A Phase 1b/2a Randomized Pilot Study to Investigate the Safety and Tolerability of Autologous T Cells With Enhanced T-Cell Receptors Specific to NY-ESO-1/LAGE-1a (GSK3377794) Alone, or in Combination With Pembrolizumab, in Advanced Non-small Cell Lung Cancer

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Introduction

- There is a high unmet medical need for patients with advanced non-small cell lung cancer (NSCLC) who have failed platinum-based chemotherapy and checkpoint inhibitors as well as for patients who have failed tyrosine kinase inhibitors targeted at genetic aberrations such as epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase/c-ros oncogene 1 (ALK/ROS1) rearrangements.
  - Only ~10%–20% of these patients receive any benefit from current treatments,[1-3] and novel therapies are needed to improve outcomes.
- Adoptive T-cell therapy uses a cancer patient's own T lymphocytes to generate an antitumor T-cell immune response.[4]
  - T-lymphocytes are obtained through leukapheresis, engineered to express tumor-specific T-cell receptors, expanded in vitro, and re-infused into the patients.[4]
- Preclinical data support the efficacy, specificity, and possible safety of, New York esophageal squamous cell carcinoma 1/cancer testis antigen 2 (NY-ESO-1/LAGE-1a) T-cell receptor-engineered patient T cells (GSK3377794) in NSCLC.
- Pembrolizumab is a potent humanized immunoglobulin G4 monoclonal antibody, which specifically blocks programmed death protein 1/programmed death-ligand 1 (PD-1/PD-L1) interaction thereby increasing the antitumor activity of T cells.[5]
- Therefore, the combination of GSK3377794 and pembrolizumab may work synergistically due to the inhibition of PD-1/PD-L1 signaling on GSK3377794 and other T cells, which may potentially further improve the therapeutic effect.

Objectives

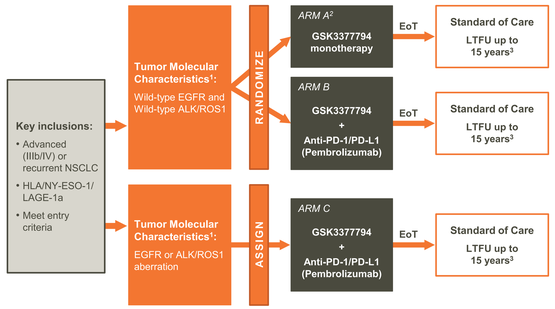
- The primary objective is to evaluate the safety of and clinical response to GSK3377794 alone or in combination with pembrolizumab in human leukocyte antigen (HLA) HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive participants with NY-ESO-1 and/or LAGE-1a-positive advanced NSCLC.
- Secondary objectives are to evaluate the duration of the antitumor activity of GSK3377794 and to describe the persistence of GSK3377794 over time.

Methods

Study Design (Protocol Amendment 2)

- This will be a Phase 1b/2a randomized, multi-arm, open-label pilot study (NCT03709706) of GSK3377794 in HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive patients aged ≥18 years whose tumors express NY-ESO-1 and/or LAGE-1a (**Figure 1**).

Figure 1. Study design



[1]Patients with NSCLC with B-RAF, HER2, and/or any other actionable genetic aberration that can be treated with targeted standard of care (NCCN recommended) are excluded; [2]option of pembrolizumab rescue therapy for patients who progress after receiving GSK3377794 monotherapy; [3]LTFU requires patient enrollment in a dedicated LTFU protocol.

EoT, end of treatment; HER2, human epidermal growth factor receptor 2; LTFU, long-term follow-up.

- 30 patients with wild-type EGFR and ALK/ROS1 will be randomized (1:1) to Arm A or B; 15 patients with EGFR or ALK/ROS1 aberrations will be assigned to Arm C.
  - Patients in Arm A will receive GSK3377794 as monotherapy, administered as a single intravenous (IV) infusion on Day 1.
  - Patients in Arm B and Arm C will receive GSK3377794 as a single IV infusion on Day 1 followed by pembrolizumab 200 mg initiated on Day 22 and continued for up to 35 cycles or until disease progression.
- Patients in Arm A who progress within 25 weeks after receiving GSK3377794 monotherapy may receive pembrolizumab therapy at the same dose and duration as Arm B and C.
- Patients who complete the treatment phase or are withdrawn from study treatment will be followed for long-term adverse events (AEs) and survival for up to 15 years (GSK Study 208750).
- This study will be conducted in accordance with ethical principles derived from the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, and International Council for Harmonisation Good Clinical Practice. All patients are required to provide informed consent at Screening, prior to any assessments or procedures.
- The first patient was screened on December 31, 2018.

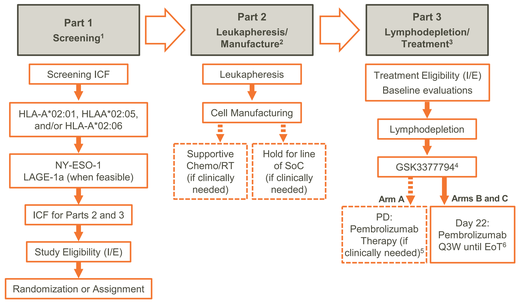
Patient Population

- This study aims to enroll up to 45 HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive patients with unresectable Stage IIIb or Stage IV NSCLC (using Response Evaluation Criteria In Solid Tumors [RECIST] v1.1) whose tumors express NY-ESO-1 and/or LAGE-1a.
- Eligible patients are either ineligible for definitive chemoradiotherapy, have recurrent disease that has progressed during or after platinum-based chemotherapy with or without anti-PD-1 agents, have terminated prior treatment due to intolerable side effects, or have refused standard approved treatment.
- Patients with B-RAF, human epidermal growth factor receptor 2 and/or any other actionable genetic aberration that can be treated with targeted standard of care (National Comprehensive Cancer Network recommended) are not eligible.
- All patients are required to provide archival tumor biopsies and, if feasible, a pretreatment biopsy following completion of their previous line of therapy.

Patient Flow

- The patient journey will consist of 3 parts: eligibility screening (Part 1), leukapheresis/manufacture (Part 2), and lymphodepletion/treatment (interventional phase) (Part 3). The study flow is summarized in **Figure 2**.

Figure 2. Patient flow



Dashed boxes and arrows indicate activities performed based on clinical need.

[1]Screening may start any time following diagnosis of advanced Stage IIIb or IV, or recurrent NSCLC; [2]leukapheresis may start following confirmation of eligibility criteria and 3 cycles of standard care. Washout periods may apply; [3]lymphodepletion starts at clinical and/or radiographic disease progression. Washout periods may apply; [4]a single dose of GSK3377794 will be administered 5 days after completion of lymphodepleting chemotherapy (Day 1); [5]patients with disease progression after receiving GSK3377794 will be offered anti-PD-1 rescue therapy with pembrolizumab following evaluation and approval; [6]the first pembrolizumab dose is administered on Day 22, then every 3 weeks up to 35 cycles, or PD.

CRS, cytokine release syndrome; ICF, informed consent form; I/E, inclusion/exclusion; PD, progressive disease; Q3W, once every 3 weeks; RT, radiotherapy; SoC, standard of care.

Part 1: Screening

- Following informed consent, blood samples will be tested for the presence of HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06. Formalin-fixed paraffin-embedded analysis will be performed on archival tumors to confirm NY-ESO-1 and/or LAGE-1a expression.

Part 2: Leukapheresis/Manufacture

- Patients will undergo leukapheresis if they have absolute neutrophil count ≥1.5 x 10^9/L, CD3 count ≥200/µL, and lymphocyte count ≥0.5 x 10^9/L.
- Leukapheresis can be initiated, in accordance with specified washout periods (**Table 1**) and recovery of blood and T-cell counts:
  - Between lines of therapy
  - After the first 3 cycles of current chemotherapy
  - During prior PD-1/PD-L1 regimens following 3 cycles of checkpoint blockade therapy
  - After 9 weeks of current tyrosine kinase inhibitor therapy
  - After radiotherapy
  - Following refusal of prior standard care.

Table 1. Concomitant treatments and washout periods

Treatment/therapy	Required washout
Cytotoxic therapy	2 weeks
Immune therapy (including monoclonal antibody therapy)	No washout for PD-1/PD-L1 checkpoint inhibitors For all others, case-by-case evaluation
Anticancer vaccine	2 months[a]
Live-virus vaccination	4 weeks
Gene therapy using an integrating vector Allogeneic hematopoietic stem cell transplant at any time	Not permitted
Corticosteroids or any other immunosuppressive therapy	2 weeks
Investigational treatment	4 weeks
Radiotherapy	No washout for palliative radiation Otherwise dependent on the dose and target of therapy
Herbal medications and other dietary supplements	2 weeks

[a]Patient will be excluded if their disease is responding to an experimental vaccine given within 6 months.

- If a patient has progressive disease and cannot remain treatment-free, supportive radiotherapy, chemotherapy, or other systemic treatments may be administered between leukapheresis and lymphodepletion, subject to the mandatory washout periods shown in **Table 1**.
- GSK3377794 manufacture will be undertaken following leukapheresis.

Part 3: Lymphodepletion/Treatment (Interventional Phase)

- Patients will receive preparative lymphodepleting chemotherapy (cyclophosphamide and fludarabine) on Days –8 to –5 (fludarabine only on Day –8). After 24 hours (Day –4), patients could receive granulocyte-colony stimulating factor support.
- On Day 1, patients will receive GSK3377794 infusion after premedication against potential infusion reactions with antihistamines and acetaminophen.
- In Arms B and C, the first pembrolizumab administration is on Day 22 (if deemed safe and to allow for recovery following lymphodepletion), then every 3 weeks up to 35 cycles or disease progression.
- Patients must not receive concomitant non-protocol chemotherapy, immune therapy, biological therapy, or investigative anticancer therapy, or undergo other anticancer locoregional therapies after T-cell administration.

Endpoints and Assessments

- The primary endpoints are overall response rate determined by Investigator response by RECIST v1.1 (percentage of patients with confirmed complete response or partial response) and safety (including frequency and severity of AEs, laboratory parameters, and vital signs).
  - Tumor assessment for disease response and progression will be assessed as defined by RECIST v1.1 and iRECIST. Computed tomography scans will be performed within 2 weeks of lymphodepletion, at Week 7, then every 6 weeks until Week 25, then every 9 weeks until Week 52, and then every 12 weeks until progression per iRECIST criteria. Tumor images will be reviewed centrally.
  - Safety will be assessed continuously. AEs will be coded using the Medical Dictionary for Regulatory Activities, and graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
- Secondary endpoints include progression-free survival, disease control rate, duration of response, time to response, and maximum persistence.
- Exploratory endpoints include overall survival, T-cell receptor diversity in the blood and tumor, levels of NY-ESO-1/LAGE-1a, and titers of anti-GSK3377794 antibodies over time.

Statistical Analysis

- The primary efficacy analysis will be performed in the modified intent-to-treat population, consisting of all patients who received GSK3377794 infusion.
- The safety population will include all patients who were enrolled in the study and underwent leukapheresis (intent-to-treat population).
- The study will use a Bayesian predictive adaptive design, allowing for data from the three treatment arms to be frequently monitored against rates of Type I and Type II errors after first interim analysis for each individual arm. The first futility analysis will be conducted when at least 10 patients become evaluable per arm. Enrollment can be stopped in any arm if futility is determined.

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