Efficacy and Safety of Lifileucel, an Investigational Autologous Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy in Patients With Advanced Melanoma Previously Treated With Anti-LAG3 Antibody

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Background

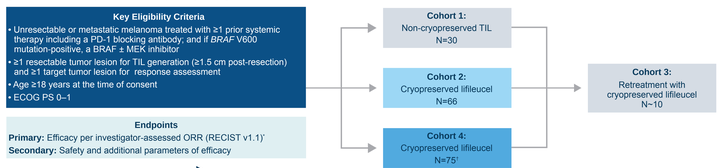
- The adoption of immune checkpoint inhibitors (ICI) in the first-line setting has substantially improved outcomes for patients with advanced melanoma[1,2]; however, treatment options are limited following disease progression on or after ICI therapy[3,4]
- The recent approval of relatlimab (anti-lymphocyte activation gene 3 [LAG3] antibody) + nivolumab in the US for patients with advanced melanoma,[5] followed by the positive opinion of the therapy by the Committee for Medicinal Products for Human Use (CHMP) for patients with advanced melanoma who have programmed death-ligand 1 (PD-L1) expression <1%,[6] provides patients with a new option for first-line treatment of advanced melanoma
  - Efficacy of second-line relatlimab + nivolumab in patients who progress after ICI treatment is modest (objective response rate [ORR] of 16%)[7] as is the efficacy of second-line ICI after progression on relatlimab + nivolumab (ORR 11%), suggesting emergence of cross-resistance[8]
- Lifileucel is a one-time, autologous tumor-infiltrating lymphocyte (TIL) cell therapy that is currently being investigated for the treatment of patients with advanced (unresectable or metastatic) melanoma in the post-ICI setting in a multicohort phase 2 study (C-144-01; NCT02360579)[9]
- In previous analyses of C-144-01 (Cohort 2), lifileucel monotherapy demonstrated encouraging efficacy, including an investigator-assessed ORR of 36% and an expected and manageable safety profile[9,10]

Objective

- In this post hoc subgroup analysis of patients enrolled in the C-144-01 study, we assessed the efficacy and safety of lifileucel in patients who progressed on or after anti-LAG3–containing therapy

Methods

Figure 1. C-144-01 (NCT02360579) Study Design and Flow Chart

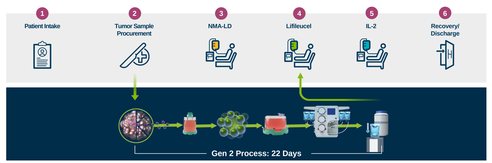


*The original primary endpoint for Cohort 2 was investigator-assessed ORR. Cohort 4 had a prospectively defined endpoint of ORR by an IRC; the primary endpoint of Cohort 2 was then amended to IRC-assessed ORR. This subanalysis uses investigator-assessed ORR for both Cohort 2 and Cohort 4.
†Planned enrollment.

Patients and Methods

- Data cut as of 15 September 2021
- Patients in Cohort 2 and Cohort 4 received the same treatment regimen, using lifileucel based on the Gen 2 manufacturing process (**Figure 1** and **Figure 2**)
- This post hoc analysis included patients from Cohorts 2 and 4 who had received prior anti-LAG3 therapy in combination with anti–PD-1 therapy
  - Patients were also classified as having either primary (best response to treatment was PD) or acquired (best response to treatment was CR, PR, SD, or unknown, but progressed later) resistance to anti-LAG3 therapy

Figure 2. Lifileucel Manufacturing and Patient Journey



Results

- 13 patients across Cohorts 2 and 4 had received prior anti-LAG3 treatment and were included in the analysis (**Table 1**)
  - Median follow-up duration was 24.4 months
  - Median number of prior therapies was 3
  - Median duration of prior anti-LAG3 treatment was 3.3 months

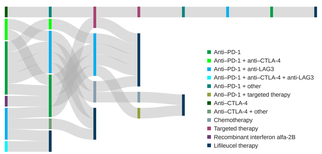
Table 1. Baseline Characteristics for Patients With Prior Anti-LAG3 Therapy

Characteristic	N=13
Age, years	
Median	57
Min, max	29, 70
Sex, n (%)	
Female	5 (38.5)
Male	8 (61.5)
Baseline ECOG PS, n (%)	
0	4 (30.8)
1	9 (69.2)
BRAF mutation status,* n (%)	
Mutated V600E or V600K	2 (15.4)
Wild type	10 (76.9)
PD-L1 status,† n (%)	
Positive	
TPS ≥1%	5 (38.5)
TPS ≥5%	4 (30.8)
Negative	
TPS <1%	3 (23.1)
TPS <5%	4 (30.8)
Liver lesions, n (%)	4 (30.8)
Liver and/or brain lesions, n (%)	5 (38.5)
Target lesion sum of diameter, mm	
Median (range)	83.0 (37.0, 267.3)
Number of target and nontarget lesions	
>3, n (%)	11 (84.6)
Baseline LDH, n (%)	
≤ULN	4 (30.8)
>1 to 2 × ULN	7 (53.8)
>2 × ULN	2 (15.4)
Number of prior therapies	
Median	3
Min, max	1, 7
Anti-LAG3 line of therapy, n (%)	
1L	4 (30.8)
2L+	9 (69.2)
Duration of anti-LAG3 therapy, months	
Median	3.3
Min, max	0.03, 9.2
Other prior therapies, n (%)	
Anti–PD-1 / PD-L1	13 (100)
Anti–CTLA-4	6 (46.2)
Anti–PD-1 + anti–CTLA-4 combination	4 (30.8)
BRAF ± MEK inhibitor	2 (15.4)

*One patient (7.7%) had a missing *BRAF* mutation status.
†Five patients (38.5%) had missing PD-L1 status.

- Anti-LAG3 therapy was used in the first-line setting in 4 patients, and in the second- or later-line settings in 9 patients (**Figure 3**)
  - All anti-LAG3 treatments were given in combinations; in 12 patients, anti-LAG3 was combined with anti-programmed cell death protein 1 (PD-1) therapy, and in 1 patient it was combined with anti–PD-1 and anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) therapies
  - Anti-LAG3 combination was used as the last therapy prior to lifileucel in 7 patients

Figure 3. Treatment Journey for Patients With Prior Anti-LAG3 Therapy



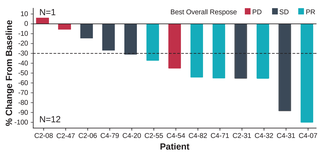
The R package networkD3 was used to generate the Sankey plot.

- Investigator-assessed ORR was 38.5% (**Table 2**, **Figure 4**), consistent with the overall study population[9,10]

Table 2. Efficacy Outcomes by Investigator Assessment per RECIST v1.1 in Patients With Prior Anti-LAG3 Therapy

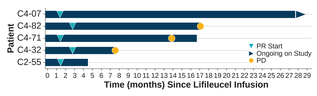
Investigator-Assessed Response, n (%)	N=13
Objective response rate	5 (38.5)
Best overall response	
CR	0
PR	5 (38.5)
SD	5 (38.5)
PD	3 (23.1)

Figure 4. Best Percentage Change From Baseline in Target Lesion SOD in Patients With Prior Anti-LAG3 Therapy



Patient C4-07 had a complete target lesion reduction; however, a non-target lesion was not completely resolved, so the best overall response was labelled as PR.

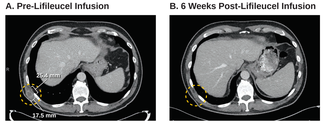
Figure 5. Time to Response, DOR, and Time on Efficacy Assessment for Patients With Prior Anti-LAG3 Therapy Who Achieved Response



A bar is presented for each patient starting from date of lifileucel infusion up to date of new anti-cancer therapy, end of assessment, death, or data cutoff date, whichever occurs earlier.

- In all responders, first response was recorded <3 months after lifileucel infusion (**Figure 5**)
- Three of 5 (60%) responses extended beyond 12 months, with 1 response still ongoing at time of data cutoff (**Figure 5**)
- Median DOR was 13.4 months (95% CI, 4.8, NR)
- Three responders had primary and 2 had acquired anti-LAG3 resistance

Figure 6. Images From a Partial Responder Pre-Lifileucel Infusion and 6 Weeks Post-Lifileucel Infusion (Patient C4-07)



- A patient (C4-07) who achieved best response of PR presented with a chest wall muscle target lesion that measured ~25.4 × 17.5 mm at baseline (**Figure 6A**) and showed 75% reduction at week 6 (**Figure 6B**) and 100% reduction at week 12 (not shown)

Table 3. TEAEs Reported in Patients With Prior Anti-LAG3 Therapy (≥30% Grade 3/4 Incidence)

Preferred Term, n (%)	Any Grade	Grade 3/4
Any TEAE*	13 (100)	12 (92.3)
Anemia	11 (84.6)	11 (84.6)
Thrombocytopenia	11 (84.6)	11 (84.6)
Febrile neutropenia	5 (38.5)	5 (38.5)
Leukopenia	7 (53.8)	4 (30.8)
Lymphopenia	6 (46.2)	4 (30.8)
Neutropenia	6 (46.2)	4 (30.8)

*TEAEs refer to all AEs starting on or after lifileucel infusion for up to 30 days; patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.

- The incidence of AEs decreased rapidly within 2 weeks of lifileucel infusion (**Figure 7**)
- TEAEs were manageable and expected (**Table 3**)
- No Grade 5 TEAEs were reported for this subpopulation

Figure 7. AEs Over Time for Patients With Prior Anti-LAG3 Therapy

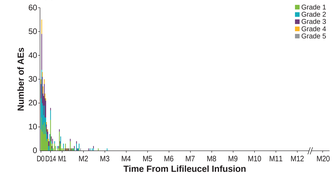
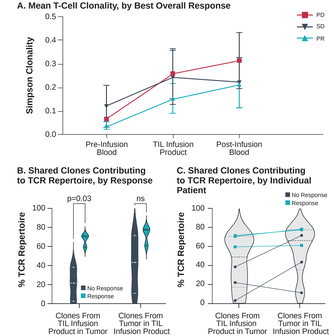


Figure 8. TCR Repertoire Analysis in Patients With Prior Anti-LAG3 Therapy



- Patient samples were assessed for both TCR repertoire clonality (n=13) and the proportions of the tumor and TIL infusion product repertoires that were composed of shared clonotypes (n=6)
  - Patients with BOR of PR trended to show greater polyclonality (lower Simpson Clonality) numerically in pre-infusion blood, TIL infusion product, and post-infusion blood samples, compared with patients achieving SD or PD (**Figure 8A**)
  - A numerically higher percentage of shared TCR repertoire between the TIL infusion product and tumor sample was observed in the responders (n=3) than in the non-responders (n=3) (p=0.03) (**Figure 8B,C**)

Conclusions

- Relapsed and refractory metastatic melanoma presents a high unmet medical need with low survival rates and with limited durable treatment options
- Treatment with lifileucel after prior anti-LAG3 failure produced a response rate consistent with the overall C-144-01 study population of patients with heavily pretreated advanced melanoma
  - Investigator-assessed ORR was 38.5%
  - Responses were durable, with 60% extending beyond 12 months
  - Responses were observed in patients with both primary and acquired anti-LAG3 resistance, suggesting that lifileucel outcomes may not be affected by prior anti-LAG3 treatment
- The safety profile of lifileucel in this patient sub-population was manageable and consistent with prior reports from the C-144-01 study
- The tumor TCR repertoire of responders showed a higher proportion of shared T-cell clones between tumor and TIL infusion product compared with non-responders, a finding that will need to be confirmed in larger datasets

Lifileucel TIL cell therapy provides a novel non-ICI–based therapeutic option for patients with advanced melanoma who progress after anti-LAG3 and ICI combination therapy

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Abbreviations

1L, first line; 2L+, second line or later; AE, adverse event; BOR, best overall response; CHMP, Committee for Medicinal Products for Human Use; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EOA, end of assessment; ICI, immune checkpoint inhibitors; ICF, informed consent form; IL-2, interleukin-2; IRC, independent review committee; LAG3, lymphocyte activation gene 3; LDH, lactate dehydrogenase; M, month; NE, not evaluable; NMA-LD, nonmyeloablative lymphodepletion; NR, not reached; ns, not significant; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOD, sum of diameters; TCR, T-cell receptor; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocytes; TPS, tumor proportion score; ULN, upper limit of normal.

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