cancer Institute, New York, NY, WashU, Washington University, School of Medicine, St. Louis, MO, University of California, Davis, CA, EU Health Science Center, Oncological Therapists, Inc., San Diego, CA

I. RATIONALE / BACKGROUND

ROR1 is a cell surface receptor tyrosine kinase that is overexpressed at high levels on many hematologic malignancies including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). Inhibitors of ROR1 have shown promise in preclinical studies, including one patient with a complete remission (CR) following treatment with cirmtuzumab (Cirm) plus ibrutinib in a phase 1 study in patients with relapsed/refractory CLL/SLL (Hue et al., 2020). In this study, we examined the safety and efficacy of Cirm in combination with ibrutinib in MCL and CLL/SLL patients.

II. STUDY DESIGN

Patients with relapsed/refractory MCL or CLL/SLL were eligible to participate. Patients were adults ≥18 years, with ≥1 prior systemic therapy, including ibrutinib, were eligible. Patients with a failing CAR-T cell therapy were also eligible. The primary endpoints were safety and efficacy of the combination regimen in a comparative study and is actively enrolling CLL pts.

III. CLINICAL RESULTS

A. COMBINATION REGIMEN

- **MCL (N=15):**
  - Evaluable R/R Pts: n=22
  - Most patients have completed the planned 1 year on study. 6 CLL pts from Part 1 and 10 pts from Part 2 have chosen to enroll into extended therapy and continue combination treatment. Most MCL pts have completed 6 months of therapy; 2 have completed 1 year and enrolled into extended therapy.
  - **CLL Part 2:** 1 discontinued due to an AE (arthralgias thought possibly related to ibrutinib).

B. SAFETY:

- **MCL** and **CLL** patients reported treatment related SAE events. SAEs were considered related to the combination therapy. Overall, addition of cirmtuzumab to ibrutinib was without any new grade 3 or higher adverse events and was consistent with the AE profile reported for ibrutinib alone.

- **Disposition After Enrollment**

- **Progression-Free Survival**

- **MCL Part 1:** MCL with a median follow-up of 9.3 months (range 0.1 to 23). In the MCL Part 1, 2 patients were enrolled. One patient achieved a partial response (PR) and the other patient had stable disease (SD).

- **CLL Part 1:** CLL with a median follow-up of 12 months (range 0.1 to 30). In the CLL Part 1, 4 patients were enrolled. One patient achieved a PR, one patient had SD, and two patients had disease progression (DP).

IV. OVERALL CONCLUSIONS

This interim analysis of a Phase 1b/2 study in patients with relapsed/refractory MCL or CLL showed promising activity of cirmtuzumab plus ibrutinib. The combination was well tolerated, and the overall safety profile of both agents was compatible with the known safety profiles of single agents. The combination was associated with rapid responses in MCL and CLL patients, with 88% achieving a best response of CR or PR, including one patient with a CR in MCL and two patients with PR in CLL. The combination was also associated with clinical benefit in MCL and CLL patients, with 100% achieving a best response of CR, PR, or SD. Overall, the addition of cirmtuzumab to ibrutinib was without any new grade 3 or higher adverse events and was consistent with the AE profile reported for ibrutinib alone.

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