VII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN

Anticuerpos biespecíficos papel en otros tumores

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Vigo, 20 y 21 de febrero de 2025

Disclosures

- **Consulting fees from**: Roche, Bayer, BMS, Janssen and Basilea.

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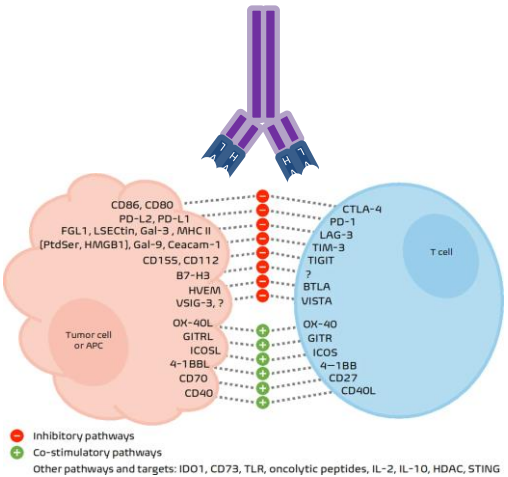
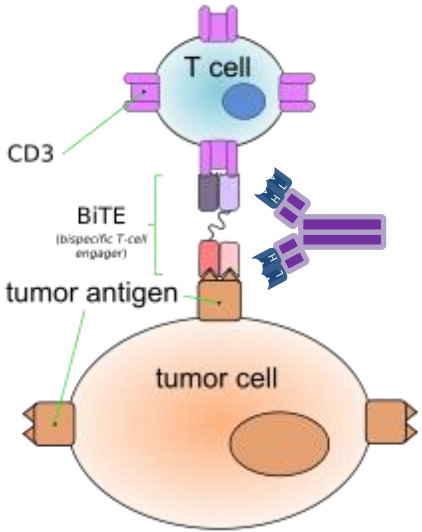
Types of bispecifics

Antibodies

Bispecific antibodies (immune bispecific)



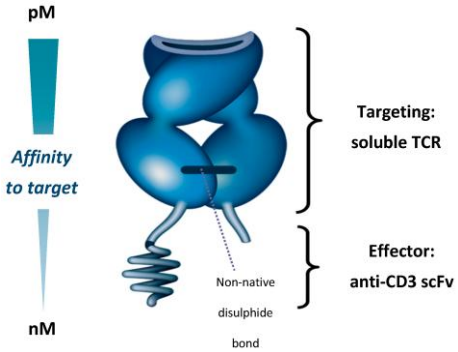
T cell engager bispecific (CD3)



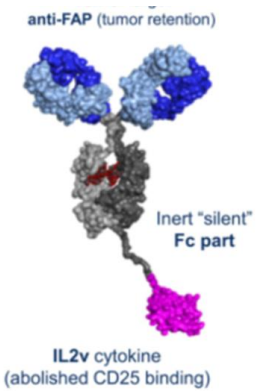
Recombinant fusion proteins

Non-antibody proteins such as cytokines, ligands, or toxins can be fused to different fragments of the antibody to generate an antibody fusion protein

i.e: Immune-mobilizing monoclonal T-cell receptor Against Cancer (ImmTAC®)

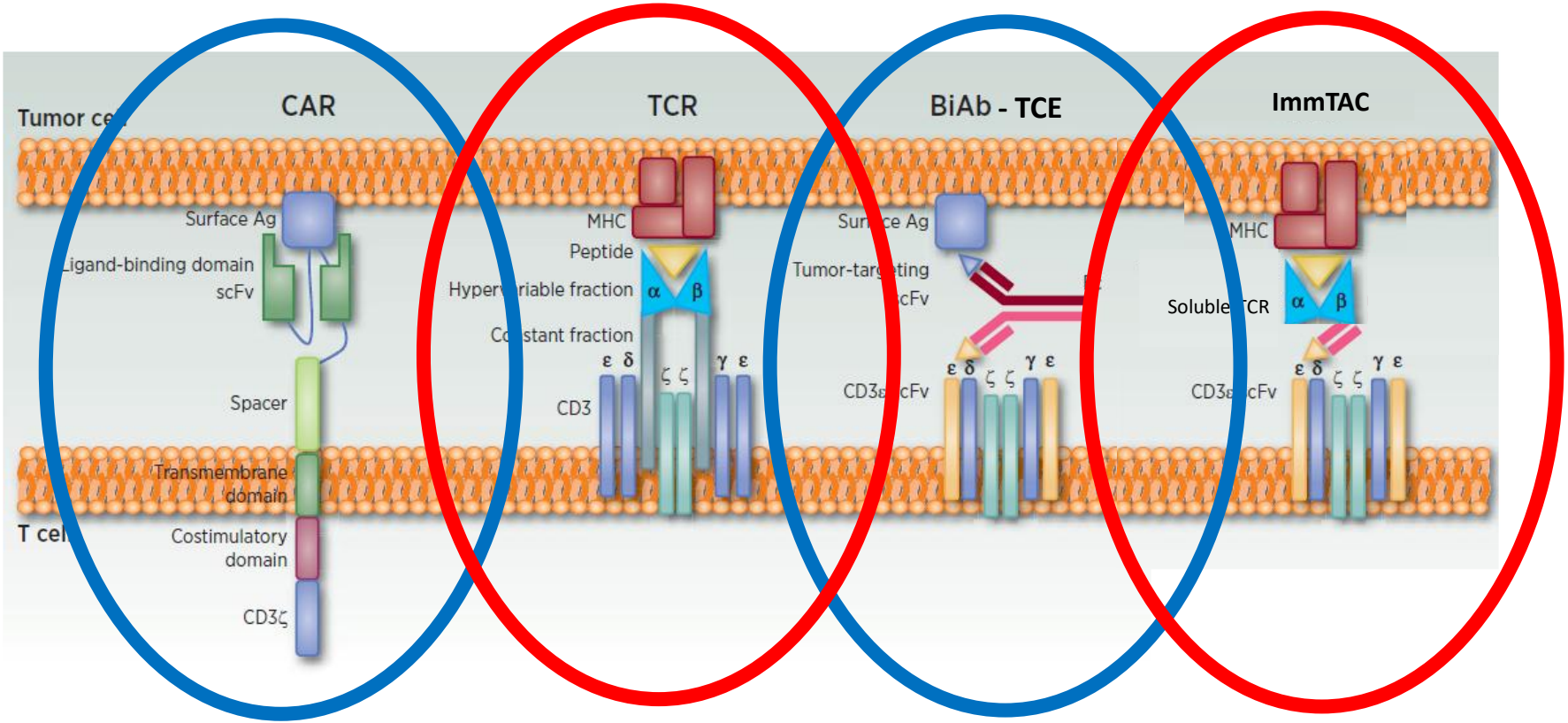


i.e: immunocytokines



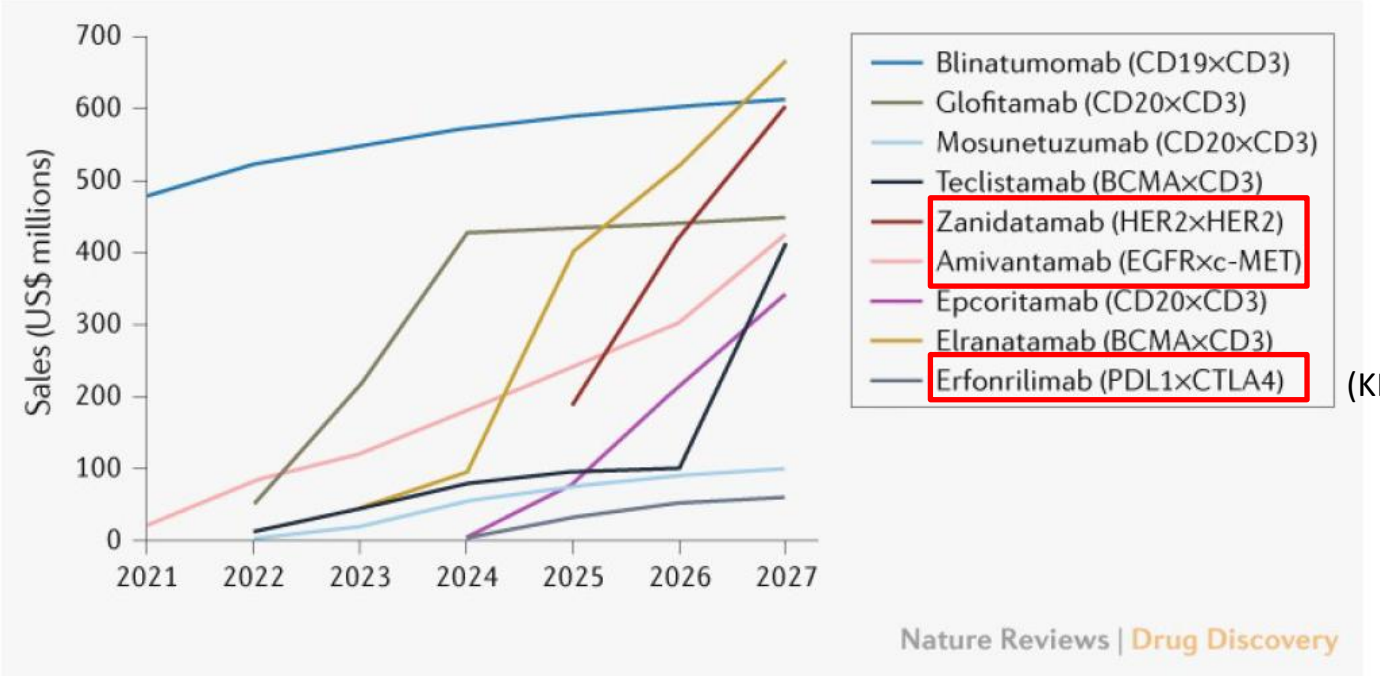
https://www.immunocore.com/

https://es.wikipedia.org/wiki/Archivo:BiTE_antibody_en.svg



Adapted from De Miguel et al, CCR 2021

Forecast global sales of select bispecific antibodies



(KN-046)

Bispecific antibodies in oncology, Esfandari et al. Nature Reviews Drug Discovery. March 2022

PARIS 2022 ESMO congress

Ubamatamab (REGN4018, MUC16xCD3 bispecific antibody) monotherapy in patients with recurrent ovarian cancer: Phase 1 dose-escalation analysis

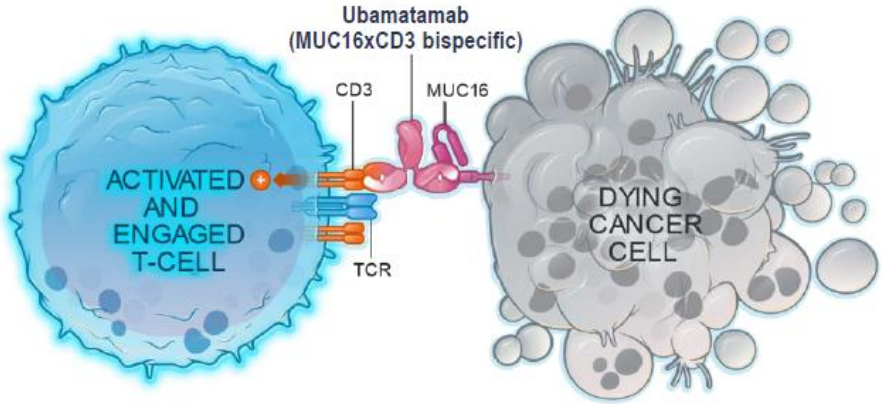
Els van Nieuwenhuysen,[1] David M O'Malley,[2] Roisin E O'Cearbhaill,[3] Kathleen N Moore,[4] Erika P Hamilton,[5] Oladapo Yeku,[6] Sara Bouberhan,[6] Suk-Young Yoo,[7] Jurriaan Brouwer-Visser,[7] Hung Kam Cheung,[7] Mary Peterman,[7] Priscila Goncalves,[7] Tamara Schmidt,[7] Min Zhu,[7] Israel Lowy,[7] Tracey Rowlands,[7] Thomas S Uldrick,[7] Elizabeth Miller,[7] Joyce F Liu[8]

[1]Leuven Cancer Institute, Leuven, Belgium; [2]The Ohio State University and The James Cancer Center, Columbus, OH, USA; [3]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [4]Stephenson Cancer Center, University of Oklahoma Health Sciences Center/Sarah Cannon Research Institute, Oklahoma City, OK, USA; [5]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [6]Massachusetts General Hospital, Boston, MA, USA; [7]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [8]Dana-Farber Cancer Institute, Boston, MA, USA

Dr David O'Malley

Ubamatamab (REGN4018) in Advanced Ovarian Cancer

- There is a high unmet need for improved therapies for women with recurrent ovarian cancer[1,2]
- The median survival is only ~12 months in the platinum resistant setting[3]



- Ubamatamab is a human bispecific antibody, developed using VelocImmune technology
- Ubamatamab is designed to bridge MUC16 on cancer cells with CD3-expressing T cells to facilitate T-cell activation and cytotoxicity[4]
- In immune-deficient mice, ubamatamab combined with human immune cells led to dose-dependent antitumor activity against intraperitoneal MUC16-expressing ovarian tumour cells and malignant ascites[5,6]

1. National Cancer Institute. Available at: https://seer.cancer.gov/statfacts/html/ovary.html. Accessed January 20, 2022; 2. Siddiqui MK et al. Gynecol Oncol. 2017;146:44–51; 3. Pujade-Lauraine et al. J Clin Oncol. 2014; 13:1302-8; 4. Crawford A et al. Sci Transl Med. 2019;11:1–13; 5. Crawford A et al. Abstract presented at AACR 2018, Chicago, USA; 6. Crawford A et al. Oral presentation at PEGS Boston Summit 2020, Virtual.

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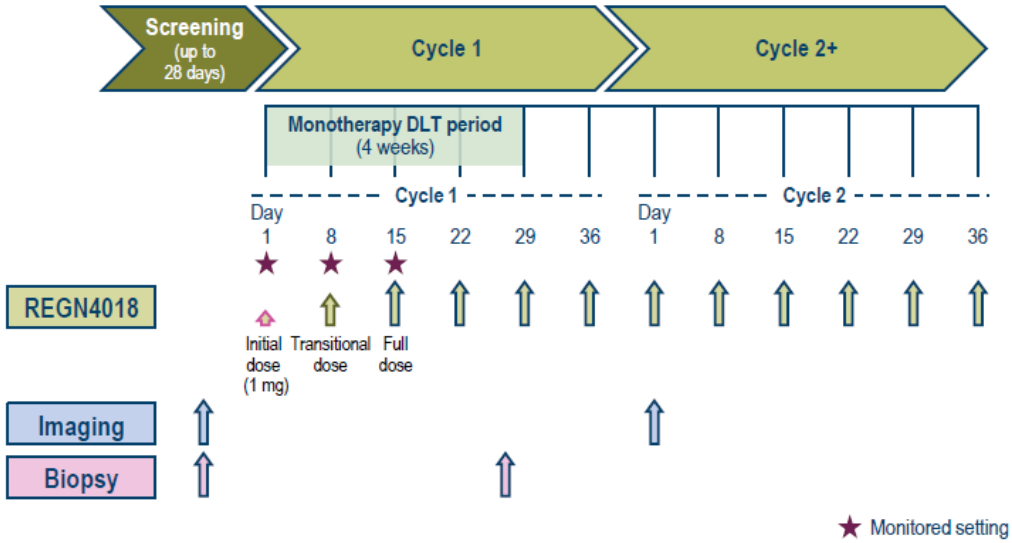
Study Design

First-in-human dose-escalation study of ubamatamab monotherapy for recurrent ovarian cancer

- Ubamatamab administered IV weekly, evaluated at doses ranging from 0.1–800 mg
- Modified 3+3 design (4+3)
- Step-up dosing for initial two doses utilized to mitigate risk of CRS via gradual increase in drug exposure
- **Primary objectives:** Safety and PK
- **Secondary objectives:** Preliminary efficacy estimate as determined by ORR per RECIST 1.1
- **Key inclusion criteria:**
  - Women ≥18 years of age
  - Relapsed advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer
  - ≥1 prior cycle of platinum-based therapy
  - CA125 ≥2X the upper limit of normal



CA-125, cancer antigen 125; CRS, cytokine release syndrome; DLT, dose limiting toxicity; IV, intravenous; ORR, objective response rate; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors.

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Baseline patient characteristics and exposure

Demographics	Total (n=78)
Age in years, median (range)	61 (31.0–80.0)
Number of lines of prior therapy, median (range)	4.5 (1–17)
Histology, n (%)	
High-grade serous	71 (91.0)
Clear cell	2 (2.6)
High-grade endometroid	1 (1.3)
Low-grade serous	1 (1.3)
Other	3 (3.8)
Other features	
CA-125 baseline serum U/mL, median (range)	709 (107–10,000)
Visceral metastases,* n (%)	26 (33)
>75% PS2+ IHC staining,** n (%)	30 (58)

- Median (range) duration of ubamatamab exposure was **12 (0.4†–145)** weeks
- Ubamatamab demonstrated linear pharmacokinetics

*Patients with investigator identified and sponsor confirmed visceral metastases, which included intraparenchymal liver (n=21), lung (n=9), pancreas (n=2), adrenal (n=2); **Patients with >75% of tumour cells with 2+ baseline MUC16 IHC staining; of 52 patients with available MUC16 score; †One patient followed for 3 days after first dose of REGN4018. Data cut-off date: March 16, 2022.
CA-125, cancer antigen 125; IHC, immunohistochemical.

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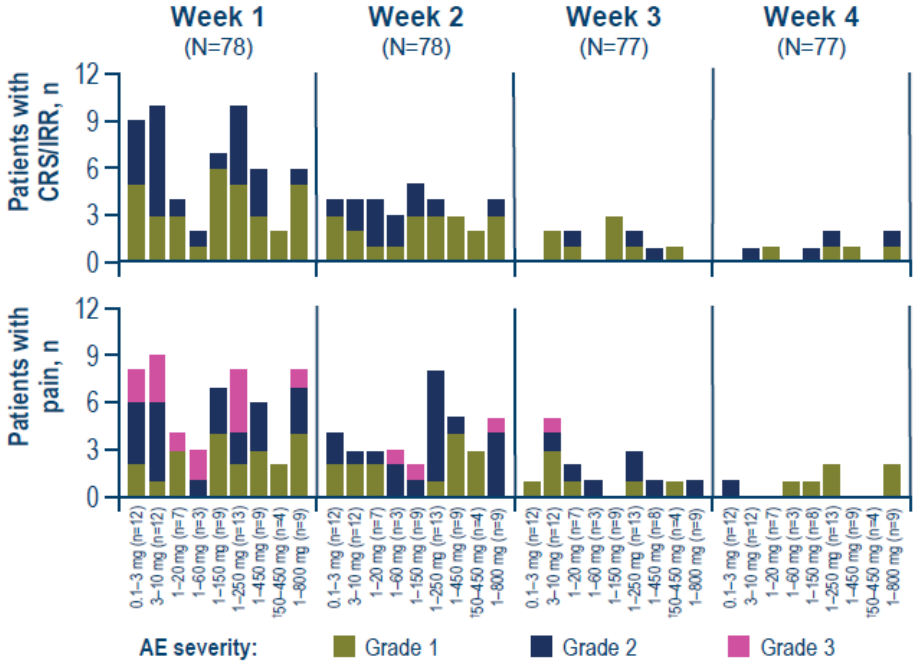
Most common ubamatamab TEAEs occurred with initial doses

	All grades (n=78)	Grade ≥3 (n=78)
Total TEAEs, n	1403	103
Patients with any TEAE, n (%)	78 (100.0)	51 (65.4)
Patients with any TEAE resulting in death,* n (%)	3 (3.8)	3 (3.8)
Primary toxicities experienced during step up dosing, n (%)		
CRS	58 (74.4)	0 (0)
Grade 1	31 (39.7)	n/a
Grade 2	27 (34.6)	n/a
Patients with any TEAE with pain	68 (87.2)	18 (23.1)
Abdominal pain	58 (74.4)	16 (20.5)
Back pain	29 (37.2)	6 (7.7)
Non-cardiac chest pain	14 (17.9)	1 (1.3)
ICANS	1 (1.3)	1 (1.3)
Other G3 AEs observed in >5% of patients, n (%)		
Anaemia	40 (51.3)	19 (24.4)
Neutropaenia	10 (12.8)	6 (7.7)

CRS/IRR and pain AEs over the first four doses of ubamatamab



*Sepsis (1), cardiac arrest (2), none attributed to ubamatamab based on sponsor assessment; †Translational dose of 2–25mg. Data cut-off date: March 16, 2022.

AEs, adverse events; CRS, cytokine release syndrome; G3, Grade 3; ICANS, immune effector cell-associated neurotoxicity syndrome; IRR, infusion-related reactions; n/a, not applicable; TEAE, treatment-emergent adverse event.

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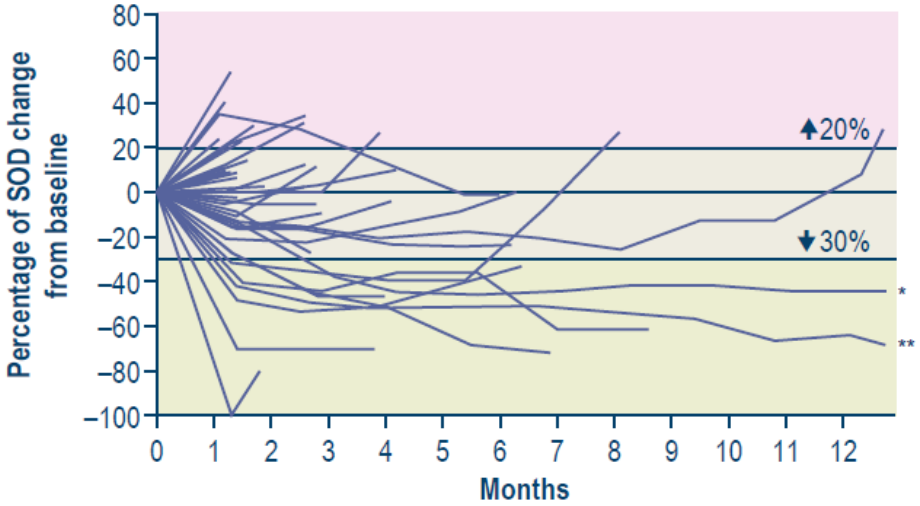
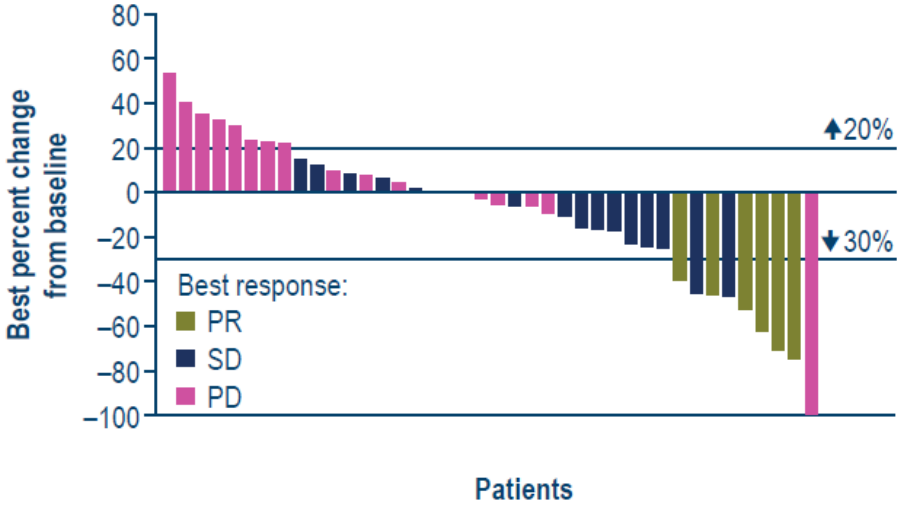
Ubamatamab results in durable anti-tumour responses

The Kaplan-Meier estimated median duration of response in patients with confirmed response was 12.2 months





*15+ months; **25+ months. Data cut-off date: March 16, 2022.

PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOD, Sum of the Diameters.

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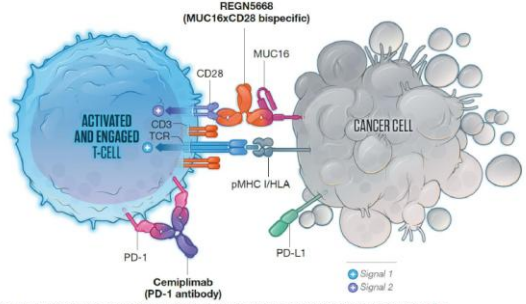
127P

REGN5668 (MUC16xCD28 bispecific antibody) with cemiplimab (anti-PD-1 antibody) in recurrent ovarian cancer: Phase 1 dose-escalation study

Roisin E O'Cearbhaill[1], Ira S Winer[2], Sara Bouberhan[3], John L Hays[4], Robert M Wenham[5], Dario R Roque[6], Oladapo O Yeku[3], Joyce F Liu[7], Bin Wang[8], Suk-Young Yoo[8], Shilpa Govindraj[8], Priyanka Madia[8], Min Zhu[8], Jurriaan Brouwer-Visser[8], Mary J Peterman[8], Tamara Schmidt[8], Brigid Barnes[8], Israel Lowy[8], David Knorr[8], Thomas S Uldrick[9], Elizabeth Miller[8]

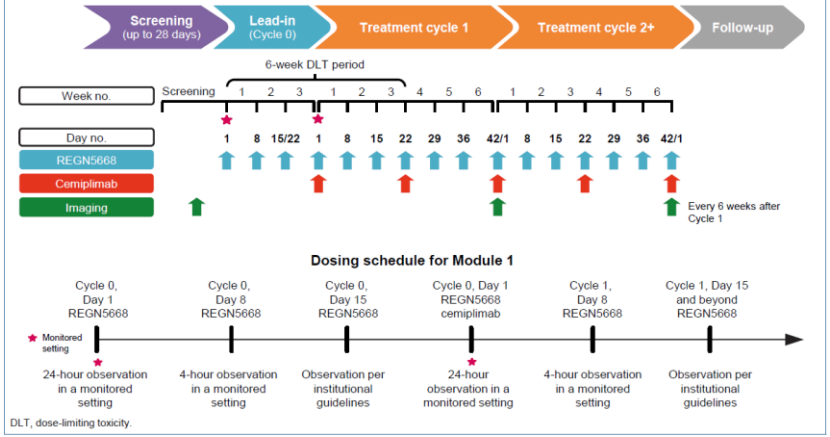
[1]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [2]Wayne State University/Karmanos Cancer Center, Detroit, MI, USA; [3]Massachusetts General Hospital, Boston, MA, USA; [4]Ohio State University Wexner Medical Center, Columbus, OH, USA; [5]Moffitt Cancer Center, Tampa, FL, USA; [6]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [7]Dana-Farber Cancer Institute, Boston, MA, USA; [8]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Figure 1. REGN5668 mechanism of action



CD28, cluster of differentiation 28; HLA, human leukocyte antigen; MUC16, mucin16; PD-(L)1, programmed cell death-(ligand) 1; pMHC, peptide-loaded major histocompatibility complex; TCR, T-cell receptor.

Figure 2. Module 1 treatment schema

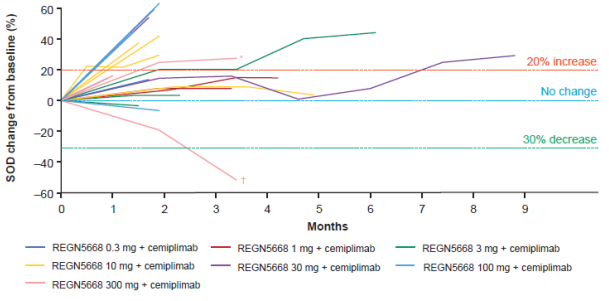


DLT, dose-limiting toxicity.

Table 2. Safety summary over the entire treatment period

	Total (N=28)	
	All grades	Grade 3§
Total TRAEs, n	107	1
Patients with any TRAE, n (%)	24 (85.7)	1 (3.6)
Patients with any TRAE resulting in death, n (%)	0	0
Patients with any TRAE observed in >10% of patients, n (%)*		
Fatigue	9 (32.1)	1 (3.6)
Nausea	8 (28.6)	0
Pain	5 (17.9)	0
Abdominal pain	2 (7.1)	0
Back pain	2 (7.1)	0
Non-cardiac chest pain	1 (3.6)	0
Diarrhoea	4 (14.3)	0
Infusion-related reaction/cytokine release syndrome	4 (14.3)	0
Cytokine release syndrome	3 (10.7)†	0
Infusion-related reaction	2 (7.1)‡	0
Anaemia	3 (10.7)	0
Aspartate aminotransferase increased	3 (10.7)	0
Dizziness	3 (10.7)	0
Dyspnoea	3 (10.7)	0
Headache	3 (10.7)	0

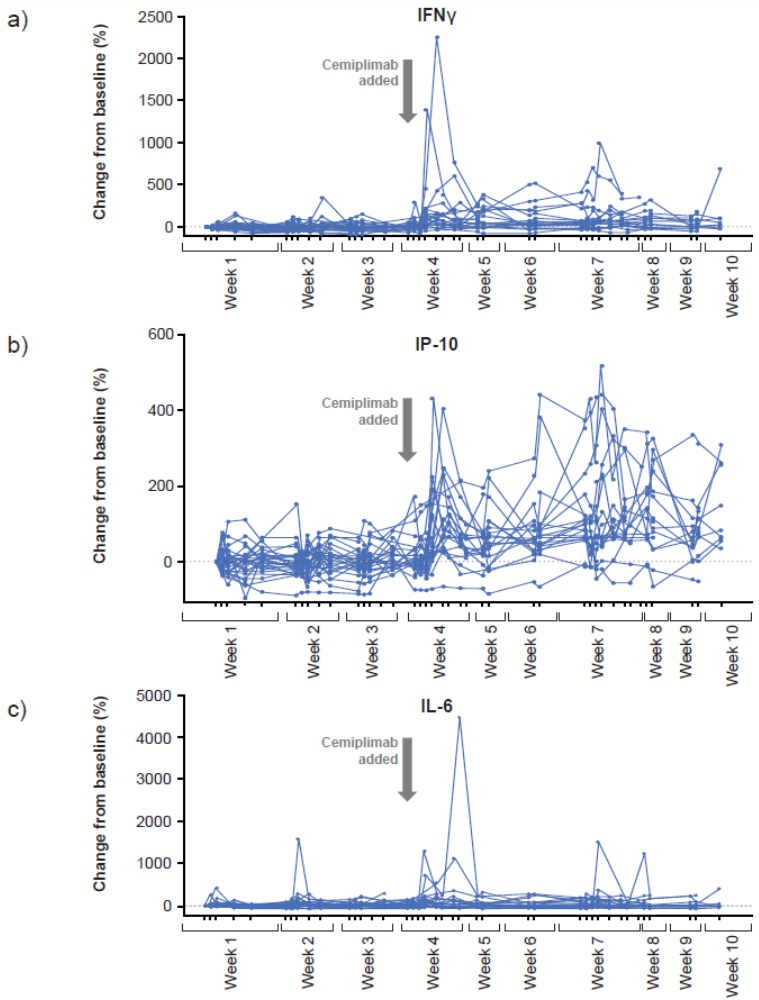
Figure 3. REGN5668 + cemiplimab: SOD change from baseline



Data cutoff date: 14 July 2023. *Treatment ongoing as of 16 November 2023; duration: 7.7 months. †Partial response with 4.1 months DOR as of last tumor assessment (10 October 2023); treatment ongoing as of 16 November 2023; duration: 8.8 months.
DOR, duration of response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOD, sum of diameters.

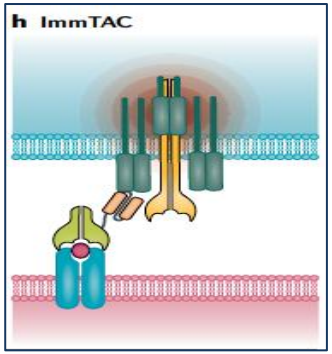
ESMO IO 2023

Figure 5. Cytokine profiles of a) IFNγ, b) IP-10 and c) IL-6



Number of patients with value at any timepoint: 26 (IFNγ), 27 (IP-10), 26 (IL-6).
IFNγ, interferon gamma; IL-6, interleukin 6; IP-10, interferon-gamma inducible protein of 10 kDa.

Immune mobilising monoclonal T-cell receptors Against Cancer (ImmTAC®)



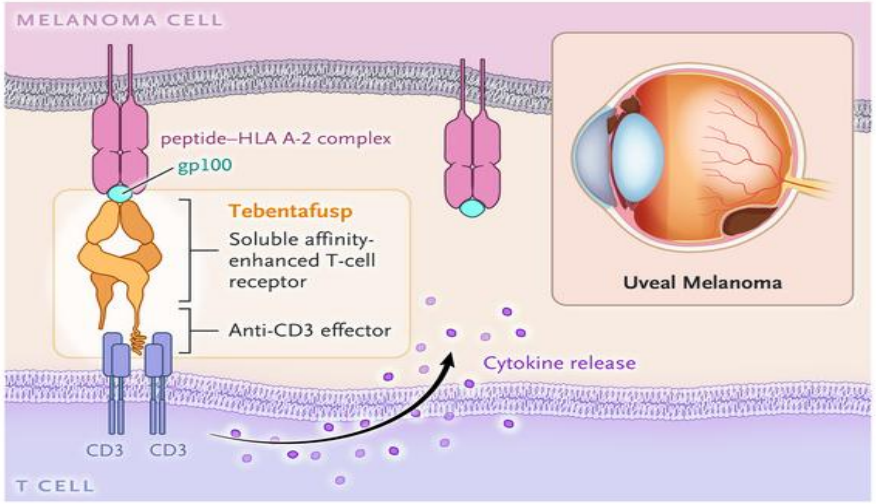
bifunctional reagents that combine a soluble TCR with affinity for an intracellular or extracellular tumor specific antigen presented in the context of peptide–MHC complexes and an anti- CD3.

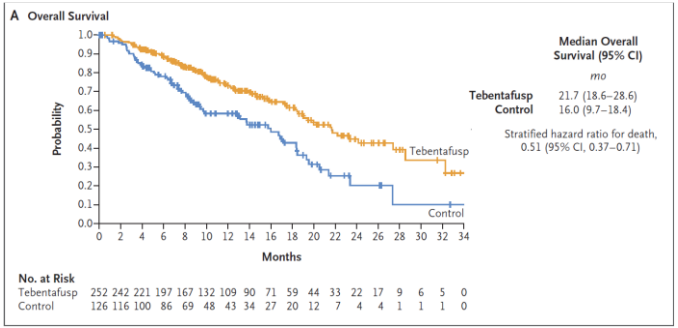
T cell-engaging therapies - BiTEs and beyond. Nat Rev Clin Oncol. 2020 Jul;17(7):418-434. doi: 10.1038/s41571-020-0347-5

The NEW ENGLAND JOURNAL of MEDICINE

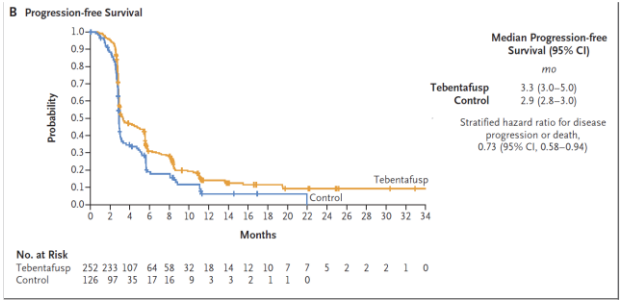
ORIGINAL ARTICLE

Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma





The estimated overall survival at 1 year was 73% (95% confidence interval [CI], 66 to 79) in the tebentafusp group and 59% (95% CI, 48 to 67) in the control group



at 6 months, the estimated progression-free survival was 31%, as compared with 19% in the control group

Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med. 2021 Sep 23;385(13):1196-1206.doi: 10.1056/NEJMoa2103485.

2024 ASCO ANNUAL MEETING

#9507

Phase 1 safety and efficacy of brenetafusp (IMC-F106C), a PRAME × CD3 ImmTAC bispecific, in post-checkpoint cutaneous melanoma (CM)

Omid Hamid[1], Anja Williams[2], Juanita Lopez[3], Daniel Olson[4], Takami Sato[5], Heather Shaw[6], Claire F. Friedman[7], Fiona Thistlethwaite[8], Mark R. Middleton[9], Celeste Lebbe[10], Vincent T. Ma[11], Benjamin Izar[12], Peter Lau[13], Oliver Bechter[14], Peter Kirk[15], Yuan Yuan[16], Shannon Marshall[16], and Diwakar Davar[17]

[1]The Angeles Clinical and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA; [2]Sarah Cannon Research Institute, London, United Kingdom; [3]The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; [4]University of Chicago, Comprehensive Cancer Center, Chicago, IL; [5]Sidney Kimmel Cancer Center, Jefferson University, Philadelphia, PA; [6]University College London Hospital, London, United Kingdom; [7]Memorial Sloan Kettering Cancer Center, New York, NY; [8]The Christie NHS Foundation and University of Manchester, Manchester, United Kingdom; [9]Medical Sciences Division, University of Oxford, Headington, Oxford, United Kingdom; [10]Université Paris Cité; Dermatolo-Oncology AP-HP Hôpital Saint-Louis, INSERM U976, Paris, France; [11]University of Wisconsin Carbone Cancer Center, Madison, WI; [12]Columbia University Medical Center, New York, NY; [13]Linear Clinical Research, Harry Perkins Institute for Medical Research, Nedlands, WA, Australia; [14]UZ Gasthuisberg - Katholieke University Leuven, Leuven, Belgium; [15]Immunocore, Abingdon, United Kingdom; [16]Immunocore, Rockville, MD; [17]University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA

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PRESENTED BY: Dr. Omid Hamid

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Phase 1 safety and efficacy of brenetafusp, a PRAME × CD3 ImmTAC T cell engager, in platinum resistant ovarian cancer (PROC)

Claire F. Friedman[1], Anja Williams[2], Juanita Lopez[3], Kaissa Ouali[4,5] Mark R. Middleton[6], Fiona Thistlethwaite[7], Omid Hamid[8], Benjamin Izar[9], Victor Moreno[10], Melissa Johnson[11], Diwakar Davar[12], Juan Martin-Liberal[13], Patricia Roxburgh[14], Kathleen Moore[15], Daniel Olson[16], Sylvie Rottey[17,18,19] Peter Kirk[20], Yuan Yuan[21], Shannon Marshall[21], Oladapo Yeku[22]

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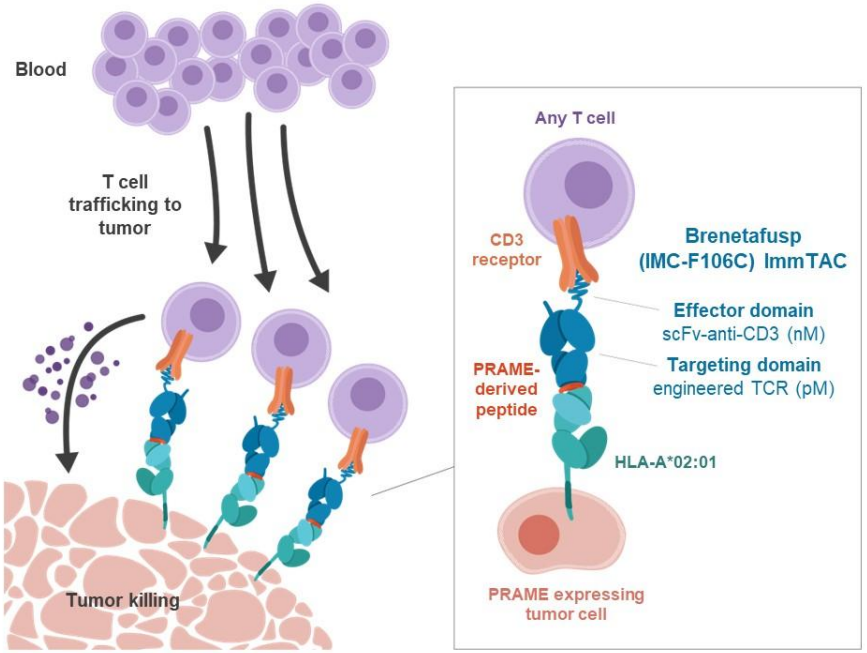
Brenetafusp: ImmTAC bispecific T cell engager targeting HLA-A2-presented peptide from PRAME



- TCR bispecific ImmTAC molecules redirect polyclonal T cells to target cancer cells by recognizing intra-/extra-cellular cancer proteins
- ImmTAC platform validated by tebentafusp (gp100 × CD3) with OS (HR 0.51) and PFS benefit (HR 0.73) in mUM[2]
- ImmTAC tolerability with immune checkpoints demonstrated with tebentafusp in cutaneous melanoma[2]
- PRAME is broadly expressed in several tumor types, including ~90% cutaneous melanoma (CM), with minimal normal tissue expression[1]

ImmTAC, Immune mobilizing T cell receptor Against Cancer; mUM, metastatic uveal melanoma; OS, overall survival; TCR, T cell receptor

1. Internal IHC data analysis and TCGA; Kaczorowski, et al. 2022 Am J Surg Pathol 2022; 46(11):1467-1476
2. Nathan P, et al. N Engl J Med 2021;385:1196-206; Hamid O, et al. J Immunother Cancer 2023;11(6):e006747

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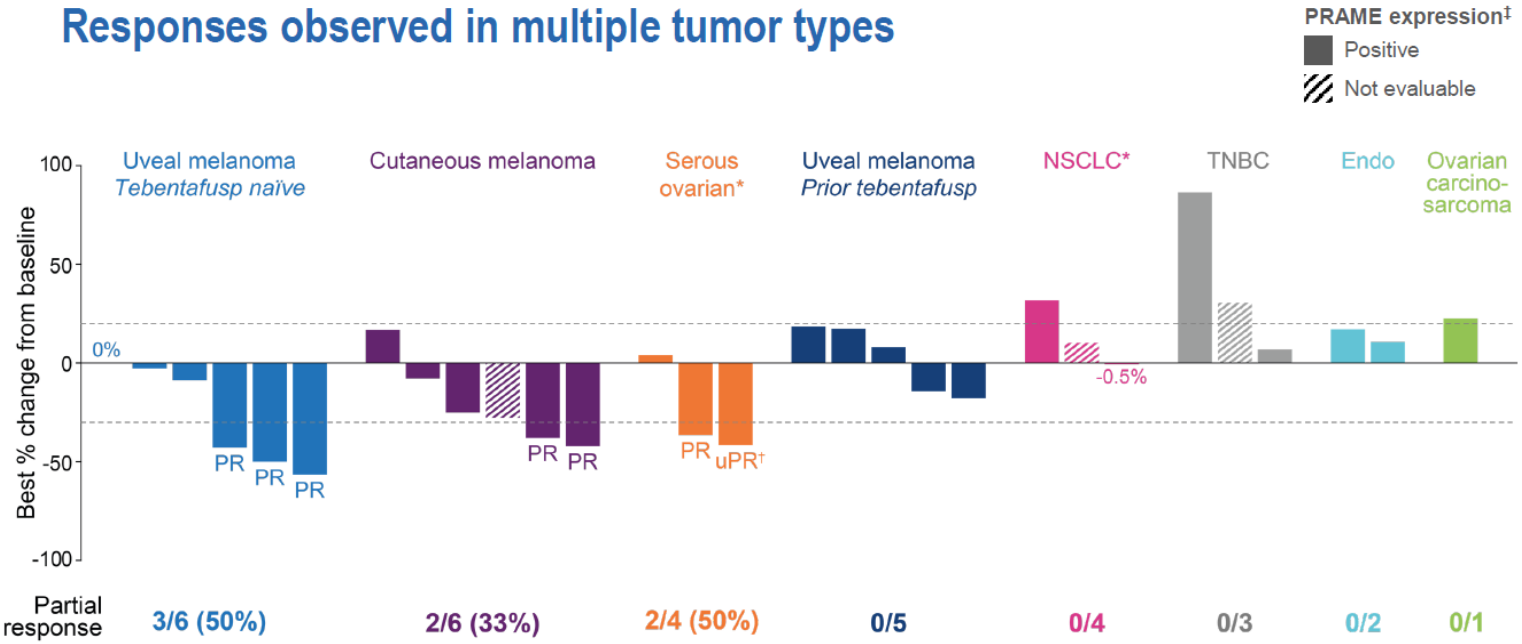
Responses observed in multiple tumor types



* Two patients (1 with NSCLC, 1 serous ovarian) discontinued treatment due to PD with scan data not available at DCO
† Ovarian cancer patient with unconfirmed PR (uPR) remains on treatment and eligible for confirmation
‡ PRAME expression assessed by IHC H-score
Two PRAME-negative patients both had PD (not shown)
Endo, endometrial carcinoma; NSCLC, non small cell lung carcinoma; TNBC, triple-negative breast cancer;

Brenetafusp Phase 1/2 Study Design (HGSOC*)

Monotherapy	Chemotherapy combinations†		
Brenetafusp ≥ 20 mcg N=37	**Gemcitabine combination** N=10	**Nab-paclitaxel combination** N=4	**PLD combination** N=2

Dosing regimen & assessments

Weekly IV infusion

1-2 step doses → **Target dose**

RECIST tumor assessment every 9 weeks
ctDNA assessment every 3 weeks

Key eligibility (HGSOC):
- Unresectable or metastatic
- HLA-A*02:01 (central testing)
- Relapsed / refractory / intolerant of standard treatments including:
  - Platinum-based chemotherapy
  - PARP inhibitor if applicable

Key objectives:
- Primary
  - Safety
  - MTD/expansion dose
  - Efficacy (expansion only)
- Additional
  - Pharmacokinetics
  - Molecular response (ctDNA)
  - Predictive biomarkers

- Tumor PRAME expression evaluated by immunohistochemistry
- Gene expression in whole blood at baseline evaluated by bulk RNA sequencing

IV, intravenous; HGSOC, high grade serous ovarian carcinoma; MTD, maximum tolerated dose; PLD, pegylated liposomal doxorubicin
* Other tumor types assessed in the study: cutaneous melanoma, NSCLC, and endometrial carcinoma (Hamid O, *et al*. Ann Oncol 2022; 33 Suppl 7: S875). † Chemotherapy dosed at regimens recommended by medical guidance.
EudraCT No. 2019-004046-16; NCT04262466. Data cut-off date: 20 MAY 2024

Table 2. Brenetafusp well tolerated as monotherapy and in combination with chemotherapy

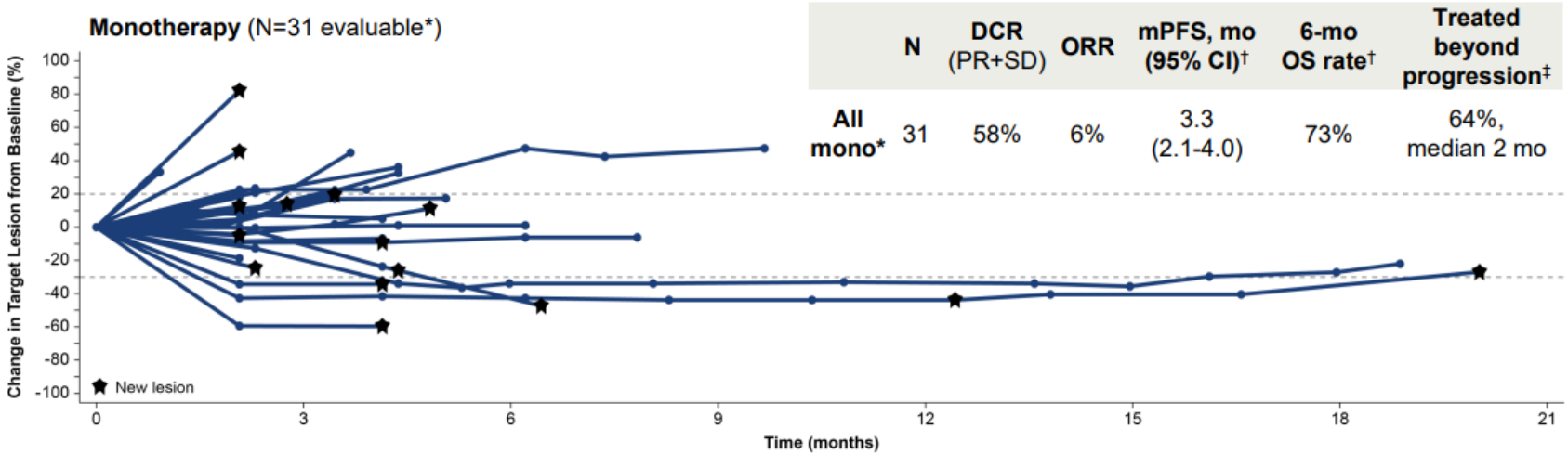
Brenetafusp related adverse events (TRAE) in ≥20%*

	Mono N=37		Chemo Combo N=16	
Preferred Term	**TRAE**	**G3/4 TRAE†**	**TRAE**	**G3/4 TRAE†**
ANY	36 (97%)	7 (19%)	16 (100%)	8 (50%)
CRS‡	21 (57%)	---	12 (75%)	---
Rash§	19 (51%)	1 (3%)	13 (81%)	---
Nausea	14 (38%)	---	4 (25%)	---
Fatigue	13 (35%)	---	6 (38%)	1 (6%)
Vomiting	12 (32%)	---	2 (13%)	---
Pyrexia	11 (30%)	---	9 (56%)	---
ALT increased	4 (11%)	1 (3%)	8 (50%)	3 (19%)
AST increased	2 (5%)	1 (3%)	8 (50%)	2 (13%)
Flushing	1 (3%)	---	4 (25%)	---

CRS, cytokine release syndrome; ALT, alanine transaminase; AST, aspartate transaminase
* Includes patients receiving target doses ≥20mcg. † Other mono G3 TRAE, each N=1: anemia, diarrhea, neutropenia, pericardial effusion, rash maculo-popular; other combo G3 TRAE, each N=1: dyspnea, fatigue, neutropenia, presyncope. ‡ CRS graded per ASTCT 2019 criteria; all other AE per CTCAE v5.0. § Rash is a composite term for a list of skin toxicities of any grade (Nathan *et al*. 2021)

- TRAE frequency and severity attenuated over time
- No TRAE leading to treatment discontinuation or death
- **Monotherapy**:
  - Most frequent TRAE was G1/G2 CRS
  - Of patients who had CRS, vast majority had G1
- **Combinations**:
  - Additional chemo-related AEs were observed and consistent with each agent

Figure 2. Clinical benefit characterized by durable disease control



	N	DCR (PR+SD)	ORR	mPFS, mo (95% CI)†	6-mo OS rate†	Treated beyond progression‡
All mono*	31	58%	6%	3.3 (2.1-4.0)	73%	64%, median 2 mo

Figure 3A. Monotherapy clinical benefit characterized by disease control and molecular response

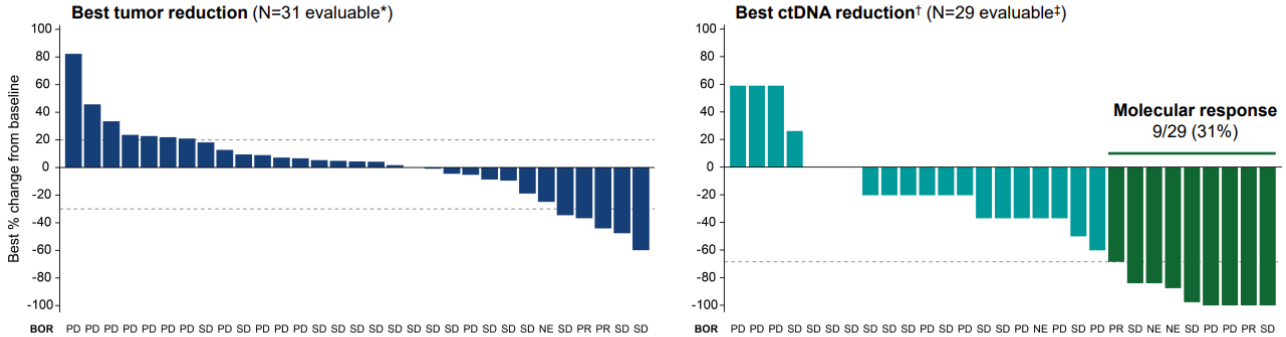


Figure 3B. Clinical benefit with brenetafusp may be enhanced with chemotherapy

Brenetafusp Phase 1/2 Study Design

Key objectives:

Primary
- Safety
- MTD/expansion dose
- Efficacy (in expansion only)

Additional
- Pharmacokinetics
- Molecular response (ctDNA)
- Predictive biomarkers

Key eligibility criteria for CM:

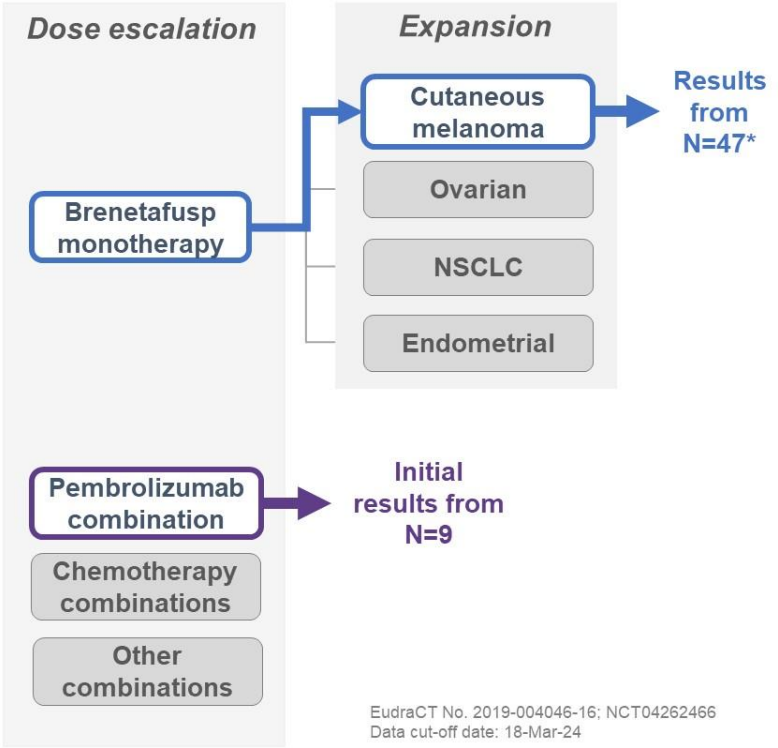
- Unresectable or metastatic
- HLA-A*02:01 (central testing)
- Previously treated with
  - immune checkpoint inhibitors
  - BRAFi/MEKi, if applicable

Weekly IV infusion

1-2 step doses | **Target dose**

RECIST tumor assessment every 9 weeks
ctDNA assessment every 3 weeks

- Previously presented Ph1 data[1]
  - Identified target doses ≥ 20 mcg as consistently pharmacodynamically and clinically active
  - Included 7 efficacy-evaluable CM pts
- Tumor PRAME expression evaluated by IHC
- Gene expression in whole blood at baseline evaluated by bulk RNASeq



EudraCT No. 2019-004046-16; NCT04262466
Data cut-off date: 18-Mar-24

IV, intravenous; MTD, maximum tolerated dose; 1. Hamid O, et al. Ann Oncol 2022; 33 Suppl 7: S875
*47 monotherapy patients at brenetafusp target dose of ≥ 20 mcg including 40 new patients and follow-up on 7 CM patients previously presented

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CM Demographics and baseline characteristics

Brenetafusp monotherapy and in combination with pembrolizumab

Characteristic	Monotherapy N=47	+ Pembro N=9
Age, yr – median (range)	64 (31-79)	65 (24-78)
Female – n (%)	19 (40%)	4 (44%)
ECOG status 0 – n (%)	27 (57%)	8 (89%)
Baseline disease status		
Stage III/IV M1a	3 (6%)	3 (33%)
Stage IV M1b/c/d	44 (94%)	6 (67%)
Brain metastasis – n (%)	10 (21%)	2 (22%)
Liver metastasis – n (%)	21 (45%)	3 (33%)
Sum of target lesions*, mm – median (range)	84 (14-309)	73 (24-117)
Prior therapy		
# lines – median (range)	2 (1-9)	4 (1-7)
Anti-PD1	47 (100%)	9 (100%)
Primary resistant† – n (%)	14 (30%)	6 (67%)
Anti-CTLA4	38 (81%)	8 (89%)
BRAF inhibitor	7 (15%)	4 (44%)
PRAME status (IHC)		
Positive‡	42 (89%)	9 (100%)
H-score§ – median	215	155

Patients were heavily pre-treated

- All received prior checkpoint inhibitors (CPI)
  - Median 2 prior anti-PD1 regimens
  - 81% prior ipilimumab – nearly all in combination with nivolumab
  - 38% had another IO, in addition to anti-PD1, anti-CTLA4
- Pembro combo pts. more heavily pre-treated
  - Higher percentage with prior BRAFi and primary resistance to anti-PD1

PRAME expression was high (median H score 215 in monotherapy)†

Includes patients receiving target doses ≥20mcg
* Sum of target lesions at baseline; one pembro combo pt had non-target lesions only
† Primary resistant to anti-PD1: progressed within 6 months of starting first anti-PD1-containing regimen
‡ PRAME positive group for efficacy analysis includes H-score ≥1 and pts with unknown PRAME IHC results; maximum H-score 300
§ Amongst IHC evaluable pts (n=38 mono, n=5 combo)

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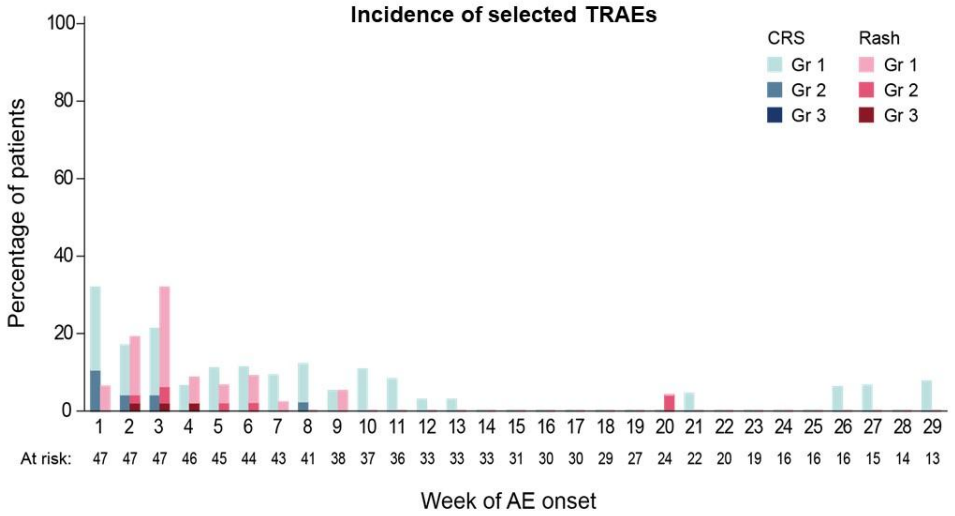
Brenetafusp monotherapy was well tolerated

TRAE in ≥ 15% of patients (N=47)

Preferred Term (%)	Any grade	Grade 3 / 4
ANY	43 (92%)	19 (40%)
Cytokine release syndrome*	24 (51%)	-
Rash (composite)†	23 (49%)	1 (2%)
Pyrexia	17 (36%)	1 (2%)
Chills	13 (28%)	-
Lymphocyte decrease	12 (26%)	11 (23%)
Pruritus	11 (23%)	-
Nausea	9 (19%)	-
Fatigue	7 (15%)	-

Includes patients receiving target doses ≥20mcg
* CRS graded per ASTCT 2019 criteria; all other AE per CTCAE v5.0
† Rash is a composite term for a list of skin toxicities of any grade (Nathan et al. 2021)
Other G3 treatment-related adverse events (TRAE, in 1 pt each): anemia, chronic inflammatory demyelinating polyneuropathy, fever, hypertension, hypotension, hypoxia, pain in extremity, tumor lysis syndrome, urticaria



- Safety consistent with previous report; no new signal with continued dosing
- Most frequent TRAE was G1/G2 CRS, consistent with mechanism
- TRAE frequency and severity attenuated over time

- The only G4 TRAEs were lymphocyte decrease (n=11) / lymphopenia (n=3), transient and related to mechanism
- No severe neutropenia observed
- 1 TRAE resulted in treatment discontinuation
- No treatment-related deaths

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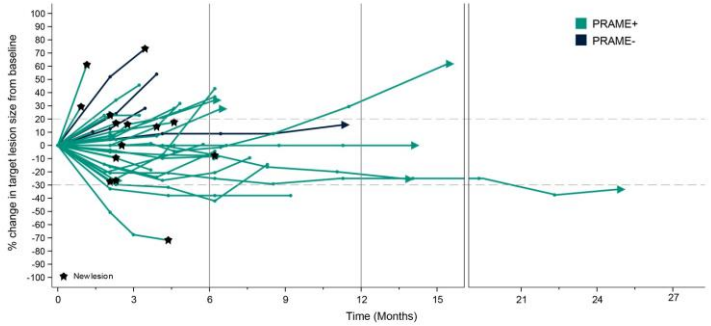
Clinical benefit characterized by durable disease control

Brenetafusp monotherapy (n= 36 evaluable*)



PRAME positive group for efficacy analysis includes H-score ≥1 and pts with unknown PRAME IHC results
* 36/47 patients had baseline and at least one tumor assessment on treatment; 10 patients had no evaluable post-baseline tumor scans and 1 had non-target lesions only at baseline

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Clinical benefit characterized by disease control

	N	DCR (PR+SD)	PR + SD with confirmed tumor reduction*	ORR
All mono	36	56%	28%	11%
PRAME+	31	58%	32%	13%
PRAME-	5	40%	0%	0%

Reduction in tumor burden is associated with clinical benefit across ImmTAC platform

Nathan NEJM[1]; Middleton CCR[2]; see ASCO 2024 poster #9529

PRAME positive group for efficacy analysis includes H-score ≥1 and pts with unknown PRAME IHC results
* Defined as patients with PR + patients SD or better who have tumor reduction that is confirmed in a subsequent scan after at least 4 weeks with no progressive disease in between
1. Nathan P, et al. N Engl J Med 2021;385:1196-206; 2. Middleton M, et al Clin Can Res; 26:5869-5878

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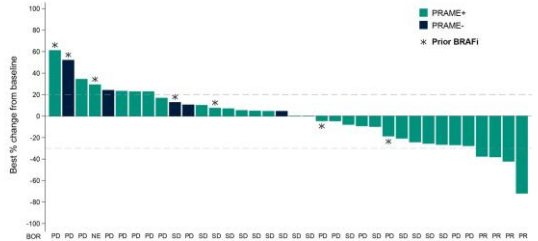
Tumor reduction observed only in PRAME+ pts

Brenetafusp monotherapy (n= 36 evaluable)



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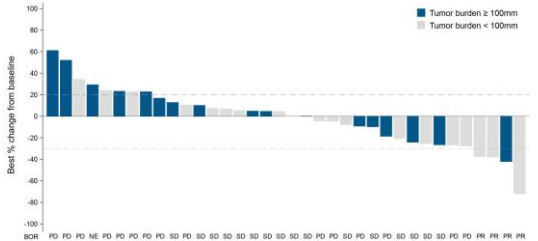
Tumor reduction observed in patients with high tumor burden

Brenetafusp monotherapy (n= 36 evaluable)



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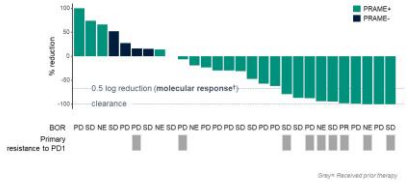
ctDNA molecular response in 42% of PRAME+ patients

Brenetafusp monotherapy (n=28 ctDNA evaluable*)



- Trend for longer PFS (HR 0.5) and OS (HR 0.3) in molecular responders
- Molecular response in patients with PR, SD and PD
- 4 pts have ≥99% ctDNA reduction

PRAME positive group includes H-score ≥1 and pts with unknown PRAME IHC results
*ctDNA evaluable: defined as ≥1 mutation detected at baseline at ≥0.5% VAF AND data from at least one on-treatment timepoint up to week 9; n=28 ctDNA evaluable, best response by week 9
†Molecular response defined as ≥0.5log10(95%) ctDNA reduction by week 9

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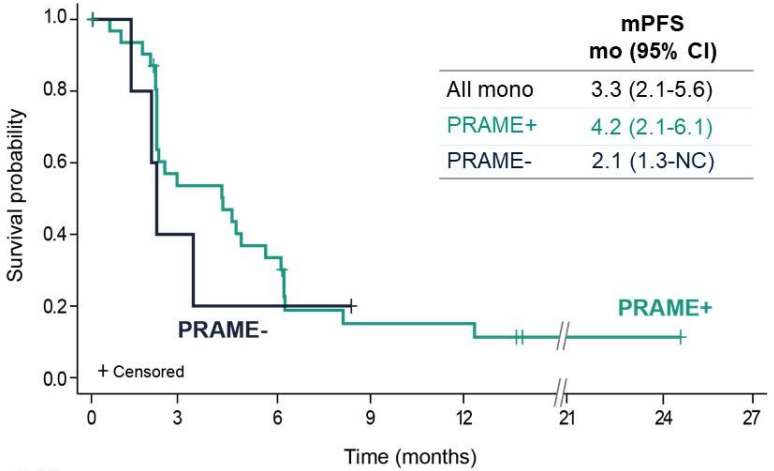
Promising initial PFS and OS, enriched in PRAME+ pts

Brenetafusp monotherapy (n= 47)

Progression free survival

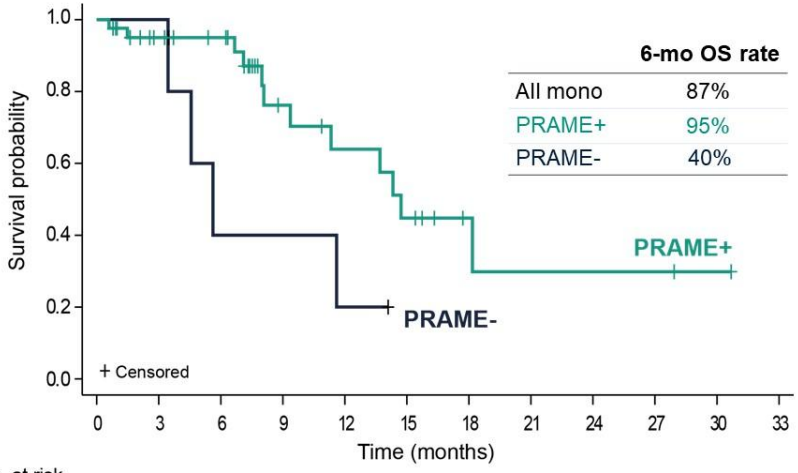


	mPFS mo (95% CI)
All mono	3.3 (2.1-5.6)
PRAME+	4.2 (2.1-6.1)
PRAME-	2.1 (1.3-NC)

No. at risk

PRAME+	42	16	10	4	4	1	1	1	1	0
PRAME-	5	2	1	0						

Overall survival



	6-mo OS rate
All mono	87%
PRAME+	95%
PRAME-	40%

No. at risk

PRAME+	42	31	26	13	10	7	3	2	2	2	1	0
PRAME-	5	5	2	2	1	0						

Median follow up 7.8 mos

PRAME positive group includes H-score ≥1 and pts with unknown PRAME IHC results

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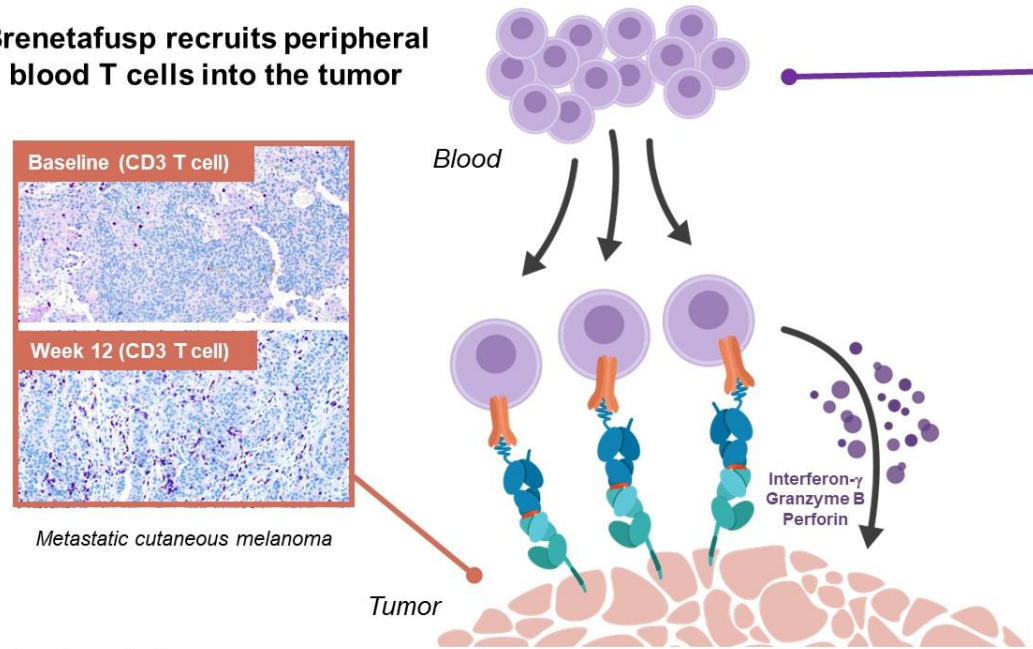
Phenotype of peripheral blood T cells, which are recruited by brenetafusp, may be important for clinical activity

Brenetafusp recruits peripheral blood T cells into the tumor



Hypothesis:
Specific T cell subsets in the blood may be associated with brenetafusp benefit

Method:

- RNAseq whole blood at baseline
- Analyzed key T cell subsets:
  - Naïve /stem cell memory T cell (T_{scm})
  - Effector
  - Exhausted
  - Regulatory

Naïve T/T_{scm} have been associated with anti-tumor activity of other T cell therapies[1].

Tscm, stem cell memory T cell

1. Gattinoni, et al. Nature Rev Cancer 2012; 12:671-684; Kishton, et al. Curr Opin Imm 2022; 74:39-45; Mehta, et al. Front Immunol 2021; 12:780442; Arcangeli, et al. J Clin Invest 2022; 123:e150807; Rosenberg, et al. Clin Cancer Res 2011; 17:4550-4557

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Novel T cell fitness (TCF) signature associated with brenetafusp benefit

TCF higher in earlier lines of therapy and highly correlated with naïve/T_{scm} cells

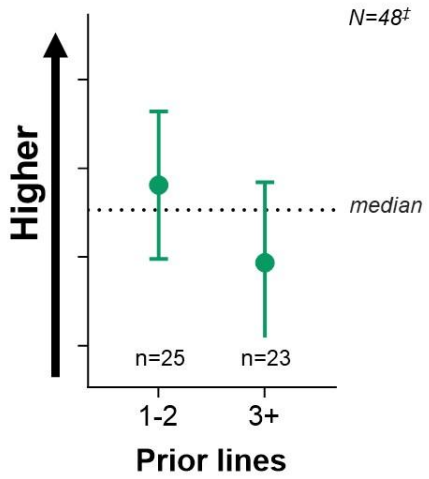
Monotherapy benefit by TCF signature

N=41†	High* n=21	Low n=20
mPFS	6 mo	2 mo
ORR	19%	0%
DCR	69%	42%

*For exploratory analysis, 'high' defined as ≥ median gene expression signature level

Other gene signatures, including T effector and exhausted T cell phenotype, not associated with clinical benefit (data not shown)

TCF signature, by line of therapy



†41 monotherapy CM patients had baseline TCF and were evaluable for tumor assessment on therapy;
‡42 monotherapy CM and 6 pembrolizumab combination patients had baseline T cell fitness evaluated

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Conclusions

- Brenetafusp is well tolerated
  - Most frequent TRAE is reversible and manageable CRS (Grade 1-2)
  - Brenetafusp can be safely combined with anti-PD1
- Promising monotherapy activity in heavily pretreated CM supports a PFS endpoint
  - Enriched in PRAME+: DCR (58%), confirmed tumor reduction (32%), molecular response (42%) and mPFS (4.2mo)
  - These endpoints best capture brenetafusp benefit and are consistent across ImmTAC platform[1-3] (*2024 ASCO poster #9529*)
- T cell fitness signature associated with brenetafusp benefit and higher in earlier lines of therapy
  - This association emerging across ImmTAC platform and reported for other T cell therapies[4]
- Data support Ph3 brenetafusp + nivolumab in 1st line mCM (PRISM-MEL301; NCT06112314)

1. Nathan P, et al. N Engl J Med 2021;385:1196-206; 2. Hassel JC & Piperno-Neumann S, et al. N Engl J Med 2023; 389:2256-2266; 3. Carvajal RD, et al. Nat Med 2022; 28:2364-2373 4. Gattinoni, et al. Nature Rev Cancer 2012; 12:671-684; Kishton, et al. Curr Opin Imm 2022; 74:39-45; Mehta, et al. Front Immunol 2021; 12:780442; Arcangeli, et al. J Clin Invest 2022; 123:e150807; Rosenberg, et al. Clin Cancer Res 2011; 17:4550-4557

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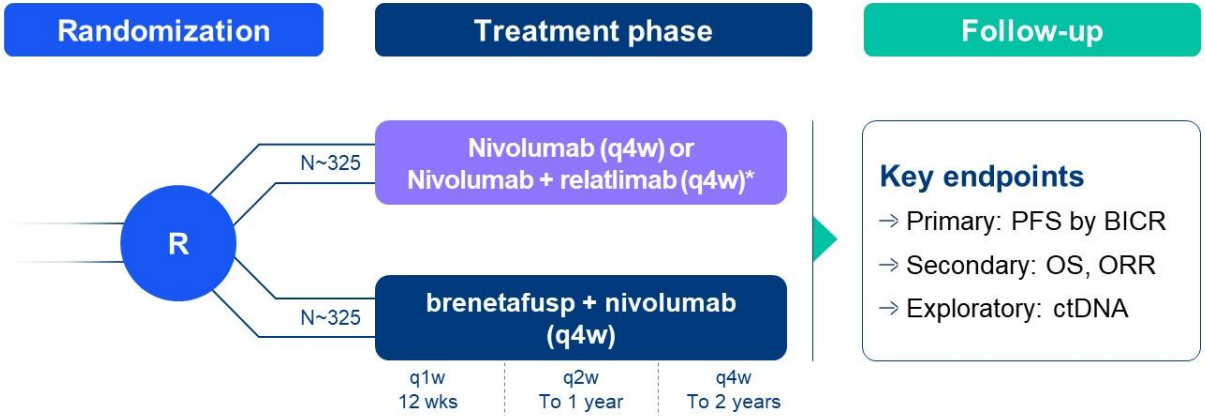
PRISM-MEL301: First-line advanced CM Phase 3



Initial randomization includes comparison of two brenetafusp regimens (~90 patients or 30/arm)

(PRISM-MEL301; NCT06112314); *see ASCO 2024 TiP poster #TPS9602*

*Use of nivolumab or nivolumab + relatlimab as control will be country specific

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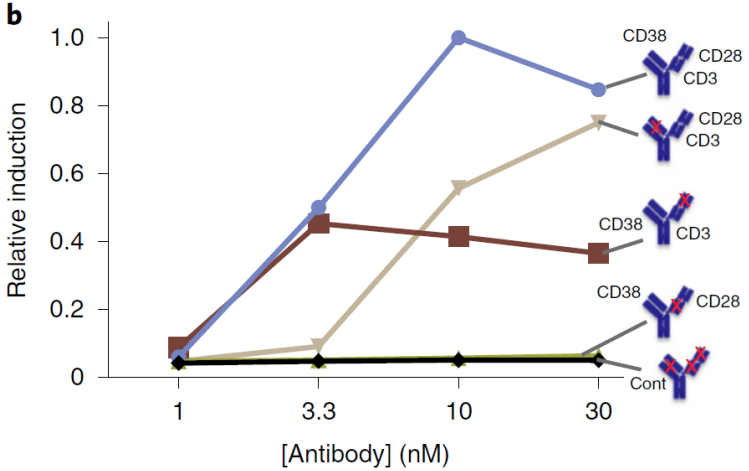
Future

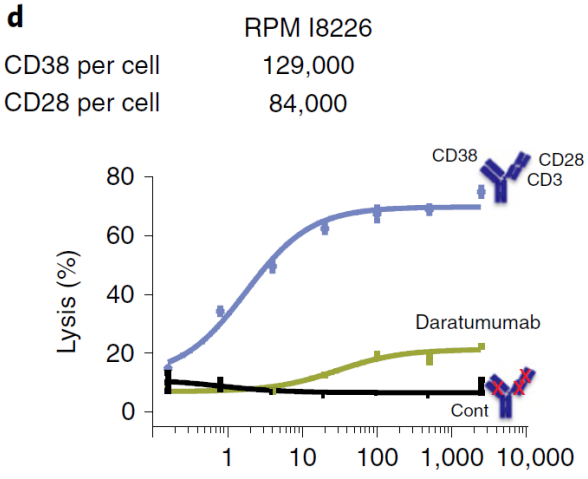
nature cancer

ARTICLES

https://doi.org/10.1038/s43018-019-0004-z

Trispecific antibodies enhance the therapeutic efficacy of tumor-directed T cells through T cell receptor co-stimulation





Trispecific antibodies enhance the therapeutic efficacy of tumor-directed T cells through T cell receptor co-stimulation. Lan Wu et al. Nature Cancer. Nov 2019

BsAbs START FJD (Feb 25)

Fármaco	Target
BNT142-01	CLDN6/CD3
BNT314-01	41BB/EpCam
BI 764532	DLL3/CD3
CLN-619	MICA/MICB-NKG2D
EGL-121	CTLA4-IL2
FS222	PDL1-41BB
GCT1078	B7H4/CD3
IMC-F106	PRAME/CD3 ImmTAC
IMC115	PRAME/CD3 ImmTAC HLE
IMC117	PIWIL/CD3 ImmTAC
INCA 33890	TGFb/PDL1
78278343PCR1001	KLK2/CD3
79032421STM1001	MSNL/CD3
LCB-2301	CEACAM5/CD3
LCB-2401	CEACAM5/CD47
MCLA129	EGFR/MET
R4018	MUC16/CD3
R5668	MUC16/CD28
R7075	EGFR/CD28
TAK-280	B7H3/CD3

Conclusion

- Bispecifics can provide a more robust immunogenic response via modulation of two different signaling pathways in the same cell or co-engaging two different cells expressing either antigens.
- T cell engagers show promising activity in solid tumors.
  - Ovary (MUC16)
- However, target expression is a hurdle (like CART for solid tumors)
- Fusion proteins with soluble TCRs (ImmTACs) have achieved the landmark of prolonging OS in a solid tumor (uveal melanoma)
  - PRAME (ovary, melanoma)
  - HLA selection and antigen selection are hurdles.

GRACIAS

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