Event-driven Management, Risk Factors, and Clinical Associations of Cytokine Release Syndrome Following Anzutresgene Autoleucel, a TCR T-cell Therapy, in Advanced Melanoma

Diwakar Davar,[1] Sapna Pradyuman Patel,[2] Leonel Fernando Hernandez-Aya,[3] Tobias A.W. Holderried,[4] Antonia Busse,[5] Apostolia Maria Tsimberidou,[6] Dejka M. Araujo,[6] Manik Chatterjee,[7] M. Alper Kursunel,[8] Maike Wagner,[8] Ana Maia,[8] Liane Preussner,[8] Haneen Aldehayat,[8] Delfi Krishna,[9] Dmitry Pankov,[9] Martin Wermke,[10] Winfried Alsdorf[11]

[1]University of Pittsburgh Medical Center (UPMC), Hillman Cancer Center, Pittsburgh, PA, USA; [2]University of Colorado Cancer Center, Aurora, CO, USA; [3]University of Miami, Miami, FL, USA; [4]University Hospital Bonn, Bonn, Germany; [5]Charite Medical University Hospital, Berlin, Germany; [6]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]Translational Oncology/Early Clinical Trial Unit (ECTU), Comprehensive Cancer Center Mainfranken, University Hospital of Wuerzburg, Wuerzburg, Germany; [8]Immatics Biotechnologies GmbH, Tuebingen, Germany; [9]Immatics US, Houston, TX, USA; [10]University Hospital Carl Gustav Carus Dresden, Dresden, Germany; [11]Department of Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

BACKGROUND

- Despite advances with immune checkpoint blockade, up to 50% of patients with advanced melanoma experience disease relapse, and survival is limited[1]
- PRAME is a cancer-associated antigen expressed in >50 cancers, including melanoma
- Anzutresgene autoleucel (anzu-cel; formerly IMA203), an autologous PRAME-directed TCR T-cell therapy, recognizes an intracellular HLA-A*02:01-presented PRAME-derived peptide and mediates a potent and specific antitumor immune response[2]
- In the ongoing phase 1b IMA203-101 trial in advanced PRAME-positive solid tumors, anzu-cel demonstrated frequent and durable activity in melanoma[3]
  - cORR: 56%
  - mDOR: 14.6 months
  - 2-year OS: 46%
- In the phase 1b trial, we evaluated the effect of immunosuppressants (anticytokines with or without corticosteroids for immune-related AE management) on the pharmacokinetics and pharmacodynamics of anzu-cel in patients with melanoma

METHODS

- Eligible patients in the ongoing phase 1b IMA203-101 trial (NCT03686124) underwent leukapheresis followed by lymphodepletion (days −6 to −3) and a one-time anzu-cel infusion (day 0); low-dose IL-2 was administered on days 1-10 (QD on days 1-5, then BID on days 6-10)
- Patients treated with anzu-cel were evaluated for associations between treatment-emergent CRS and patient and disease characteristics, serum cytokines, and T-cell exposure
  - CRS assessment, grading, and management initially followed the Neelapu et al 2018 recommendations[4] and transitioned to the Neelapu 2019 recommendations[5] in March 2024
  - Baseline patient and disease characteristics assessed included age, number of prior systemic therapies, baseline tumor burden, sum of target and nontarget lesions, presence of liver metastases, LDH level, cell dose, and depth of response
  - Serum concentrations of inflammatory and immune activation mediators (IFN-γ, IL-10, IL-15, IL-18, IL-6, IL-7, IL-8, IP-10, MCP-1, and TNF-α) were evaluated from baseline through the first 4 weeks following anzu-cel infusion (days −3, 0, 2, 3, 7, 14, and 28); peak fold change from baseline was also calculated for each cytokine
- An exploratory analysis evaluated associations between serum cytokines (IFN-γ, IL-10, IL-15, IL-18, IL-6, IL-7, IL-8, IP-10, MCP-1, and TNF-α) and response
- Following anzu-cel infusion, the impact of AE management with concomitant immunosuppressants (an anticytokine therapy with or without systemic corticosteroids within 28 days postinfusion) on cellular kinetics and serum cytokines was investigated

RESULTS

- In the phase 1b IMA203-101 trial, 33 patients with metastatic melanoma received anzu-cel
- The data cutoff was September 24, 2025
- CRS occurred in all 33 patients, consistent with the expected mechanism of action of anzu-cel, and was predominantly grade 1-2 (grade 1: 36%, grade 2: 45%, grade 3: 18%, grade 4: 0%; **Table 1**)
- IL-2 dose modifications were implemented in 70% of patients (interruption: 33%, discontinuation: 15%, reduction: 3%, not initiated: 18%)
  - Among patients with grade 1 CRS, 25% had IL-2 dose modifications; 93% and 100% of patients with grade 2 and 3 CRS, respectively, had IL-2 dose modifications
- CRS was actively managed with tocilizumab in 73% of patients and corticosteroids in 33% of patients
  - All 6 patients with grade 3 CRS were treated with tocilizumab; 4 of these patients were also treated with corticosteroids
  - Siltuximab could have been given as an alternative to tocilizumab but was not administered to any patient
- The median duration of systemic corticosteroid and/or anticytokine treatment was 6 days (range: 1-49; **Table 2**)

RESULTS

Table 1. Anticytokine use, corticosteroid use, and IL-2 dose modifications for AE management within days 0-28 after anzu-cel infusion by CRS grade (all patients; N=33)

	Any-grade CRS	Grade 1 CRS	Grade 2 CRS	Grade 3 CRS
Patients with CRS, n (%)	33 (100)	12 (36)	15 (45)	6 (18)
Therapies administered for CRS, No. of patients (%)[a,b]	24 (73)	3 (25)	15 (100)	6 (100)
Tocilizumab	24 (73)	3 (25)	15 (100)	6 (100)
Anakinra	1 (3)	0	0	1 (17)
Corticosteroids (any)	11 (33)	0	7 (47)	4 (67)
Dexamethasone	11 (33)	0	7 (47)	4 (67)
Anticytokine therapies and/or corticosteroids administered for any reason, No. of patients (%)[a,c]	27 (82)	6 (50)	15 (100)	6 (100)
Tocilizumab	25 (76)	4 (33)	15 (100)	6 (100)
Anakinra	4 (12)	1 (8)	1 (7)	2 (33)
Corticosteroids (any)[d]	15 (45)	1 (8)	9 (60)	5 (83)
Dexamethasone	11 (33)	0	7 (47)	4 (67)
Methylprednisolone	1 (3)	0	1 (7)	0
Prednisone	3 (9)	1 (8)	1 (7)	1 (17)
Hydrocortisone	3 (9)	0	3 (20)	0
No. of IL-2 doses received per patient, median (range)[e]	9 (2-15)	15 (3-15)	7.5 (2-12)	2 (2-12)
Patients with IL-2 dose modification, n (%)[a]	23 (70)	3 (25)	14 (93)	6 (100)
Interruption + rechallenge, n (%)	11 (33)	3 (25)	6 (40)	2 (33)
Discontinuation, n (%)	5 (15)	0	2 (13)	3 (50)
Dose reduction, n (%)	1 (3)	0	1 (7)	0
IL-2 never initiated, n (%)[f]	6 (18)	0	5 (33)	1 (17)
No. of IL-2 doses received per patient with IL-2 dose modifications, median (range)[e]	8 (2-13)	13 (8-13)	8 (2-12)	2 (2-12)

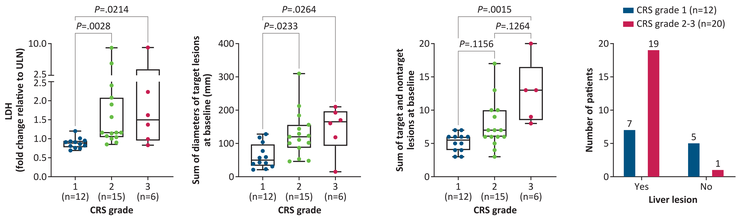
[a] Percentages were based on the number of patients with the respective CRS grade.
[b] Medications were included if treatment started day 0-28 after infusion on day 0.
[c] Systemic corticosteroid and anticytokine therapies were identified regardless of concomitant medication indication.
[d] Systemic corticosteroids were restricted to oral, subcutaneous, intravenous, intramuscular, or intraperitoneal administration.
[e] Patients who never initiated IL-2 were excluded when calculating the range.
[f] Six patients did not receive IL-2 per investigator discretion.

Table 2. Initiation and duration of systemic corticosteroid and anticytokine treatments within days 0-28 after anzu-cel infusion

	Patients, n (%)	Day of Treatment Initiation, median (range)[a]	Duration of Treatment, median (range), days[b]	Duration of Treatment, No. of patients (%)[c]		
				≤3 Days	≤7 Days	>7 Days
Any systemic corticosteroid and/or anticytokine therapy[d,e]	27 (82)	2 (0-27)	6 (1-49)	11 (41)	18 (67)	9 (33)
Tocilizumab	25 (76)	2 (0-5)	2 (1-29)	15 (60)	22 (88)	3 (12)
Anakinra	4 (12)	8.5 (3-15)	4.5 (1-12)	2 (50)	3 (75)	1 (25)
Corticosteroids (any)[f,g]	15 (45)	4 (1-27)	7 (1-49)	4 (27)	9 (60)	6 (40)
Dexamethasone	11 (33)	4 (1-7)	5 (1-21)	4 (36)	8 (73)	3 (27)
Methylprednisolone	1 (3)	15 (15-15)	10 (10-10)	0	0	1 (100)
Prednisone	3 (9)	25 (14-27)	11 (2-29)	1 (33)	1 (33)	2 (67)
Hydrocortisone	3 (9)	2 (1-9)	24 (7-49)	0	1 (33)	2 (67)

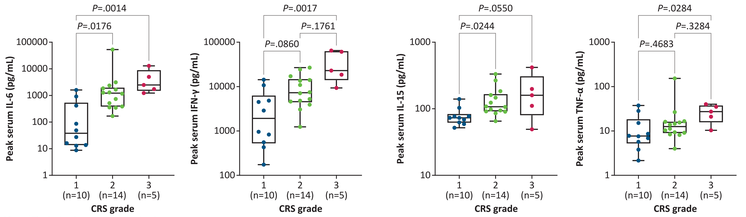
[a] Day of treatment initiation was determined as the number of days from anzu-cel infusion (day 0) to the earliest medication start date for each patient.
[b] Duration of treatment was calculated as the number of days from the first treatment start date through the last treatment end date (inclusive).
[c] Percentages for duration categories were based on patients with an evaluable treatment duration for the respective therapy.
[d] Medications were included if treatment started day 0-28 after infusion on day 0.
[e] Systemic corticosteroid and anticytokine therapies were identified regardless of concomitant medication indication.
[f] Systemic corticosteroids were restricted to oral, subcutaneous, intravenous, intramuscular, or intraperitoneal administration.
[g] Patients could receive more than one type of corticosteroid.

Figure 1. Associations between CRS by grade and baseline disease characteristics



- Greater CRS severity was associated with advanced disease markers at baseline, including a higher LDH level, a greater sum of diameters of target lesions, a greater sum of target and nontarget lesions, and the presence of liver metastases (**Figure 1**)

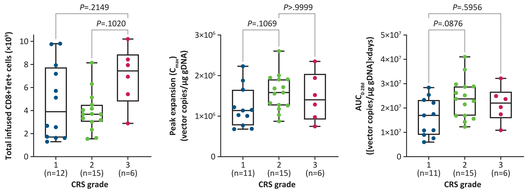
Figure 2. Associations between CRS by grade and posttreatment peak serum cytokine levels[a]



[a] Four of 33 patients withdrew consent prior to cytokine analysis.

- Immunomodulatory cytokine increases generally followed a stepwise increase from CRS grade 1 to 2 to 3 for IL-6, IFN-γ, IL-15, and TNF-α, suggesting increasing immune activation with increasing CRS severity (**Figure 2**)
  - IL-8, MCP-1, and IP-10 also showed a similar stepwise pattern between increasing peak serum levels and increasing CRS severity (data not shown)
  - No associations between CRS severity and other evaluated cytokines were observed
- IL-6 fold induction was greater with higher-grade CRS (grade 1 vs grade 3: *P*=.0221; data not shown)

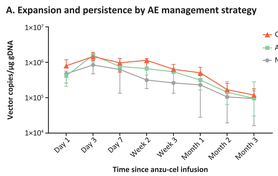
Figure 3. Associations between CRS by grade and T-cell dose and exposure



- Among patients administered the RP2D (1-10 billion TCR T cells), CRS severity was associated with baseline tumor burden
- No statistically significant correlation was observed between CRS severity and infused T-cell dose, peak T-cell expansion, or AUC_{0-28d}, although a trend toward increased CRS severity with a higher T-cell dose was observed (**Figure 3**)

Figure 4. Anzu-cel expansion, persistence, and cellular kinetics by AE management strategy

A. Expansion and persistence by AE management strategy



- Patients who had generally lower anzu-cel expansion did not require corticosteroids or an anticytokine (**Figure 4a**)
- AE management with corticosteroids with or without an anticytokine did not adversely impact anzu-cel cellular kinetics (**Figure 4b**)
- Patients who had generally lower cytokine induction did not require corticosteroids or an anticytokine (**Supplementary Figure S1**)

B. Cellular kinetics by AE management strategy

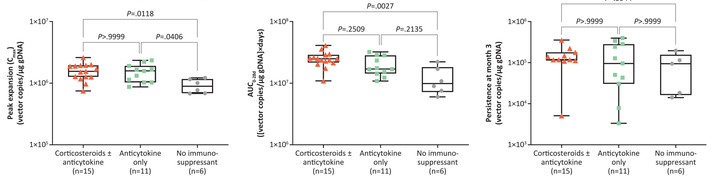
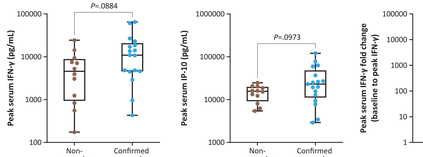


Figure 5. Associations between response and peak serum cytokine levels[a]



[a] Four of 33 patients withdrew consent prior to cytokine analysis.
[b] One patient had missing baseline samples; therefore, fold change could not be calculated.

- Confirmed responders with evaluable cytokine data (n=17/29; 59%) showed greater IFN-γ fold induction than nonresponders, with numerical trends toward higher peak serum IFN-γ and IP-10 levels, suggesting enhanced immune activation; further validation is required (**Figure 5**)
  - No associations between response and other cytokines were observed

CONCLUSIONS

- Higher-grade CRS was associated with features of advanced disease (elevated LDH, greater tumor burden, and liver metastases) and heightened inflammatory responses
- CRS events in the phase 1b IMA203-101 trial were manageable with standard interventions
- Enhanced Tc1-type immune activation (IFN-γ and IP-10) was associated with both CRS severity and clinical response, linking anzu-cel pharmacology with antitumor activity
- AE management with anticytokine therapy with or without corticosteroids did not appear to adversely affect anzu-cel cellular kinetics
- Patients with lower cytokine induction did not require anticytokine therapy or corticosteroids
- These findings support evaluation of anzu-cel in earlier lines of treatment for patients with lower tumor burdens and may inform risk stratification, monitoring, and management of patients at increased risk for CRS

REFERENCES:
1. Zaremba A, et al. *Eur J Cancer*. 2021;155:268-280.
2. Wermke M, et al. *Nat Med*. 2025;31(7):2365-2374.
3. Davar D, et al. *J Clin Oncol*. 2026;44(suppl_16):9508.
4. Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62.
5. Neelapu SS. *Hematol Oncol*. 2019;37(suppl_1):48-52.

The following supplementary materials are available through the Quick Response (QR) code
- PDF of this poster
- Figure S1. Cytokines by AE management strategy

Copies of this poster obtained through the QR code are for personal use only and may not be reproduced without written permission of the authors.
Please contact medinfo@immatics.com for additional information.

ABBREVIATIONS: AE, adverse event; anzu-cel, anzutresgene autoleucel; AUC_{0-28d}, area under the curve from day 0 to day 28; BID, twice daily; CD8, cluster of differentiation 8; C_{max}, maximum concentration; cORR, confirmed objective response rate; CRS, cytokine release syndrome; gDNA, genomic DNA; HLA, human leukocyte antigen; IFN-γ, interferon gamma; IL, interleukin; IP-10, interferon gamma–inducible protein 10; LDH, lactate dehydrogenase; MCP-1, monocyte chemoattractant protein 1; mDOR, median duration of response; OS, overall survival; PRAME, preferentially expressed antigen in melanoma; QD, once daily; RP2D, recommended phase 2 dose; Tc1, type 1 cytotoxic T cell; TCR, T-cell receptor; TNF-α, tumor necrosis factor alpha; ULN, upper limit of normal.

ACKNOWLEDGMENTS:
- We thank the patients, their families, and their caregivers for participating in this study
- We thank the study investigators, site personnel, and independent data monitoring committee
- We thank all colleagues and collaborators who directly or indirectly contributed to data generation and analysis for this study
- This study was funded by Immatics US, Inc
- Medical writing support was provided by Decera Clinical, funded by Immatics US, Inc

Presented at the Society for Immunotherapy of Cancer (SITC) 41st Anniversary Annual Meeting ● Phoenix, AZ, USA ● November 6-8, 2026