XVII SIMPOSIUM
BASES BIOLÓGICAS DEL CÁNCER
E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

SALAMANCA, 22 Y 23 DE MAYO DE 2025

Cuando la precisión se duplica: la nueva era de los anticuerpos biespecíficos

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Anticuerpos biespecíficos

- ❑ INTRODUCCIÓN
- ❑ CLASIFICACIÓN
  - ❑ FUNCIONAL
  - ❑ ESTRUCTURAL
- ❑ HISTORIAS DE EXITO
- ❑ RETOS
  - ❑ BIOMARCADORES
  - ❑ VIA DE ADMINISTRACIÓN
  - ❑ DOSIFICACIÓN
  - ❑ TOXICIDAD
- ❑ CONCLUSIONES

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Anticuerpos biespecíficos: Introducción

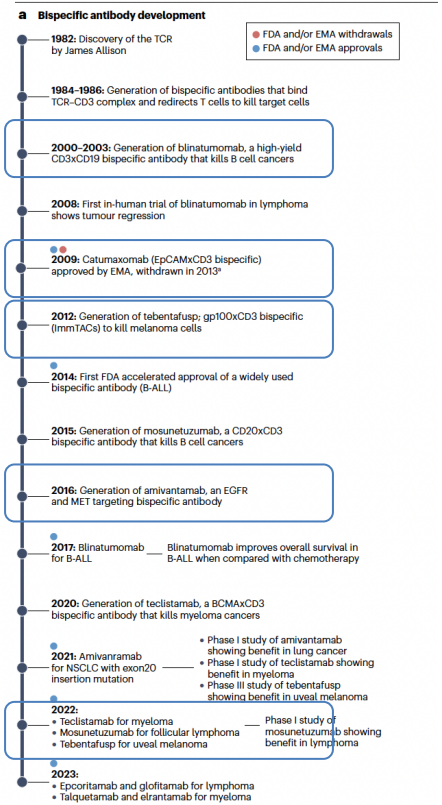

Table 1 | Approved bispecific antibodies for cancer therapy

bsAb	International non-proprietary name	Targets	MoA	Format	Year of first approval/ region[a]	Indications	Company
Removab	Catumaxomab	EpCAM×CD3ε	TDCC	Quadroma mouse/rat 1+1	2009 Withdrawn EU 2013	Ovarian ascites, intraperitoneal	Trion Pharma/ Fresenius
Blincyto	Blinatumomab	CD19×CD3ε	TDCC	BiTE 1+1	2014 United States/EU, Japan	ALL	Amgen
Rybrevant	Amivantamab	EGFR×MET	Signalling inhibition, ADCC	Duobody 1+1	2021 United States/EU	NSCLC EGFR exon 20 insert mutation	J&J
KIMMTRAK	Tebentafusp	gp100-HLA-A*02×CD3ε	TDCC	scFv-TCR fusion 1+1	2022 United States/EU	Uveal melanoma	Immunocore
Lunsumio	Mosunetuzumab	CD20×CD3ε	TDCC	KiH 1+1 IgG	2022 United States/EU	Relapsed/refractory follicular NHL	Roche group
Kaitanni	Cadonilimab	PD1×CTLA4	Dual checkpoint inhibition	IgG-scFv tetrabody 2+2	2022 China	Hepatocellular carcinoma	Akeso Bio
Tecvayli	Teclistamab	BCMA×CD3ε	TDCC	Duobody 1+1	2022 United States/EU	Relapsed/refractory multiple myeloma	J&J
Columvi	Glofitamab	CD20×CD3ε	TDCC	CrossMAb 2+1	2023 United States/EU	Relapsed/refractory DLBCL	Roche group
(T)Epkinly	Epcoritamab	CD20×CD3ε	TDCC	Duobody 1+1	2023 United States/EU, Japan	Relapsed/refractory DLBCL	Genmab, Abbvie
Talvey	Talquetamab	GPRC5D×CD3ε	TDCC	Duobody 1+1	2023 United States/EU	Relapsed/refractory multiple myeloma	J&J
Elrexfio	Elranatamab	BCMA×CD3ε	TDCC	bsAb 1+1	2023 United States/EU	Relapsed/refractory multiple myeloma	Pfizer

ADCC, antibody-dependent cellular cytotoxicity; ALL, acute lymphocytic leukaemia; BCMA, B cell maturation antigen; BiTE, bispecific T cell engager; bsAb, bispecific antibody; DLBCL,

Tarlatamab CD3-DLL3 BiTe. 2024

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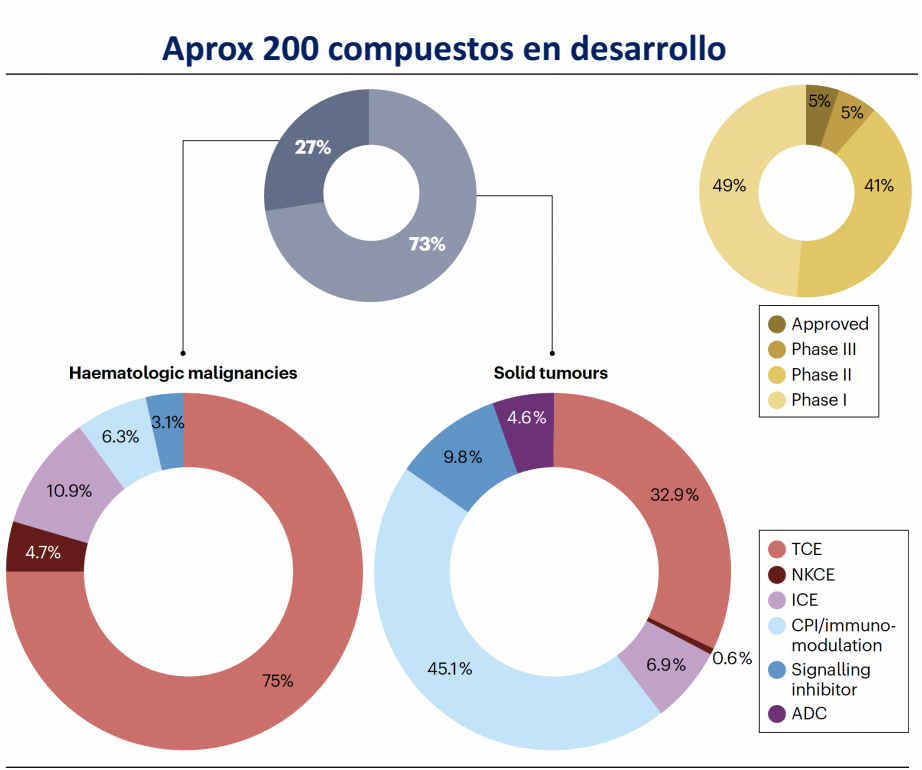
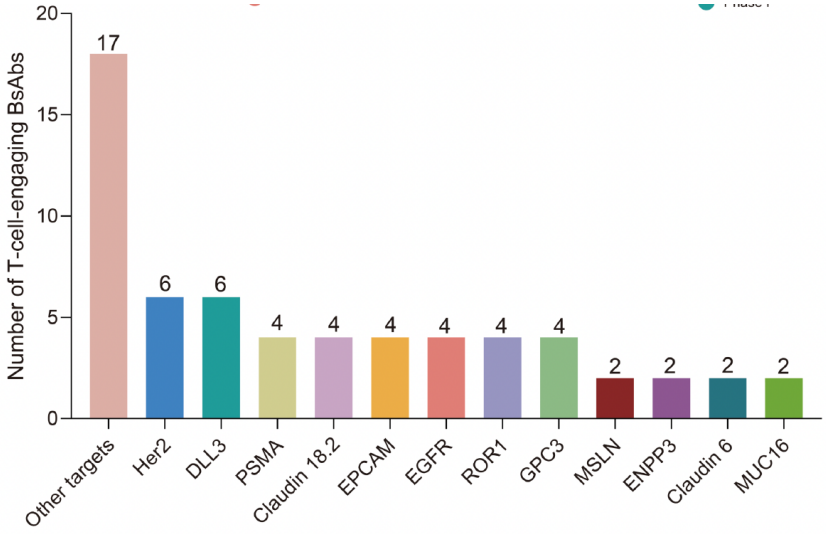


90% en EC fase I/II



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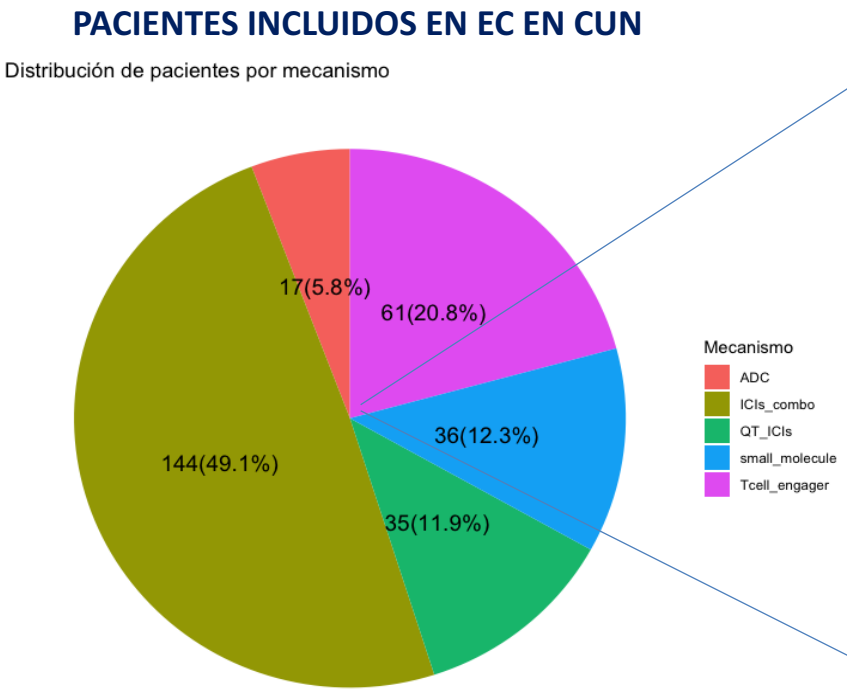
Anticuerpos biespecíficos: Introducción

PACIENTES INCLUIDOS EN EC EN CUN



ENSAYOS CLÍNICOS EN CUN

ENSAYO	MECANISMO	TIPO
BP43693	PDL1/LAG3	ICI-ICI
NP41300	PD1/LAG3	ICI-ICI
ARTEMIDE	PD1/TIGIT	ICI-ICI
D9570C0001	PD1/TIM3	ICI-ICI
FS222	PDL1/4-1BB	ICI-ICI
BI1463	FAP/4-1BB	ICI-ICI
GCT1046	PDL1/4-1BB	ICI-ICI
GCT1042	CD40/4-1BB	ICI-ICI
BNT314	EpCAM/4-1BB	ICI+TA
BP449956	LTBR-FAP	ICI+TA
BP41629	PD1/IL2v	ICI+Citocina
ANV600	PD1/IL2RB	ICI+Citocina
NM21-1480	PDL1/4-1BB/HAS	Tri
AFM24	CD16/EGFR	NKE
MCL-129	EGFR/MET	TAA-TAA
R4018	CD3-MUC16	TCE
IMC-F106	CD3-PRAME	TCE
AMX818	CD3-HER2	TCE
AMG509	CD3-STEAP1	TCE
AMX500	CD3-PSMA	TCE
GCT1078	CD3-B7H4	TCE
1438-001	CD3-DLL3	TCE
GO45296	CD3-CCR8	TCE

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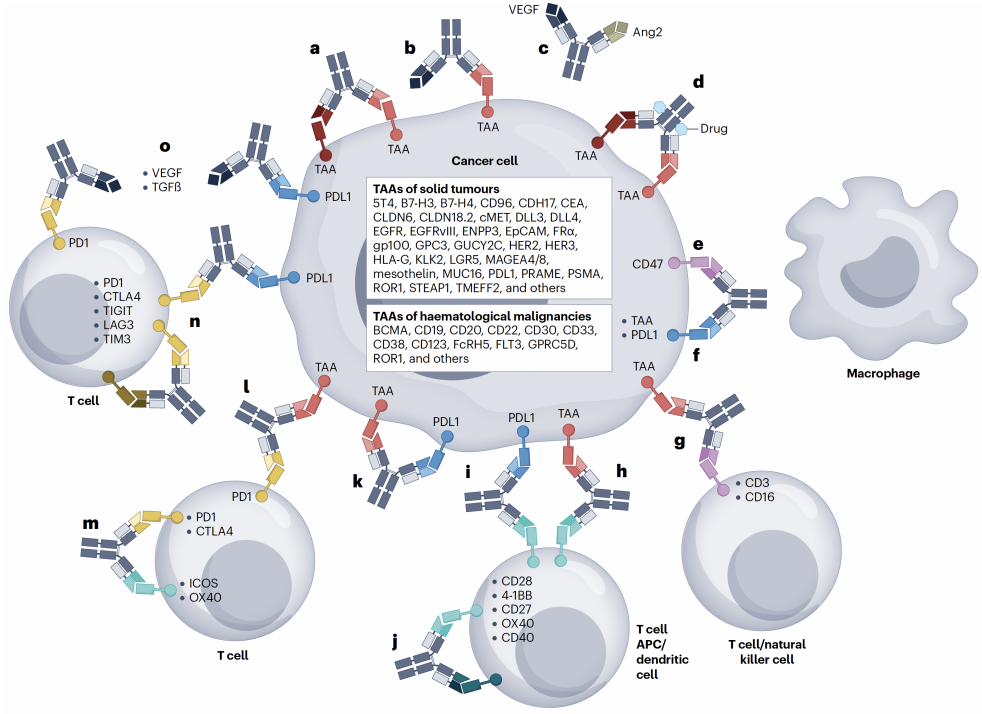
Anticuerpos biespecíficos: Clasificación

- Dual Immune-chekpoints blockade
  - Co-inhibitory
  - Co-stimulatory
- Oncogenic Pathway inhibition
- IMMUNE CELL ENGAGERS
  - T cell engagers
  - NK cell engagers
  - Innate cell engagers:
    - Macrophages
    - Fibroblasts



Klein et al. Nat rev Drug Disc 2024

Anticuerpos biespecíficos: Clasificación

- Dual Immune-chekpoints blockade
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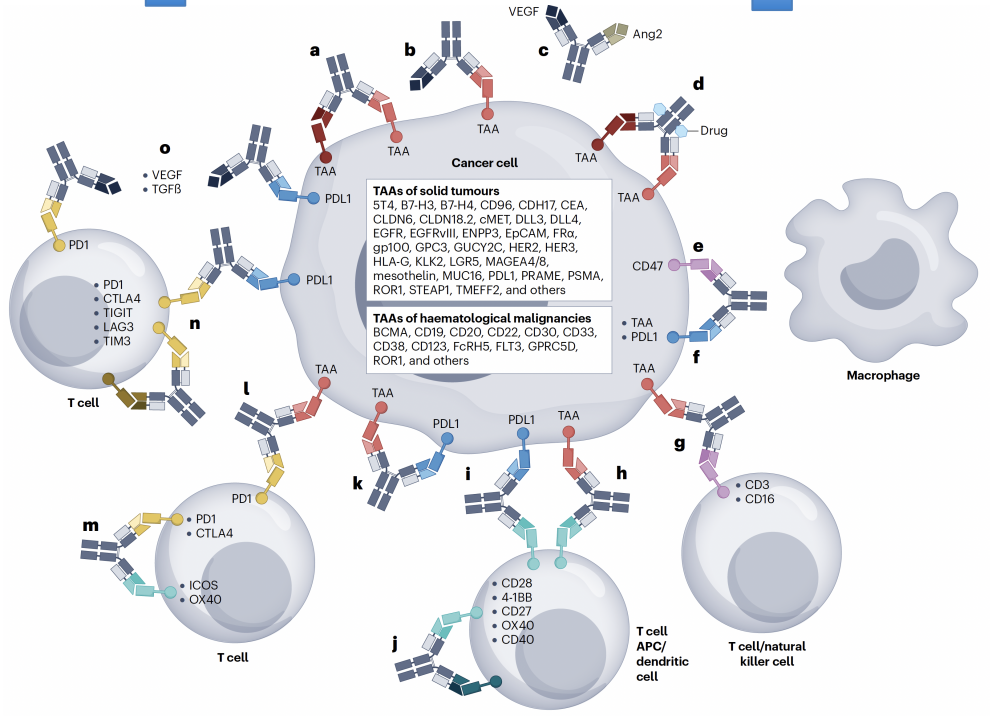

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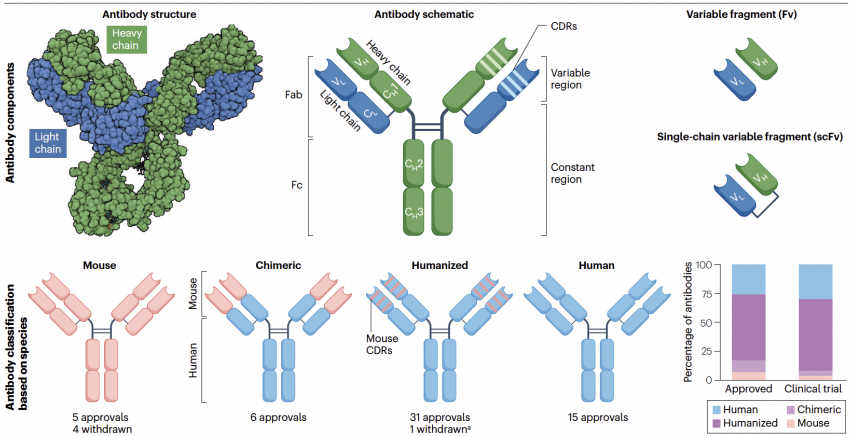
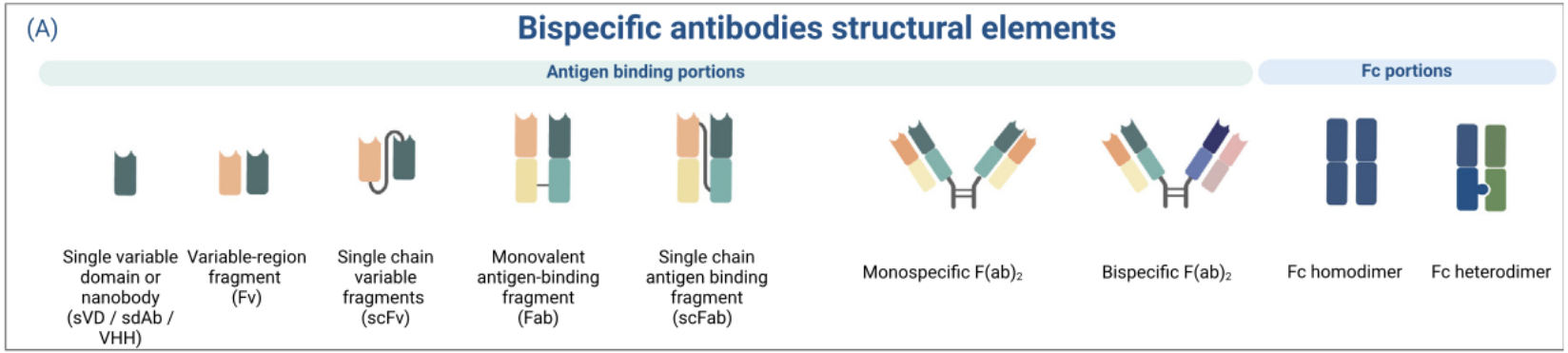
Anticuerpos biespecíficos: Clasificación





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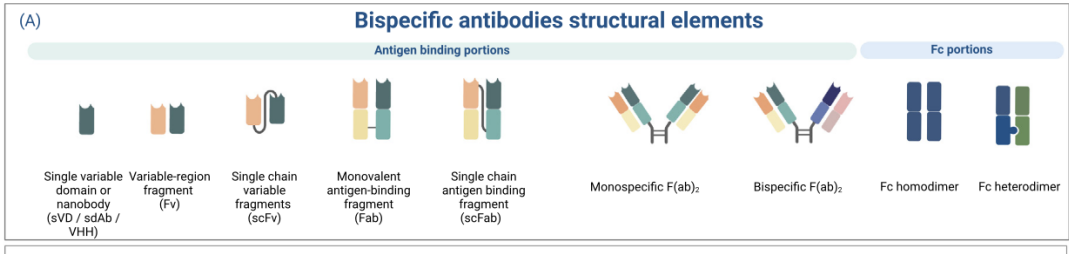
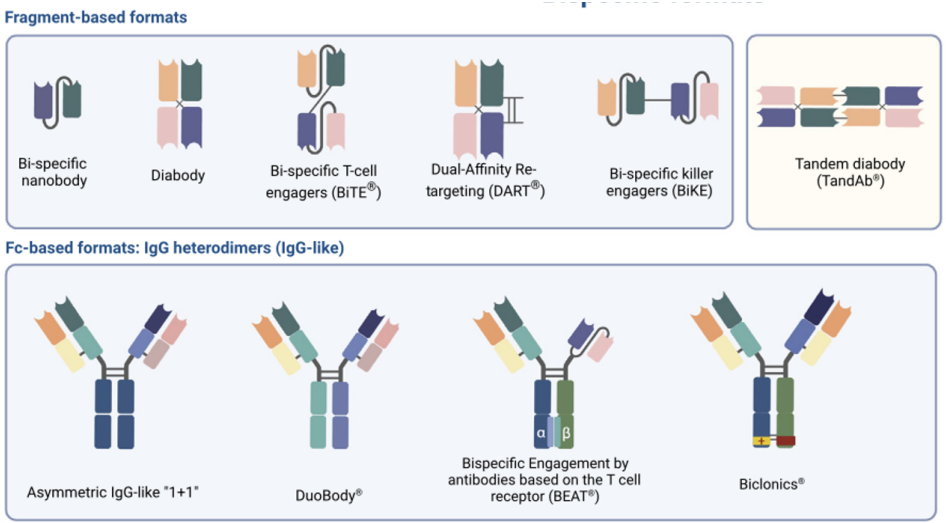
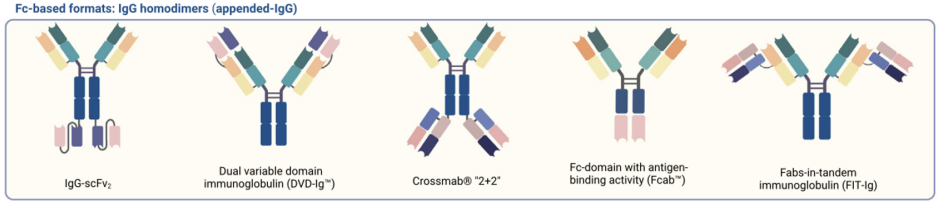
Herrera et al. Trends in Cancer. 2024

Anticuerpos biespecíficos: Clasificación







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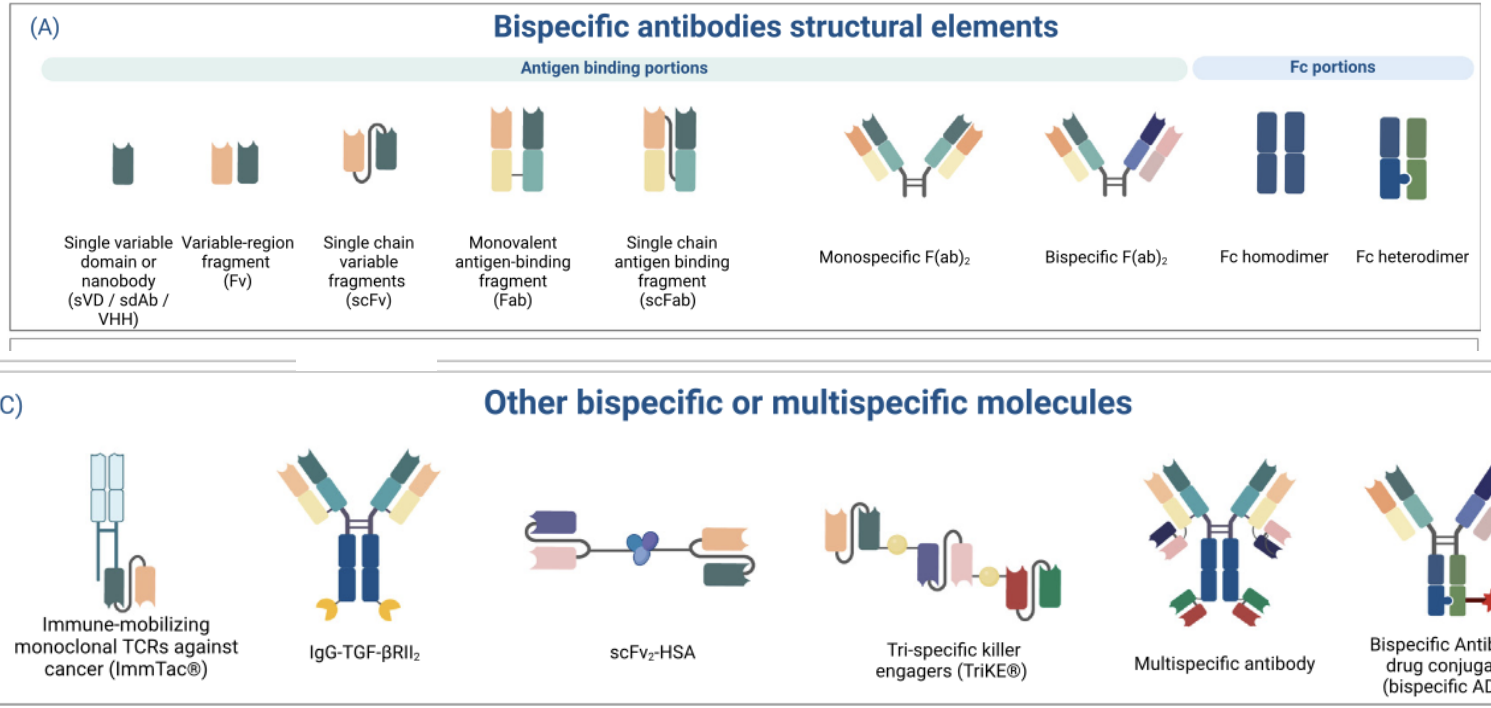

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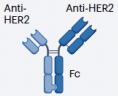
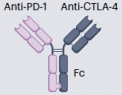
Anticuerpos biespecíficos: éxitos

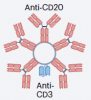
Table 2 (continued) | Bispecific antibodies approved or nearing approval by the FDA and EMA

Target	Antibody	Structure	Format	Major indications	Adverse effects
Receptor blockers					
EGFRxcMET	Amivantamab		IgG1 (half-life extension) Fc afucosylation (enhanced ADCC) K409R, F405L mutation (for Fab exchange) ~146 kDa	Lung cancer	Skin rash Stomatitis Muscle pain Cytopenia Electrolyte abnormality Embryo–fetal toxicity
Her2xHer2	Zanidatamab (in clinical trial)		Two anti-HER2 scFvs (bind two distinct HER2 epitopes) IgG1 (half-life extension) ~125 kDa	HER2⁺ cancers	Diarrhoea Infusion reaction Cardiac failure
PD1xCTLA4	Volrustomig MEDI5752 (in clinical trial)		IgG1 (half-life extension) L234F, L235E, P331S mutation (reduced FcγR binding) ~145 kDa (estimated)	Multiple solid tumours	Checkpoint inhibitor-associated irAEs: Diarrhoea Thyroid disorders Skin rash Hepatotoxicity

ADCC, antibody-dependent cellular cytotoxicity; ALL, acute lymphoblastic leukaemia; CRS, cytokine release syndrome; Ig, immunoglobulin; irAEs, immune-related adverse events; IV, intravenous; kDa, kilodalton; scFv, single-chain variable fragment; TLS, tumour lysis syndrome. Fc-bearing bispecific antibodies also carry Fc mutations that enable pairing of the heterogenous heavy chains (not shown).

Agent	Target	Indication and activity	Common grade ≥3 adverse events	Year of approval
Blinatumomab[77–80]	CD3×CD19	RR B-ALL: CR/CRh in 43–44%, mRFS 5.9 months, mOS 6.1–6.9 months	Neutropenia (37.8–41%), infection (34.1%), elevated circulating liver enzymes (6–12.7%), neurological events (9.4–11%), CRS (4.9%)	2014[a], 2017 (FDA); 2015[a], 2018 (EMA), 2020 (NMPA) Subsequently, expanded to include patients with MRD⁺ B-ALL
Mosunetuzumab[68]	CD3×CD20	RR FL: CRR 60%, ORR 80%, mPFS 17.9 months, mOS NR	Neutropenia or reduced neutrophil count (26%), hypophosphataemia (17%), anaemia (8%), increased serum ALT (5%), CRS (2%)	2022[a] (EMA), 2022[a] (FDA)
Tebentafusp[240,247]	CD3×gp100–HLA-A*02:01	HLA-A*02:01-positive uveal melanoma: ORR 11%, mPFS 3.4 months, mOS 21.6 months	Rash (19%), elevated circulating liver enzymes (10%), pyrexia (5%), pruritus (5%), CRS (1%)	2022 (FDA), 2022 (EMA)
Teclistamab[115,117]	CD3×BCMA	RR MM: CRR 39.4%, ORR 63%, mPFS 11.3 months, mOS 18.3 months	Neutropenia (64.2%), anaemia (37.0%), lymphopenia (32.7%), thrombocytopenia (21.2%), CRS (0.6%)	2022[a] (FDA), 2022[a] (EMA)
Glofitamab[81]	CD3×CD20	RR DLBCL: CRR 39%, ORR 52%, mPFS 4.9 months, mOS 12 months	Neutropenia (27%), thrombocytopenia (6%), anaemia (6%), CRS (4%)	2023[a] (FDA), 2023[a] (EMA), 2023[a] (NMPA)
Amivantamab[196–200]	EGFR×MET	Advanced-stage NSCLC harbouring *EGFR* exon 20 insertion mutations (in combination with chemotherapy): ORR 73%, mPFS 11.4 months, mOS NR	Neutropenia (33%), rash (11%), leukopenia (11%), anaemia (11%), thrombocytopenia (10%)	2021[a] (FDA)
Epcoritamab[84]	CD3×CD20	RR DLBCL: CRR 38.9%, mPFS 4.4 months, mOS NR	Neutropenia (14.6%), anaemia (10.2%), thrombocytopenia (5.7%), CRS (2.5%)	2023[a] (FDA) 2023[a] (EMA)
Elranatamab[118–120]	CD3×BCMA	RR MM: ORR 61%, estimated 15-month PFS 50.9%, estimated 15-month OS 56.7%	Neutropenia (48.8%), anaemia (37.4%), lymphopenia (25.2%), thrombocytopenia (23.8%)	2023[a] (FDA), 2024[a] (EMA)
Cadonilimab[188]	PD-1×CTLA4	Advanced-stage cervical cancer: ORR 32.3%, mPFS 3.7 months, mOS NR	Anaemia (5%), reduced appetite (4%), dyspnoea (2%)	2022 (NMPA)
Talquetamab[197]	GPRC5D×CD3	RR MM: ORR 72%, mDOR 9.5 months, mPFS NR	Lymphopenia (47%), anaemia (33%), neutropenia (26%), leukopenia (16%)	2023[a] (FDA)
Tarlatamab[181,182]	CD3 x DLL3	RR SCLC: ORR 40%, mDOR 9.7 months, mPFS 4.9 months	CRS (26%), neutropenia (8%)	2024[a] (FDA)

Table 2 | Bispecific antibodies approved or nearing approval by the FDA and EMA

Target	Antibody	Structure	Format	Major indications	Adverse effects
T cell engagers					
CD19xCD3	Blinatumomab		Lacks Fc (short half-life ~2 h) ~54 kDa	B cell precursor ALL	CRS Neurotoxicity Infection Cytopenia TLS
CD20xCD3	Mosunetuzumab		IgG1 Fc (half-life extension) N297G mutation (aglycosylation and reduced ADCC) ~146 kDa	Lymphoma	CRS Neurotoxicity Infection Cytopenia Embryo–fetal toxicity
	Epcoritamab		IgG1 Fc (half-life extension) L234F, L235E, D265A mutation (reduced ADCC) ~146 kDa	Lymphoma	CRS Neurotoxicity Infection Cytopenia TLS
	Glofitamab		Two anti-CD20 scFvs linked with one anti-CD3 scFv IgG1 Fc (half-life extension) P329G, L234A, L235A mutation (reduced ADCC) ~194 kDa	Lymphoma	CRS Neurotoxicity Infection Cytopenia
	Imvotamab (in clinical trial)		IgM pentamer (ten CD20-binding sites) Albumin fusion (half-life extension) ~960 kDa	Lymphoma	CRS Cytopenia Hypophosphatemia
BCMAxCD3	Teclistamab		IgG4 Fc (half-life extension) S228P (hinge stabilization), and F234A and L235A mutation (reduced FcγR binding) ~143 kDa	Multiple myeloma	CRS Neurotoxicity Infection Cytopenia Hepatotoxicity Embryo–fetal toxicity
	Elranatamab		IgG2 Fc (half-life extension) ~145 kDa	Multiple myeloma	CRS Neurotoxicity Cytopenia
GPRC5DxCD3	Talquetamab		IgG4 Fc (half-life extension) S228P (hinge stabilization), and F234A and L235A mutation (reduced FcγR binding) ~147 kDa	Multiple myeloma	CRS Neurotoxicity Cytopenia Skin rash Hepatotoxicity Embryo–fetal toxicity
GP100xCD3	Tebentafusp		Lacks Fc, MW above renal filtration cut-off (half-life 6–8 h) ~75–77 kDa	Melanoma	CRS Skin rash Hepatotoxicity Embryo–fetal toxicity

Suman Paul et al. Cancer therapy with anibodies. Nat Rev cancer 2024

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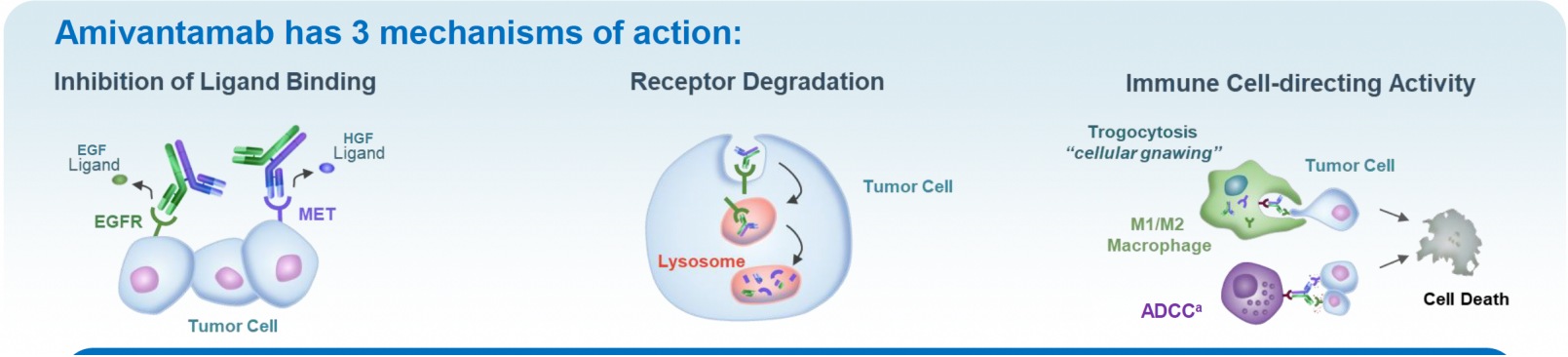
Anticuerpos biespecíficos: Oncogenic pathways



- in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations.
- in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.
- as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

Anticuerpos biespecíficos: Oncogenic pathways

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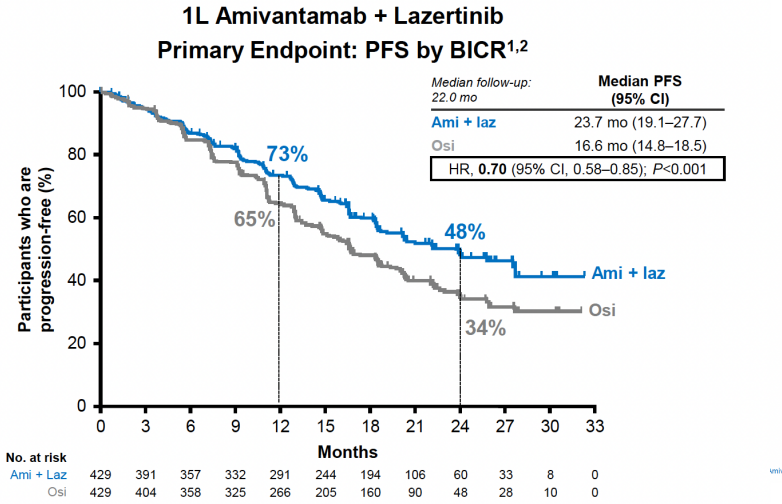
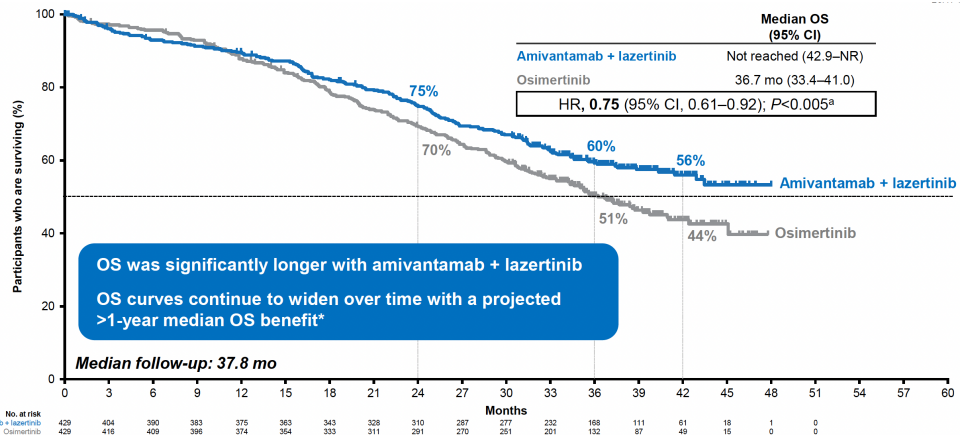
Amivantamab Plus Lazertinib vs Osimertinib in First-line *EGFR*-mutant Advanced NSCLC

Final Overall Survival from the Phase 3 MARIPOSA Study

James Chih-Hsin Yang[1], Yu Jung Kim[2], Se-Hoon Lee[3], Baogang Liu[4], Yurii Ostapenko[5], Shun Lu[6], Adlinda Alip[7], Ernesto Korbenfeld[8], Josiane Mourão Dias[9], Pongwut Danchaivijitr[10], Nicolas Girard[11], Enriqueta Felip[12], Hidetoshi Hayashi[13], Alexander I Spira[14], Benjamin Besse[15], Tao Sun[16], Mariah Ennis[17], Seema Sethi[17], Joshua M Bauml[17], Byoung Chul Cho[18]





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AEs by preferred term (≥20% of participants in either group)	Amivantamab + lazertinib (n=421)		Osimertinib (n=428)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Related to EGFR inhibition				
Paronychia	291 (69)	49 (12)	127 (30)	2 (<1)
Rash	271 (64)	73 (17)	136 (32)	3 (<1)
Diarrhea	133 (32)	9 (2)	200 (47)	4 (<1)
Dermatitis acneiform	127 (30)	37 (9)	55 (13)	0
Stomatitis	126 (30)	5 (1)	92 (21)	1 (<1)
Pruritus	107 (25)	2 (<1)	75 (18)	1 (<1)
Related to MET inhibition				
Hypoalbuminemia	216 (51)	26 (6)	29 (7)	0
Peripheral edema	162 (38)	8 (2)	29 (7)	1 (<1)
Other				
Infusion-related reaction	275 (65)	27 (6)	0	0
ALT increased	170 (40)	28 (7)	66 (15)	8 (2)
AST increased	139 (33)	15 (4)	68 (16)	6 (1)
Constipation	130 (31)	0	70 (16)	0
COVID-19	125 (30)	8 (2)	112 (26)	9 (2)
Anemia	114 (27)	20 (5)	112 (26)	10 (2)
Decreased appetite	114 (27)	4 (1)	84 (20)	7 (2)
Nausea	99 (24)	5 (1)	65 (15)	1 (<1)
Hypocalcemia	96 (23)	11 (3)	37 (9)	0
Asthenia	84 (20)	13 (3)	54 (13)	7 (2)
Muscle spasms	84 (20)	3 (<1)	36 (8)	0
Thrombocytopenia	74 (18)	4 (1)	92 (21)	6 (1)

Begin Amivantamab + Lazertinib

IRR Prophylactic Regimen (SKIPPirr)[1]

2 Days to 1 hour before start
Oral 8-mg dexamethasone BID 2 days and 1 day prior and 8-mg 1 hour before first infusion[a]

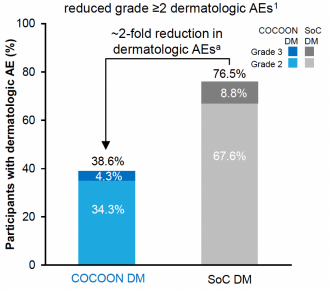
VTE Prophylactic Regimen (PALOMA-2, PALOMA-3)[2,3]

First 4 months
Oral anticoagulants as per NCCN or local guidelines

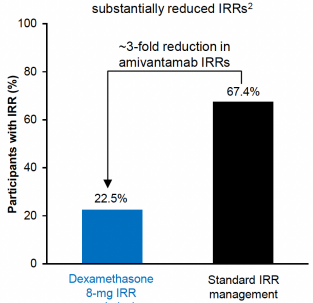
Dermatologic Prophylactic Regimen (COCOON)[b]

Antibiotic prophylaxis	**Weeks 1–12** 100-mg BID doxycycline or minocycline	**Weeks 13+** 1% Topical clindamycin lotion on the scalp daily
Nail cleaning agent	**Weeks 1+** 4% Chlorhexidine on the fingernails and toenails daily for 12 months	
Long-acting skin hydration	**Weeks 1+** Ceramide-based moisturizer at least daily for 12 months[c]	

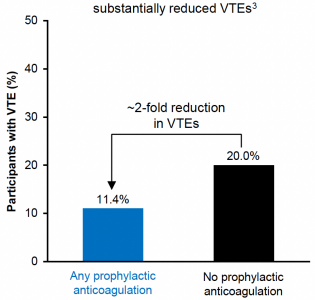
COCOON DM regimen substantially reduced grade ≥2 dermatologic AEs[1]



SKIPPirr regimen substantially reduced IRRs[2]



Prophylactic anticoagulation substantially reduced VTEs[3]



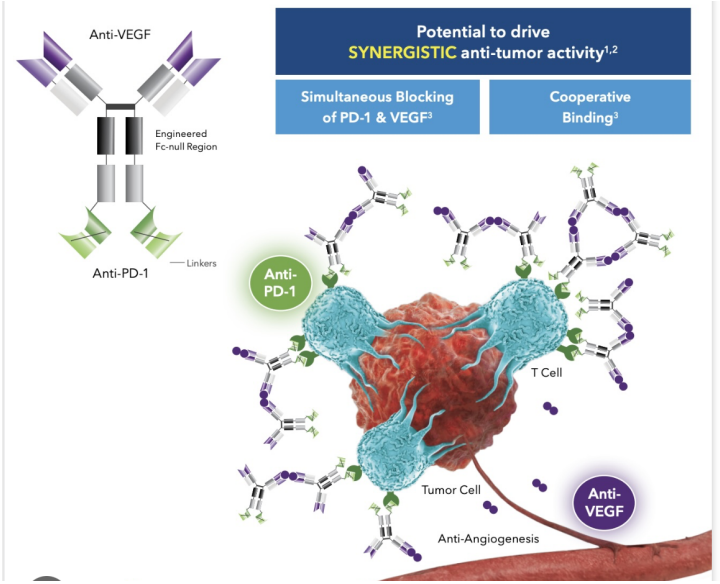
COCOON

Data from COCOON will be presented on Thursday, 27 March 2025 at 16:50–16:55 CET

Anticuerpos biespecíficos: Oncogenic pathways + ICIs

Ivonescimab versus pembrolizumab for PD-L1-positive non-small cell lung cancer (HARMONi-2): a randomised, double-blind, phase 3 study in China

Anwen Xiong, Lei Wang*, Jianhua Chen*, Lin Wu*, Baogang Liu, Jun Yao, Hua Zhong, Jie Li, Ying Cheng, Yulan Sun, Hui Ge, Jifang Yao, Qin Shi, Ming Zhou, Bolin Chen, Zhengxiang Han, Jinliang Wang, Qing Bu, Yanqiu Zhao, Junqiang Chen, Ligong Nie, Gaofeng Li, Xingya Li, Xinmin Yu, Yinghua Ji, Daqiang Sun, Xiaohong Ai, Qian Chu, Yu Lin, Jiqing Hao, Dingzhi Huang, Chengzhi Zhou, Jinlu Shan, Hongzhong Yang, Xuewen Liu, Jing Wang, Yanhong Shang, Xiaodong Mei, Jie Yang, Dongmei Lu, Mingxiu Hu, Zhongmin Maxwell Wang, Baiyong Li, Michelle Xia, Caicun Zhou*



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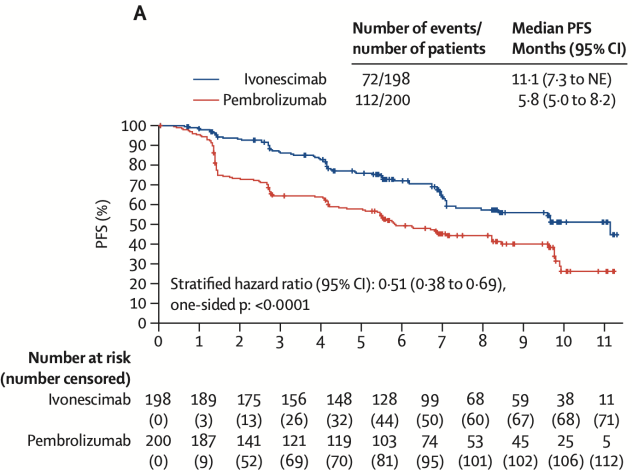
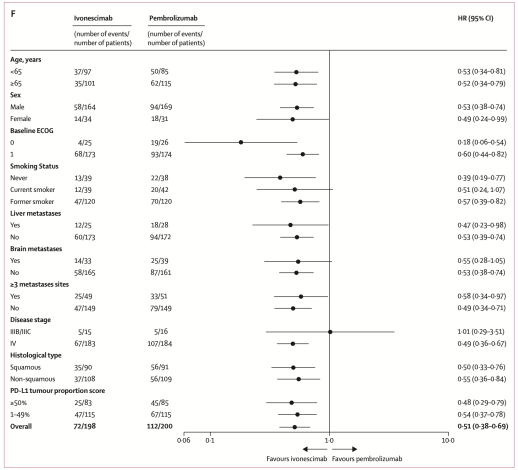
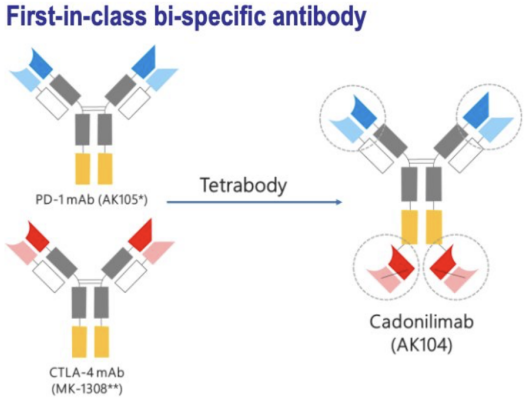




	Ivonescimab (n=197)		Pembrolizumab (n=199)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-related adverse events in ≥10% of patients*				
Proteinuria	62 (32%)	6 (3%)	20 (10%)	0
Aspartate aminotransferase increased	39 (20%)	1 (1%)	31 (16%)	0
Hypercholesterolemia	32 (16%)	0	20 (10%)	0
Blood bilirubin increased	31 (16%)	2 (1%)	23 (12%)	1 (1%)
Hypertension	31 (16%)	10 (5%)	5 (3%)	1 (1%)
Alanine aminotransferase increased	29 (15%)	1 (1%)	24 (12%)	1 (1%)
Hypothyroidism	28 (14%)	0	19 (10%)	0
Anaemia	26 (13%)	3 (2%)	29 (15%)	1 (1%)
Hypoalbuminemia	23 (12%)	1 (1%)	22 (11%)	0
Amylase increased	22 (11%)	3 (2%)	6 (3%)	0
Hyperglycaemia	22 (11%)	1 (1%)	23 (12%)	2 (1%)
Blood uric acid increased	21 (11%)	0	16 (8%)	0
Hypertriglyceridemia	20 (10%)	4 (2%)	14 (7%)	1 (1%)
Arrhythmia	20 (10%)	0	21 (11%)	0
Rash	15 (8%)	1 (1%)	28 (14%)	0
Immune-related adverse event in ≥2% of patients				
Any	59 (30%)	14 (7%)	56 (28%)	16 (8%)
Hypothyroidism	18 (9%)	0	12 (6%)	0
Hyperthyroidism	12 (6%)	0	13 (7%)	0
Blood thyroid-stimulating hormone increased	4 (2%)	0	3 (2%)	0
Immune-mediated lung disease	5 (3%)	2 (1%)	8 (4%)	3 (2%)
Hyperglycaemia and type-1 diabetes	4 (2%)	2 (1%)	3 (2%)	1 (1%)
Rash	3 (2%)	0	6 (3%)	0
Hepatic function abnormal	3 (2%)	3 (2%)	4 (2%)	3 (2%)
Adrenal insufficiency	2 (1%)	0	5 (3%)	2 (1%)
Possible VEGF-related adverse events				
Any	94 (48%)	20 (10%)	42(21%)	2 (1%)
Proteinuria	62 (31%)	6 (3%)	20 (10%)	0
Hypertension	31 (16%)	10 (5%)	5 (3%)	1 (1%)
Haemorrhage†	29 (15%)	2 (1%)	22 (11%)	1 (1%)
Arterial thromboembolism	2 (1%)	2 (1%)	1 (1%)	0
Venous thromboembolism	0	0	1 (1%)	0

Anticuerpos biespecíficos: Immune-modulation



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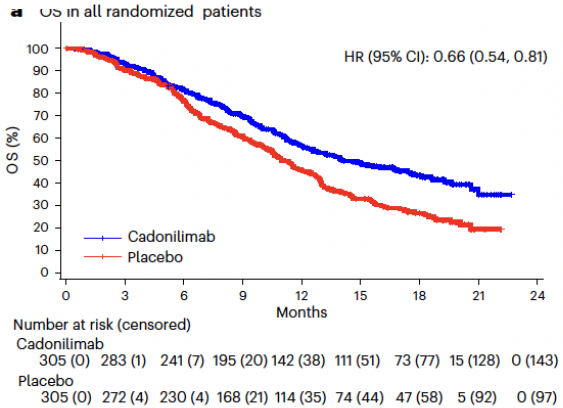
Article | Published: 22 January 2025

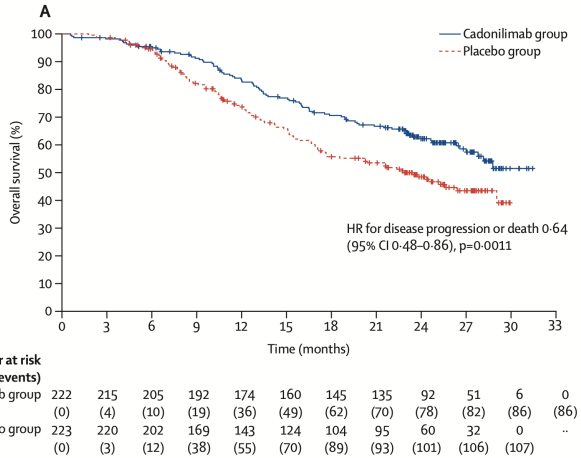
First-line cadonilimab plus chemotherapy in HER2 negative advanced gastric or gastroesophageal junction adenocarcinoma: a randomized, double-blind, phase 3 trial

Lin Shen, Yanqiao Zhang, Ziyu Li, Xiaotian Zhang, Xiangyu Gao, Bo Liu, Yusheng Wang, Yi Ba, Ruixing Zhang, Jingdong Zhang, Ye Chen, Jian Chen, Mingzhu Huang, Yang Fu, Mulin Liu, Zheng Liu, Jun Zhao, Wei Li, Jia Wei, Changzheng Li, Nong Xu, Zengqing Guo, Bangwei Cao, ... Jiafu Ji

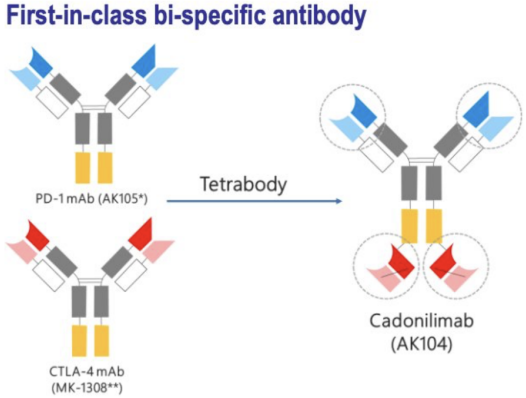


Cadonilimab plus platinum-based chemotherapy with or without bevacizumab as first-line treatment for persistent, recurrent, or metastatic cervical cancer (COMPASSION-16): a randomised, double-blind, placebo-controlled phase 3 trial in China

Xiaohua Wu, Yang Sun, Hongying Yang, Jing Wang, Hanmei Lou, Dan Li, Ke Wang, Hui Zhang, Tao Wu, Yuzhi Li, Chunyan Wang, Guiling Li, Yifeng Wang, Dapeng Li, Ying Tang, Mei Pan, Hongyi Cai, Weihu Wang, Bing Yang, Hua Qian, Qiuhong Tian, Desheng Yao, Ying Cheng, Bing Wei, Xiumin Li, Tao Wang, Min Hao, Xiaohong Wang, Tiejun Wang, Juntao Ran, Hong Zhu, Lijing Zhu, Xianling Liu, Yunxia Li, Lihong Chen, Qingshan Li, Xiaojian Yan, Fei Wang, Hongbing Cai, Yunyan Zhang, Zhiqing Liang, Funan Liu, Yi Huang, Bairong Xia, Pengpeng Qu, Genhai Zhu, Youguo Chen, Kun Song, Meili Sun, Zhengzheng Chen, Qiang Zhou, Lina Hu, Guzhalinuer Abulizi, Hongyan Guo, Sihai Liao, Yijing Ye, Ping Yan, Qiu Tang, Guoping Sun, Ting Liu, Dongmei Lu, Mingxiu Hu, Zhongmin M Wang, Baiyong Li, Michelle Xia



Anticuerpos biespecíficos: T cell engagers (Bite)



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OS (%)

Table 2 | Adverse events related to the trial regimen

	Cadonilimab group (*n*=305)		Placebo group (*n*=304)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	302 (99.0)	201 (65.9)	296 (97.4)	163 (53.6)
Serious adverse event	117 (38.4)	93 (30.5)	78 (25.7)	66 (21.7)
Adverse event leading to discontinuation	73 (23.9)	47 (15.4)	20 (6.6)	16 (5.3)
Adverse event leading to death	5 (1.6)	5 (1.6)	7 (2.3)	7 (2.3)
Cadonilimab- and placebo-related deaths	5 (1.6)	5 (1.6)	5 (1.6)	5 (1.6)
Adverse events with an incidence of ≥10% in either group				

Cadonilimab plus platinum-based chemotherapy with or without bevacizumab as first-line treatment for persistent, recurrent, or metastatic cervical cancer (COMPASSION-16): a randomised, double-blind, placebo-controlled phase 3 trial in China

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	Cadonilimab (n=226)*		Placebo (n=219)	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Any treatment-emergent adverse events	225 (>99%)	193 (85%)	219 (100%)	176 (80%)
Anaemia	154 (68%)	38 (17%)	163 (74%)	56 (26%)
White blood cell count decreased	151 (67%)	64 (28%)	162 (74%)	79 (36%)
Neutrophil count decreased	137 (61%)	92 (41%)	144 (66%)	101 (46%)
Nausea	99 (44%)	0	90 (41%)	0
Platelet count decreased	93 (41%)	32 (14%)	89 (41%)	27 (12%)
Alopecia	90 (40%)	0	83 (38%)	0
Vomiting	90 (40%)	2 (1%)	66 (30%)	2 (1%)
Hypothyroidism	75 (33%)	2 (1%)	27 (12%)	0
Decreased appetite	72 (32%)	2 (1%)	50 (23%)	0
Urinary tract infection	66 (29%)	13 (6%)	56 (26%)	11 (5%)
Hypoesthesia	60 (27%)	2 (1%)	55 (25%)	2 (1%)
COVID-19	60 (27%)	3 (1%)	47 (21%)	0
Alanine aminotransferase increased	59 (26%)	3 (1%)	41 (19%)	2 (1%)
Aspartate aminotransferase increased	59 (26%)	5 (2%)	38 (17%)	2 (1%)
Weight decreased	59 (26%)	5 (2%)	36 (16%)	2 (1%)
Proteinuria	58 (26%)	6 (3%)	47 (21%)	5 (2%)
Rash	56 (25%)	7 (3%)	16 (7%)	1 (<1%)
Constipation	51 (23%)	0	44 (20%)	0
Hypokalaemia	47 (21%)	14 (6%)	38 (17%)	10 (5%)
Pyrexia	47 (21%)	1 (<1%)	24 (11%)	0
Diarrhoea	45 (20%)	5 (2%)	44 (20%)	3 (1%)

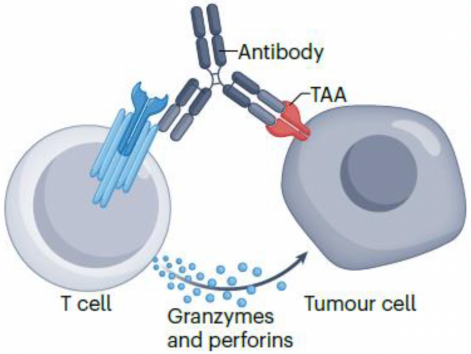
Anticuerpos biespecíficos: T cell engagers (Bite)

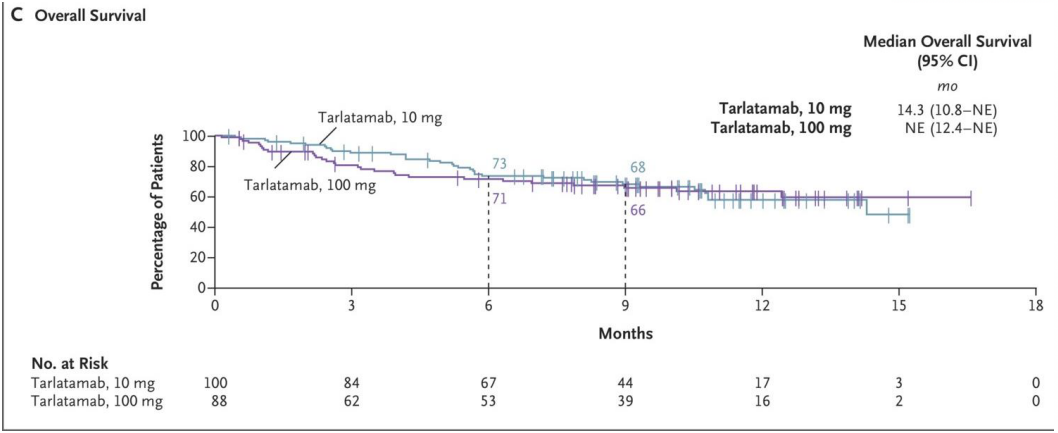
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

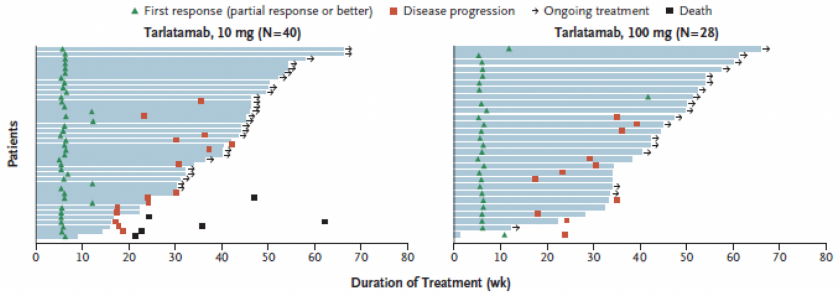
Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer

M.-J. Ahn, B.C. Cho, E. Felip, I. Korantzis, K. Ohashi, M. Majem, O. Juan-Vidal, S. Handzhiev, H. Izumi, J.-S. Lee, R. Dziadziuszko, J. Wolf, F. Blackhall, M. Reck, J. Bustamante Alvarez, H.-D. Hummel, A.-M.C. Dingemans, J. Sands, H. Akamatsu, T.K. Owonikoko, S.S. Ramalingam, H. Borghaei, M.L. Johnson, S. Huang, S. Mukherjee, M. Minocha, T. Jiang, P. Martinez, E.S. Anderson, and L. Paz-Ares, for the DeLLphi-301 Investigators*





Variable	Tarlatamab, 10 mg (N=100)	Tarlatamab, 100 mg (N=88)
Best overall response — no. (%)		
Objective response		
Confirmed complete response	1 (1)	7 (8)
Confirmed partial response	39 (39)	21 (24)



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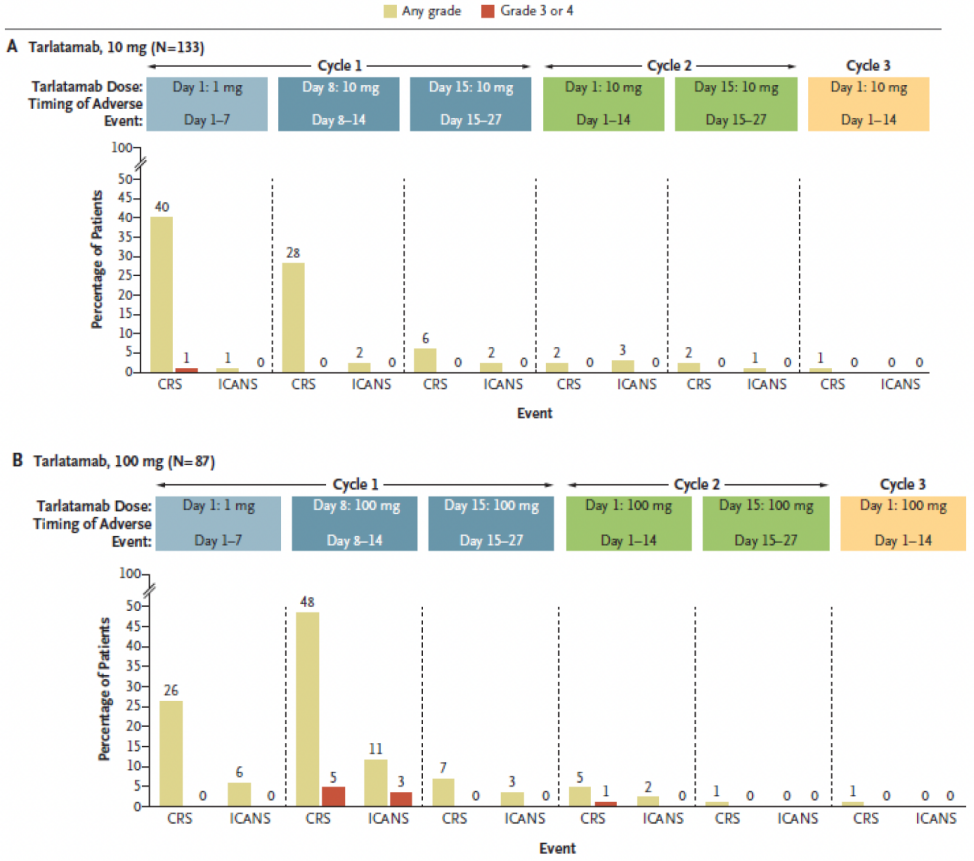
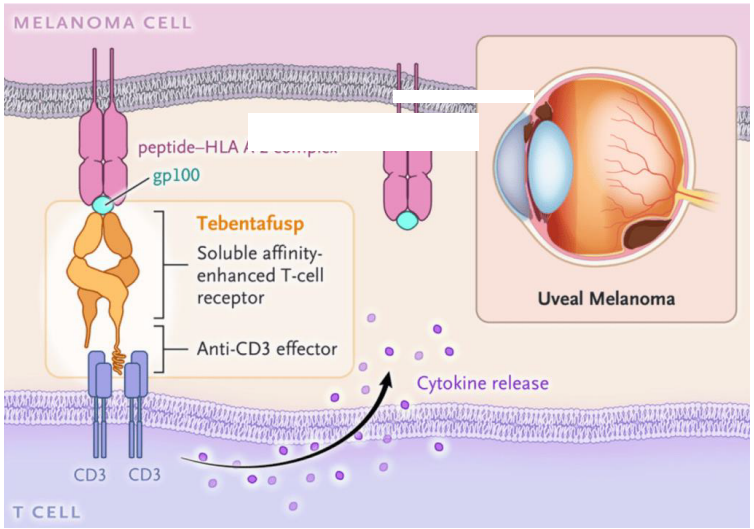


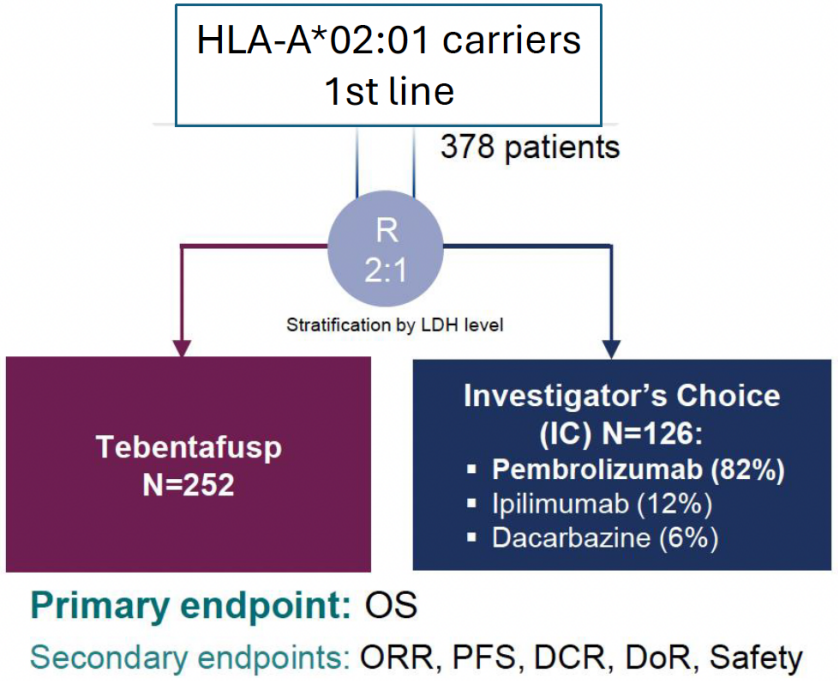
Anticuerpos biespecíficos: T cell engagers (ImmTac)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Three-Year Overall Survival with Tebentafusp in Metastatic Uveal Melanoma





Hassel, N Engl J Med 2023

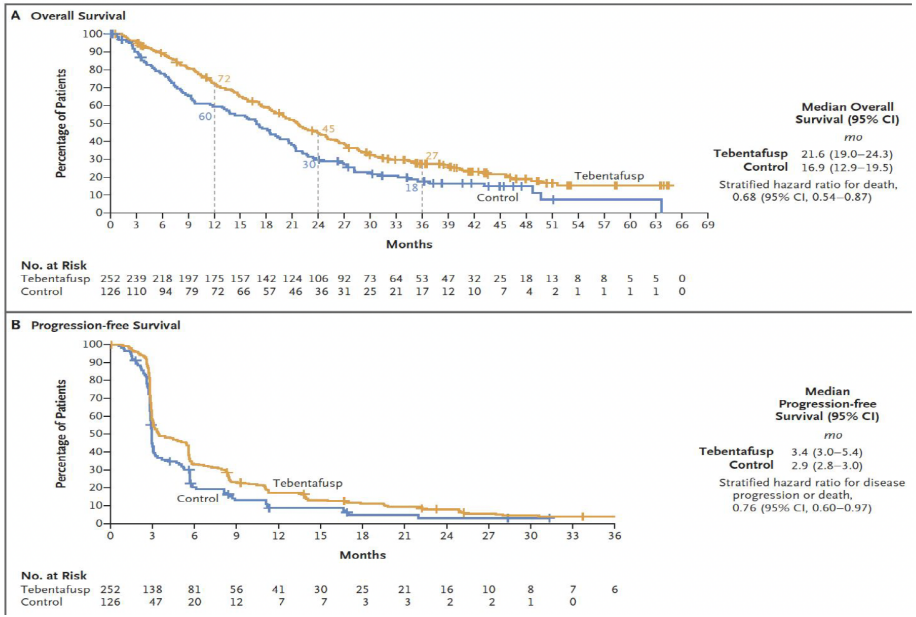
Anticuerpos biespecíficos: T cell engagers (ImmTac)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Three-Year Overall Survival with Tebentafusp in Metastatic Uveal Melanoma

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)



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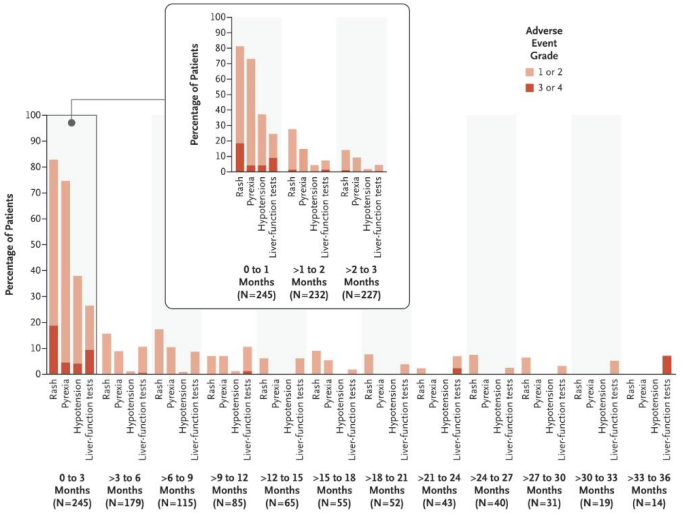
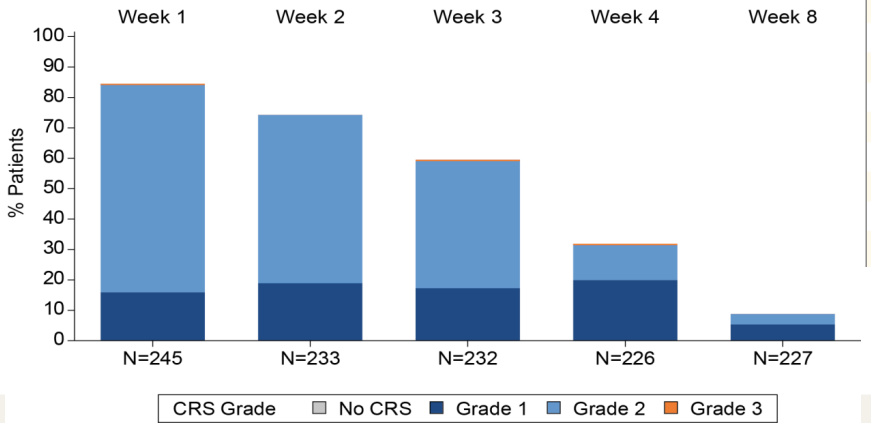
Anticuerpos biespecíficos: T cell engagers (ImmTac)





Event	Tebentafusp Group (N=245)		Control Group (N=111)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any treatment-related adverse event	243 (99)	109 (44)	91 (82)	19 (17)
Cytokine release syndrome†	217 (89)	2 (1)	3 (3)	0
Rash‡	203 (83)	45 (18)	27 (24)	0
Pyrexia	185 (76)	9 (4)	3 (3)	0
Pruritus	169 (69)	11 (4)	23 (21)	0
Chills	114 (47)	1 (<1)	3 (3)	0
Nausea	105 (43)	2 (1)	21 (19)	0
Fatigue	101 (41)	7 (3)	29 (26)	1 (1)
Hypotension	93 (38)	8 (3)	0	0
Dry skin	72 (29)	0	4 (4)	0
Vomiting	64 (26)	1 (<1)	7 (6)	0
Erythema	56 (23)	0	1 (1)	0
Headache	53 (22)	1 (<1)	3 (3)	1 (1)
Aspartate aminotransferase increased	47 (19)	11 (4)	9 (8)	0
Alanine aminotransferase increased	43 (18)	7 (3)	8 (7)	2 (2)
Lipase increased	32 (13)	9 (4)	7 (6)	6 (5)
Diarrhea	31 (13)	2 (1)	16 (14)	3 (3)
Lymphopenia	22 (9)	6 (2)	2 (2)	0
Hyperbilirubinemia	21 (9)	5 (2)	2 (2)	0
Hypophosphatemia	19 (8)	7 (3)	1 (1)	0
Hypertension	15 (6)	9 (4)	2 (2)	1 (1)

Hassel, N Engl J Med 2023

Anticuerpos biespecíficos: nuevos conceptos

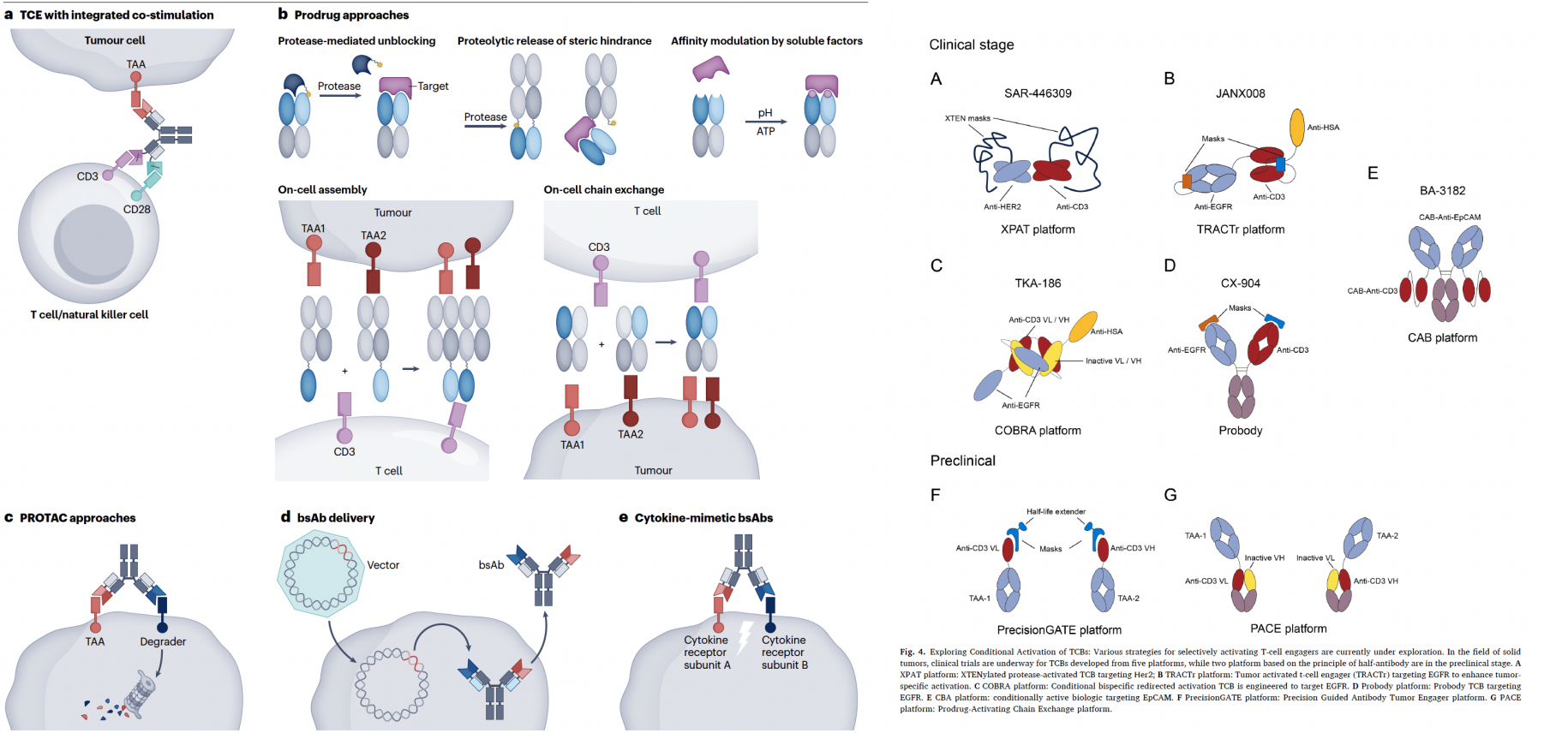


Fig. 4. Exploring Conditional Activation of TCBs: Various strategies for selectively activating T-cell engagers are currently under exploration. In the field of solid tumors, clinical trials are underway for TCBs developed from five platforms, while two platform based on the principle of half-antibody are in the preclinical stage. **A** XPAT platform: XTENylated protease-activated TCB targeting Her2; **B** TRACTr platform: Tumor activated t-cell engager (TRACTr) targeting EGFR to enhance tumor-specific activation. **C** COBRA platform: Conditional bispecific redirected activation TCB is engineered to target EGFR. **D** Probody platform: Probody TCB targeting EGFR. **E** CBA platform: conditionally active biologic targeting EpCAM. **F** PrecisionGATE platform: Precision Guided Antibody Tumor Engager platform. **G** PACE platform: Prodrug-Activating Chain Exchange platform.

Klein et al. Nat rev Drug Disc 2024

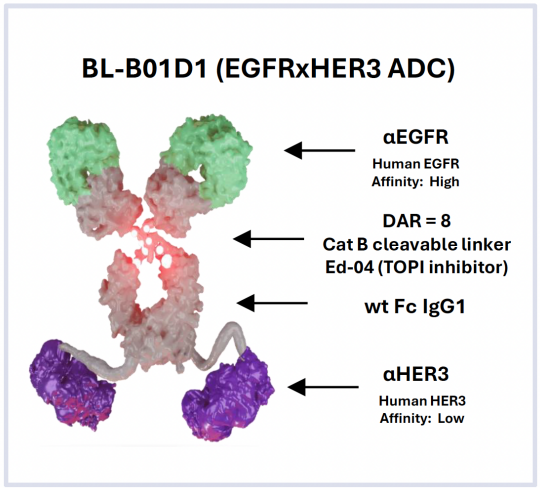
Anticuerpos biespecíficos: nuevas drogas

BARCELONA 2024 ESMO congress

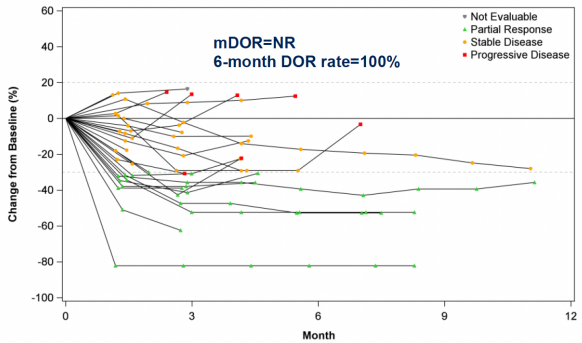
BL-B01D1, an EGFR x HER3 Bispecific Antibody-drug Conjugate (ADC), in Patients with Locally Advanced or Metastatic Urothelial Carcinoma (UC)

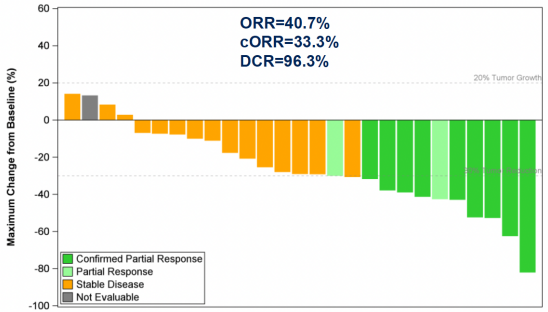
Dingwei Ye[1]

Xiaojie Bian[1], Tiejun Yang[2], Shusuan Jiang[3], Manming Cao[4], Sa Xiao[5], Hongwei Wang[6], Hai Zhu[6], Yi Zhu[1]



Patients at 2.2 mg/kg D1D8 Q3W (N=27)





Anticuerpos biespecíficos: nuevas drogas

Developmental Therapeutics—Molecularly Targeted Agents and Tumor Biology

Primary Track: Developmental Therapeutics—Molecularly Targeted Agents and Tumor Biology

Presentations

14:45 GMT-5

DB-1310, a HER3-targeted ADC, in pts with advanced solid tumors: Preliminary results from the phase 1/2a trial.

Presenter: Aaron Lisberg, MD | Division of Hematology/Oncology, University of California, Los Angeles

Abstract: 3000

14:57 GMT-5

Phase I study of iza-bren (BL-B01D1), an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with driver genomic alterations (GA) outside of classic EGFR mutations.

Presenter: Yunpeng Yang | Department of Medical Oncology, Sun Yat-Sen University Cancer Center

Abstract: 3001

15:09 GMT-5

Phase I study of iza-bren (BL-B01D1), an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic small cell lung cancer (SCLC).

Presenter: Yan Huang | Department of Medical Oncology, Sun Yat-Sen University Cancer Center

Abstract: 3002

15:21 GMT-5

Safety and efficacy of TQB2102, a novel bispecific anti-HER2 antibody–drug conjugate, in patients with advanced solid tumors: Preliminary data from the first-in-human phase 1 trial.

Presenter: Rui-Hua Xu, MD, PhD | Department of Medical Oncology, University Cancer Center State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine

Abstract: 3003

15:33 GMT-5

Is HER3 the Neu HER2 or Is It Too Soon?

Discussant: Lillian L. Siu, MD, FASCO, FRCPC | Princess Margaret Cancer Centre

15:45 GMT-5

Panel Question and Answer

Panel Speaker: Panel Discussion | ASCO

15:57 GMT-5

Efficacy and safety of the DLL3/CD3 T-cell engager obrixtamig in patients with extrapulmonary neuroendocrine

Anticuerpos biespecíficos: nuevas drogas

Developmental Therapeutics—Immunotherapy

Primary Track: Developmental Therapeutics—Immunotherapy

Presenters summarize their novel research findings and provide background on their methodologies. Discussants analyze the significance of each abstract within the co current knowledge, highlighting clinical application and implications for future research and practice. Abstract presenters and discussants answer questions during a mc panel discussion.

Presentations

15:00 GMT-5

Assessment of efficacy of LBL-024, a novel and uniquely designed bispecific antibody against PD-L1 and 4-1BB, combined with etoposide/platinum-based chemotherapy in treatment-naive advanced extrapulmonary neuroendocrine carcinoma (EP-NEC): A multicenter phase Ib/II trial.

Presenter: Panpan Zhang, MD | Peking University Cancer Hospital

Abstract: 2500

15:12 GMT-5

First-in-human phase I/II trial evaluating BNT142, a first-in-class mRNA encoded, bispecific antibody targeting Claudin 6 (CLDN6) and CD3, in patients (pts) with CLDN6-positive advanced solid tumors.

Presenter: Timothy A. Yap, MD, PhD | The University of Texas MD Anderson Cancer Center

Abstract: 2501

15:24 GMT-5

Efficacy and safety results of a first-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein IBI363 in patients (pts) with immunotherapy-treated, advanced acral and mucosal melanoma.

Presenter: Jun Guo, MD | Peking University Cancer Hospital & Institute

Abstract: 2502

15:36 GMT-5

The Power of Two: Leveraging Bispecifics in Solid Tumors

Anticuerpos (bi/tri/multi)específicos

Table 2. Tri-and tetraspecific antibodies in clinical trials as of Nov 2022

Drug name	Specificity	Indication	Clinical trial	Phase	Sponsor
SAR442257 (CODV-Fab)	CD38/CD3/CD28	MM, NHL	NCT04401020	1	Sanofi
SAR443216 (CODV-Fab)	HER2/CD3/CD28	HER2+ solid tumors	NCT05013554	1	Sanofi
SAR443579 (ANKET)	CD123/CD16/NKp46	AML, MDS	NCT05086315	1/2	Sanofi
CB307 (Humabody)	PSMA/CD137/HSA	PSMA+ tumors	NCT04839991	1	Crescendo Biologics
HPN217 (TriTAC)	BCMA/HSA/CD3	MM	NCT04184050	1	Harpoon Therapeutics
HPN328 (TriTAC)	DLL3/HSA/CD3	SCLC	NCT04471727	1/2	Harpoon Therapeutics
HPN424 (TriTAC)	PSMA/HSA/CD3	Prostate cancer	NCT03577028	1/2	Harpoon Therapeutics
HPN536 (TriTAC)	MSLN/HSA/CD3	MSLN+ tumors	NCT03872206	1/2	Harpoon Therapeutics
MP0317 (DARPin)	CD40/FAP/HSA	Advanced Solid Tumors	NCT05098405	1	Molecular Partners
MP0310 (DARPin)	CD137/FAP/HSA	Advanced Solid Tumors	NCT04049903	1	Molecular Partners
GTB-3550 (TriKE)	CD16/IL-15/CD33	AML	NCT03214666*	1/2	GT Biopharma
DF1001 (TriNKET)	HER2/CD16/NKG2D	HER2+ solid tumors	NCT04143711	1/2	Dragonfly Therapeutics
GB263T	EGFR/cMET/cMET*	NSCLC	NCT05332574	1/2	Genor Biopharma
NM21-1480 (scMATCH3)	PDL-1/CD137/HSA	NSCLC	NCT04442126	1/2	Numab Therapeutics
GNC-035	CD3/CD137/PD-L1/ROR1	Breast cancer	NCT05160545	1	Sichuan Baili/Systimmune
GNC-038	CD3/CD137/PD-L1/CD19	NHL	NCT04606433	1	Sichuan Baili/Systimmune
GNC-039	CD3/CD137/PD-L1/EGFRvIII	Glioma	NCT04794972	1	Sichuan Baili/Systimmune
TAK-186	EGFR/CD3/HSA	CCR, NSCLC, SCCHN	NCT04844073	1/2	Takeda

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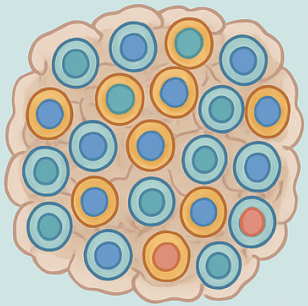
Anticuerpos biespecíficos

- ❑ INTRODUCCIÓN
- ❑ CLASIFICACIÓN
  - ❑ FUNCIONAL
  - ❑ ESTRUCTURAL
- ❑ HISTORIAS DE EXITO
- ❑ **RETOS**
  - ❑ **BIOMARCADORES**
  - ❑ **VIA DE ADMINISTRACIÓN**
  - ❑ **DOSIFICACIÓN**
  - ❑ **TOXICIDAD**
- ❑ CONCLUSIONES

Anticuerpos biespecíficos: Retos

LIMITED EFFICACY

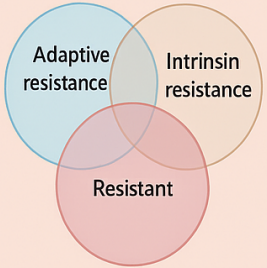


Tumor microenviron-viroment

Poor tumor penetration

Tumor heterogeneity

RESISTANCE MECHANISMS

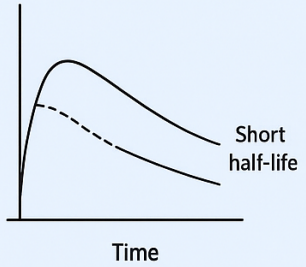


Antigen escape

Checkpoint upregulation

Immunogenicity (ADAs)

DOSING/ ADMINISTRATION

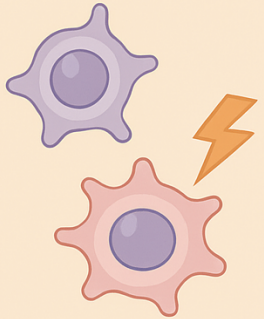


PKs (Cmax, exposure)

Short half-life

IV/SC

SAFETY



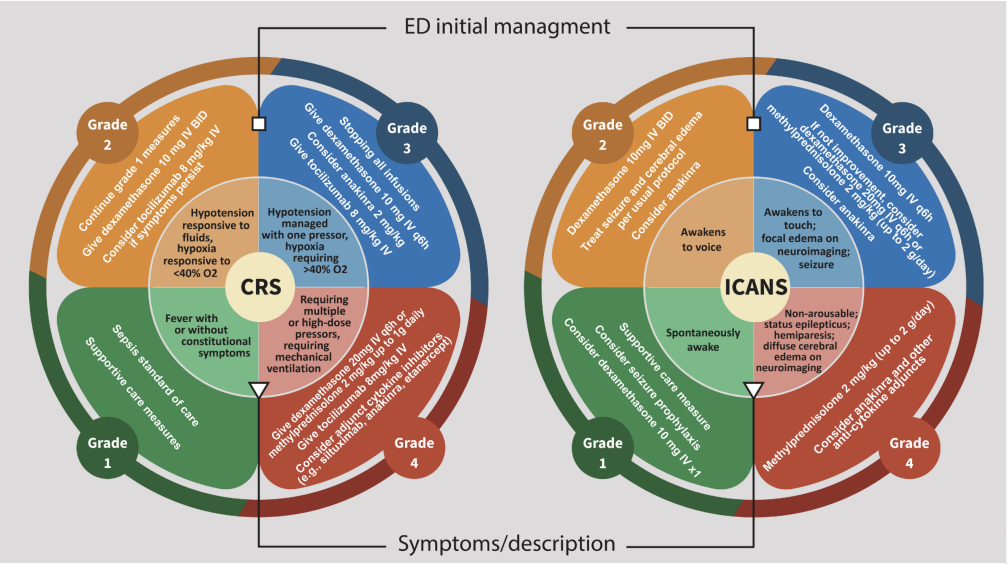
CRS

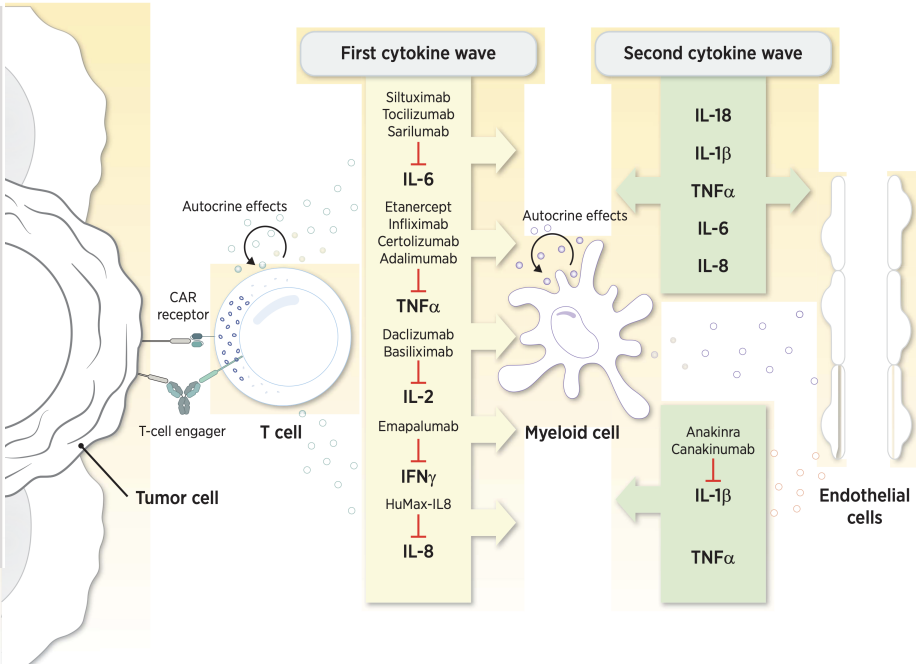
Off-target toxicity

Imagen generada por IA

Anticuerpos biespecíficos: Retos

Retos: Toxicidad





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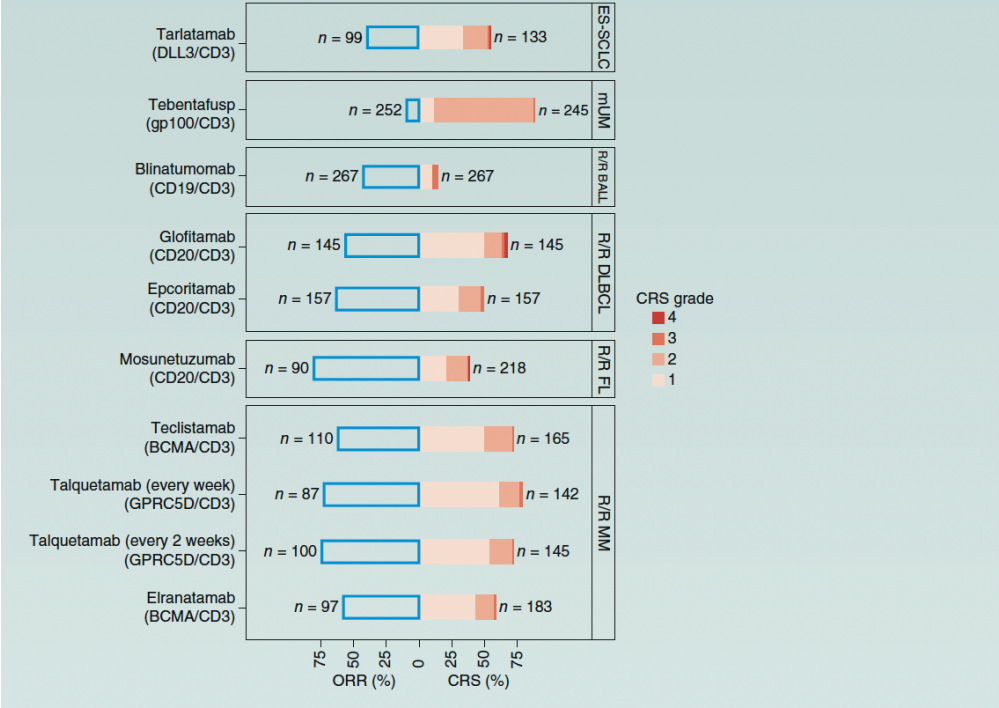
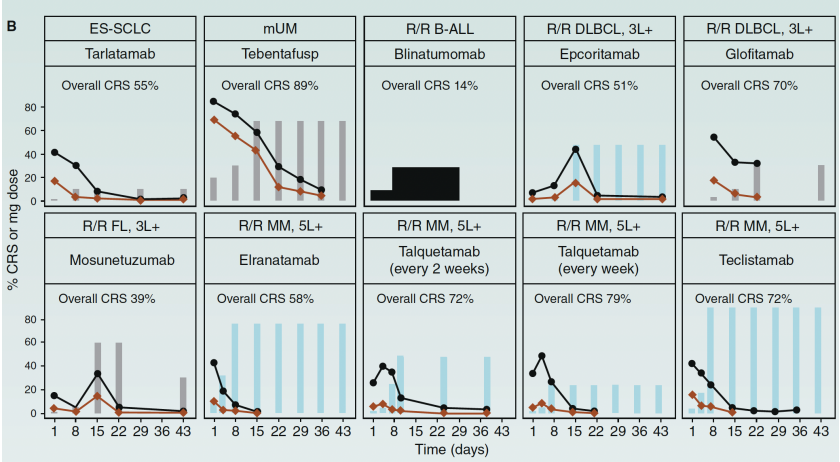
Luri-Rey. Clin Can Research 2024

Anticuerpos biespecíficos: Retos





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Anticuerpos biespecíficos

- ❑ INTRODUCCIÓN
- ❑ CLASIFICACIÓN
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- ❑ HISTORIAS DE EXITO
- ❑ RETOS
  - ❑ BIOMARCADORES
  - ❑ VIA DE ADMINISTRACIÓN
  - ❑ DOSIFICACIÓN
  - ❑ TOXICIDAD
- ❑ **CONCLUSIONES**

Anticuerpos biespecíficos: Conclusiones

- ❑Los Ac biespecíficos han demostrado claramente eficacia en contextos específicos.
- ❑Las posibilidades para desarrollar nuevos compuestos son prácticamente ilimitadas.
- ❑Debemos profundizar en la búsqueda de biomarcadores y en la comprensión biológica y mecanistíca (Selección de pacientes)
- ❑CUIDADO…las toxicidades puede también ser sumatorias + Nuevas toxicidades (CRS, ICANS…)
- ❑Actitud proactiva en el manejo de toxicidades

Muchas gracias

imatos@unav.es