Lung Cancer UPDATES
ASCO HIGHLIGHTS
30 MAYO - 03 JUNIO 2025
Chicago, USA

Iniciativa científica de:
GECP lung cancer research

Enfermedad avanzada: Anticuerpos conjugados (ADCs)

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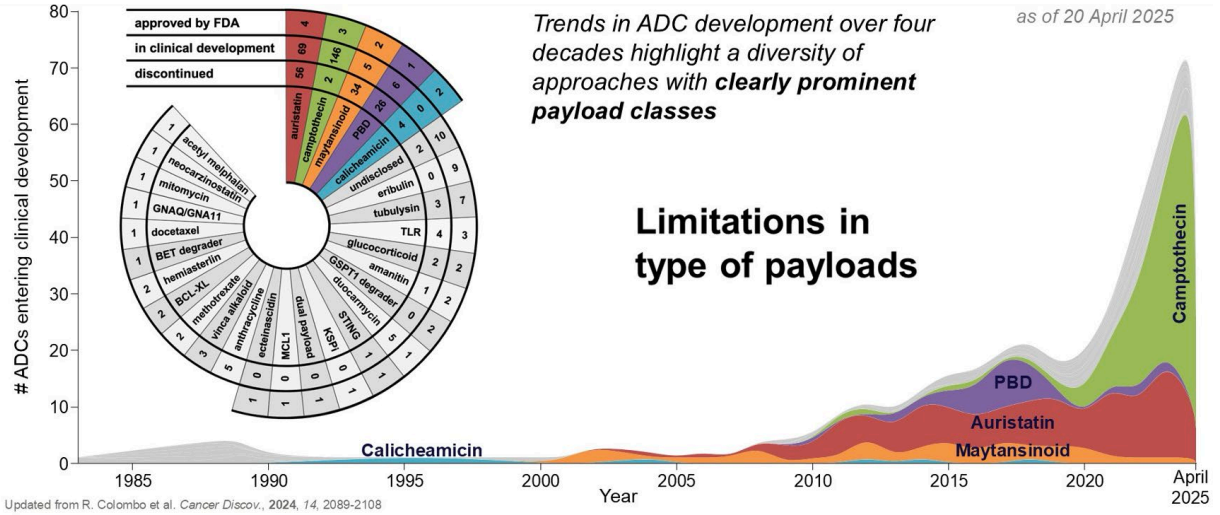
ADCs: entre la “bala mágica” y una “quimioterapia fashion”

450 ADCs have entered the clinic:

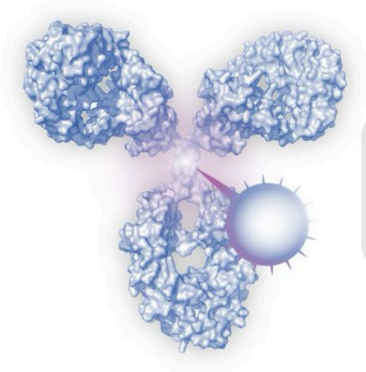
- **13 approved by US FDA**
  +3 additional by China NMPA
  +1 additional by UK MHRA and Japan PMDA
- **271 in clinical development**
- **163 discontinued**

What have we learned from this rich history?

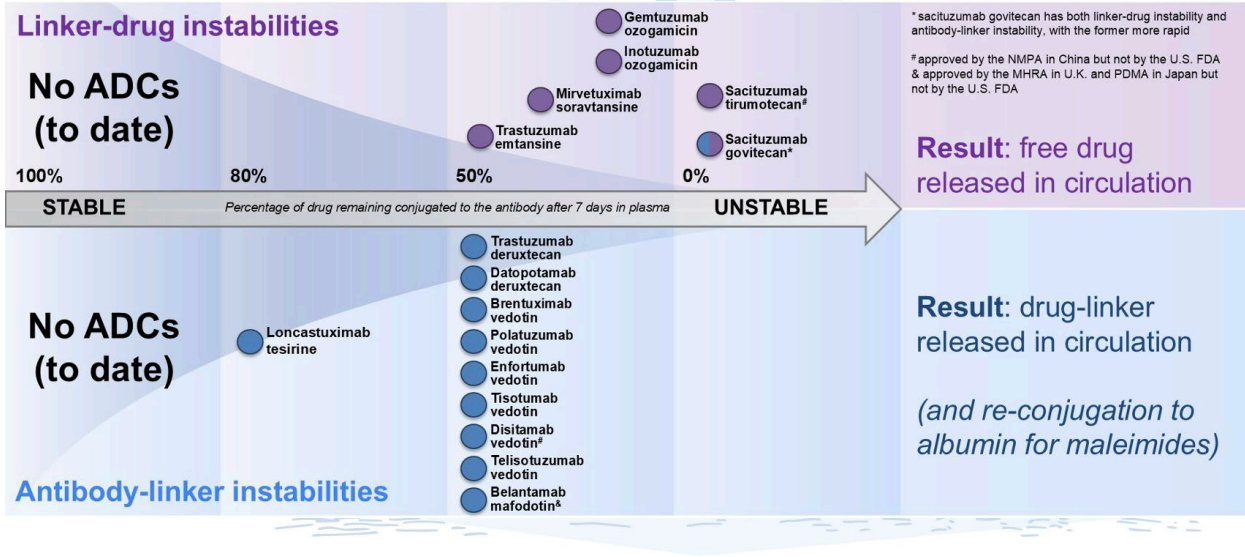
ADCs on file, manually curated, as of 23 May 2025

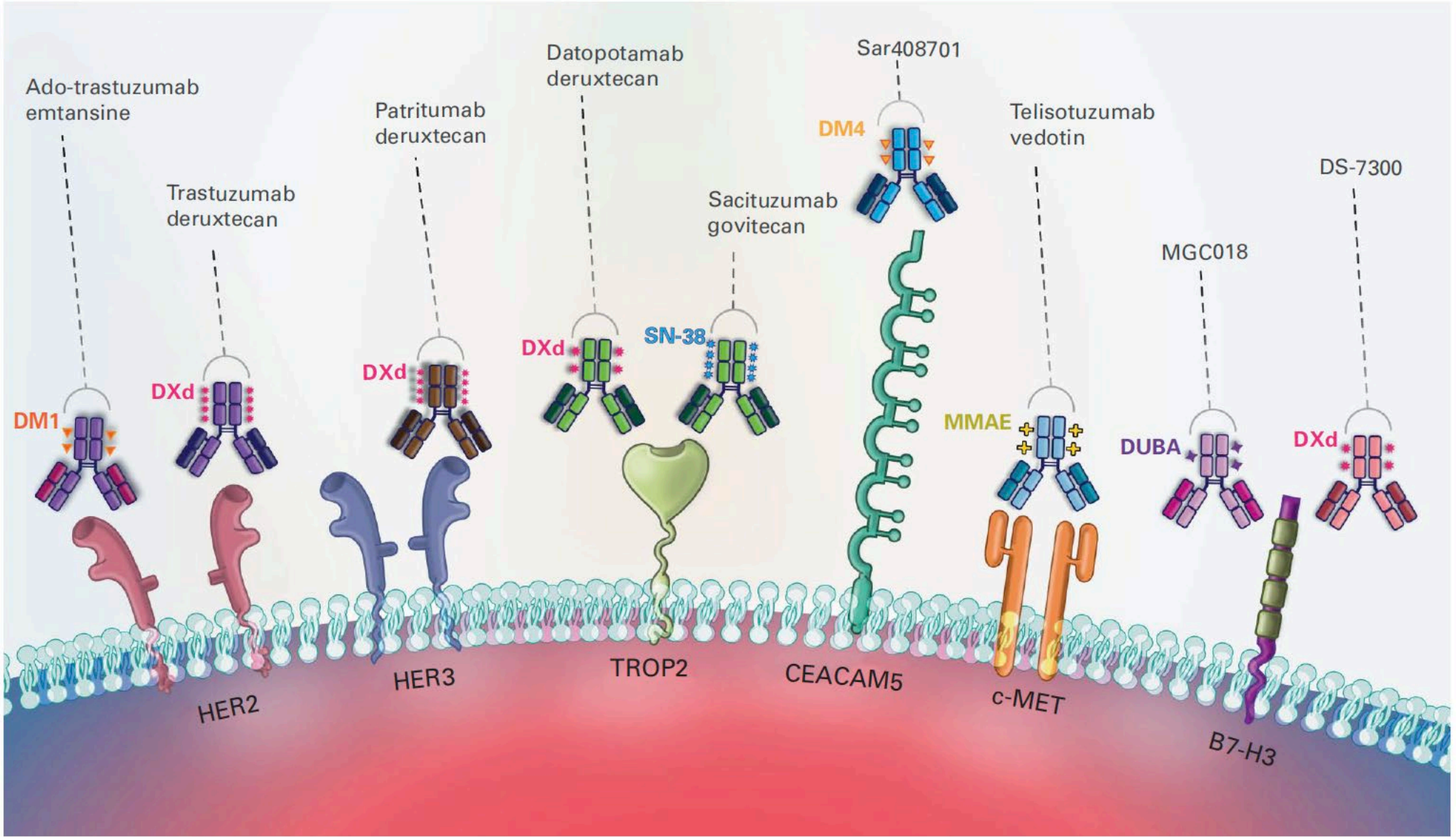


Many opportunities have been identified for optimization…



Antibody	Linker	Payload
• Target binding	• Stability	• Potency
• Hydrophobicity	• Cleavage	• Mechanism
• pI/charge	• Charge	• Bystander
• Conjugation site	• Hydrophobicity	• Hydrophobicity
• Fc-binding	• DAR	• Efflux



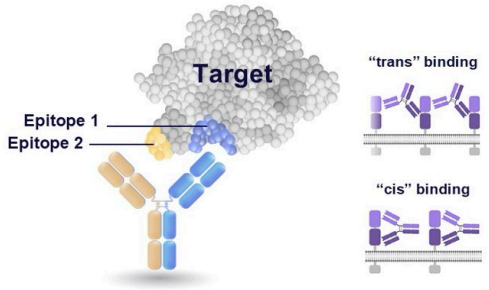


Passaro A : J Clin Oncol 41:3747-3761 © 2023

La complejidad creciente de los ADCs

GECP lung cancer research

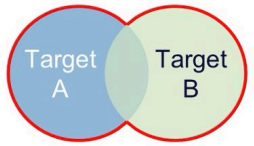
Biparatopic: bind distinct epitopes of same target antigen



- Designed for better internalization
- Could generate receptor crosslinking
- Not suitable for every target (need to engage non-overlapping epitopes of the same target antigen)

Bispecific: bind two different target antigens

Target A or target B (A ∪ B)

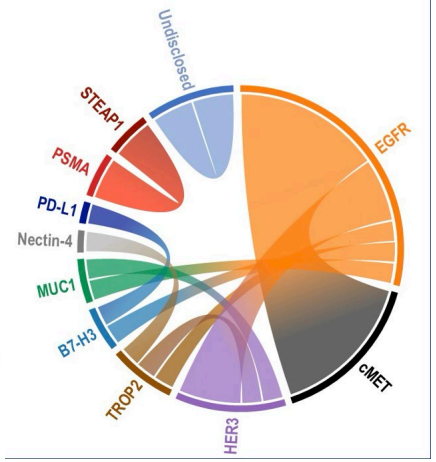


- *Broader patient population*
- *May bypass target resistance*
- *Complex formats (2+2, 2+1)*
- *May impact PK*
- *Possible toxicities related to both targets*

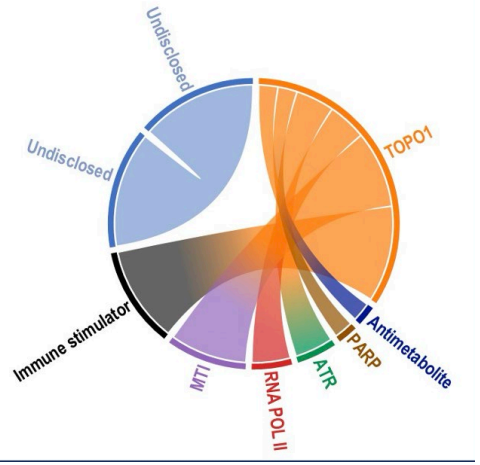
Target A and target B (A ∩ B)

- *Enhanced specificity*
- *Simpler formats (1+1)*
- *Narrow patient population*
- *Need co-expression and engagement to both targets*

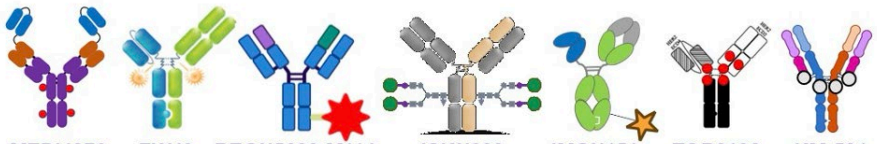
Pairs of targets used for bispecific ADCs



Pairs of payloads used in dual-payload ADCs



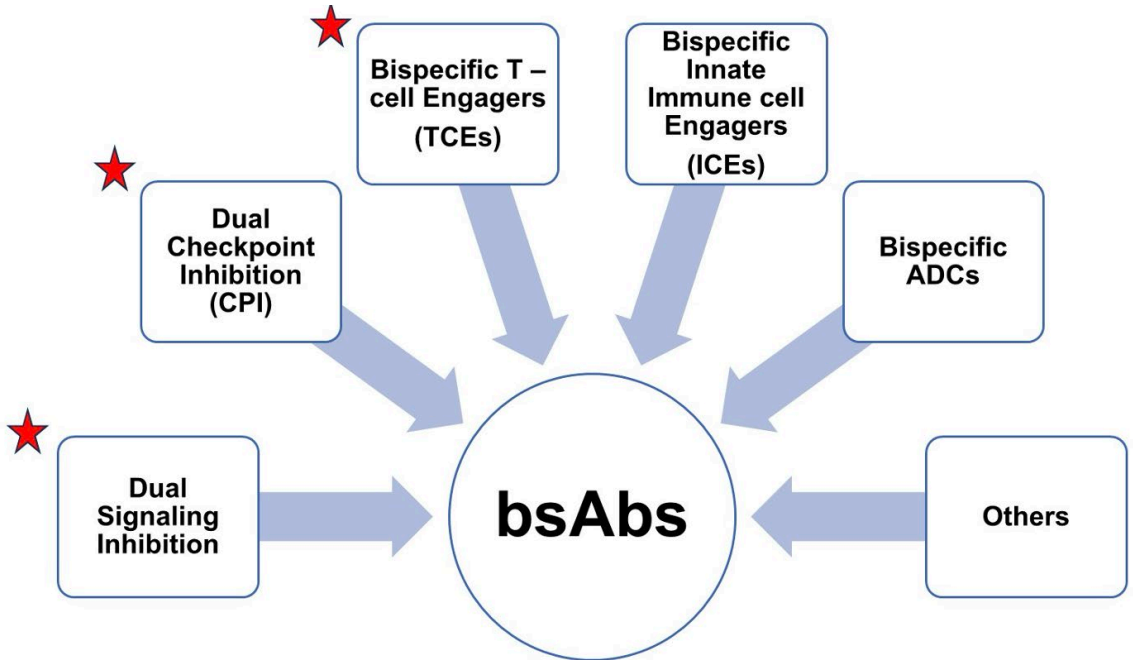
ADC	Year entering clinical development	Target	Payload class	Drug status
MEDI4276	2015	HER2 x HER2	Tubulysin	Discontinued
ZW49	2019	HER2 x HER2	Auristatin	Discontinued
REGN5093-M114	2021	cMET x cMET	Maytansinoid	Discontinued
JSKN003	2022	HER2 x HER2	Camptothecin	In clinical development
IMGN151	2023	FRα x FRα	Maytansinoid	In clinical development
TQB2102	2023	HER2 x HER2	Camptothecin	In clinical development
KM-501	2023	HER2 x HER2	Auristatin	In clinical development

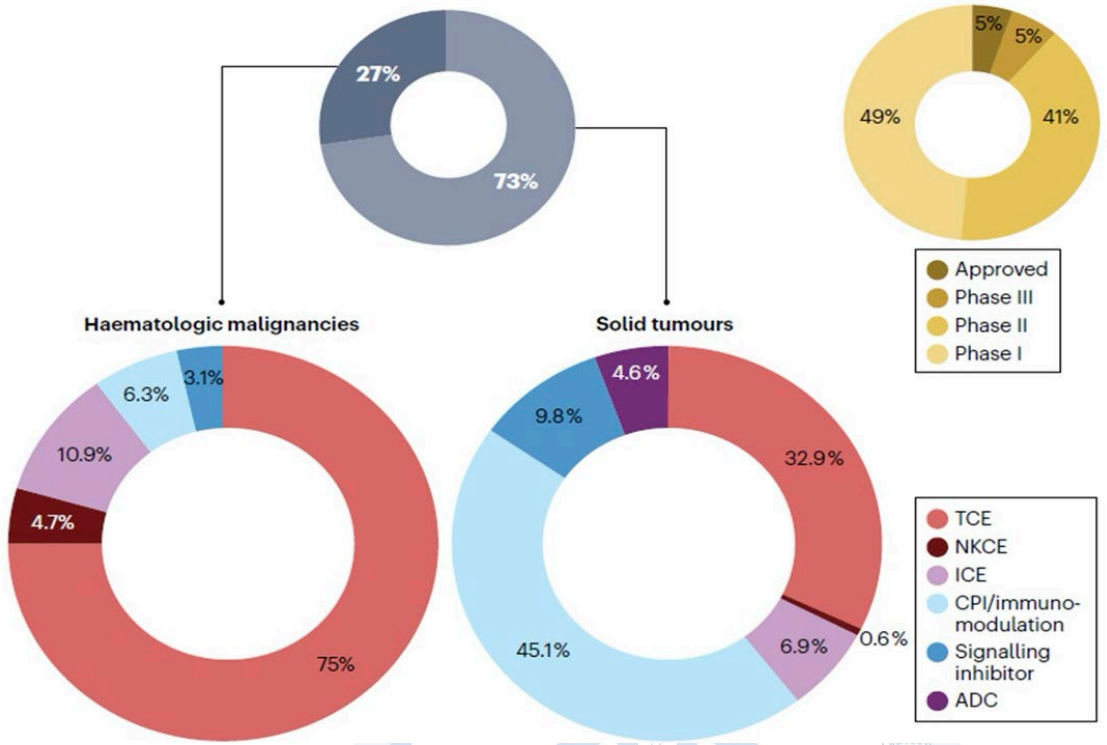


ADC	Year entering clinical development	Target 1	Target 2	Payload class	Drug status
M1231	2021	EGFR	MUC1	Hemiasterlin	Discontinued
BL-B01D1	2022	EGFR	HER3	Camptothecin	In clinical development
AZD9592	2022	EGFR	cMET	Camptothecin	In clinical development
ABBV-969	2024	PSMA	STEAP1	Camptothecin	In clinical development
JSKN016	2024	TROP2	HER3	Camptothecin	In clinical development
IBI3001	2024	EGFR	B7-H3	Camptothecin	In clinical development
IBI3005	2024	EGFR	HER3	Camptothecin	In clinical development
BL-B16D1	2024	*Undisclosed*	*Undisclosed*	Auristatin	In clinical development
DM001	2024	EGFR	TROP2	Camptothecin	In clinical development
DB-1419	2024	B7-H3	PD-L1	Camptothecin	In clinical development
DM005	2024	EGFR	cMET	Camptothecin	In clinical development
MK-2750 (SKB571)	2024	*Undisclosed*	*Undisclosed*	Camptothecin	In clinical development
ALK202	2024	EGFR	cMET	Camptothecin	In clinical development
GEN1286	2024	EGFR	cMET	Camptothecin	In clinical development
DM002	2025	MUC1	HER3	Camptothecin	In clinical development
DXC-008	2025	PSMA	STEAP1	*Undisclosed*	In clinical development
HS-20122	2025	EGFR	cMET	Camptothecin	In clinical development
TQB6411	2025	EGFR	cMET	Camptothecin	In clinical development
AK146D1	2025	TROP2	Nectin-4	Camptothecin	In clinical development
KY-0301	2025	EGFR	cMET	Auristatin	In clinical development
JS212	2025	EGFR	HER3	*Undisclosed*	In clinical development

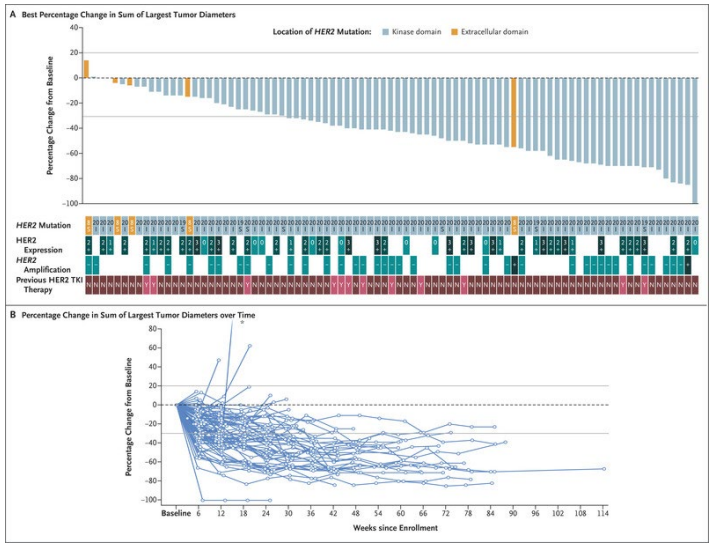
ADC	Payload 1	Payload 2	Target	Drug status
KH815	TOPO1	RNA POL II	TROP2	In clinical development
IBI3020	Undisclosed	Undisclosed	CEACAM5	In clinical development
ADC2192	Undisclosed	Undisclosed	TROP2	Preclinical
ADC2202	Undisclosed	Undisclosed	HER2	Preclinical
BR113	TOPO1	Immune stimulator	TROP2	Preclinical
CB-120	Exatecan	ATR	TROP2	Preclinical
CTPH-02	MMAE	Undisclosed	HER2	Preclinical
DXC018	TOPO1	Antimetabolite	HER2 x HER2	Preclinical
HMBD-802	TOPO1	ATR	HER2	Preclinical
IMD2113	TOPO1	TLR7/8 agonist	EGFR x TROP2	Preclinical
IMD2126	TOPO1	TLR7/8 agonist	PD-L1	Preclinical
IMD562	TOPO1	TLR7/8 agonist	HER2	Preclinical
JSNK021	TOPO1	MMAE	EGFR x HER2	Preclinical
KHN922	TOPO1	RNA POL II	CEACAM5	Preclinical
TJ102	Undisclosed	Undisclosed	CDH6 x FRα	Preclinical
Unnamed (Acepodia)	Undisclosed	Undisclosed	GPC3	Preclinical
Unnamed (Araris)	TOPO1	TOPO1	NaPi2b	Preclinical
Unnamed (Araris)	TOPO1+TOPO1	MMAE	Nectin4	Preclinical
Unnamed (GeneQuantum)	TOPO1	Immune stimulator	TROP2	Preclinical
Unnamed (Medilink)	TOPO1	MTI	HER2	Preclinical
Unnamed (Pinotbio)	TOPO1	MTI	HER2	Preclinical
Unnamed (Sutro)	TOPO1	PARP	Undisclosed	Preclinical

Ac biespecíficos

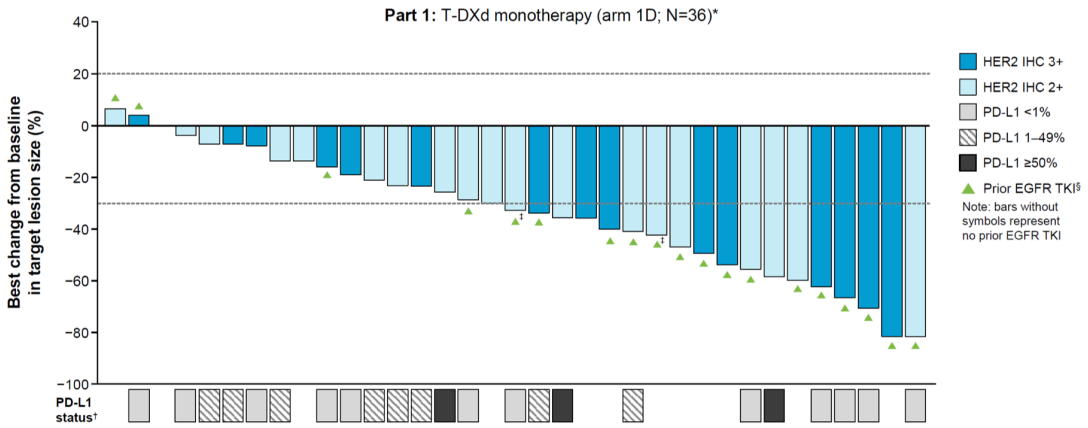




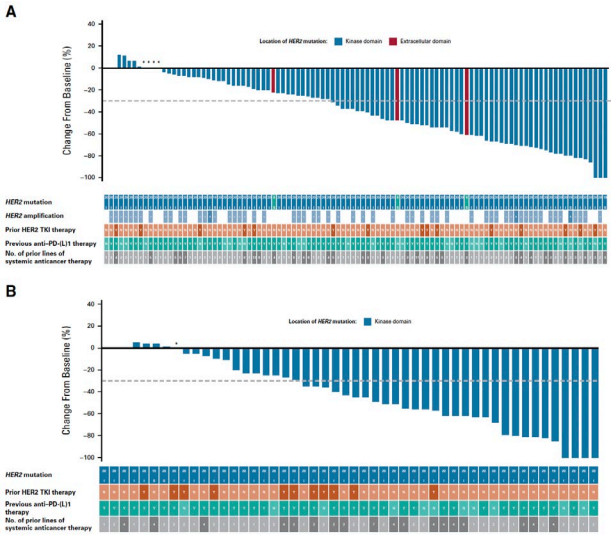
Mutaciones HER2: Trastuzumab-Deruxtecan: DESTINY-Lung



N Engl J Med 2022;386:241-51.
DOI: 10.1056/NEJMoa2112431



Planchard D et al / WCLC 2024



JCO 2023 Sept 11 DOI https://doi.org/10.1200/JCO.23.01361

Patient population (N≈264)

- Unresectable, locally advanced (not amenable to curative therapy), or metastatic nonsquamous NSCLC with *HER2* exon 19 or 20 mutations[a]
- Naive to systemic therapy in the locally advanced or metastatic setting
- No known other targetable oncogenic mutations/alterations

[a] *HER2* mutations may be detected in tissue or ctDNA.
[b] Crossover is not permitted.
[c] Investigator's choice of cisplatin or carboplatin.

Randomization 1:1

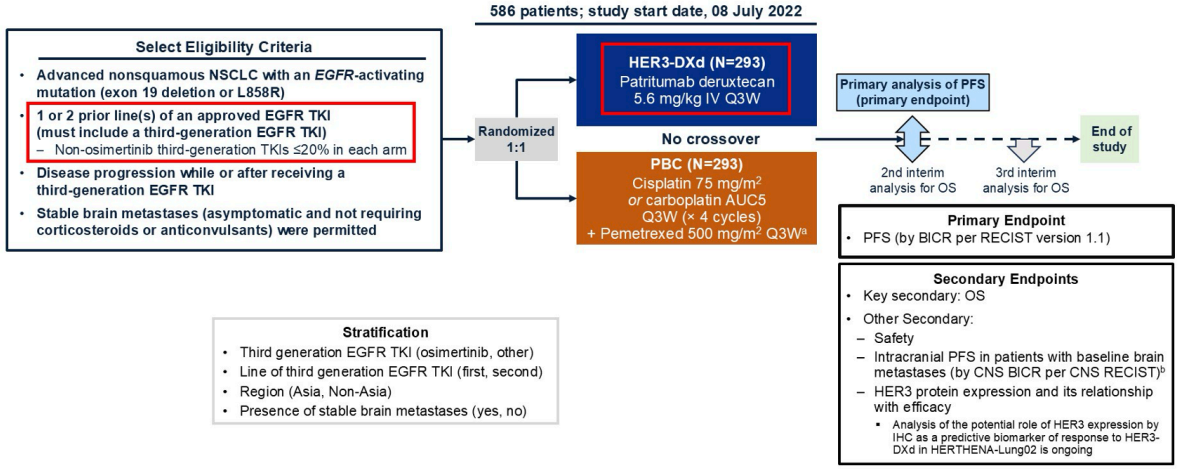
Arm 1: T-DXd[b]

Arm 2: Standard of care[b]
platinum[c] (cisplatin or carboplatin)
+ pemetrexed
+ pembrolizumab

DESTINY-Lung04

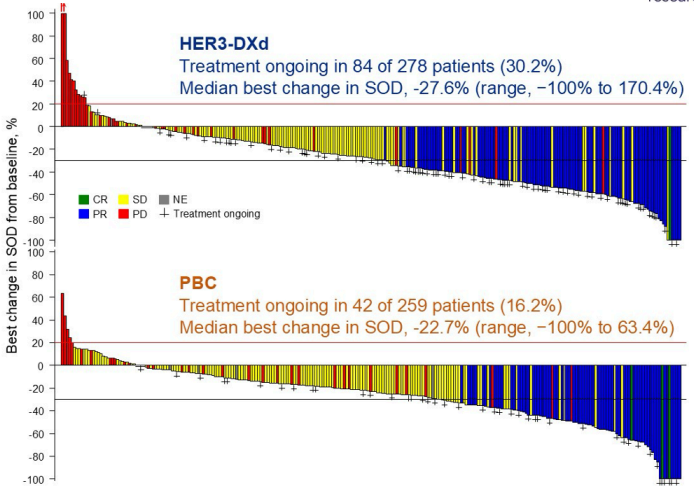
Recruiting

HERTHENA Lung02 Patritumab-Deruxtecan / Mok T et al

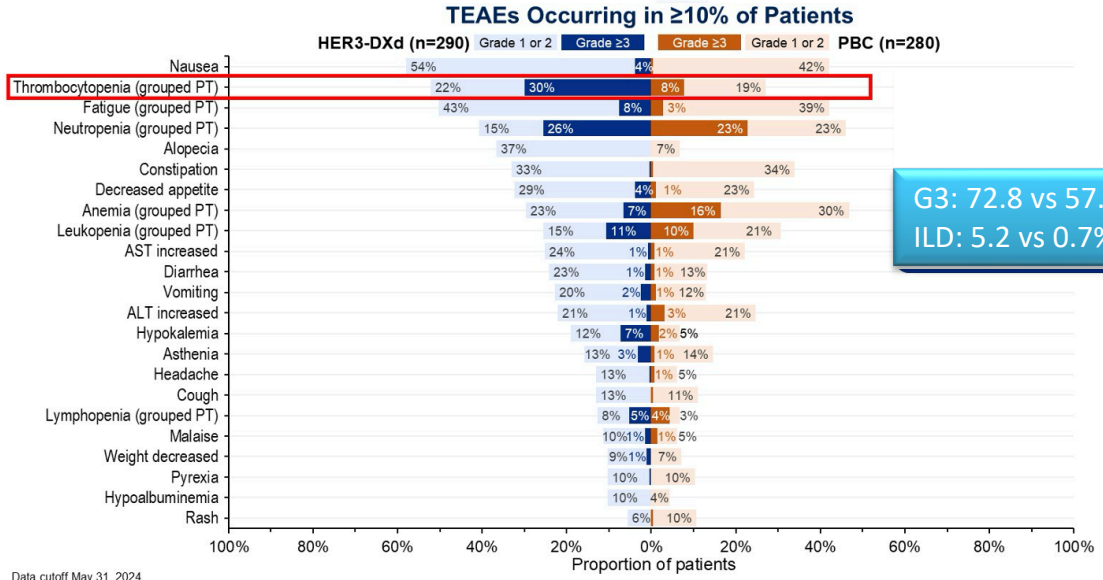


Responses by BICR per RECIST		HER3-DXd (N=293)	PBC (N=293)
Confirmed ORR (95% CI), %		**35.2 (29.7-40.9)**	**25.3 (20.4-30.6)**
Best overall response, n (%)	CR	1 (0.3)	3 (1.0)
	PR	102 (34.8)	71 (24.2)
	SD[a]	133 (45.4)	148 (50.5)
	PD	40 (13.7)	35 (11.9)
	NE	17 (5.8)[b]	36 (12.3)[c]
BOR to be confirmed, n (%)		2 (0.7)[d]	2 (0.7)[d]
DCR (95% CI), %		80.5 (75.5-84.9)	75.8 (70.4-80.6)
Median TTR (range), mo		1.5 (0.3-8.1)	1.5 (1.2-6.9)
Median DOR (95% CI), mo		5.7 (5.1-7.3)	5.4 (4.1-5.6)

Data cutoff May 31, 2024.



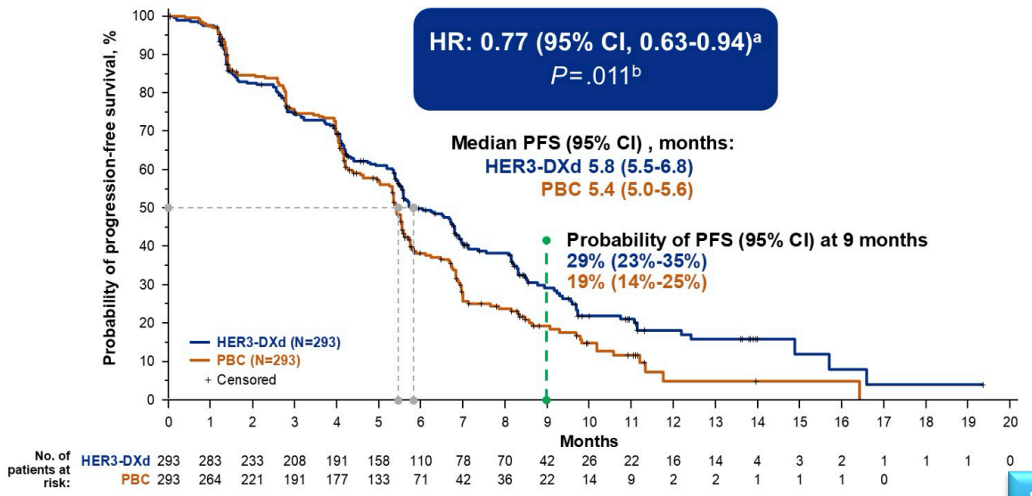
Baseline characteristics		HER3-DXd (N=293)	PBC (N=293)
Age, median (range), years		64 (35-82)	64 (34-86)
Female, n (%)		184 (62.8)	175 (59.7)
Asian, n (%)		176 (60.1)	178 (60.8)
Smoking history, n (%)	Never	187 (63.8)	185 (63.1)
	Ever	106 (36.2)	108 (36.9)
Time since initial NSCLC diagnosis, median (range), months		24.2 (2.5-121.1)	24.1 (3.2-146.1)
ECOG PS at baseline, n (%)	0	110 (37.5)	102 (34.8)
	1	183 (62.5)	190 (64.8)
	2[a]	0	1 (0.3)
History of brain metastasis, n (%)[b]		127 (43.3)	132 (45.1)
Brain metastasis at baseline (by CNS BICR per CNS RECIST), n (%)[c]		105 (35.8)	95 (32.4)
EGFR activating mutations, n (%)	Ex19del	177 (60.4)	178 (60.8)
	L858R	113 (38.6)	112 (38.2)
	Dual Ex19del and L858R	3 (1.0)	3 (1.0)
Prior EGFR TKI, n (%)	Only 3rd-generation	225 (76.8)	223 (76.1)
	3rd- and 1st/2nd-generation	68 (23.2)	70 (23.9)
Line of treatment for prior 3rd-generation EGFR TKI, n (%)	First line	226 (77.1)	227 (77.5)
	Second line	67 (22.9)	66 (22.5)
Type of prior 3rd-generation EGFR TKI, n (%)	Osimertinib	266 (90.8)	263 (89.8)
	Other 3rd-generation[d]	27 (9.2)	30 (10.2)



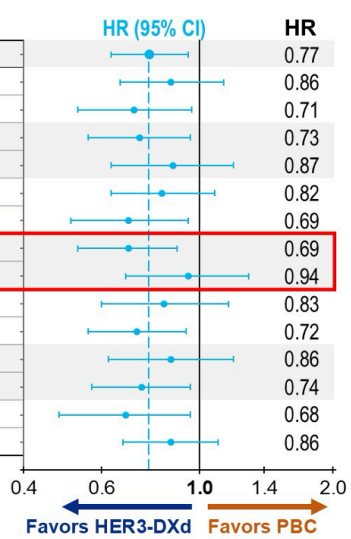
G3: 72.8 vs 57.1%
ILD: 5.2 vs 0.7%

Data cutoff May 31, 2024.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBC, platinum-based chemotherapy; PT, preferred term; TEAE, treatment emergent adverse event.

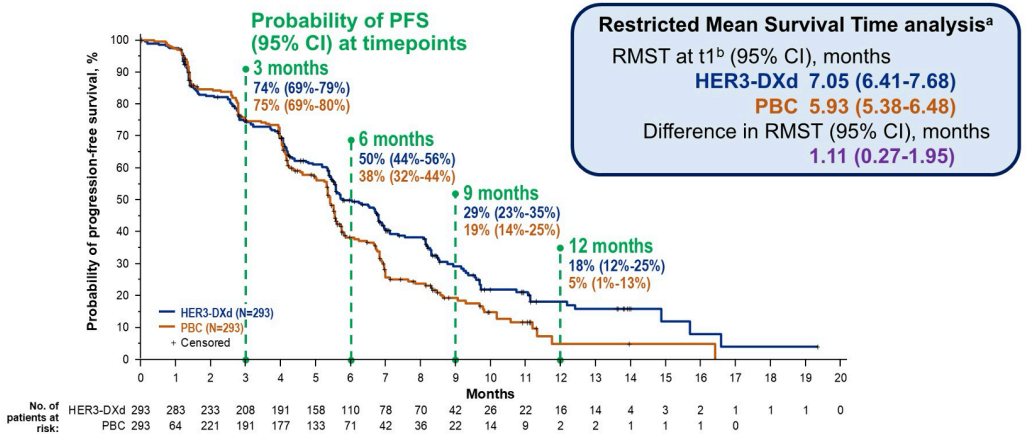
HERTHENA Lung02 Patritumab-Deruxtecan / Mok T et al



Subgroup		No. of events/n HER3-DXd	PBC	HR
Overall		194/293	195/293	0.77
Age	<65 y	105/153	108/149	0.86
	≥65 y	89/140	87/144	0.71
Sex	Female	117/184	116/175	0.73
	Male	77/109	79/118	0.87
Region	Asia	105/160	107/160	0.82
	Non-Asia	89/133	88/133	0.69
EGFR activating mutation	Ex19del	113/177	124/178	0.69
	L858R	79/113	69/112	0.94
Brain metastasis at baseline (by BICR per RECIST)	Yes	78/98	69/91	0.83
	No	116/195	126/202	0.72
Smoking status	Ever	76/106	73/108	0.86
	Never	118/187	122/185	0.74
ECOG PS at screening	0	69/111	65/103	0.68
	1	125/182	130/190	0.86



Mediana f-u 1[illegible]



Restricted Mean Survival Time analysis[a]

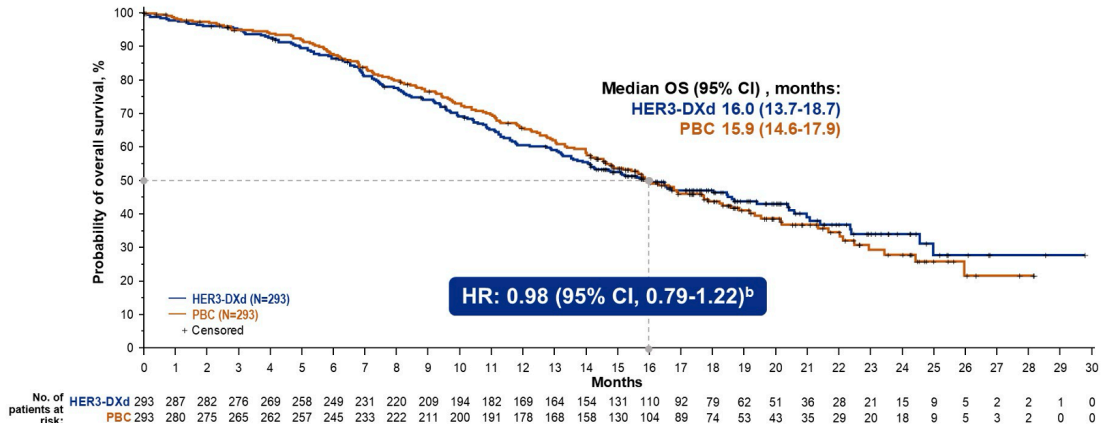
RMST at t1[b] (95% CI), months

HER3-DXd 7.05 (6.41-7.68)

PBC 5.93 (5.38-6.48)

Difference in RMST (95% CI), months

1.11 (0.27-1.95)



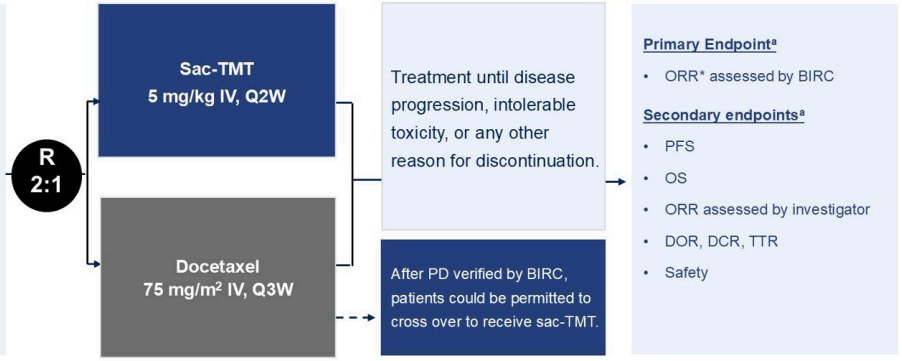
MERCK

Patritumab Deruxtecan Biologics License Application for Patients With Previously Treated Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer Voluntarily Withdrawn

Sacituzumab-Tirumotecan: Opti-TROP Lung 03 / Zhang L et al

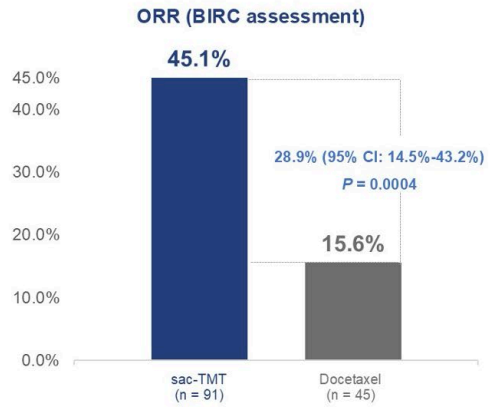
Key Eligibility
- ECOG score 0 or 1
- Nsq-NSCLC (stage IIIB/IIIC ineligible for surgery or radical radiotherapy or stage IV)
- EGFR-sensitizing mutations, including 19-Del and L858R
- Progression after prior combination or sequential treatment with EGFR-TKIs and platinum-based chemotherapy

Stratification factors:
- Brain metastases (present vs. absent)



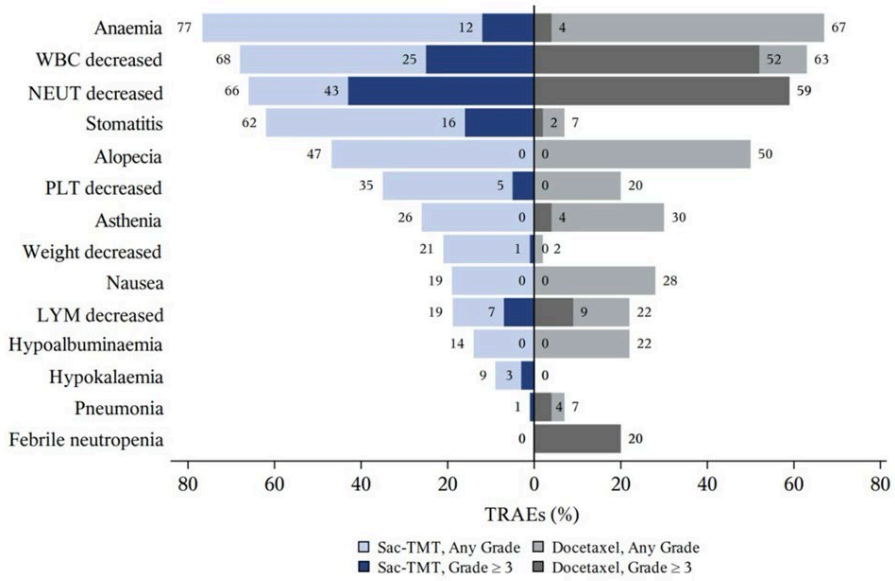
- Tumor assessments will be performed every 6 weeks (± 7 days) within 48 weeks after randomization
- After 48 weeks of randomization, tumor assessments will be performed every 12 weeks (± 7 days).

	Sac-TMT (n = 91)	Docetaxel (n = 45)
cORR, n (%) (95% CI)	41 (**45.1**) (34.6, 55.8)	7 (**15.6**) (6.5, 29.5)
Difference (95% CI)	**28.9 (14.5, 43.2)**	
One-sided P-value	0.0004	
DCR, n (%) (95% CI)	75 (82.4) (73.0, 89.6)	27 (60.0) (44.3, 74.3)
Difference (95% CI)	22.3 (6.0, 38.7)	
DOR, n (%)	26 (63.4)	6 (85.7)
Median DOR, months (95% CI)	**7.0** (5.4, 9.1)	**5.1** (3.1, NE)

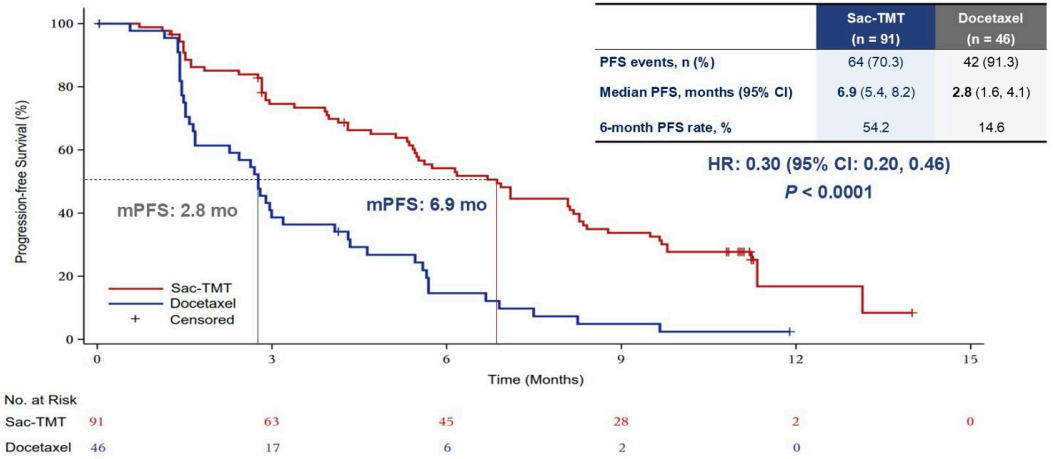


	Sac-TMT (n = 91)	Docetaxel (n = 46)
Median age (range)	57.0 (37, 75)	55.0 (34, 74)
≥65 years, n (%)	19 (20.9)	8 (17.4)
Male, n (%)	38 (41.8)	22 (47.8)
Histologic type: adenocarcinoma, n (%)	91 (100)	46 (100)
Clinical stage at enrollment, n (%)		
Stage IIIb	2 (2.2)	1 (2.2)
Stage IV	89 (97.8)	45 (97.8)
ECOG PS 1, n (%)	76 (83.5)	37 (80.4)
Brain metastases, n (%)	18 (19.8)	10 (21.7)
Liver metastases, n (%)	18 (19.8)	7 (15.2)
EGFR mutation type#, n (%)		
19-Del	43 (47.3)	32 (69.6)
L858R	48 (52.7)	14 (30.4)

	Sac-TMT (n = 91)	Docetaxel (n = 46)
T790M gene status, n (%)		
Positive	19 (20.9)	10 (21.7)
Negative	32 (35.2)	13 (28.3)
Unknown	40 (44.0)	23 (50.0)
Prior anti-tumor therapy lines (including EGFR-TKI), n (%)		
1*	9 (9.9)	5 (10.9)
2	52 (57.1)	20 (43.5)
>2	30 (33.0)	21 (45.7)
Prior EGFR-TKI therapy, n (%)		
3rd generation EGFR-TKI in 1st line	54 (59.3)	26 (56.5)
3rd generation EGFR-TKI in 2nd line	30 (33.0)	18 (39.1)
No 3rd generation EGFR-TKI used	7 (7.7)	2 (4.3)
Prior antiangiogenic therapy, n (%)	60 (65.9)	33 (71.7)
Prior immunotherapy, n (%)	15 (16.5)	6 (13.0)

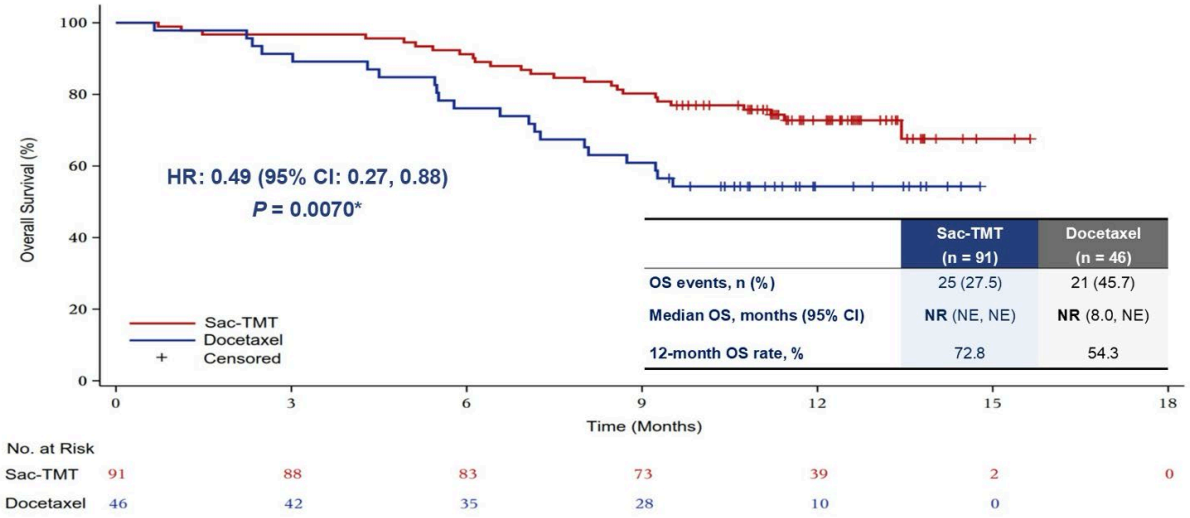


Sacituzumab-Tirumotecan: Opti-TROP Lung 03 / Zhang L et al



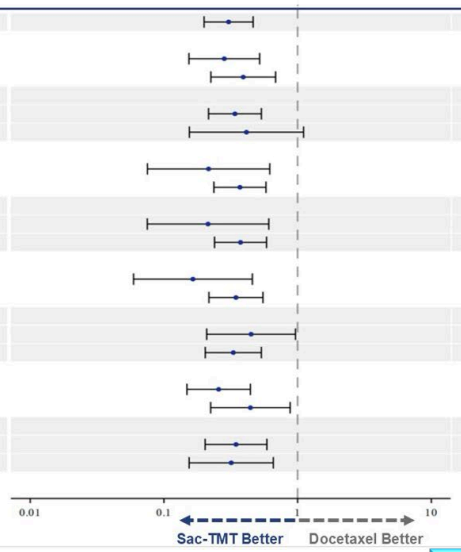
	Sac-TMT (n = 91)	Docetaxel (n = 46)
PFS events, n (%)	64 (70.3)	42 (91.3)
Median PFS, months (95% CI)	6.9 (5.4, 8.2)	2.8 (1.6, 4.1)
6-month PFS rate, %	54.2	14.6

HR: 0.30 (95% CI: 0.20, 0.46)
P < 0.0001



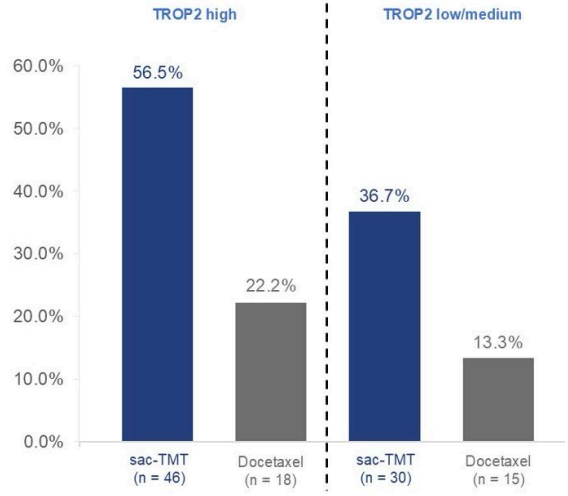
	Sac-TMT (n = 91)	Docetaxel (n = 46)
OS events, n (%)	25 (27.5)	21 (45.7)
Median OS, months (95% CI)	NR (NE, NE)	NR (8.0, NE)
12-month OS rate, %	72.8	54.3

Subgroup	Events / No. of Subjects Sac-TMT	Docetaxel	HR (95% CI)
All Subjects	64/91	42/46	0.30 (0.20, 0.46)
Sex			
Male	28/38	20/22	0.28 (0.15, 0.52)
Female	36/53	22/24	0.39 (0.22, 0.68)
Age			
< 65	53/72	35/38	0.34 (0.22, 0.54)
≥ 65	11/19	7/8	0.41 (0.16, 1.11)
ECOG PS			
0	10/15	8/9	0.22 (0.08, 0.62)
1	54/76	34/37	0.37 (0.24, 0.58)
Liver Metastases			
Yes	12/18	7/7	0.21 (0.08, 0.61)
No	52/73	35/39	0.37 (0.24, 0.59)
Brain Metastases			
Yes	16/18	9/10	0.16 (0.06, 0.46)
No	48/73	33/36	0.35 (0.22, 0.55)
Smoking History			
Yes	16/20	12/14	0.45 (0.21, 0.96)
No	48/71	30/32	0.33 (0.20, 0.54)
Prior EGFR-TKI therapy			
3rd generation EGFR-TKI in 1st line	38/54	24/26	0.26 (0.15, 0.44)
3rd generation EGFR-TKI in 2nd line	21/30	16/18	0.44 (0.22, 0.88)
EGFR Mutation Type			
19-Del	29/43	31/32	0.35 (0.20, 0.59)
L858R	35/48	11/14	0.32 (0.15, 0.66)



date: Dec 31, 2024.

TROP2 Expression Levels	Sac-TMT (n = 76)	Docetaxel (n = 33)
TROP2 high, n (%)	46 (60.5)	18 (54.5)
cORR, n (%) (95% CI)	26 (**56.5**) (41.1, 71.1)	4 (**22.2**) (6.4, 47.6)
Difference (95% CI)	**34.3 (10.3, 58.3)**	
TROP2 low/medium, n (%)	30 (39.5)	15 (45.5)
cORR, n (%) (95% CI)	11 (**36.7**) (19.9, 56.1)	2 (**13.3**) (1.7, 40.5)
Difference (95% CI)	**23.3 (-1.0, 47.7)**	

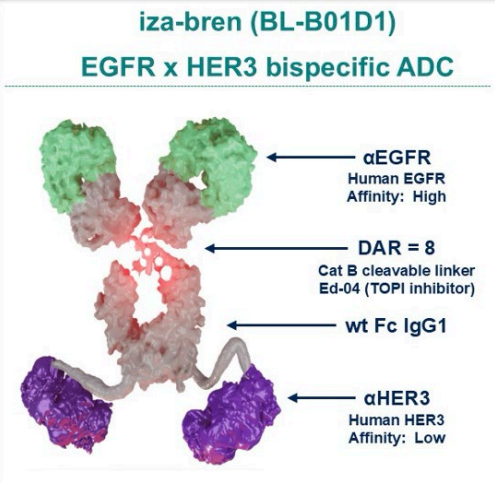


Mediana f-u 12.2 meses

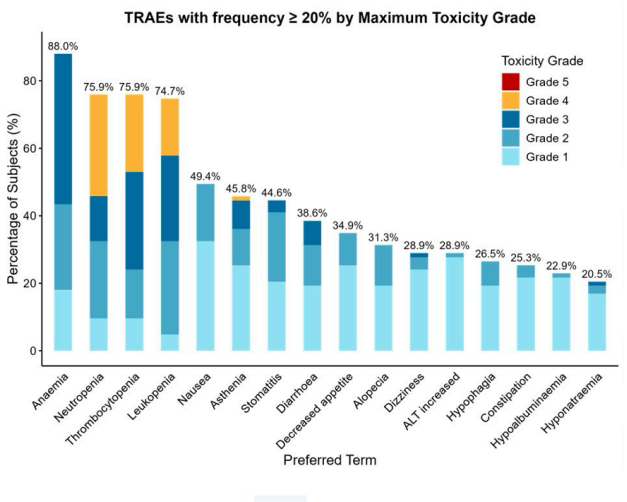
Alternativas terapéuticas en 2L EGFR mut+

Study	Regimen	Phase	PFS	HR for PFS	OS	Gr ≥ 3 tox	Remarks
MARIPOSA-2	**Amivantamab + chemo**	III	6.3 vs 4.2	0.48 (0.36-0.64); P < 0.001	17.7 vs 15.3; HR=0.73, P=0.039	72% vs 48%	Approved in US, EU, Japan, China, etc; OS data still immature
	Amivantamab + lazertinib + chemo		8.3 vs 4.2	0.44 (0.35-0.56); P < 0.001	NA	92% vs 48%	
HARMONi (Global)	**Ivonescimab + chemo vs chemo (Press release!)**	III	Not disclosed (HARMONi-A: 7.1 vs 4.8)	0.52 (0.41-0.66); P<0.00001	HR 0.79 (95% CI, 0.62-1.01); P=0.057	56% vs 50%	OS immature. Drug approved in China
IMpower150	**Atezo + bev + pacli + carbo (ABCP vs BCP)**	III (subset)	NR	NR	27.8 vs 18.1; HR, 0.74 (0.38-1.46)	52.1% vs 54.5%	Exploratory subset analysis
ATTLAS	**Atezo + bev + pacli + carbo (ABCP) vs chemo**	III	8.5 vs 5.6	0.62 (0.45-0.86); P=0.004	20.6 vs 20.2; HR. 2.02 (0.69-1.46), P=0.975	40.4% vs 21.6%	PFS positive, OS negative
SACHI (*MET*amp)	**Osi + savolitinib vs chemo**	III	8.2 vs 4.5	0.34 (0.23-0.49); P<0.0001	22.9 vs 17.7; HR, 0.84 (0.55-1.29)	57% vs 57%	Only available in China
HERTHENA-Lung02	**HER3-DXd vs chemo**	III	5.8 vs 5.4	0.77 (0.63-0.94); P=0.011	16.0 vs 15.9; HR, 0.98 (0.79-1.22)	57.9% vs 46.1%	Drug will not be marketed
OptiTROP-Lung03	**Sacituzumab tirumotecan vs docetaxel**	II	6.9 vs 2.8	0.30 (0.20-0.46); P<0.0001	NR vs NR; HR, 0.49 (0.27-0.88); P=0.0070	56% vs 71.7%	FDA breakthroug therapy designation

Iza-Bren DL (BL-B01D1) ADC biespecífico EGFR-HER3 / Zhang L et al



	2.5mg/kg D1D8Q3W (N = 83)
TRAEs, n (%)	83 (100)
Treatment-related SAEs, n (%)	30 (36.1)
≥Grade 3 TRAEs, n (%)	66 (79.5)
TRAEs leading to death, n (%)	1 (1.2)
TRAEs leading to discontinuation of study drug, n (%)	2 (2.4)
TRAEs leading to dose reduction, n (%)	46 (55.4)
TRAEs leading to drug delay, n (%)	44 (53.0)



Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Presence of driver genomic alterations outside of classic EGFR mutations (19del and L858R)
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Failed standard treatment
- Received no more than one prior line of chemotherapy

Treatment

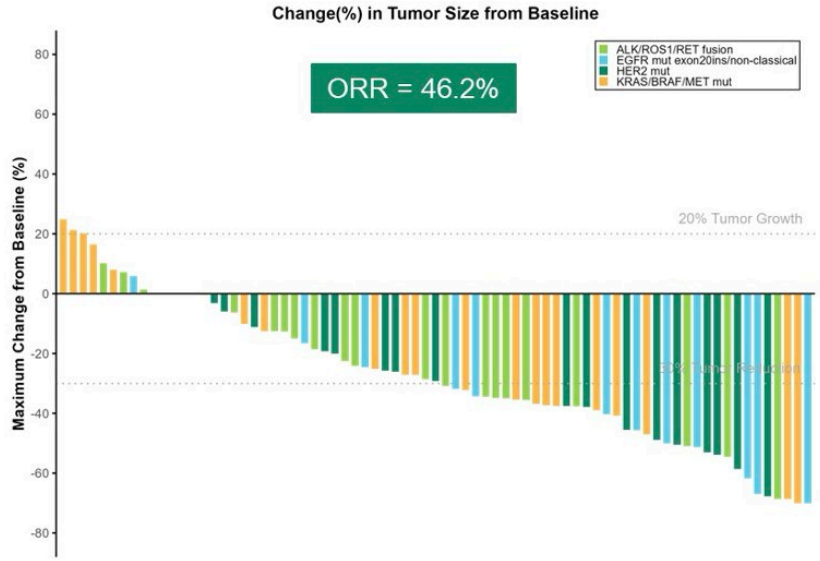
iza-bren
2.5 mg/kg
D1D8 Q3W

Endpoints

Primary
- Safety

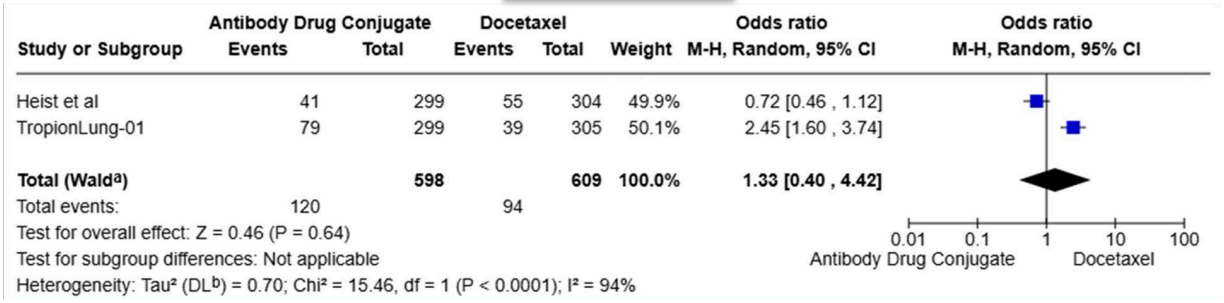
Secondary
- ORR, DCR and DoR

Exploratory
- PFS and OS



Metanálisis ADCs dirigidos a TROP2 2L / Abstract #8575

ORR Rate

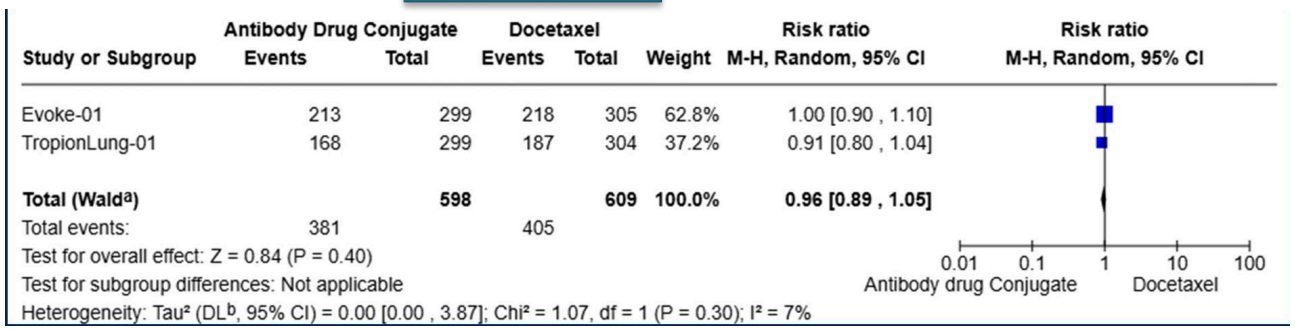


Study or Subgroup	Antibody Drug Conjugate Events	Total	Docetaxel Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Heist et al	41	299	55	304	49.9%	0.72 [0.46 , 1.12]
TropionLung-01	79	299	39	305	50.1%	2.45 [1.60 , 3.74]
Total (Wald[a])		**598**		**609**	**100.0%**	**1.33 [0.40 , 4.42]**
Total events:	120		94			

Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.70; Chi² = 15.46, df = 1 (P < 0.0001); I² = 94%

Odds ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Antibody Drug Conjugate Docetaxel

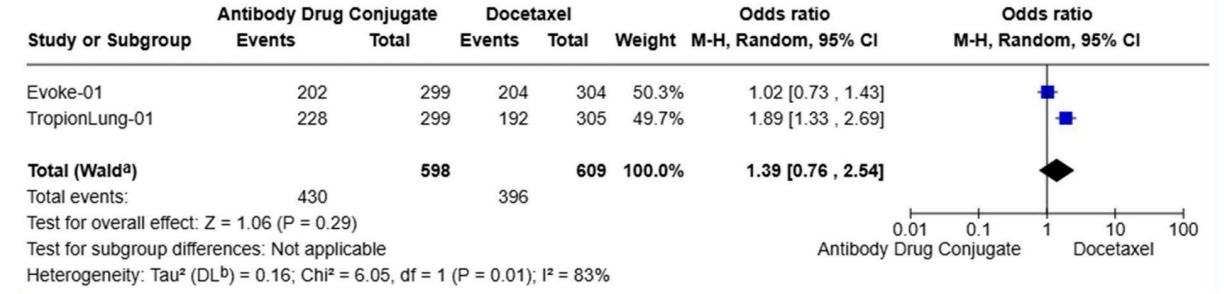
Event Rate



Study or Subgroup	Antibody Drug Conjugate Events	Total	Docetaxel Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Evoke-01	213	299	218	305	62.8%	1.00 [0.90 , 1.10]
TropionLung-01	168	299	187	304	37.2%	0.91 [0.80 , 1.04]
Total (Wald[a])		**598**		**609**	**100.0%**	**0.96 [0.89 , 1.05]**
Total events:	381		405			

Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b], 95% CI) = 0.00 [0.00 , 3.87]; Chi² = 1.07, df = 1 (P = 0.30); I² = 7%

Risk ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Antibody drug Conjugate Docetaxel

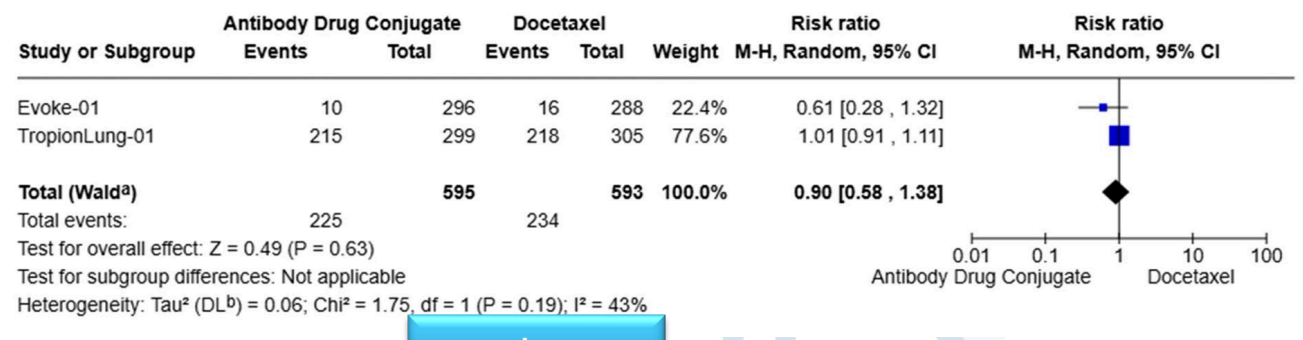


Study or Subgroup	Antibody Drug Conjugate Events	Total	Docetaxel Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Evoke-01	202	299	204	304	50.3%	1.02 [0.73 , 1.43]
TropionLung-01	228	299	192	305	49.7%	1.89 [1.33 , 2.69]
Total (Wald[a])		**598**		**609**	**100.0%**	**1.39 [0.76 , 2.54]**
Total events:	430		396			

Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.16; Chi² = 6.05, df = 1 (P = 0.01); I² = 83%

Odds ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Antibody Drug Conjugate Docetaxel

Death Rate



Study or Subgroup	Antibody Drug Conjugate Events	Total	Docetaxel Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Evoke-01	10	296	16	288	22.4%	0.61 [0.28 , 1.32]
TropionLung-01	215	299	218	305	77.6%	1.01 [0.91 , 1.11]
Total (Wald[a])		**595**		**593**	**100.0%**	**0.90 [0.58 , 1.38]**
Total events:	225		234			

Test for overall effect: Z = 0.49 (P = 0.63)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.06; Chi² = 1.75, df = 1 (P = 0.19); I² = 43%

Risk ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Antibody Drug Conjugate Docetaxel

DCR Rate

Outcome	Datopotamab Deruxtecan				Sacituzumab Govitecan			
	Rate	95% CI	P-Value	I^2	Value	95% CI	P-Value	I^2
ER	0.52	(0.26, 0.78)	<0.001	97%	0.45	(0.21, 0.69)	<0.001	91%
DCR	0.77	(0.73, 0.80)	<0.001	0%	0.68	(0.63, 0.73)	<0.001	0%
ORR	0.29	(0.23, 0.36)	<0.001	50%	0.14	(0.11, 0.18)	<0.001	0%
G3AER	0.34	(0.22, 0.47)	<0.001	86%	0.75	(0.57, 0.94)	<0.001	91%
DDR	0.07	(0.03, 0.12)	0.002	69%	0.07	(0.01, 0.13)	0.20	74%

TROPION Lung02 Dato-Dx+Pembro+/-QT / Levy B et al

- Phase 1b study of Dato-DXd + pembrolizumab ± Pt-CT in a/mNSCLC without actionable genomic alterations[a]

Key eligibility criteria

- a/mNSCLC
- Dose escalation[b]: ≤2 lines of prior therapy[c]
- Dose expansion
  - ≤1 line of Pt-CT (cohorts 1 and 2)[c]
  - Treatment-naive (cohort 2)[c,d]
  - Treatment-naive (cohorts 3–6)[c]

1L patients only	Dato-DXd IV Q3W	+ Pembrolizumab IV Q3W	+ Pt-CT IV Q3W	
Cohort 1 (n=2):	4 mg/kg	+ 200 mg		Doublet
Cohort 2 (n=40):	6 mg/kg	+ 200 mg		Doublet
Cohort 3 (n=14):	4 mg/kg	+ 200 mg	+ Carboplatin AUC 5	Triplet
Cohort 4 (n=26):	6 mg/kg	+ 200 mg	+ Carboplatin AUC 5	Triplet
Cohort 5 (n=8):	4 mg/kg	+ 200 mg	+ Cisplatin 75 mg/m^2	Triplet
Cohort 6 (n=6):	6 mg/kg	+ 200 mg	+ Cisplatin 75 mg/m^2	Triplet

Objectives

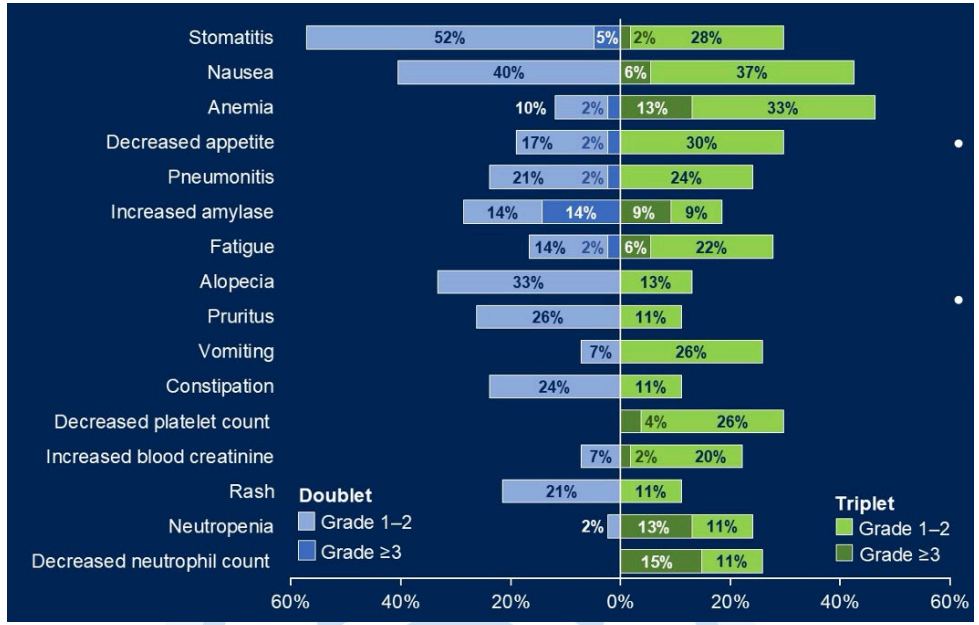
Primary: Safety and tolerability

Secondary: Efficacy

	All 1L (N=96)	
	Doublet (n=42)	Triplet (n=54)
Age, median (range), years	65 (48–83)	64 (33–78)
Male, n (%)	32 (76.2)	34 (63.0)
Asian race, n (%)	31 (73.8)	23 (42.6)
Histology, n (%)		
Nonsquamous	32 (76.2)	40 (74.1)
Squamous	10 (23.8)	14 (25.9)
History of brain metastases, n (%)	4 (9.5)	10 (18.5)
ECOG PS 1, n (%)	24 (57.1)	33 (61.1)
Dato-DXd dosing, n (%)		
4 mg/kg	2 (4.8)	22 (40.7)
6 mg/kg	40 (95.2)	32 (59.3)
PD-L1 expression[a], n (%)		
<50%	30 (71.4)	40 (74.1)
≥50%	5 (11.9)	10 (18.5)
NE	7 (16.7)	4 (7.4)

TROPION Lung02 Dato-Dx+Pembro+/-QT / Levy B et al

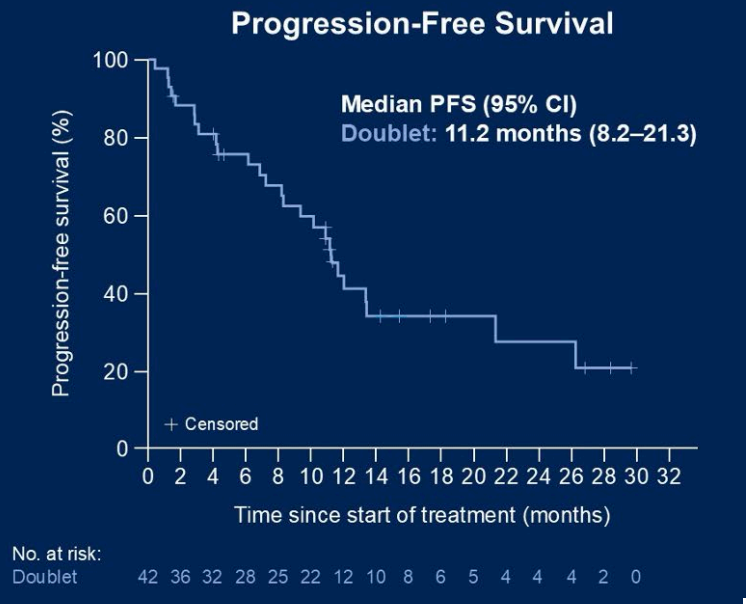
Event, n (%)	All 1L (N=96)	
	Doublet (n=42)	Triplet (n=54)
TRAEs	39 (92.9)	54 (100)
Grade ≥3	17 (40.5)	30 (55.6)
Associated with death	0	0
TRAEs associated with dose modifications		
Dose reduction of any drug	8 (19.0)	14 (25.9)
Dose reduction of Dato-DXd	8 (19.0)	7 (13.0)
Discontinuation of any drug	14 (33.3)	20 (37.0)
Discontinuation of Dato-DXd	13 (31.0)	16 (29.6)
Serious TRAEs	5 (11.9)	12 (22.2)
Grade ≥3	4 (9.5)	9 (16.7)
AESIs		
Oral mucositis/stomatitis	26 (61.9)	22 (40.7)
Grade 3	2 (4.8)	1 (1.9)
Adjudicated drug-related ILD/pneumonitis	11 (26.2)	14 (25.9)
Grade 3	2 (4.8)	1 (1.9)
Ocular surface events	9 (21.4)	18 (33.3)
Grade 3	1 (2.4)	2 (3.7)



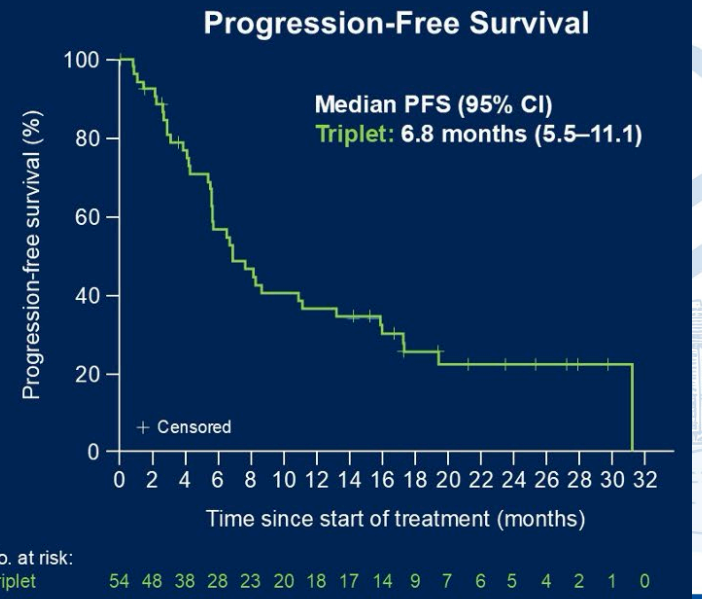
Mediana duración tto:
9.7 meses Dato-Dx-Pembro
5.3 meses Dato-Dx-Pembro-QT

TROPION Lung02 Dato-Dx+Pembro+/-QT / Levy B et al

	Doublet (n=42)
Confirmed ORR*, n (%)	**23 (54.8)**
95% CI	38.7–70.2
Median DOR, months	**20.1**
95% CI	9.7–NE
DCR, n (%)	**37 (88.1)**
95% CI	74.4–96.0
Median TTR, months	**1.4**
Range	1.2–7.0
Median PFS, months	**11.2**
95% CI	8.2–21.3
Median OS, months	**NE**
95% CI	19.2–NE

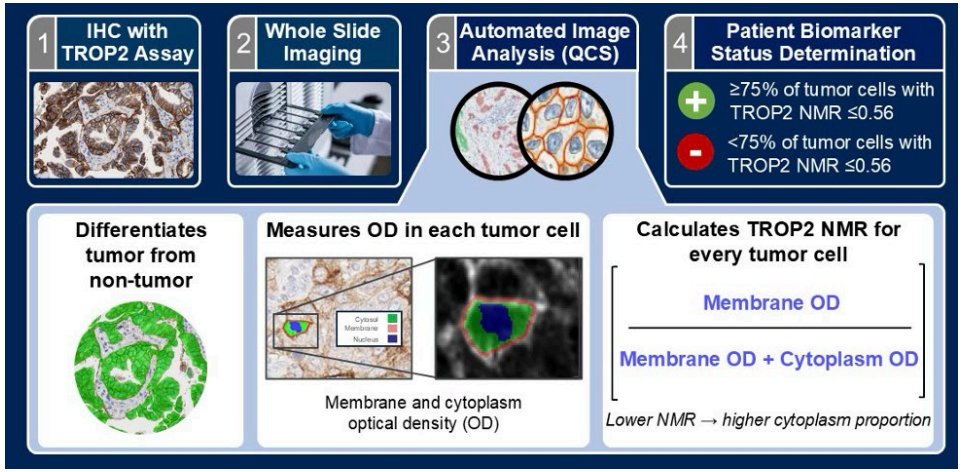


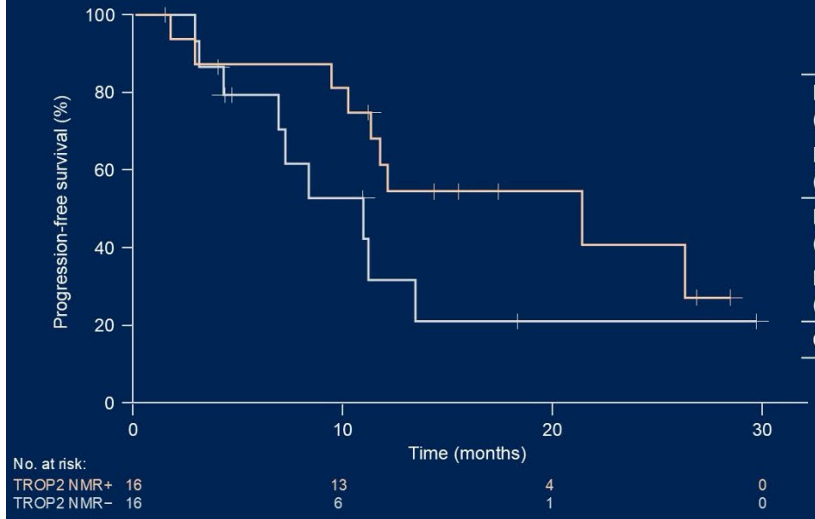
	Triplet (n=54)
Confirmed ORR*, n (%)	**30 (55.6)**
95% CI	41.4–69.1
Median DOR, months	**13.7**
95% CI	5.7–NE
DCR, n (%)	**48 (88.9)**
95% CI	77.4–95.8
Median TTR, months	**1.4**
Range	1.2–9.6
Median PFS, months	**6.8**
95% CI	5.5–11.1
Median OS, months	**17.4**
95% CI	9.1–NE



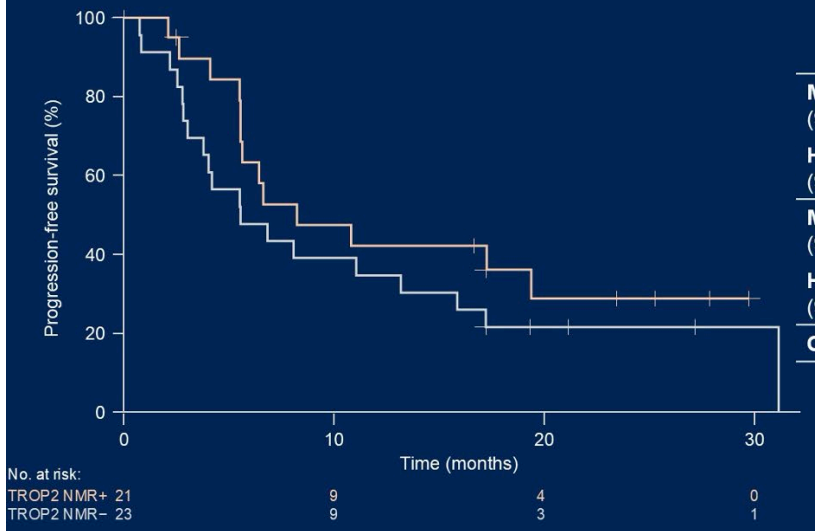
TROPION Lung02 Dato-Dx+Pembro+/-QT / Levy B et al

	Doublet		Triplet	
	PD-L1 <50%	PD-L1 ≥50%	PD-L1 <50%	PD-L1 ≥50%
N	30	5	40	10
ORR,% (95% CI)	53.3% (34.3–71.7)	100% (47.8–100)	55.0% (38.5-70.7)	60.0% (26.2–87.8)
BoR (%)				
CR	3.3%	0	2.5%	10.0%
PR	50%	100%	52.5%	50.0%
DOR, months (95% CI)	12.0 (8.0–NE)	NE (5.5–NE)	14.6 (5.3–NE)	NE 4.1–NE





	TROP2 NMR+ (n=16)	TROP2 NMR− (n=16)	1L ITT (n=42)
Median PFS (95% CI)	21.3 mo (10.2–NE)	10.9 mo (4.2–13.4)	11.2 mo (8.2–21.3)
HR (95% CI)	0.50 (0.19–1.29)		-
Median OS (95% CI)	NE (26.2–NE)	NE (14.3–NE)	NE (19.2–NE)
HR (95% CI)	0.35 (0.07–1.72)		-
ORR	68.8%	62.5%	54.8%



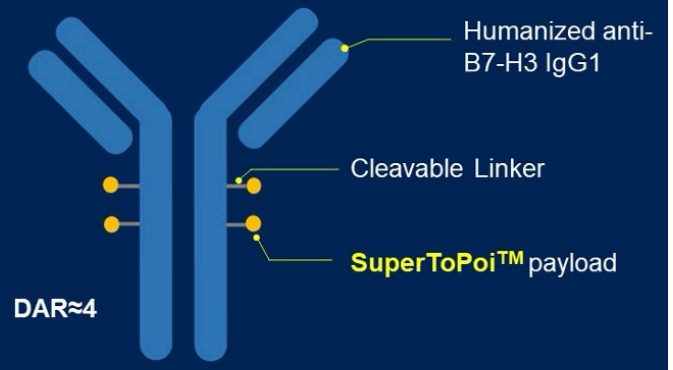
	TROP2 NMR+ (n=21)	TROP2 NMR− (n=23)	1L ITT (n=54)
Median PFS (95% CI)	8.2 mo (5.6–NE)	5.5 mo (3.0–13.2)	6.8 mo (5.5–11.1)
HR (95% CI)	0.67 (0.33–1.36)		-
Median OS (95% CI)	26.9 mo (7.1–NE)	13.3 mo (6.4–NE)	17.4 mo (9.1–NE)
HR (95% CI)	0.71 (0.31–1.59)		-
ORR	61.9%	52.2%	55.6%

EE CC activos en 1L con ADCs anti-TROP2

Clinical Trial Name	Phase	Treatment	Status
TROPION-Lung07	3	Dato-DXd Plus Pembro +/-Chemo in 1L nonsquamous NSCLC	Recruiting
TROPION-Lung08	3	Dato-DXd Plus Pembro vs. Pembro in 1L nonsquamous NSCLC with PD-L1 ≥50%	Recruiting
EVOKE-03	3	Pembro vs. Sacituzumab Govitecan Plus Pembro in 1L NSCLC with PD-L1 ≥50%	Recruiting
TroFuse-007	3	Sacituzumab Tirumotecan (Sac-TMT) Plus Pembro vs. Pembro Alone in 1L NSCLC with PD-L1 ≥ 50%	Recruiting
TroFuse-023	3	Pembro +/- Sac-TMT in 1L maintenance for squamous NSCLC	Recruiting

MHB088C ADC B7H3 / Zhou C et al

Structure of MHB088C



Patient eligibility

- Histologically- or cytologically-confirmed SCLC
- ECOG PS of 0 or 1
- 1~3 prior lines of systemic therapies

- Cohort 1: 1.6 mg/kg Q2W (n=30~50)
- Cohort 2: 2.0 mg/kg Q2W (n=30~50)
- Cohort 3: 2.4 mg/kg Q3W (n=30~50)

- Primary endpoint: ORR by RECIST v1.1
- Secondary endpoints: Safety, DCR, DOR, PFS, OS

Antibody vs Ifinatamab

- **3~4 times** higher cell binding activities
- **2~3 times** higher internalization rate

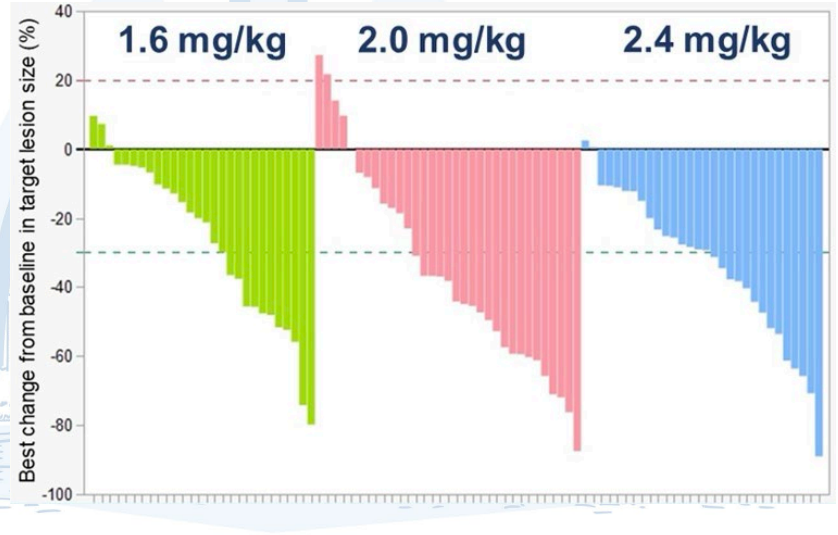
Proprietary linker

- **Stable in plasma**

SuperTopoi™ payload

- **5~10 times more potent** than DXd
- Short half-life

Dosing Regimen	1.6 mg/kg Q2W (n=28)	2.0 mg/kg Q2W (n=33)	2.4 mg/kg Q3W (n=30)
Median follow-up (m)	9.2	6.2	8.3
Unconfirmed ORR (%) (95% CI)	42.9 (24.5, 62.8)	57.5 (39.2, 74.5)	46.7 (28.3, 65.7)
Confirmed ORR (%) (95% CI)	21.4 (8.3, 41.0)	42.4 (25.5, 60.8)	43.3 (25.5, 62.6)
DCR (%) (95% CI)	89.3 (71.8, 97.7)	87.9 (71.8, 96.6)	93.3 (77.9, 99.2)



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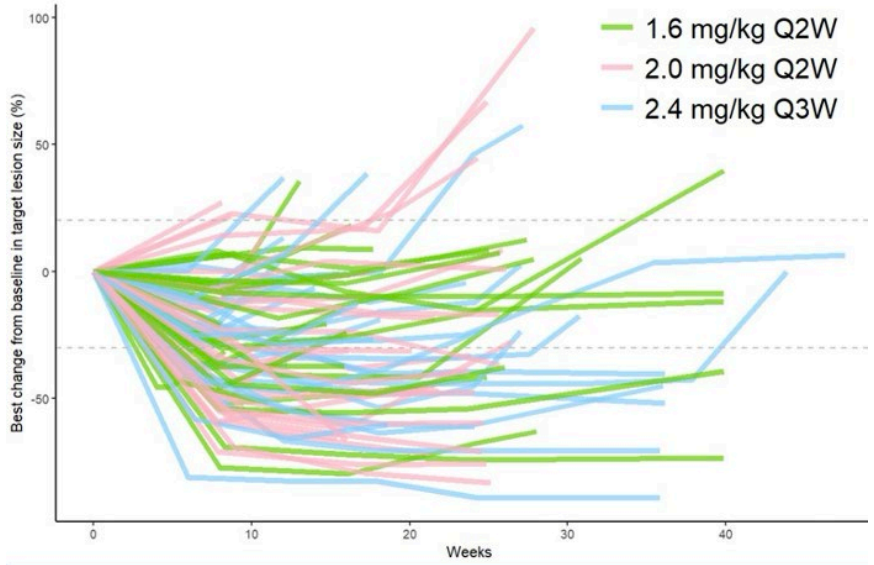
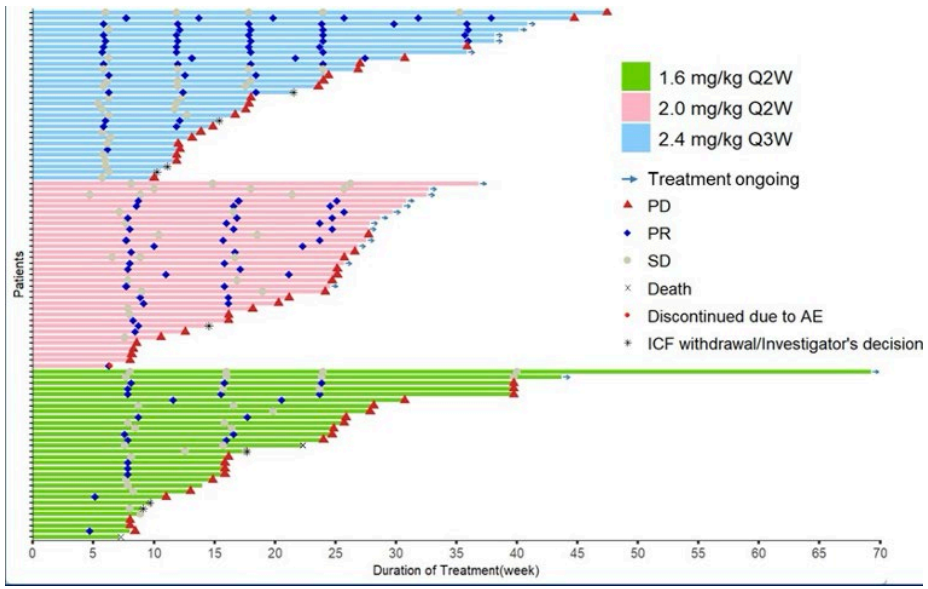
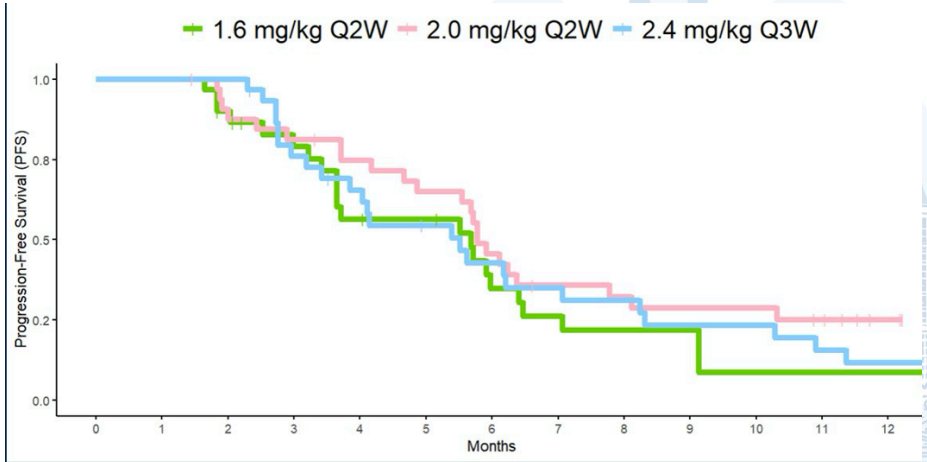




TEAEs (Grade ≥3), n (%)	1.6 mg/kg Q2W (N=30)	2.0 mg/kg Q2W (N=33)	2.4 mg/kg Q3W (N=30)	Total (N=93)
Neutropenia	3 (10.0)	3 (9.1)	12 (40.0)	18 (19.4)
White blood cell count decreased	3 (10.0)	2 (6.1)	6 (20.0)	11 (11.8)
Lymphocyte count decreased	7 (23.3)	3 (9.1)	0	10 (10.8)
Anaemia	1 (3.3)	4 (12.1)	1 (3.3)	6 (6.5)
Hyponatraemia	3 (10.0)	2 (6.1)	0	5 (5.4)
Platelet count decreased	1 (3.3)	1 (3.0)	3 (10.0)	5 (5.4)
Pneumothorax	0	0	2 (6.7)	2 (2.2)
Atrial fibrillation	2 (6.7)	0	0	2 (2.2)
Alanine aminotransferase increased	1 (3.3)	0	0	1 (1.1)
Gamma-glutamyltransferase increased	0	1 (3.0)	0	1 (1.1)
Aspartate aminotransferase increased	1 (3.3)	0	0	1 (1.1)
Bilirubin conjugated increased	1 (3.3)	0	0	1 (1.1)
Blood bilirubin increased	1 (3.3)	0	0	1 (1.1)
Febrile neutropenia	0	0	1 (3.3)	1 (1.1)
Hypokalaemia	1 (3.3)	0	0	1 (1.1)
Cachexia	1 (3.3)	0	0	1 (1.1)
Hypomagnesaemia	1 (3.3)	0	0	1 (1.1)
Pulmonary embolism	0	1 (3.0)	0	1 (1.1)
Haemoptysis	1 (3.3)	0	0	1 (1.1)
Pneumonitis	1 (3.3)	0	0	1 (1.1)
Respiratory failure	1 (3.3)	0	0	1 (1.1)
Infection	0	1 (3.0)	0	1 (1.1)
Pneumonia	0	1 (3.0)	0	1 (1.1)
Anal abscess	1 (3.3)	0	0	1 (1.1)
Upper respiratory tract infection	1 (3.3)	0	0	1 (1.1)
Diarrhoea	1 (3.3)	0	0	1 (1.1)
Cerebral infarction	1 (3.3)	0	0	1 (1.1)



Dosing Regimen	1.6 mg/kg Q2W (n=28)	2.0 mg/kg Q2W (n=33)	2.4 mg/kg Q3W (n=30)
Median DOR (95% CI), months	4.2 (3.8, NA)	4.2 (2.5, NA)	6.9 (4.1, NA)
Median PFS (95% CI), months	5.6 (3.7, 6.3)	5.7 (4.0, 6.1)	5.5 (3.8, 7.1)

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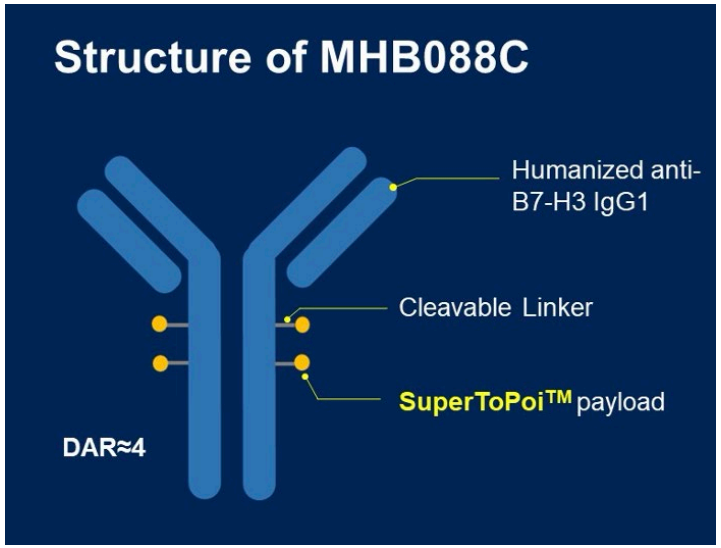
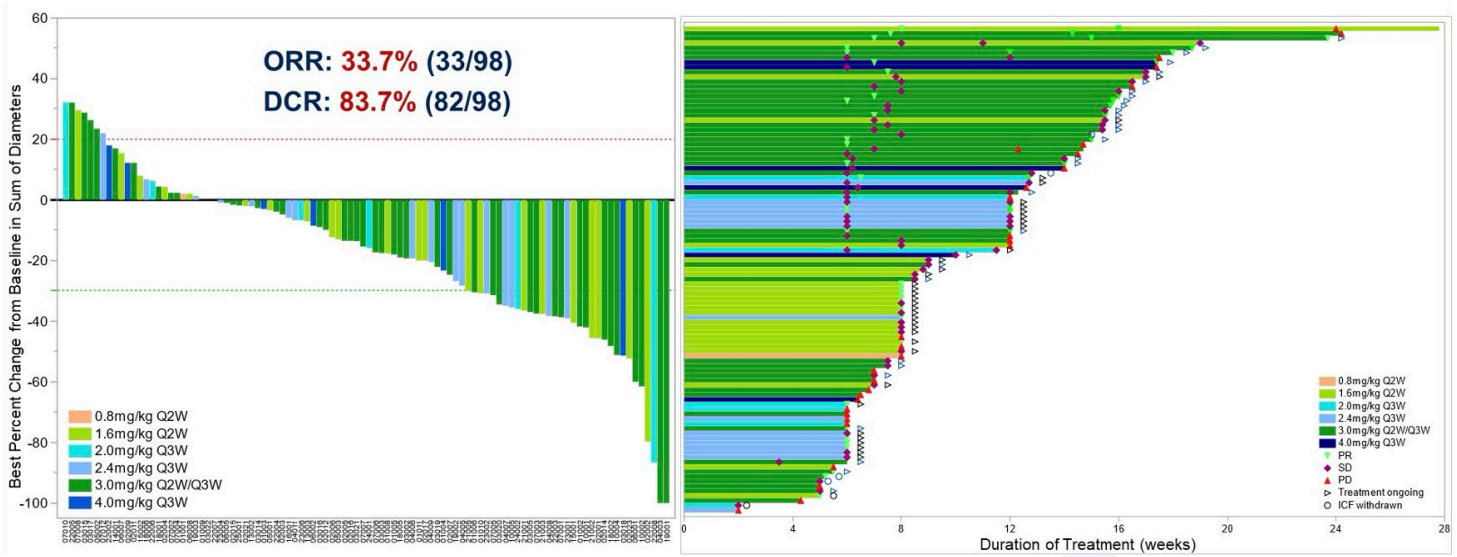
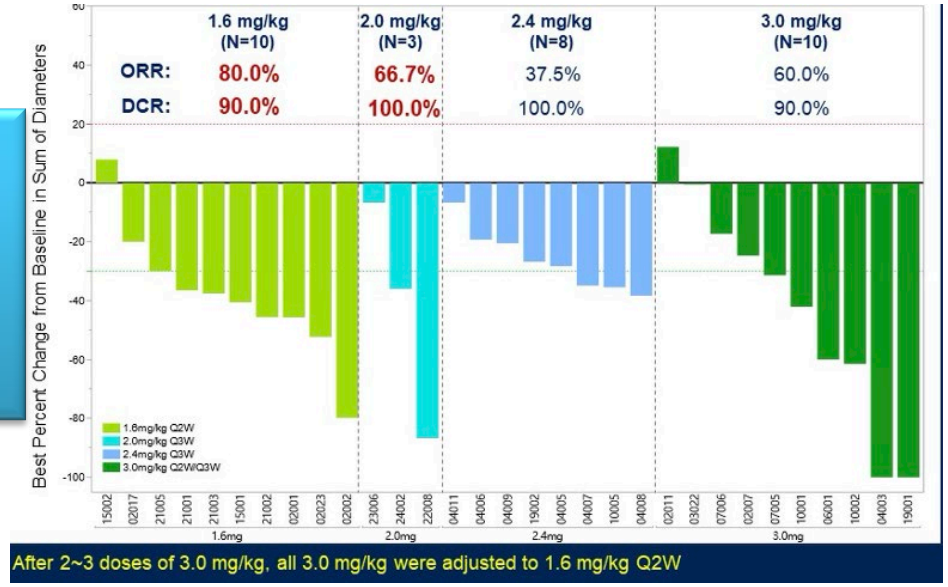




- 53 p SCLC
- 31 evaluables para respuesta
- ORR 61.·%
- DCR 93.5%



Grade≥3 TRAEs, n (%)	1.6 mg/kg Q2W (N=48)	2.0 mg/kg Q3W (N=8)	2.4 mg/kg Q3W (N=24)	3.0mg/kg Q2W / Q3W (N=51)
Neutrophil count decreased	**2 (4.2)**	**0**	4 (16.7)	23 (45.1)
Platelet count decreased	**2 (4.2)**	**0**	3 (12.5)	14 (27.5)
Anaemia	**1 (2.1)**	**1 (12.5)**	1 (4.2)	9 (17.6)

ADCs en Cáncer Broncopulmonar Microcítico

Compound.	Payload	Phase	Activity	% grade ≥3 TRAEs including deaths
Ifinatamab deruxtecan/ I-DXd	Topoisomerase I inhibitor, DAR4	II IDeate-Lung01 (Global) (NCT05280470)[1]	n=42 treated at 12mg/kg with confirmed ORR in 54.8%. Intracranial response 66.7% in n=6 (8mg/kg) and 50% in n=10 (12mg/kg).	Observed in 36.4% and one death. One ILD that lead to discontinuation.
GSK5764227	Topoisomerase inhibitor, DAR4	1a/b ARTEMIS-001 study (China) (NCT05276609)[2]	n=56 treated at doses 8.0-10mg/kg Q3W. ORR 61%. Tumour shrinkage in target lesion in 96.2% pts, deep response in 44.2%.	>10% neutropenia, leukopenia, thrombocytopenia
YL201	Topoisomerase inhibitor, DAR8	I/II dose escalation and expansion (China) (NCT05434234)[3]	n=72. ORR 63.9%, DCR 91.7%, mPFS-6.3mo, mDoR- 5.7mo.	Neutropenia 31.7%, leukopenia 29.5%, Anemia 25%, ILD 1.3% (3 cases). *7 deaths (2.6%) considered linked to drug
BNT324	Topoisomerase inhibitor, DAR6	II (Global) (NTC05914116)[4]	n=73, ORR 31.5% at 6-9mg/kg dose, higher in no prior topotecan 60.9%, DCR 89%	Observed in 23.8-51.9%. Neutropenia 15.9%, anemia 7%, thrombocytopenia 6.3%
MHB088C	SuperTopoi inhibitor-5-10x >potent than DXd, DAR4	II (China)	N=91 treated at doses 1.6-2.4mg/kg, ORR 42.4% (2mg/kg), DCR 87.9%, mPFS 5.7mo.	~10% haematologic AEs, 1 case of ILD (grade 2), 1 death related to drug

Resumen

- Los ADCs tienen un desarrollo clínico creciente
- Son fármacos complejos cuyos diferentes componentes pueden ser determinantes de la eficacia y efectos secundarios
- Importancia del epítopo y de su rol oncogénico
- Resultados limitados en 2L sin alteraciones oncogénicas
- Necesidad de biomarcadores predictivos validados y de difusión en práctica clínica
- Resultados iniciales en Carcinoma microcítico