PHARMACOKINETIC AND IMMUNOLOGIC DATA FROM A PHASE I STUDY OF THE CLICK CHEMISTRY-BASED THERAPY SQ3370 IN ADVANCED SOLID TUMORS AND SOFT-TISSUE SARCOMA PROVIDES PROOF-OF-CONCEPT FOR THE CAPAC PLATFORM

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Background Conventional chemotherapeutics lack specificity for tumor tissue and usually have a narrow therapeutic index. SQ3370, a novel therapy that activates doxorubicin (Dox) at the tumor site while minimizing systemic exposure, is based on intratumoral injection of a prodrug-activating hyaluronic acid-based biopolymer (SQL70) followed by five daily intravenous (IV) doses of an attenuated prodrug of Dox (SQP33). SQ3370 utilizes Shasqi's proprietary Click Activated Prodrugs Against Cancer (CAPAC) platform where mutually-reactive click chemistry groups in the two components allow release of active Dox specifically at the tumor site. In animals, SQ3370 allowed for an 8.95-fold increase in dosing with minimal systemic adverse events and no cardiotoxicity. SQ3370 treatment of mouse tumor models showed improved overall survival, enhanced T-cell infiltration, and a robust anti-tumor response against both biopolymer-injected and non-injected lesions,¹ suggesting that SQ3370 promotes activation of the native immune system against the tumor.

Methods SQ3370-001 (NCT04106492) is a phase 1 trial open to patients with relapsed/refractory soft-tissue sarcoma or other advanced, potentially anthracycline-responsive solid tumors with an injectable local or metastatic lesion and ≥ 300 mg/m² prior exposure to Dox (or equivalent). Primary objectives include safety, tolerability, and recommended Phase 2 dose. Additional objectives include preliminary efficacy, plasma and tumor biopsy pharmacokinetics (PK), and immune response by peripheral blood mass cytometry/tumor IHC.

Results To date, ten patients have been enrolled. SQ3370 treatment has been well-tolerated with no dose-limiting toxicities observed. Plasma PK appeared consistent with preclinical data; rapid conversion of SQP33 prodrug to active Dox occurred but slowed as the residence time of the injected biopolymer lengthened. Systemic exposure to active Dox peaked on days 1–2 post biopolymer injection, followed by a decline on days 3–5. Preliminary tumor analysis shows that substantial local exposure to Dox continues 2 weeks after the last SQP33 dose. Immune response analysis of early patient samples suggests increased tumor immune cell infiltration that dynamically changes with each cycle of treatment.

Conclusions SQ3370 appears to be well-tolerated and demonstrates proof-of-concept for the first click-chemistry-based therapy in the clinic. Preclinical and clinical PK are consistent; high tumor exposure can be achieved, so far without the typical clinical adverse events seen with IV Dox and potentially improving the therapeutic index of a frequently-used chemotherapeutic agent.

Trial Registration NCT04106492

REFERENCE

1. Srinivasan S, Yee NA, Wu K, et al. SQ3370 activates cytotoxic drug via click chemistry at tumor and elicits sustained responses in injected and non-injected lesions. *Advanced Therapeutics* 2021;4(3):2000243.

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