2025 SMR CONGRESS

Anzutresgene Autoleucel (IMA203), a PRAME-directed T-cell receptor T-cell therapy, demonstrated broad organ penetration in patients with heavily pretreated advanced or metastatic melanoma in a phase 1 trial

Martin Wermke[1], Winfried Alsdorf[2], Sapna P. Patel[3], Manik Chatterjee[4], Christoffer Gebhardt[5], Leonel Fernando Hernandez-Aya[6], Tobias A.W. Holderried[7], Apostolia Maria Tsimberidou[8], Norbert Hilf[9], Mohammad Hossain[10], Delfi Krishna[10], M. Alper Kursunel[9], Dmitry Pankov[10], Katrin Aslan[9], Marilena Letizia[9], Diwakar Davar[11], Antonia Busse[12], Cedrik M. Britten[9]

[1]University Hospital Dresden, Dresden, Germany; [2]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]University of Colorado, Aurora, CO; [4]University Hospital Wuerzburg, Wuerzburg, Germany; [5]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [6]University of Miami, Miller School of Medicine, Miami, FL; [7]University Hospital Bonn, Bonn, Germany; [8]University of Texas MD Anderson Center, Houston, TX; [9]Immatics Biotechnologies GmbH, Tuebingen, Germany; [10]Immatics US Inc, Houston, TX; [11]University of Pittsburgh, Pittsburgh, PA; [12]Charité University Medicine Berlin, Berlin, Germany.

PLENARY SESSION 7 – Understanding and Optimizing the Immunotherapy Response
Abstract #270
Monday, October 27th, 2025

Background

- Melanoma is an aggressive malignancy with a high propensity for metastasis[1]
- Current immune-based therapies including checkpoint inhibitors have improved survival for advanced/metastatic disease, but have limited efficacy in metastatic sites due to organ-specific immunosuppressive microenvironments[2-6]
- Successful T-cell trafficking and infiltration into tumor sites are key determinants of therapeutic efficacy in solid tumors, as impaired access to metastatic lesions limits immune-mediated tumor clearance[7]
- Anzutresgene autoleucel (anzu-cel), previously IMA203, is an autologous T cell receptor (TCR) T-cell therapy engineered to recognize intracellular PRAME-derived peptides presented by HLA-A*02:01 and initiate a potent and specific anti-tumor response[8]
- In a phase 1 trial (NCT03686124), anzu-cel demonstrated a confirmed ORR of 56% (18/32) with durable clinical benefit at RP2D in heavily pretreated advanced metastatic melanoma[9]
- Here, we characterize the efficacy and underlying trafficking potential of anzu-cel across different metastatic sites at the RP2D

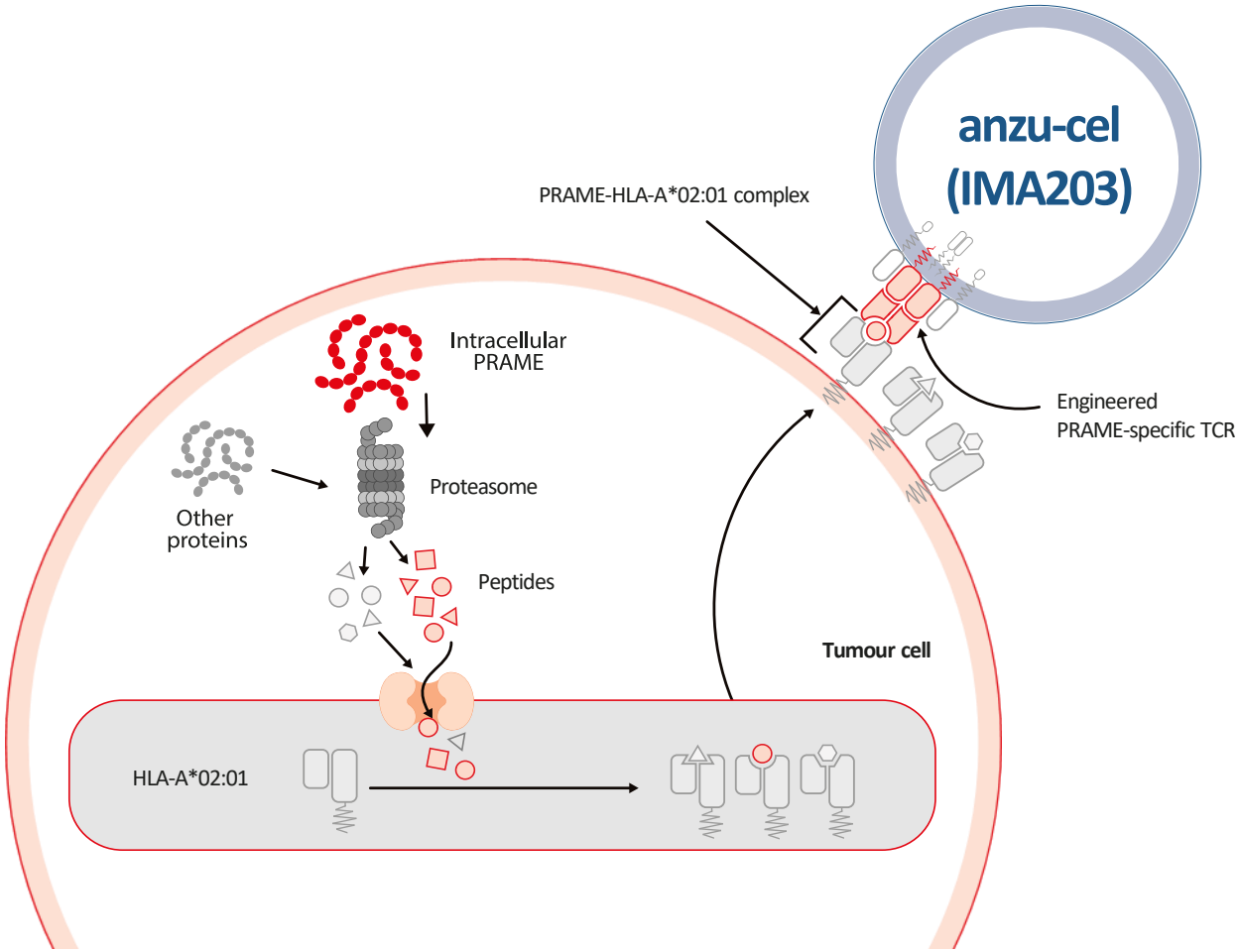
HLA, human leukocyte antigen; ORR, objective response rate; PRAME, preferentially expressed antigen in melanoma; RP2D, recommended phase 2 dose; TCR, T-cell receptor.

1. Wagstaff W, et al. *Genes Dis.* 2022;9:1608-1623. 2. Larkin J, et al. *N Engl J Med.* 2015;373:23-34. 3. Robert C, et al. *N Engl J Med*. 2015;372:2521-2532. 4. Robert C, et al. *N Engl J MEd.* 2015;372:320-330. 5. Ma Y, et al. *Front Immunol.* 2025;16:1608215. 6. Lim SY, et al. *Nat Commun.* 2023;14:1516. 7. Kirtane K, et al. *J Immunother Cancer*. 2021;9:e002723. 8. Wermke M, et al. *Nat Med*. 2025;31:2365-2374. 9. Wermke M, et al. Presented at : ASCO 2025. Abstr 2508.

Anzu-cel TCR T-cell Therapy Is Designed to Target PRAME

PRAME is expressed in more than 50 cancers

Indication	% PRAME+ Patients[a]
Cutaneous melanoma	**95%**
Uterine carcinoma	95%
Uterine carcinosarcoma	95%
Synovial sarcoma	95%
Uveal melanoma[b]	**90%**
Mucosal melanoma	90%
Ovarian carcinoma (clear cell, endometroid)	85%
Squamous cell NSCLC	70%
Triple-negative breast carcinoma	65%
Small cell lung cancer	45%
Oesophageal carcinoma subtype	45%
Kidney carcinoma subtype	40%
Cholangiocarcinoma	35%
HER2-enriched breast carcinoma	30%
Adenocarcinoma NSCLC	25%
Head & neck squamous cell carcinoma	25%
Hepatocellular carcinoma	20%
Bladder carcinoma	20%



[a]Data on file: PRAME target prevalence is based on a proprietary mass spec-guided expression threshold applied to RNAseq and/or IHC data (approximate values; values between 95-100% shown as 95%); [b]PRAME target prevalence in uveal melanoma based on IMADetect® qPCR testing of screening biopsies from 61 clinical trial patients demonstrates substantial higher prevalence of ~90% compared to prevalence based on TCGA data of 50%, TCGA: early & late-stage primary tumor samples, Immatics clinical trials: primarily late-stage/metastatic tumor samples; HER2, Human epidermal growth factor receptor 2; HLA, human leukocyte antigen; NSCLC, non-small cell lung cancer; PRAME, preferentially expressed antigen in melanoma; TCR, T-cell receptor.

Wermke M, et al. Nat *Med.* 2025;31(7):2365-2374.

Phase 1 Study of Anzu-cel, an Autologous TCR T-cell Therapy Targeting PRAME

NCT03686124

Key Objectives

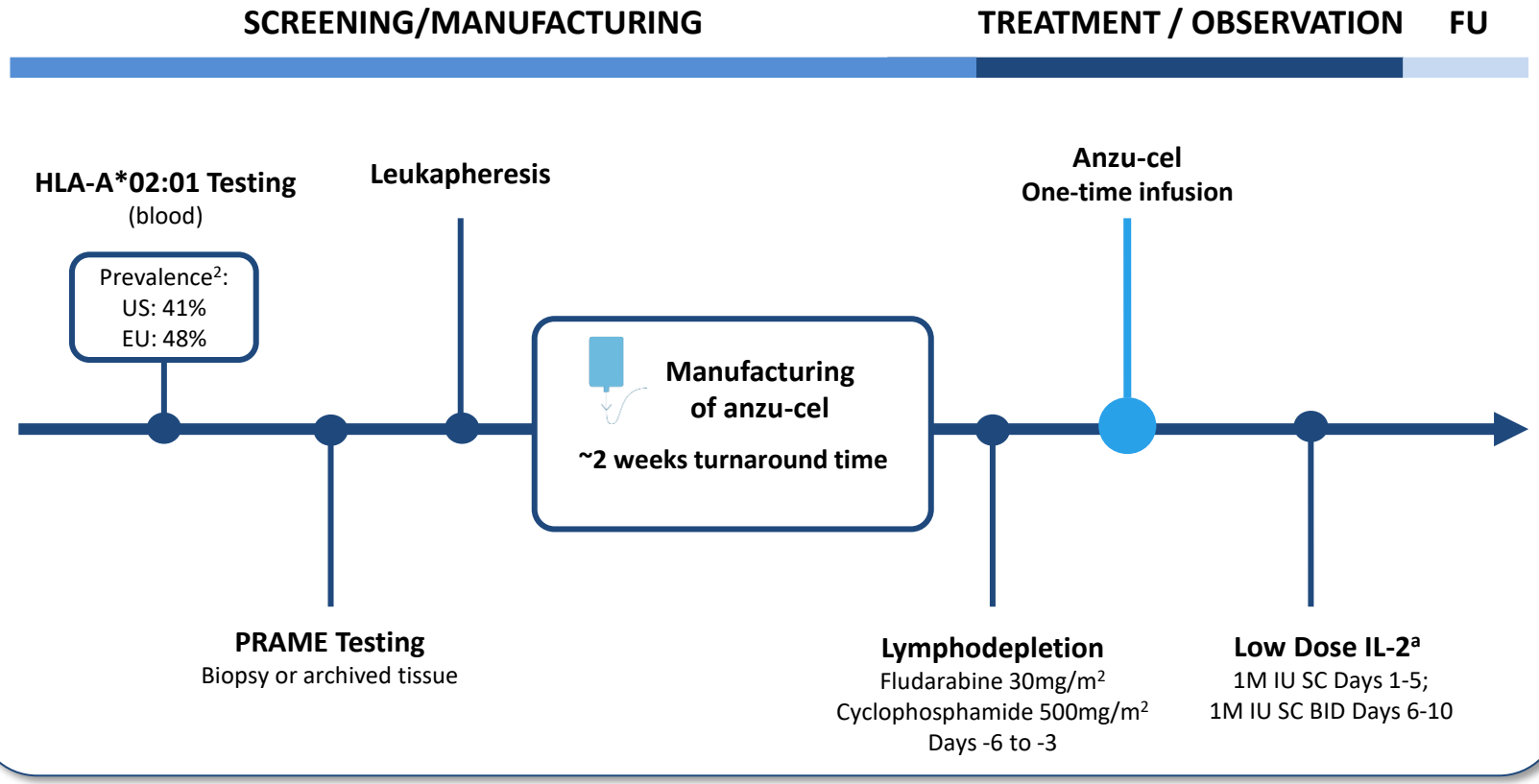
Primary:
- Tolerability
- Determination of RP2D

Secondary:
- Anzu-cel T-cell engraftment, persistence
- Efficacy

Key Eligibility Criteria

- Confirmed advanced and/or metastatic solid tumor
- Patients ≥ 18 years of age
- ECOG performance status 0-1
- HLA-A*02:01 positive (blood)
- PRAME positive (mRNA)
- No active brain metastasis

Patient Journey



Data cutoff: April 7, 2025. Manufacturing success rate as of Apr 7, 2025

[a] Outpatient administration at investigator's discretion.

BID, twice daily; ECOG, Eastern Cooperative Oncology Group; FU, follow-up; HLA, human leukocyte antigen; IL, interleukin; IU, international unit; mRNA, messenger RNA; RP2D, recommended phase 2 dose at 1-10x109 TCR T cells; SC, subcutaneous TCR, T-cell receptor.

1. Wermke M, et al. ASCO 2025. Oral presentation 2508. 2. Gragert et al. 2013 and census numbers.

Anzu-cel Phase 1 Study: Baseline Characteristics & Treatment Experience of the Melanoma Efficacy Population

Baseline Characteristic	All Melanoma (n=33)
Age, median (range)	57 (31, 79)
Female, n (%)	16 (49)
Baseline ECOG status 1, n (%)	13 (39)
LDH ≥ ULN, n (%)	19 (58)
AJCC stage*, % (CM, MM, UkM only)	(n=17)
IIIb/IIIc/IV M1a	0
IV M1b/c/d	100
AJCC stage*, % (UM only)	(n=16)
IV M1a/b/c	19 / 75 / 6
Median target lesion SPD, cm (range)	10 (2, 31)
Liver metastasis, n (%)	79
Brain metastasis, n (%)	3

Prior Therapies	All Melanoma (n=33)
Systemic therapies, median (range)	2 (0, 6)
Prior ICI treatment, median (range)	1 (0, 4)
≥1 line of ICI treatment, % (n/N)	82 (27/33)
Prior tebentafusp, % (n/N)	33 (11/33)

Median infused TCR T-cell dose:
4.04×10^9 (range: 1.30, 10.20) cells

***AJCC 8th ed.**
M1a: largest tumor size ≤3 cm
M1b: 3.1-8 cm
M1c: >8 cm

Data cutoff: April 7, 2025.
CM, cutaneous melanoma; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; LDH, lactate dehydrogenase; MM, mucosal melanoma; SPD, sum of product diameters; TCR, T-cell receptor; UkM, melanoma of unknown primary; UM, uveal melanoma.

Anzu-cel Safety Profile Across All Dose Levels

NCT03686124[1]

TEAEs in ≥20% of patients

Preferred terms, n (%)	N=74 Any grade	N=74 Grade ≥3
Blood and lymphatic system disorders	73 (98.6)	73 (98.6)
Neutropenia[a]	68 (91.9)	67 (90.5)
Anemia	57 (77.0)	38 (51.4)
Thrombocytopenia[a]	50 (67.6)	27 (36.5)
Leukopenia	39 (52.7)	38 (51.4)
Lymphopenia	39 (52.7)	39 (52.7)
Gastrointestinal disorders	65 (87.8)	2 (2.7)
Nausea	45 (60.8)	0 (0.0)
Diarrhea[a]	28 (37.8)	1 (1.4)
Vomiting	25 (33.8)	1 (1.4)
Constipation	23 (31.1)	0 (0.0)
General disorders and administration site conditions	49 (66.2)	2 (2.7)
Fatigue	29 (39.2)	1 (1.4)
Pyrexia	22 (29.7)	1 (1.4)
Edema peripheral	17 (23.0)	0 (0.0)
Investigations	35 (47.3)	10 (13.5)
Aspartate aminotransferase increased	29 (39.2)	5 (6.8)
Alanine aminotransferase increased	28 (37.8)	7 (9.5)
Blood creatinine increased	15 (20.3)	2 (2.7)
Skin and subcutaneous tissue disorders	35 (47.3)	6 (8.1)
Rash	18 (24.3)	0 (0.0)
Rash maculo-popular	18 (24.3)	6 (8.1)
Metabolism and nutrition disorders	33 (44.6)	6 (8.1)
Hyponatraemia	22 (29.7)	3 (4.1)
Hypokalaemia	21 (28.4)	3 (4.1)

Adverse events of special interest

AESIs, n (%)	N=74 Any grade
CRS, any grade	**70 (94.6)**
Grade 1	27 (36.5)
Grade 2	35 (47.3)
Grade 3[a]	8 (10.8)
ICANS, any grade	**10 (13.5)**
Grade 1	4 (5.4)
Grade 2	3 (4.1)
Grade 3	3 (4.1)
HLH, any grade	**2 (2.7)**
Grade 1	0 (0.0)
Grade 2	1 (1.4)
Grade 3	1 (1.4)

No Grade 4 or 5 AESIs were observed

- Tolerability consistent with previous report
- Most frequent TEAEs were anticipated **cytopenias associated with lymphodepletion**
- Expected and **manageable CRS, mostly Grade 1/2,** consistent with mechanism of action
- **Infrequent**, manageable, and mostly **mild ICANS**
- **No anzu-cel—related Grade 5 events**
- Tolerability in the melanoma subset generally consistent with the full anzu-cel tolerability profile

Data cutoff: April 7, 2025.

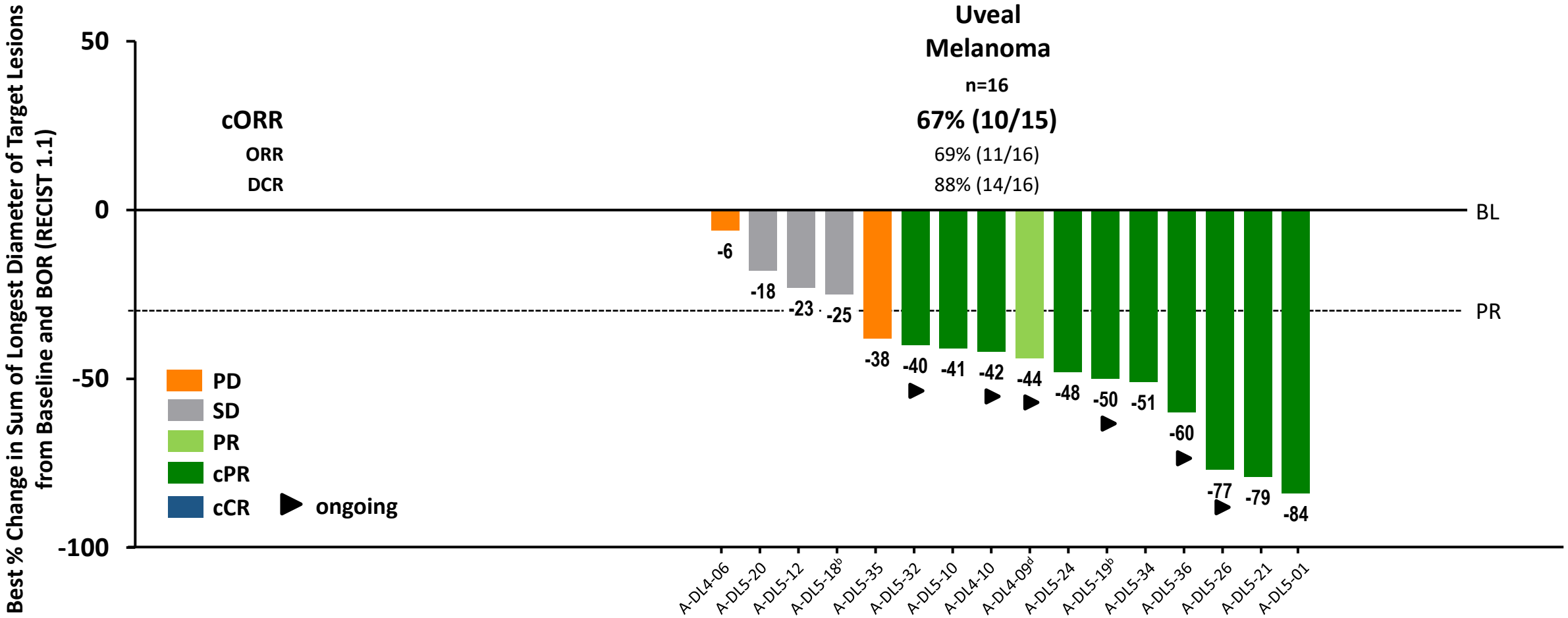
Patients are counted only once per adverse event and severity classification. [a] Two patients with disease progression after first anzu-cel infusion received exploratory second anzu-cel infusion. They had these ≥ Grade 3 TEAEs only after second infusion, which are included in the table: First patient: CRS, diarrhea; Second patient: neutropenia, thrombocytopenia.

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; HLH, hemophagocytic lymphohistiocytosis; TEAE, treatment-emergent adverse event.

1. Wermke M, et al. ASCO 2025. Oral presentation 2508.

Best Overall Response at RP2D

NCT03686124



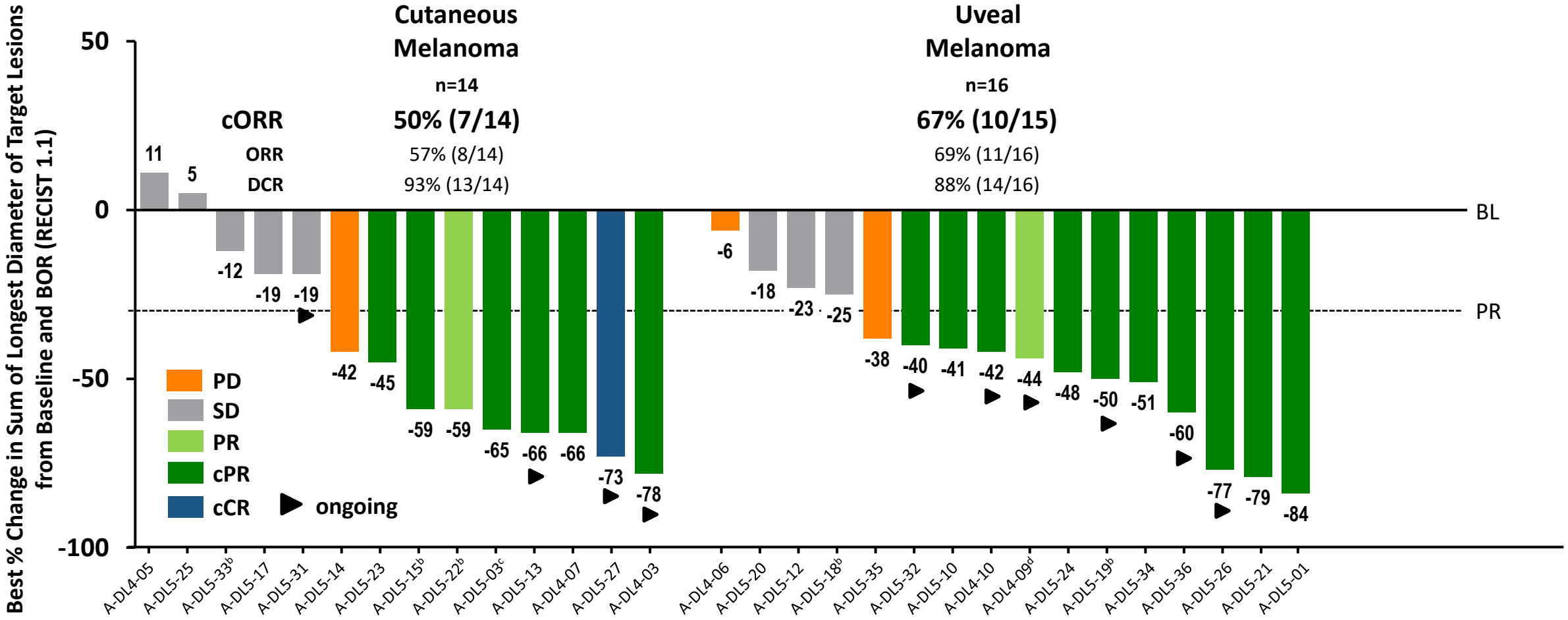
Data cutoff: April 7, 2025.

[a] Includes melanoma (other); [b] Maximum change of target lesions and RECIST1.1 response at different timepoints; [c] Patient out of study due to PD (external assessment); [d] Patient out of study at data-cut (withdrew consent).
n=3: mucosal melanoma n=2, melanoma of unknown primary n=1; Melanoma efficacy population excludes 1 uveal melanoma patient with ongoing unconfirmed PR from cORR.
BOR, best overall response; cCR, confirmed complete response; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SD, stable disease

1. Wermke M, et al. ASCO 2025. Oral presentation 2508.

Best Overall Response at RP2D

NCT03686124



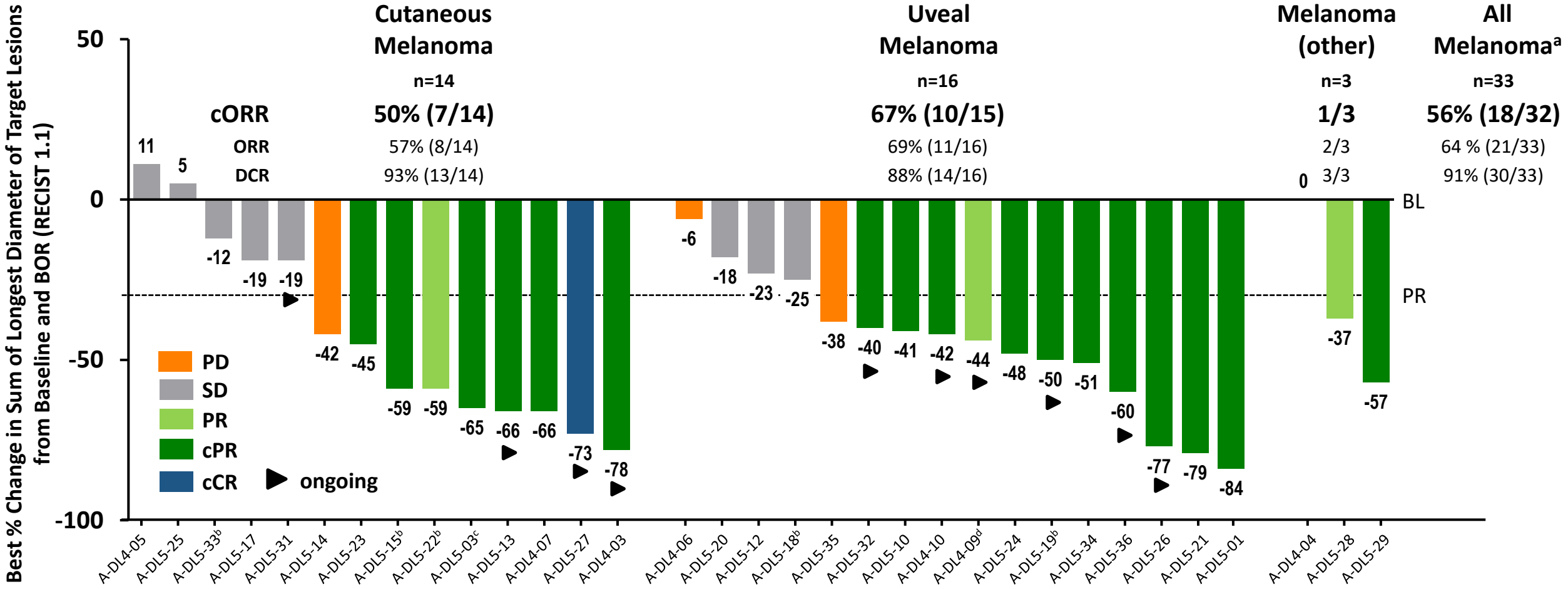
Data cutoff: April 7, 2025.

[a] Includes melanoma (other); [b] Maximum change of target lesions and RECIST1.1 response at different timepoints; [c] Patient out of study due to PD (external assessment); [d] Patient out of study at data-cut (withdrew consent).
n=3: mucosal melanoma n=2, melanoma of unknown primary n=1; Melanoma efficacy population excludes 1 uveal melanoma patient with ongoing unconfirmed PR from cORR.
BOR, best overall response; cCR, confirmed complete response; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SD, stable disease

1. Wermke M, et al. ASCO 2025. Oral presentation 2508.

Best Overall Response at RP2D

NCT03686124



Data cutoff: April 7, 2025.

[a] Includes melanoma (other); [b] Maximum change of target lesions and RECIST1.1 response at different timepoints; [c] Patient out of study due to PD (external assessment); [d] Patient out of study at data-cut (withdrew consent).

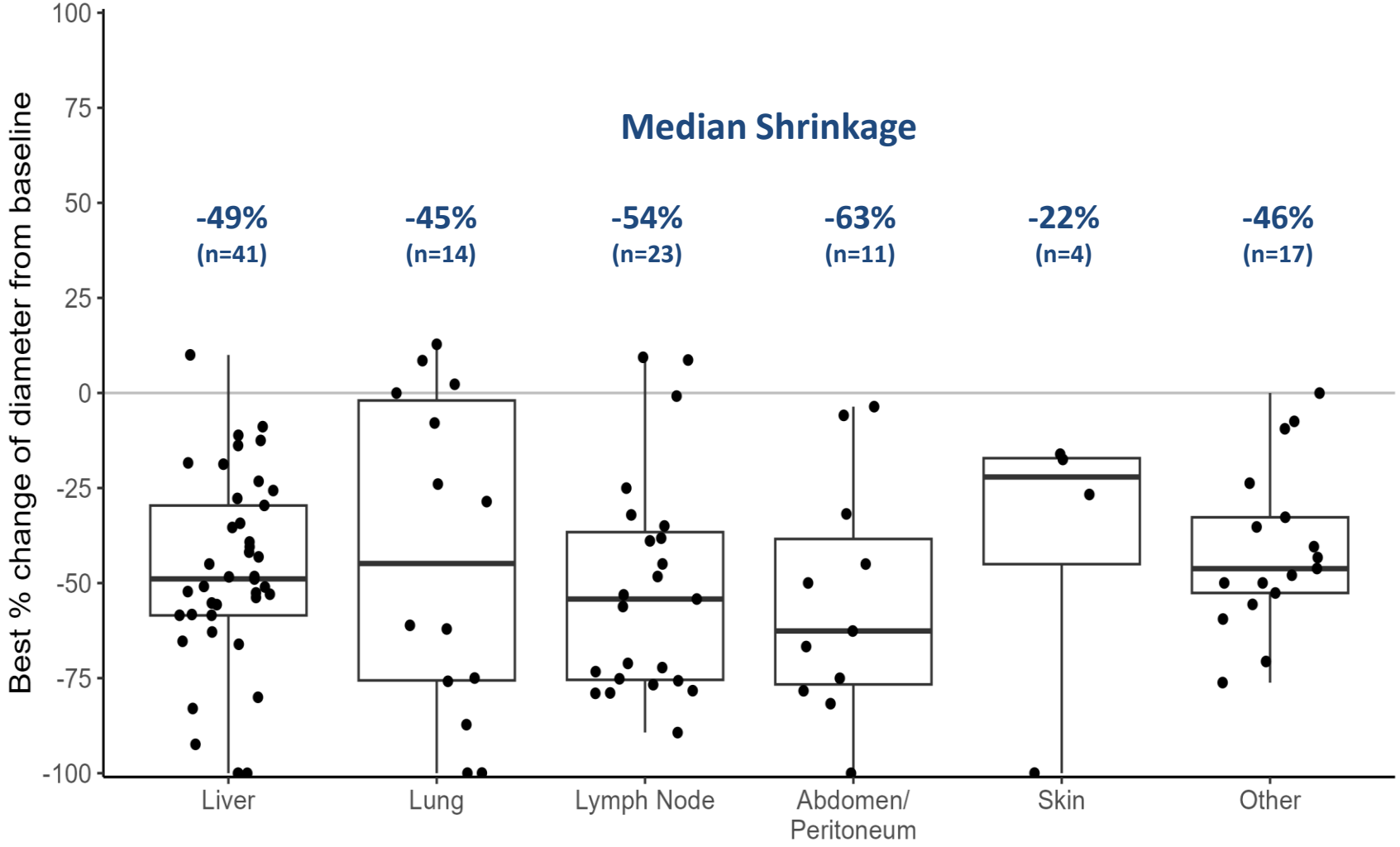
n=3: mucosal melanoma n=2, melanoma of unknown primary n=1; Melanoma efficacy population excludes 1 uveal melanoma patient with ongoing unconfirmed PR from cORR.

BOR, best overall response; cCR, confirmed complete response; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SD, stable disease

1. Wermke M, et al. ASCO 2025. Oral presentation 2508.

Anzu-cel in the Melanoma Efficacy Population: Responses of Metastatic Lesions

- Lesion-level analysis showed shrinkage across multiple metastatic sites, including difficult-to-treat organs like the liver
- Some lesions achieved complete resolution, and even patients with progressive disease had shrinkage in select lesions



Data cutoff: April 7, 2025.

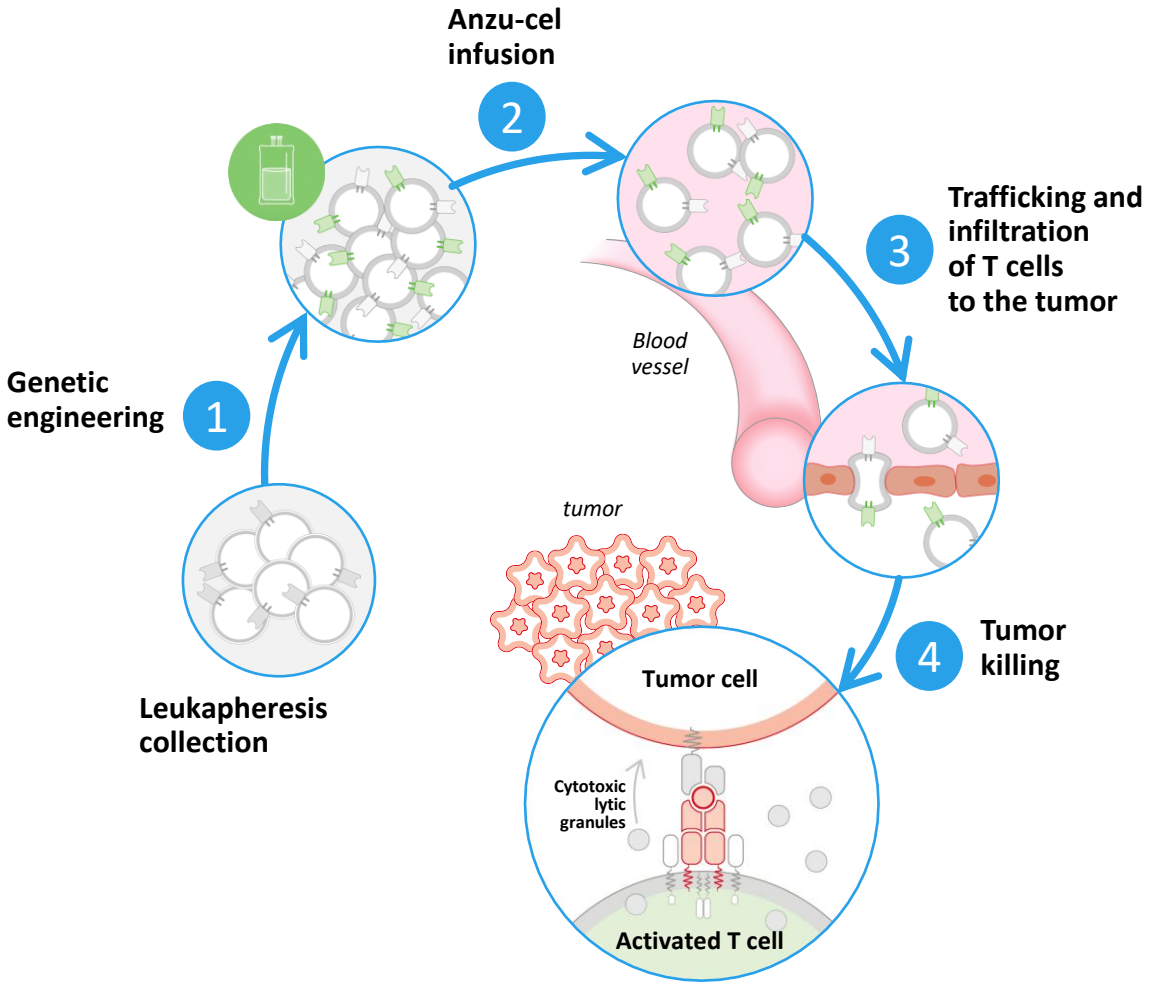
[a] Other: brain, kidney, pelvis, pericardium, pleura, bone, adrenal, retroperitoneum, rectum, soft tissue, gluteal, dorsal.

Each data point represents shrinkage of a target lesion, respectively.

T Cell Trafficking and Tumor Infiltration

- Chemokine receptors guide T-cell migration and homing to specific tissues[1,2]
- Expression pattern determines organ-specific trafficking and tumor infiltration[2]
- Upregulation of certain receptors (eg, CCR5, CXCR3) enhances effector T-cell localization to inflamed or tumor sites[2-4]
- We analyzed 3 receptors (CXCR3, CCR2, and CCR5) which cover 6 ligands (CXCL9/10; CCL2/3/4/5) identified as key drivers of $CD8^+$ T-cell trafficking/infiltration in melanoma metastases[5]

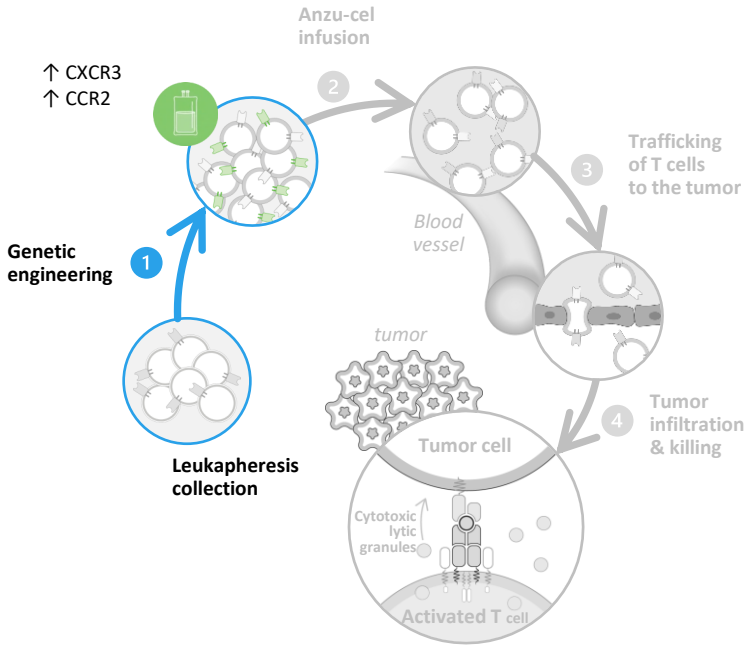
Receptor	Ligand	Function
CXCR3[2]	CXCL9, CXCL10	Migration of activated T cells to inflamed/tumor tissue
CCR2[6]	CCL2	Recruitment of monocytes and memory T cells
CCR5[4]	CCL3, CCL4, CCL5	Enhances T cell migration to inflamed/tumor microenvironments; facilitates effector cell entry

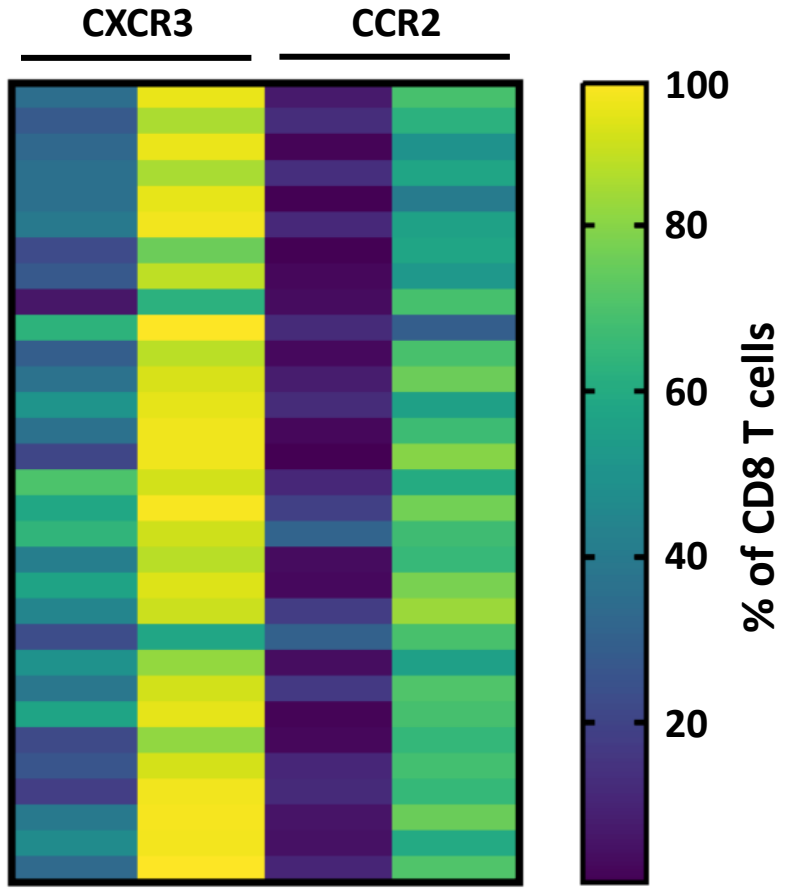


CCR, C-C chemokine receptor; CXCR, C-X-C chemokine receptor; PBMC, peripheral blood mononuclear cell; TCR, T-cell receptor.

1. Hughes CE, et al. *FEBS J.* 2018;285:2944-2971. 2. Nagarsheth N, et al. *Nat Rev Immunol.* 2017;17:559-572. 3. Idorn M, et al. *Oncoimmunology*. 2018;7:e1450715. 4. de Oliveira CE, et al. *Dis Markers.* 2014;2014:126954. 5. Harlin H, et al. *Cancer Res.* 2009; 69: 3077–3085. 6. Fujimura N, et al. *Sci Rep*. 2015;5:11664

Final Anzu-cel Products Were Significantly Enriched for Chemokine Receptors Involved in Immune Cell Migration (CXCR3, CCR2)





Sample	Leuk.	Final	Leuk.	Final
% of CD8 T cells	36%	91%*	7%	66%*
	P<0.0001		*P*<0.0001	

Chemokine receptors such as **CXCR3** and **CCR2** enable T cell trafficking and infiltration into the tumor microenvironment[1,2]

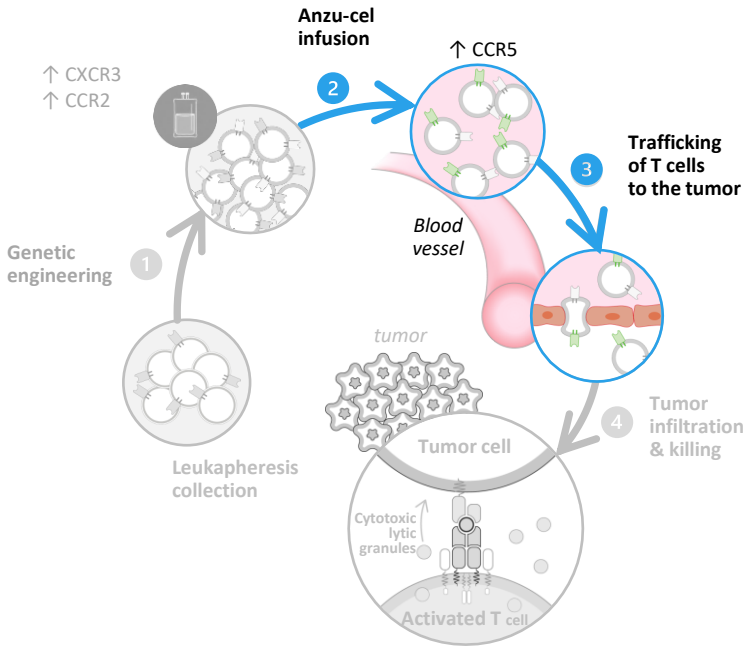
Statistical analysis was performed using two-tailed Wilcoxon matched pairs test n=31

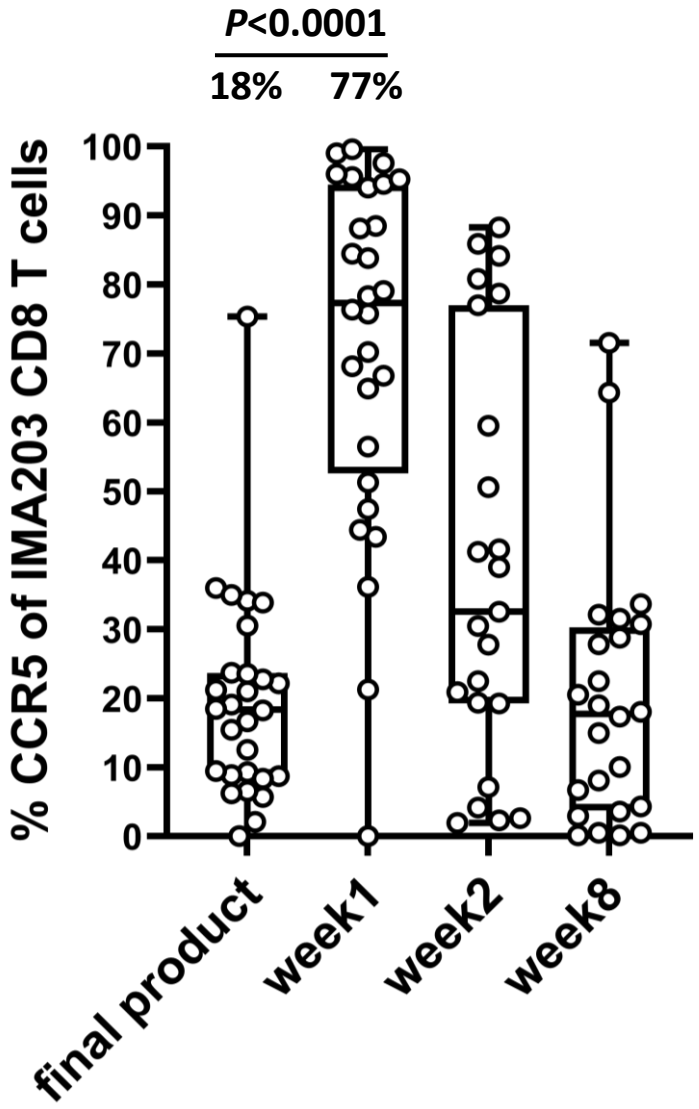
*Median expression of CXCR3 and CCR2 are 92% and 70%, respectively in the subset of anzu-cel TCR expressing CD8 T cells

CD, cluster of differentiation; CCR, C-C chemokine receptor; CXCR, C-X-C chemokine receptor; Leuk, leukapheresis; TCR, T-cell receptor.

1. Nagarsheth N, et al. *Nat Rev Immunol*. 2017;17:559-572. 2.. Fujimura N, et al. *Sci Rep*. 2015;5:11664

CCR5 is Induced on Anzu-cel TCR T Cells upon Activation Post-Infusion





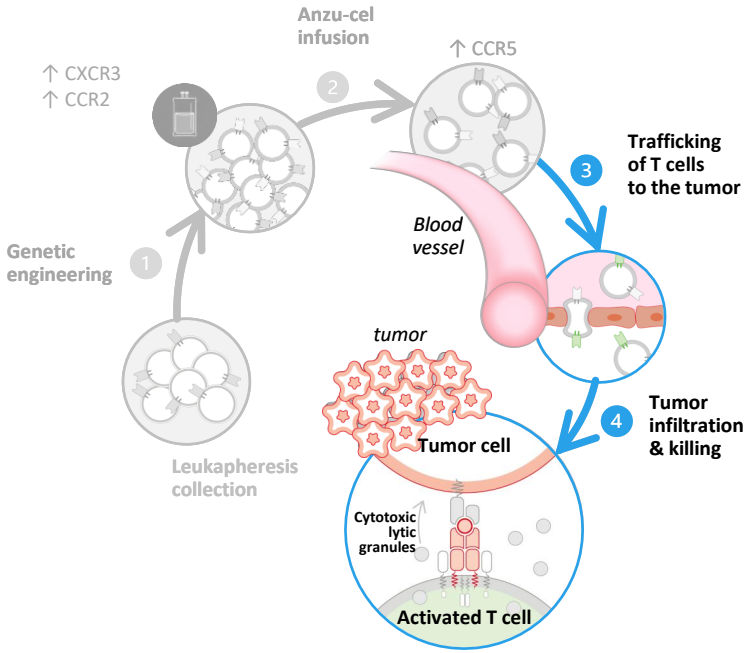
CCR5 facilitates migration of activated effector T cells into inflamed and tumor tissues following immune activation[1]

Statistical analysis was performed using two-tailed Wilcoxon matched pairs test.
FP, week1 n=28; week 2 n=23; week8 n=24

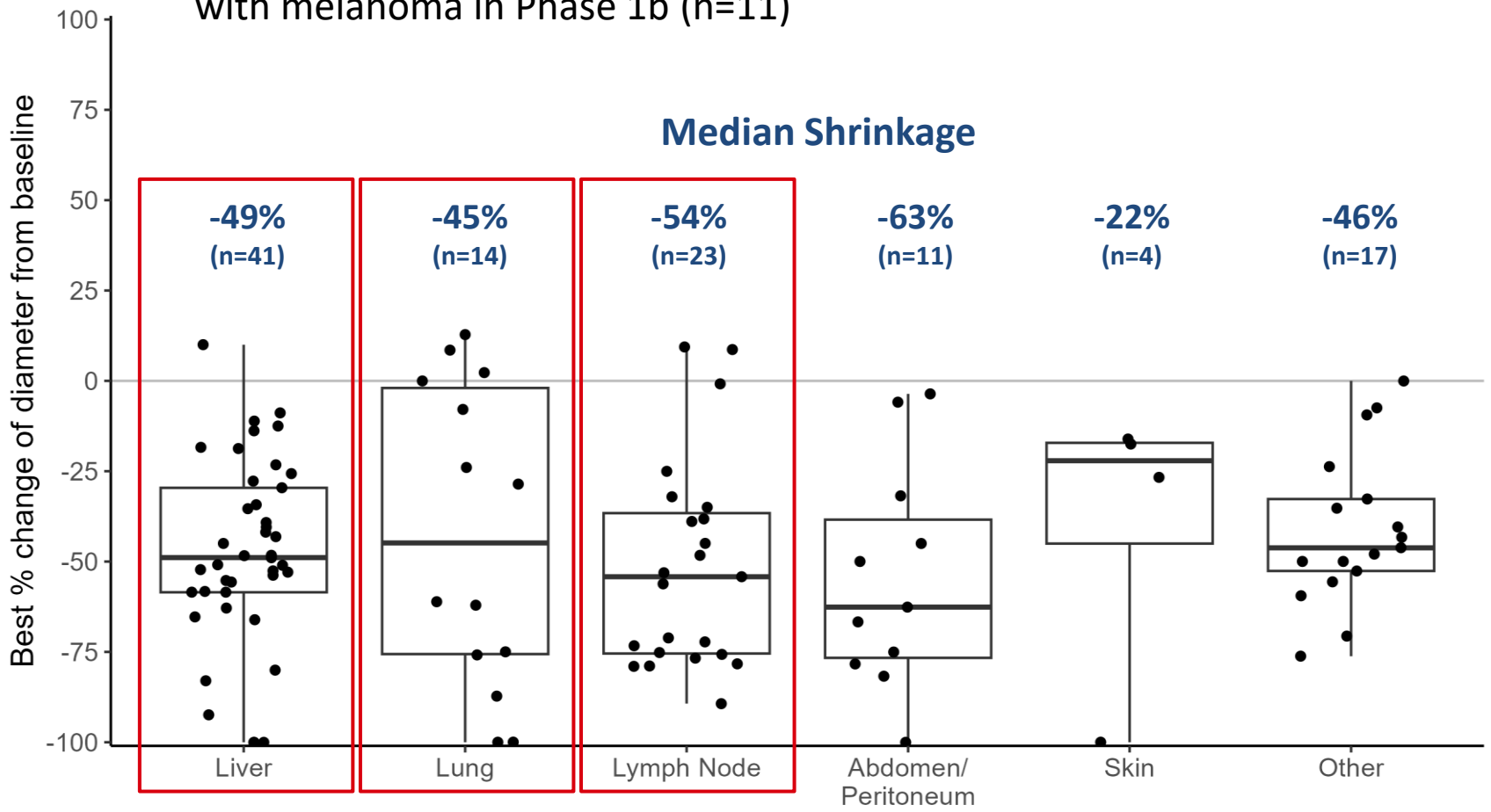
CD, cluster of differentiation; CCR, C-C chemokine receptor, TCR, T-cell receptor.

1. de Oliveira CE, et al. *Dis Markers.* 2014;2014:126954.

Anzu-cel in the Melanoma Efficacy Population: Responses of Metastatic Lesions



- Anzu-cel TCR T-cells were detected in evaluable samples from all patients with melanoma in Phase 1b (n=11)



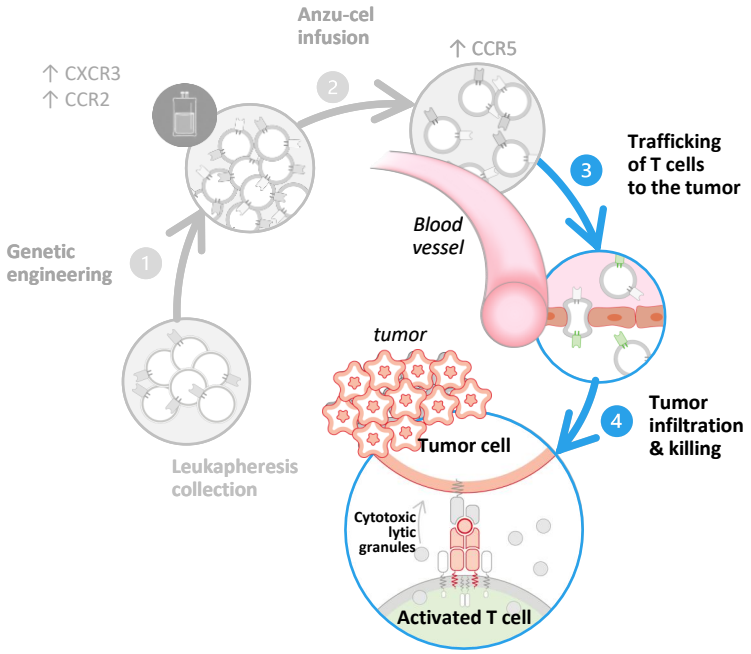
Data cutoff: April 7, 2025.

[a] Other: brain, kidney, pelvis, pericardium, pleura, bone, adrenal, retroperitoneum, rectum, soft tissue, gluteal, dorsal.

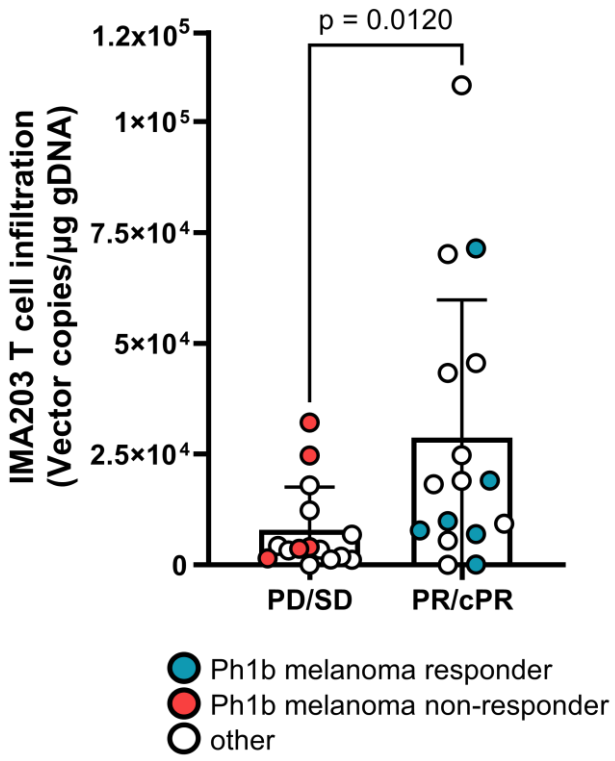
Each data point represents shrinkage of a target lesion, respectively.

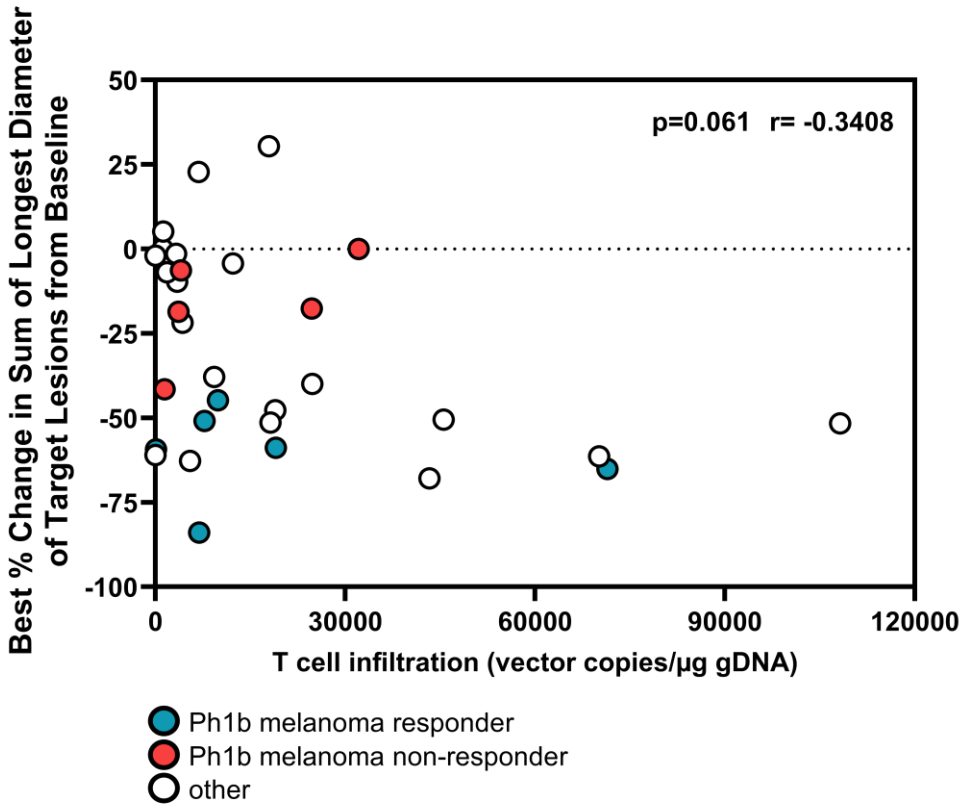
TCR, T-cell receptor

Anzu-cel TCR T-cell Infiltration Was Detected in Post-Treatment Biopsies and Correlates with Clinical Responses



- Higher degrees of infiltration were associated with clinical responses





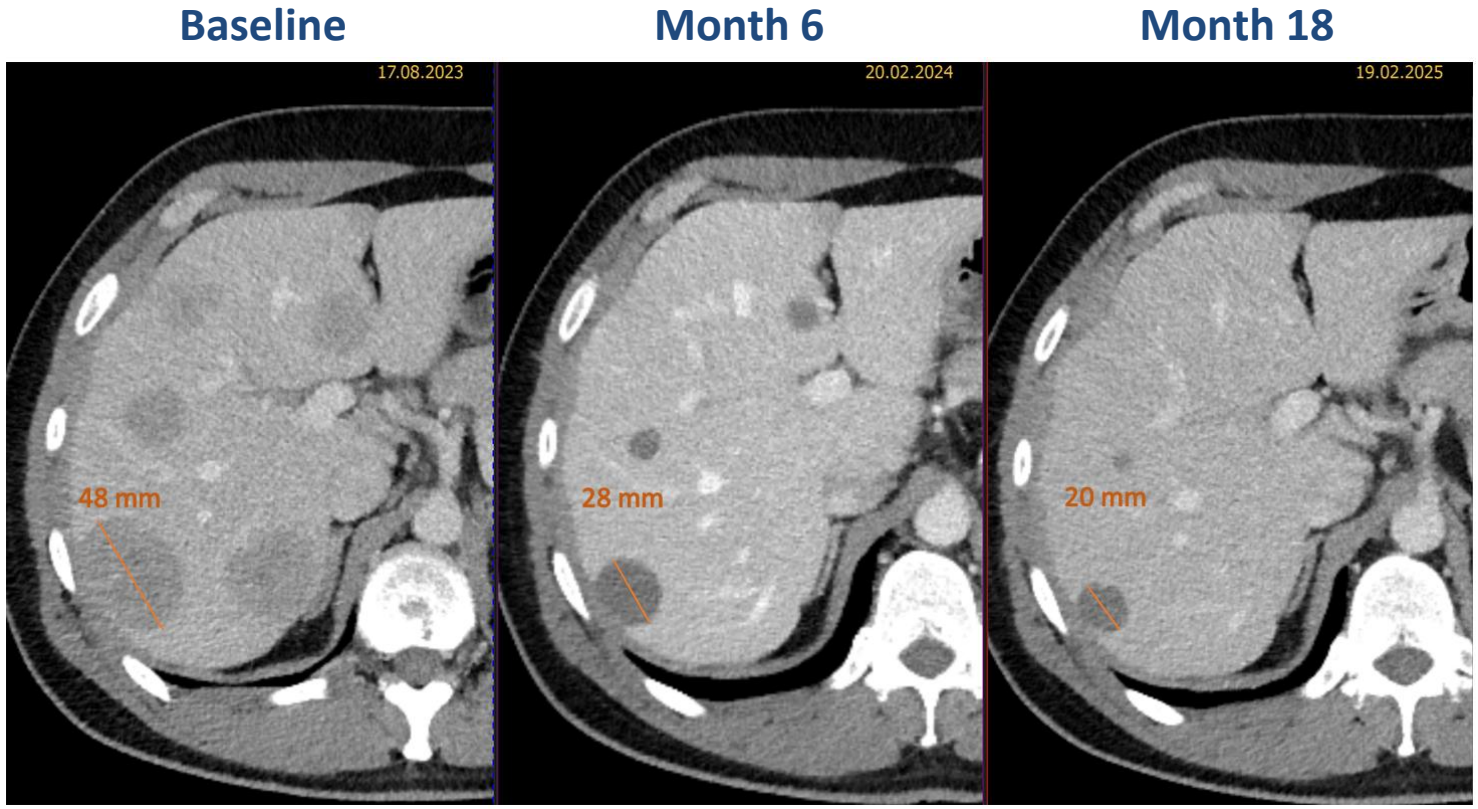
Statistical testing: Mann-Whitney U statistical test (right), spearman correlation (left) n=31

cCR, confirmed complete response; gDNA, genomic DNA; PD, progressive disease; PR, partial response; SD, stable disease; TCR, T-cell receptor.

Patient Case: Cutaneous Melanoma

A-DL5-13

- 37 years of age, male
- Prior lines of treatment: 3
  - Treatment type: 3 lines of ICI
  - Time from diagnosis to anzu-cel infusion: 4.5 years
  - Anzu-cel infusion: August, 2023
- Tumor burden: 12.8 cm
  - 4 target lesions; 2 lung (1.6 & 1.3 cm) and 2 liver (5.1 & 4.8 cm)
- T-cell dose
  - 9.8×10^9 infused TCR T-cells
- Best overall response
  - cPR (-65.6%)
  - Duration of response: 16.7 months



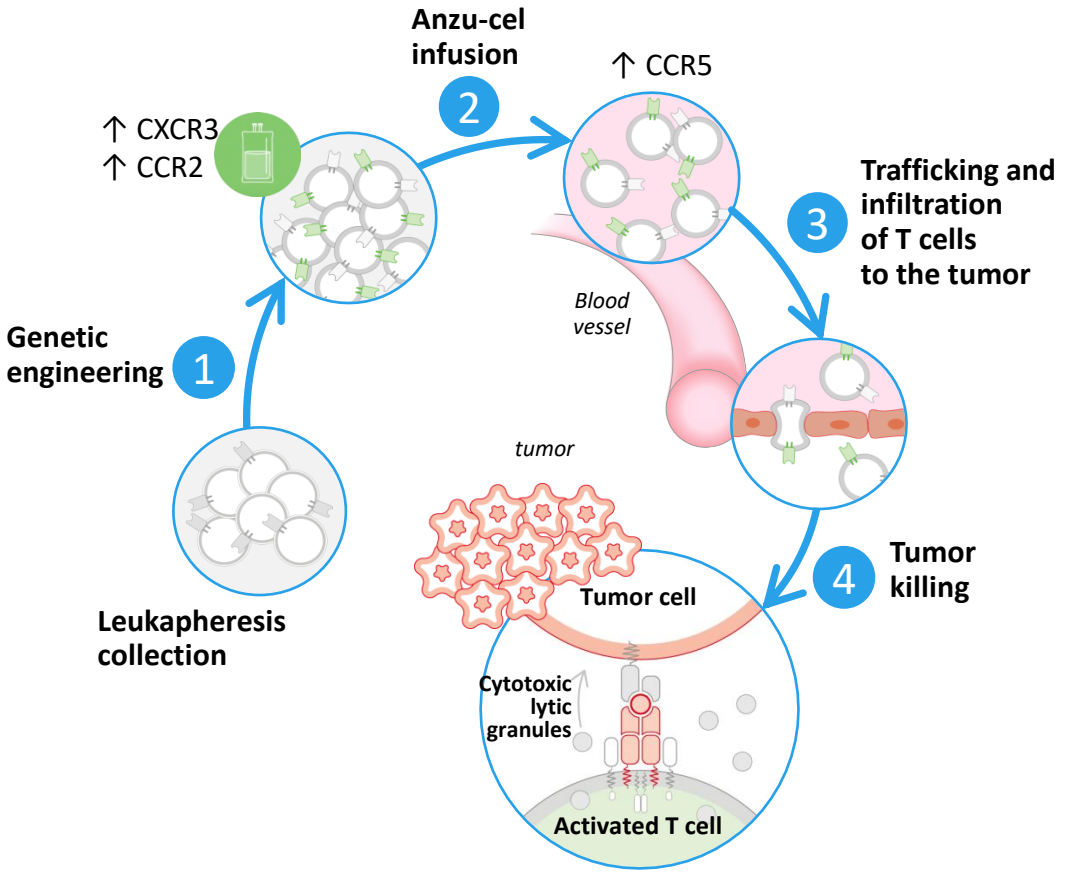
Data cutoff: April 7, 2025.

CT scans courtesy of treating physician (Dr. Chatterjee, University Clinic Würzburg); BOR: best overall response; cPR: confirmed partial response; ICI, immune checkpoint inhibitor; SOD: sum of diameter; TL: target lesion; TCR, T-cell receptor.

Conclusions

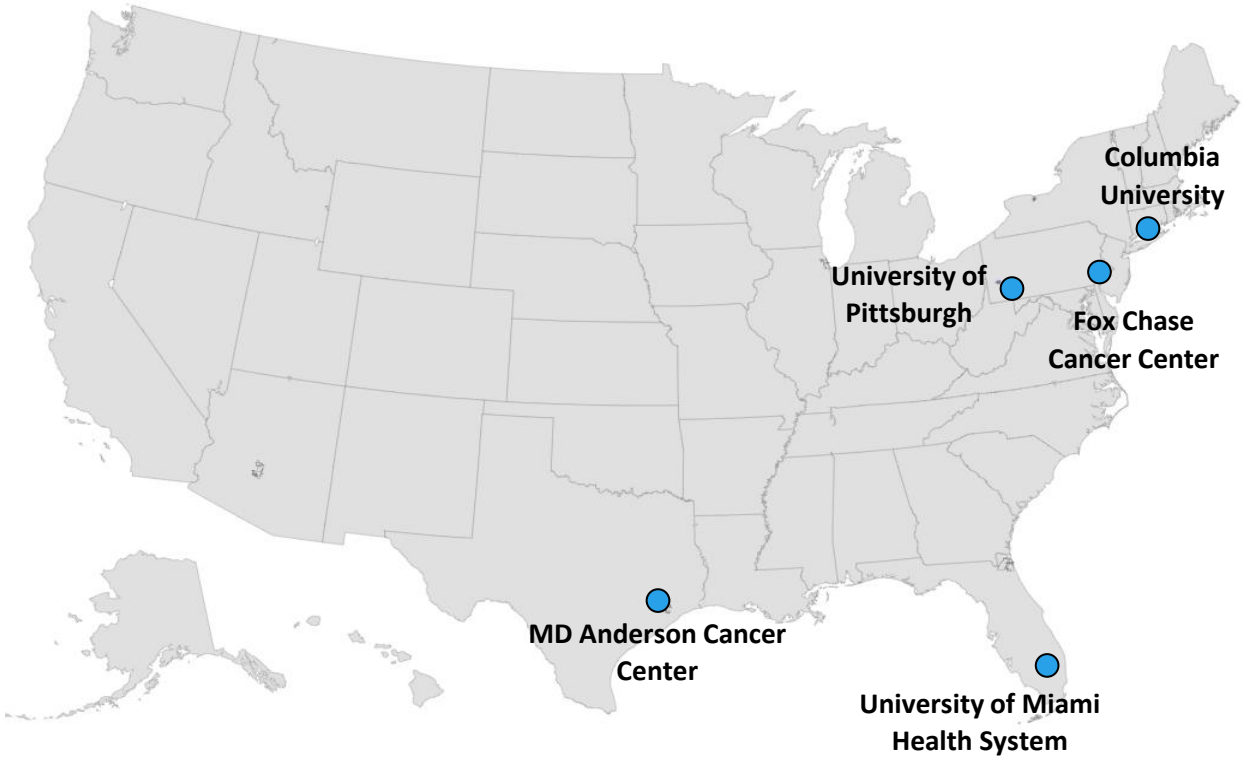
Anzutresgene autoleucel, a novel PRAME-directed TCR T-cell therapy, demonstrated broad organ penetration in patients with heavily pretreated advanced or metastatic melanoma

- Anzu-cel products are enriched for CXCR3 and CCR2 expression that allow migration across tumor-associated chemokine gradients
- CCR5 expression increases post-infusion, indicating that anzu-cel TCR T-cells adaptively enhance their migratory capacity upon activation
- Anzu-cel TCR T-cells were detected in all analyzed tumor biopsies, including traditionally immune-cold sites such as liver metastases
- A registration-directed phase 3 trial (SUPRAME; NCT06743126) is enrolling patients with previously treated advanced or metastatic cutaneous melanoma



Thank You to the Patients, their Families and the Participating Clinical Trial Sites

United States



Germany

Access the presentation by scanning the QR code.

For more information: martin.wermke@ukdd.de / medinfo@immatics.com

Medical writing support: Christopher Waldapfel, PharmD, Immatics US Inc; Clinical Care Solutions