Safety and Activity of Autologous T Cells With Enhanced NY-ESO-1–Specific T-Cell Receptor (GSK3377794) in HLA-A*02+ Previously-Treated and -Untreated Patients With Advanced Metastatic/Unresectable Synovial Sarcoma: A Master Protocol Study Design (IGNYTE-ESO)

Poster No. 459

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Background

Unmet need

Response rates to anthracycline-based chemotherapy, a first-line treatment in advanced metastatic/unresectable synovial sarcoma (SS), are low (<30%) and often not durable[1]

Study rationale

NY-ESO-1 is a member of the cytoplasmic cancer/testis family of tumor antigens detectable in many cancer types, including SS

- SS comprises ~5%–10% of soft-tissue sarcomas[2]
- Previous clinical studies using adoptively transferred T cells against NY-ESO-1 have reported objective responses in 40%–60% of patients with **HLA-A*02+** bearing **NY-ESO-1+** SS[3–5]

Genetically engineered **NY-ESO-1–specific** T cells (**NY-ESO-1** 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–specific** TCR

Unlike CAR-T cells that recognize cell surface proteins, TCRs can recognize antigenic epitopes of intracellular proteins that are processed and presented on the surface of the cancer cell in the context of **HLA**

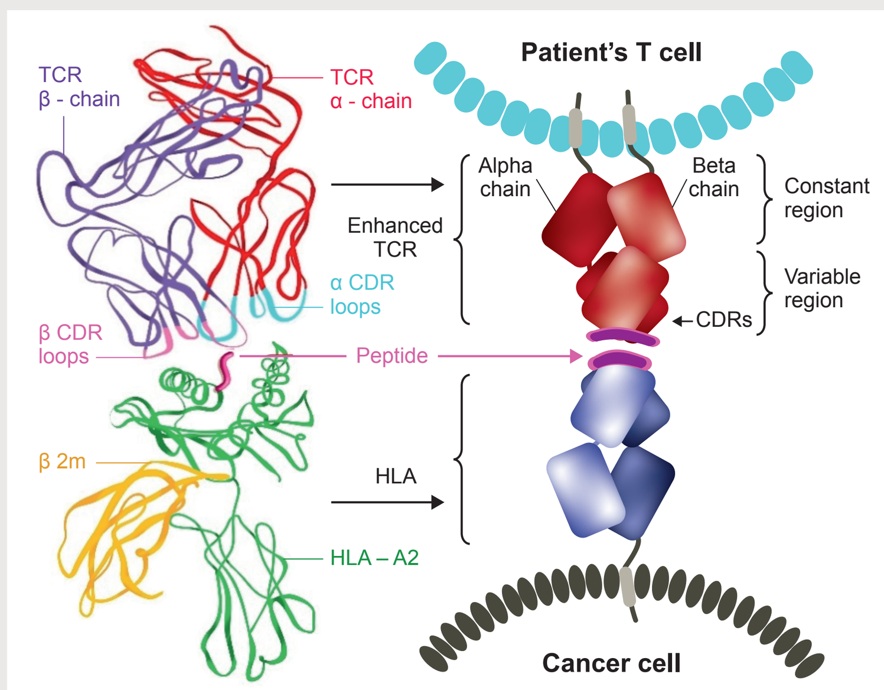
Ongoing Phase I and II trials are evaluating **GSK3377794** as a first-line and second-line therapy for treatment of hematologic malignancies and solid tumors, including SS

Mechanism of action

NY-ESO-1 is expressed in various malignancies, but is absent in healthy, normal, adult tissue, with the exception of germ cells of the adult testis

- Because testis germ cells have low HLA expression,[6] off-target side effects would be expected to be limited when targeting NY-ESO-1

NY-ESO-1 is one of the most immunogenic proteins described in human cancer, based on its capacity to elicit simultaneous antibody and CD8+ T-cell responses in vivo



Summary

- **GSK3377794 has shown encouraging clinical activity in earlier clinical trials**
- **This larger clinical trial is being initiated to establish and further discern the efficacy and safety of GSK3377794 in patients with biomarker-selected metastatic SS**
- **This innovative Master Protocol study design permits evaluation of NY-ESO-1– specific T cells in other NY-ESO-1+ tumor types in HLA-A*02:01, HLA-A*02:05, ± HLA-A*02:06 allele positive patients within separate substudies**
- **Enrollment began in December 2019**

Study design

This trial (IGNYTE-ESO; NCT03967223) has a Master Protocol design consisting of a core protocol and allowing for multiple independent substudies to investigate the activity of **NY-ESO-1–specific** T cells in multiple tumor types; overall sample size is not fixed. The first 2 substudies are non-randomized, single-arm investigations of **GSK3377794** in patients with metastatic SS

The protocol may be amended to include additional substudies to investigate other **NY-ESO-1+** or **LAGE-1a+** positive tumor types and other NY-ESO-1–specific T cells, potentially in combination with other agents

Substudy 1

Previously **untreated** patients who:

1. HLA-A*02:01, HLA-A*02:05, HLA-A*02:06 – have ≥1 positive allele
2. have **NY-ESO-1+** advanced metastatic or unresectable SS

(N=10)

Substudy 2

Previously **treated** patients who:

1. HLA-A*02:01, HLA-A*02:05, HLA-A*02:06 – have ≥1 positive allele
2. have **NY-ESO-1+** advanced metastatic or unresectable SS
3. have progressed following anthracycline-based chemotherapy

(N=55 planned to ensure that ≥45 receive treatment)

Master Protocol design (IGNYTE-ESO)

TCR engineered NY-ESO-1–specific T cells → Long-term follow-up and safety

Substudy 1	Advanced metastatic or unresectable SS	Previously untreated	HLA-A*02 participants with NY-ESO-1 positive tumors	GSK3377794
Substudy 2	Advanced metastatic or unresectable SS	Progressed post chemo	HLA-A*02 participants with NY-ESO-1 positive tumors	GSK3377794
Potential additional substudy	Other tumor types			NY-ESO-1–specific T cells alone or combined with other agents
Potential additional substudy	Other tumor types			NY-ESO-1–specific T cells alone or combined with other agents

Key inclusion criteria

- ≥10 years of age
- Measurable disease
- Positive for HLA-A*02:01, HLA-A*02:05 ± HLA-A*02:06
- Tumor expression of NY-ESO-1
- Adequate organ function
- ECOG performance status 0–1

Key exclusion criteria

- Central nervous system metastases
- Clinically significant systemic illness
- Prior gene therapy with integrating vector or NY-ESO-1–specific T cells, vaccine, or targeting antibody
- Prior autoimmune disease or allogeneic hematopoietic stem-cell transplant

Primary Endpoints

- **Substudy 1:** Overall response rate per RECIST v1.1 assessed by investigators
- **Substudy 2:** Overall response rate per RECIST v1.1 assessed by independent central review

Secondary Endpoints

- Time to and duration of response
- Disease control rate
- Progression-free survival
- Overall survival (Substudy 2)
- Adverse events, including serious adverse events
- Presence and titers of anti-GSK3377794 antibodies over time (Substudy 2)

Exploratory Endpoints

- Correlation of T-cell persistence with safety, clinical response, and phenotype of infused T cells
- Relationship between antigen expression and treatment response
- Potential immune response to GSK3377794 (Substudy 1)
- Impact on quality of life and daily functioning

PART 1 Eligibility screening

- Target Expression Screening HLA-A*02* and NY-ESO-1
- Leukapheresis Eligibility Screening – 28 days prior to apheresis

PART 2 Leukapheresis & Manufacture

- Leukapheresis
- Manufacturing of NY-ESO-1 T cells GSK3377794

PART 3 Lymphodepletion, Treatment & Follow-up

- Treatment Eligibility Confirmed – Days -13 to -8
- Lymphodepletion Cy × 2 days Flu × 4 days – Days -7 to -4
  - **Fludarabine** 30 mg/m²/day x 4 days (Day -7 to -4)
  - **Cyclophosphamide** 1800 mg/m²/day x 2 days (Day -5 to -4)
- GSK3377794 Infusion – Day 1
- Follow-up
  - **Response evaluation:** RECIST 1.1
  - **Primary endpoints:** ORR
  - **Secondary endpoints:** TTR, DOR, DCR, PFS, OS, safety

PART 4 Long-term Follow-up (Study 208750)

- Long-term Follow-up – Up to 15 years after GSK3377794 infusion

Abbreviations

CAR-T, chimeric antigen receptor T cells; CDR, complementarity-determining region; Cy, cyclophosphamide; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; Flu, fludarabine; HLA, human leukocyte antigen; NY-ESO, New York esophageal squamous cell carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SS, synovial sarcoma; TCR, T-cell receptor; TTR, time to response

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Encore statement

These data are presented on behalf of the original authors with their permission. A similar presentation (P453) was presented at the SITC Annual Meeting, National Harbor, MD, USA, Nov 6–10, 2019.

Disclosures

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Ethics approval statement

This Master Protocol (IGNYTE-ESO) will be conducted under approval by the appropriate institutional review boards and independent ethics committees

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