Master protocol to assess the safety and recommended Phase 2 dose of next generation NY-ESO-1–specific TCR T-cells in HLA-A*02 patients with synovial sarcoma and non-small cell lung cancer

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*At time of study design

Background

Therapeutic areas

- Soft tissue sarcomas (STS) are rare, accounting for <1% of all cancers.[1,2]
  - Synovial sarcoma (SS) is a rare form of STS[2], accounting for 5–10% of all STS subtypes.[2]
    - Patients with metastatic SS have a median survival of 16.2 months and an estimated 1-year mortality rate of 41%.[1,3]
    - The 5-year survival in the overall SS population between 2003–2012 was reported at 60.5%.[4]
    - The 5-year survival rate for patients who present with metastatic disease is 10%.[5]
- Lung cancer is one of the most common forms of cancers worldwide, with non-small cell lung cancer (NSCLC) accounting for up to 84% of lung cancer cases.[6]
  - A high proportion of patients have advanced stage disease at diagnosis.[7]
  - In a non-selected population with NSCLC, the 5-year survival rate for patients with metastatic disease was 5%.[8]
  - Five-year survival rates of 29.6% and 25.0% have been reported in treatment-naïve and previously treated patients, respectively, who had metastatic NSCLC and high programmed death-ligand 1 (PD-L1) expression and were treated with pembrolizumab monotherapy.[9]
  - Thus, there remains a need for novel therapies for patients with recurrent/metastatic NSCLC who have failed standard-of-care therapies.[10,11]

NY-ESO-1 TCR T-cell therapy

- The cancer/testis antigen family members NY-ESO-1 and LAGE-1a are intracellular proteins selectively expressed in cancer cells, including sarcomas and NSCLC.[12,13]
  - 20–30% of lung tumors express NY-ESO-1 and ~15% express LAGE-1a.[12,13]
  - Up to 80% of SS tumors express NY-ESO-1.[12]
- Letetresgene autoleucel (lete-cel; GSK3377794) is an autologous T-cell therapy that uses CD4+ and CD8+ T cells that have been genetically modified to express a T-cell receptor (TCR) recognizing an epitope of NY-ESO-1 and/or LAGE-1a bound to HLA-A*02 (more specifically HLA-A*02:01, A*02:05, or A*02:06).
  - Lete-cel has shown promising clinical activity in patients with SS[14] and is currently being investigated in patients with myxoid/round cell liposarcoma (MRCLS) (NCT02992743)[15], NSCLC (NCT03709706)[16], and SS or MRCLS (NCT03967223).[17]

Next generation NY-ESO-1–specific TCR T-cell therapies

- Next-generation NY-ESO-1–specific TCR T-cell therapies have been designed to enhance anticancer activity of NY-ESO-1 TCR T cells by incorporating additional genetic modifications.
  - **GSK3901961** incorporates the co-expression of the CD8α chain with the NY-ESO-1 TCR to induce stabilization of TCR-HLA class I interaction on CD4+ T cells. Preclinical evidence suggests this may:

enhance proliferation and persistence of TCR T cells

increase helper functions including CD4+ T-cell expression of Th1 cytokines and chemokines

enhance activity of tumor-specific effector cells

  - **GSK3845097** co-expresses a dominant negative transforming growth factor-β (TGF-β) type II receptor that may enhance efficacy by:

reducing TGF-β pathway activation

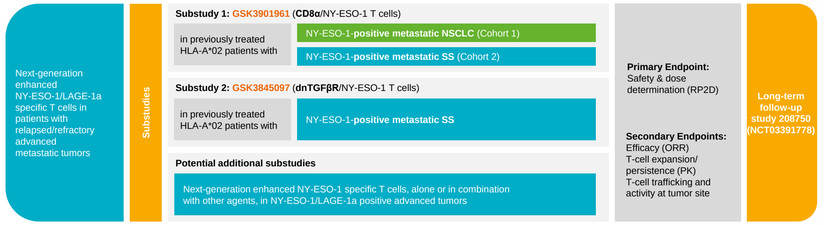
maintaining T-cell proliferation

maintaining cytokine production

maintaining cytotoxicity within the tumor microenvironment

- A Phase 1 first-in-human master protocol (NCT04526509) has been designed to enable independent substudies to investigate the activity of these and potentially other novel NY-ESO-1 TCR T-cell therapies, possibly in combination with other agents, in multiple tumor types (**Figure 1**).[18]

Figure 1: NCT04526509 Master Protocol Design



dnTGFβR, dominant-negative transforming growth factor-β (TGF-β) receptor II; HLA, human leukocyte antigen; LAGE-1a, L antigen family member 1 isoform A; NSCLC, non-small cell lung cancer; NY-ESO-1, New York Esophageal Squamous Cell Carcinoma-1; ORR, overall response rate; PK, pharmacokinetics; RP2D, recommended Phase 2 dose; SS, synovial sarcoma.

Study objective

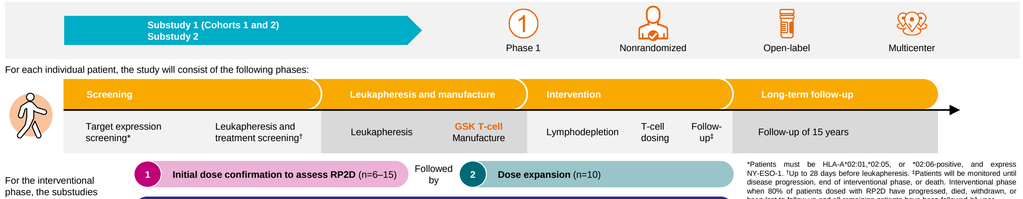
To evaluate the safety, tolerability, and recommended Phase 2 dose (RP2D) of **GSK3901961** and **GSK3845097** and potentially other agents (**Figure 1**).

- Substudy 1 will assess **GSK3901961** in patients with NY-ESO-1-positive metastatic NSCLC (Cohort 1) or SS (Cohort 2).
- Substudy 2 will assess **GSK3845097** in patients with NY-ESO-1-positive metastatic SS.

Study design

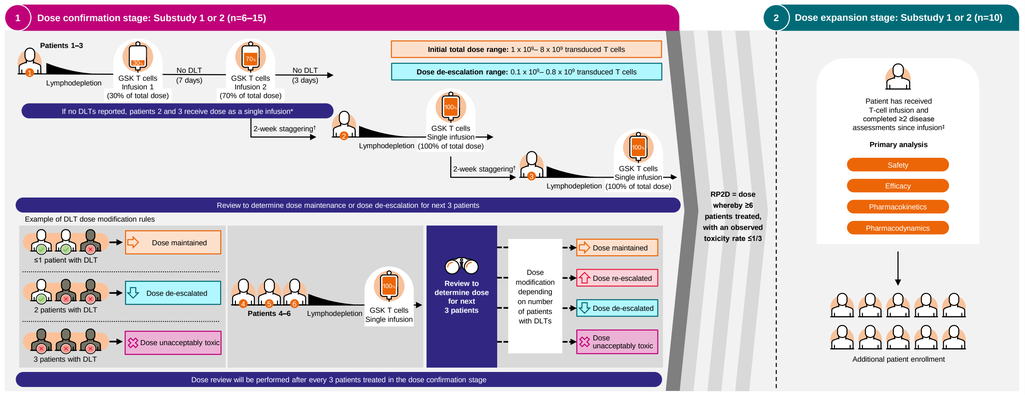
- For each patient, the study consists of screening, leukapheresis and manufacture, intervention, and long-term follow-up phases (**Figure 2**).

Figure 2: Patient Treatment Timeline



- For both substudies, the interventional phase has 2 stages: initial dose confirmation to assess RP2D followed by dose expansion (n=~48 for both dose confirmation and expansion in substudies 1 and 2 combined) (**Figure 3**).

Figure 3: Dose Confirmation and Dose Expansion Phases



*If dose limiting toxicities (DLTs) are reported for the patients receiving split doses, additional patients may be treated with a split-dose regimen at the discretion of the sponsor in consultation with the participating investigators and the dose selection committee (DSC). †At each dose level, dose administration in the first 3 patients will be staggered: initiation of the lymphodepleting regimen in the 2nd and 3rd patient will be separated by a minimum of 2 weeks from the complete dose administered to the prior patient to enable close monitoring of toxicities in each patient and DSC consultation if needed. ‡Includes patients who have died or progressed or were withdrawn from this study. DLT, dose-limiting toxicity; DSC, dose selection committee; RP2D, recommended Phase 2 dose.

Study population

	Key inclusion criteria		Key exclusion criteria	
Substudies 1 and 2 (NSCLC and SS)	• ≥18 years of age • Measurable disease per RECIST v1.1 criteria	• Expression of HLA-A*02:01, A*02:05, or A*02:06 • Expression of NY-ESO-1 in tumor archival or fresh biopsy	• Prior malignancy that is not in complete remission or clinically significant systemic illness • Previous treatment with genetically modified NY-ESO-1-specific T cells, NY-ESO-1 vaccine, or NY-ESO-1 targeting antibody	• Prior gene therapy using an integrating vector • Previous allogeneic hematopoietic stem cell transplant within the last 5 years or solid organ transplant
Substudies 1 and 2 (SS only)	• Histologically confirmed advanced (metastatic or unresectable) SS diagnosis • Presence of t(X;18) translocation	• Received, completed, or intolerant to treatment with anthracycline or anthracycline with ifosfamide for advanced (metastatic or unresectable) disease and has progressed	• Central nervous system metastases (Allowable for NSCLC participants on a case-by-case basis)	
Substudy 1 (NSCLC only)	• Histologically or cytologically confirmed Stage IV NSCLC	• Receiving or previously received ≥1 prior line(s) of standard-of-care treatment including programmed death receptor-1/programmed death ligand-1 checkpoint blockade therapy, and received or be intolerant to platinum-containing chemotherapy	• Received or failed ≥3 lines of systemic therapy	

HLA, human leukocyte antigen; NSCLC, non-small cell lung cancer; NY-ESO-1, New York Esophageal Squamous Cell Carcinoma-1; RECIST, response evaluation criteria in solid tumors; SS, synovial sarcoma.

Study endpoints

Primary endpoints

- Safety (adverse events)
  - AEs
  - SAEs
  - AESIs
- Tolerability (dose-limiting toxicities)

Secondary endpoints

- Investigator-assessed overall response rate per RECIST v1.1
- Duration of response
- Expansion/persistence over time (maximum expansion/persistence (C_{max}) , time to C_{max} and area under the time curve from zero to time *t* (AUC[0-t])
- Infiltration and phenotype of transduced T cells in tumor (RNA, DNA, and/or protein levels)

Exploratory endpoints

- Laboratory parameters
- Overall survival
- Anti-GSK3901961 and anti-GSK3845097 antibody titers for the respective substudies
- Disease control rate
- Correlation of T cell persistence with safety, clinical response, and with phenotype of infused T cells
- Mechanisms of pharmacological activity as measured by biomarkers (TCR diversity, changes in cytokine and tumor microenvironment)
- Relationship between antigen expression (NY-ESO-1) and treatment response

Current status

- The study is currently open and recruiting.

AE, adverse events; AESIs, adverse events of special interest; AUC (0-t), area under the concentration-time curve over the dosing interval; NY-ESO-1, New York Esophageal Squamous Cell Carcinoma-1; RECIST, response evaluation criteria in solid tumors; SAE, serious adverse events; TCR, T-cell receptor.

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