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Phase 1 Clinical Results of SQ3370, a Doxorubicin-based Click Chemistry Therapeutic in Advanced Solid Tumor Patients

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Introduction

- Shasqi's aim is to safely activate highly effective treatments at tumors using our **C**lick **A**ctivated **P**rotodrugs **A**gainst **C**ancer (**CAPAC®**) platform (**Fig. 1**).
- CAPAC has two separate components: tumor targeted activators and protodrugs. This separation allows for optimization of the therapeutic index throughout development, including in the clinic.

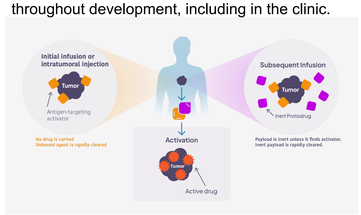


Figure 1. Local tumor targeting using CAPAC. An inert, systemically administered protodrug is activated at the tumor by the targeting agent using click chemistry.

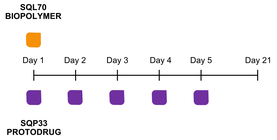
- SQ3370 combines the targeting agent SQL70, a tetrazine-modified sodium hyaluronate biopolymer with SQP33, a *trans*-cyclooctene-modified protodrug of doxorubicin (Dox).
- Here, we report the final safety, PK and immune results from the P1 study of SQ3370.

Study Design

- Phase 1, first-in-human, single-arm, open-label, dose-escalation study of SQ3370 in patients with locally advanced or metastatic solid tumors that are refractory/relapsed following, or otherwise ineligible for, standard of care therapy.
- The study has an accelerated titration design comprising initial single-patient cohorts and subsequent Rolling 6.
- **Study Objectives:** Safety, tolerability of SQ3370, and determination of the maximum tolerated dose (MTD), if possible, the recommended Phase 2 dose (RP2D).

21-day Treatment Cycle:

- 10 mL or 20 mL of SQL70 biopolymer is injected on Day 1
- SQP33 protodrug is infused after SQL70 biopolymer injection on Day 1 through Day 5 (5 doses)



Results

Table 1: Demographics and patient characteristics for those who received at least one dose of SQ3370

	10 mL SQL70 N = 30[a]	20 mL SQL70 N = 8
Median age in years (range)	62 (26-92)	58 (23-84)
Female, n (%)	17 (56.7)	4 (50.0)
White, n (%)	26 (86.7)	7 (87.5)
ECOG[b] 1, n (%)	17 (56.7)	8 (100.0)
Prior surgery, n (%)	26 (86.7)	8 (100.0)
Prior radiotherapy, n (%)	14 (46.7)	5 (62.5)
Received prior systemic anti-cancer therapy, n (%)	28 (93.3)	7 (87.5)
Median number of prior systemic anti-cancer therapy (range)	2 (0-7)	2 (0-7)
Received prior Doxorubicin, n (%)	14 (46.7)	7 (87.5)
Response from previous therapy (CR or PR), n (%)	1 (3.3)	0 (0.0)
Diagnosis of sarcoma[c], n (%)	20 (66.7)	6 (75.0)
Metastases at study entry, n (%)	25 (83.3)	5 (62.5)
Median number of metastatic sites (range)	2 (1-5)	3 (1-3)

[a]N=38 were enrolled and evaluable for safety; N=37 evaluable for DLT (1pt excluded who developed COVID-19 Day 2/Cycle 1), 28 evaluable for efficacy.
[b]ECOG 0 and 1 pts were eligible
[c]Other solid tumors included: breast cancer (N=2); gynecologic cancers (N=2); myoepithelioma (N=1), Merkel cell (N=1), and squamous cell of the supraclavicular fossa (N=1).
(Data Cut: 2022-12-15; safety population)

Results Continued

SQ3370; Activation of SQP33 at the Tumor by SQL70 Results in Intratumoral Release of Dox and Systemic Dox PK

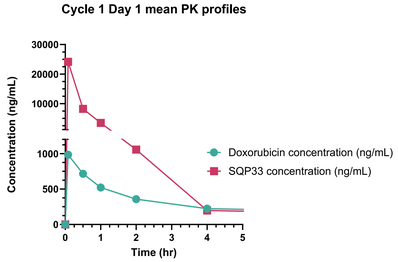


Figure 2: C_{max} of SQP33 and Dox Cycle 1 Day 1 at 12x, the RP2D. Within 3 hours of SQL70 biopolymer injection, patients were infused with SQP33. Plasma samples were collected pre-infusion and 5-, 30-, 60-, 120-, and 240-min post-infusion. Validated LC-MS/MS methods were used to quantify levels of SQP33 and Dox in the plasma.

Impact of Prior Immunotherapy Status on T-cell Activity and Tumor Cell Apoptosis

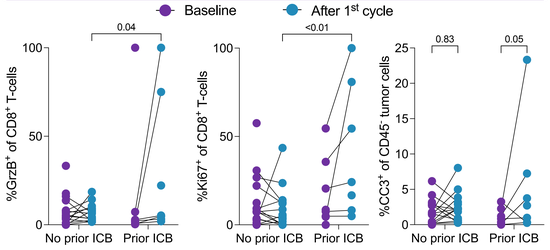


Figure 3. Increased cytotoxic T-cell activity in patient tumors with prior immune checkpoint blockade (ICB). Relative cytotoxic activity (GrzB) and proliferation (Ki67) in $CD8^+$ T-cells, and cleaved caspase 3 (CC3)-mediated tumor cell apoptosis increased after 1 cycle of SQ3370 (4x to 15x Dox molar equiv) in prior ICB vs ICB naïve patients. *P*-values: Two-Way ANOVA with *post-hoc* Šídák's test.

C_{max} of SQP33 vs Dox Dose and SQL70 Injections Cycle 1 Days 1-5

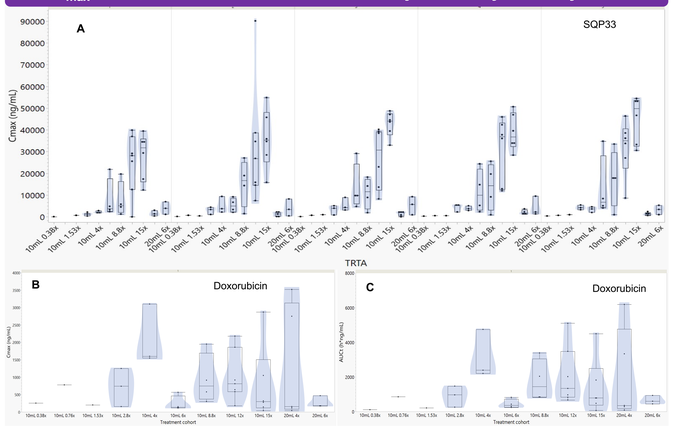


Figure 4: C_{max} of SQP33 (A) and Dox (B) Days 1-5 of Cycle 1, and AUC_t of doxorubicin for Cycle 1, Day 1 (C). Box and Violin plots comparison of PK parameter for SQP33 and Dox. The horizontal solid line in the box represents the arithmetic mean value. The dashed line represents median values. The box represents the 1st and 3rd quartile (25th and 75th percentile), the whisker bars represent fences of 1.5x IQR (interquartile range) or min/max range if smaller than 1.5x IQR, and markers represent outlier points (outside fences). Shaded areas show the distribution of data density.

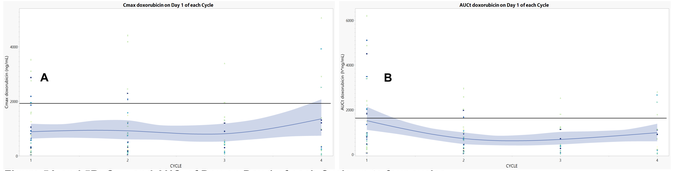


Figure 5A and 5B: C_{max} and AUC_t of Dox on Day 1 of each Cycle up to four cycles. C_{max} and AUC on Day 1 for each cohort were plotted against cycles. The smooth spline is represented by a horizontal line, intersecting at the mean. Confidence intervals are shown as shaded areas. Solid black line represents the average reported Dox C_{max} and AUC_t following a single infusion at 75 mg/m² in sarcoma patients.[2]

Safety

Dox Equiv. Dose*
10 mL SQL70 biopolymer

	< 1x (N=2)		1.53x (N=1)		2.8x (N=3)		4x (N=3)		6x (N=4)		8.8x (N=4)		12x (N=7)		15x (N=6)		Total (N=30)	
Preferred Term	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)
Nausea	1 (100)	0	1 (100)	0	2 (66.7)	1 (33.3)	2 (66.7)	0	3 (75.0)	0	1 (25.0)	0	4 (57.1)	0	3 (50.0)	0	17 (56.7)	1 (3.3)
Fatigue	1 (100)	0	1 (100)	0	3 (100)	0	1 (33.3)	0	1 (25.0)	0	1 (25.0)	0	3 (42.9)	1 (14.3)	4 (66.7)	0	15 (50.0)	1 (3.3)
Constipation	1 (100)	0	1 (100)	0	1 (33.3)	0	0	0	1 (25.0)	0	1 (25.0)	0	2 (28.6)	0	2 (33.3)	0	9 (30.0)	0

Dox Equiv. Dose*
Hematological Toxicity: 10 mL SQL70 biopolymer

	< 1x (N=2)		1.53x (N=1)		2.8x (N=3)		4x (N=3)		6x (N=4)		8.8x (N=4)		12x (N=7)		15x (N=6)		Total (N=30)	
Preferred Term	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)	All n (%)	Gr≥3 n (%)
Anaemia	0	0	0	0	1 (33.3)	0	1 (33.3)	1 (33.3)	1 (25.0)	1 (25.0)	2 (50.0)	1 (25.0)	1 (14.3)	1 (14.3)	1 (16.7)	1 (16.7)	7 (23.3)	5 (16.7)
Neutropenia	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (25.0)	1 (25.0)	2 (28.6)	2 (28.6)	2 (33.3)	0	4 (13.3)	3 (10.0)
Thrombo-cytopenia	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (25.0)	1 (25.0)	2 (28.6)	1 (14.3)	0	0	4 (13.3)	2 (6.7)

Dox Equiv. Dose*
20 mL SQL70 biopolymer

	4x (N=5)		6x (N=3)		Total (N=8)	
Preferred Term	All n (%)	Gr ≥3 n (%)	All n (%)	Gr ≥3 n (%)	All n (%)	Gr ≥3 n (%)
Decreased appetite	2 (40.0)	0	2 (66.7)	0	4 (50.0)	0
Diarrhoea	2 (40.0)	0	0	0	2 (40.0)	0
Nausea	2 (40.0)	0	2 (66.7)	0	4 (50.0)	0

Dox Equiv. Dose*
Hematological Toxicity: 20 mL SQL70 biopolymer

	4x (N=5)		6x (N=3)		Total (N=8)	
Preferred Term	All n (%)	Gr ≥3 n (%)	All n (%)	Gr ≥3 n (%)	All n (%)	Gr ≥3 n (%)
Anaemia	4 (80.0)	3 (60.0)	0	0	4 (50.0)	3 (37.5)
Neutropenia	2 (40.0)	2 (40.0)	0	0	2 (25.0)	2 (25.0)

Table 2. Treatment emergent adverse events (TEAE) reported in ≥ 25% patients regardless of causality.
Safety population: Patients with a least one dose of SQ3370. The most frequent Grade ≥3 TEAE for 10 mL or 20 mL biopolymer subgroups was anemia. No dose-limiting toxicities (DLTs) have been observed and no TEAEs that led to death were considered related to SQ3370 by the Investigator. *Where 1x = 75 mg/m² of Dox.

Summary

- Biopolymer activator converts inert protodug (SQP33) into active Dox at the tumor via a click chemistry reaction.
- PK data suggests:
  - There is rapid release of Dox at all dose levels with increasing exposure, demonstrating selective activation
  - PK profiles are reproducible and consistent across cycles
  - C_{max} of Dox occurs shortly after the start of the SQP33 infusion; overall there is a reduced C_{max} compared with conventional Dox.
  - A nearly linear dose response is observed (up to 8.8x) plateauing at 12x, as measured by systemic Dox C_{max}.
  - Dosing above 250 mg/m² did not result in additional release of Dox
  - SQ3370 maintains a similar AUC and biphasic clearance of Dox compared to conventional Dox
- SQ3370 administration did not result in many of the toxicities that might be expected with conventional Dox:
  - MTD was not reached in patients receiving up to 15x (1127 mg/m²) per cycle compared to standard Dox dose (75 mg/m²). 12x (894 mg/m²) per cycle was selected as the RP2D.
  - Myelosuppression and GI toxicities were not dose limiting; no febrile neutropenia cases were reported, and only 14% required G-CSF
  - The altered safety profile of Dox is likely a result of a reduced C_{max}
- SQ3370 has unique immunomodulatory activity; it increased cytotoxic T-cell activity in tumors and induced an increasing trend of tumor cell apoptosis in patients with prior immune checkpoint blockade therapy. More details in our previous presentation at AACR 2023, details can be obtained by scanning the QR code to the right.

Conclusions

- In this study, we have demonstrated our ability to activate an inert Dox protodrug at the tumor using an intratumorally injected activator, providing clinical validation of CAPAC.
- CAPAC can enhance exposure while minimizing systemic toxicity.
- Separation of payload and tumor targeted activator allows you to continually optimize activity and limit toxicity, including in the clinic.

Additional Information

- We would like to thank all patients and their families for participating in our clinical trial, clinicalTrials.gov identifier: NCT04106492
- **References:** 1. Srinivasan et al., 2023 https://www.biorxiv.org/content/10.1101/2023.03.28.534654v1; 2. Cancer Medicine 2020;9:882-893
- Data source: SQ3370-001, as of 2022-12-15

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