First-in-human Phase I Study of SQ3370, a Click Activated Protodrug Therapy, in Patients with Advanced Solid Tumors

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CAPAC™ and SQ3370 Overview

Cancer immunotherapies have been very successful in recent times; however, they benefit only a subset of patients and have varying response rates across tumor types. Conversely, conventional chemotherapies are effective in a large group of patients, but have limited dosing capabilities, lack specificity, and often result in systemic adverse events. While conventional Dox is known to induce immune activation[1] and enhance tumor responsiveness to checkpoint inhibitors[2], its benefit is limited by cumulative dose cardiotoxicity.

Shasqi's lead candidate, **SQ3370**, has the potential to bridge this gap. SQ3370 utilizes Shasqi's proprietary **C**lick **A**ctivated **P**rotodrugs **A**gainst **C**ancer (**CAPAC**™) platform, a click chemistry-based approach that activates cancer drugs at a specific tumor with minimal systemic toxicity. Unlike targeted therapies, the CAPAC™ platform is agnostic to tumor characteristics that can vary across patients and hence applicable to several types of tumors. SQ3370 consists of 2 components, SQL70 biopolymer and SQP33 protodrug. SQL70 is a tetrazine-modified sodium hyaluronate biopolymer which functions by activating the protodrug inside the body and does not contain a therapeutically active ingredient. SQP33 is a trans-cyclooctene (TCO)-modified protodrug of Doxorubicin (Dox) with attenuated cytotoxic activity.

In syngeneic mouse models, SQ3370 improved overall survival and induced a robust anti-tumor response against biopolymer-injected tumors compared to conventional Dox. Surprisingly, SQ3370 also induced regression in non-injected tumors, suggesting the activation of an immune-mediated anti-tumor response. SQ3370 is the first click chemistry-based treatment to be used in humans.

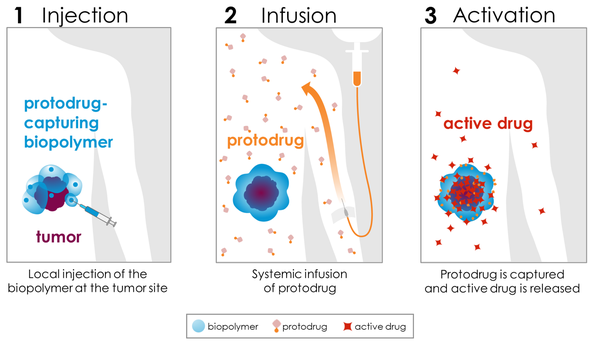


Figure 1: (**1**) SQL70 biopolymer is locally injected at the tumor site and (**2**) SQP33 protodrug is infused systemically. (**3**) SQP33 protodrug is activated by SQL70 biopolymer at the tumor site through a rapid covalent reaction between tetrazine and trans-cyclooctene moieties, followed by chemical rearrangement to release active Dox.

[1]**Mattarollo, S.R.,**et al. Cancer Res 2011; [2]**Zitvogel L.**, et al. Immunity 2013.

Treatment

- A fixed amount of SQL70 biopolymer is injected on Day 1 of each 21-day cycle into a single lesion.
- SQP33 protodrug is infused after the SQL70 biopolymer injection on Day 1 once-daily until Day 5 (5 doses) for each 21-day cycle.

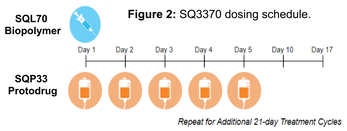
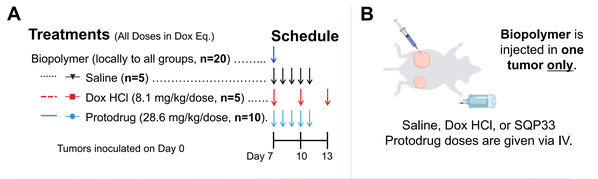


Figure 2: SQ3370 dosing schedule.

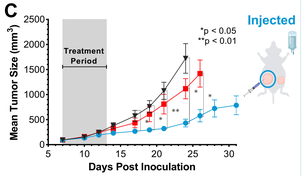
- The starting daily dose of SQP33 protodrug for this clinical study is 8 mg/m^2/day (5.72 mg/m^2/day Dox equivalents [Eq]).
  - The starting human dose of SQP33 protodrug with a fixed amount of SQL70 biopolymer was determined in accordance with ICH S9 guidelines, which propose using 1/6th of the human equivalent highest non-severely toxic dose (HNSTD) taken from a Good Laboratory Practice (GLP) toxicology study in the relevant species.
- Patients may continue to receive treatment until they have either no injectable (as determined by the investigator) lesions, radiographic progression of disease per RECIST v1.1, unacceptable toxicity, or other treatment discontinuation criteria are met.

SQ3370 Improves Survival, Tumor Growth Inhibition and Systemic Anti-Tumor Response in Mice

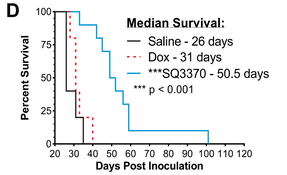
Efficacy of SQ3370 in Dual-Tumor Syngeneic Mice Compared to Dox HCl



SQ3370 Inhibits Injected Tumors



SQ3370 Enhances Survival over Dox



Non-injected Tumor Growth - SQ3370 Induces Systemic Anti-Tumor Response

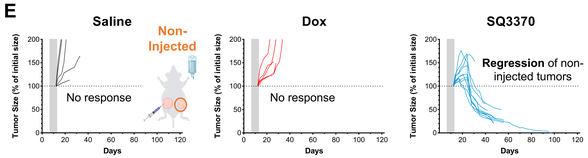


Figure 3: *C57BL/6* mice received 2 SC-flank MC38 inoculations (Injected and Non-injected tumors). SQL70 Biopolymer was injected ONLY in the larger tumor. Mice received Saline, Dox HCl, or SQP33 treatment. Plots show mean ± SEM.

Revised and reproduced from: ***N.A. Yee****, et al. Poster presented at AACR Annual Meeting 2020 (abstract 7764).*

Study Objectives

Primary

- Assess the safety and tolerability of SQ3370, including determination of the maximum tolerated dose (MTD) and/or recommended Phase 2 dose.

Secondary

- Characterize the pharmacokinetic (PK) profile of SQP33 protodrug and active doxorubicin (Dox) following SQ3370 treatment.
- Assess preliminary signals of SQ3370 anti-tumor activity.

Exploratory

- Assess the concentration of active Dox and SQP33 following SQ3370 treatment at the local site through analysis of tumor biopsies.
- Assess immune response through biomarker analysis of tumor biopsies and peripheral blood specimens.

Study Design

- This multicenter, Phase 1, first-in-human, single-arm, open-label, dose-escalation study will evaluate the safety and tolerability, PK, and preliminary efficacy of SQ3370 in patients with locally advanced or metastatic solid tumors that are refractory/relapsed following, or otherwise ineligible for, standard of care therapy.
  - ClinicalTrials.gov identifier: **NCT04106492.**

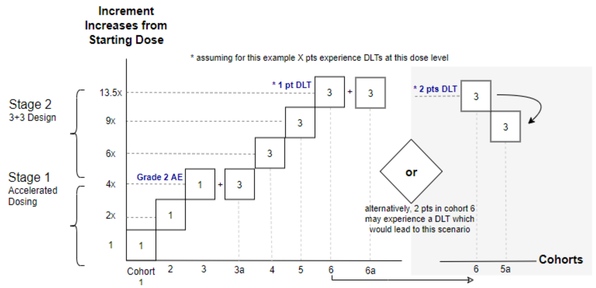


Figure 4: Dose-escalation trial design.

- The dose-escalation portion of the study will initially consist of a single-patient accelerated titration design (Stage 1) and then switch to a 3+3 design (Stage 2).

Assessments

- Tumor response will be assessed by the investigators using RECIST guidelines version 1.1.
- Blood (plasma) samples for determination of PK levels of SQP33 protodrug and active Dox following SQ3370 treatment to be collected from all patients
  - PK bioanalysis will be conducted using a validated LC/MS method. Blood SQP33 protodrug and active Dox, following SQ3370 treatment, parameters will be calculated (if possible) from plasma SQP33 protodrug concentration, including C_{max} , T_{max} , AUC_t , AUC_{inf} , and CL/F.
- AEs and SAEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.
- Tumor biopsies and PBMCs will be collected to assess immune response and the concentration of active Dox and SQP33 at the local site following SQ3370 treatment.

Key Inclusion Criteria

- ≥ 18 years old
- local or advanced/metastatic solid tumor that is
  - responsive to anthracyclines
  - either refractory/relapsed or is ineligible for standard of care therapy
  - injectable defined as able to be injected with ultrasound guidance or palpable
  - not near vital structures or within a visceral organ
  - accessible for repeated intratumoral or peritumoral injection
- ECOG status score of 0-1
- Adequate
  - **Hematologic Function**:
    - ANC ≥ 1500 µL
    - Hemoglobin ≥ 9 g/dL
    - Platelet Count ≥ 100,000/µL
  - **Hepatic Function**:
    - Bilirubin ≤ 1.2 mg/dL
    - AST and ALT ≤ 3-times ULN
  - **Renal Function**:
    - Creatine Clearance ≥ 45 mL/min (Cockcroft-Gault)
  - **Coagulation Function**:
    - INR ≤ 1.5
    - PTT ≤ 5 seconds above ULN
- Resolution to Grade ≤ 1 of clinically significant toxicity of prior anti-cancer treatments

Key Exclusion Criteria

- Lifetime exposure to
  - >225 mg/m^2 Dox HCl, Doxil/Caelyx
  - 450 mg/m^2 of Epirubicin
  - 135 mg/m^2 of Daunorubicin
- Anticoagulants at therapeutic doses/known to cause abnormal coagulation/increase bleeding (incl. low dose ASA prophylaxis, oral Xa inhibitors, LMWH)
- CHF, severe myocardial insufficiency, cardiac arrythmia, or:
  - LVEF < 45%, QTc > 470 msec, history of QT prolongation, history/signs of active CAD, clinically significant cardiac arrhythmias, LBBB, high grade AV block
- Recent:
  - Chemotherapy, radiotherapy, other investigational product administration
  - Major surgery
  - Transfusion
  - Serious or systemic infection
- Positive HBsAb, and either positive HBsAg and/or detectable HBV DNA
- Resolved or treated hepatitis C virus
- Immunodeficiency
- Symptomatic pleural effusion, ascites, or pericardial fluid requiring drainage
- CNS metastases and/or carcinomatous meningitis or symptomatic brain mets
- Treated malignancies (exc. Palliative radiation) within 2 years (excl. resected NMSC, cervical CIS, and non-metastatic breast or prostate cancer)
- History of allergic reactions to the Investigational Product

Statistical Methods

- **Sample Size:**
  Sample size for the dose-escalation portion of the study is not predefined. Total enrollment will depend on the DLTs observed and number of escalation cohorts. Patients will be replaced if they are enrolled into the study but do not receive (for reasons other than AEs/SAEs) a minimum of 4 doses of SQP33 protodrug.
- **Safety/Tolerability:**
  Electrocardiogram, vital signs, and clinical laboratory data (observed and change from baseline) will be summarized by time point and treatment using descriptive statistics. The number and percentage of patients reporting any treatment-emergent AE will be summarized by system organ class and preferred term for each treatment (coded using Medical Dictionary for Regulatory Activities). Treatment-emergent AEs will be further classified by severity and relationship to treatment.
- **Efficacy**:
  Tumor dynamics will be summarized by dose, cycle, and overall follow-up. RECIST based tumor response and ORR status will be summarized. Additionally, sub-set analyses will be performed on both injected and non-injected individual lesions.

Progress to Date

- As of October 1, 2020, the trial has begun at sites in the US and Australia, and 2 patients have been enrolled.

Summary

- Shasqi's CAPAC based lead candidate, SQ3370, is the first therapeutic in the clinic to utilize click chemistry – an innovative mechanism that is agnostic to tumor characteristics.
- CAPAC provides a new tool for oncologists by activating chemotherapeutics at the site of the tumor and minimizing systemic toxicity.
- SQ3370 is supported by broad *in vivo* anti-tumor activity, has a positive therapeutic window in preclinical model systems, and may achieve systemic immune-mediated anti-tumor responses.

Additional info

- For more information please visit https://www.shasqi.com/.
- Visit Our SITC Preclinical Poster (Abstract ID: 82) For Our Latest Findings.
- Presented at the Society for Immunotherapy of Cancer Virtual Annual Meeting, November 9–14, 2020.