Duration of cytopenias in patients with advanced melanoma receiving the lifileucel regimen: analysis of data from a phase 2 trial

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Introduction

- Adoptive cell therapy with tumor-infiltrating lymphocytes (TIL) has been demonstrated to be effective in adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if *BRAF* V600 mutation positive, a *BRAF* inhibitor with or without a MEK inhibitor [1–3]
- Nonmyeloablative lymphodepletion (NMA-LD) optimizes the activity of the infused TIL cells by reducing competition for homeostatic cytokines and eliminating immunosuppressive cells, including Treg and myeloid-derived suppressor cells[4]
- Myelosuppression with NMA-LD results in transient bone marrow toxicity in the form of cytopenias (i.e., lymphopenia, neutropenia, thrombocytopenia, etc.) after TIL infusion[4,5]
- Lifileucel TIL cell therapy is approved for the treatment of patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and, if *BRAF* V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor[6]

USPI Boxed Warning

- The US prescribing information (USPI) includes a Boxed Warning indicating that patients should be monitored for prolonged severe cytopenia[6] based on a high incidence of investigator-reported grade ≥3 hematologic adverse events that did not resolve to grade ≤2 or lasted >30 days after lifileucel infusion
- Because adverse event (AE) reporting relies on investigator judgment, abnormal laboratory test values are reported as AEs if the investigator judges them to be clinically significant
- Changes in hematologic parameters are accurately reflected in the laboratory data because each value can be graded and correlated to an AE term

Hematologic Events by Laboratory Data and Transfusion Records

- Laboratory data collected at regular intervals provide an objective measure of the impact of the lifileucel regimen on patients' hematologic parameters during and after treatment
- The objective of the present analysis is to characterize effects of the lifileucel regimen on hematologic parameters during and after treatment using laboratory measurements to assess severity and duration of hematologic events
- We also evaluated the incidence and timing of platelet and red blood cell (RBC) transfusions during and after treatment

Methods

- The lifileucel regimen includes a preparative course of NMA-LD consisting of cyclophosphamide 60 mg/kg IV daily for 2 days followed by fludarabine 25 mg/m^2 IV daily for 5 days before the single infusion of lifileucel; beginning 3 to 4 hours after lifileucel infusion, patients receive intravenous interleukin-2 (IL-2) at 600,000 IU/kg IV every 8 to 12 hours for up to a maximum of 6 doses to support cell expansion
- We analyzed hematologic laboratory parameters from 156 patients who received the lifileucel regimen in cohorts 2 and 4 of the phase 2 C-144-01 trial (NCT02360579)[2]
  - Abnormal results were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
- Blood was drawn for assessment of complete blood count with differential at every patient visit, including:
  - Screening, baseline (Day -7, prior to the start of NMA-LD), daily on Days -6 through Day 4, Day 14, every 6 weeks through Month 6, and every 3 months thereafter until progressive disease, start of new therapy, or end of study (5 years or 60 months)

Results

- All 156 patients (100%) had hematologic lab abnormalities of grade 3/4 in the period from the start of NMA-LD to 30 days post lifileucel infusion
  - By Day -5, all patients achieved grade 3/4 lymphopenia as intended (**Figure 1**)
  - 100% of patients developed grade 3/4 neutropenia (**Figure 2**) and leukopenia (**Figure 3**)
  - 94.2% of patients had grade 3/4 thrombocytopenia (**Figure 4**), and 72.4% had grade 3/4 anemia (**Figure 5**)
- In a majority of patients, grade 3/4 cytopenia had resolved to grade ≤2 by Day 30 after lifileucel infusion. The percentages of patients with resolution of cytopenia are as follows: lymphopenia, 86.5%; neutropenia, 98.1%; leukopenia, 98.1%; thrombocytopenia, 96.6%; and anemia, 96.5%
- At Month 6 after lifileucel infusion, the percentage of patients with lymphopenia of grade ≤2 was 95% and 100% for other cytopenias

Figure 1. Prevalence of Grade 3/4 Lymphopenia

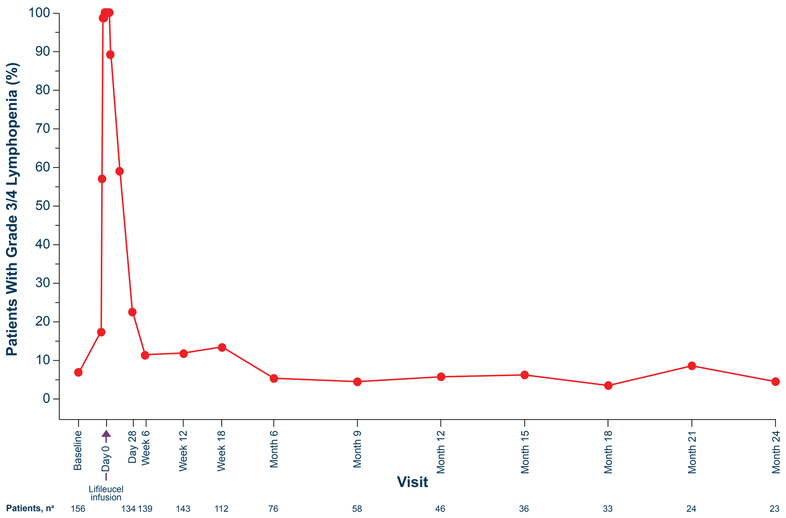


Figure 2. Prevalence of Grade 3/4 Neutropenia

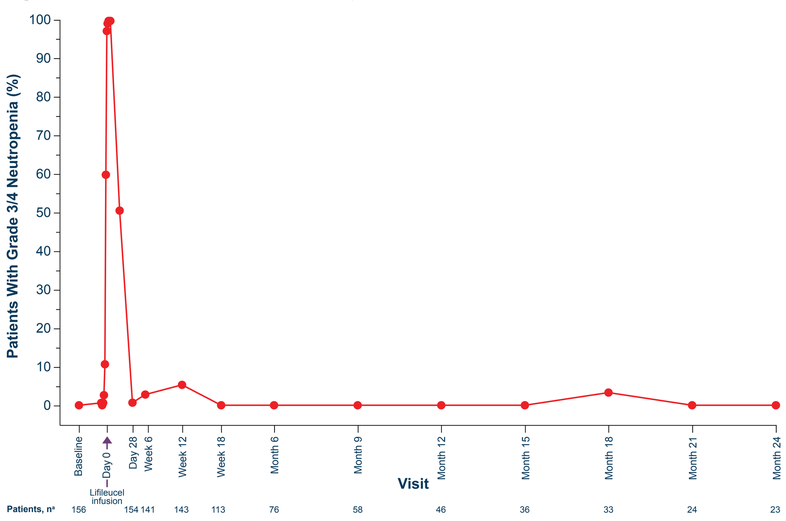


Figure 3. Prevalence of Grade 3/4 Leukopenia

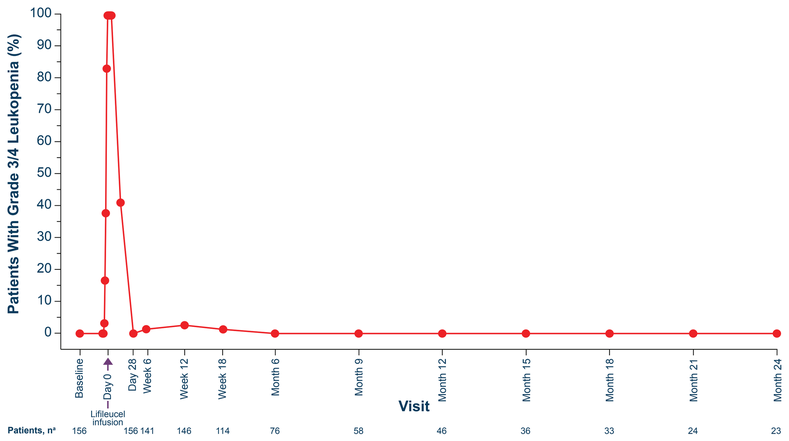


Figure 4. Prevalence of Grade 3/4 Thrombocytopenia

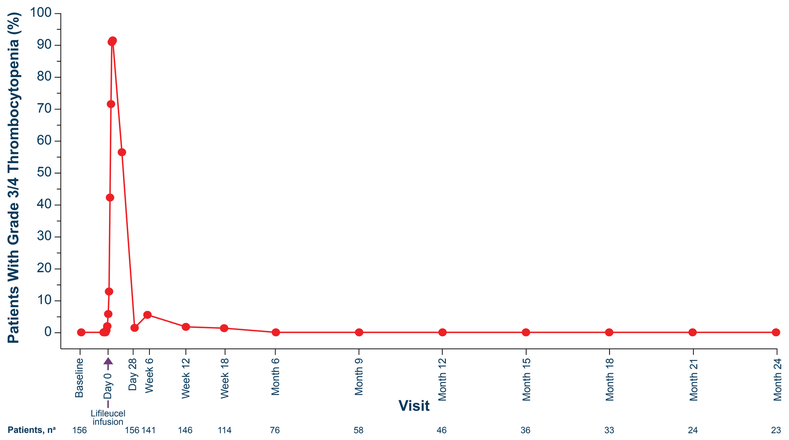
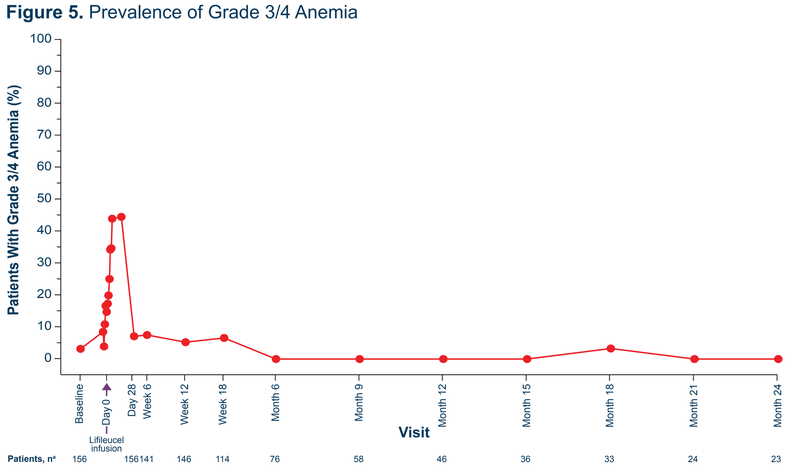
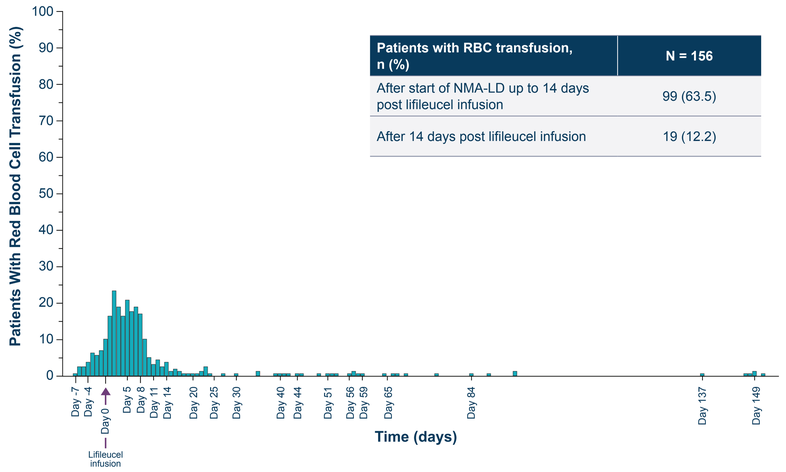


Figure 5. Prevalence of Grade 3/4 Anemia



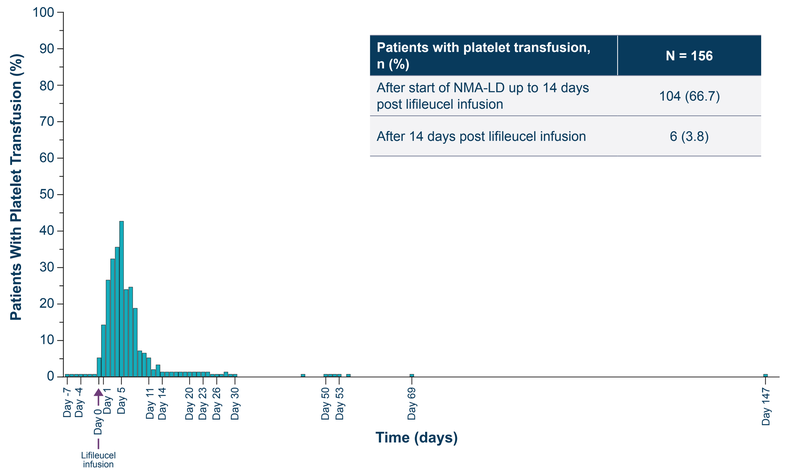
- The majority of platelet and RBC transfusions occurred in the first 14 days after the initiation of NMA-LD (**Figures 6 and 7**)

Figure 6. Frequency of RBC Transfusion over Time after the Start of NMA-LD



Patients with RBC transfusion, n (%)	N = 156
After start of NMA-LD up to 14 days post lifileucel infusion	99 (63.5)
After 14 days post lifileucel infusion	19 (12.2)

Figure 7. Frequency of Platelet Transfusion over Time after the Start of NMA-LD



Patients with platelet transfusion, n (%)	N = 156
After start of NMA-LD up to 14 days post lifileucel infusion	104 (66.7)
After 14 days post lifileucel infusion	6 (3.8)

Conclusions

- **These data show that the majority of grade 3/4 cytopenias resulting from the one-time administration of the lifileucel regimen resolve by Day 30 after lifileucel infusion and that clinically relevant prolonged cytopenia is a rare observation**
- **Cytopenia for the majority of patients recover to grade ≤2 by Day 30**
- **Most platelet and RBC transfusions were administered prior to Day 14 post lifileucel infusion; the need for transfusions declined steeply thereafter**

[a]Results are limited to patients for whom data were available at each post-baseline visit. There may have been adverse events reported in patients who did not have laboratory data reported.

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Abbreviations

AE, adverse event; CTCAE, Common Toxicity Criteria for Adverse Events; IL-2, interleukin-2; IV, intravenous; NMA-LD, nonmyeloablative lymphodepletion; PD-1, programmed cell death protein 1; RBC, red blood cell; TIL, tumor-infiltrating lymphocytes; USPI, United States Prescribing Information

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Disclosures

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