A CIVO INTRATUMOR MICRODOSE PHASE 0 TRIAL OF SUBASUMSTAT (TAK-981) IN COMBINATION WITH CETUXIMAB OR AVELUMAB REVEALS TYPE 1 INTERFERON INDUCTION AND IMMUNE ACTIVATION IN HEAD AND NECK CANCER PATIENTS

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Background Subasumstat (TAK-981) is an investigational drug designed to induce type I interferon (IFN) signaling via inhibition of the SUMO activating enzyme (SAE). In parallel to Phase I trials of intravenous (IV) dosing, we completed a Phase 0 intratumoral (IT) microdosing trial in head and neck cancer (HNC) using the Comparative In Vivo Oncology (CIVO) platform in order to understand effects of subasumstat within the native tumor microenvironment (TME). A major advantage of the CIVO platform is the ability to compare responses to up to 8 different drugs and combinations in the same human tumor. Here we present data from a Phase 0 trial evaluating TME responses to subasumstat alone or in combination with cetuximab or avelumab.

Methods We enrolled 12 patients with a confirmed diagnosis of HNC and planned surgical resection. Patients’ surface accessible and ≥2 cm diameter tumors (either primary sites or metastatic to cervical lymph nodes or parotid) were injected with a 3, 5, or 8-needle CIVO device containing vehicle, subasumstat, cetuximab, avelumab, and combinations thereof co-formulated with a fluorescent tracking marker for injection site identification and visualization. Tumors were resected 24 to 96 hours after injection, processed, and analyzed at a central site using multiplex ISH / IHC and molecular profiling via GeoMx Digital Spatial Profiling (DSP). In each tumor, biomarker responses were resolved to individual injection sites, quantified, and compared by injection contents.

Results Consistent with our reports from the interim analysis of this study, subasumstat IT microdoses induced IFN signaling and activation of both innate immune cells and CD8+ T cells in the TME.1 Combinations of subasumstat with avelumab or cetuximab led to enhanced and prolonged IFN signaling and increased expression of CD86 and granzyme B within the TME. GeoMx DSP revealed key similarities and differences between cetuximab and avelumab combination sites, including inflammatory markers, chemokines, and stromal markers.

Conclusions IT microdosing with CIVO provides early insights into investigational agents that can only be obtained in the native, intact TME. This is the first reported trial we know of where side-by-side evaluation of an investigational agent, two different biologics, and combinations thereof all in the same patient tumor was achieved. Results provide the first evidence in human tumors that subasumstat combinations can enhance immune cell activation in the TME. They also provide mechanistic rationale for further evaluating combinations of subasumstat with anti-EGFR antibodies and/or checkpoint blockade in human tumors.

Trial Registration NCT04065555: Intratumoral Microdosing of TAK-981 in Head and Neck Cancer