TPS6110 **Poster Session**

A phase II study of ACR-368 and low dose gemcitabine combination therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma.

Robin Park, Dan Paul Zandberg, Jean-Marie Cuillerot, Erick Gamelin, Satish Stephen Maharaj, Kedar Kirtane, Guilherme Rabinowits, Christine H. Chung; Department of Head and Neck-Endocrine Oncology, Moffitt Cancer Center, Tampa, FL; UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; Acrivon Therapeutics Inc., Watertown, MA

Background: Safe and efficacious therapeutic options for patients with recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) beyond the 1st line palliative treatment, for which the standard of care is PD-1 inhibitor with/without chemotherapy, are limited. Therefore, developing novel therapeutic strategies in this setting remains a critical unmet need. ACR-368 (prexasertib) is a potent, selective CHK1/2 inhibitor which impairs DNA damage repair (DDR) and induces cancer cell apoptosis. ACR-368 has shown single agent activity in a phase Ib trial of patients with advanced squamous cell carcinomas including heavily treated R/M HNSCC. Pre-clinical studies suggest down-regulation of DDR pathways downstream to CHK1/2 is a major resistance mechanism to ACR-368 that can be overcome with low doses of nucleoside analogs that increase replication stress. Work conducted at Acrivon Therapeutics using their AP3 platform uncovered protein signaling features linked to ACR-368 resistance that demonstrated low-dose gemcitabine (LDG) may sensitize cancer cells to ACR-368 treatment. Furthermore, combining LDG with ACR-368 induces synergistic cancer cell regression in *in vitro* and *in vivo* models of HNSCC. Therefore, combined ACR-368 and LDG warrant further evaluation. **Methods:** This is a multi-center, parallel-arm, open-label, phase II trial evaluating combined ACR-368 with LDG in patients with R/M HNSCC. Eligible patients must have been treated with 1 prior line of PD-1/L1 inhibitor with/without chemotherapy with no limitation on the number of prior therapies received in the R/M setting. Patients must agree to a biopsy after the lead-in LDG infusion and at disease progression or end of treatment. OncoSignature is a proprietary predictive biomarker designed to predict response from ACR-368 that will be evaluated as a companion diagnostic. Lead-in LDG 10 mg/m2 IV will be administered before Cycle 1 only followed by ACR-368 105 mg/m2 IV Q2W and LDG 10 mg/m2 Q2W until discontinuation due to disease progression, intolerance, or consent withdrawal. Patients with HPV-unrelated R/M HNSCC will be assigned to Cohort A and patients with HPV-related R/M HNSCC to Cohort B. Primary objective is to determine objective response rates (ORR) in Cohort A and Cohort B, respectively. Study will enroll 14 patients in Cohort A and 29 patients in Cohort B to detect an increase in ORR from 0 to 19% and 5 to 22%, in respective cohorts (type I, II errors, both 10%). Secondary objectives include safety, duration of response, progression-free survival, and overall survival. Exploratory objectives include evaluating potential predictive biomarkers and the effect of lead-in LDG on OncoSignature by comparing pre- and post-LDG tumors. Since recruitment began 09-25-2024, 5 of planned 43 patients have been enrolled as of 01-22-2025. Clinical trial information: NCT06597565. Research Sponsor: Acrivon.