#OncoPrecision26

VIII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN

Vigo, JUEVES
19 de FEBRERO de 2026

2ª MESA: T-cell engagers

MELANOMA

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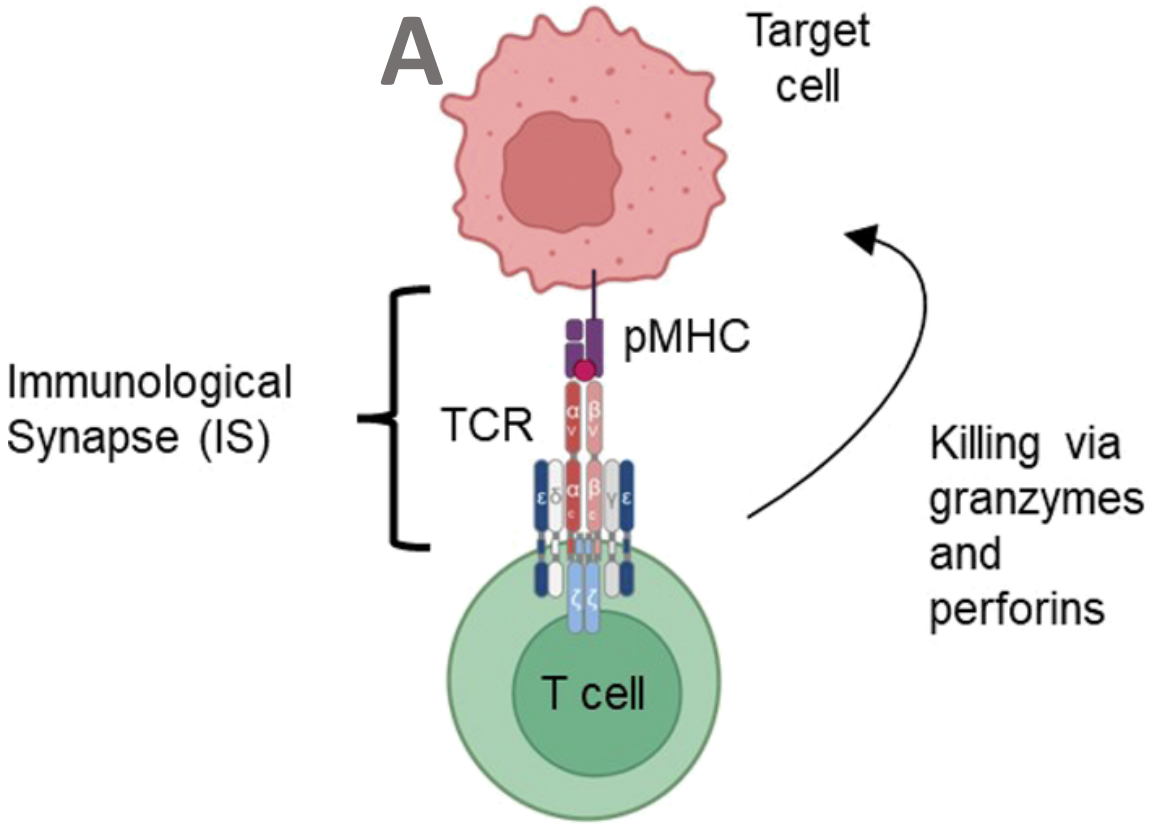
T cell engagers (TCEs)

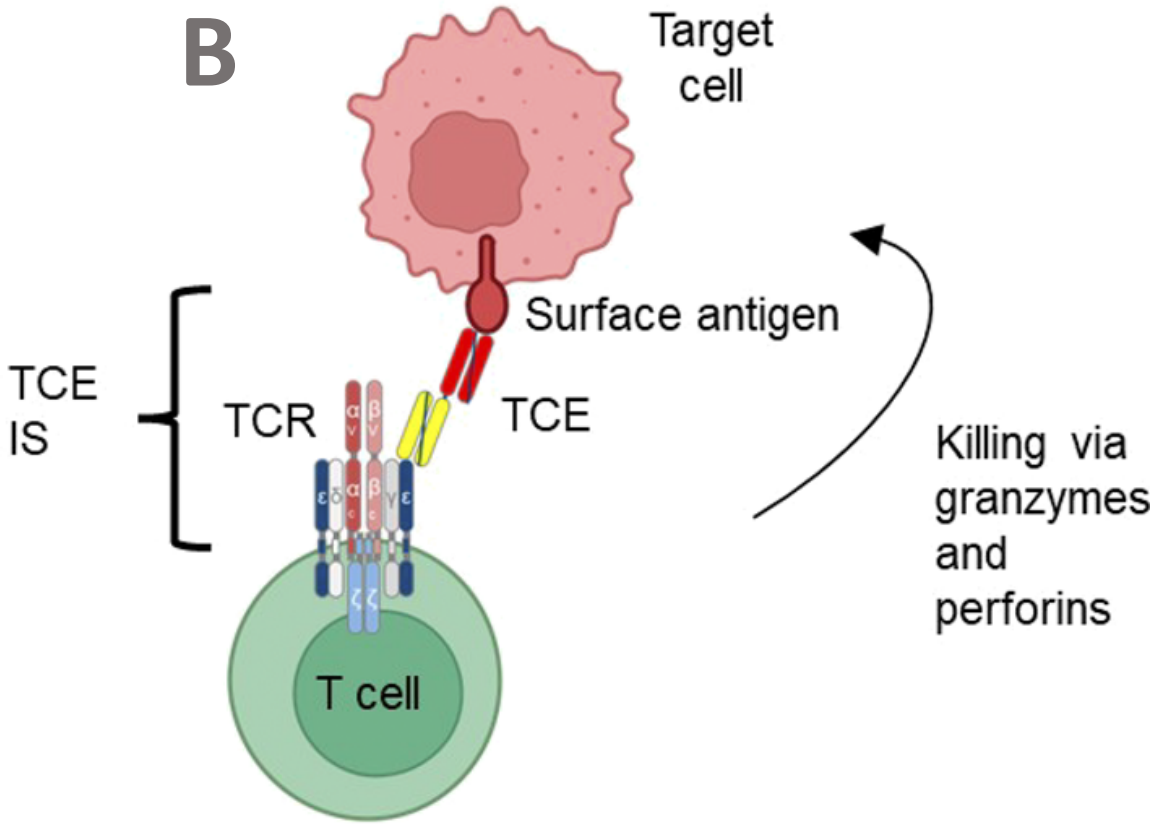
Engineered immunotherapeutic molecules designed to transiently reprogram cytotoxic T lymphocytes for target cell elimination by **simultaneously binding the T cell receptor and a specific surface antigen on the target cell** *(tumour cells, infected cells, autoimmune cells, …)*, triggering potent cytotoxic responses.

Baeuerle PA et al. J. Exp. Med (2026) 223 (2): e20251652
Albayrak G et al. BJC (2025) 133:1241–1249
Bucci L et al. Nat Med (2024) 30: 1593–1601

T cell engagers in Oncology

Unlike **ICI and TILs**, which **depend on the presence of pre-existing tumor specific lymphocytes (A)**, **T-cell engagers' function by homing lymphocytes toward cancer cells regardless of their native antigen target (B)**.



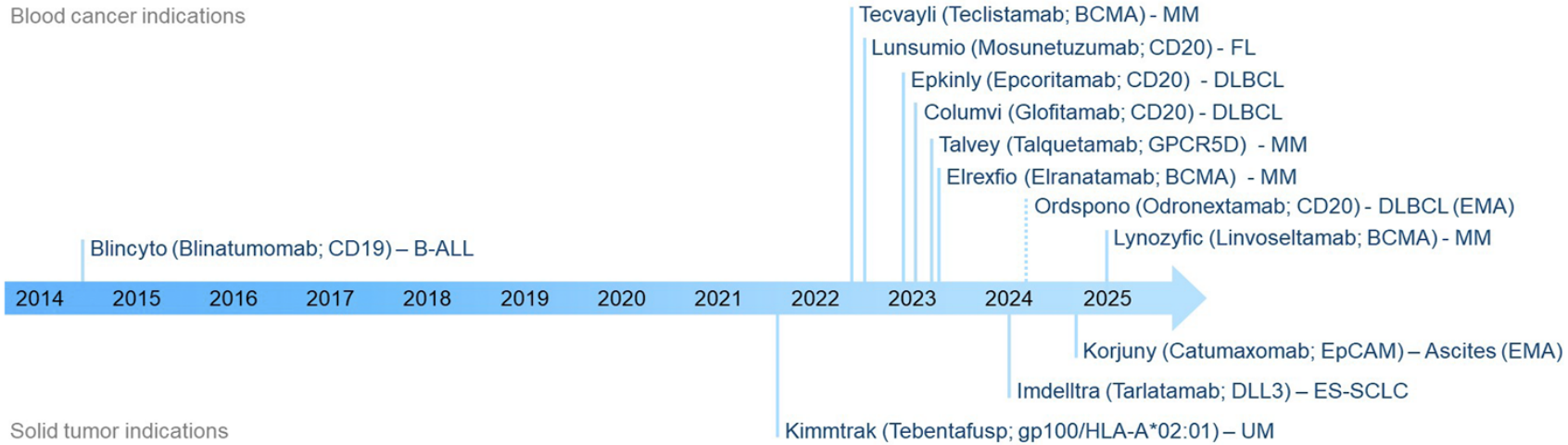


JEM | Journal of Experimental Medicine

Baeuerle PA et al. J. Exp. Med (2026) 223 (2): e20251652

T cell engagers in Oncology

- **TCEs** represent a major breakthrough in immunotherapy, offering a **new method to activate T cells for the targeted destruction of cancer cells.**
- **FDA** and **EMA** have approved TCE-based therapies for **malignant ascites**, **hematologic malignancies**, **uvM** and **SCLC**, and currently are a **growing promise for other solid tumors**.

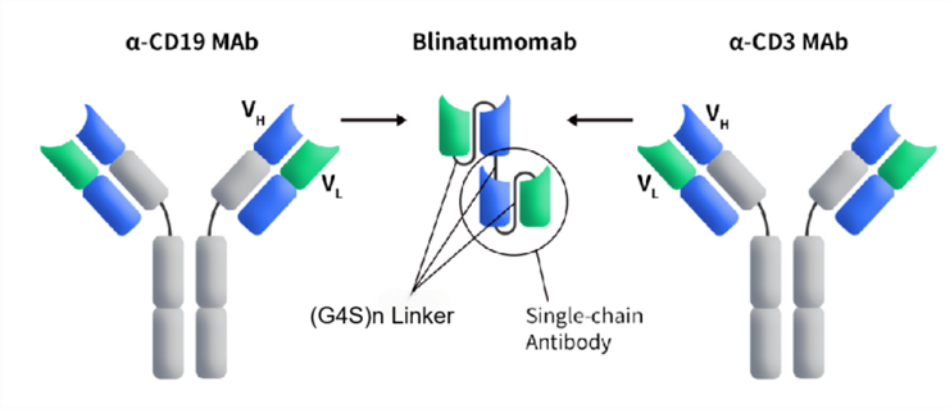


JEM | Journal of Experimental Medicine

J Exp Med. 2026;223(2): 20251652

Bi-specific T-cell engager (BiTE)

The most well-established process for inducing this effect utilizes **2 single chain variant fragments (scFvs) joined by a G4S linker*** in a structure known as a **bi-specific T-cell engager** (BiTE).



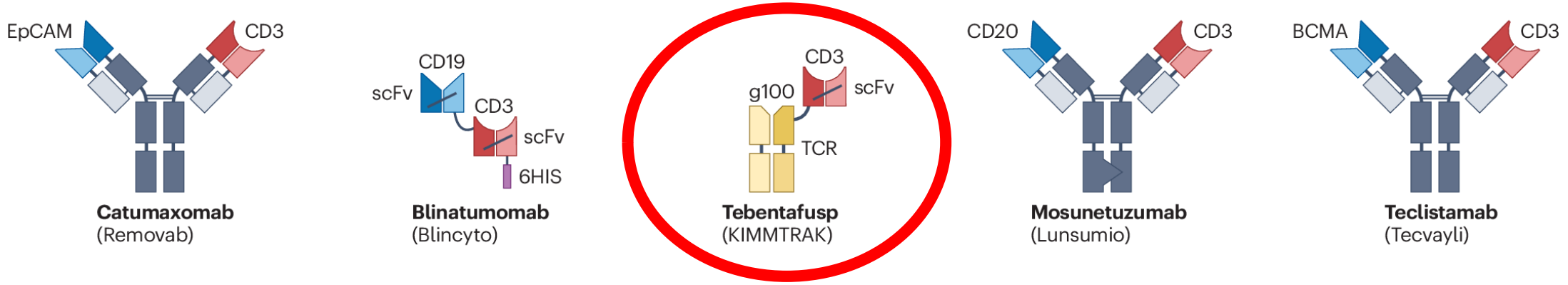
https://www.dimabio.com/blog/exciting-launch-the-new-anti-g4s4-antibody-is-here

- *common, flexible, and non-immunogenic synthetic peptide sequence used in protein engineering to connect protein domains:* Gly-Gly-Gly-Gly-Ser

Bispecific antibodies and **ImmTACs** (Immune-mobilizing monoclonal T-cell receptor Against Cancer) are **TCEs** currently under clinical trials in different malignancies

Albayrak G et al. BJC (2025) 133:1241–1249;

"**mab**" (*Monoclonal Antibodies*) and "**fusp**" (*Fusion Proteins*) are **distinct classes of therapeutic agents with different structural compositions, mechanism of actions, and International Nonproprietary Name (INN) classifications.**



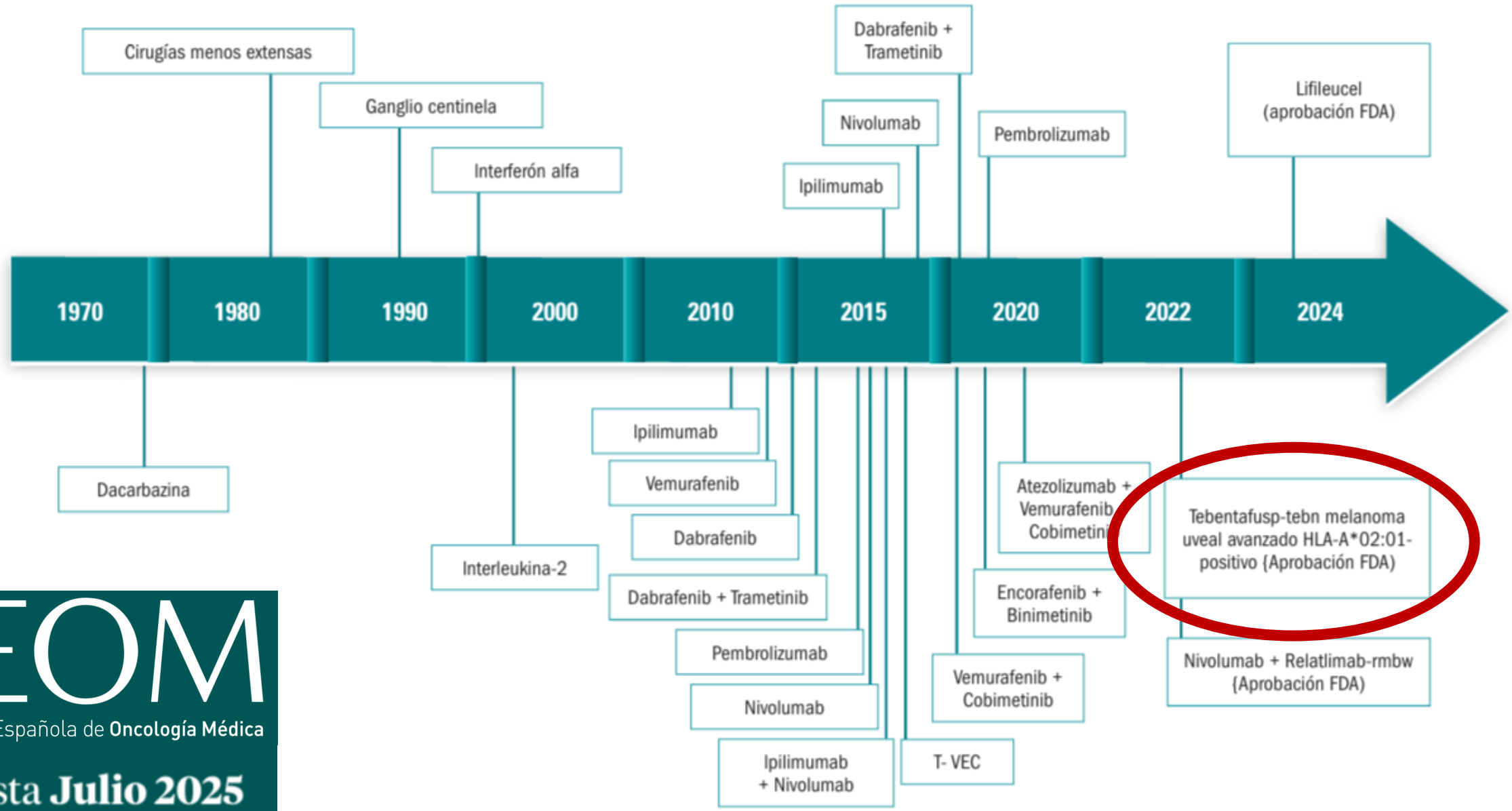
The primary difference lies in their construction:

- **mab denotes an immunoglobulin (antibody) derivative**, while
- **fusp denotes a protein engineered by fusing a targeting domain (often antibody-based) to another, non-immunoglobulin, functional protein.**

Klein et al, Nat Rev Drug Discovery, 2024

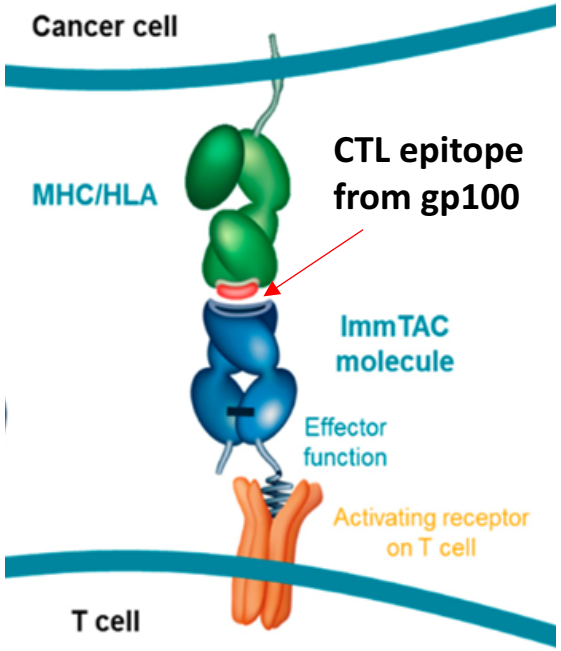
Modificación de diapositiva cedida por el Dr. J.J. Lasarte

Avances en Melanoma



SEOM
Sociedad Española de Oncología Médica
Revista Julio 2025

Tebentafusp (Kimmtrak)



- Is technically an **ImmTAC** (Immune-mobilizing monoclonal T-cell receptor Against Cancer), a first-in-class **bispecific fusion protein**, *not a conventional monoclonal antibody*, though it is often grouped with antibody-based therapies.
- Functions as a **T-cell engager** by combining an affinity-enhanced soluble **T-cell receptor (TCR) specific for the gp100 peptide** with an **anti-CD3 scFv effector domain** to redirect T cells to kill tumor cells.
- FDA approved in 2022 for treating HLA-A*02:01-positive metastatic uveal melanoma.
- EMA approved in 2023.
- SNS approved in 2024.

MINISTERIO DE SANIDAD | DIRECCIÓN GENERAL DE CARTERA COMÚN DE SERVICIOS DEL SNS Y FARMACIA | agencia española de medicamentos y productos sanitarios

REvalMed SNS

Comisión Permanente de

INFORME DE POSICIONAMIENTO TERAPÉUTICO
IPT 127-2023/V1/10042023

Informe de Posicionamiento Terapéutico de tebentafusp

Unfortunately, only about 50% of Caucasian patients express the HLA-A*02:01 allele. Consequently, tebentafusp can be offered only to a subset of patients.

es de **4/1.000.000 habitantes y año** (**164 casos**) según datos procedentes de 11 registros españoles de tumores.

INFORME DE POSICIONAMIENTO TERAPÉUTICO
IPT 127-2023/V1/10042023

Informe de Posicionamiento Terapéutico de tebentafusp (Kimmtrak®) en melanoma uveal irresecable o metastásico en pacientes adultos con antígeno leucocitario humano (HLA)-A*02:01 positivo

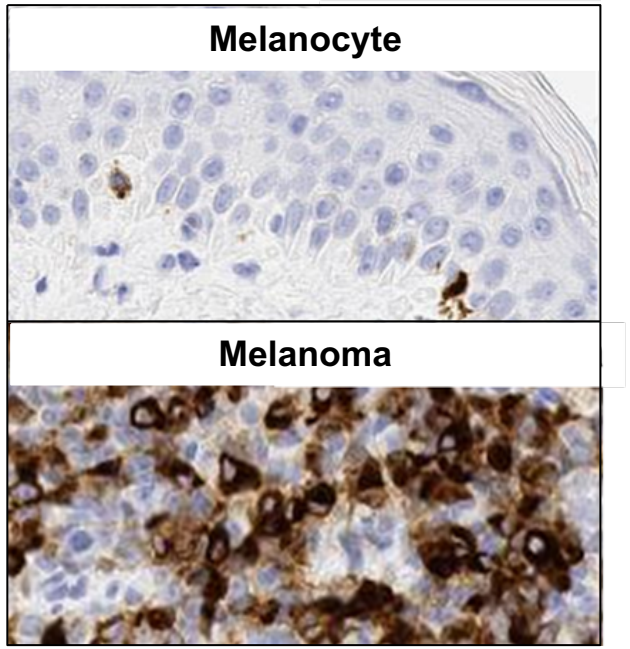
Fecha de primera publicación: 10/04/2023

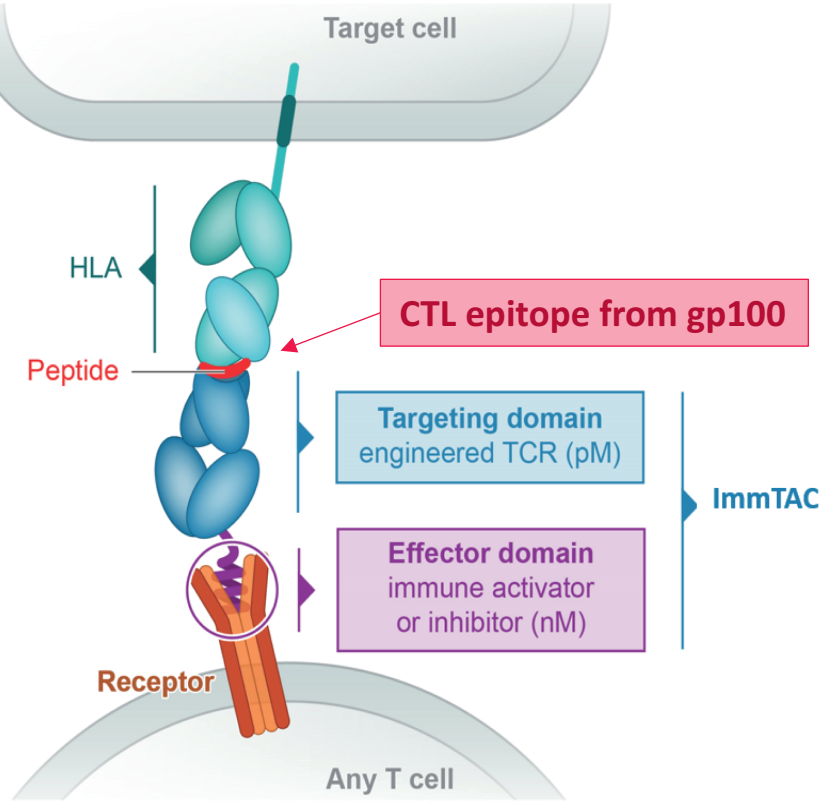
La ratio coste-eficacia de tebentafusp supone 523.060,19€ por cada año de vida ganado, de acuerdo con los resultados obtenidos en el estudio IMCgp100-202. Teniendo en cuenta que es muy probable que tenga una gran penetración, el impacto presupuestario puede situarse en 13,6 millones de euros al año.

Background

Uveal Melanoma (UM)

- **Rare melanoma type with low mutational burden**
- Frequent liver metastases; **poor benefit from IO**
- **No standard of care once metastatic**
- **12-mo OS up to 52% in first line** clinical trials[1,2,3]
- Commonly **expresses gp100** (melanocytic protein)





Tebentafusp

- Bispecific, soluble TCR therapeutic
- **Affinity-enhanced TCR fused to anti-CD3**
- **Designed to redirect T cells to gp100+** melanocytic cells

ImmTAC, Immune mobilizing T cell receptor Against Cancer; TCR, T cell receptor.

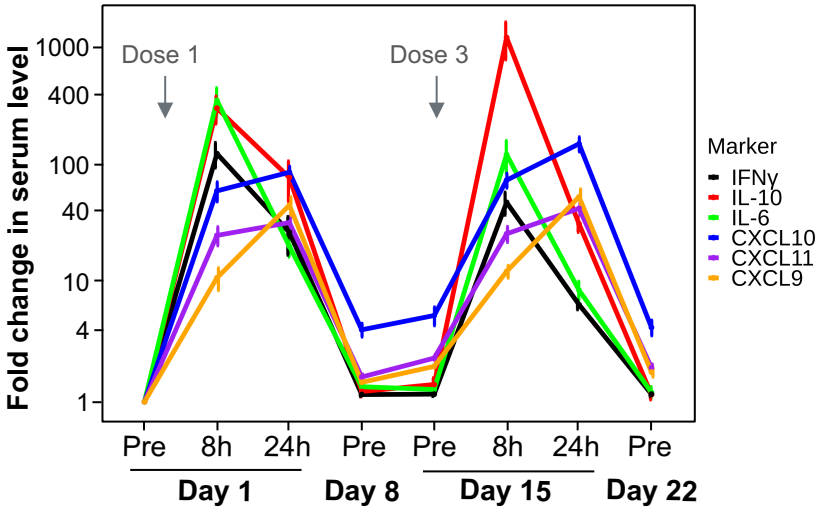
1. Piulats JM, et al. *J Clin Oncol* 2021;39(6):586–98; 2. Rantala ES, et al. *Melanoma Res* 2019;29(6):561–8; 3. Khoja L, et al. *Ann Oncol* 2019;30(8):1370–80

OS, overall survival.

Biomarkers consistent with proposed mechanism of action (IMCgp100-102)

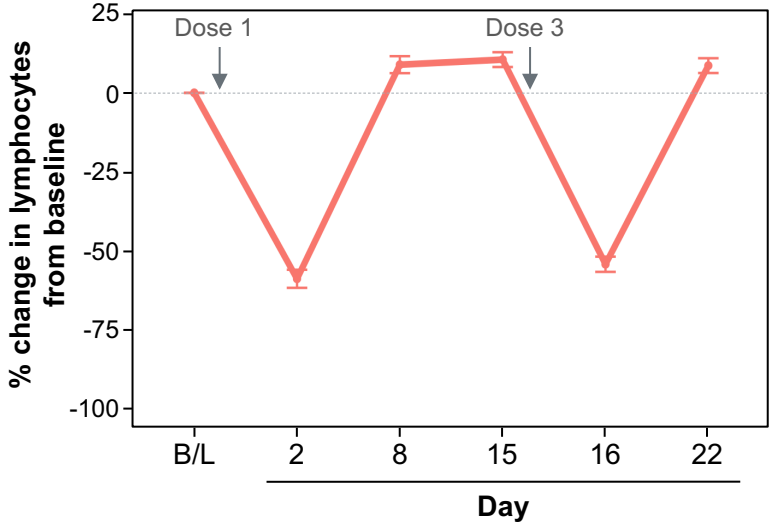
Cytokine induction

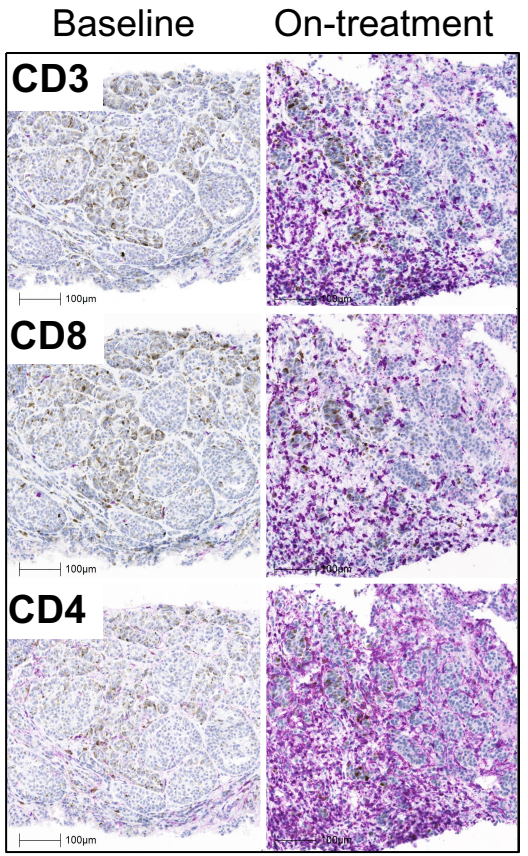
Peripheral blood



T cell trafficking

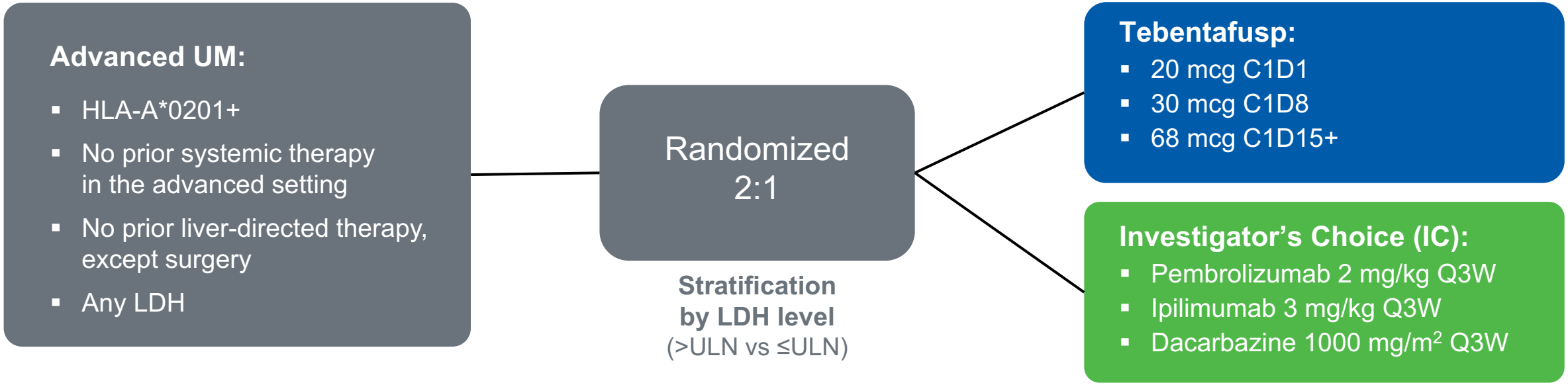
Peripheral blood ⇢ Tumor





Please see 2021 AACR poster 517 for additional information

IMCgp100-202 – study design



Co-primary endpoints

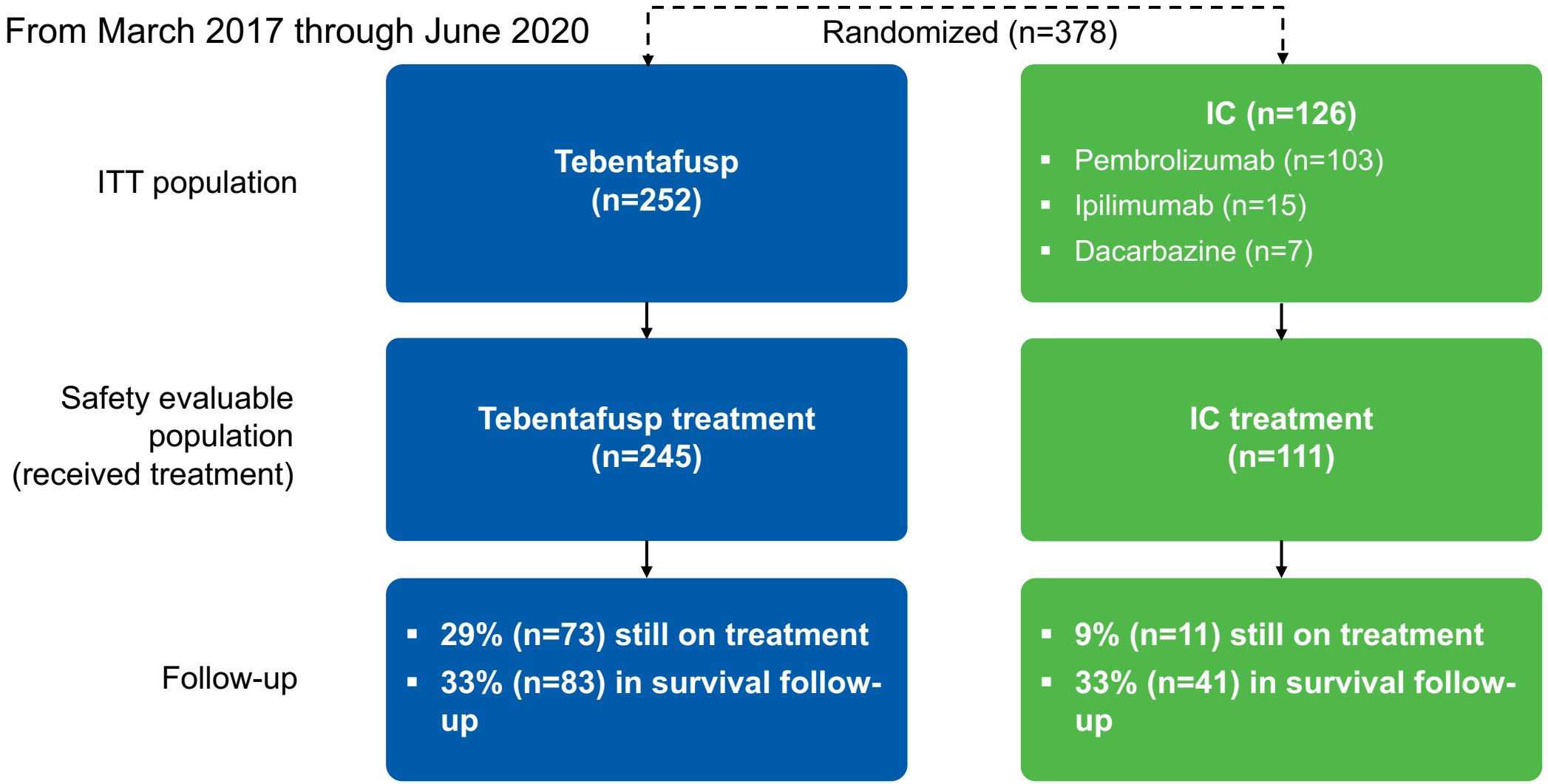
- **OS in randomized patients to tebentafusp vs IC treatment (ITT)**
- **OS in randomized patients to tebentafusp with rash during Wk 1 vs IC treatment**

Key secondary endpoints

- **ORR and PFS by investigator assessment**

Data cut-off date: October 13, 2020; data snapshot date: January 22, 2021.
ITT, intent-to-treat; ORR, overall response rate; PFS, progression free survival.

Consort diagram



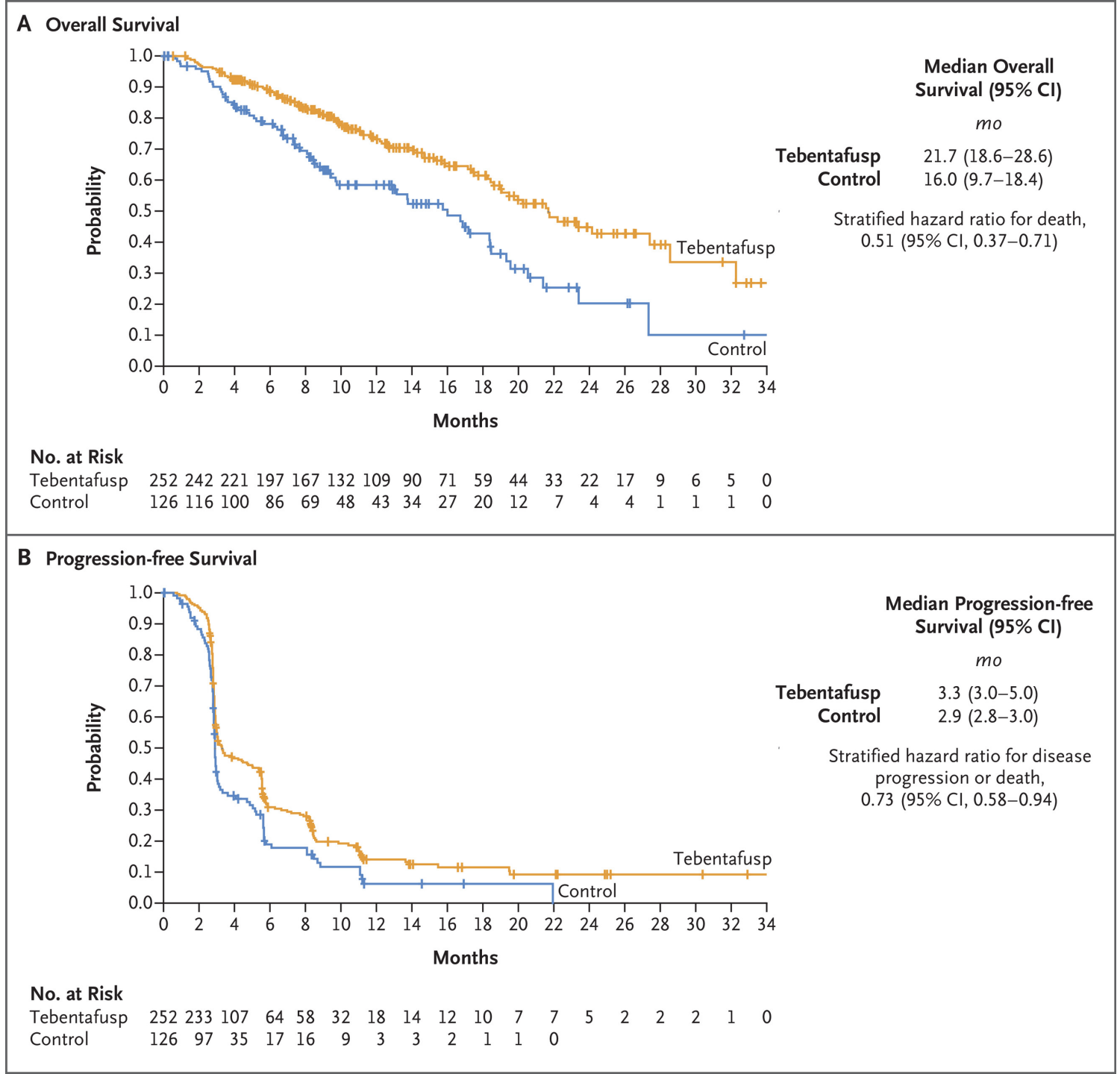
ORIGINAL ARTICLE

Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma

Paul Nathan, M.D., Ph.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D.,

N Engl J Med 2021;385:1196-206.

1y OS: 73% (95%CI, 66-79) *vs* 59% (95%CI, 48-67).
mD of OS: 21.7m *vs* 16m.
HR for Death: 0.51 (95%CI, 0.37 to 0.71; P<0.001)
6m PFS: 31%, *vs* 19% (HR for disease progression or death, 0.73; 95% CI, 0.58 to 0.94; P=0.01)
OR: 9% vs 5%.
mD OR: 9.9m vs 9.7m
% CR, PR, or SD≥12 w: 46% vs 27%.



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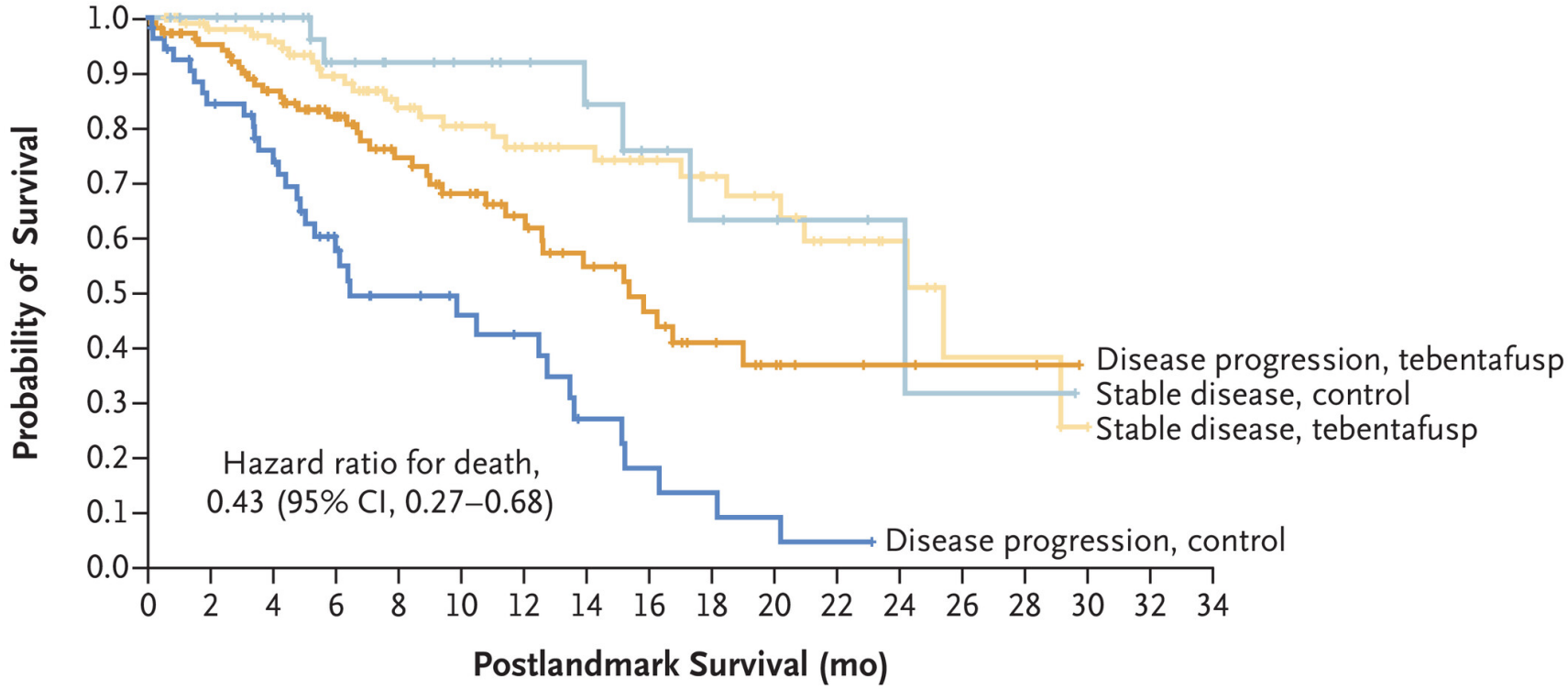
mOS among patients who had PD before day 100: 15.3m (95% CI, 12.0 - not reached) *vs* 6.5m (95% CI, 4.9 -13.4).



No. at Risk

Stable disease, tebentafusp	101	89	82	67	53	45	37	32	26	21	17	12	7	3	3	0
Stable disease, control	34	32	29	20	17	15	13	10	7	5	4	3	2	1	1	0
Disease progression, tebentafusp	105	92	78	62	47	38	29	22	17	11	6	4	3	2	2	0
Disease progression, control	53	42	35	23	16	13	11	6	4	3	2	1	0			

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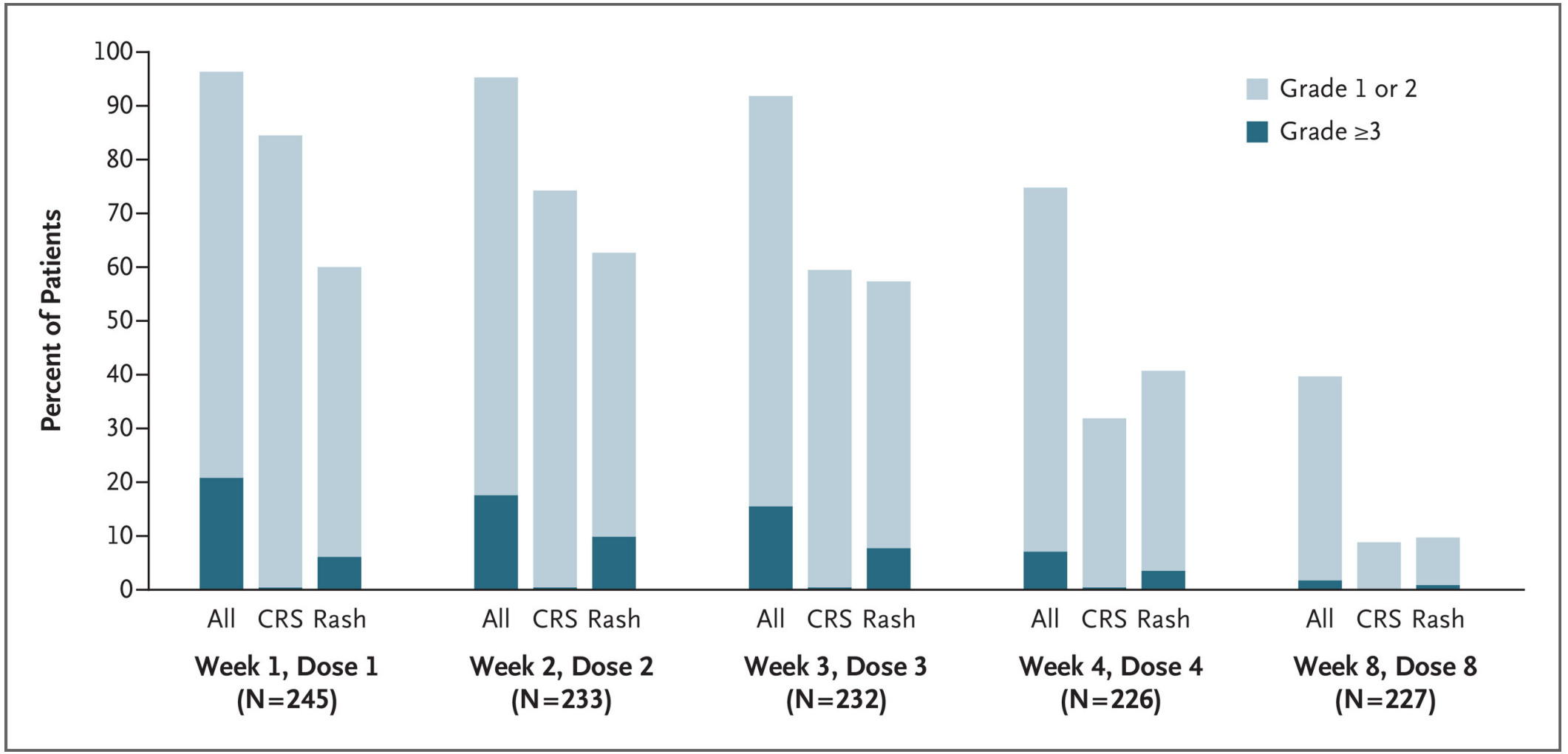
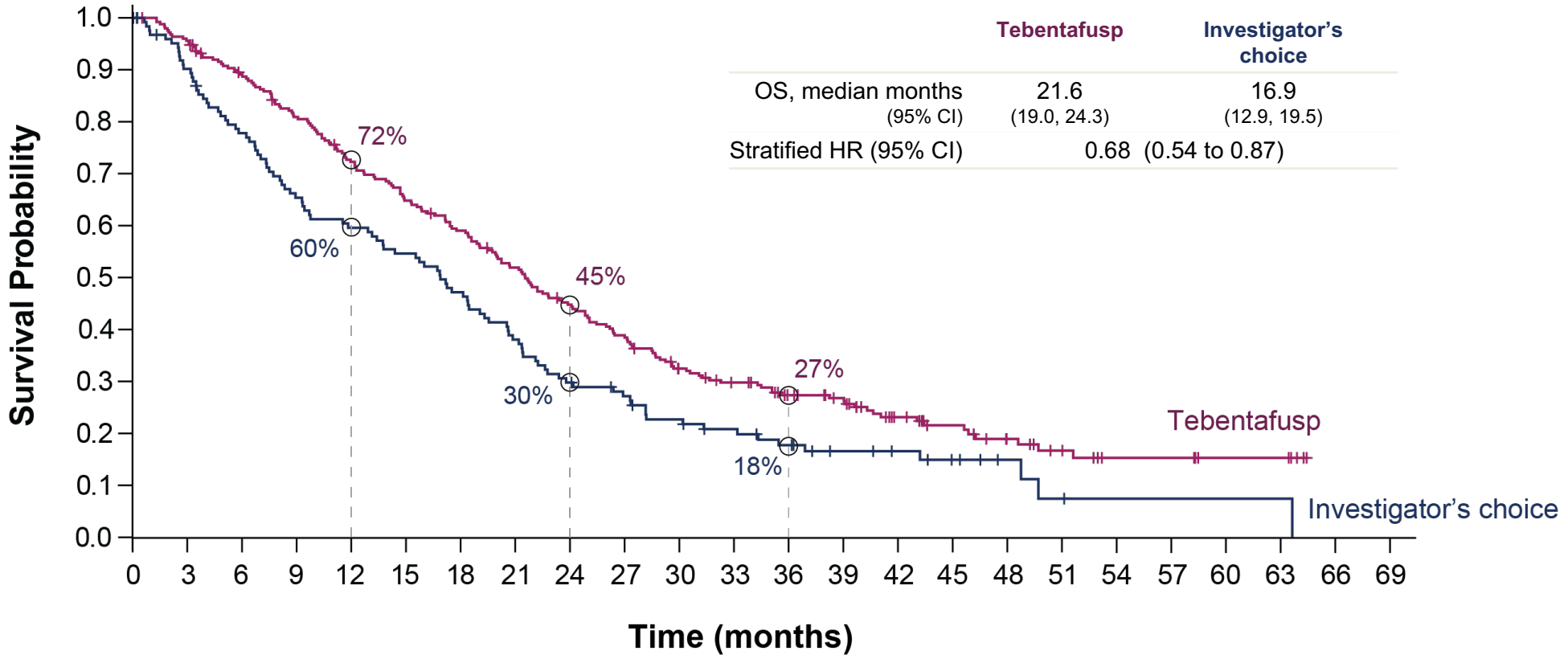
Incidence and Severity of Treatment-Related Adverse Events after Initial Doses of Tebentafusp.

Patients who had G1-2 or G3 or higher treatment-related adverse events after the initial doses of tebentafusp. (CRS: cytokine release syndrome)



3-year update: OS in ITT

OS benefit of tebentafusp maintained vs IC at 3-year follow-up



	Tebentafusp	Investigator's choice
OS, median months (95% CI)	21.6 (19.0, 24.3)	16.9 (12.9, 19.5)
Stratified HR (95% CI)	0.68 (0.54 to 0.87)	

No. at risk

Tebentafusp	252	239	218	197	175	157	142	124	106	92	73	64	53	47	32	25	18	13	8	8	5	5	0
IC	126	110	94	79	72	66	57	46	36	31	25	21	17	12	10	7	4	2	1	1	1	1	0

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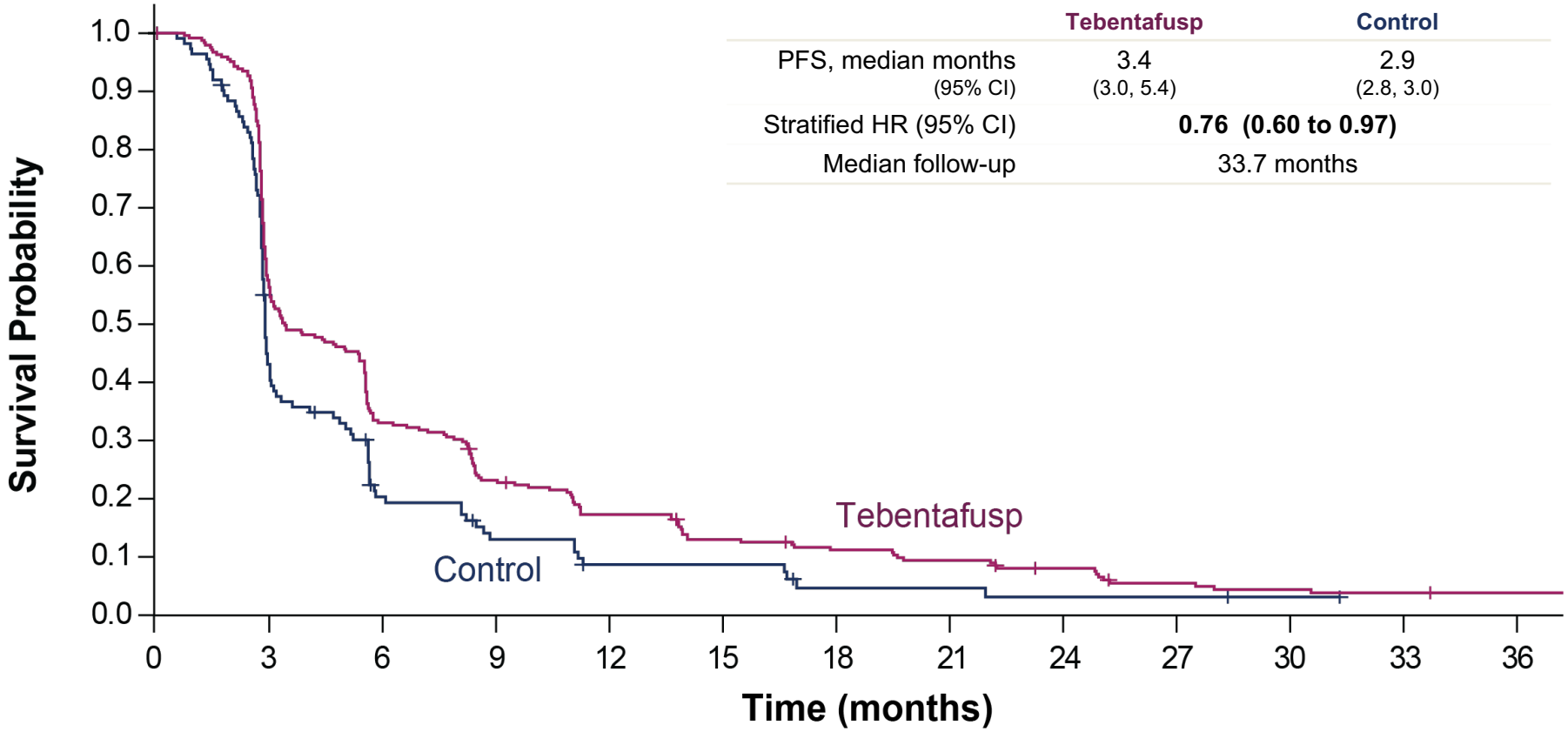
Minimum / median follow-up for OS: 36 months / 43.3 months

OS: overall survival; ITT: intention-to-treat; IC: investigator's choice

3-year update: PFS in ITT



	Tebentafusp	Control
PFS, median months (95% CI)	3.4 (3.0, 5.4)	2.9 (2.8, 3.0)
Stratified HR (95% CI)	**0.76 (0.60 to 0.97)**	
Median follow-up	33.7 months	

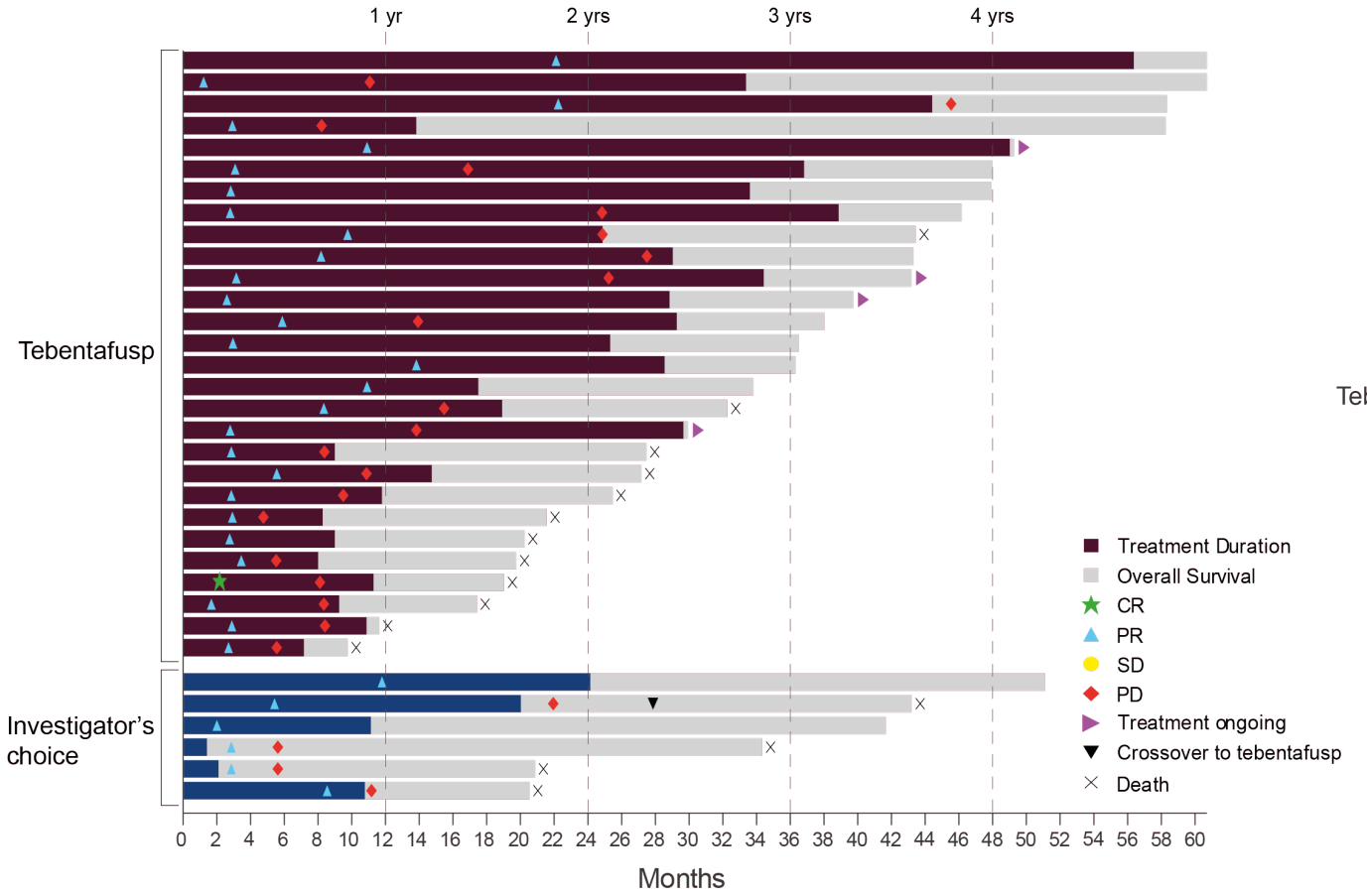
No. at risk

Tebentafusp	252	138	81	56	41	30	25	21	16	10	8	7	6
Control	126	47	20	12	7	7	3	3	2	2	1	0	

Disease control rate of 46% tebentafusp vs 27% IC

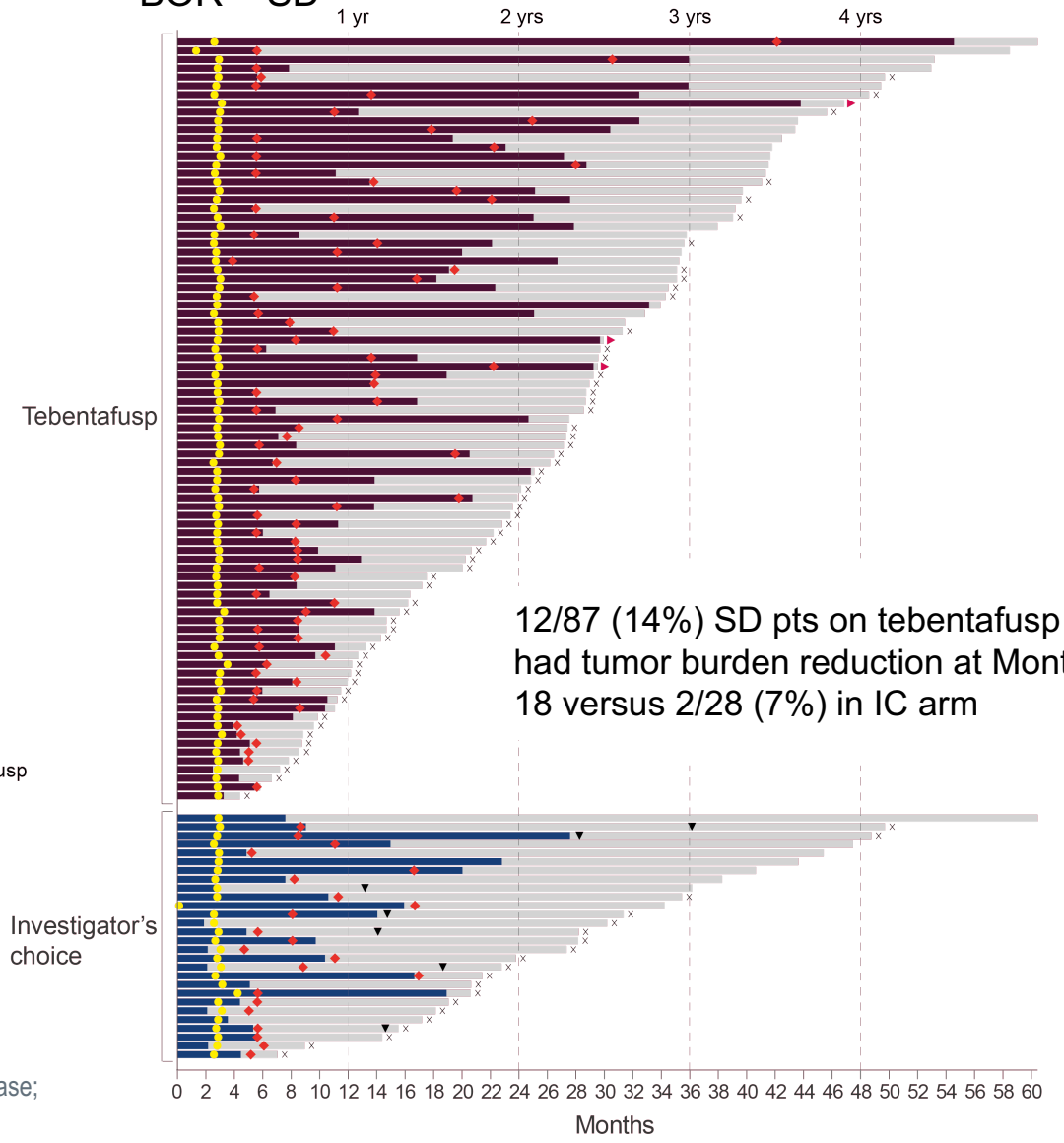
Median duration of response 11.1 months for tebentafusp and 9.7 months for control

BOR = CR/PR



9/28 (32%) tebentafusp responders maintained response for at least 18 months versus none in IC arm

BOR = SD



12/87 (14%) SD pts on tebentafusp had tumor burden reduction at Month 18 versus 2/28 (7%) in IC arm

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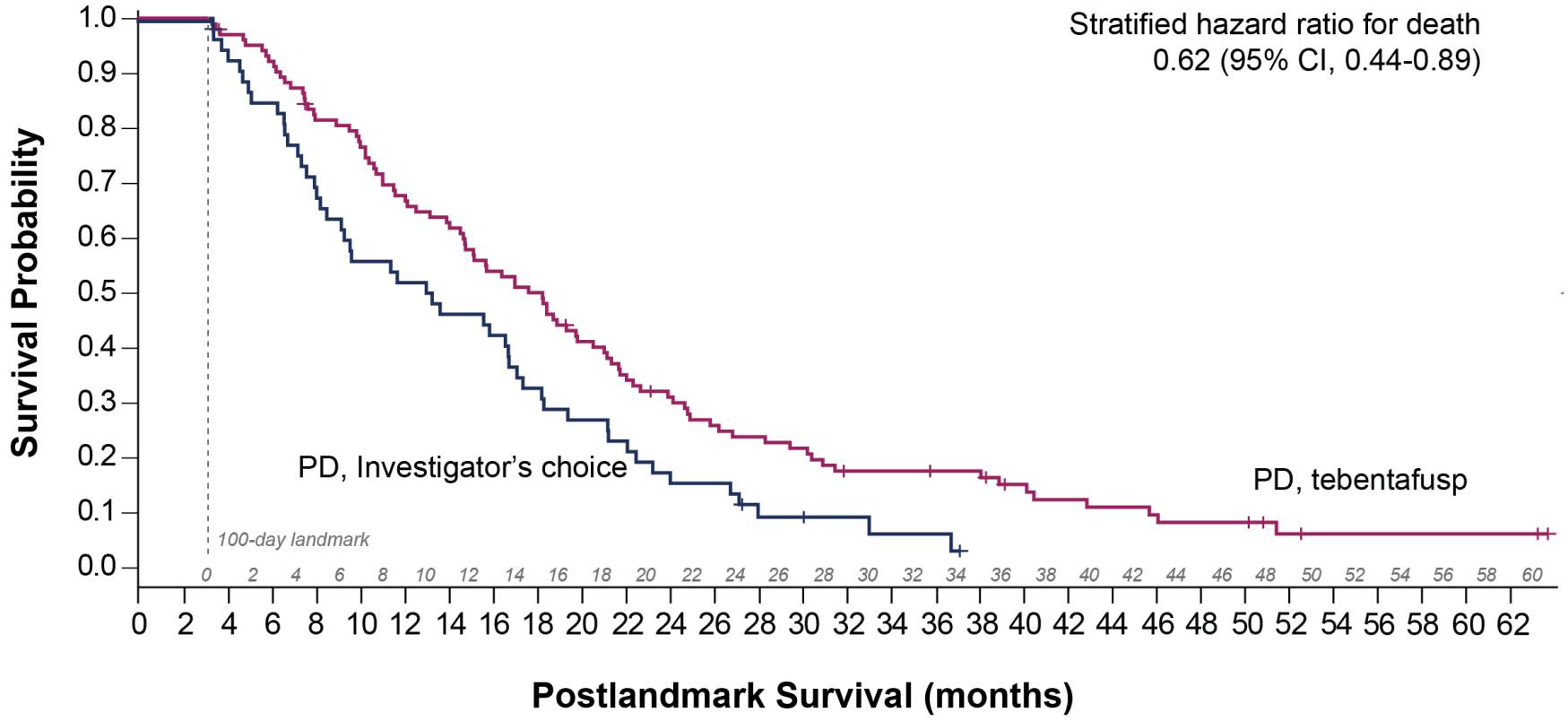
CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; IC: investigator's choice

Post-day 100 OS in patients with BOR PD

OS benefit seen even in patients with BOR of PD



No. at risk

Tebentafusp	104	98	90	82	71	66	58	52	45	39	32	26	23	22	18	16	16	15	12	9	8	8	6	6	4	2	2	2	2	2	2
IC	53	44	40	33	29	26	24	18	15	14	10	8	7	4	3	2	2	1	0												

MADRID 2023 ESMO congress

Patients could receive treatment beyond initial radiographic progression if they were clinically stable, still deriving benefit, and showed no signs of unacceptable toxicity

BOR: Best objective response; IC: investigator's choice; OS: overall survival; PD: progressive disease

Table 1. Tumor Response.

Response	Tebentafusp (N = 252)	Control (N = 126)*
Best overall response — no. of patients (%)		
Complete response	1 (<1)	0
Partial response	27 (11)	6 (5)
Stable disease	87 (35)	28 (22)
Progressive disease	132 (52)	82 (65)
Not evaluable or not applicable	5 (2)	10 (8)
Objective response — no. of patients (%)	28 (11)	6 (5)
Stratified odds ratio for objective response, tebentafusp vs. control (95% CI)†	2.46 (1.00–6.06)	Reference
Disease control at 12 wk — no. of patients (%)‡	115 (46)	34 (27)
Stratified odds ratio for disease control, tebentafusp vs. control (95% CI)§	2.34 (1.45–3.76)	Reference

* Patients in the control group received the investigator's choice of single-agent therapy with pembrolizumab, ipilimumab, or dacarbazine.

† The 95% confidence intervals were calculated with the use of the exact Clopper–Pearson method.

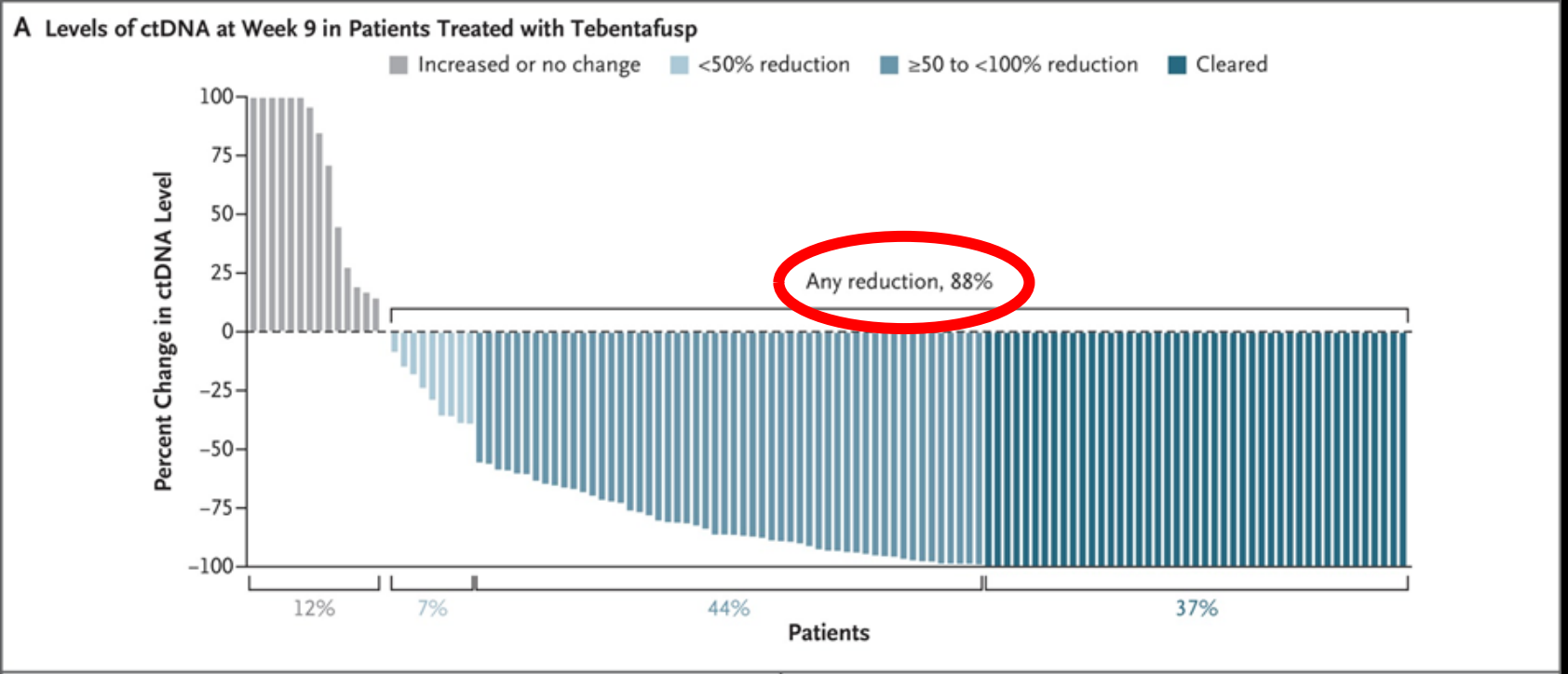
‡ Disease control was defined as a complete response, a partial response, or stable disease that persisted for at least 12 weeks.

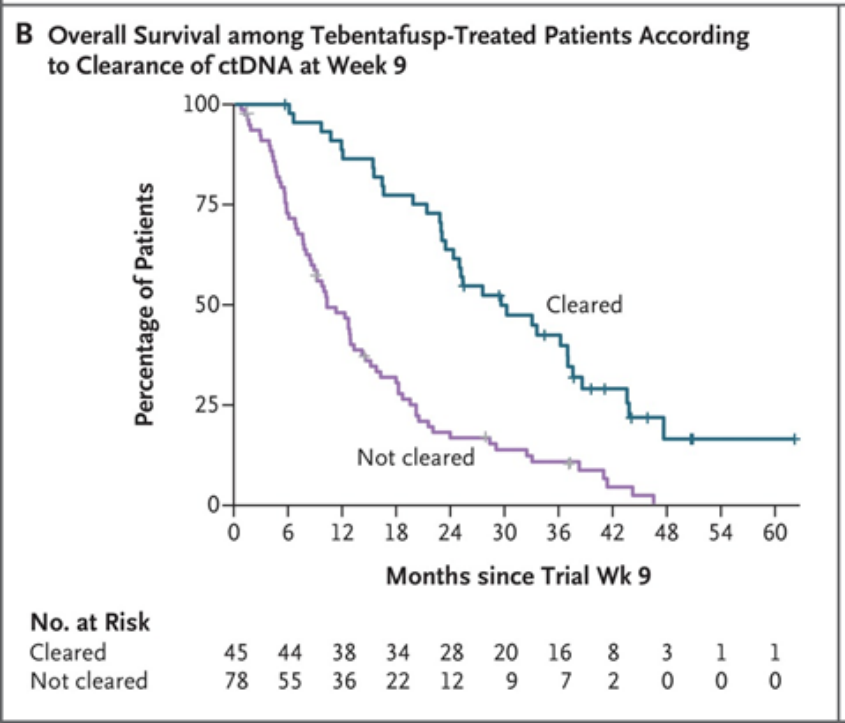
§ The odds ratio and 95% confidence interval were calculated with a Stratified Cochran–Mantel–Haenszel test, with stratification according to lactate dehydrogenase (LDH) status (i.e., LDH level higher than the upper limit of the normal range or less than or equal to the upper limit of the normal range).

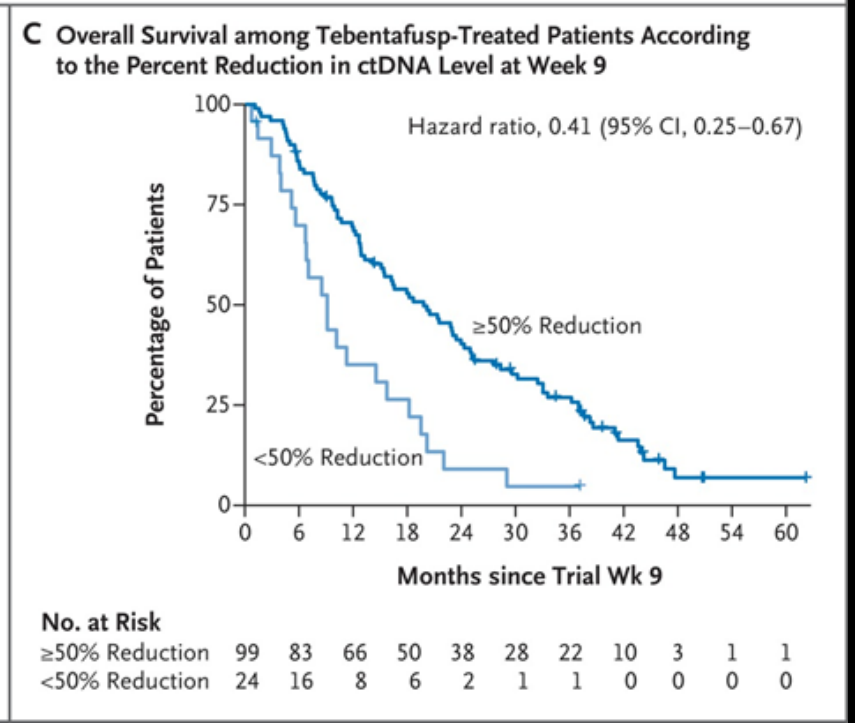
Hassel JC et al.
NEJM 2023;389:2256-2266

The NEW ENGLAND JOURNAL of MEDICINE

Dynamics of Circulating Tumor DNA (ctDNA) and Association with Overall Survival in Patients Treated with Tebentafusp.







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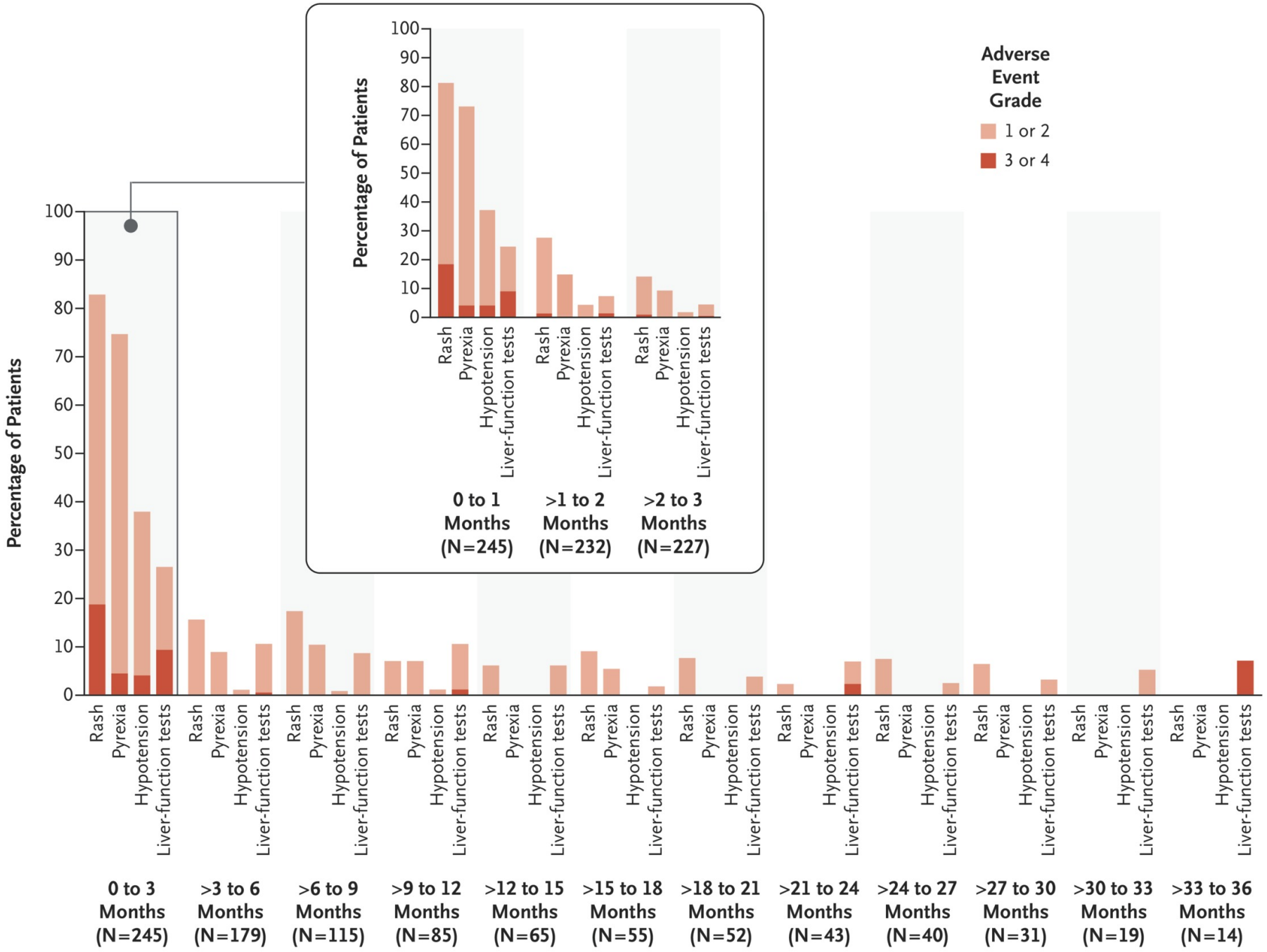


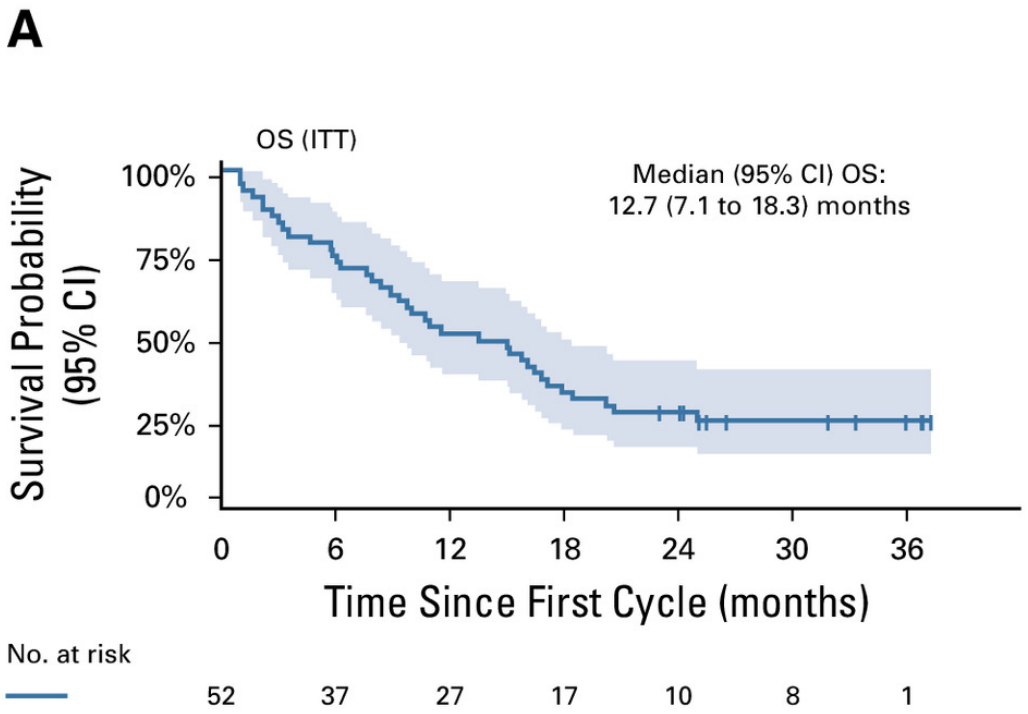
Long-term Frequency and Severity of Selected Treatment-Related Adverse Events with Tebentafusp.

Hassel JC et al.
NEJM 2023;389:2256-2266

The NEW ENGLAND JOURNAL of MEDICINE

Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: GEM-1402

Piulats JM, et al. J Clin Oncol 39, 586-598(2021)



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ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Overall survival from tebentafusp versus nivolumab plus ipilimumab in first-line metastatic uveal melanoma: a propensity score-weighted analysis

J. M. Piulats[1,2,3*], C. Watkins[4], M. Costa-García[2], L. del Carpio[1,2], S. Piperno-Neumann[5], P. Rutkowski[6], J. C. Hassel[7], E. Espinosa[8], L. de la Cruz-Merino[9], S. Ochsenreither[10], A. N. Shoushtari[11,12], M. Orloff[13], A. K. S. Salama[14], H. M. Goodall[15], J.-F. Baurain[16] & P. Nathan[17]

- To investigate the OS benefit of tebentafusp over nivolumab - ipilimumab based on an indirect comparison to GEM-1402.
- Although comparisons of treatments across studies can be biased by differences in patient characteristics, this limitation can be addressed using **propensity score modeling**.
- … analysis based on individual data from patients who received **tebentafusp or pembrolizumab in IMCgp100-202** (median duration of FU of 43.3 months; data cut-off 3 July 2023) and **nivolumab plus ipilimumab in GEM-1402** (median duration of follow-up of 35 months; data cut-off of August 2023).

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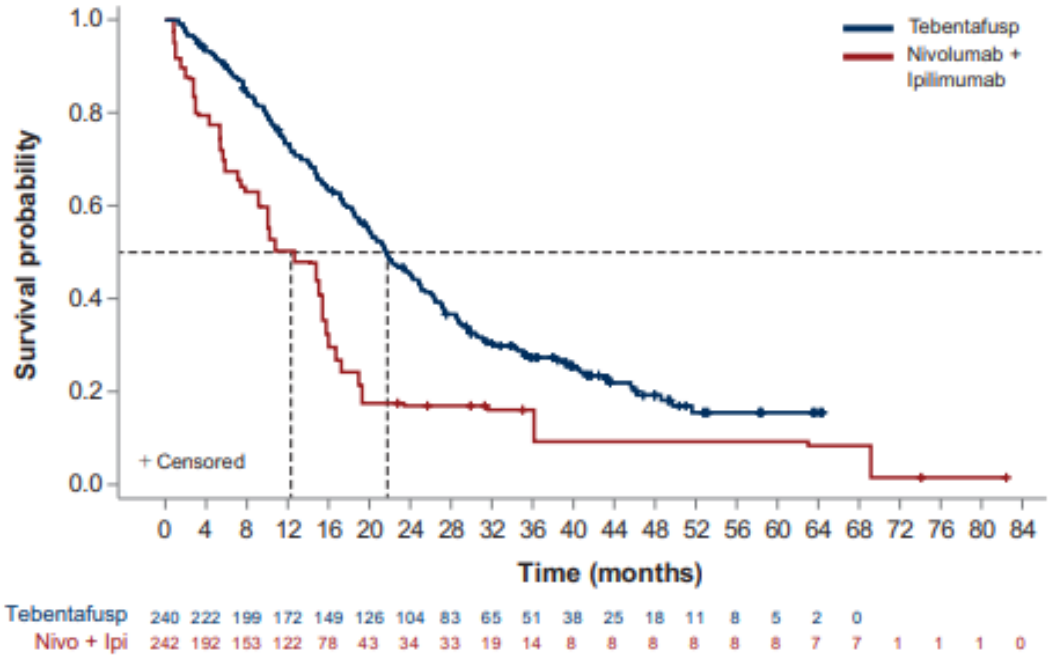
J. M. Piulats[1,2,3*], C. Watkins[4], M. Costa-García[2], L. del Carpio[1,2], S. Piperno-Neumann[5], P. Rutkowski[6], J. C. Hassel[7], E. Espinosa[8], L. de la Cruz-Merino[9], S. Ochsenreither[10], A. N. Shoushtari[11,12], M. Orloff[13], A. K. S. Salama[14], H. M. Goodall[15], J.-F. Baurain[16] & P. Nathan[17]

In conclusion, …

"using a <u>patient-level propensity score-weighted analysis</u>, Tebentafusp also demonstrated an OS benefit versus Nivolumab plus Ipilimumab"

*… the HLA-A*02:01 haplotype was found not to be associated with OS in mUM (based on an analysis from an independent cohort of 40 mUM patients treated at a single institution)*

A



B

Model	Tebe N	Nivo + Ipi N	HR (95% CI)
PS-based IPTW analyses			
Complete case, IPT ATT weights (primary)	240	242	0.53 (0.35-0.78)
Multiple imputation, IPT ATT weights	252	255	0.55 (0.38-0.79)
Complete case, IPT ATT stabilized weights	202	38	0.50 (0.32-0.76)
Complete case, IPT ATE weights	284	287	0.54 (0.37-0.79)
Complete case, IPT ATC weights	44	45	0.61 (0.41-0.92)
Other models			
Complete case, multivariate Cox analysis	240	45	0.41 (0.28-0.62)
Unadjusted analyses			
Unadjusted complete case	240	45	0.63 (0.44-0.90)
Unadjusted multiple imputation	252	52	0.66 (0.47-0.93)

Bispecific T-Cell Engagers in MuvM Clinical Efficacy

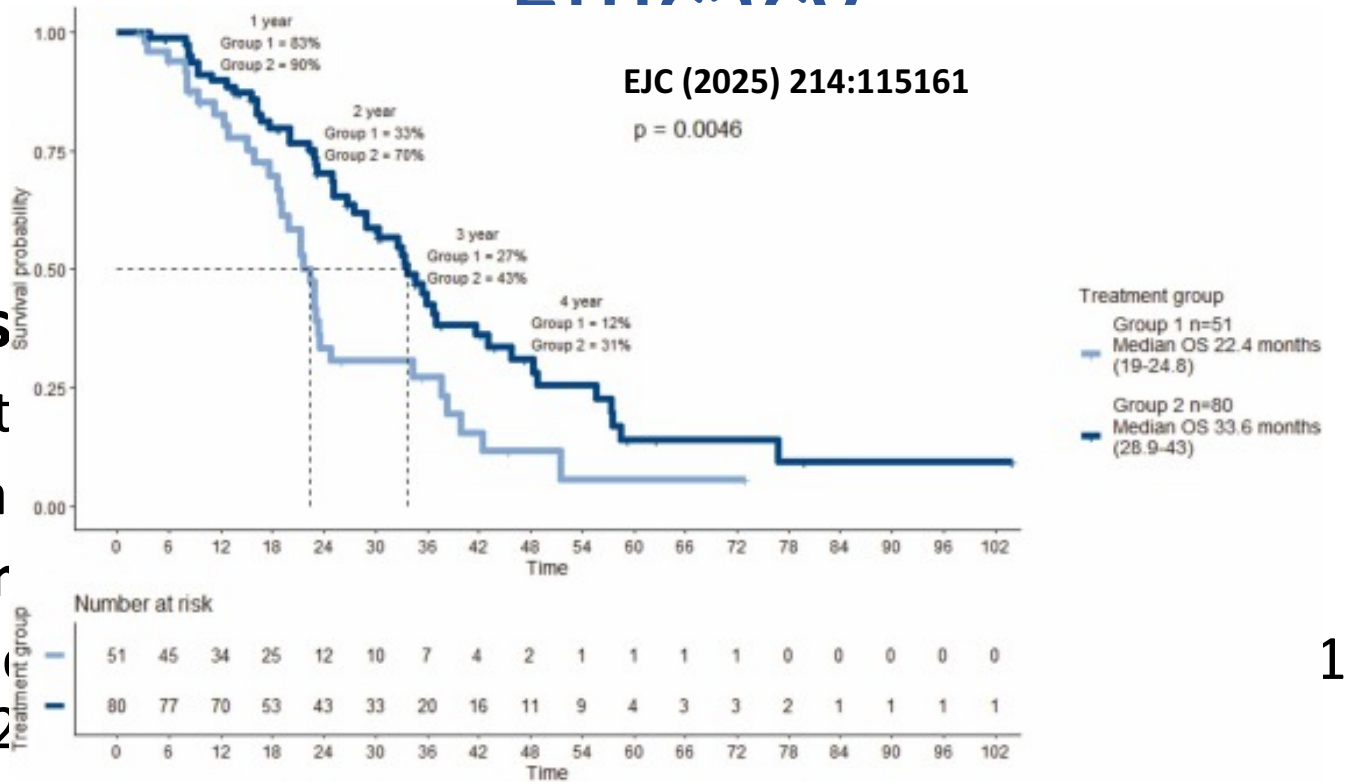
A total of **15 clinical reports** encompassing ~1150 HLA-A*02:01+ patients have explored BiTCE therapy in MuvM:

- **14** evaluate the **gp100-directed ImmTAC tebentafusp** including thee pivotal phase III trial analyzed at 12 months by Nathan et al. (2021) and at 36 months by Hassel et al. (2023): **OS benefit of tebentafusp at 3 years: 27% vs 18%.**
- **1** the **NY-ESO-1–targeted IMCnyeso** (López et al. 2025): non objective responses in 3 evaluable MuvM patients and 3 McutM patients.

Early-phase trials and real-world cohorts corroborate tebentafusp activity reporting **median OS 17–25 months** (e.g., Sacco 17.4 mo; Carvajal 25.5 mo; *Nattan 19mo*) and documenting ORR values up to 23% in selected series.

Kleinrok J. et al. J. Clin. Med. 2026, 15, 641

Bispecific T-Cell Engagers in MUM Clinical Efficacy



- Consistent **s**
  - early treat
  - normal ba
  - higher **lym**
  - complete
    34.6 vs. 12

12, median OS of

- A multi-center sequencing study indicates that giving ICI before tebentafusp may further improve outcomes (median OS 33.6 vs. 22.4 months; Dimitriou et al. 2025).

Kleinrok J. et al. J. Clin. Med. 2026, 15, 641

ClinicalTrials.gov **Search Details:** Viewing 1-4 out of **4** studies for: melanoma | Other terms: T cell engager

- A Study of RO7293583 in Participants With Unresectable Metastatic Tyrosinase Related Protein 1 (**TYRP1**)-Positive Melanomas. *Front Oncol. 2024 TYRP1-TCB is a novel BiTE antibody comprising two TYRP1-binding domains and one CD3e-binding domain (2 + 1 format); 20 TYRP1+ melanoma (cut:10; uv:6; muc :3; up:1)* ***OR:0; SD:12; 1yThx 1/20***
- Radiation Combined With BIspecific T-Cell Engager in **DLL3** Expressing Tumors. *Recruiting*. US.
- Neoadjuvant **Tebentafusp** for Uveal Melanoma. *Recruiting. US.*
- **Tebentafusp** in HLA-A*0201 Positive Previously Untreated Metastatic Uveal Melanoma (with an integrated circulating tumor DNA (ctDNA) biomarker.). *Recruiting. US.*

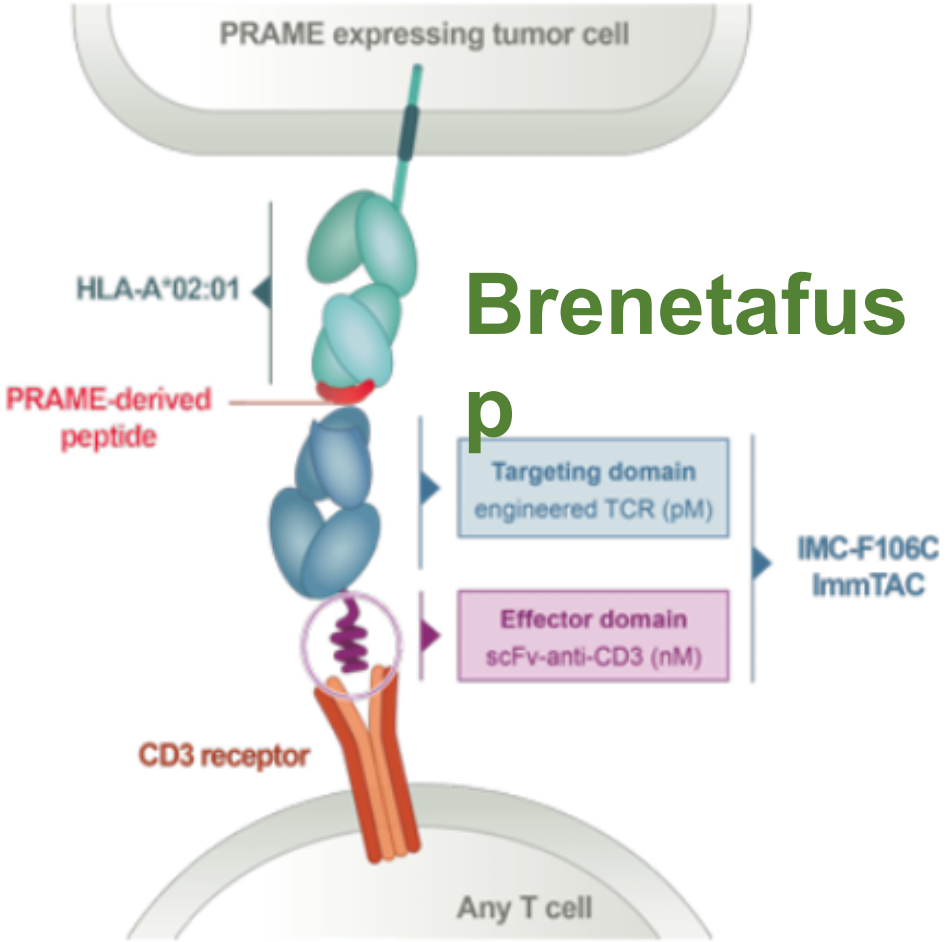
ClinicalTrials.gov

Search Details: Viewing 1-6 out of **6** studies for: melanoma | Other terms: Bispecific Antibody | Not yet recruiting, Recruiting studies

- **Tebentafusp** Regimen Versus Investigator's Choice in Previously Treated **Advanced Melanoma** (TEBE-AM)

Hospital Universitari Vall d'Hebron
Hospital Clínico de Barcelona
Hospital General Universitario Gregorio Marañon
Hospital Universitario Ramon y Cajal
Hospital Regional Universitario de Málaga
Hospital General Universitario de Valencia

IMC-F106C-301
A Phase 3 Randomized, Controlled Study of IMC-F106C Plus Nivolumab Versus Nivolumab Regimens in HLA-A*02:01-Positive Participants With Previously Untreated Advanced Melanoma (PRISM-MEL-301)



- **Complejo Hospitalario Universitario A Coruña (CHUAC)**
- **Hospital Universitario Marques de Valdecilla (HUMV)**
- **Clinica Universidad de Navarra (CUN) – Pamplona**
- **Hospital Universitario Miguel Servet (HUMS)**
- **Hospital Universitari Vall d'Hebron, Hospital Universitario Dexeus, Hospital Duran i Reynals , Hospital Clinic de Barcelona**
- **Hospital Clinico Universitario de Valencia , Universitari i Politecnic La Fe de Valencia (Hospital La Fe)**
- **Hospital General Universitario Gregorio Marañon Clinica Universidad de Navarra (CUN) – Madrid hospital Universitario Ramon y Cajal - Hospital Universitario 12 de Octubre (H12O) Hospital Universitario La Paz Centro Integral Oncologico Clara Campal (CIOCC)**
- **Hospital Universitario Reina Sofia Hospital Universitario Virgen de las Nieves (HUVN) H. Regional Universitario de Malaga H Universitario Virgen Macarena Hospital Universitario Virgen del Rocio**
- **Hospital Universitario Virgen de la Arrixaca (HUVA)**
- **Hospital Universitario Insular de Gran Canaria**

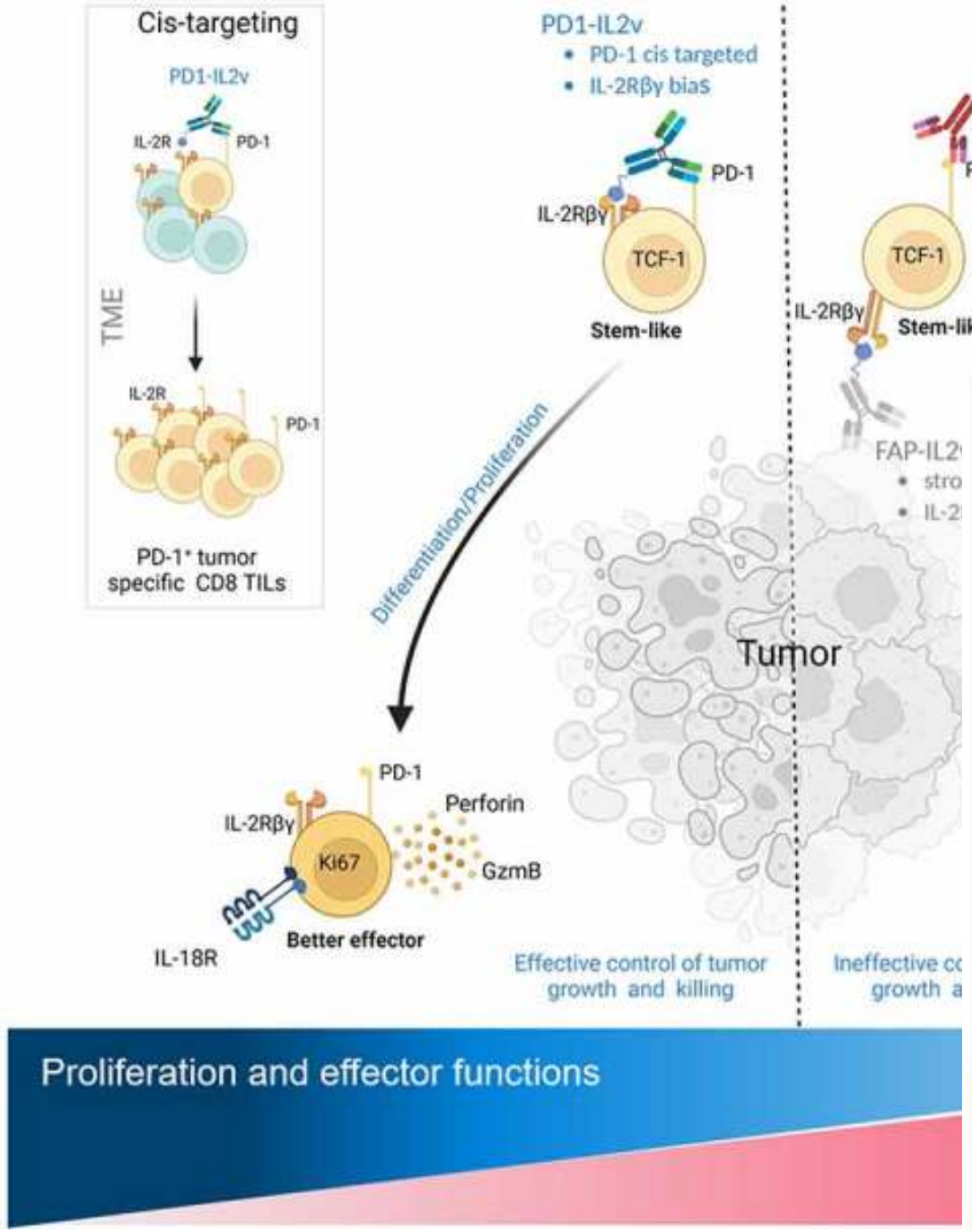
Conclusions

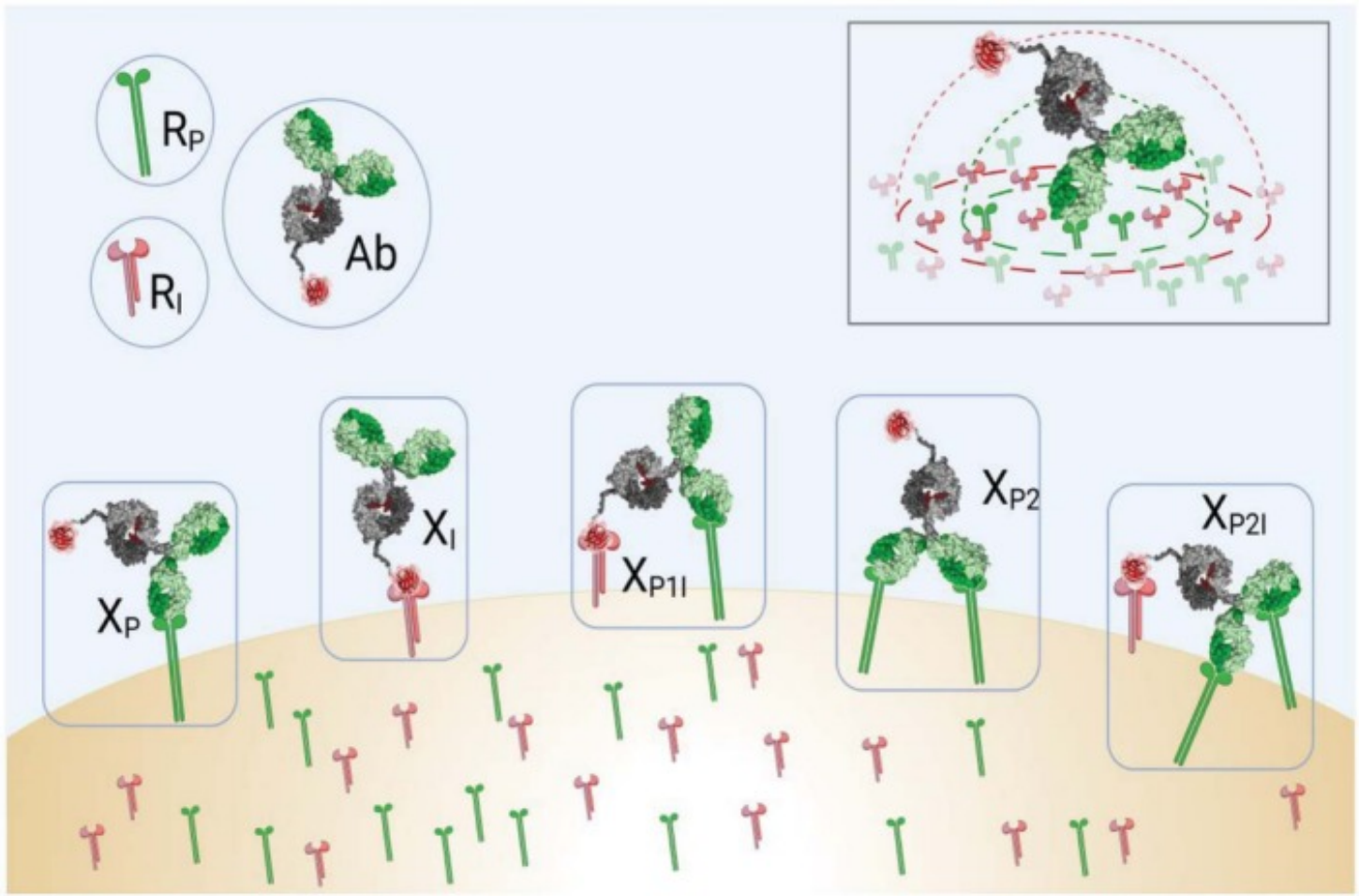
- **TCE are active in ocular melanoma** and there are preliminary evidences that may also being active in cutaneous melanoma.
- **Tebentafusp** (an IMMTAC – TCE) is the most active therapy **in HLA-A*02:01+ MuvM**, with an **OS benefit at 3 years (27% vs 18%)**, greater disease control, including durable responses and tumor shrinkage, and higher rate of ctDNA reduction.
- Most of the Tebentafusp TRAE occurred within the first month on therapy and decreased in frequency and severity thereafter, but side effects management training is mandatory.
- There is an urgent need for alternative systemic treatment strategies for HLA-A*02:01-negative MuvM patients and for HLA-A*02:01+ MuvM who progress after tebentafusp.
- There is a strong rationale to study TCEs in uveal and non-uveal melanoma. **Participation in clinical trials is encouraged.**

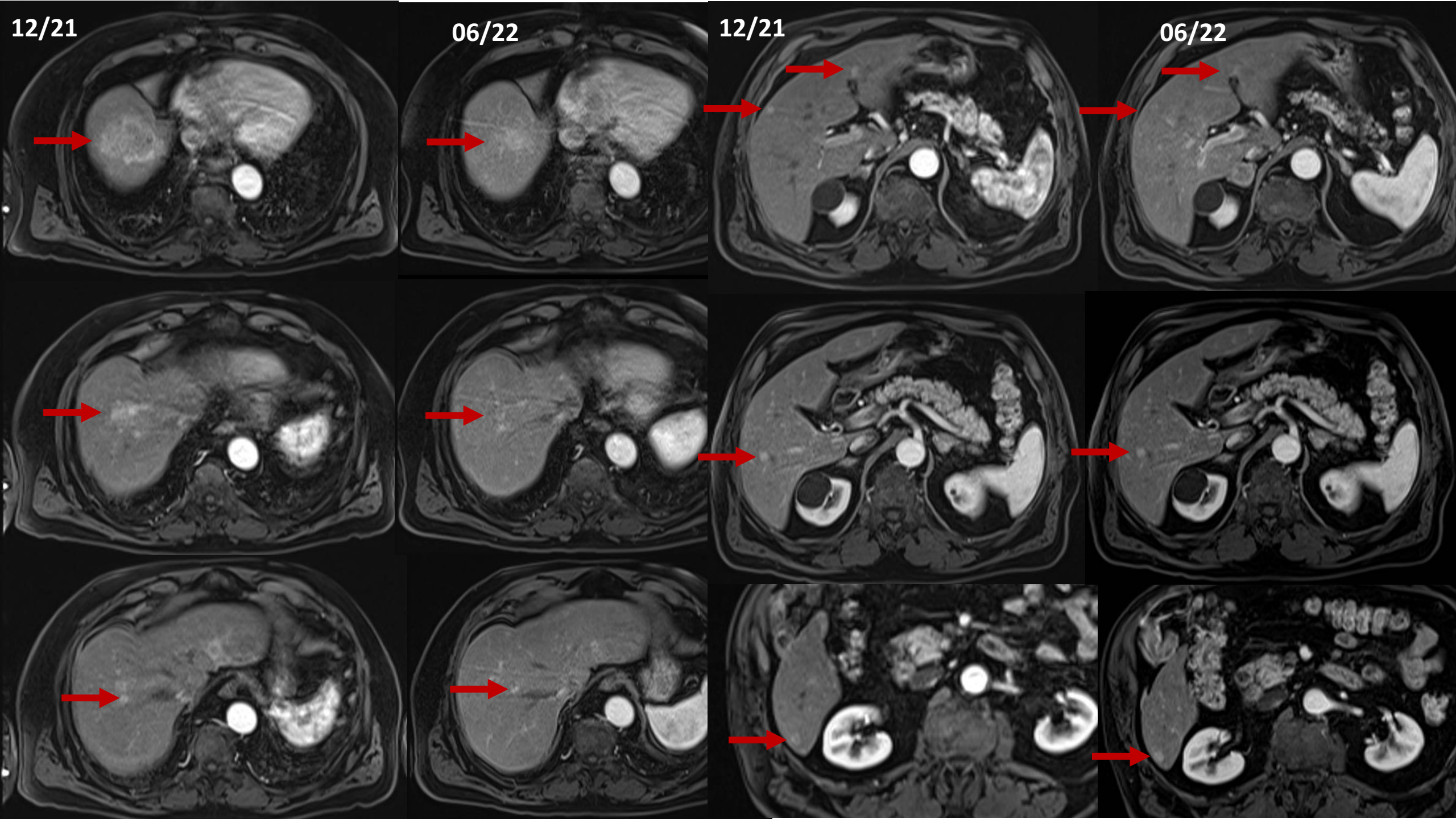
PD1-IL2v (RO7284755, eciskafusp alfa)

An antibody-cytokine fusion protein

Binding in cis-configuration to the PD-1 receptor (**PD-1**) and IL-2$\beta\gamma$ receptor (**IL-2R$\beta\gamma$**) has been shown to **lead to differentiation of CD8 T cells to better effectors**,






12/21
06/22
12/21
06/22

- 2015 Uveal melanoma – BrachiThx
- 2018 Small lung nodules (?)
- 2021 (Spt) Lung & liver P
  (Dec) Med Onc P → HLAA*02:01+
  Tebentafusp EAP
- 2022 (Jun) TAC Tx-RM hep RP
  G1 asthenia, Vitiligo STOP Tebentafusp (16)
  (Oct) TAC Tx-RM hep P **Tebentafusp EAP**
  (Nov) **G1 asthenia** STOP Tebentafusp (4)
  (Dec) TAC Tx-RM hep P
- 2023 (Apr) Exitus