Supplemental Materials

Supplemental Methods

Supplemental assessments:

In patients who achieved ≥ PR, the time to response (TTR; defined as the time from lete-cel infusion to initial date of confirmed response) and duration of response (DoR (time from the initial date of confirmed response to the date of progressive disease or death due to disease under study) were assessed.

Assessments for clinical response and progression were to be performed Q3W from Week 3 to Week 24, then Q6W to Week 72, and then Q12W until confirmed disease progression, death, or study withdrawal. T-cell peak expansion (C_{max}), time to C_{max} (T_{max}), and area under the curve (AUC) from zero to time t (AUC_{0-t}) were assessed as secondary endpoints using DNA-based quantitative (q)PCR to estimate transgene copy numbers (copies/µg gDNA).

Exploratory endpoints included OS (defined as the time from lete-cel infusion to death due to any cause), lete-cel kinetics in peripheral blood mononuclear cells (PBMCs) and/or bone marrow samples, and serum cytokine levels pre- and post–lete-cel infusion (and their association with CRS and response). Serum samples were collected at baseline and at each visit post lete-cel infusion. For patients with suspected CRS, serum samples were collected approximately every other day until resolution or if an alternative diagnosis was established. Serum cytokines, including interleukin (IL)-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, IL-2Rα, IL-10, IL-13, IL-1Ra, IL-8, IL-12, IL-15, IL-2, and granulocyte-macrophage colony-stimulating factor (GM-CSF), were measured by Meso Scale Discovery (MSD) immunoassay. At screening, bone marrow samples were assessed for NY-ESO-1/LAGE-1a expression via RNA-based RT-quantitative PCR.

Supplemental statistics:

Cytopenias were reported as pooled terms: anemia included anemia/red blood cell count decreased; leukopenia included leukopenia/white blood cell decreased;

thrombocytopenia included thrombocytopenia/platelet count decreased; lymphopenia included lymphopenia/lymphocyte count decreased; and neutropenia included neutropenia/neutrophil count decreased.

OS was not mature at the time of the analysis. The study was not powered to compare efficacy or safety data between the study arms. Results of all analyses were therefore summarized descriptively. Potential biomarker correlates of clinical response were summarized graphically in a post-hoc analysis as longitudinal profiles with the lower limit of detection displayed when applicable.

Treatment-limiting toxicity (TLT) definition

The following toxicities were considered to be TLTs:

- Any ≥ grade 4 adverse event (AE) except for the exclusions listed below:
  - Grade 3 non-infectious pneumonitis
  - Any other grade 3 AE (excluding pneumonitis) that does not improve to grade 2 within 7 days after onset despite medical management and supportive care
- Any AE that prevents dosing of pembrolizumab at Week 3, has not resolved to an acceptable level by Week 6, and consequently precludes a subject randomized to Arm 2 from initiating pembrolizumab was counted as a TLT
- An AE not listed above could be defined as a TLT after consultation with the Sponsor, the Investigators, and the Safety Review Team based on the emerging safety profile
- The following toxicities were not considered to be TLTs:
  - Grade 3/4 leukopenia, lymphopenia, neutropenia, or febrile neutropenia
  - Grade 3/4 thrombocytopenia not associated with significant bleeding
  - Grade 3 anemia
  - Grade 4 CRS or toxicities related to CRS resolving to grade ≤ 2 within 7 days
  - Other grade 3 laboratory abnormality determined to be not clinically significant by the investigator

- Grade 3/4 fever and chills
- Grade 3/4 hypoalbuminemia or abnormal electrolytes responding to supplementation/correction
- AEs related to the cancer or its progression

63 **Supplemental Table 1. Summary of treatment-emergent SAEs**

Patients, n (%)	Arm 1 (lete-cel) (N = 3)		Arm 2 (lete-cel + pembrolizumab) (N = 3)		Total (N = 6)	
	Total	Grade ≥3	Total	Grade ≥3	Total	Grade ≥3
Treatment-emergent SAEs	2 (67)	1 (33)	1 (33)	1 (33)	2 (33)	2 (33)
Pancytopenia[a]	1 (33)	1 (33)	0	0	1 (17)	1 (17)
Back pain	1 (33)	0	0	0	1 (17)	0
Pneumonia	1 (33)	1 (33)	0	0	1 (17)	1 (17)
Tumor-related pain	1 (33)	0	0	0	1 (17)	0

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65 Treatment-emergent SAEs in the mITT population, including all patients who received lete-cel. Safety was assessed per NCI-
66 CTCAE Version 4.0.[26]
67 AE, adverse event; lete-cel, letetresgene autoleucel; mITT, modified intention-to-treat; N, patients in mITT population; n, patients
68 with available data; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; SAE, serious adverse
69 event.
70 [a]Indicates a treatment-related AE, defined as those related to lymphodepletion or lete-cel infusion with definite, probable, and
71 possible study drug relationship; AEs are listed in descending order of total frequency.
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Supplemental Table 2. Response and PFS outcomes

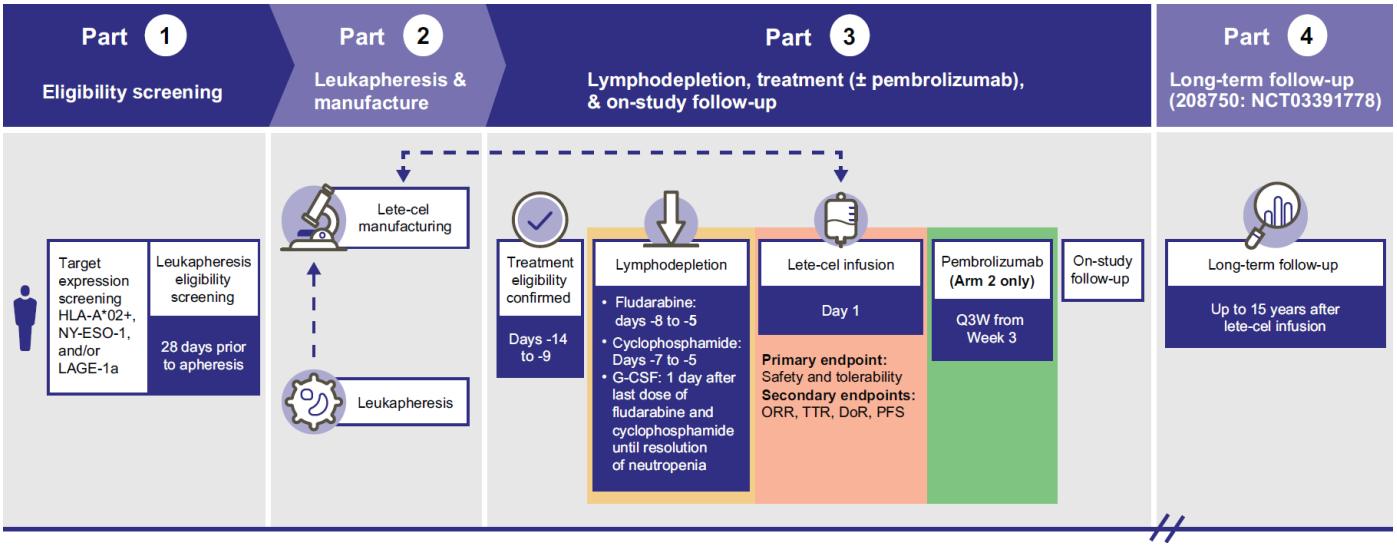
	Arm 1 (lete-cel) (N = 3)	Arm 2 (lete-cel+ pembrolizumab) (N = 3)	Total (N = 6)
Best responses, n (%)			
sCR	0	0	0
CR	1 (33)	0	1 (17)
VGPR	0	1 (33)	1 (17)
PR	0	1 (33)	1 (17)
SD	2 (67)	1 (33)	3 (50)
ORR, % (95% CI)[a]	33.3% (0.8–90.6%)	66.7% (9.4–99.2%)	50.0% (11.8–88.2%)
PFS, range, months	n = 3 1.31–5.16	n = 2[b] 2.76–2.79	n = 5 1.31–5.16

Efficacy outcome in the mITT population, including all patients who received lete-cel.

CI, confidence interval; CR, complete response; IMWG, International Myeloma Working Group; lete-cel, letetresgene autoleucel; mITT, modified intention-to-treat; N, patients in mITT population; n, patients with available data; ORR, overall response rate; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

[a]ORR defined as a PR or better per IMWG Uniform Response Criteria 2016. 95% CI calculated using exact (Clopper-Pearson) method; [b]One patient was censored, follow-up ended at 2.1 months.

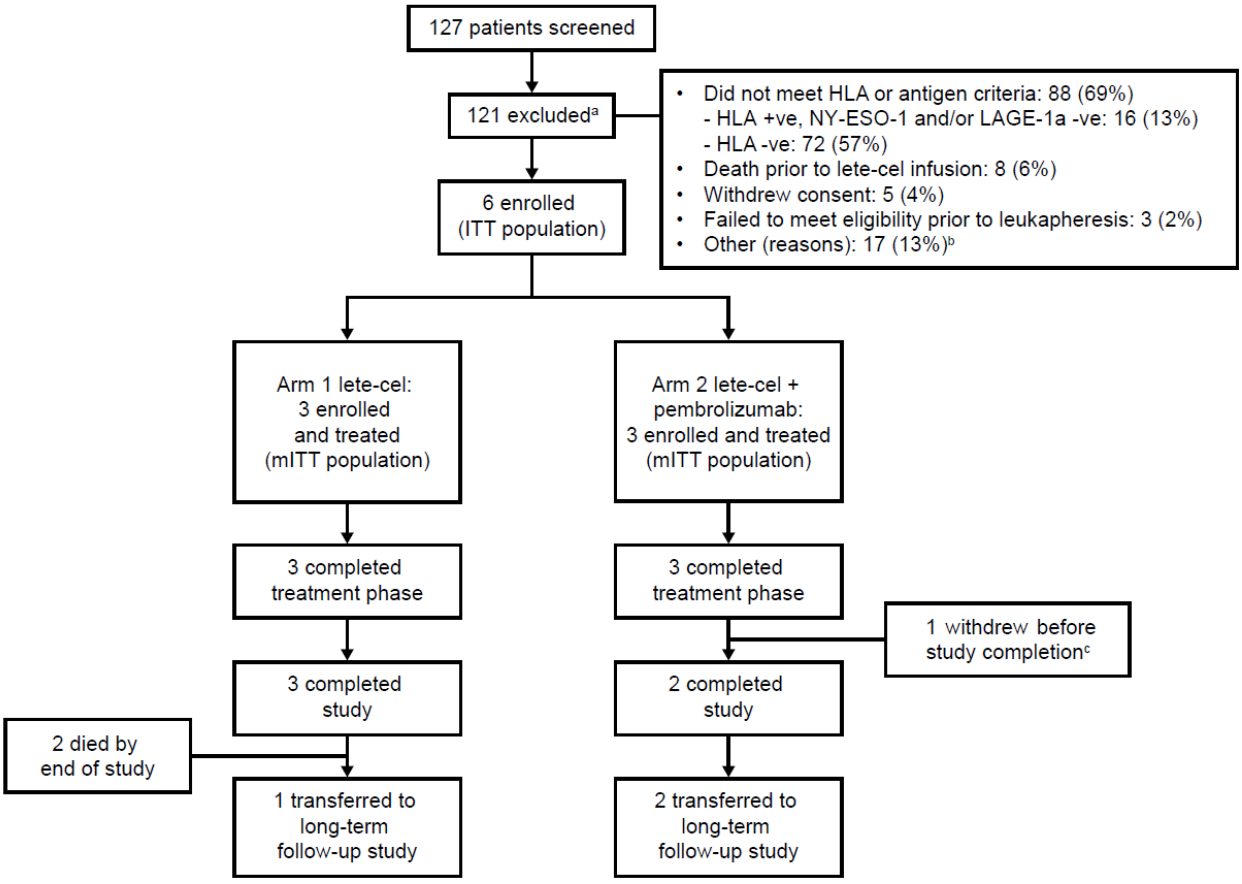
Supplemental Figure 1. Study design



Study design schematic demonstrating the 3 parts of this study and long-term follow-up in a separate study. For the first 5 patients, enrollment was randomized 1:1 to Arms 1 and 2. Following protocol amendment and starting with patient 6, enrollment to Arm 1 was to be completed prior to resumption of enrollment into Arm 2.

DoR, duration of response; G-CSF, granulocyte colony-stimulating factor; HLA, human leukocyte antigen; LAGE-1a, L antigen family member 1 isoform A; lete-cel, letetresgene autoleucel; NY-ESO-1, New York esophageal squamous cell carcinoma-1; ORR, overall response rate; PFS, progression-free survival; Q3W, every 3 weeks; TTR, time to response.

Supplemental Figure 2. Patient disposition



Patient disposition from screen in this study (NCT03168438) to transfer to long-term follow-up study (NCT03391778).

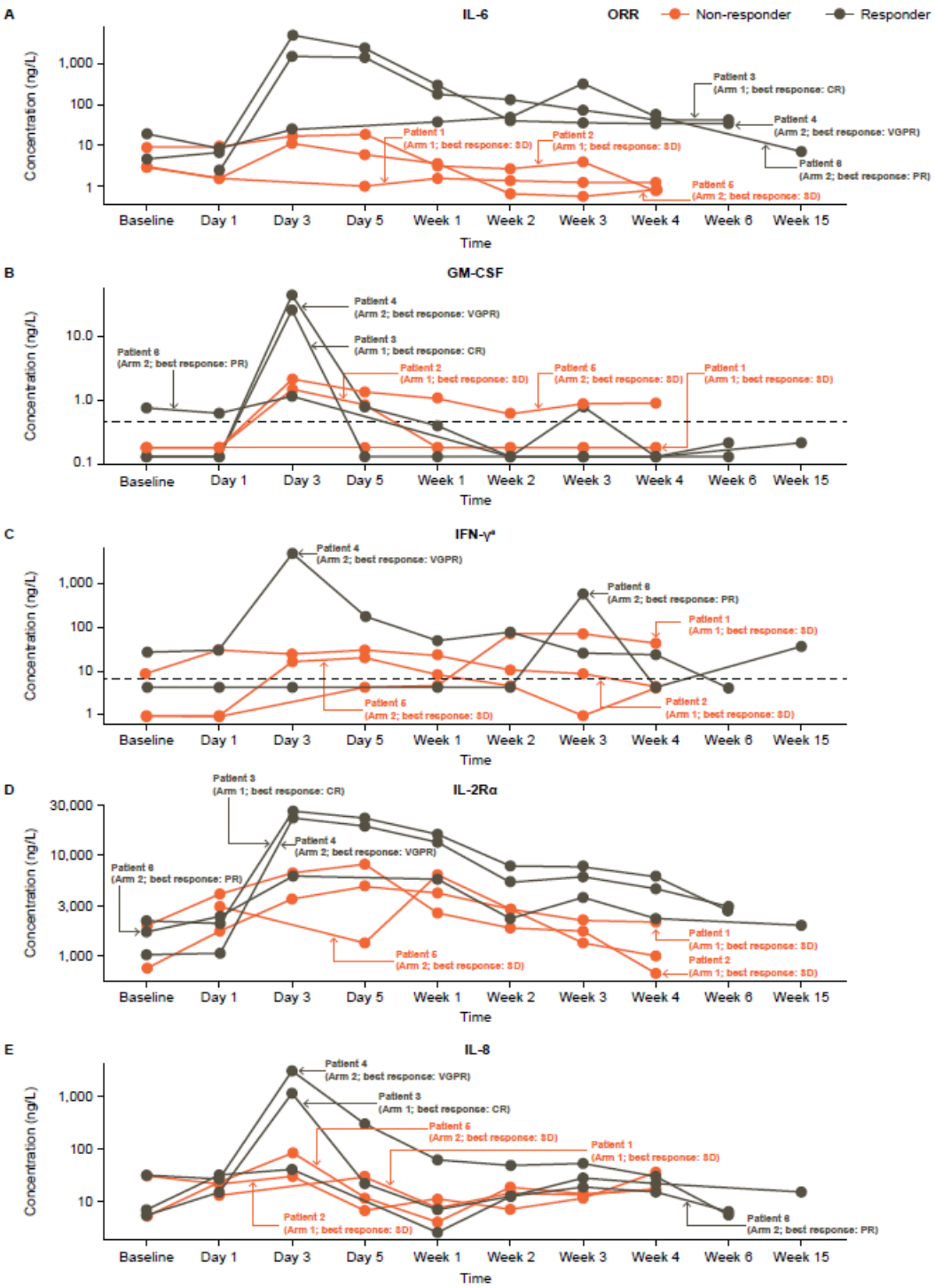
[a]Of the total 127 patients screened for HLA, 55 were positive for at least one of the eligible alleles. Of these 55 patients, 39 patients were identified as positive for antigen expression.

[b]Other reasons included: bone marrow assessment not completed prior to enrollment closing (n = 6); did not meet other sponsor's requirements (n = 4); patient started other clinical trial (n = 3); investigator and sponsor decision (n = 1); had diagnosis of plasma cell leukemia (n = 1); patient passed away before consent could be obtained (n = 1); and ineligible due to cardiac assessment (n = 1).

[c]One patient in Arm 2 was withdrawn from the study (declined long-term follow-up) prior to completion of the treatment phase.

+ve, positive; -ve, negative; HLA, human leukocyte antigen; ITT, intention-to-treat; LAGE-1a, L antigen family member 1 isoform A; lete-cel, letetresgene autoleucel; mITT, modified intention-to-treat; NY-ESO-1, New York esophageal squamous cell carcinoma-1.

Supplemental Figure 3. Cytokine levels over time by patient

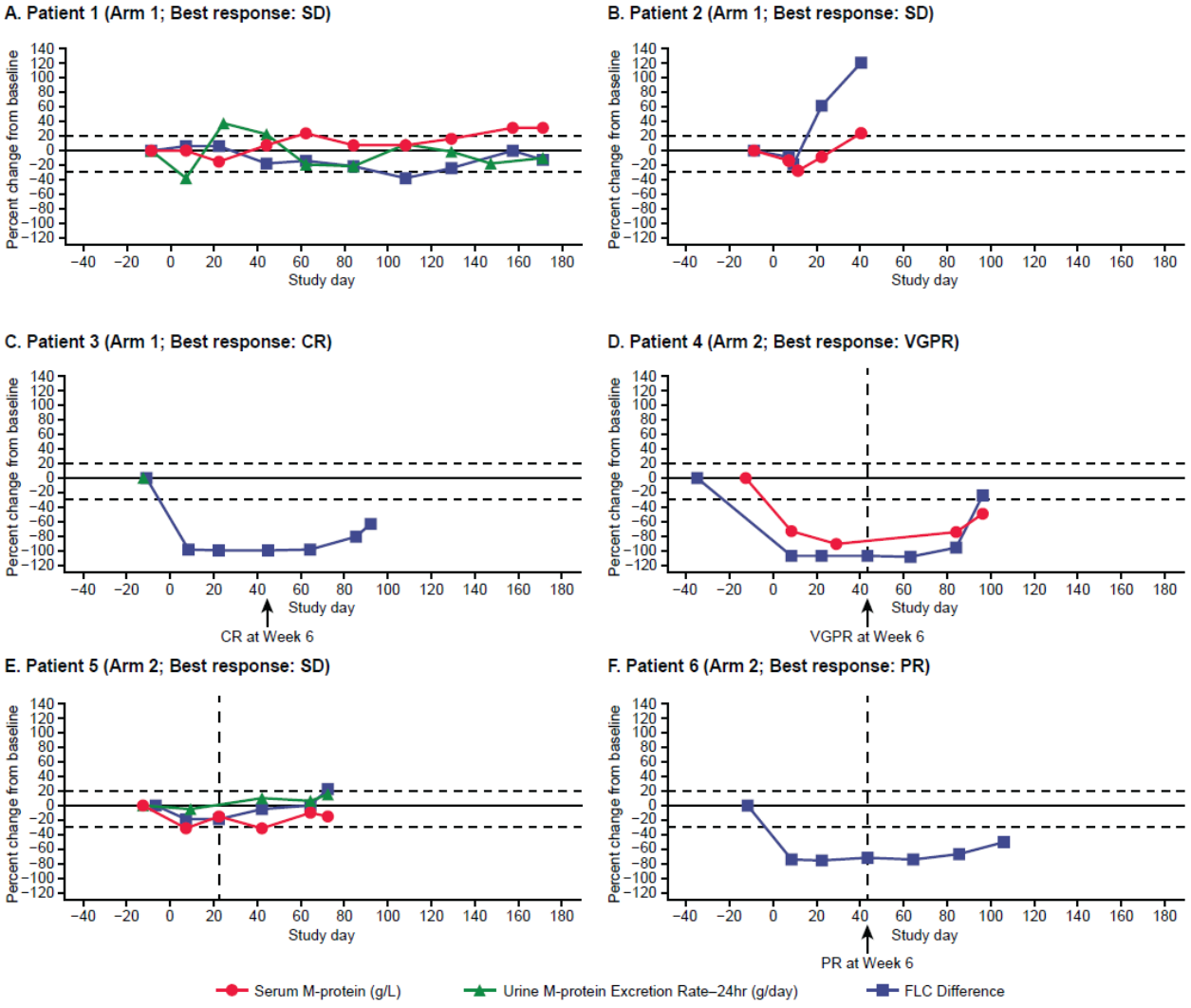


Expression of IL-6 (**A**), GM-CSF (**B**), IFN-γ (**C**), IL-2Rα (**D**), and IL-8 (**E**) over time in responders (brown lines, defined as patients who achieved an ORR [PR or better] per IMWG Uniform Response Criteria 2016) compared with non-responders (orange lines). Dotted lines represent LLOQ.

CR, complete response; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; IL-2Rα, interleukin-2 receptor alpha; lete-cel, letetresgene autoleucel; LLOQ, lower limit of quantitation; MM, multiple myeloma; PR, partial response; SD, stable disease; VGPR, very good partial response.

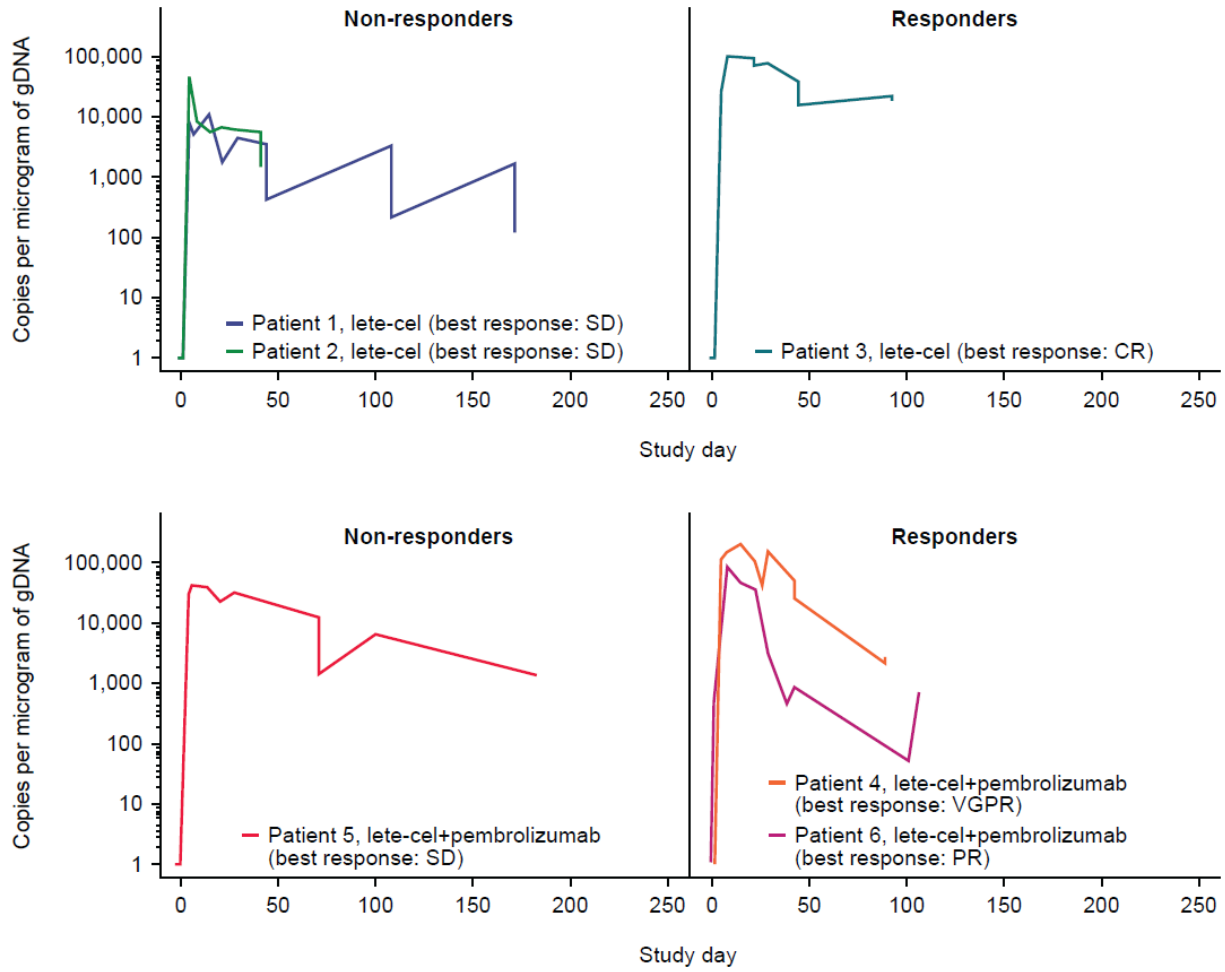
[a]Patient 3 not shown (data only available at 1 timepoint).

Supplemental Figure 4. Change in biomarker levels by patients



Percent change in serum M-protein (g/L; red line), urine monoclonal protein excretion rate – 24hr (g/day; green line), and free light chain (blue line) in all patients with available data (Arm 1: patients 1–3 [A-C]; Arm 2: patients 4–6 [D-F]). Vertical dotted lines for patients 4–6 indicate the date of first pembrolizumab dose. Clinical response per IMWG Uniform Response Criteria 2016.
CR, complete response; FLC, free light chain; M-protein, myeloma protein, PR, partial response; SD, stable disease; VGPR, very good partial response.

Supplemental Figure 5. T-cell persistence over time in individual patients



T-cell persistence over time in responders and non-responders in each treatment arm. Clinical response defined as a ≥ PR per IMWG Uniform Response Criteria 2016).

CR, complete response; gDNA, genomic DNA; IMWG, International Myeloma Working Group; lete-cel, letetresgene autoleucel; PR, partial response; SD, stable disease; VGPR, very good partial response.