Safety, tolerability and activity 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: a Phase 1b/2a randomised pilot study

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Background

Unmet need

An unmet need exists for patients with advanced 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 EGFR mutation and 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.

Clinical rationale

Adoptive cell therapy using autologous engineered TCR-T against NY-ESO-1 is a promising treatment for recurrent or high-risk solid and haematologic malignancies with encouraging activity demonstrated.

- Previous clinical trials using autologous T cells directed against NY-ESO-1/LAGE-1a have shown objective responses between 40% and 60% in synovial sarcoma, metastatic melanoma and multiple myeloma.[4-6]

Unlike CAR-T agents that primarily target cell surface proteins and have demonstrated substantial activity in haematological malignancies, engineered TCR-T can be directed to target intracellular antigens and hence ideal for solid tumours.

NY-ESO is a cancer testis antigen expressed across a broad number of cancers including high expression in NSCLC.[7,8]

Genetically engineered NY-ESO-1/LAGE1a specific T cells (GSK3377794) are autologous CD4$^+$ and CD8$^+$ T cells transduced with a self-inactivating lentiviral vector to express an affinity-enhanced NY-ESO-1- and LAGE-1a-specific T-cell receptor.

Pembrolizumab is a monoclonal antibody that blocks PD-1/PD-L1 interaction and increases anti-tumour activity in anti-tumour T cells; combination of NY-ESO-1 specific T-cells and an anti-PD-1 antibody has previously shown in a pre-clinical model significantly enhanced control of tumour growth when compared with NY-ESO-1-specific T-cell monotherapy in preclinical models.[9]

Trial

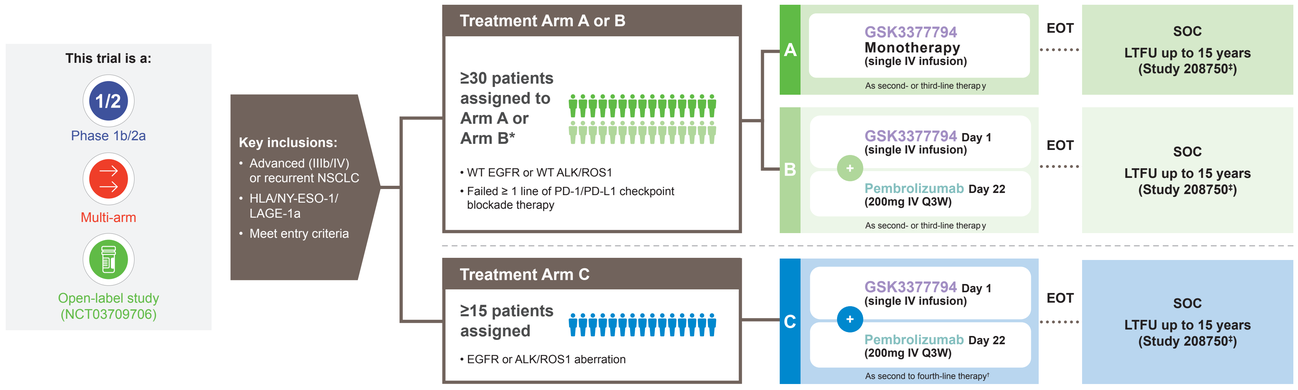
NY-ESO-1/LAGE-1a T-cell receptor engineered patient T cells (GSK3377794) will be used in combination with pembrolizumab to potentially improve clinical benefit in HLA-A2+ patients with NY-ESO-1 and/or LAGE-1a positive Stage IIIb/IV NSCLC.

Objectives

The primary objectives are to determine the clinical response to GSK3377794 alone or in combination with pembrolizumab, and assess the safety and tolerability of these regimens.

The secondary objectives are to evaluate the duration of anti-tumour activity of GSK3377794 and to describe the persistence of GSK3377794 over time.

Study design (protocol amendment 2)



*≥15 evaluable patients per arm; †after failing SOC targeted therapies per NCCN guidelines[10]; ‡patients who complete the treatment phase or are withdrawn from study treatment will be enrolled in study 208750, a dedicated LTFU protocol, and followed for observation of long-term AEs and survival for up to 15 years.

Main inclusion criteria

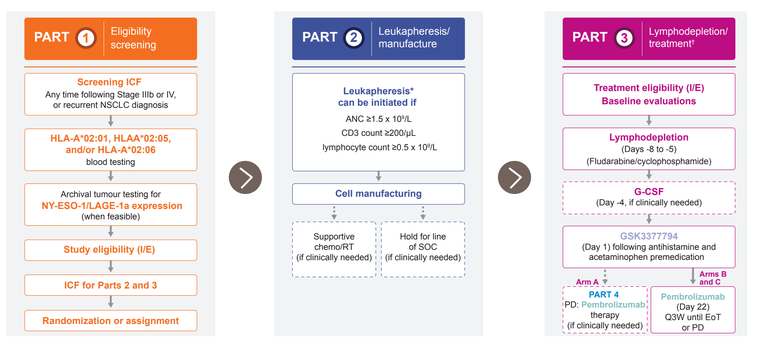
- Age ≥18 years
- Recurrent or unresectable Stage IIIb/IV (per RECIST v1.1) NSCLC patients who are either:
  - ineligible for SOC chemoradiotherapy, or
  - have received PD-1/PD-L1 therapy or appropriate targeted therapy, or
  - have terminated prior treatment due to intolerable side effects, or
  - have refused SOC
- HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive
- NY-ESO-1 and/or LAGE-1a-expressing tumour

Main exclusion criteria

- BRAF/any other actionable genetic aberration that can be treated with targeted SOC (NCCN recommended[10]), other than EGFR mutations or ALK/ROS1 translocations

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**).



Any patients receiving GSK3377794 monotherapy with PD before or at the 25-week scan will have the option of pembrolizumab combination therapy following evaluation and approval.

If a patient has PD 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.

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

*Leukapheresis can be initiated subject to the mandatory washout periods following eligibility confirmation and in 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 TKI therapy, after radiotherapy or following refusal of prior SOC; †patients must not receive concomitant non-protocol chemotherapy, immune therapy, biological therapy, or investigative anti-cancer therapy, or undergo other anti-cancer locoregional therapies after T-cell administration.

Mandatory washout periods for concomitant treatment only (not for leukapheresis)

Treatment/therapy	Required washout
Cytotoxic therapy	2 weeks
Immune therapy (including mAb therapy)	No washout for PD-1/PD-L1 checkpoint inhibitors. For all others, case by case evaluation.
Anti-cancer vaccine	2 months*
Live-virus vaccination	4 weeks
Gene therapy using an integrating vector Allogeneic haematopoietic 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

*Patients will be excluded if their disease is responding to an experimental vaccine given within 6 months.

Endpoints and Assessments

Primary

ORR

- Response and progression will be investigator assessed (RECIST 1.1/iRECIST)
- Baseline CT scans will be performed within 2 weeks of lymphodepletion, and then 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
- Tumour images may be reviewed centrally

Safety will be continually assessed including:

- Frequency and severity of AEs coded using MedDRA and graded based on NCI-CTCAE v4.03
- AE/SAE/AEs of special interest (protocol-defined) leading to dose delays and or treatment withdrawal
- Laboratory parameters
- Vital signs
- ECGs

Secondary

- PFS
- DCR
- DoR
- TTR
- Maximum persistence

Exploratory

- OS
- TCR diversity in the blood and tumour
- NY-ESO-1/LAGE1a levels
- Titres of anti-GSK3377794 antibodies over time

Statistical analysis

Primary efficacy analysis will be performed in the mITT population. >> mITT population is defined as all patients who received GSK3377794 infusion.

All safety analyses will be performed using the ITT population. >> ITT population defined as all patients who were enrolled in the study (i.e. underwent leukapheresis).

The study is using a Bayesian decision framework for evaluating activity at interim and final analyses; this allows any arm to be halted due to futility at interim time points.

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Abbreviations

AE, adverse event; ALK/ROS1, anaplastic lymphoma kinase/c-ros oncogene 1; BRAF, B-Raf; chemo, chemotherapy; CAYT-1, cmvneo antigen receptor 7 cells; CRS, cytokine release syndrome; DLR, disease control rate; DoR, duration of response; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; HLA, human leukocyte antigen; ICF, informed consent form; I/E, inclusion/exclusion; iRECIST, Modified RESIST 1.1 for Immune-based Therapeutics; ITT, intent-to-treat; IV, intravenous; LAGE-1a, cancer testis antigen 2; LTFU, long-term follow-up; mAb, monoclonal antibody; MedDRA, Medical Dictionary for Regulatory Activities; mITT, modified intent-to-treat; NCCN, National Comprehensive Cancer Network; non-TX CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; NY-ESO-1, New York esophageal squamous cell carcinoma 1; ORR, objective response rate; PD, progressive disease; PD-1, programmed death protein 1; PD-L1, PD-1 ligand; PFS, progression-free survival; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumours; SAE, serious adverse event; SOC, standard of care; TCR, T-cell receptor; TCR-T, T-cell receptor T cells; TKI, tyrosine kinase inhibitor; TTR, time to response; WT, wild-type.

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