

Response Durability With Anzutresgene Autoleucel (Anzu-cel), a PRAME-directed T-cell Receptor T-cell Therapy, in Advanced Melanoma

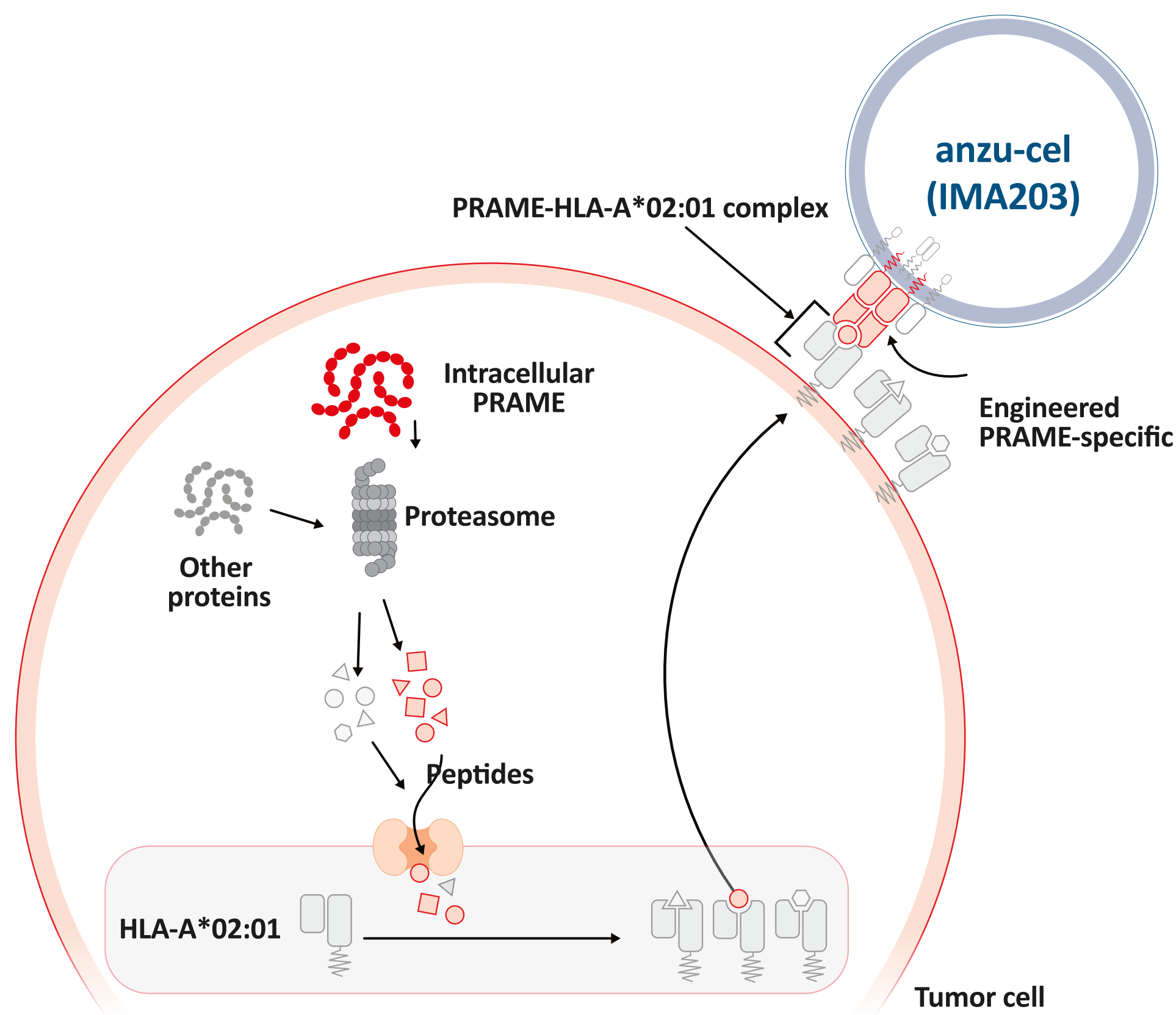
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BACKGROUND

- For patients with advanced melanoma, treatment options after first-line therapy provide limited responses and poor survival, highlighting the need for new systemic therapies with durable disease control^{1,3}
 - 2-year survival is approximately 40% in cutaneous melanoma following first-line immune checkpoint inhibitors and approximately 40% in previously treated uveal melanoma
- TCR T-cell therapies enable immune recognition of intracellular tumor antigens presented by cell-surface HLA, expanding the therapeutic landscape beyond targets accessible to conventional immunotherapies⁴
- Anzutresgene autoleucel (Anzu-cel, IMA203) is a one-time autologous TCR T-cell therapy targeting the cancer-associated antigen PRAME, which is expressed in >50 cancers and represents a novel immunotherapy target for melanoma (Figure 1)⁵
- Results from IMA203-101 (NCT03686124) demonstrate a predictable and manageable tolerability profile and rapid, deep, and durable systemic antitumor activity with anzu-cel⁶
- Here we characterize durable clinical benefit, including baseline characteristics associated with extended PFS (>12 months), and provide a longitudinal assessment of hematologic recovery
 - In addition to conventional cytopenia reporting, immune effector cell-associated hematotoxicity (ICAH) criteria, developed to characterize the depth and duration of neutropenia following CAR T-cell therapy, were applied to evaluate early and late hematotoxicity, supportive care requirements, and associated infectious complications

Figure 1. Anzu-cel Mechanism of Action



METHODS

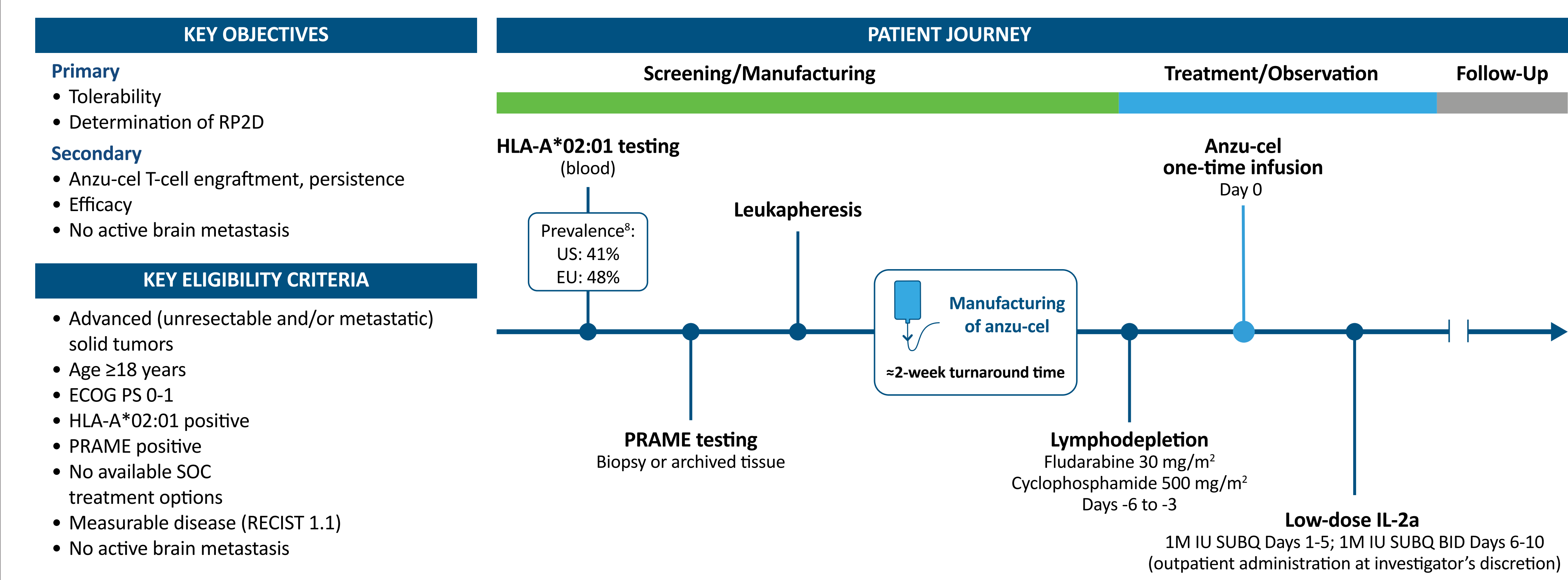
- IMA203-101 (NCT03686124) is an ongoing phase 1 study evaluating anzu-cel in patients with PRAME-positive solid tumors (Figure 2)
- Data cutoff: Sept 24, 2025 (median follow-up for PFS: 20 months)
- Univariate Cox proportional hazards regression models were used to evaluate a subset of clinical factors associated with PFS
 - The current presentation is a part of a broader exploratory analysis to examine variables across the patient journey including baseline characteristics, starting apheresis material, manufacturing, treatment, and postinfusion treatment course
 - This analysis was conducted in a cohort of patients with advanced melanoma who were treated with anzu-cel at cell doses between 1-10 billion TCR T cells (N=33); clinical variables evaluated in patients with melanoma with complete data included age, sex, ECOG performance status, target lesions, largest target lesion, LDH, prior lines of ICI therapy, infused cell dose, and effector-to-tumor (E:T) ratio
 - Variables were evaluated individually, without adjustment for other clinical or treatment characteristics
 - 5 patients were censored due to ongoing PFS <12 months (n=3) or withdrawal of consent (n=2)

- Hematologic recovery was characterized using ANC measurements following anzu-cel one-time infusion
- Late neutropenia-associated ICAHT (N-ICAHT) was assessed using EHA/EBMT consensus ANC thresholds developed for CAR T-cell therapy (Table 1)^{7,10}
- For this analysis, late N-ICAHT required ≥2 ANC measurements meeting the applicable threshold between days 28 (±3) to 100, including ≥1 qualifying ANC measurement between days 35-60

Table 1. Late N-ICAHT Grading

Parameter, n (%)	ANC (cells/μL)
Grade 1	≤1500
Grade 2	≤1000
Grade 3	≤500
Grade 4	≤100

Figure 2. IMA203-101 study design



ABBREVIATIONS: ANC, absolute neutrophil count; BID, twice daily; CAR, chimeric antigen receptor; cCR, confirmed complete response; cORR, confirmed objective response rate; cPR, confirmed partial response; CRS, cytokine release syndrome; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; E:T, effector cell to tumor burden ratio; FU, follow-up; HLA, human leukocyte antigen; HLH, hemophagocytic lymphohistiocytosis; ICAHT, immune effector cell-associated hematotoxicity; ICANS, immune effector cell-associated neurotoxicity syndrome; ICI, immune checkpoint inhibitor; IL, interleukin; IU, international unit; LDH, lactate dehydrogenase; N-ICAHT, neutropenia-associated ICAHT; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRAME, preferentially expressed antigen in melanoma; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SD, standard deviation; SLD, sum of the longest diameters; SOC, standard of care; SUBQ, subcutaneous; TCR, T-cell receptor; ULN, upper limit of normal.

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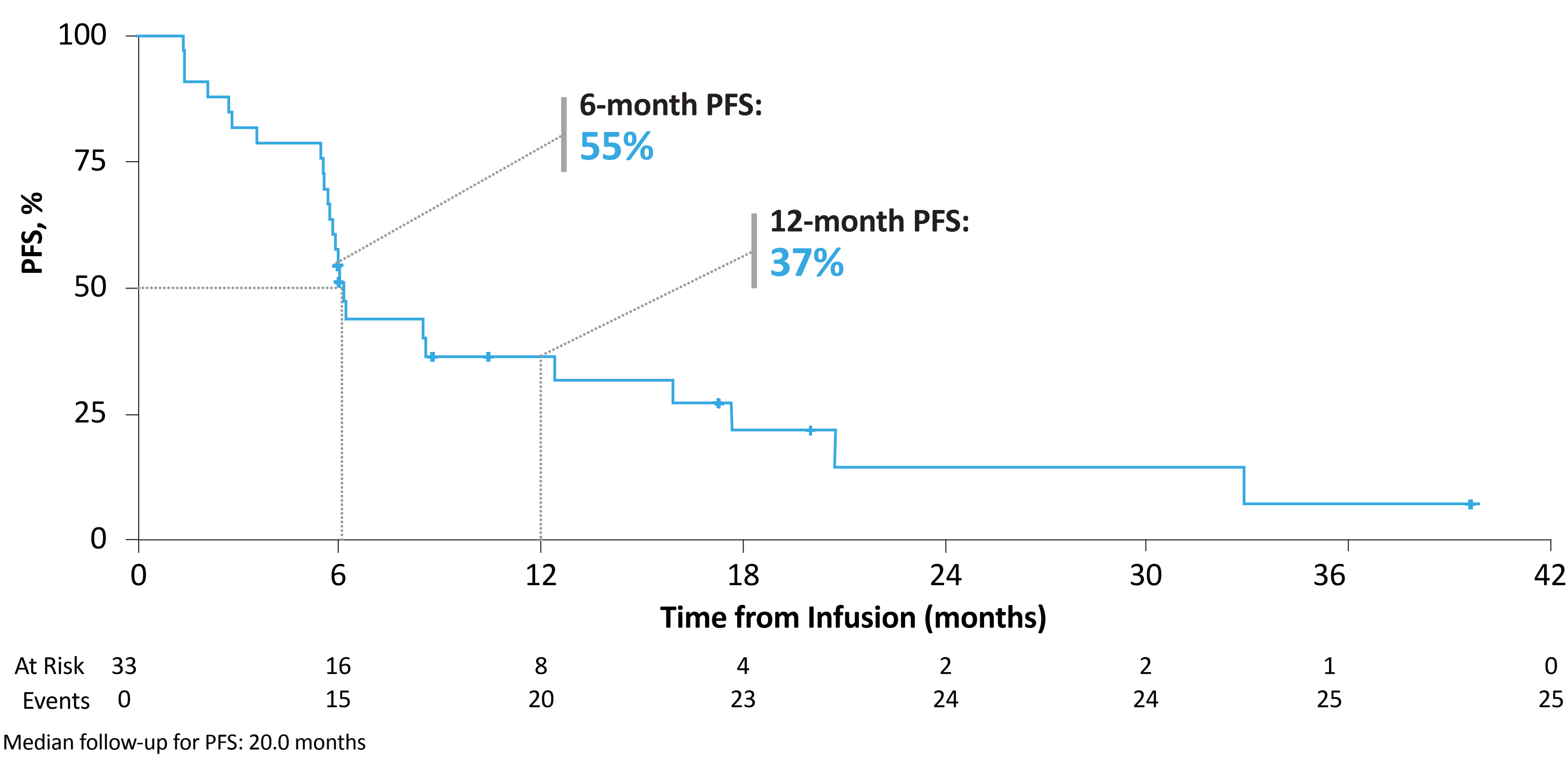
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RESULTS

- For all patients with melanoma, the median PFS was 6.1 months (range, 1.4-39.6+; Figure 3); median PFS for cutaneous melanoma was 6.0 months (1.4-39.6+) and for uveal melanoma was 8.5 months (1.4-32.9)⁶
- The median OS was 16.2 months (range, 2.4-39.6+ months)⁶
 - 12-month OS for all melanoma: 70%; cutaneous: 72%; uveal: 71%
 - 24-month OS: 46%; cutaneous: 45%; uveal: 57%
- The confirmed ORR was 56% (n=18/32) for all patients with melanoma (cCR=1; cPR=17)⁶
 - The median DoR was 14.6 months for all patients with melanoma (range, 4.2-38.2+ months); 6 of 18 (33%) responses were ongoing at data cutoff

Figure 3. Time-to-Event Analyses



- A total of 8 patients had PFS >12 months and 20 patients had PFS <12 months
- Patients with PFS >12 months had a range of baseline and treatment characteristics (Table 2)
- In exploratory univariate Cox proportional hazards analyses, each clinical variable was evaluated separately. No variable showed a statistically significant association with PFS, as all 95% confidence intervals for the hazard ratios included 1 (Figure 4)
- Point estimates suggested longer PFS with lower LDH, a lower sum of target-lesion diameters, and a higher E:T ratio.
 - These findings are hypothesis-generating; the absence of statistical significance does not exclude clinically meaningful associations

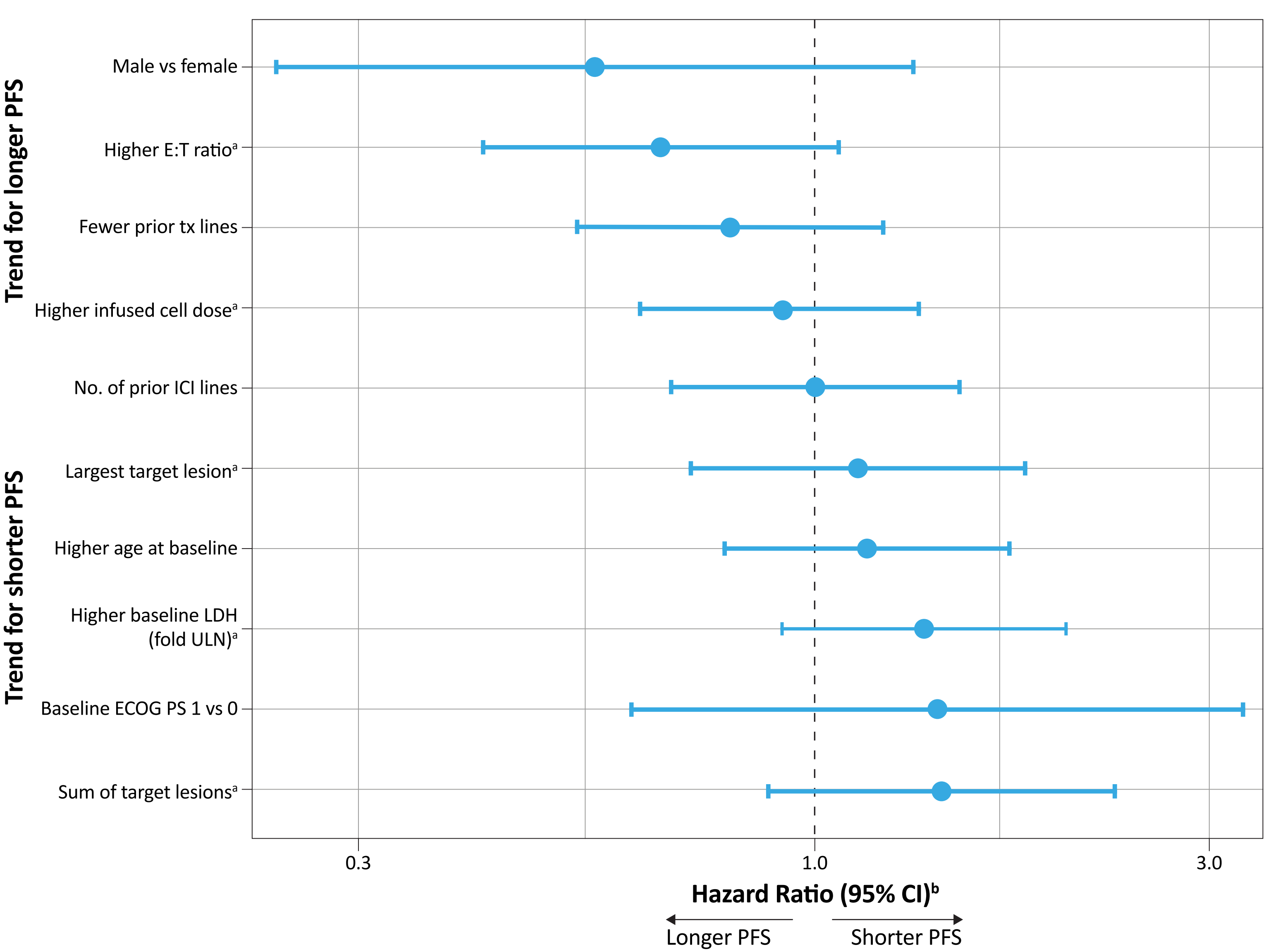
Table 2. Clinical Characteristics by PFS Category (>12 or <12 months)

Baseline Characteristics	All (N=33)	Patients Evaluable for PFS categorization ^a PFS >12 Months (n=8)	PFS <12 Months (n=20)
Median age, years (range)	57 (31-79)	47 (31-71)	61 (37-79)
Female, n (%)	16 (48)	2 (25)	11 (55)
ECOG PS 0, n (%)	20 (61)	6 (75)	11 (55)
ECOG PS 1, n (%)	13 (39)	2 (25)	9 (45)
Median prior lines of systemic treatment (range)	2 (0-6)	3 (1-5)	2 (0-6)
Median prior lines of ICI treatment (range)	1 (0-4)	1 (0-3)	1 (0-4)
≥1 line of ICI treatment, n (%)	27 (82)	6 (75)	18 (90)
Median target lesion SLD, cm (range)	10.4 (1.5-31.0)	10.1 (1.5-12.8)	11.9 (2.1-31.0)
Largest target lesion, cm (range)	4.1 (1.1-13.8)	4.0 (1.5-6.6)	4.1 (1.1-13.8)
Elevated LDH at baseline, n (%)	19 (58)	5 (63)	12 (60)
Median LDH x ULN (range)	1 (0.7-9.1)	1.02 (0.69-1.20)	1.11 (0.76-9.07)
Treatment Experience	All	PFS >12 Months	PFS <12 Months
Median infused TCR T cell dose, ×10 ⁹ (range)	4.04 (1.30-10.20)	6.16 (1.3-10.20)	3.52 (1.55-9.76)
Median effector cell to tumor burden ratio (range) ^b	0.0433 (0.0113-0.6800)	0.071 (0.037-0.680)	0.038 (0.011-0.097)
Median PFS, month (range)	6.1 (1.4-39.6+)	20.7 (12.4-39.6+)	5.6 (1.4-8.6)
Median OS, month (range)	16.2 (2.4-39.6+)	NE (15.9-39.6+)	11.4 (2.4-33.4+)
ORR, % (n/N)	64 (21/33)	88 (7/8)	45 (9/20)
cORR, % (n/N)	56 (18/32)	88 (7/8)	35 (7/20)

^a 5 patients were censored due to ongoing PFS <12 months (n=3) or withdrawal of consent (n=2).

^b Calculated by infused TCR T-cell dose divided by the sum of target lesions.

Figure 4. Univariate Analysis of Clinical Characteristics and PFS



^a Variables were log-transformed prior to modeling; Hazard ratios are reported per SD increase of the corresponding log-transformed variable. E:T ratio calculated by infused TCR T-cell dose divided by the sum of target lesions.
^b Hazard ratios are reported per 1-SD (standard deviation) increase for all variables except ECOG PS (1 vs 0) and sex (male vs female).
Interpreting the hazard ratios: HR >1 indicates a higher estimated hazard of disease progression or death; HR <1 indicates a lower estimated hazard; HR=1 indicates no difference. Each model evaluates one variable without adjustment for other variables.

- The safety profile of anzu-cel was previously reported in detail.⁴ The most common AEs were lymphodepletion-related cytopenias. CRS was early-onset (grade 1: 36%, grade 2: 46%, grade 3: 18%); ICANS (grade 1: 6%, grade 3: 6%) and HLH (grade 2: 3%, grade 3: 3%) were infrequent
- This exploratory analysis provides temporal and clinical context for previously reported cytopenias, extending incidence reporting to characterize neutrophil recovery, supportive-care use, and clinical events during the later postinfusion period
- Late N-ICAHT was observed in 8 of 33 patients (24%) including grade 3-4 N-ICAHT in 2 patients (6%; Table 3; Figure 5)
- Growth factor support was used in 6 of 8 patients (75%) with N-ICAHT: 4/6 with grade 1-2 N-ICAHT and 2/2 with grade 3-4 N-ICAHT
- One patient experienced pneumonia requiring hospitalization during the N-ICAHT period
- Both grade 3-4 N-ICAHT events improved to grade ≤2 by day 78 postinfusion
- All N-ICAHT events resolved at a median of 78 days postinfusion (range, 51-272)

Table 3. Incidence and Grade of Late N-ICAHT

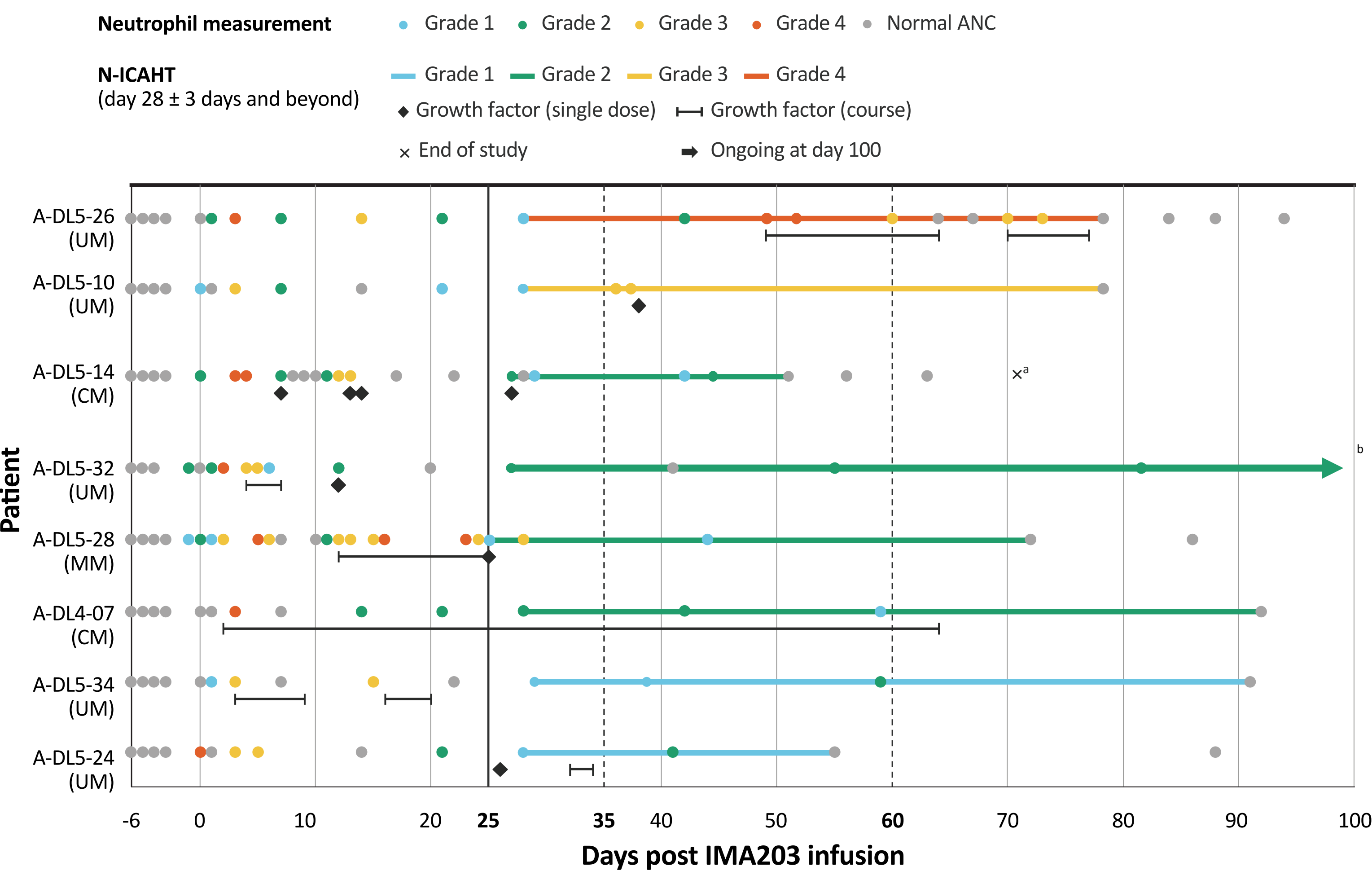
Parameter	All Melanoma Patients (N=33), n (%)
Late N-ICAHT beyond day 28 ^a	8 (24.2)
Grade 1	2 (6.1)
Grade 2	4 (12.1)
Grade 3	1 (3.0)
Grade 4	1 (3.0)

^a Late N-ICAHT grade was based on the second-lowest absolute neutrophil count between days 28 to 100 postinfusion and required ≥2 neutropenic measurements during this period, including ≥1 between days 35-60. Measurements before the day 28 visit were not used for late N-ICAHT grading but were considered when determining neutropenia onset and duration. Day 28 visits could have occurred up to 3 days before or after day 28.

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- Tobias A.W. Holderried is currently affiliated with the Medical University of Graz in Graz, Austria

Figure 5. Late N-ICAHT Duration and Growth Factor Use



^a Patient died from PD.
^b N-ICAHT remained without further worsening and resolved on day 272.
N-ICAHT grades defined as grade 1 ≤1500 cells/μL; grade 2 ≤1000 cells/μL; grade 3 ≤500 cells/μL; grade 4 ≤100 cells/μL.
ANC values were used for this analysis; grading is based on the 2nd lowest ANC value.
Patients with at least 2 ANC values below thresholds between days 28 (±3) to 100, with 1 abnormal ANC value occurring between days 35-60.
ANC measurements before day 25 are displayed for context but are not used to define late N-ICAHT eligibility.
Growth factor use shown as a diamond for a single-day dose or a line for a multi-day course (per-patient administration data).

CONCLUSIONS

- Durable clinical benefit following anzu-cel for treatment of advanced melanoma was observed in patients with varied baseline and treatment characteristics⁴
 - No variable evaluated individually showed a statistically significant association with PFS
 - Point estimates suggested longer PFS with lower LDH, a lower sum of target-lesion diameters, and a higher E:T ratio; these findings remain hypothesis-generating and warrant further evaluation
- Durable benefit was achieved with a one-time treatment and a time-limited treatment burden
- Late N-ICAHT occurred in a minority of patients and resolved by data cutoff
- These findings support continued postinfusion monitoring of complete blood counts in the subset of patients with incomplete hematologic recovery or recurrent cytopenias, with supportive care guided by clinical need and protocol recommendations

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