A Phase 1/2 Study of KSQ-001EX: An autologous Tumor Infiltrating Lymphocyte Therapy engineered to inactivate the *SOCS1* gene, in Patients with Select Advanced Solid Tumors

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SOCS1 identified as top target in enhancing T cell anti-tumor immunity in CRISPR/Cas9 screens

While clinical responses of unmodified TIL therapies have been observed in metastatic melanoma, the effectiveness and durability of TIL therapy may be limited by the immunosuppressive tumor microenvironment and the baseline functionality of transferred T cells (Dafni 2019). In a series of *in vivo* genome-wide CRISPR/Cas9 screens conducted in syngeneic mouse tumor models, SOCS1, a negative regulator of cytokine signaling and T cell function, was identified as a top target for enhancing T cell anti-tumor immunity (Schlabach 2023). SOCS1 inactivation was found to enhance tumor infiltration and anti-tumor functionality of TIL, including enhanced cytotoxicity and IFNγ production. Based on these findings, KSQ-001EX, an engineered autologous TIL therapy with CRISPR/Cas9 mediated inactivation of SOCS1, was developed.

KSQ-001EX shows enhanced cytotoxicity and IFNγ production in comparison to No EP control, consistent with the biology of SOCS1 editing

A. Genome-Wide In Vivo CRISPR Screens Identified SOCS1 as One of the Top Targets in Enhancing T Cell Activity

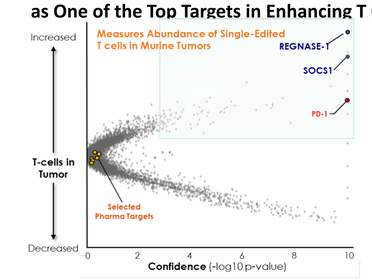


Figure A: Library containing OT1 T cells were infused into B16-OVA tumor bearing animals; after takedown and tissue processing, abundance of gRNA for each target was assessed by NGS.

B. Enhanced In Vivo Efficacy of SOCS1 Edited OT1 T cells

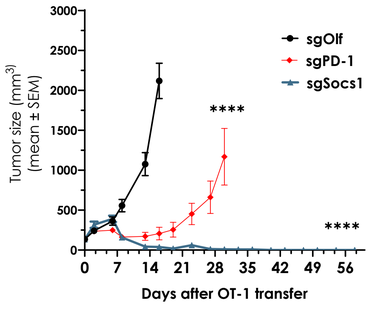


Figure B: B16-OVA tumor bearing animals were dosed with olfactory receptor (biologically irrelevant target) edited, PD1 edited, and SOCS1 edited OT1 T cells, with changes in tumor volume monitored following cell infusion.

C. Enhanced MHC Class I Dependent Production of IFNγ Against Autologous Tumor (AT)

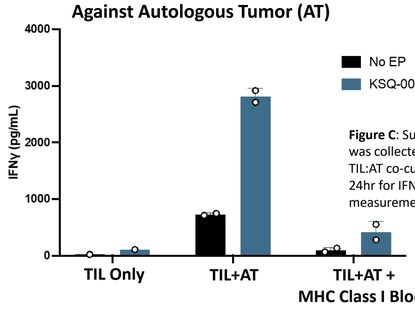


Figure C: Supernatant was collected from TIL:AT co-cultures at 24hr for IFNγ measurement.

KSQ-001EX FIH STUDY DESIGN

Phase 1: Dose Confirmation

Safety Lead-in Cohort 1 (n=6)
KSQ-001EX
Standard LDC
No IL-2
Melanoma/NSCLC/HNSCC

→

Safety Lead-in Cohort 2 (n=6)
KSQ-001EX
Standard LDC
High-dose IL2 (up to 6 doses)^
Melanoma/NSCLC/HNSCC

^IL-2 dose: 600,000 IU/kg q 8-12 hrs

Evaluate data to determine ED →

Phase 2: Expansion

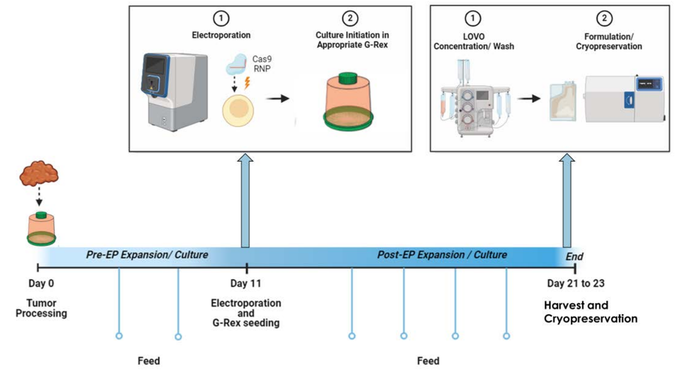
Arm A: Melanoma
KSQ-001EX @ ED
(n=20)

Arm B: HNSCC
KSQ-001EX @ ED
(n=20)

Arm C: NSCLC
KSQ-001EX @ ED
(n=20)

ED: expansion dose; HNSCC: head and neck squamous cell carcinoma; LDC: Lymphodepleting chemotherapy; MDACC: MD Anderson Cancer Center; NSCLC: Non-small cell lung cancer

KSQ-001EX Manufacturing

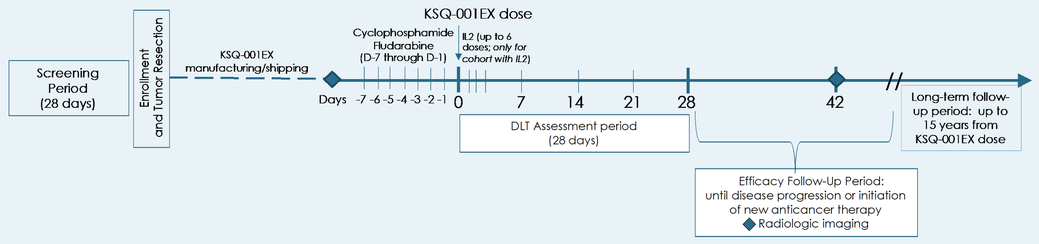


KSQ-001EX manufacturing process consists of:

- TIL activation and extravasation from tumor for 11 days
- CRISPR engineering by electroporation (EP)
- Post-EP expansion of 10 to 12 days.
- TIL expansion throughout the process is supported by IL-2.

CTMC+

Treatment Schema



Key Inclusion Criteria

- Diagnosed with one of the following tumor types:
  - Unresectable, incurable and/or metastatic histologically and/or cytologically confirmed melanoma (Stage IIIC/IIID or Stage IV) that has progressed following at least 1 line of prior systemic therapy including treatment with anti-PD-1/PD-L1 inhibitor alone or in combination with anti-CTLA-4 inhibitor or anti-LAG-3 antibody.
  - Histologically and/or cytologically confirmed primary diagnosis of NSCLC which has progressed on standard therapy which includes treatment with platinum-based chemotherapy and checkpoint inhibitor therapy (either given in combination or sequentially)
    - Participants with tumors that have known actionable molecular alteration such as EGFR, ALK, ROS-1, BRAF, RET, MET and KRAS must have progressed on standard directed molecular therapy in addition to platinum-based chemotherapy
  - Locally advanced, recurrent and/or metastatic histologically and/or cytologically confirmed HNSCC that has been previously treated with at least 1 and no more than 3 lines of prior therapy
    - Participants must have received a platinum-containing chemotherapy regimen for the treatment of primary tumor in locally advanced, or metastatic setting
    - Participants must have received an anti-PD-1/PD-L1 as monotherapy or in combination with chemotherapy
- Resectable lesion(s) for KSQ-001EX manufacturing (tumor ≥ 1.5cm^2 or at least 5 core biopsies)
- At least 1 measurable lesion per RECIST v1.1 (Eisenhauer 2009) following tumor resection for KSQ-001EX manufacturing
- Age: ≥18 - 70 years old; Life expectancy ≥ 12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

Key Exclusion Criteria

- Prior organ allograft or prior cell therapy that included LDC or myeloablative chemotherapy regimen
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, Grade ≥2 colitis or Crohn's disease], systemic lupus erythematosus, sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis], rheumatoid arthritis, etc.]) with some exceptions
- Hypersensitivity to antibiotics of the aminoglycoside group (eg, streptomycin, gentamicin) or penicillin
- Uveal and/or ocular melanoma
- Large cell neuroendocrine NSCLC (defined as pathology with > 10% neuroendocrine components)
- Symptomatic and/or untreated brain metastases (of any size or number) including active leptomeningeal or parenchymal metastases. Note: Participants with definitively treated brain metastases may be considered for enrollment if stable (defined as stable for 1-month post-central nervous system directed therapy) and does not require ongoing steroid treatment

Objectives

Phase 1 Primary Objective
- To evaluate the safety and tolerability of KSQ-001EX in adult participants with advanced solid tumors (melanoma, HNSCC, NSCLC)

Phase I Secondary Objectives
- Determine expansion dose
- Assess the safety and tolerability of KSQ-001EX in participants with advanced solid tumors (melanoma, HNSCC, NSCLC)
- Evaluate preliminary antitumor activity of KSQ-001EX in participants with advanced solid tumors
- Evaluate the feasibility of the manufacturing process.

Phase 2 Primary Objectives
- To assess the anti-tumor activity of KSQ-001EX in patients with advanced malignant solid tumors

Phase 2 Secondary Objectives
- Assess the safety and tolerability of KSQ-001EX in patients with advanced solid tumors (melanoma, HNSCC, NSCLC)
- Evaluate anti-tumor activity of KSQ-001EX in patients with advanced malignant solid tumors
- Evaluate overall survival (OS)
- Evaluate the feasibility of the manufacturing process

Endpoints

Phase I Primary Endpoint
- Incidence of dose-limiting toxicities (DLTs)

Phase I Secondary Endpoints
- Incidence and severity of treatment-emergent adverse events (TEAEs) and change from Baseline in laboratory results
- Objective response rate (ORR), duration of response (DOR), time to response (TTR) as assessed by the Investigator, per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Manufacturing success rate

Phase 2 Primary Endpoint
- ORR per RECIST v1.1

Phase 2 Secondary Endpoints
- Incidence and severity of TEAEs and change from Baseline in laboratory results
- Complete response rate (CRR), DOR, TTR, progression-free survival (PFS) per RECIST v1.1
- OS
- Manufacturing success rate

Comprehensive Biomarker Plan

Expansion/Persistence	Infiltration	Safety Monitoring	Correlative Analysis
- On-target editing and TCRseq of the blood - Cellularity Panels - Immune cell population characterization	- On-target editing and TCRseq of the tumor - Tumor micro-environment	- Off-target editing - T-cell clonal growth - Cytokine and inflammatory markers	- Tumor characteristics - Drug product attributes -MoA/Response

FIH study provides opportunity to evaluate KSQ-001EX dosed with and without IL-2 in 3 indications

First-in-human clinical study (NCT 06237881) evaluating KSQ-001EX in patients with metastatic melanoma, non-small cell lung cancer (NSCLC), and head and neck squamous cell carcinoma (HNSCC).

Phase 1: Approximately 6 patients with melanoma, NSCLC or HNSCC dosed with LDC and KSQ-001EX in Safety Lead-in Cohort 1 with no IL-2 administration followed by Safety Lead-in Cohort 2 where patients will also be dosed with IL-2.
In phase 2, patients with melanoma, HNSCC, and NSCLC will be enrolled in indication-specific cohorts.

This is currently a single-institution study that is actively enrolling/recruiting patients.