CD8α-enhanced NY-ESO-1-specific TCR T cells (GSK3901961) in HLA-A*02 patients with NSCLC: master protocol substudy 1

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Background

Therapeutic area

- NSCLC accounts for up to 85% of lung cancer cases, and a high proportion of patients have advanced or metastatic disease at diagnosis.[1,2]
  - The 5-year survival rate for patients with metastatic disease is 5% in a non-selected population.[3] A 5-year survival rate of >25% has been reported for patients with high PD-L1 expression who received pembrolizumab monotherapy.[4]
  - Despite this, there remains an unmet clinical need for novel therapies for patients with recurrent/metastatic NSCLC who have failed standard-of-care therapies.[5–7]

NY-ESO-1 TCR T-cell therapy

- NY-ESO-1 and LAGE-1a are intracellular proteins of the cancer/testis antigen family expressed in 20–30% and ~15% of NSCLC tumors, respectively.[8–9]
- Letetresgene autoleucel (lete-cel; GSK3377794) consists of autologous CD4+ and CD8+ T cells that have been genetically modified to express a 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 encouraging clinical activity in patients with SS[10,11] and is currently being investigated in SS[12] and NSCLC.[13]

For references, see slide at end of poster presentation.
HLA-A, human leukocyte antigen-A; LAGE-1a, L antigen family member 1 isoform A; lete-cel, letetresgene autoleucel; NSCLC, non-small-cell lung cancer; NY-ESO-1, New York esophageal antigen-1; PD-L1, programmed cell death ligand 1; SS, synovial sarcoma; TCR, T-cell receptor

Background

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

- Next-generation NY-ESO-1–specific TCR T-cell therapies based on lete-cel have been developed using novel constructs that incorporate additional genetic modifications to enhance anticancer activity of NY-ESO-1 TCR T cells.

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 that compared to lete-cel, this may:

enhance proliferation and persistence of TCR T cells

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

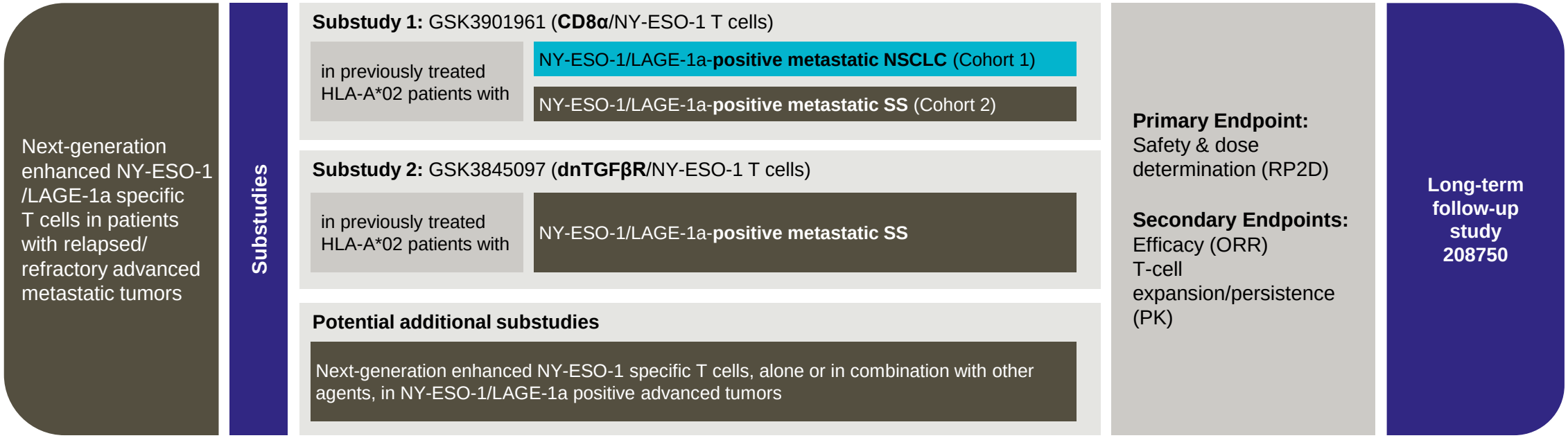
enhance activity of tumor-specific effector cells, including CD4+ T-cell granzyme B expression

For references, see slide at end of poster presentation.
HLA-A, human leukocyte antigen-A; lete-cel, letetresgene autoleucel; NY-ESO-1, New York esophageal antigen-1; TCR, T-cell receptor; Th1, T helper type 1

Background

A master protocol (NCT04526509) has been designed to allow independent substudies to investigate the activity of these novel NY-ESO-1 TCR T-cell therapies, potentially in combination with other agents, in multiple tumor types.

Figure: NCT04526509 Master Protocol Design



Study objective

Substudy 1 (Cohort 1) will assess the safety and tolerability, and determine the RP2D of **GSK3901961** in NY-ESO-1- and/or LAGE-1a-positive patients with metastatic NSCLC.

dnTGFβR, dominant-negative transforming growth-factor β receptor; HLA-A, human leukocyte antigen-A; LAGE-1a, L antigen family member 1 isoform A; lete-cel, letetresgene autoleucel; NSCLC, non-small-cell lung cancer; NY-ESO-1, New York esophageal antigen-1; ORR, overall response rate; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SS, synovial sarcoma; TCR, T-cell receptor

Study design

Substudy (cohort 1)

1 Phase I

Nonrandomized

Open-label

Multicenter

For each individual patient, the study will consist of the following phases:

Screening		Leukapheresis and manufacture		Intervention			Long-term follow-up
Target expression screening*	Leukapheresis and treatment screening†	Leukapheresis	GSK3901961 Manufacture	Lymphodepletion	T-cell dosing	Follow up‡	Follow-up of 15 years

For the interventional phase, the substudy consists of 2 stages:

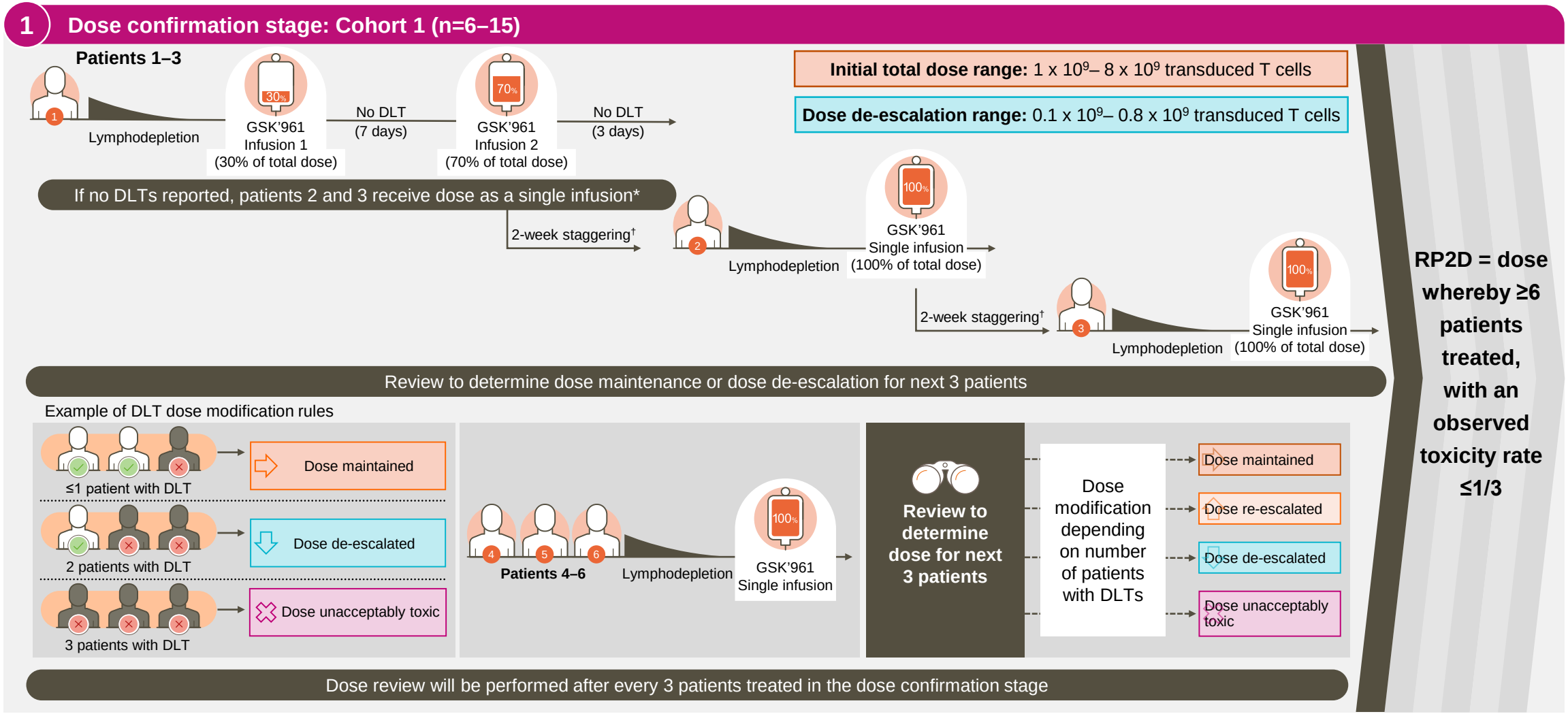
1 **Initial dose confirmation to assess RP2D** (n=6–15) followed by 2 **Dose expansion** (n=10)

To find the RP2D, modified toxicity probability interval 2 (mTPI-2) design will be implemented[14]

*Patients must be HLA-A*02:01-,*02:05-, or *02:06-positive, and express NY-ESO-1/LAGE-1a. †Up to 28 days before leukapheresis. ‡Patients will be monitored until disease progression, end of interventional phase, or death. Interventional phase when 80% of patients dosed with RP2D have progressed, died, withdrawn, or are lost to follow-up and all remaining patients have been followed ≥1 year.
For references see slide at end of poster presentation.
RP2D, recommended phase 2 dose

Study design

Part 1: Dose confirmation stage



*If 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.

For references see slide at end of poster presentation. DLT, dose-limiting toxicity; HLA-A, human leukocyte antigen-A; RP2D, recommended phase 2 dose

Study design

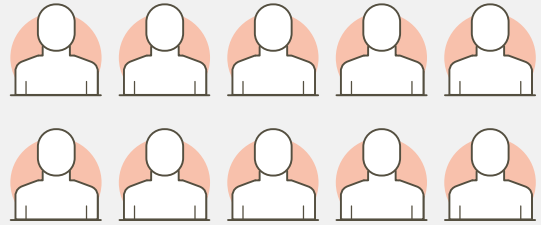
Part 2: Dose confirmation stage

2 Dose expansion stage: Cohort 1 (n=10)

Patient has received T-cell infusion and completed ≥2 disease assessments since infusion*

Primary analysis

- Safety
- Efficacy
- Pharmacokinetics
- Pharmacodynamics



Additional patient enrolment

*Includes patients who have died or progressed or were withdrawn from this study.

Study population

Substudy 1

Key inclusion criteria

- ≥18 years
- Histologically or cytologically confirmed Stage IV NSCLC
- Patient must have received or be receiving ≥1 prior lines of treatment including PD-1/PDL-1checkpoint blockade therapy
- Patient must have received or be intolerant to platinum doublet chemotherapy
- Patients must be HLA-A*02:01-, *02:05-, or *02:06-positive, and express NY-ESO-1/LAGE-1a on tumor archival or fresh biopsy

Key exclusion criteria

- Patients with actionable genetic aberrations (eg, EGFR, ALK/ROS1)
- Patients with prior NY-ESO-1–targeted therapies (vaccine, antibody, cell therapies), or who have received and failed ≥3 systemic therapies

ALK/ROS1, anaplastic lymphoma kinase/c-ros oncogene 1; EGFR, epidermal growth factor receptor; HLA-A, human leukocyte antigen-A; LAGE-1a, L antigen family member 1 isoform A; NSCLC, non-small-cell lung cancer; NY-ESO-1, New York esophageal antigen-1; PD-L1, programmed cell death ligand 1; PD-1, programmed death receptor-1

Study objectives and endpoints

Substudy 1

Primary endpoints

- Dose-limiting toxicities
- AEs
- SAEs
- AESIs

Secondary endpoints

- Investigator-assessed overall response rate per RECIST v1.1
- Duration of response
- Maximum expansion/persistence (C_{max})
- Time to C_{max}
- Area under the time curve from zero to time
- Phenotype of infiltrating transduced T cells (RNA, DNA, and/or protein levels)

Exploratory endpoints

- Overall survival
- Progression-free survival
- Disease control rate
- Time to response
- Anti-GSK3901961 titers

Current status

The study is currently open and recruiting.

AEs, adverse events; AESIs, adverse events of special interest; C_{max}, maximum expansion/persistence; RECIST, response evaluation criteria in solid tumor; SAEs, serious adverse events

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