IGNYTE-ESO: a master protocol to assess safety and activity of letetresgene autoleucel (lete-cel; GSK3377794) in HLA-A*02+ patients with synovial sarcoma or myxoid/round cell liposarcoma (Substudies 1 and 2)

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Background

Unmet need

There is an unmet need for effective therapies in many metastatic or advanced stage solid tumor types, including soft tissue sarcomas (STS) for which novel immunotherapies present a promising therapeutic option.

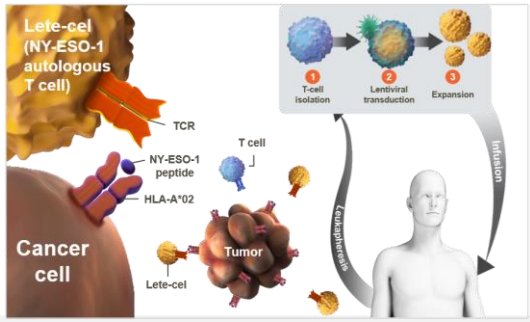
- Synovial sarcoma (SS) and myxoid/round cell liposarcoma (MRCLS), both of which harbor chromosomal translocations, each represent approximately 5%–10% of STS.[1-3]
  - Objective response rates to standard therapies among patients with metastatic, recurrent, and/or unresectable SS and MRCLS are poor, particularly after failure of first-line systemic chemotherapy.[3,4]
    - For second-line treatment, a recent multicenter study identified a <15% response rate among 249 patients with advanced SS.[3]
    - Although response rates in individual studies can be high,[5] data among a larger cohort (n=101) indicated <20% response rates to first- and second-line treatments in patients with advanced MRCLS.[3]

Letetresgene autoleucel (lete-cel; GSK3377794)

New-York esophageal squamous cell carcinoma 1 (NY-ESO-1) is an immunogenic cancer testis antigen present in several types of tumors, including 70%–80% of SS and 80%–90% of MRCLS tumors.[2,6]

- Letetresgene autoleucel (lete-cel; GSK3377794) is an autologous T-cell therapy using genetically modified T-cell receptors to target cancer cells expressing NY-ESO-1 (**Figure 1**).[7]
- Unlike CAR-T cells that recognize cell surface proteins, T-cell receptors can recognize antigenic epitopes of intracellular proteins that are processed and presented on the surface of the cancer cell in the context of human leukocyte antigen (HLA).[8]

Figure 1. Lete-cel mechanism of action



HLA-A*02 denotes subtypes HLA-A*02:01, HLA-A*02:05, and HLA-A*02:06.
HLA, human leukocyte antigen; lete-cel, letetresgene autoleucel; NY-ESO-1, New York esophageal squamous cell carcinoma-1; TCR, T-cell receptor.

- A Phase I clinical study (NCT01343043) identified response rates to lete-cel of 20–50% and a manageable safety profile among patients with advanced/metastatic SS.
- A pilot study (NCT02992743) is evaluating the safety and antitumor activity of lete-cel in advanced MRCLS[9]; interim analysis results from this study are displayed in poster 11521.

Study design

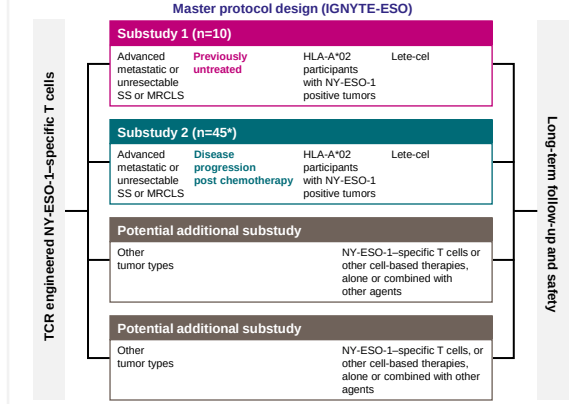
IGNYTE-ESO (NCT03967223) is a master protocol that enables evaluation of multiple cell therapies in multiple tumor types and treatment stages across separate substudies.

The first 2 substudies are single-arm, open-label, multicenter trials investigating lete-cel in biomarker-selected advanced metastatic or unresectable SS/MRCLS (**Figure 2**).

- Substudy 1: Previously untreated patients
- Substudy 2: Patients with disease progression following prior treatment with anthracycline-based chemotherapy

The protocol may be amended in the future to add additional substudies for different patient populations or tumor types.

Figure 2. Study Design



*Intended sample size for treatment with commercial vector supply and manufacturing process.
HLA, human leukocyte antigen; lete-cel, letetresgene autoleucel; MRCLS, myxoid/round cell liposarcoma; NY-ESO-1, New York esophageal squamous cell carcinoma-1; SS, synovial sarcoma; TCR, T-cell receptor.

Study population

Key inclusion criteria	Key exclusion criteria
• ≥10 years of age • Advanced metastatic or unresectable SS or MRCLS • Measurable disease • Positive for HLA-A*02:01, A*02:05 and/or A*02:06 • Tumor expression of NY-ESO-1 • Adequate organ function • ECOG performance status 0–1 or equivalent	• Central nervous system metastases • Clinically significant other systemic illness besides SS or MRCLS • Prior gene therapy with any NY-ESO-1–specific T cells, vaccine, or targeting antibody; or with the integrating vector • Prior autoimmune disease or allogeneic hematopoietic stem-cell transplant

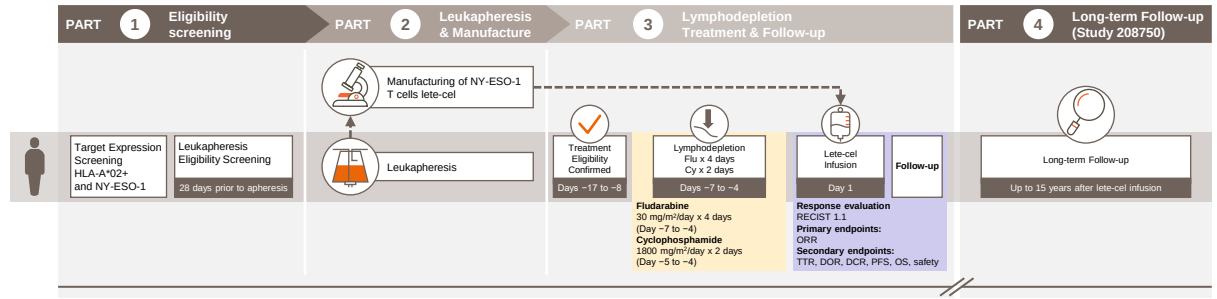
ECOG, Eastern Cooperative Oncology Group.

Study phases

Figure 3 displays the patient journey for both substudies, which includes leukapheresis for lete-cel manufacture, lymphodepletion chemotherapy, lete-cel infusion, and follow-up.

- Lymphodepletion prior to lete-cel infusion may enhance immune reconstitution via facilitation of T-cell expansion and trafficking; it may also enhance the activity of the adoptively transferred cells by decreasing activity of regulatory T cells.[10–12]

Figure 3. Patient journey



Cy, cyclophosphamide; DCR, disease control rate; DoR, duration of response; flu, fludarabine; HLA, human leukocyte antigen; lete-cel, letetresgene autoleucel; NY-ESO-1, New-York esophageal squamous cell carcinoma 1; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; RECIST, TTR, time to response.

Study objectives and endpoints

Table 2 describes the endpoints for each substudy.

Table 2. Study objectives and endpoints

	Substudy 1	Substudy 2
Primary endpoint	Overall response rate (ORR) per RECIST v1.1 assessed by investigators; no formal hypotheses were evaluated statistically	ORR per RECIST v1.1 assessed by central independent review • ORR will be compared with the historical control assuming at least 90% power with 0.025 one-sided type I error
Secondary endpoints	**Efficacy** • Time to response • Duration of response • Disease control rate • Progression-free survival • Overall survival* **Safety** • Adverse event frequency/severity • Serious adverse events • Adverse events of special interest **Pharmacokinetic** • Maximum transgene expansion (C_{max}) • Time to C_{max} • Area under the time curve from zero to time (AUC_{0-t})	

*Secondary endpoint for Substudy 2 only; exploratory endpoint for Substudy 1.
RECIST, Response Evaluation Criteria in Solid Tumors.

Status[13]

- Enrollment began in December 2019.
- Recruitment is ongoing.

Summary

There is an unmet need for safe and effective novel therapies in patients with solid tumors such as SS and MRCLS, with promising results observed using autologous TCR T-cell immunotherapy.

- A previous Phase I study has shown that lete-cel infusion has persistent clinically meaningful activity with a manageable safety profile in patients with previously treated advanced SS.[7]
  - Additionally, recent interim analysis results from a pilot study of lete-cel in advanced MRCLS identified durable partial responses (ORR, 40%) and prolonged stable disease along with a manageable safety profile in this population (please see poster 11521).[9]

Lete-cel is currently being investigated in multiple tumor types as a single agent (including in SS and MRCLS) or in combination with pembrolizumab (including in non-small cell lung cancer).

Substudies 1 and 2 of the IGNYTE-ESO master protocol study will examine the efficacy, safety, and pharmacokinetics of lete-cel in previously untreated (Substudy 1) patients or patients who have progressed following treatment with anthracycline-based chemotherapy (Substudy 2) with biomarker-selected advanced metastatic or unresectable SS or MRCLS.

This innovative study design allows additional patient populations, tumor types, and other cell-based therapies with different combination strategies to be assessed in separate substudies.

Enrollment began in December 2019, and the study is currently ongoing.

Disclosures

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, Deciphera, and Merck, paid to her institution. **JN** reports a paid consulting or advisory role for Bayer. **FT** reports paid consulting or advisory roles for BMS, Octimet, Achilles Therapeutics, Evelo Therapeutics, GSK, T-knife, and Zellunz; travel, accommodations, and expenses from GSK and Zellunz; other financial relationships with iMatch; honoraria from Bayer; research funding from Pfizer, Genmab, Novartis, Synthon, 3-V Biosciences, Actuate Therapeutics, Agalimmune, AstraZeneca, Bayer, BerGenBio, Blueprint Medicines, Boehringer Ingelheim, Carrick Therapeutics, CytomX Therapeutics, Eisai, Lilly, Ignyta, Immutep, Incyte, Janssen, Kinex, MacroGenics, Merck, Millennium Pharmaceuticals, Octimet, Orion Pharma GmbH, Redx Pharma, Sierra Oncology, Takeda, Tarveda Therapeutics, Adaptimmune, Aveo, BMS, GSK, Medimmune, MSD, Abbvie, and Roche, paid to her institution. **ARAR** reports paid consulting or advisory roles for Merck, Bayer, and Adaptimmune; 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and has received research funding from TRACON Pharmaceuticals, paid to his institution. **AC** has an immediate family member with paid consulting or advisory roles for DePuy companies and a patent pending for hormone supplementation of tendon and ligament repair; and reports research funding from Blueprint Medicines, TRACON Pharmaceuticals, and GSK. **KNG** has nothing to disclose.

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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 BSG Congress, Virtual Format, February 24–25, 2021 (poster number 914542).

Ethics statement

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

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