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POSTER ABSTRACTS

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Tazemetostat in Combination with Lenalidomide and Rituximab in Patients with Relapsed/Refractory Follicular Lymphoma: Updated Phase 1b Results of Symphony-1 with 22.5 Months Follow-up

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Background: Tazemetostat (TAZ), an enhancer of zeste homolog 2 (EZH2) inhibitor, is approved by the US Food and Drug Administration for the treatment of patients with relapsed/refractory (R/R) follicular lymphoma (FL) whose disease has mutant (MT) *EZH2* and who have received ≥2 prior therapies, or patients with R/R FL who have no satisfactory alternative treatment options. We previously reported the efficacy and safety of TAZ in combination with lenalidomide and rituximab (R ^{2}) in patients with R/R FL from the SYMPHONY-1 study (EZH-302; NCT04224493) after complete enrollment and following the phase 1b safety run-in period. Here, we report the updated efficacy and safety results after a median follow-up of 22.5 months.
Methods: Phase 1b evaluated TAZ at 3 dose levels (400, 600, and 800 mg orally twice daily [BID]) in 28-day cycles with standard-dose R ^{2}. After the initial 12 months of combination therapy, tazemetostat 800 mg BID was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Primary endpoints of the phase 1b portion were safety and determination of the recommended phase 3 dose (RP3D). Secondary endpoints included pharmacokinetic (PK) parameters. Efficacy analysis was performed on the intent-to-treat (ITT) population, including best overall response, progression-free survival (PFS), and duration of response (DOR) per investigator assessment, according to Lugano 2014 response criteria.
Results: As of July 10, 2023, 44 patients were enrolled and receiving TAZ + R ^{2} (400 [n=6], 600 [n=19], or 800 mg [n=19]). Median age was 67 years, 31.8% of patients had received >1 prior therapy, and patients had a median of 1 prior line of therapy (range, 1-4). Overall, 81.8% (n=36) of patients had wild-type (WT) *EZH2* FL, 34.1% (n=15) of patients had rituximab-refractory disease, and 27.3% (n=12) of patients had POD24. Median durations of treatment exposure for TAZ, lenalidomide, and rituximab were 13.3, 10.8, and 4.6 months, respectively. In the 800-mg cohort, the median relative dose intensity was 94.1%, 92.9%, and 100% for TAZ, lenalidomide, and rituximab, respectively. No dose-limiting toxicities were observed in phase 1b, and no new safety signals were identified as of the data cutoff. The RP3D of TAZ was determined to be 800 mg BID in combination with R ^{2}. The most common grade 3-4 TEAE was neutropenia (40.9%; n=18). The most frequent type of dose modification due to TEAEs for any study treatment was drug interruption (70.5%), followed by dose reduction (38.6%) and treatment discontinuation (20.5%); protocol-mandated dose modifications included simultaneous dose interruption and/or reduction of TAZ and lenalidomide for neutropenia and thrombocytopenia. Of the 44 patients, 42 patients were evaluable for tumor assessment and 2 patients had no postdose tumor assessments. Of 42 patients evaluable for tumor assessment, 23 (54.8%) had a complete response, 17 (40.5%) had a partial response, and 2 (4.8%) had stable disease. The ORR in the ITT population was 90.9% (n=40/44). The ORRs in patients with WT *EZH2* and MT *EZH2* were 88.9% (n=32/36) and 100% (n=7/7), respectively. The ORR in patients with rituximab-refractory disease was 93.3% (n=14/15) and in patients with POD24 was 91.7% (n=11/12). With a median follow-up

of 22.5 months, median PFS and median DOR were not reached. In the ITT population, 18-month PFS and DOR estimates were 79.5% and 81.0%, respectively; in the 800-mg cohort (n=19), 18-month PFS and DOR estimates were 94.4% and 100%, respectively. PFS appeared to be dose dependent, with durable response in the 800-mg cohort.

Conclusions: The safety profile of TAZ + R ^{2} combination therapy was consistent with previous reports, with no new safety signals identified in the phase 1b data of this study. The 12 months of initial combination therapy resulted in long-lasting remission. Dose-dependent response was seen with durable response in patients receiving TAZ 800 mg, regardless of their mutation status. The 2-arm randomized phase 3 portion will further explore the efficacy and safety of TAZ 800 mg + R ^{2} in ≈500 patients with R/R FL who completed ≥1 prior systemic therapy.

Disclosures Salles: *Molecular Partners:* Consultancy; *ATB Therapeutics:* Consultancy; *Kite/Gilead:* Consultancy; *Merck:* Consultancy, Honoraria; *Debiopharm:* Consultancy; *AbbVie:* Consultancy, Honoraria; *Genmab:* Consultancy; *Genentech, Inc./F. Hoffmann-La Roche Ltd:* Consultancy, Research Funding; *Novartis:* Consultancy; *Nurix:* Consultancy; *Orna:* Consultancy; *Nordic Nanovector:* Consultancy; *Incyte:* Consultancy; *Ipsen:* Consultancy, Research Funding; *BMS/Celgene:* Consultancy; *Loxo/Lilly:* Consultancy; *Janssen:* Consultancy, Research Funding; *Owkin:* Current holder of *stock options* in a privately-held company; *EPIZYME:* Consultancy; *BeiGene:* Consultancy. **Park:** *Seattle Genetics:* Research Funding; *BMS:* Research Funding; *Epizyme:* Membership on an entity's Board of Directors or advisory committees; *ADC Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Morphosys:* Membership on an entity's Board of Directors or advisory committees. **Phillips:** *Abbvie, AstraZeneca, Bayer, Beigene, BMS, Cardinal Health, Epizyme, Incyte, Karyopharm, Pharmacyclics, Seattle Genetics:* Consultancy; *Abbvie, Bayer:* Research Funding. **Amengual:** *Incyte:* Consultancy; *Epizyme:* Honoraria; *AstraZeneca:* Consultancy. **Andorsky:** *AstraZeneca:* Consultancy; *AbbVie:* Consultancy. **Campbell:** *Amgen, AstraZeneca, CSL Behring, Janssen, Novartis, Roche:* Consultancy; *Amgen, Celgene (BMS), Janssen, Novartis, Roche:* Research Funding. **McKay:** *AstraZeneca:* Consultancy; *Abbvie:* Consultancy; *Beigene:* Consultancy; *Celgene/BMS:* Consultancy; *Gilead/Kite:* Consultancy, Honoraria, Other: Travel to scientific conferences; *Incyte:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria, Other: Travel to scientific conferences; *Roche:* Consultancy; *Takeda:* Consultancy, Other: Travel to scientific conferences. **Leonard:** *AbbVie, AstraZeneca, Astellas, Bayer, BeiGene, BMS, Calithera, Constellation, Eisai, Epizyme, GenMab, Grail, Incyte, Janssen, Karyopharm, Lilly, Merck, Mustang Bio, Pfizer, Roche/Genentech, Seagen, Second Genome, Sutro:* Consultancy; *National Cancer Institute, Leukemia and Lymphoma Society, Genentech, Epizyme, Janssen:* Research Funding. **Chen:** *Ipsen:* Current Employment. **Chen:** *Ipsen:* Current Employment. **Bannerji:** *Ipsen:* Current Employment. **Kapopara:** *Ipsen:* Current Employment. **Szanto:** *Ipsen:* Current Employment. **Morschhauser:** *F. Hoffmann-La Roche Ltd, AbbVie, BMS, Genmab, Gilead, Novartis:* Consultancy; *F. Hoffmann-La Roche Ltd, Gilead, AbbVie:* Membership on an entity's Board of Directors or advisory committees.

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