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

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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 rate in the overall SS population during 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]
- 70–80% of SS tumors express NY-ESO-1.[12,14]

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.

- Lete-cel has shown promising clinical activity in patients with SS[14] and is currently being investigated in other solid tumors, including in myxoid/round cell liposarcoma (MRCLS) (NCT02992743),[15] NSCLC (NCT03709706),[16] and SS or MRCLS (NCT03967223).[17]

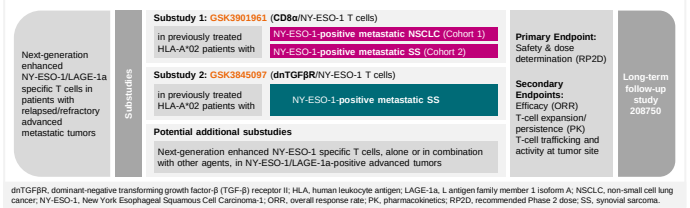
Next-generation NY-ESO-1–specific TCR T-cell therapies

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



dnTGFBR, 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

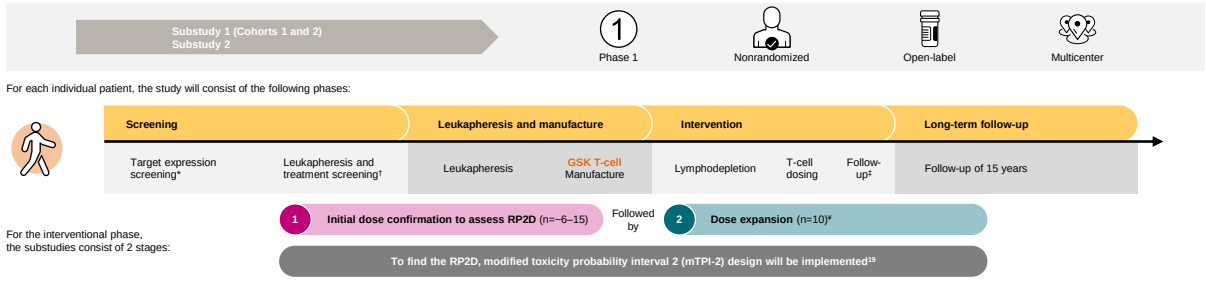
To evaluate the safety, tolerability, and recommended Phase 2 dose (RP2D) of GSK3901961 and GSK3845097 and potentially other agents (**Figure 1**).

- 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**).

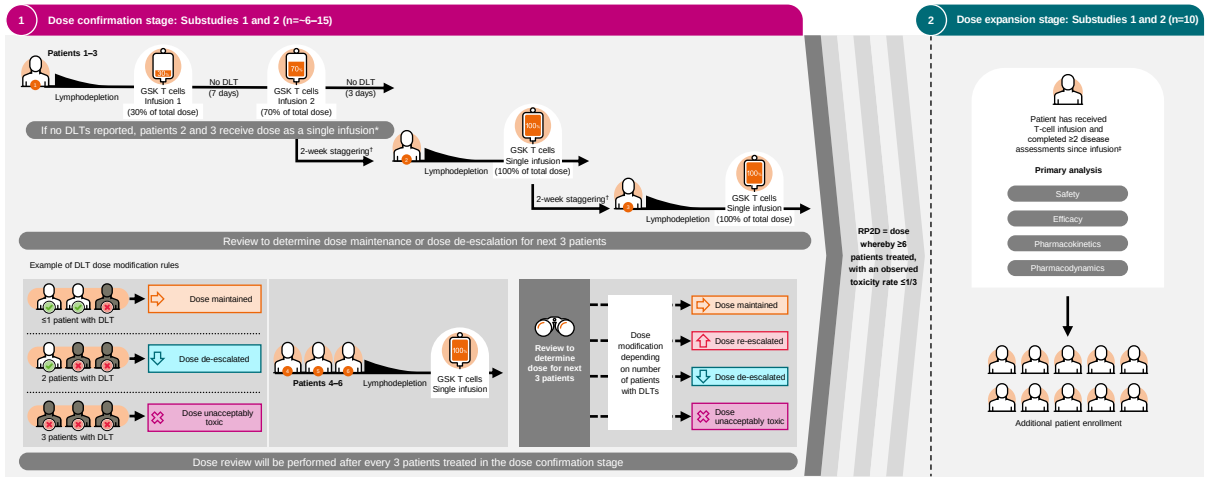
Figure 2: Patient Treatment Timeline



*Patients must be HLA-A*02:01,*02:05-, or *02:06-positive, and express NY-ESO-1. †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 been lost to follow-up and all remaining patients have been followed ≥1 year. ¥Total evaluable at RP2D in each cohort of each substudy. HLA, human leukocyte antigen; NY-ESO-1, New York Esophageal Squamous Cell Carcinoma-1; RP2D, recommended Phase 2 dose.

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.

Disclosures

AJS reports an uncompensated relationship with Iovance Biotherapeutics. **MA** reports paid consulting or advisory roles for GSK and Shattuck Labs; and has received research funding from Lilly, BMS, Novartis, GSK, Jounce Therapeutics, Adaptimmune, Merck, Genentech, Nektar, and Shattuck Labs. **TKO** reports paid consulting or advisory roles for Novartis, Celgene, Lilly, Sandoz, AbbVie, Eisai, G1 Therapeutics, Takeda, Seattle Genetics, BMS, MedImmune, BerGenBio, Lilly, Amgen, AstraZeneca, PharmaMar, Boehringer Ingelheim, EMD Serono, Xcovery, Bayer, Heron Therapeutics, ARMO Biosciences, and Merck; serving on speakers' bureaus for AbbVie; and, through his institution, holds patents or other intellectual property pertaining to overcoming acquired resistance to chemotherapy, diagnostic methods related to selective chemotherapy treatments, modulation of DR4 and its implications in EGFR-target cancer therapy, and soluble FAS ligand as a biomarker of thyroid cancer recurrence; reports other relationships with Roche/Genetech and EMD Serono; owns stocks/shares in Cambium Medical Technologies; has received research funding from Novartis, Astellas Pharma, Celgene, Bayer, Stem CentRx, Regeneron, AstraZeneca/MedImmune, AbbVie, G1 Therapeutics, BMS, United Therapeutics, Amgen, Loxo/Lilly, Fujifilm, Pfizer, Aeglea Biotherapeutics, Incyte, and Merck, paid to his institution; reports research funding from Corvus Pharmaceuticals; and reports an uncompensated relationship with Reflexion Medical. **SPDA** reports paid consulting or advisory roles for Amgen, EMD Serono, GSK, Immune Design, Immunocore, Incyte, Merck, Adaptimmune, and Nektar; travel, accommodations, and expenses from Adaptimmune, EMD Serono, and Nektar, and research support from EMD Serono, Amgen, Incyte, Nektar, BMS, Decipherx, and Merck, paid to her institution. **BHL** and **JY** have nothing to disclose. **JN** reports a paid consulting or advisory role for Bayer. **KH** reports paid consulting or advisory roles for Perthera, Iovance Biotherapeutics, BMS, Geneplus, and Mirati Therapeutics, and has received research funding from BMS, Mirati Therapeutics, Adaptimmune, Genentech/Roche, GSK, Amgen, Iovance Biotherapeutics, AbbVie, and BeiGene, paid to his institution. **DL** reports paid consulting or advisory roles for Epizyme, Blueprint Medicines, and Foundation Medicine; 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owns stocks/shares in Vanguard funds; has received honoraria from Ipsen; and has received research funding from Bayer, BMS, Benta Pharma Industries, Novartis, Incyte, Genentech/Roche, RGX, Mirati Therapeutics, and GSK, paid to his institution. **BAVT** reports a leadership role for Polaris; reports paid consultancy or advisory roles for EMD Serono, Novartis, Epizyme, Daiichi Sankyo, Pfizer, Adaptimmune, Bayer, GSK, Lilly, Cytokinetics INC, Apexigen Inc, and Decipherx; has participated in speakers bureaus/paid presentations for Adaptimmune, GSK, Lilly, and Novartis; has received research funding from GSK, Merck, Pfizer, and Tracon; has received travel, accommodations, and expenses from Lilly, Adaptimmune, and Advenchen Laboratories; and holds patents/licensing agreements on the use of ME1 as a biomarker, ALEXT3102, and for work performed with Accuronix Therapeutics. **ANH** is a former employee of and holds stocks/shares in GSK and receives royalties from Atara Biotherapeutics. **TF** is an employee of and holds stocks/shares in GSK. **EB** is a former employee of GSK. **AS** is an employee of and holds stocks/shares in GSK; 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Encore statement

These data are presented on behalf of the original authors with their permission. An earlier version of this work was previously presented at the AACR Congress, Virtual Format, April 10–15, 2021 (poster number CT219).

Ethics statement

The Master Protocol (NCT04526509) will be conducted under approval by the appropriate review boards and independent ethics committees.

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