Poster #569

A Phase 1/2 Study of KSQ-004EX: Autologous Tumor Infiltrating Lymphocytes, Engineered to Inactivate Genes Encoding SOCS1 and Regnase-1, in Patients with Select Advanced Solid Tumors

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FIH Study Provides Opportunity to Evaluate KSQ-004EX in 6 Solid Tumor Indications

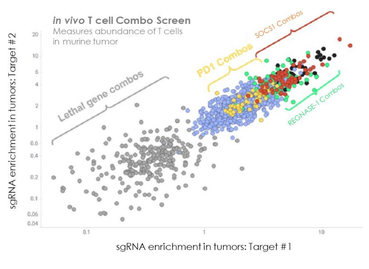
First-in-human clinical study (NCT06598371) evaluating KSQ-004EX in patients with metastatic melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and cervical cancer.

Phase 1: Approximately 6-12 patients with melanoma, NSCLC, HNSCC, CRC, PDAC, or cervical cancer will be dosed with LDC and KSQ-004EX in escalating dose levels. IL-2 may be added to previously tested dose levels in phase 1. In phase 2, patients with melanoma, NSCLC, HNSCC, CRC, PDAC, and cervical cancer will be enrolled in indication-specific cohorts.

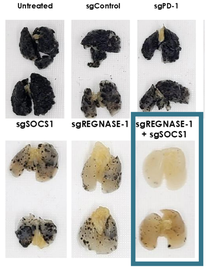
This is currently a single-institution study that is actively enrolling/recruiting patients.

SOCS1 and Regnase-1 Identified as Top Combination Enhancing Efficacy of TIL

A: In vivo combination CRISPR screen in OT1 CD8⁺ T cells identifies SOCS1 and Regnase-1 as the top dual-edit



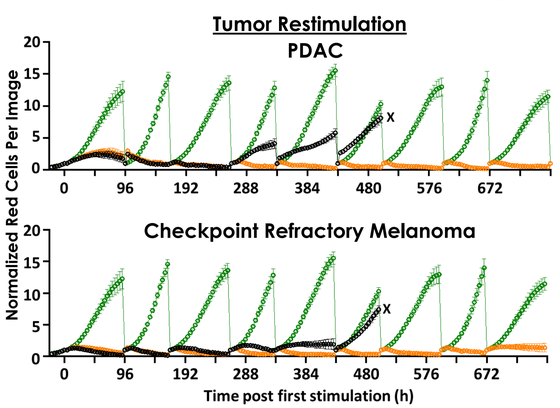
B: Dual-inactivation of SOCS1 and Regnase-1 in PMEL CD8⁺ T cell Control B16F10 Tumors in Lungs



A: CRISPR screens were performed in the B16-OVA model with OT1 T cells;
B: Target validation studies were performed in the disseminated B16F10 model with adoptively transferred gene-edited PMEL T cells.

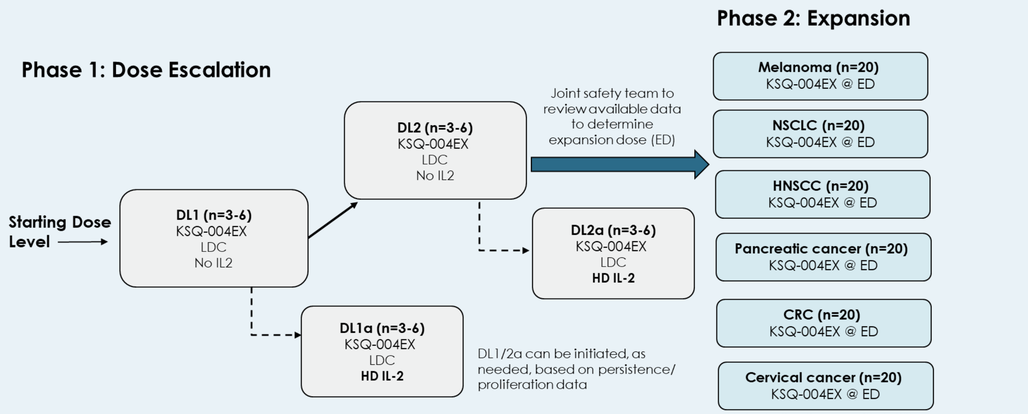
Enhanced KSQ-004EX Functionality Against A375-OKT3 cells in Serial Re-Stim Setting

KSQ-004EX Clears Tumor in a Chronic Re-Stimulation Assay Against A375-OKT3 cells



Cytotoxicity assessed by Incucyte across 8 rounds of re-stimulation. No EP cells are unedited control TIL. Two representative donors are shown. Data shows Mean ± SD (n=10 replicates per condition). X indicates that No EP samples were removed due to lack of tumor control.

KSQ-004EX FIH Study Design



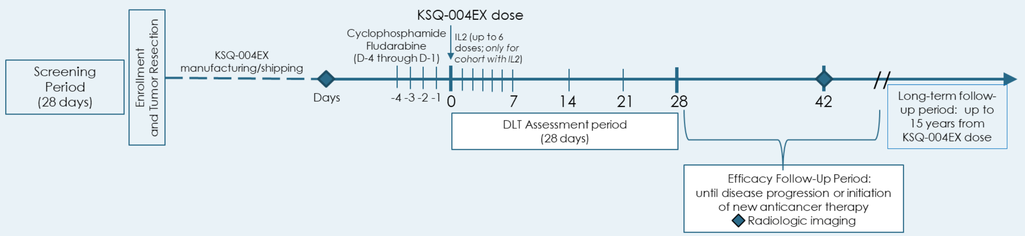
LDC regimen consisting of Cyclophosphamide 750 mg/m^2 administered on Days -4, -3, and -2. Fludarabine 30 mg/m^2 administered on Days -4, -3, -2, and -1

Note: Indication-specific futility assessment (FA) after 10 pts/indication in Expansion

A modified LDC regimen consisting of Cyclophosphamide 750 mg/m^2 administered on Days -3 and -2 and Fludarabine administered at 30 mg/m^2 on Days -3, -2, and -1 may be added to DL1 or DL2

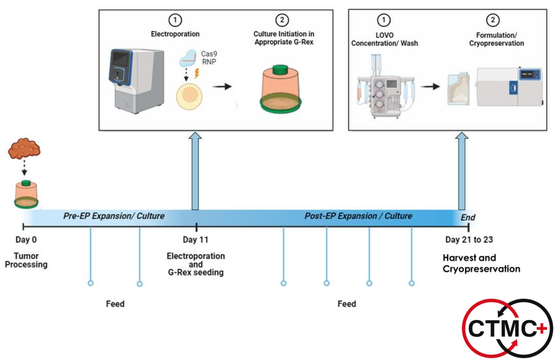
CRC: colorectal cancer; ED: expansion dose; HNSCC: head and neck squamous cell carcinoma; MDACC: MD Anderson Cancer Center; NSCLC: Non-small cell lung cancer

Treatment Schema

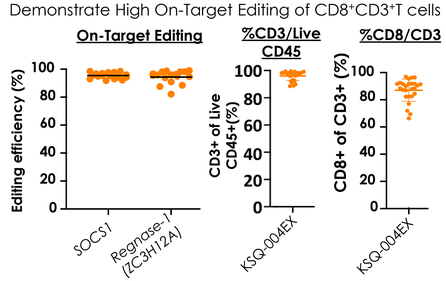


KSQ-004EX Manufacturing Using KSQ's Proprietary ExPRESS Process

A: ExPRESS, a ~22-day streamlined process for KSQ-004EX Manufacture

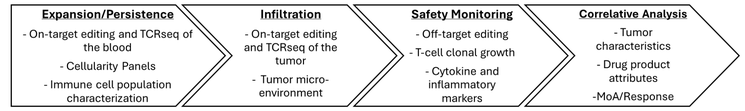


B: Pre-clinical lots of KSQ-004EX Generated from ExPRESS Demonstrate High On-Target Editing of CD8⁺CD3⁺T cells



KSQ-004EX preclinical lots (n=26) generated from melanoma (n=8), HNSCC (n=3), NSCLC (n=10), ovarian carcinoma (n=2), breast carcinoma (n=1), CRC (n=1), and PDAC (n=1). On-target editing was assessed for each target. Cellularity was evaluated using flow cytometry. *ZC3H12A* is the gene symbol for Regnase-1.

Comprehensive Biomarker Plan



Key Inclusion Criteria

- Diagnosed with one of the following tumor types:
  - Unresectable, incurable and/or metastatic histologically and/or cytologically confirmed cutaneous, acral, or unknown primary melanoma (Stage IIIC or Stage IV) that has progressed following at least 1 and no more than 3 lines of prior therapy in the advanced/metastatic setting, one of which includes treatment with anti-PD-1/PD-L1 inhibitor alone or in combination with anti-CTLA-4 inhibitor or in combination with anti-LAG-3 antibody
  - Histologically and/or cytologically confirmed primary diagnosis of NSCLC which has progressed on at least 1 line and no more than 4 lines of prior therapy in the advanced/metastatic setting, including platinum-based chemotherapy and checkpoint inhibitor therapy (either given in combination or sequentially)
    - Patients 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 4 lines of prior therapy in the advanced/metastatic setting
    - Patients must have received a platinum-containing chemotherapy regimen for the treatment of primary tumor in locally advanced, or metastatic setting
  - Advanced, metastatic histologically and/or cytologically confirmed colorectal adenocarcinoma that has progressed following at least 1 and no more than 3 lines of prior therapy
    - Patients with dMMR/MSI-H or KRASG12C BRAF V600E mutation must have progressed on standard directed therapy
  - Locally advanced, recurrent, or metastatic histologically and/or cytologically confirmed PDAC that has progressed following at least 1 and no more than 3 lines of prior therapy in the advanced/metastatic setting
  - Recurrent, metastatic, or persistent histologically and/or cytologically confirmed squamous cell carcinoma (SCC), adenosquamous carcinoma, or adenocarcinoma of the cervix that is not amenable to curative treatment with surgery and/or radiation therapy that has progressed following at least 1 and no more than 3 lines of prior therapy in the advanced/metastatic setting
- Resectable lesion for KSQ-004EX manufacturing (tumor ≥ 1.5 cm^2 or at least 5 core needle biopsies)
- At least 1 measurable lesion per RECIST v1.1 (Eisenhauer 2009) following tumor resection for KSQ-004EX manufacturing
- Age: ≥18 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
- Mucosal, 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
- Evaluate safety and tolerability of KSQ-004EX in adult patients with advanced solid tumors (melanoma, NSCLC, HNSCC, CRC, PDAC, and cervical cancer)

Phase 1 Secondary Objectives
- Determine expansion dose
- Assess safety and tolerability of KSQ-004EX in patients with advanced solid tumors (melanoma, NSCLC, HNSCC, CRC, PDAC, and cervical cancer)
- Evaluate preliminary antitumor activity of KSQ-004EX in patients with advanced solid tumors
- Evaluate feasibility of the manufacturing process

Phase 2 Primary Objectives
- Assess anti-tumor activity of KSQ-004EX in patients with advanced malignant solid tumors

Phase 2 Secondary Objectives
- Assess safety and tolerability of KSQ-004EX in patients with advanced solid tumors (melanoma, NSCLC, HNSCC, CRC, PDAC, and cervical cancer)
- Evaluate anti-tumor activity of KSQ-004EX in patients with advanced malignant solid tumors
- Evaluate overall survival (OS)
- Evaluate feasibility of the manufacturing process