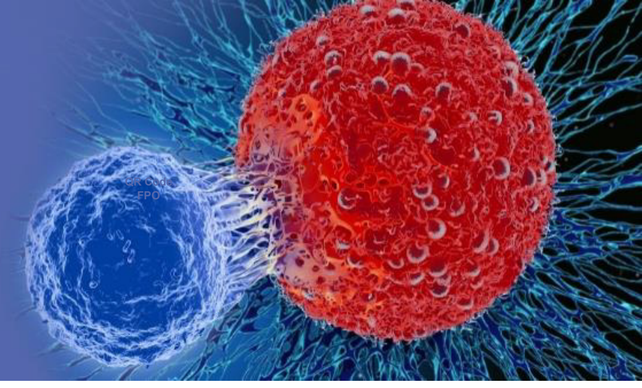
Primary Analysis of Efficacy and Safety of Letetresgene Autoleucel (Lete-cel) as First-Line Treatment for Unresectable or Metastatic Synovial Sarcoma (SyS); Substudy 1 of IGNYTE-ESO



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Introduction

- Letetresgene autoleucel (lete-cel) is an autologous T-cell therapy targeting NY-ESO-1 (**Figure 1**), which is expressed in synovial sarcoma (SyS) and myxoid/round cell liposarcoma (MRCLS)
- Lete-cel efficacy has been demonstrated in pilot studies for patients with metastatic or unresectable SyS and MRCLS[1]
- We explored the feasibility, efficacy, and safety of lete-cel in the first-line setting for treatment-naïve patients with metastatic or unresectable SyS or MRCLS

Methods

- IGNYTE-ESO is a master protocol with two substudies (NCT03967223)
- Substudy 1 is an open-label pilot study of lete-cel in treatment-naïve patients with metastatic or unresectable SyS or MRCLS
  - The target enrollment was 10 patients
  - Key eligibility criteria: Age ≥10 years; human leukocyte antigen (HLA)-A*02:01, A*02:05, or A*02:06; NY-ESO-1+ (≥30% of cells 2+/3+); optional bridging therapy consisting of up to two cycles of doxorubicin between apheresis and lymphodepletion (LD); and measurable disease
- Patients received fludarabine (range: 60–120 mg/m^2) and cyclophosphamide (range: 1800–3600 mg/m^2) for LD chemotherapy, and a transduced T-cell dose between 1 and 15x10^9. LD dose reduction was required for age ≥60 years and renal impairment
- Response was assessed at Weeks 6, 12, 18, and 24, then every 3 months until disease progression, death, or withdrawal
- The primary efficacy endpoint was investigator-assessed overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Secondary endpoints included disease control rate (DCR), time to response (TTR), duration of response (DOR), progression-free survival (PFS), and safety. To characterize the cellular pharmacokinetics of lete-cel, we report the area under the curve (AUC) from Time 0 to Day 28, and maximum serum concentration (C_{max})
- The primary analysis was conducted when all enrolled patients had received T-cell infusion and completed at least two post-baseline disease assessments or withdrawn

Demographics and baseline characteristics

- From January 2020 to May 2022, 52 patients were screened for inclusion in this substudy: 26 were HLA negative, four were NY-ESO-1 negative, and testing was not completed for two
- Of the 20 who met HLA and NY-ESO-1 criteria, seven were enrolled and received leukapheresis, and five received LD (**Table 1**) and T-cell infusion (**Table 2**)
  - The two patients who did not receive LD and T-cell infusion became not eligible (n=1 diagnosed with a second malignancy, n=1 received more than two cycles of doxorubicin bridging therapy)
  - None had received any prior lines of systemic therapy for metastatic disease
  - There was one adolescent patient
  - One patient received radiotherapy between leukapheresis and LD
  - One patient received bridging chemotherapy, with two cycles of doxorubicin
  - Study accrual was slow and did not reach its goal of 10 enrolled patients

Table 1. LD regimens received cumulatively over 3–4 days

Patient	Fludarabine	Cyclophosphamide
101	120 mg/m^2	3600 mg/m^2
102	60 mg/m^{2,a,b}	2400 mg/m^{2,a,b}
103	120 mg/m^2	2700 mg/m^2
104	120 mg/m^2	2700 mg/m^2
105	90 mg/m^{2,a}	1800 mg/m^{2,a}

[a]Dose reduced for age ≥60 years. [b]Dose reduced for renal function.
LD, lymphodepletion.

Table 2. Demographics and baseline characteristics

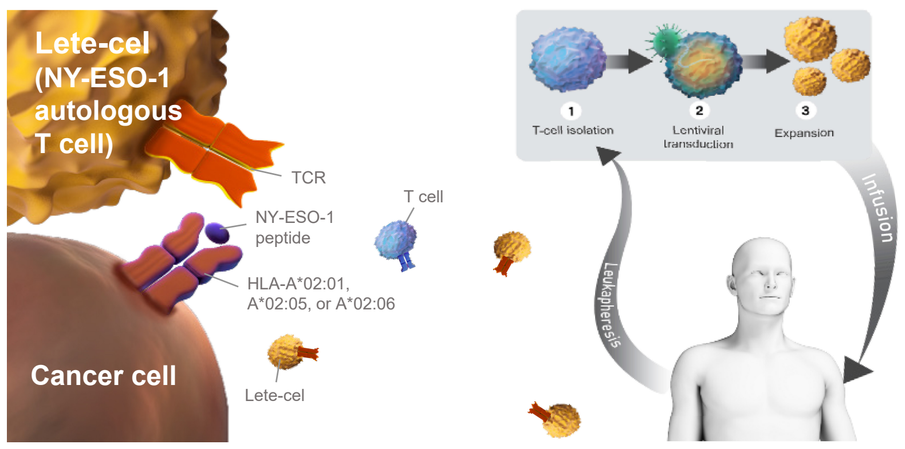
Characteristic	N=5
Synovial sarcoma	5 (100)
Primary site, n (%) Extremities Trunk Lung Mediastinum	 2 (40) 1 (20) 1 (20) 1 (20)
Male, n (%)	2 (40)
Female, n (%)	3 (60)
Race, White, n (%)	5 (100)
Age, years, median (min, max)	57 (16, 63)
One HLA allele positive: A*02:01 – other, n (%) Two allele positive: A*02:01 – A*02:01, n (%)	4 (80) 1 (20)
Tumor cells positive for NY-ESO-1,[a] median (min, max)	100 (70, 100)
Tumor histology type, n (%) Monophasic Not available	 4 (80) 1 (20)
Prior radiotherapy regimens before leukapheresis, n (%) 0 1 >1	 2 (40) 2 (40) 1 (20)
Received neoadjuvant and adjuvant chemotherapy, n (%)	1 (20)
Disease Stage IV at screening with TNM Stage M1 distant metastases, n (%)	5 (100)
Time from diagnosis of locally advanced or metastatic disease to leukapheresis, months, median (min, max)	2.4 (1.6, 5.9)
Time from leukapheresis to T-cell infusion, months, median (min, max)	2.3 (2.1, 11.3)
Transduced cell dose, median (min, max)	5.4x10^9 (2.6, 9.2)

[a]≥30% of cells staining at 2+ or 3+ intensity by immunohistochemistry.
HLA, human leukocyte antigen; max, maximum; min, minimum.

T-cell persistence

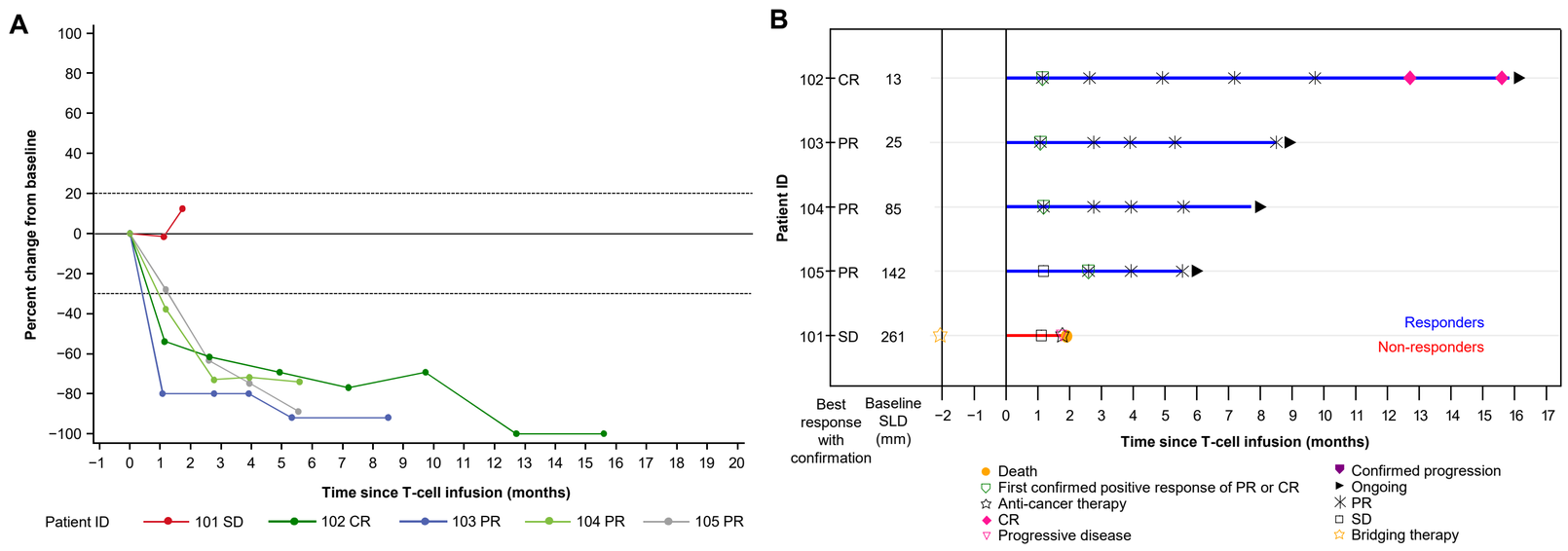
- Geometric means for T-cell persistence were 1,911,783 (% coefficient of variation [CV]: 53.7) copies per µg genomic DNA (gDNA) times days for $AUC_{(0–28d)}$, and 119,702 (%CV: 68.3) copies per µg gDNA for C_{max}, consistent with T-cell persistence in other studies of lete-cel[1,2]
- The four patients who responded to therapy continued to have detectable T-cell persistence during follow-up (**Figure 4**)

Figure 1. Lete-cel mechanism of action



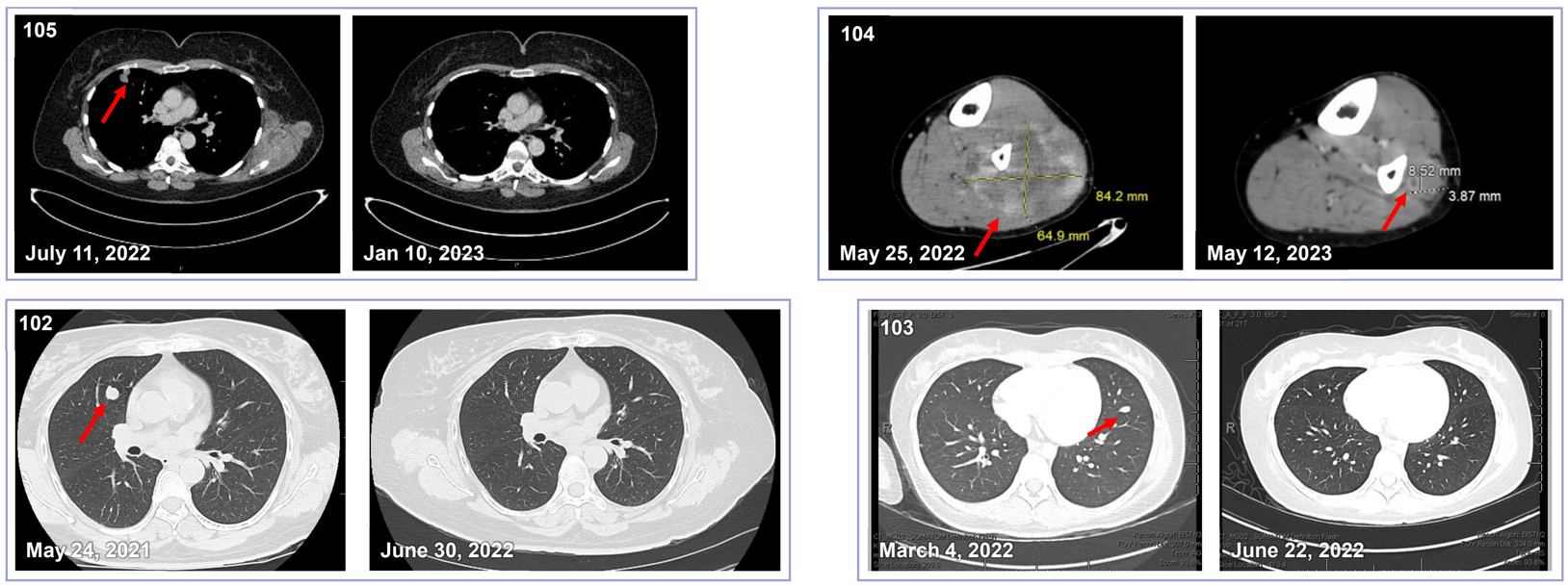
HLA, human leukocyte antigen; lete-cel, letetresgene autoleucel; TCR, T-cell receptor.

Figure 2. A. Spider plot of investigator-assessed percentage change from baseline in target lesion diameter per RECIST v1.1. B. Swimmer's plot of duration on interventional phase



Interventional phase is defined as the time between LD and the time at which the patient either progresses, dies, or withdraws from treatment. Best overall response with confirmation by RECIST v1.1. 20% threshold, RECIST threshold for progressive disease; −30% threshold, RECIST threshold for partial response.
CR, complete response; LD, lymphodepletion regimen; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SLD, sum lesion diameter.

Figure 3. Representative CT scans for the 4 responding patients at baseline and best response



CT, computed tomography.

Figure 4. T-cell persistence by concentration over time

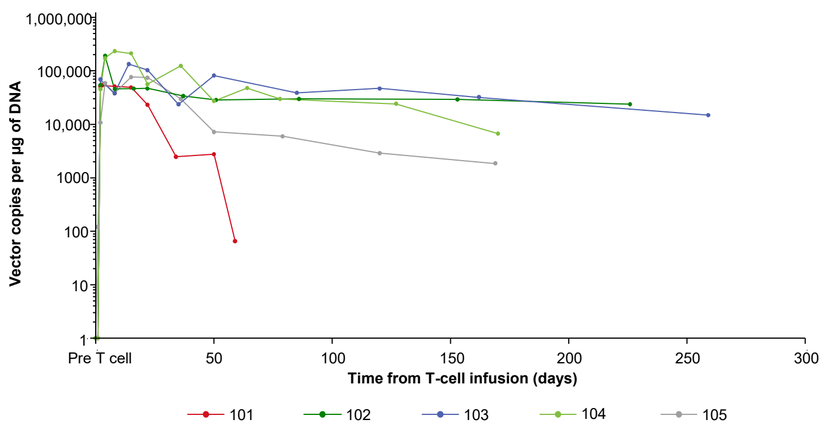


Table 3. Treatment-emergent adverse events of special interest

Adverse event, n (%)	N=5
Cytokine release syndrome	5 (100)
Graft-versus-host disease	2 (40)
Neutropenia/neutrophil count decreased	3 (60)
Platelet count decreased	2 (40)
White blood cell count decreased	2 (40)
Anemia	1 (20)

Efficacy

- The ORR was 80% (95% CI: 28.4–99.5%), with one complete response (CR) and three partial responses (PRs) (**Figure 2**), with representative images shown in **Figure 3**
- One patient had stable disease lasting <12 weeks as best confirmed response, yielding a DCR of 80% (95% CI: 28.4–99.5%)
  - This patient developed clinical disease progression, Grade 5 hemoptysis from pulmonary metastases, and died from their disease
- Median TTR was 1.2 (range: 1.1–2.6) months for the four patients with CR/PR
- The median DOR and PFS are not mature, as response was ongoing among the four responders at the time of this analysis
- For the four responders, at the time of this analysis:
  - DOR was censored at 3.0, 4.4, 7.5, and 14.5 months
  - PFS was censored at 5.6, 5.6, 8.5, and 15.6 months

Safety

- All patients had at least one treatment-emergent adverse event (TEAE) (**Table 3**)
  - Three patients had at least one serious TEAE
- The most common TEAEs were cytokine release syndrome (CRS) 100%, all T-cell related; Grade 1 (60%), Grade 2 (20%), Grade 3 (20%), alanine transaminase increase (60%), neutropenia/neutrophil count decreased (60%), and fatigue (60%)
- All five occurrences of CRS resolved; four were treated with tocilizumab. Median (range) time to onset was 2 days (1–8) and duration was 9 days (3–13)
- T-cell–related serious TEAEs were CRS (20%) and graft versus host disease (20%) (both Grade 3)
- Three (60%) patients had treatment-emergent cytopenia, maximum Grade 4
- Two (40%) patients developed graft-versus-host disease predominated by rash
  - Based on clinical diagnosis without pathologic confirmation, both considered T-cell related
  - One case was serious (Grade 3) and the other was non-serious (Grade 2)
- One patient died due to progressive disease; they developed Grade 5 hemoptysis from pulmonary metastasis that was treated with arterial embolization followed by radiation, but neither were effective

Conclusions

- This study highlights the challenges of enrolling patients with advanced/metastatic treatment-naïve rare sarcoma in a cell therapy trial
- Encouraging efficacy was seen in this small population of treatment-naïve patients in the advanced/metastatic setting with 80% ORR, with all responses ongoing at the time of this analysis
- The TEAEs in this substudy are consistent with the known safety profile of lete-cel
- All responders had detectable T-cell persistence through follow-up

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References

1. D'Angelo SP, et al. *Cancer Discov*. 2018;8:944–57.
2. Nishihori T, et al. *Blood Adv*. 2023;7:1168–77.

Footnotes and Abbreviations Used in Text

AUC, area under the curve; C_{max}, maximum concentration; CR, complete response; CRS, cytokine release syndrome; CV, coefficient of variation; DCR, disease control rate; DOR, duration of response; HLA, human leukocyte antigen; LD, lymphodepletion; lete-cel, letetresgene autoleucel; MRCLS, myxoid/round cell liposarcoma; ORR, overall response rate; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SyS, synovial sarcoma; TEAE, treatment-emergent adverse event; TTR, time to response.

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