ACTengine IMA203 TCR-T Targeting PRAME Shows Deep and Durable Anti-Tumor Activity in Heavily Pretreated Solid Cancer Patients

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Declaration of Interests

Martin Wermke

Financial Interests

Amgen, Invited Speaker, Personal
AstraZeneca, Advisory Board, Personal
Bayer, Advisory Board, Personal
Boehringer Ingelheim, Advisory Board, Personal
Boehringer-Ingelheim, Invited Speaker, Personal
Bristol Myers Squibb, Advisory Board, Personal
Daiichi Sankyo, Advisory Board, Personal
EMD Merck Serono, Invited Speaker, Personal
GWT TUD GmbH, Invited Speaker, Personal
ImCheck Therapeutics, Advisory Board, Personal
Immatics, Advisory Board, Personal
ISA Therapeutics, Other, Personal, Member of DSMC
Janssen, Invited Speaker, Personal
Novartis, Invited Speaker, Personal
Novartis, Advisory Board, Personal
Pfizer, Advisory Board, Personal
Regeneron, Advisory Board, Personal
Synlab GmbH, Invited Speaker, Personal
Tacalyx GmbH, Advisory Board, Personal
Zymeworks, Advisory Board, Personal
Roche, Funding, Institutional, Financial interest

Non-Financial Interests

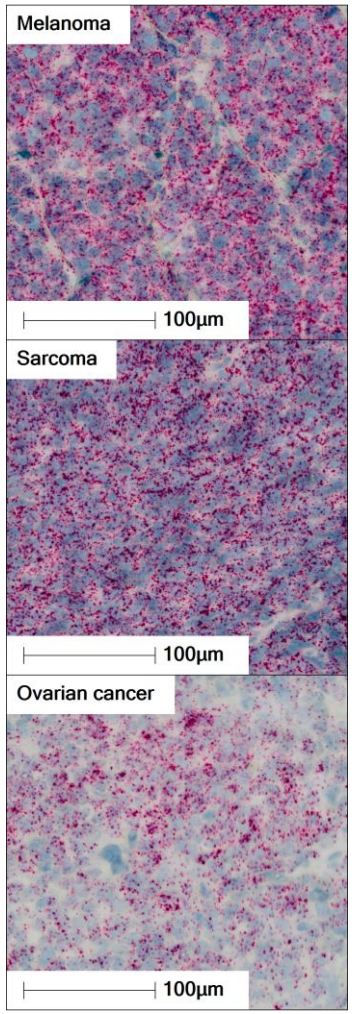
AstraZeneca, Other, Congress Travel Cost Support
Boehringer Ingelheim, Other, Congress Travel Cost Support
Daiichi Sankyo, Other, Congress Travel Cost Support
EMD Merck Serono, Other, Congress Travel Cost Support
Immatics, Other, Congress Travel Cost Support
Iovance, Other, Congress Travel Cost Support
Janssen, Other, Congress Travel Cost Support

The Multi-Cancer Opportunity of PRAME

PRAME Prevalences

Indication	% PRAME positive patients
Uterine Carcinosarcoma	100%
Sarcoma Subtypes	up to 100%
Uterine Carcinoma	95%
Cut. Melanoma	95%
Uveal Melanoma[2]	90%
Ovarian Carcinoma	85%
Squamous NSCLC	70%
TNBC	65%
Small Cell Lung Cancer	45%
Kidney Carcinoma Subtypes	up to 40%
Cholangiocarcinoma	35%
Adeno NSCLC	25%
Breast Carcinoma	25%
HNSCC	25%
Esophageal Carcinoma	25%
HCC	20%
Bladder Carcinoma	20%

PRAME RNA detection (ISH)

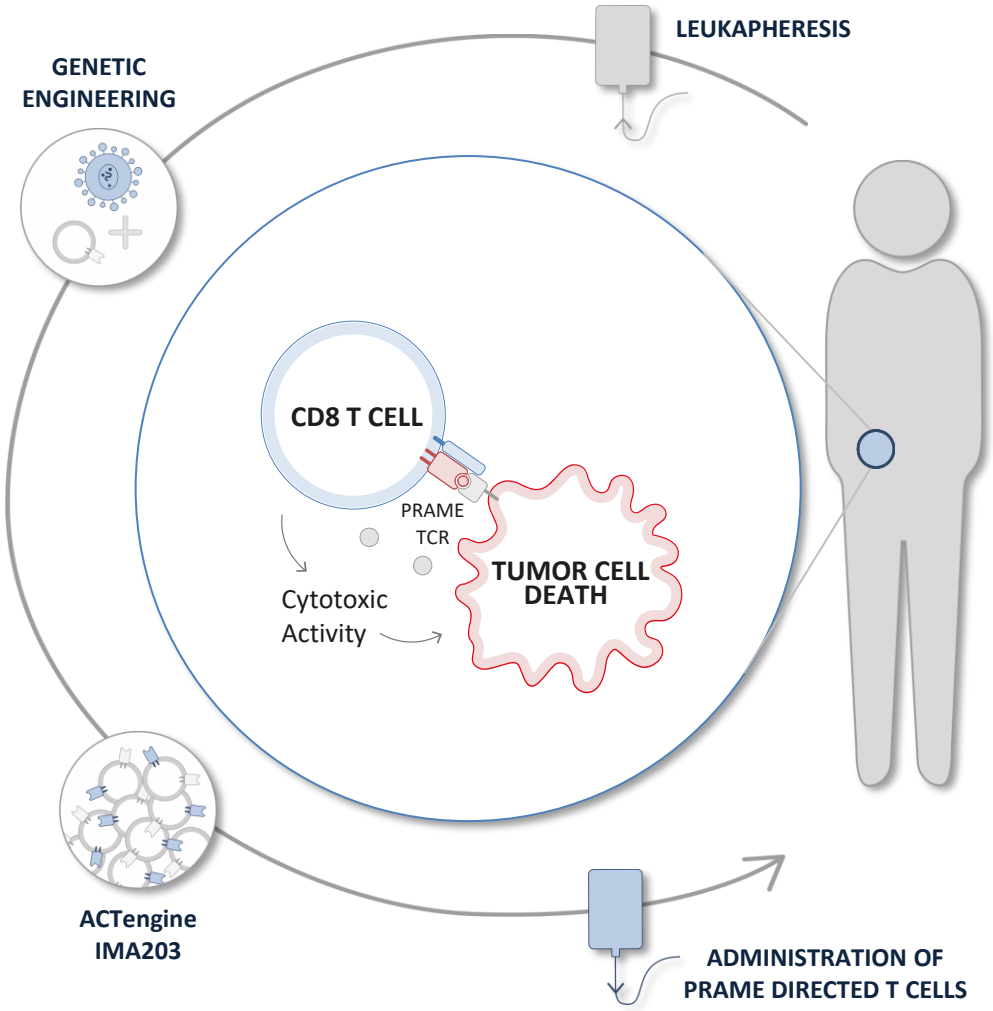


PRAME fulfills all properties of an ideal target for TCR-based therapies

- High prevalence[1]
- High target density
- Homogeneous expression
- “Clean” expression profile[3]

[1]Target prevalence based on TCGA (SCLC: in-house) RNAseq data combined with proprietary mass spec-guided RNA expression threshold; [2]Uveal melanoma target prevalence based on IMADetect qPCR testing of screening biopsies from 61 trial patients; [3]presented at SITC 2022

IMA203 – Mechanism of Action



- Autologous T cells transduced with PRAME specific TCR
- Targets HLA-A*02:01-presented PRAME peptides
- Engineered $CD8^+$ T cells designed to specifically recognize and destroy PRAME-positive tumor cells

[1] Data not shown here, published in Bajwa *et al.* 2021 Journal for Immunotherapy of Cancer; [2] Melenhorst *et al.* 2022 Nature, Bai *et al.* 2022 Science Advances

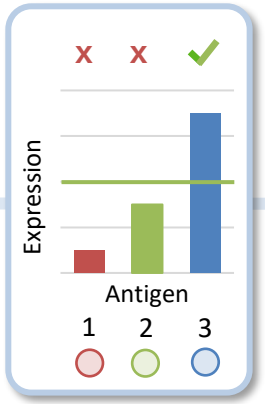
Patient Flow

SCREENING/MANUFACTURING | TREATMENT / OBSERVATION | LTFU

HLA-A*02 Testing

Leukapheresis

Lymphodepletion
Fludarabine 30mg/m^2 and
Cyclophosphamide 500mg/m^2
for 4 days



Target Profiling
IMADetect mRNA assay using Immatics' MS-guided threshold; Biopsy or archived tissue

ACTengine Manufacturing
by Immatics

IMA203

Process time of 14 days
7-day manufacturing process
applying CD8/CD4 T cell selection
7-day QC release testing

Low Dose IL-2
1m IU, daily d1-5
and twice daily d6-10

ACTengine IMA203 Infusion

Key Objectives and Eligibility Criteria

Key Objectives

Primary: Tolerability

- Investigation of Adverse Events
- Determination of a RP2D

Secondary: Biological and Clinical Activity

- IMA203 T cell engraftment, persistence
- Objective responses (RECIST1.1) & Duration of Response

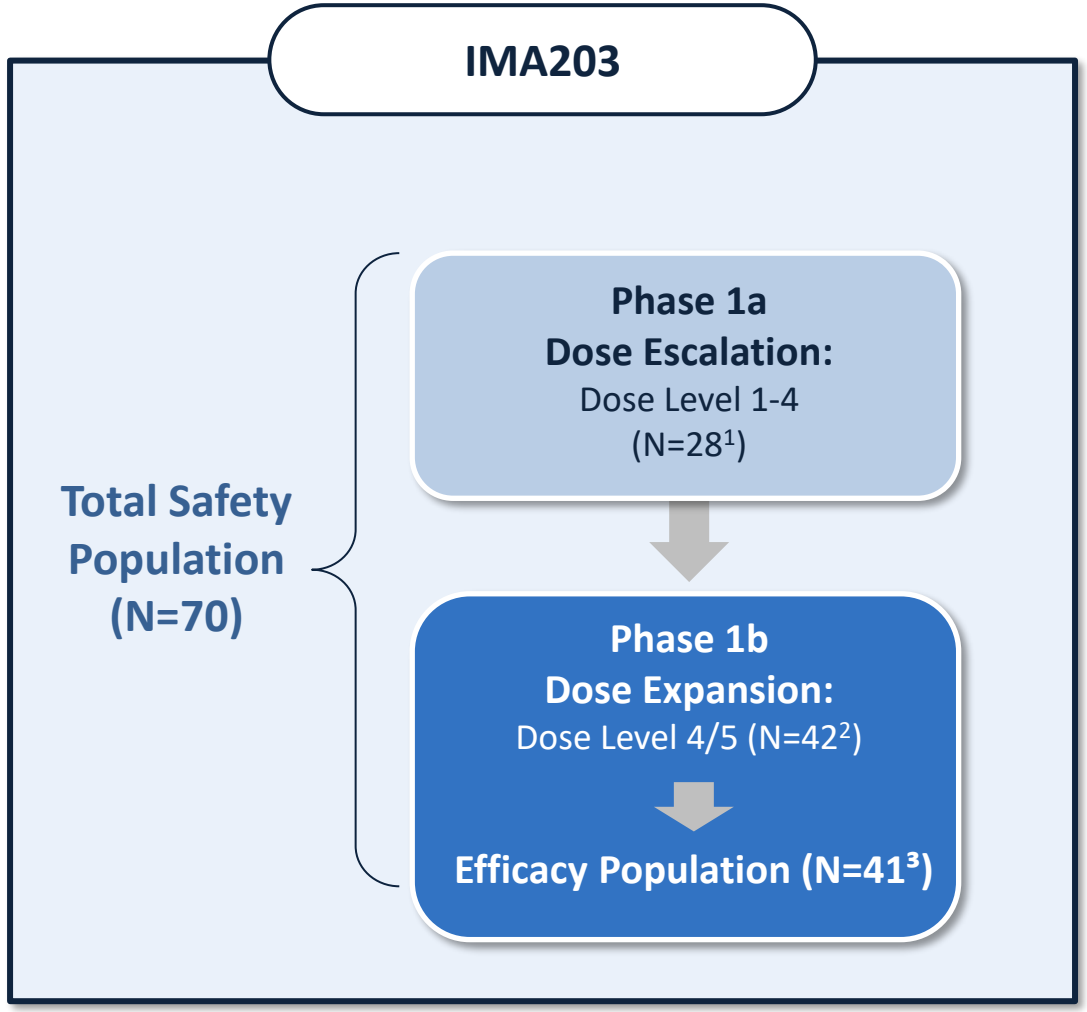
Exploratory

- IMA203 tumor infiltration

Key Eligibility Criteria

- Patients ≥ 18 years of age with ECOG 0 / 1
- HLA-A*02:01 and PRAME positive
- Patients having received, or not been eligible for all available indicated SOC treatment
- Adequate organ function
- No active brain metastasis
- No serious autoimmune disorder
- No immunosuppressive medication

Phase 1 Trial Design in Advanced Solid Tumors



Session 205b: Rapid Oral Abstract-Clinical

Saturday, Nov. 9, 2024

12:30–1:30 p.m.

Grand Ballroom C

Data cut-off Aug 23, 2024; [1] Includes one patient who started lymphodepletion but did not receive IMA203 TCR-T cells. [2] Includes one patient who started lymphodepletion with T cell infusion scheduled after data-cut; [3] All infused patients, first tumor assessment post infusion pending for 2/28 melanoma patients at data-cut.

Patient Characteristics

	Total Safety Population		Efficacy Population[2]	
	All Comers (Phase 1a and Phase 1b)		All Comers (Phase 1b, at RP2D)	
Number of patients	**Total**	**N=70[1]**	**Total**	**N=41**
	Melanoma	N=41	Melanoma	N=28
	Other	N=29	Others	N=13
Prior lines of systemic treatment (median, min, max)	3 (0, 9)		3 (0, 9)	
Thereof CPI (melanoma only) (median, min, max)	2 (0, 4)		1 (0, 4)	
LDH at baseline >1 x ULN [% of patients]	64.3		63.4	
Baseline tumor burden Median Target lesion sum of diameter [mm] (min, max)	117.8 (15.0, 309.8)		104.0 (15.0, 309.8)	
Liver/brain lesions at baseline [% of patients]	65.7		75.6	
Dose level	DL1-5		DL4/5	
Total infused dose TCR-T cells [x10^9]	2.09 (0.08, 10.2)		4.68 (1.0, 10.2)	

Data cut-off Aug 23, 2024; [1] All patients who started lymphodepletion. [2] All infused patients; IMA203 DL4: 0.2-1.2x10^9 TC-T cells/m^2 BSA, IMA203 DL5: 1.201 - 4.7x10^9 TCR-T cells/m^2 BSA.

Tolerability Profile of IMA203 Across Dose Levels in Phase 1a/b

Adverse event (System organ class, Preferred term)	≥ Grade 3 No.	≥ Grade 3 %
Patients with any adverse event	70	100.0
Adverse Events of Special Interest	**9**	**12.9**
Cytokine release syndrome	8	11.4
ICANS	3	4.3
Blood and lymphatic system disorders	**70**	**100.0**
Neutropenia	62	88.6
Lymphopenia	39	55.7
Leukopenia	38	54.3
Anaemia	36	51.4
Thrombocytopenia	24	34.3
Febrile neutropenia	2	2.9
Cytopenia	1	1.4
Leukocytosis	1	1.4
Infections and infestations	**10**	**14.3**
Urinary tract infection	2	2.9
Appendicitis	1	1.4
COVID-19	1	1.4
Cytomegalovirus infection reactivation	1	1.4
Enterococcal infection	1	1.4
Human herpesvirus 6 encephalitis	1	1.4
Infection	1	1.4
Orchitis	1	1.4
Sepsis[1, 2]	1	1.4
Septic shock[1]	1	1.4
Investigations	**10**	**14.3**
Alanine aminotransferase increased	6	8.6
Aspartate aminotransferase increased	5	7.1
Blood creatinine increased	2	2.9
Blood alkaline phosphatase increased	1	1.4
Blood bilirubin increased	1	1.4
Blood fibrinogen decreased	1	1.4
Lymphocyte count increased	1	1.4
Respiratory, thoracic and mediastinal disorders	**10**	**14.3**
Hypoxia	4	5.7
Pleural effusion	2	2.9
Bronchial obstruction	1	1.4
Dyspnoea	1	1.4
Epistaxis	1	1.4
Laryngeal inflammation	1	1.4
Respiratory failure	1	1.4

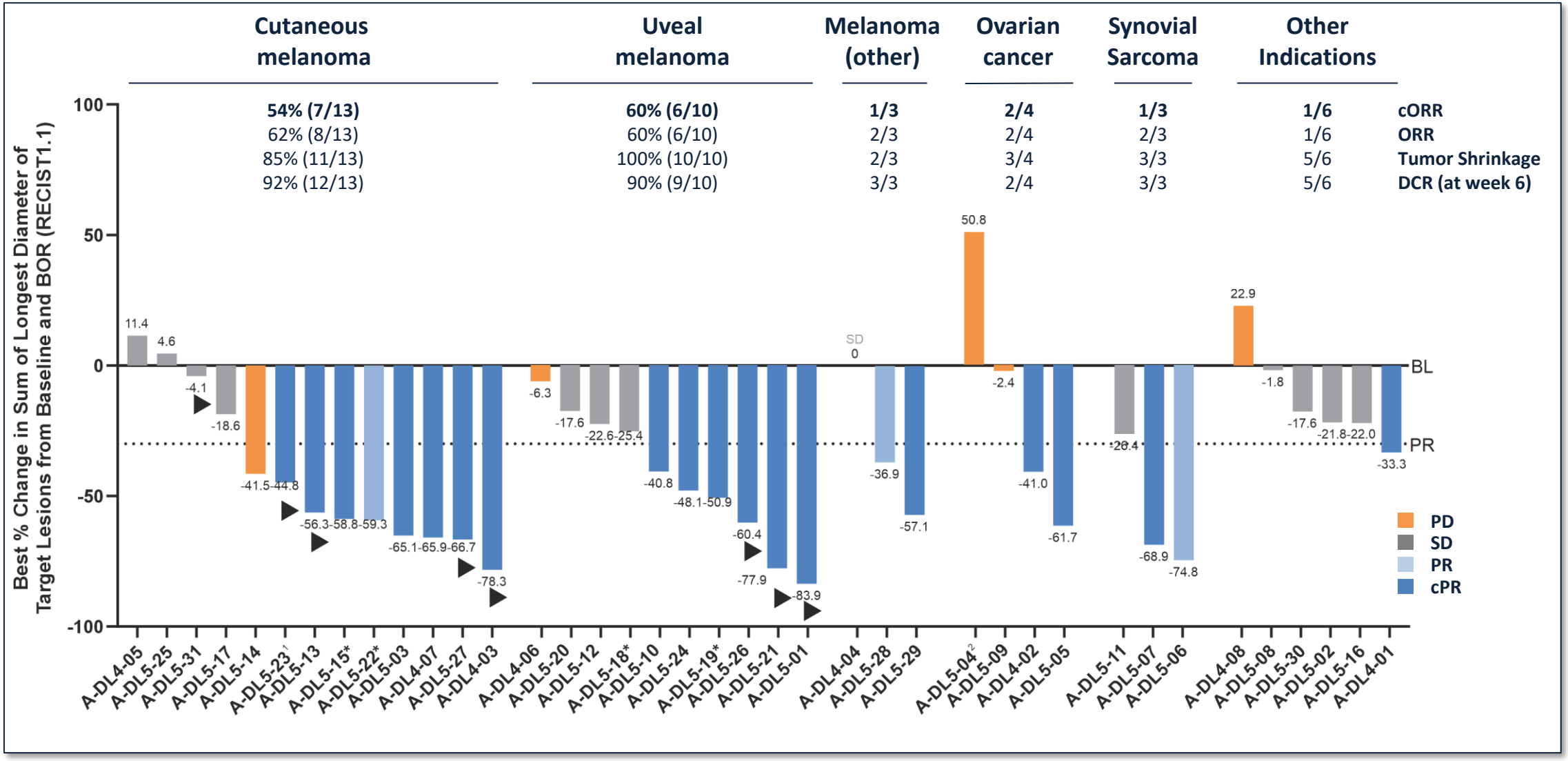
Adverse event (System organ class, Preferred term)	≥ Grade 3 No.	≥ Grade 3 %
table continued…		
Metabolism and nutrition disorders	**7**	**10.0**
Hypokalaemia	3	4.3
Hyponatraemia	3	4.3
Hypophosphataemia	2	2.9
Dehydration	1	1.4
Failure to thrive	1	1.4
Vascular disorders	**7**	**10.0**
Hypertension	6	8.6
Hypotension	1	1.4
Renal and urinary disorders	**6**	**8.6**
Acute kidney injury	4	5.7
Nephritis	1	1.4
Proteinuria	1	1.4
Gastrointestinal disorders	**5**	**7.1**
Abdominal pain	3	4.3
Diarrhoea	1	1.4
Ileus	1	1.4
Vomiting	1	1.4
General disorders and administration site conditions	**4**	**5.7**
Fatigue	1	1.4
General physical health deterioration[1]	1	1.4
Pyrexia	1	1.4
Swelling face	1	1.4
Skin and subcutaneous tissue disorders	**4**	**5.7**
Rash maculo-papular	3	4.3
Eczema	1	1.4
Cardiac disorders	**3**	**4.3**
Atrial fibrillation[3]	3	4.3
Eye disorders	**2**	**2.9**
Periorbital oedema	1	1.4
Ulcerative keratitis	1	1.4
Injury, poisoning and procedural complications	**2**	**2.9**
Humerus fracture	1	1.4
Infusion related reaction	1	1.4
Musculoskeletal and connective tissue disorders	**2**	**2.9**
Back pain	1	1.4
Muscle spasms	1	1.4

Adverse event (System organ class, Preferred term)	≥ Grade 3 No.	≥ Grade 3 %
table continued…		
Nervous system disorders	**2**	**2.9**
Headache	1	1.4
Posterior reversible encephalopathy syndrome	1	1.4
Endocrine disorders	**1**	**1.4**
Inappropriate antidiuretic hormone secretion	1	1.4
Hepatobiliary disorders	**1**	**1.4**
Cholangitis	1	1.4
Immune system disorders	**1**	**1.4**
Haemophagocytic lymphohistiocytosis	1	1.4
Reproductive system and breast disorders	**1**	**1.4**
Vaginal haemorrhage	1	1.4

- Expected cytopenias
- Expected CRS (11% Grade 3, no Grade 4)
- Infrequent ICANS (4% Grade 3, no Grade 4)
- No IMA203-related Grade 5 events
- MTD not reached

All treatment-emergent adverse events (TEAEs) with ≥ Grade 3 regardless of relatedness to study treatment n=70. [1] Fatal Adverse events were not considered related to any study drug; [2] Patient died from sepsis of unknown origin and did not receive IMA203 TCR-T cells; [3] DLT: Dose limiting toxicity in phase 1a at DL2 reported on March 17, 2021; Data cut-off Aug 23, 2024.

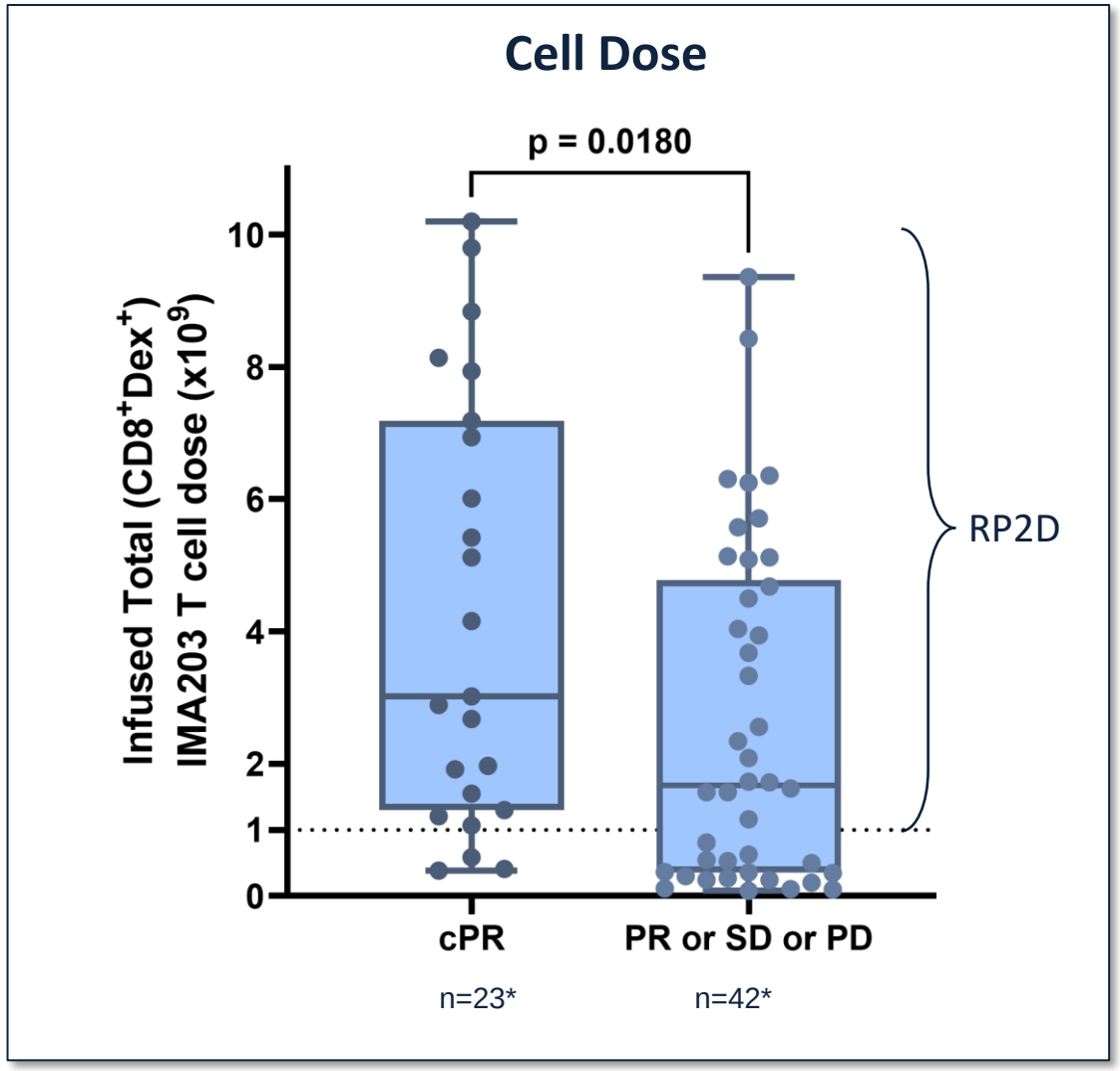
Best Overall Response IMA203 - Dose Expansion (n=41#)

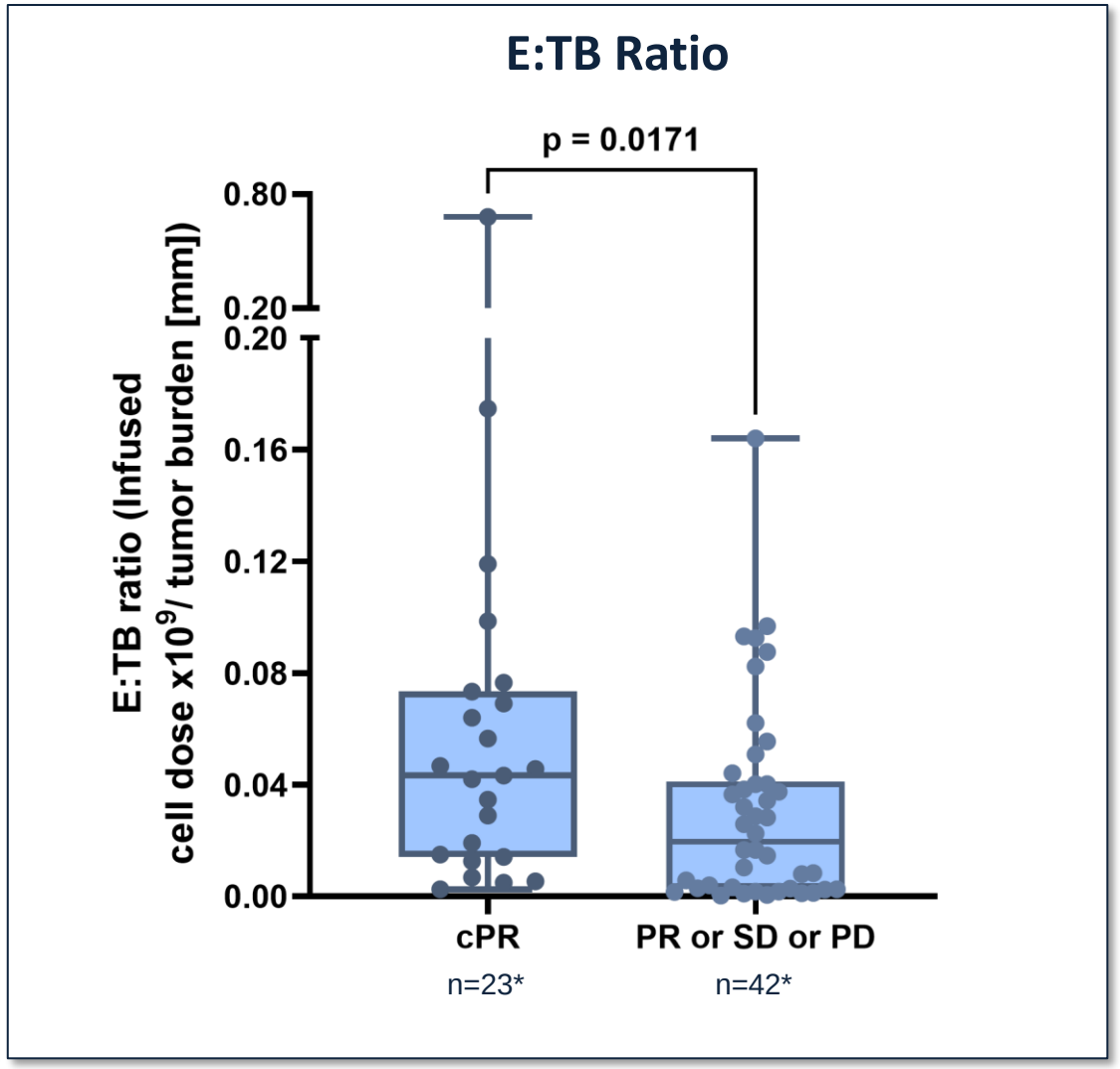


Data cut-off Aug 23, 2024; #First tumor assessment post infusion pending for 2/28 melanoma patients at data-cut; *Maximum change of target lesions and RECIST1.1 response at different timepoints.

[1]Patient A-DL5-23 is off study at data cut-off; [2] Patient received one dose nivolumab erroneously.

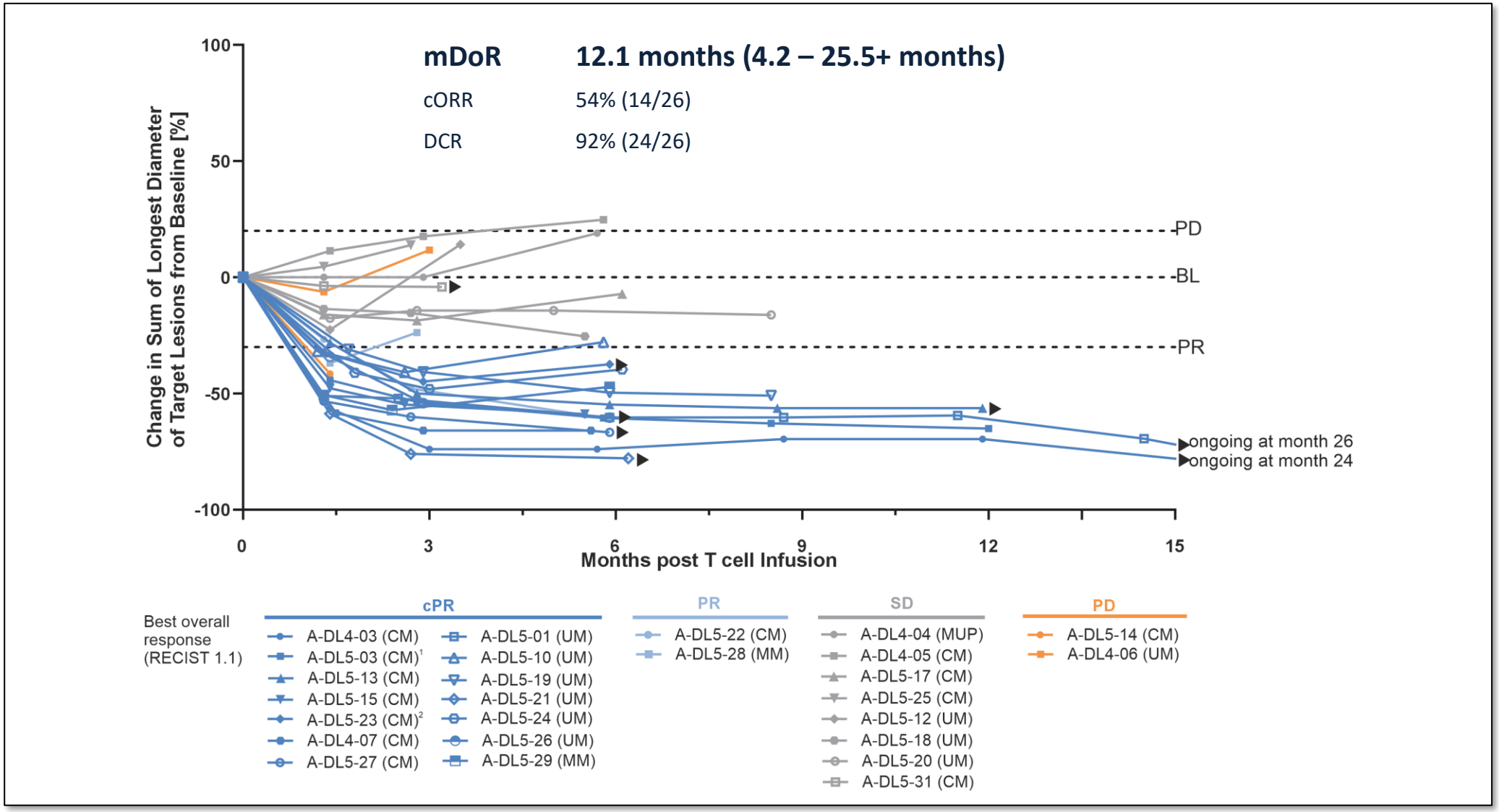
IMA203 Cell Dose and E:TB Ratio Associated with Clinical Activity





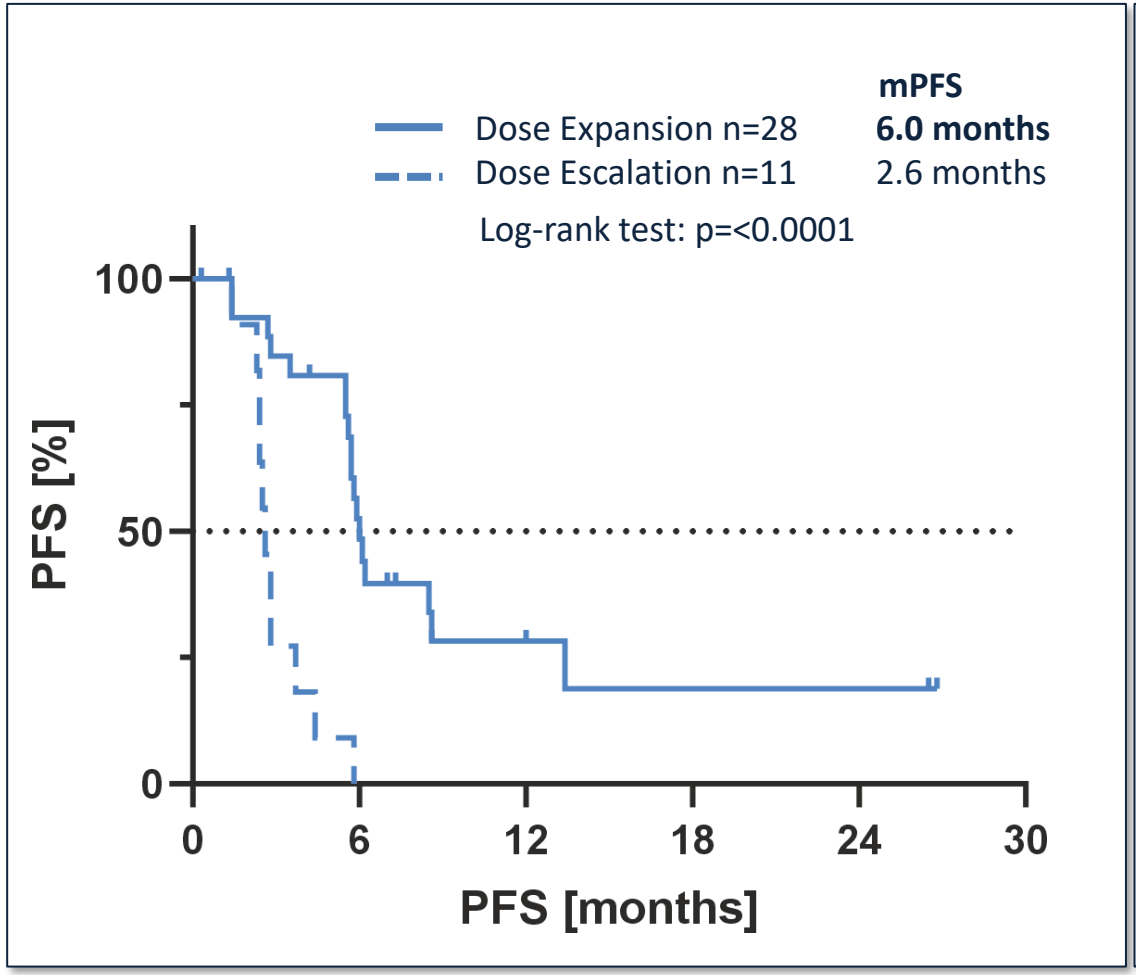
Data cut-off Aug 23, 2024; All dose levels and all indications shown; *no data available yet for patients recently treated; Mann-Whitney U test

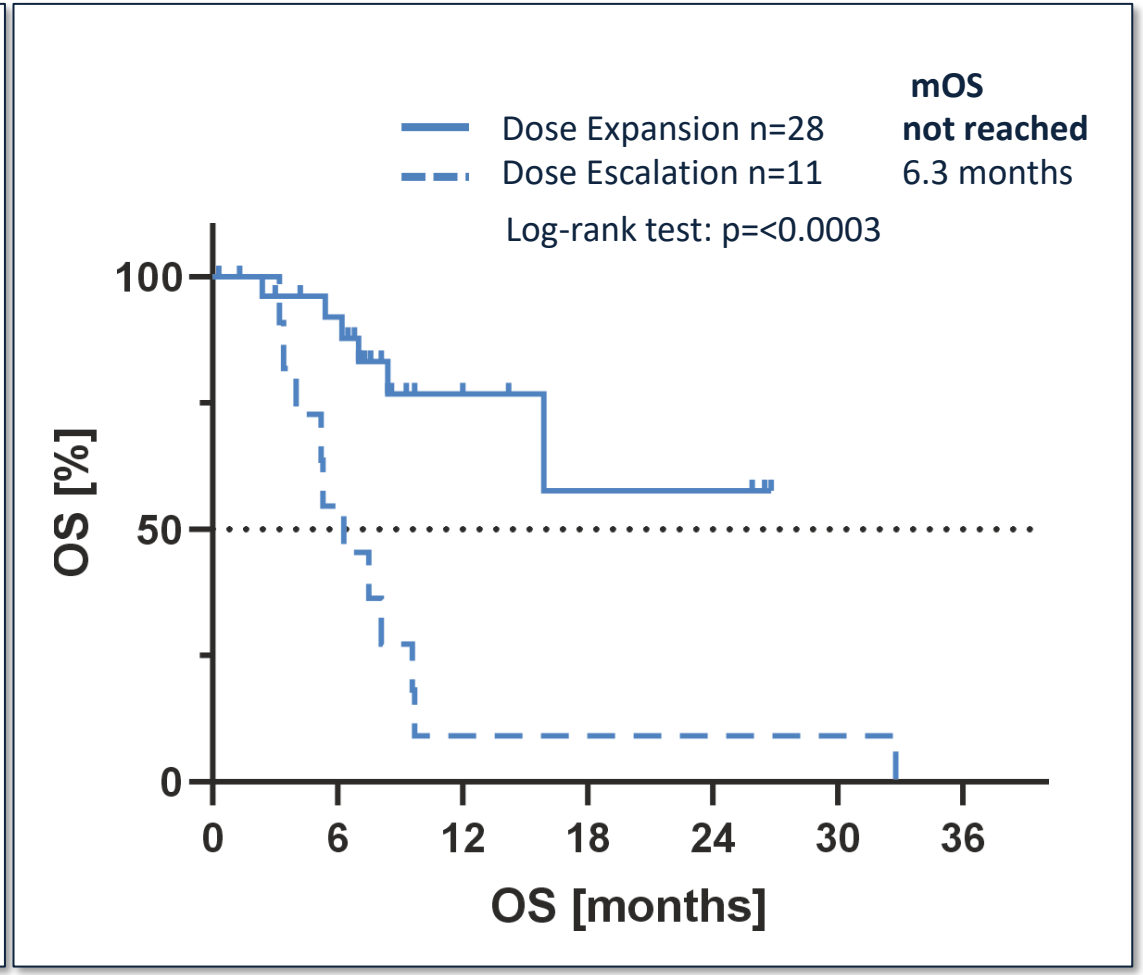
Response Over Time of IMA203 in Melanoma



Data cut-off Aug 23, 2024; #First tumor assessment post infusion pending for 2/28 melanoma patients at data-cut; [1]Patient out of study due to PD (external assessment) [2]Patient A-DL5-23 is off study at data cut-off.

Significant Shift in PFS and OS from Dose Escalation to Dose Expansion in Melanoma Patients





Data cut-off Aug 23, 2024; Overall survival (OS) and progression-free survival (PFS) censored at data-cut

SUPRAME: Registration-enabling Randomized Phase 3 Trial

Trial Design Following Recent Type D Meeting with FDA and SA Meeting with PEI[1]

Patient Population:
unresectable or metastatic melanoma post-treatment with a checkpoint inhibitor (2L+)

N=360

Randomization 1:1

ACTengine® IMA203

N=180

Investigator's choice
of selected approved treatments

N=180

- Nivolumab/Relatlimab
- Nivolumab
- Ipilimumab
- Pembrolizumab
- Lifileucel (US)
- Chemotherapy

Endpoints

- **Primary Endpoint**
  - **PFS**
- **Secondary Endpoints**
  - Safety
  - ORR + DOR
  - No OS detriment
  - Patient-reported outcomes (EORTC QLQ-C30, EQ-5D-5L)

Next Steps

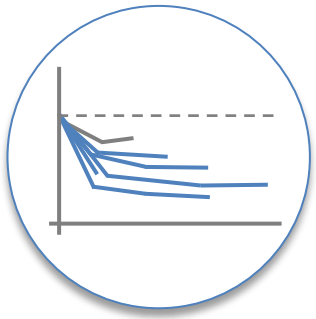
- SUPRAME Phase 3 trial is projected to commence in **December 2024**
- Pre-specified interim analysis planned after approx. 200 patients enrolled
- Full enrollment anticipated by late **2026**

mPFS: median progression-free survival, ORR: objective response rate; [1] Scientific Advice Meeting with Paul-Ehrlich-Institute, the German regulatory authority

ACTengine IMA203 TCR-T Monotherapy Targeting PRAME

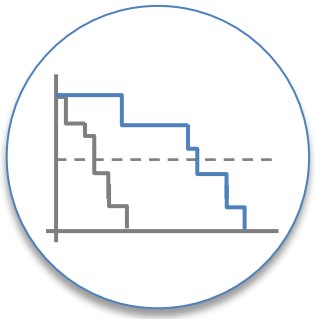
Tolerability

Favorable tolerability profile:
mostly mild to moderate CRS;
infrequent ICANS
(5.7% Gr1, 4.3% Gr2, 4.3% Gr3);
no treatment related deaths



Anti-Tumor Activity & Durability

54% (14/26) cORR and
92% (24/26) DCR;
12.1 months mDOR and
ongoing responses for
over two years in
melanoma patients

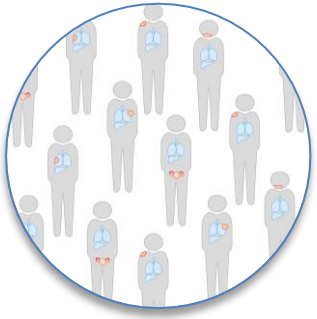


PFS & OS

PFS of 6 months and OS
not reached in
melanoma patients
(mFU 8.6 months)

Biological Data

T cell dose and E:TB ratio
are significantly
associated with clinical
response



Broad Reach

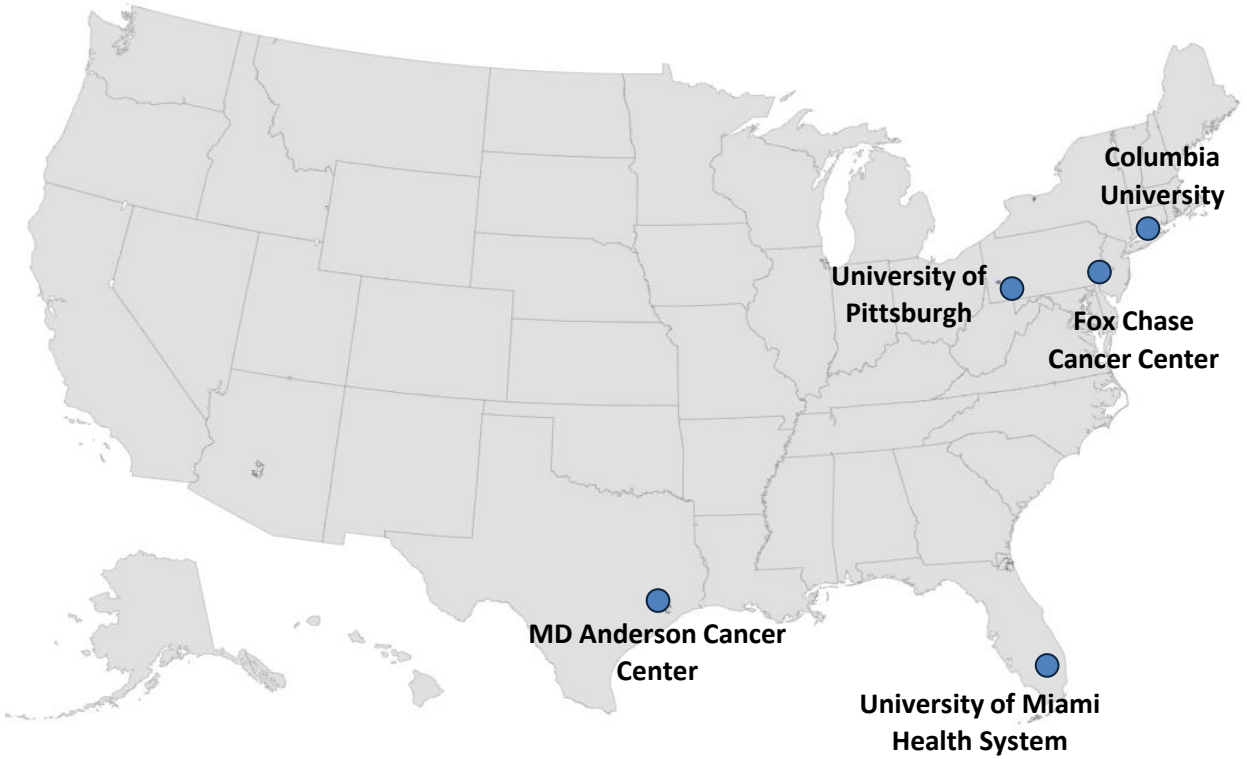
FDA RMAT designation
received in multiple PRAME
expressing cancers including
cutaneous and uveal
melanoma

SUPRAME Phase 3 trial in cutaneous melanoma patients is projected to commence in **December 2024**

Data cut-off Aug 23, 2024

Thank you Patients, Families, participating IMA203 Clinical Trial Sites

United States



Germany

Sponsor: Immatics

Appendix

All Patients: Patient Characteristics

	Total Safety Population	Total Efficacy Population[2]	Melanoma Dose Escalation Population	Melanoma Efficacy Population[2]
	All Comers (Phase 1a and Phase 1b)	All Comers (Phase 1b, at RP2D)	Melanoma (Phase 1a)	Melanoma (Phase 1b, at RP2D)
Number of patients	**Total** **N=70**[1] Melanoma **N=41** Other **N=29**	**Total** **N=41** Melanoma N=28 Others N=13	**Total** **N=11** Cutaneous melanoma N=8 Uveal melanoma N=2 Mucosal melanoma N=1	**Total** **N=28** Cutaneous melanoma N=13 Uveal melanoma N=12 Melanoma of unknown primary N=1 Mucosal melanoma N=2
Prior lines of systemic treatment (median, min, max)	3 (0, 9)	3 (0, 9)	4 (2, 7)	2 (0, 6)
Thereof CPI (melanoma only) (median, min, max)	2 (0, 4)	1 (0, 4)	2 (1, 4)	1 (0, 4)
LDH at baseline >1 x ULN [% of patients]	64.3	63.4	81.8	60.7
Baseline tumor burden Median Target lesion sum of diameter [mm] (min, max)	117.8 (15.0, 309.8)	104.0 (15.0, 309.8)	117.5 (37.0, 211.0)	107.5 (15.0, 309.8)
Liver/brain lesions at baseline [% of patients]	65.7	75.6	63.6	82.1
Dose level	DL1-5	DL4/5	EC1/DL3/DL4	DL4/5
Total infused dose TCR-T cells [$x10^9$]	2.09 (0.08, 10.2)	4.68 (1.0, 10.2)	0.586 (0.10, 2.09)	4.1 (1.3, 10.2)

Data cut-off Aug 23, 2024; [1] All patients who started lymphodepletion. [2] All infused patients;
EC1: 0.06-0.12x10^9 TCR-T cells/m^2 BSA; DL3: 0.2-0.48x10^9 TCR-T cells/m^2 BSA ; DL4: 0.2-1.2x10^9 TCR-T cells/m^2 BSA, DL5: 1.201 - 4.7x10^9 TCR-T cells/m^2 BSA

Baseline Characteristics of Melanoma Patients in Phase 1a and Phase 1b

Focus on Cutaneous and Uveal Melanoma

	Melanoma Dose Escalation Population		Melanoma Efficacy Population[1]	
Indication	**Cutaneous Melanoma (N=8)**	**Uveal Melanoma (N=2)**	**Cutaneous Melanoma (N=13)**	**Uveal Melanoma (N=12)**
Prior lines of systemic treatment (median, min, max)	4.5 (2, 7)	2 (2, 2)	2 (1, 5)	2.5 (0, 6)
Thereof CPI (melanoma only) (median, min, max)	2.5 (2, 4)	1 (1,1)	2 (1, 3)	1 (0, 4)
LDH at baseline >1 x ULN [% of patients]	75.0	100.0	69.2	58.3
Baseline tumor burden Median Target lesion sum of diameter [mm] (min, max)	106.3 (37.0, 211.0)	153,5 (109.9, 198.0)	123.0 (15.0, 309.8)	107.5 (38.6, 210.0)
Liver/brain lesions at baseline [% of patients]	50.0	100.0	69.2	91.7
Dose level	EC1/DL4	EC1, DL3	DL4/DL5	DL4/DL5
Total infused dose TCR-T cells [$x10^9$]	1.115 (0.099, 2.09)	0.417 (0.248, 0.586)	4.04 (1.3, 10.2)	4.33 (1.62, 8.43)

Cutaneous melanoma patients in Phase 1b had similar prior CPI exposure, higher tumor burden and higher incidence of liver/brain lesions compared to Phase 1a

Data cut-off Aug 23, 2024; [1] All infused melanoma patients in Ph1b dose expansion;
EC1: 0.06-0.12x10^9 TCR-T cells/m^2 BSA; DL3: 0.2-0.48x10^9 TCR-T cells/m^2 BSA ; DL4: 0.2-1.2x10^9 TCR-T cells/m^2 BSA, DL5: 1.201 - 4.7x10^9 TCR-T cells/m^2 BSA