11515 **Poster Discussion Session**

RINGSIDE phase 2/3 trial of AL102 for treatment of desmoid tumors (DT): Phase 2 results.

Mrinal M. Gounder, Robin Lewis Jones, Rashmi Chugh, Mark Agulnik, Arun S. Singh, Brian Andrew Van Tine, Vladimir Andelkovic, Edwin Choy, Jeremy Howard Lewin, Ravin Ratan, Gary B. Gordon, Jonathan Yovell, Andres A. Gutierrez, Bernd Kasper; Memorial Sloan Kettering Cancer Center, New York, NY; Sarcoma Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom; Michigan Medicine, Ann Arbor, MI; City of Hope Comprehensive Cancer Center, Durarte, CA; University of California Los Angeles Translational Oncology Research, Santa Monica, CA; Washington University School of Medicine, St. Louis, MO; Princess Alexandra Hospital, Brisbane, Australia; Massachusetts General Hospital, Boston, MA; Peter MacCallum Cancer Centre, Melbourne, Australia; University of Texas MD Anderson Cancer Center, Houston, TX; Ayala Pharmacuticals, Highland Park, IL; Ayala Pharmaceutical, Wilmington, DE; Ayala Pharmaceuticals, Monmouth Junction, NJ; Universität Heidelberg, Mannheim Cancer Center (MCC), Sarkom Zentrum, Mannheim, Germany

Background: For patients with desmoid tumors (DT, aggressive fibromatosis), systemic therapy that results in tumor regression, symptom improvement and durable tolerability is needed. Gamma secretase inhibitors (GSIs) have demonstrated antitumor activity against DT. AL102 is a potent, orally available, selective GSI under investigation for treatment of DT. **Methods:** RINGSIDE (AL-DES-01) is a Phase 2/3 study for patients with progressing DT. In the open-label Phase 2 study (Part A), adults with progressing DT (≥10% unidimensional growth within 18 months or DT-related pain requiring non-opioid medication) were randomized to three dosing regimens: 1.2 mg QD, 2 mg intermittent BIW (2 days on 5 days off), or 4 mg intermittent BIW. Patients who complete Phase 2 roll over into an open-label extension (OLE). RINGSIDE Phase 3 (Part B) is a double-blind, placebo-controlled study evaluating the chosen dose regimen from Phase 2 (1.2 mg once daily) utilizing PFS as the primary endpoint. We report updated efficacy and safety results from RINGSIDE Phase 2. **Results:** Enrollment of all 42 patients into Phase 2 was completed as of March 2022. As of January 3, 2023, median time on study was 10.5 months (range 0.8 – 14.7) and 30 patients (71.4%) were still on study, 10 (23.8%) of whom rolled over to the OLE. Mean age was 39.9 years, 73.8% were women and 69% had received prior desmoid cancer therapy. The best response in the evaluable population as assessed by blinded independent central review (BICR) was partial response (PR) in 6/12 patients (50%) for 1.2 mg QD, 3/13 patients (23.1%) for 4 mg BIW, and 5/11 patients (45.5%) for 2 mg BIW. Disease control rate was 100%, 91%, and 97% in these groups, respectively. A consistent pattern of deeper, more rapid and maintained response was observed with 1.2 mg QD. Median volume change (BICR) from baseline was -51.9% for 1.2 mg QD, -9.5% for 4 mg BIW, and -15.2% for 2 mg BIW at Week 16 and -76.4%, -35.5%, and -51.2%, respectively, at Week 28. Similar patterns were observed for % changes from baseline in T2 signal intensity, suggesting reduction of tumor cellularity. Consistent with the mechanism of action of GSIs, the five most common Grade 1-2 treatment-emergent adverse events (TEAEs) were diarrhea, nausea, fatigue, alopecia, and dry skin. Grade 3 drug-related TEAEs were reported in 26.2% of patients across all tested doses. There were no Grade 4, Grade 5, or serious TEAEs related to AL102 per investigator assessment. There were no new safety signals. **Conclusions:** In this Phase 2 study, AL102 was safe and generally well tolerated across all tested doses. The safety profile was consistent with the GSI class of drugs. Tumor response, volume reduction and T2 signal reduction were observed earlier in the 1.2 mg QD group, with deeper and maintained treatment responses. This dose was selected for study in RINGSIDE Phase 3, which is currently enrolling in multiple countries. Clinical trial information: NCT04871282. Research Sponsor: Ayala Pharmaceuticals.