16th CONGRESS Lung ON CANCER

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GECP lung cancer research

Is the future conjugated? ADCs in lung cancer treatment

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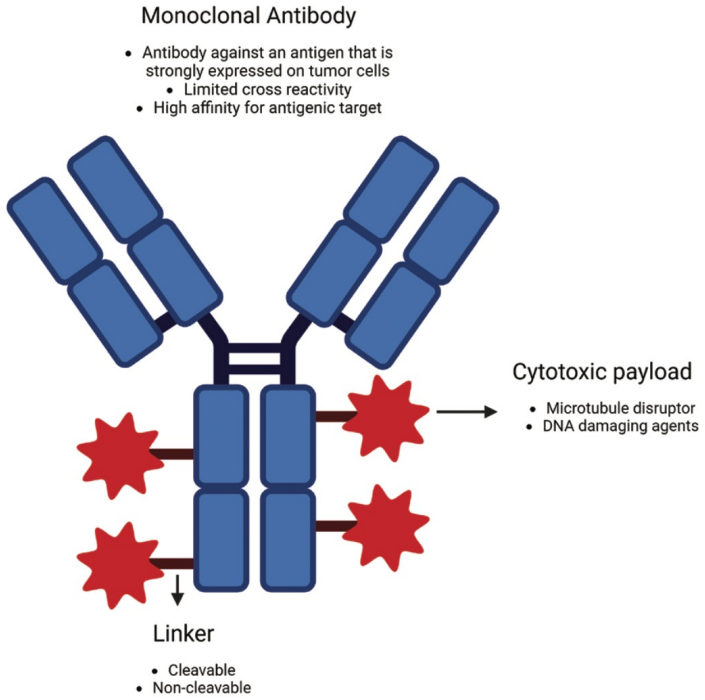
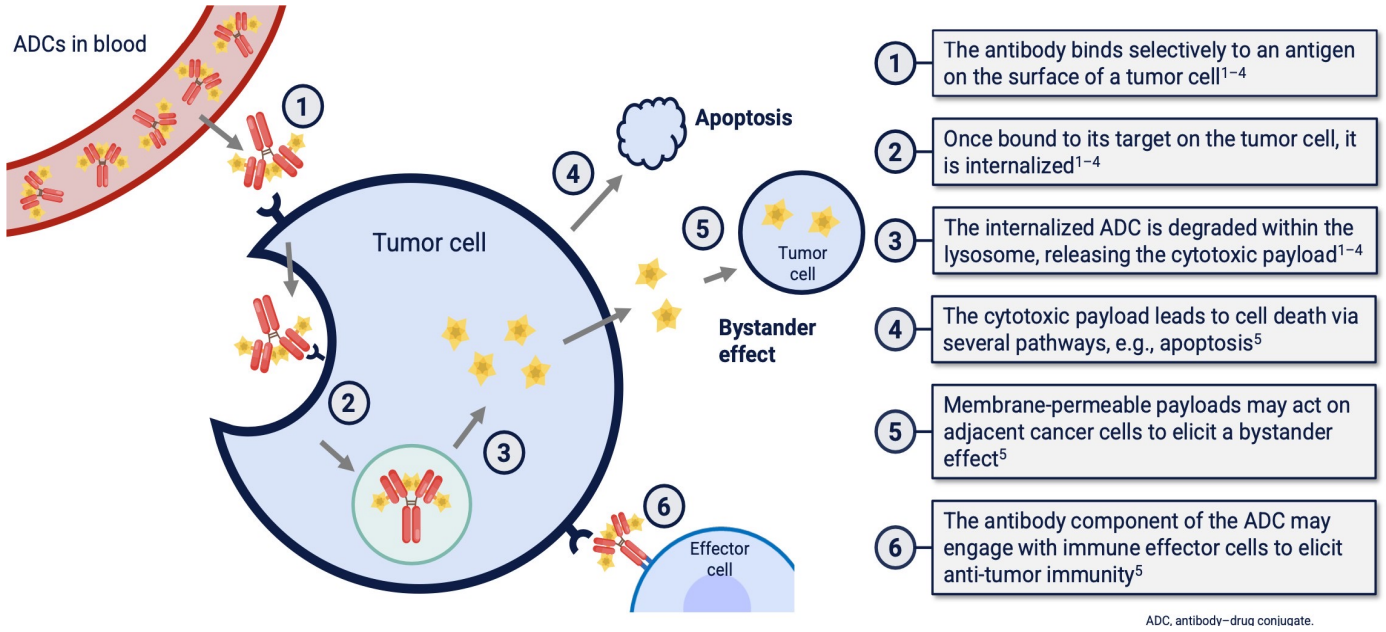
Declaration of interests

Dr. Fusco discloses the following conflicts of interest:

- Fees for lectures from Regeneron and Pierre Fabre
- Travel and accomodation expenses from Johnson & Johnson, Roche, AstraZeneca

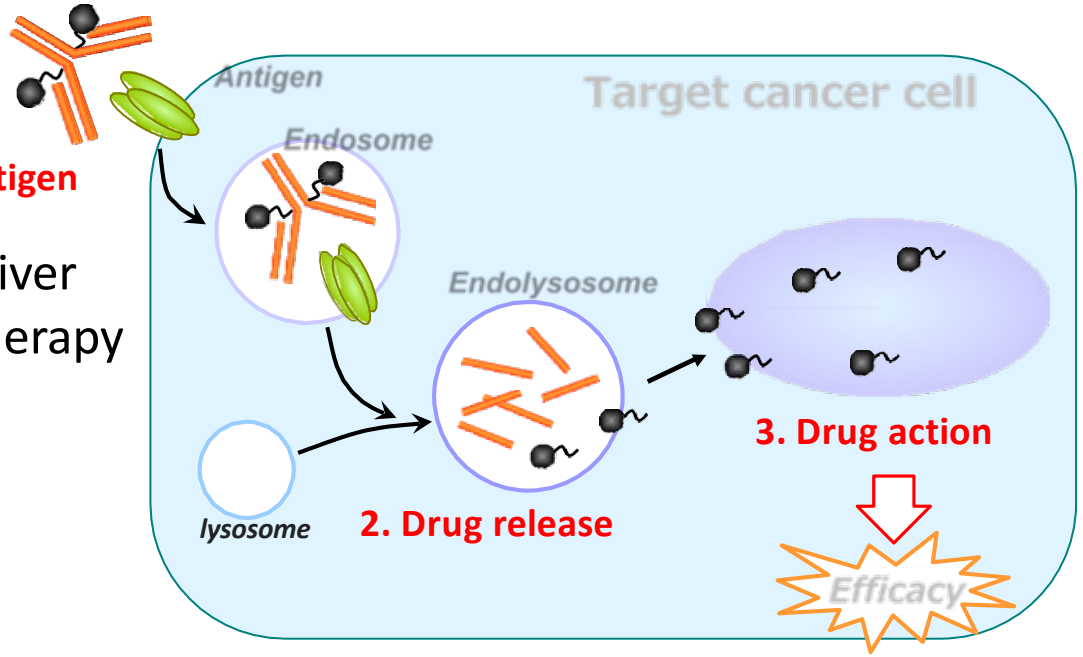
ADCs: How they work





1. Drago JZ, et al. Nat Rev Clin Oncol. 2021; 2. Khongorzul P, et al. Mol Cancer Res. 2020;
3. Coleman N, et al. NPJ Precis Oncol. 2023; 4. Kostova V, et al. Pharmaceuticals. 2021;
5. Fu Z, et al. Signal Transduct Target Ther. 2022; Bhardwaj PV, et al. The Oncologist 2023

ADCs: Chemotherapy, targeted therapy, or immunotherapy?



1: If the antigen is a driver
ADCs work as target therapy

3: Immunological effect

2: If the activity is dependent on drug release
ADCs work as chemotherapy (bystander effect included)

1. Drago JZ, et al. Nat Rev Clin Oncol. 2021; 2. Khongorzul P, et al. Mol Cancer Res. 2020;
3. Coleman N, et al. NPJ Precis Oncol. 2023; 4. Kostova V, et al. Pharmaceuticals. 2021;
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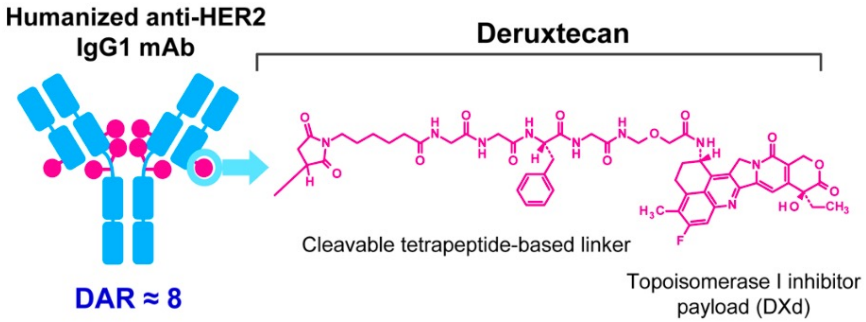
Targeting HER2 in NSCLC

Tratuzumab Deruxtecan (T-DXd)



DESTINY-Lung01 trial

Phase 2 study of T-DXd, a novel antibody-drug conjugate, in patients with HER2-overexpressing or HER2-mutated metastatic NSCLC (NCT03505710)

Key eligibility criteria
- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- ECOG PS of 0 or 1

Cohort 1: HER2-overexpressing[a] (IHC 3+ or IHC 2+) T-DXd 6.4 mg/kg q3w n = 49

Cohort 1a: HER2-overexpressing (IHC 3+ or IHC 2+) T-DXd 5.4 mg/kg q3w n = 41

Cohort 2: HER2-mutated T-DXd 6.4 mg/kg q3w n = 42 *(Encore to be presented at WCLC: abstract 1419)*[b]

Cohort 2 expansion: HER2-mutated T-DXd 6.4 mg/kg q3w n = 49

Primary end point
- ORR

Secondary end points
- PFS
- OS
- DOR
- DCR
- Safety and tolerability

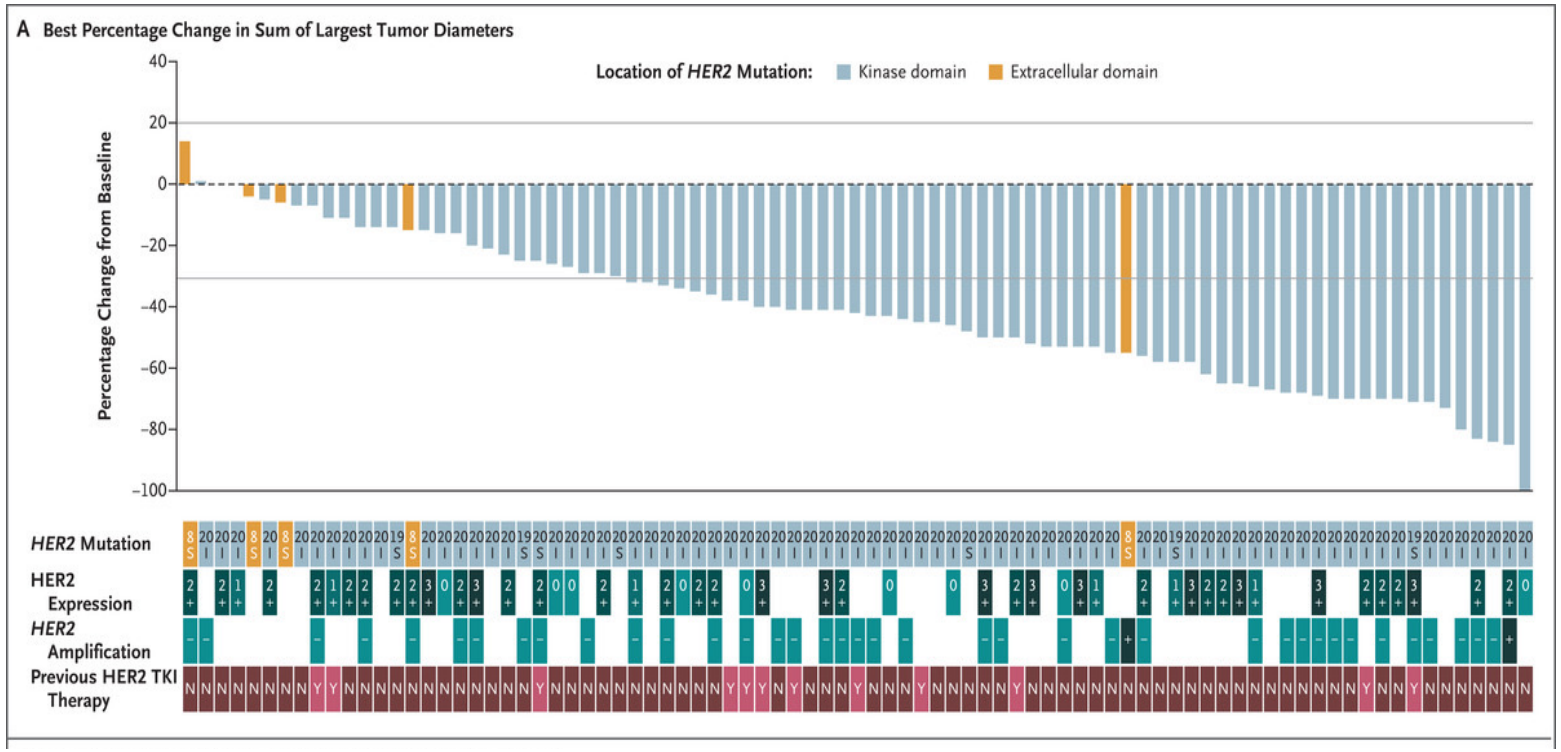
Interim analysis of cohort 1

Data cutoff: May 31, 2020

Nakada T et al, Translat Regulat Sci 2021; Li B, et al. NEJM 2021

Targeting HER2 in NSCLC

DESTINY-Lung01: Tratuzumab Deruxtecan (T-DXd) in pretreated HER2 mutant NSCLC



	Outcome (95% CI) N=91
ORR	55% (44-65)
mDOR	9.3 mos (5.7-14.7)
mPFS	8.2 mos (6.0-11.9)
mOS	17.8 mos (13.8-22.1)

Li B, et al. NEJM 2021

DESTINY-Lung03: Phase 1b, multicenter, open-label, dose-escalation study of T-DXd in HER2-OE NSCLC

Patient population

- Aged ≥18 years
- Centrally assessed HER2-OE (IHC 3+/2+)* unresectable, locally advanced or metastatic nonsquamous NSCLC
- Measurable disease per RECIST v1.1
- WHO/ECOG performance status 0–1
- Patients in Part 1 had one or two prior lines of therapy; those with therapy-targetable alterations must have had prior appropriate targeted therapy

Part 1: dose escalation† (enrollment complete)

Arm 1A: T-DXd + durvalumab + cisplatin
Arm 1B: T-DXd + durvalumab + carboplatin

Part 1: T-DXd monotherapy (enrollment complete)

Arm 1D: T-DXd 5.4 mg/kg IV Q3W (N=36)

Part 3: dose confirmation and expansion (currently recruiting)

T-DXd + volrustomig ± carboplatin

Part 4: safety run-in and expansion (currently recruiting)

T-DXd + rilvegostomig ± carboplatin

Key endpoints: T-DXd monotherapy (arm 1D)

Secondary:

- ORR
- DOR
- DCR
- PFS

(Investigator assessed)

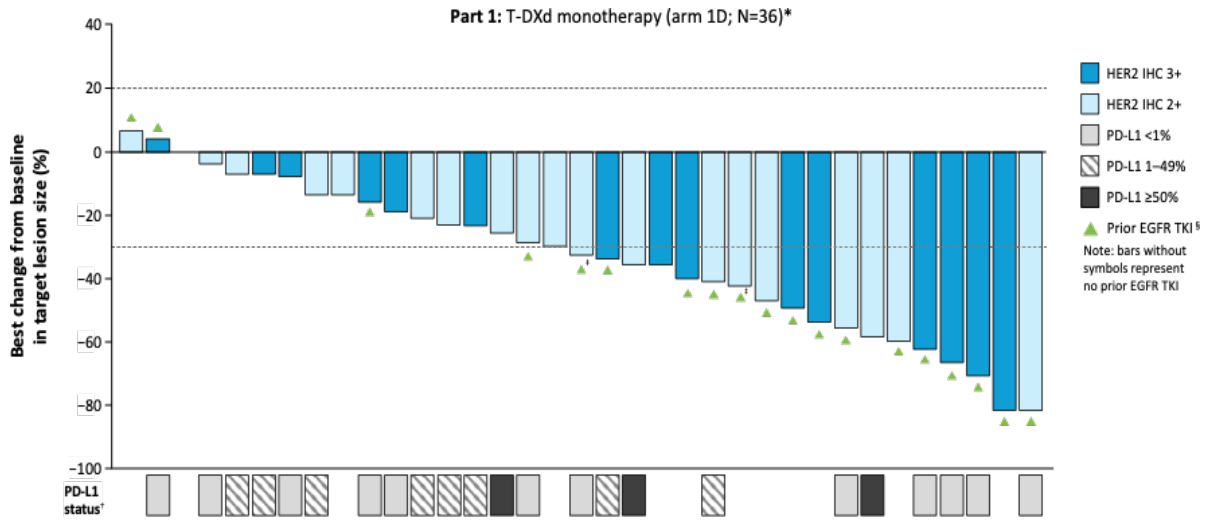
- OS
- Safety and tolerability

Exploratory:

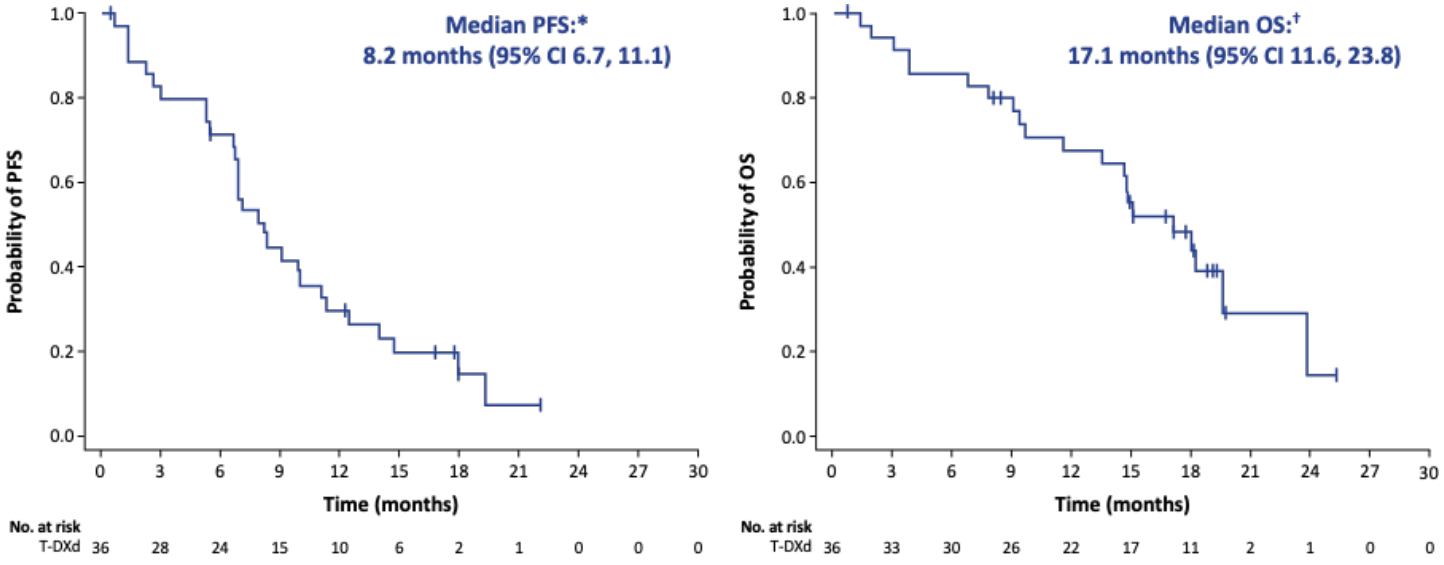
- Efficacy outcomes by:
  - HER2 IHC status
  - Prior EGFR TKI exposure‡

Planchard D, et al. WCLC 2024

DESTINY-Lung03: Efficacy



Confirmed ORR=44.4%



Planchard D, et al. WCLC 2024

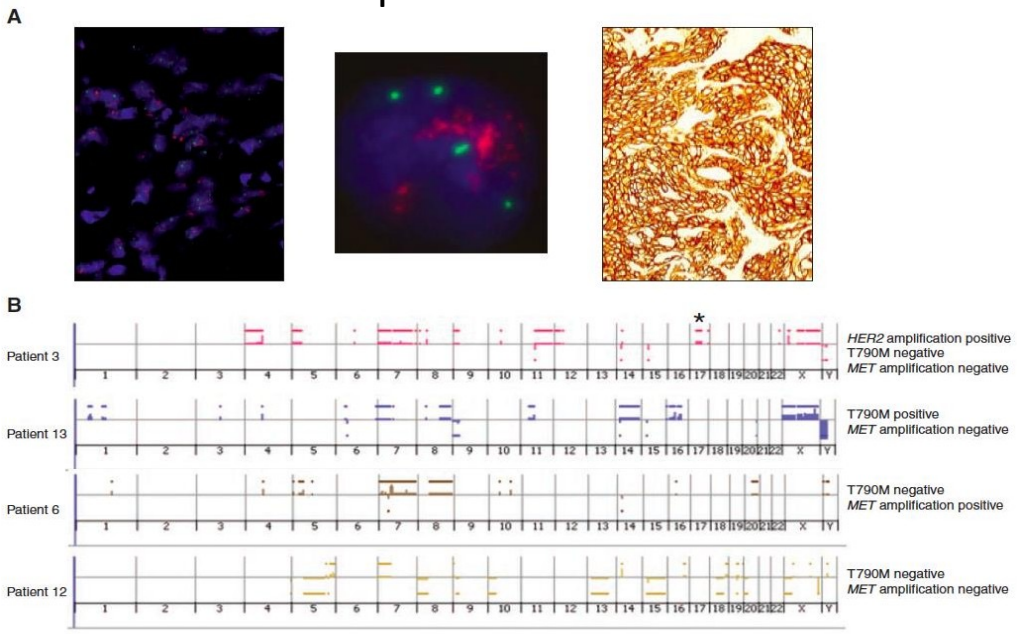
Efficacy driven by EGFR mutations

Part 1: T-DXd monotherapy (arm 1D)	HER2 IHC 3+ (n=16)	HER2 IHC 2+ (n=20)	Prior EGFR TKI (n=19)**	No prior EGFR TKI (n=17)**
Confirmed ORR, % (n)*† 95% CI	56.3 (9) 29.9, 80.3	35.0 (7) 15.4, 59.2	68.4 (13) 43.5, 87.4	17.6 (3) 3.8, 43.4
DCR at 12 weeks, % (95% CI)*‡	81.3 (54.4, 96.0)	75.0 (50.9, 91.3)	84.2 (60.4, 96.6)	70.6 (44.0, 89.7)
Median DOR, months (95% CI)*§	12.5 (5.5, NE)	6.6 (4.5, 11.0)	11.7 (5.5, NE)	4.6 (4.5, NE)
Median PFS, months (95% CI)*¶	6.9 (5.3, 17.9)	8.2 (5.4, 10.0)	8.2 (6.7, 19.3)	7.1 (1.4, 10.0)
Median OS, months (95% CI)‖	16.4 (6.8, NE)	17.1 (9.4, 23.8)	19.6 (13.5, NE)	14.7 (3.9, 18.0)

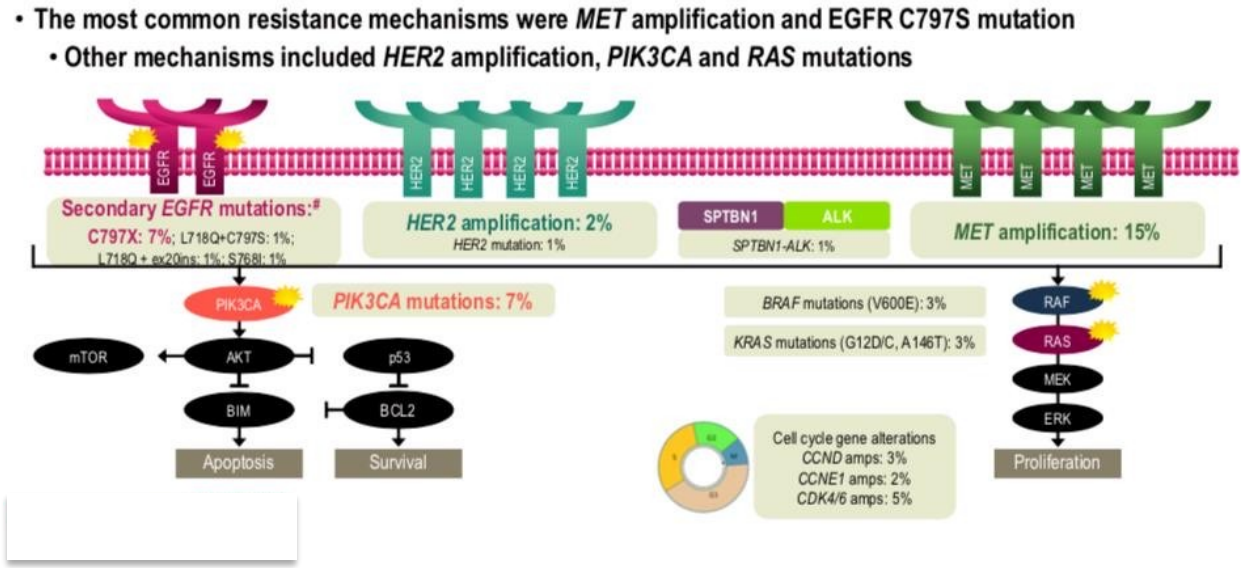
Planchard D, et al. WCLC 2024

HER2 gene copy number modulates EGFR-TKI sensitivity and it is a mechanism of resistance

High levels of *HER2* amplification induces aquired resistance



HER2 amplification is a mechanism of resistance to osimertinib



Takezawa K, et al. Cancer Discovery 2012; Ramalingam SS, et al. Ann Oncol 2018

Need for options after resistance to TKIs and immunotherapy: The challenge is to BEAT DOCETAXEL

Docetaxel

In non-oncogene addicted NSCLC anti-TROP2 ADCs work as chemotherapy: TROPION LUNG01 (Dato-DXd versus TXT)

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without actionable genomic alterations[a]
- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

- **Dato-DXd** 6 mg/kg Q3W (N=299)
- **Docetaxel** 75 mg/m² Q3W (N=305)

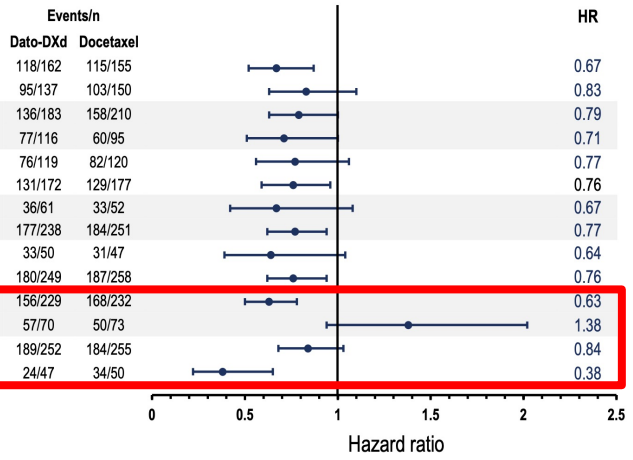
Dual Primary Endpoints
- PFS by BICR
- OS

Secondary Endpoints
- ORR by BICR
- DOR by BICR
- Safety

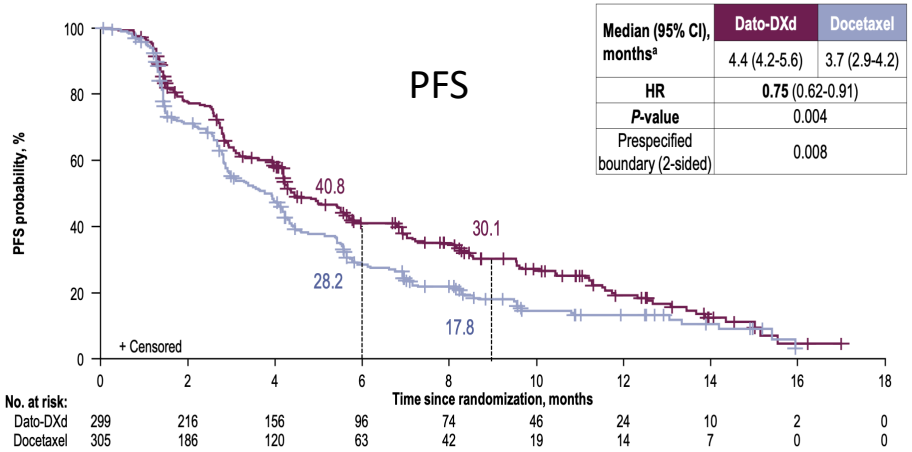
Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

PFS in subgroups

		Events/n Dato-DXd	Events/n Docetaxel	HR
Age at randomization	<65 years	118/162	115/155	0.67
	≥65 years	95/137	103/150	0.83
Sex	Male	136/183	158/210	0.79
	Female	77/116	60/95	0.71
Race	Asian	76/119	82/120	0.77
	Non-Asian	131/172	129/177	0.76
Smoking status	Never	36/61	33/52	0.67
	Former/current	177/238	184/251	0.77
Brain metastasis at baseline	With	33/50	31/47	0.64
	Without	180/249	187/258	0.76
Histology	Non-squamous	156/229	168/232	0.63
	Squamous	57/70	50/73	1.38
Actionable genomic alterations[a]	Absent	189/252	184/255	0.84
	Present	24/47	34/50	0.38



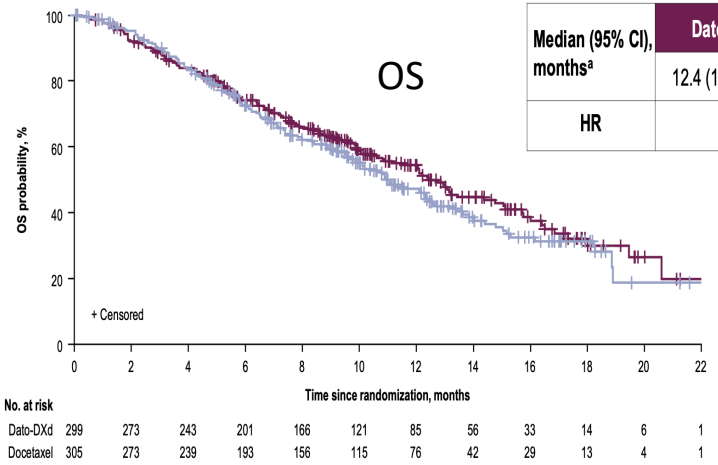
PFS



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	0.75 (0.62-0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

OS



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8-14.8)	11.0 (9.8-12.5)
HR	0.90 (0.72-1.13)	

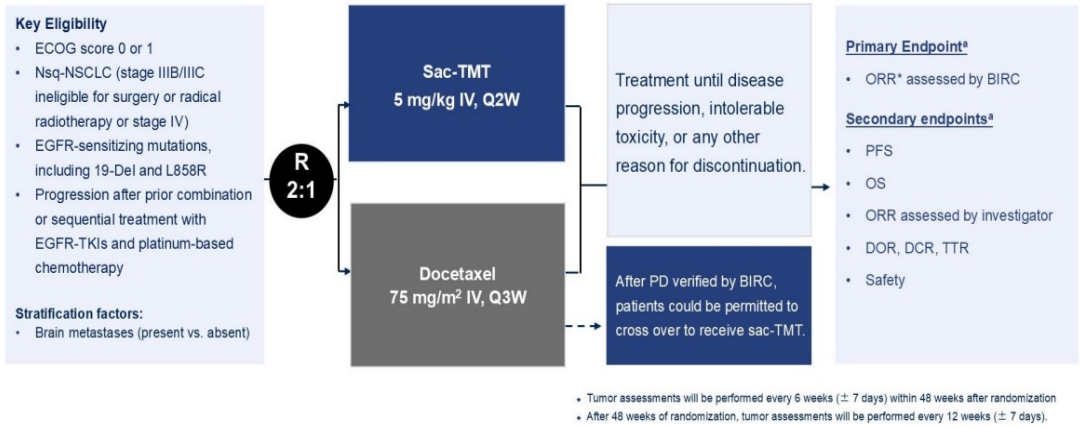
Information fraction at interim analysis (events/total events required): **74%.**

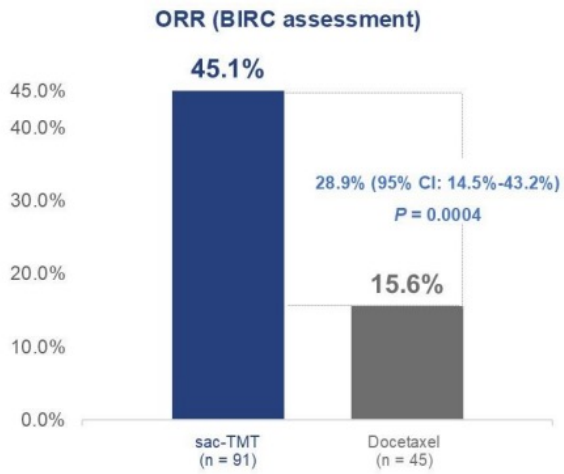
Non-squamous HR (95% CI): **0.77** (0.59-1.01); **Squamous HR** (95% CI): **1.32** (0.87-2.00)

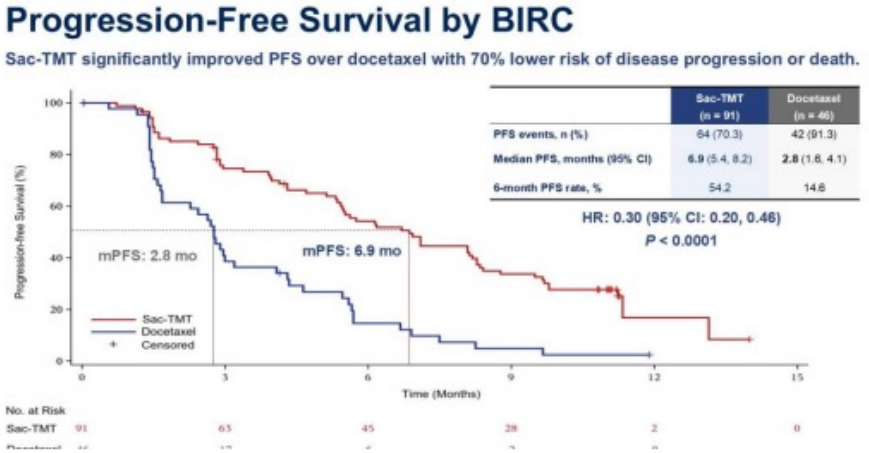
Ahn MJ, et al. ESMO 2023

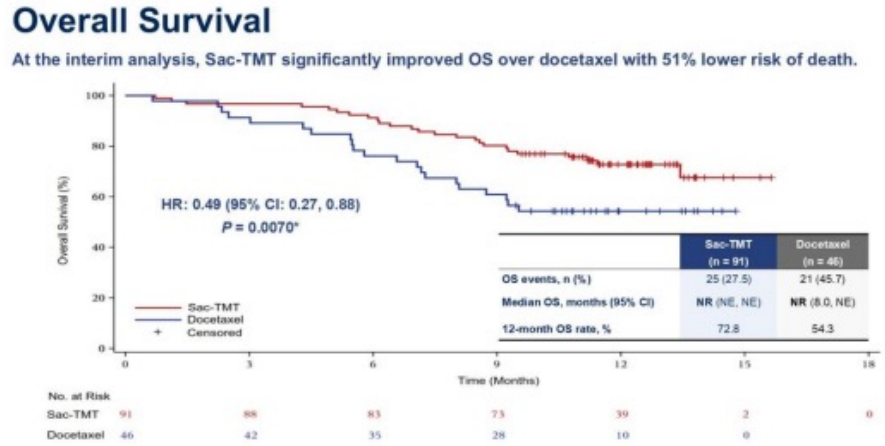
Sacituzumab tirumotecan in pretreated EGFR mutant NSCLC

OptiTROP-Lung03









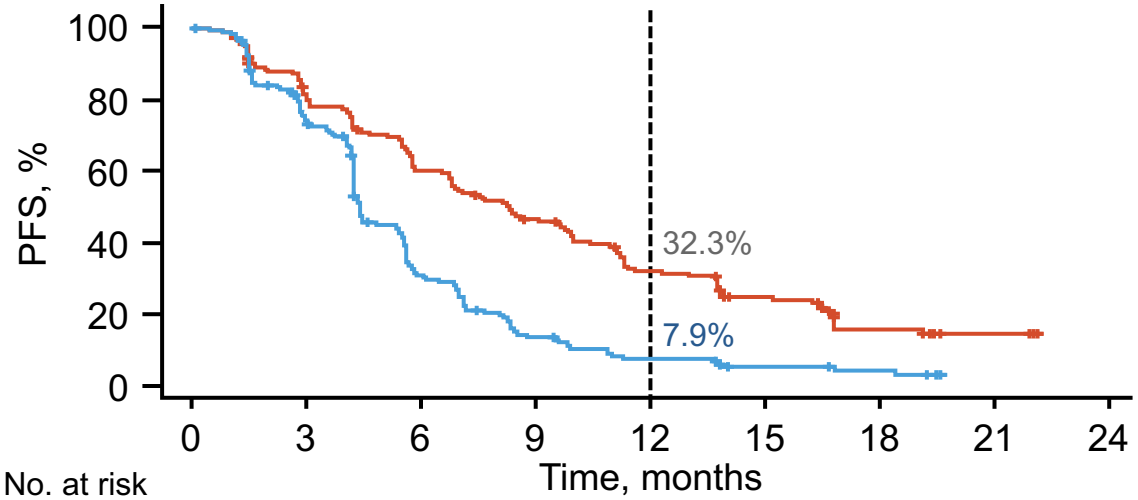
Zhang L, et al. ASCO 2025

Sacituzumab tirumotecan in pretreated EGFR mutant NSCLC

OptiTROP-Lung04, phase III trial

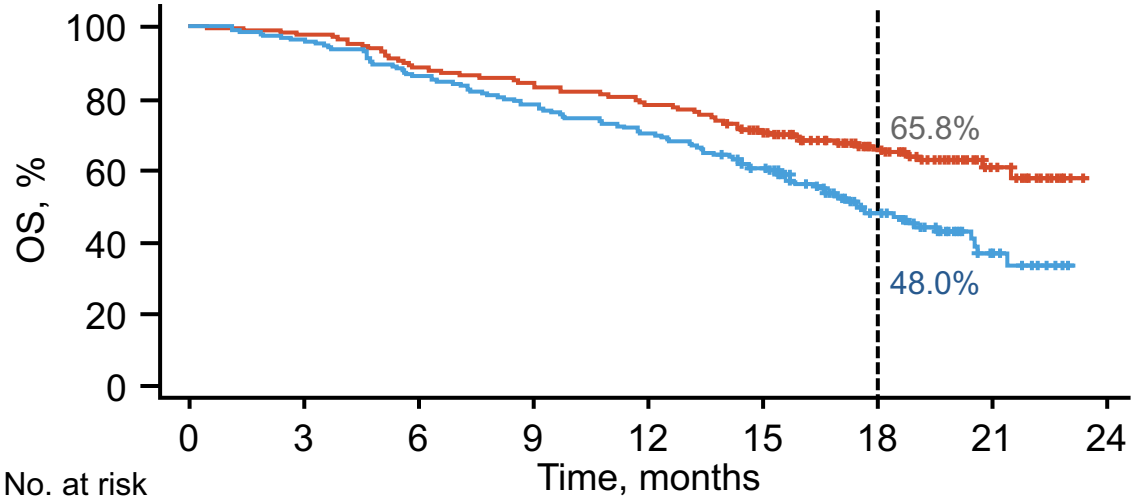
PFS by BICR

	Sacituzumab tirumotecan (n=188)	Chemotherapy (n=188)
PFS events, n (%)	144 (76.6)	159 (84.6)
mPFS, mo (95%CI)	8.3 (6.7, 9.9)	4.3 (4.2, 5.5)
12-mo PFS, mo (95%CI)	32.3 (25.5, 39.2)	7.9 (4.4, 12.8)
HR (95%CI); p-value	0.49 (0.39, 0.62); <0.0001	



OS

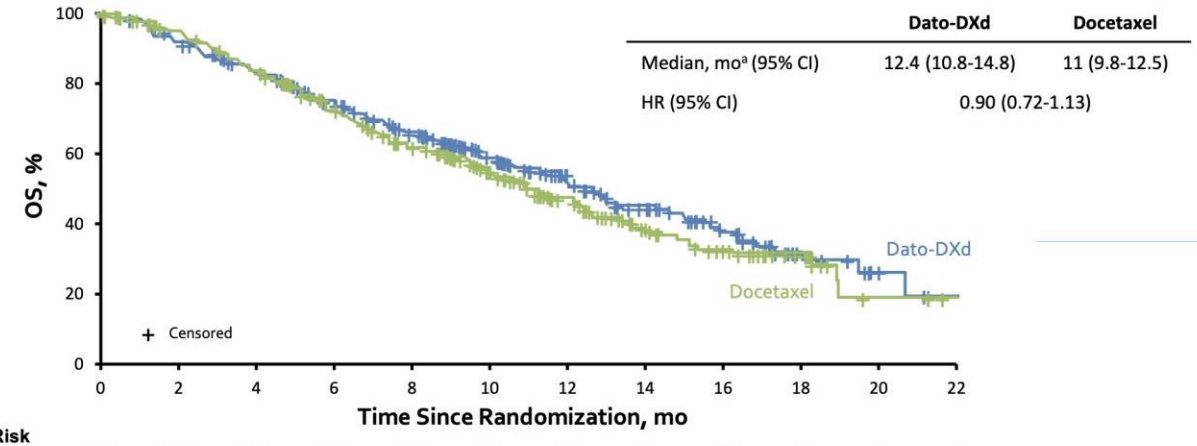
	Sacituzumab tirumotecan (n=188)	Chemotherapy (n=188)
OS events, n (%)	67 (35.6)	101 (53.7)
mOS, mo (95%CI)	NR (21.5, NE)	17.4 (15.7, 20.4)
18-mo OS, mo (95%CI)	65.8 (58.3, 72.3)	48.0 (40.2, 55.4)
HR (95%CI); 2-sided p-value*	0.60 (0.44, 0.82); 0.001*	



Zhang L et al. ESMO 2025 and Ann Oncol 2025

Do ADCs work as immunotherapy? No evidence of effect on long- term survival

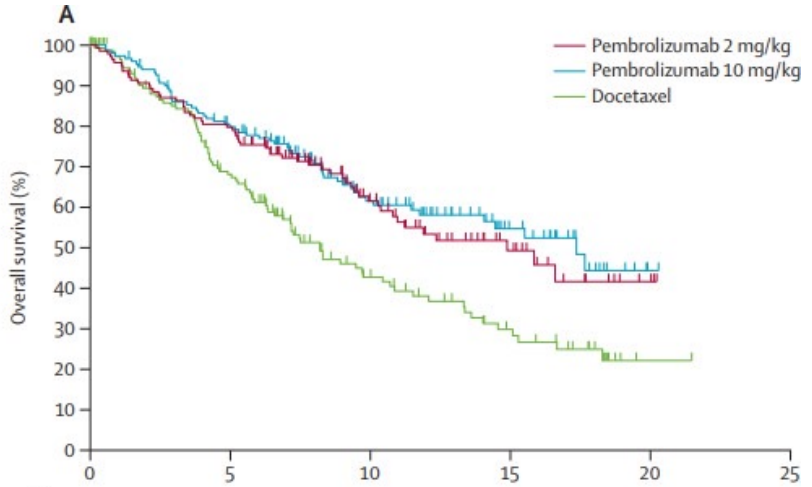
Dato DXd in TROPION Lung 01



	Dato-DXd	Docetaxel
Median, mo[a] (95% CI)	12.4 (10.8-14.8)	11 (9.8-12.5)
HR (95% CI)	0.90 (0.72-1.13)	

No. at Risk												
Dato-DXd	299	273	243	201	166	121	85	56	33	14	6	1
Docetaxel	305	273	239	193	156	115	76	42	29	13	4	1

Pembrolizumab in pretreated NSCLC*, KEYNOTE-010



Number at risk						
Pembrolizumab 2 mg/kg	139	110	51	20	3	0
Pembrolizumab 10 mg/kg	151	115	60	25	1	0
Docetaxel	152	90	38	19	1	0

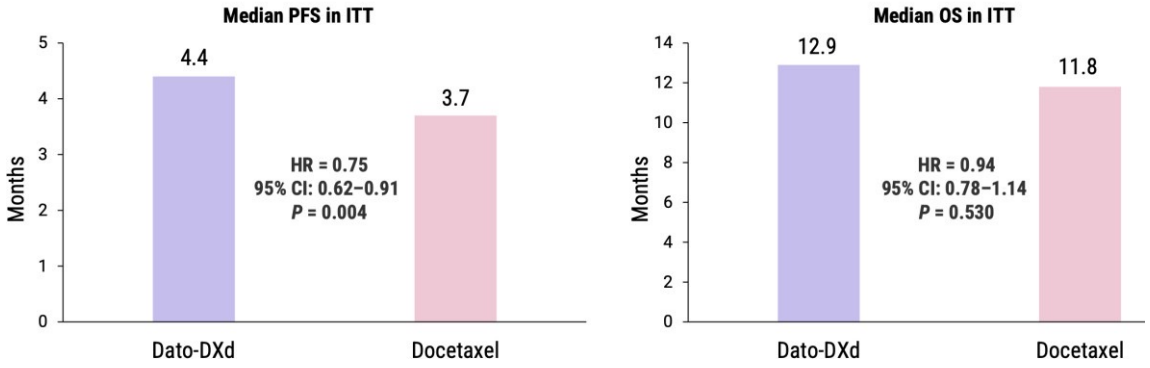
*PD-L1 tumour proportion score of 50% or greater

Ahn M,et al. ESMO 2023; Herbst R, et al. Lancet 2015

No ADCs showed OS improvement over standard chemotherapy in non-oncogene-addicted NSCLC in phase III trials

TROPION-Lung01: Results

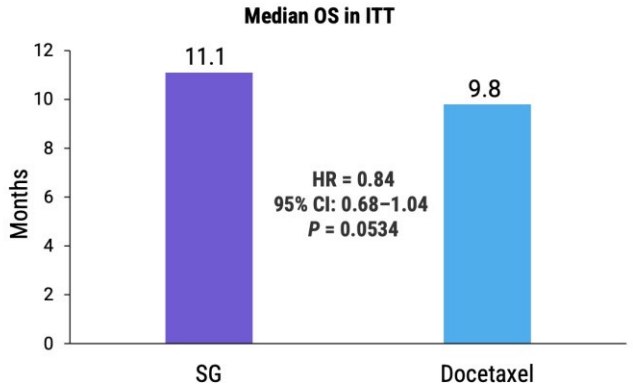
Phase 3 study examining datopotamab deruxtecan vs docetaxel in pre-treated patients with advanced/metastatic NSCLC with or without actionable genomic alterations



EVOKE-01: Efficacy

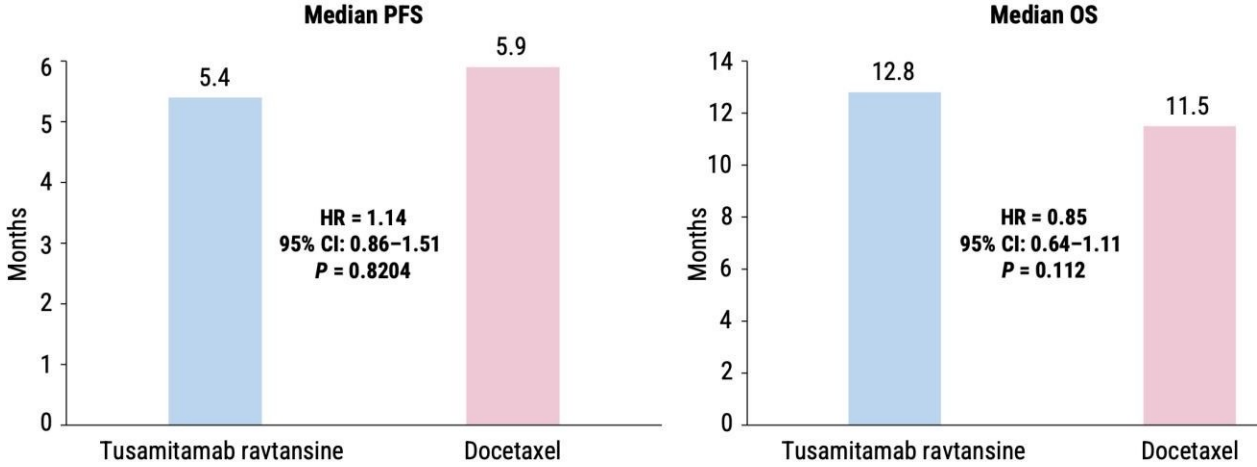
Phase 3 study examining sacituzumab govitecan vs docetaxel in patients with mNSCLC progressing on or after PBC and anti-PD-(L)1 treatment

- Patients were randomised to receive either 10 mg/kg sacituzumab govitecan on Day 1 and 8 or 75 mg/m^2 docetaxel on Day 1 of each 21-day cycle



CARMEN-LC03: Results[1,2]

Phase 3, randomised, open-label, study examining tusamitamab ravtansine vs docetaxel in patients with pretreated, advanced, non-squamous CEACAM5-positive NSCLC

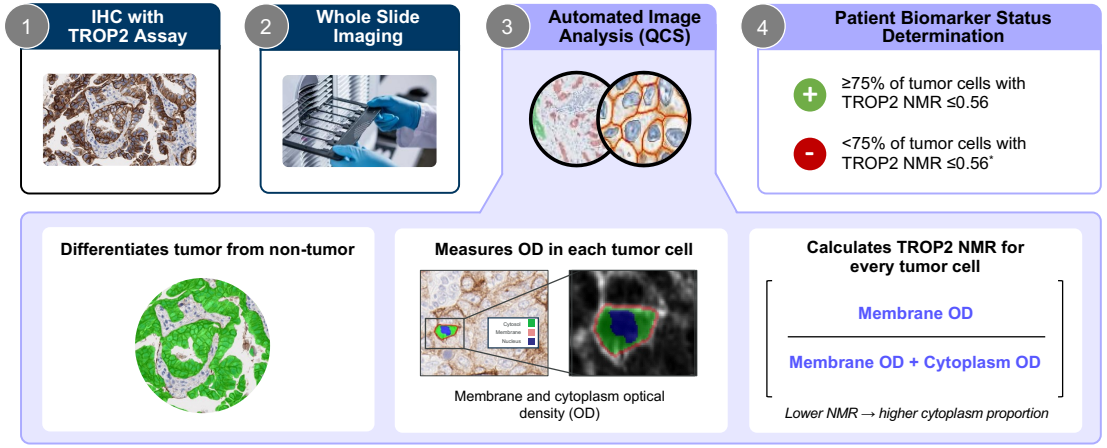


Ahn MJ, et al. JCO 2025; Paz-Ares L, et al. JCO 2024; The ASCO post Aug 2025

Improving ADCs efficacy: are Biomarkers and Digital Pathology the key?

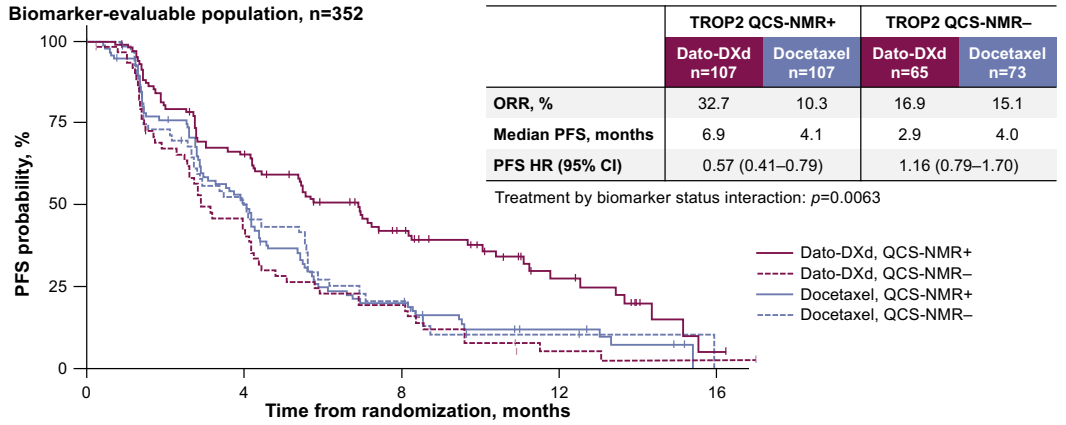
TROPION-Lung01 TROP2 QCS: TROP2 Normalized Membrane Ratio (NMR) Measured by Quantitative Continuous Scoring (QCS)

QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2



*Or >25% of cells with an NMR >0.56.
IHC, immunohistochemistry; NMR, normalized membrane ratio; OD, optical density (a measure of staining intensity); QCS, quantitative continuous scoring; TROP2, trophoblast cell-surface antigen 2.

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the biomarker-evaluable population



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Treatment by biomarker status interaction: p=0.0063

Data cutoff: March 29, 2023. PFS HR (95% CI) by TROP2 QCS-NMR status (+ vs -) within treatment: Dato-DXd: 0.48 [0.33–0.69]; Docetaxel: 0.97 [0.66–1.39].
BEP, biomarker evaluable population; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; NMR, normalized membrane ratio; ORR, objective response rate; PFS, progression-free survival; QCS, quantitative continuous scoring; TROP2, trophoblast cell-surface antigen 2; vs, versus.

Garassino MC et al. WCLC 2024

Improving ADCs efficacy: biomarker selection

Telisotuzumab Vedotin in MET overexpressing NSCLC

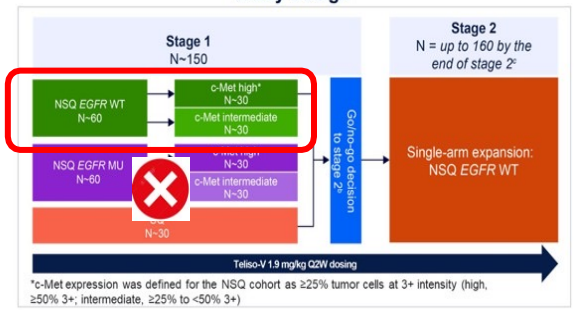
LUMINOSITY is a phase 2, multicenter, non-randomized, 2-stage study (NCT03539536)

Eligible Patients
- ≥18 years
- Advanced/metastatic NSCLC
- c-Met OE by IHC[a]
- Received ≤2 prior lines of systemic therapy in the advanced/metastatic setting, including cytotoxic CTx (≤1 line), immunotherapy (sequential or combined with CTx), and therapy targeting driver gene alterations (if eligible)

Primary Endpoint
- ORR assessed by ICR per RECIST v1.1

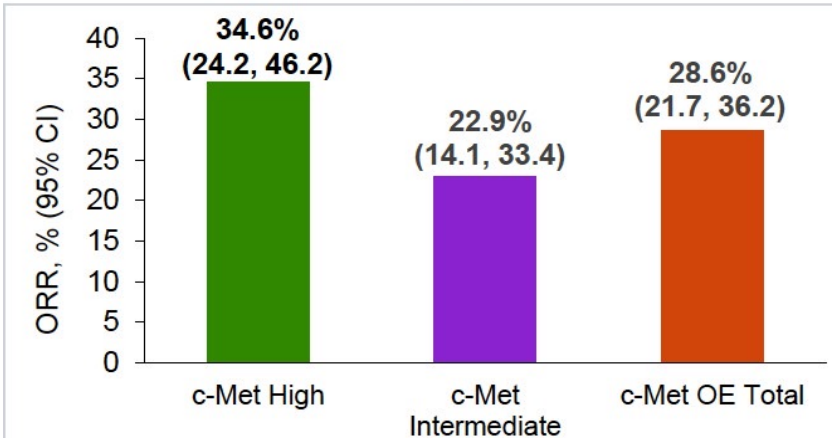
Secondary Endpoints
- DCR, DOR, PFS, and OS

Study Design



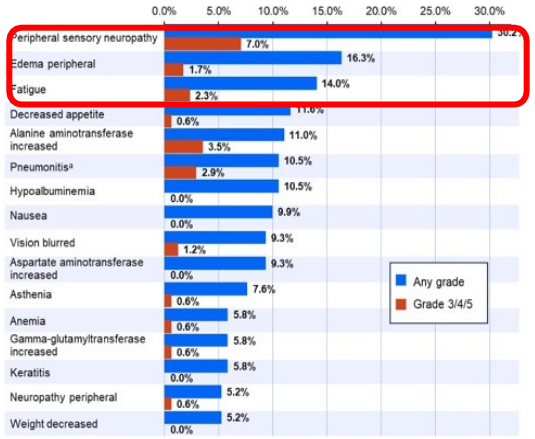
- The SQ and *EGFR* MU NSQ cohorts met stopping criteria
- The *EGFR* WT NSQ cohort met criteria for expansion in stage 2

ORR



Safety: Treatment-related adverse events occurring in >5% of patients

TRAEs



Events (N=172)	TRAE[b]
Any grade	140 (81.4)
Grade ≥3	48 (27.9)
Serious	21 (12.2)
Leading to Teliso-V discontinuation	37 (21.5)
Leading to death	2 (1.2)

- No new safety signals were observed with Teliso-V
- TRAEs leading to death were ILD and respiratory failure in one patient each
- Possible pneumonitis/ILD cases were formally adjudicated retrospectively (see slide 11)

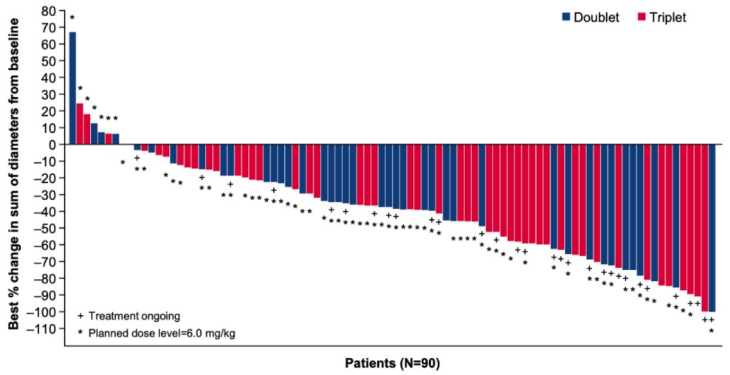
Camidge R, ASCO 2024

ADCs: First-Line Potential?

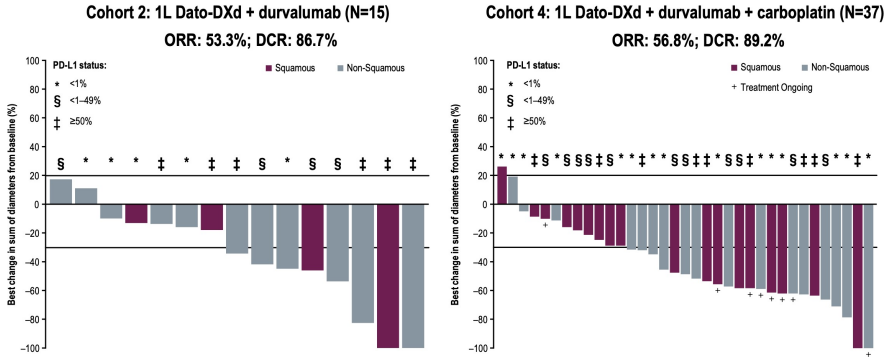
Work in progress…

Anti-TROP2 ADC - Ready for the first LINE?

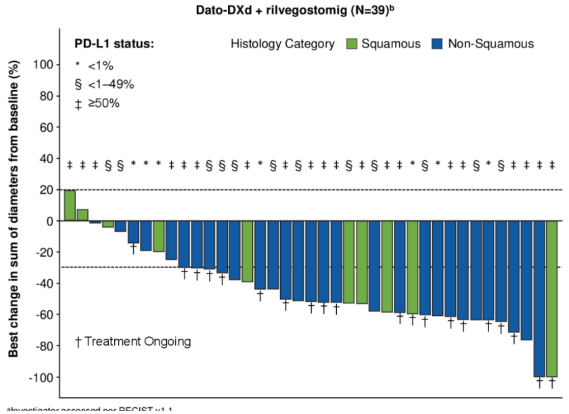
TROPION-Lung02: First-line
– Dato-DXd + chemo/pembro: RR 56%, DCR 89%
– Dato-DXd + pembro: RR 52%, DCR 88%



TROPION-Lung04: First-line
– Dato-DXd + durva: RR 53.3%, DCR 86.7%
– Dato-DXd + chemo/durva: RR 56.8%, DCR 89.2%



TROPION-Lung04: First-line
Cohort 5 Dato-DXd + Rilvegostomig: ORR 57.5%, DCR 95%

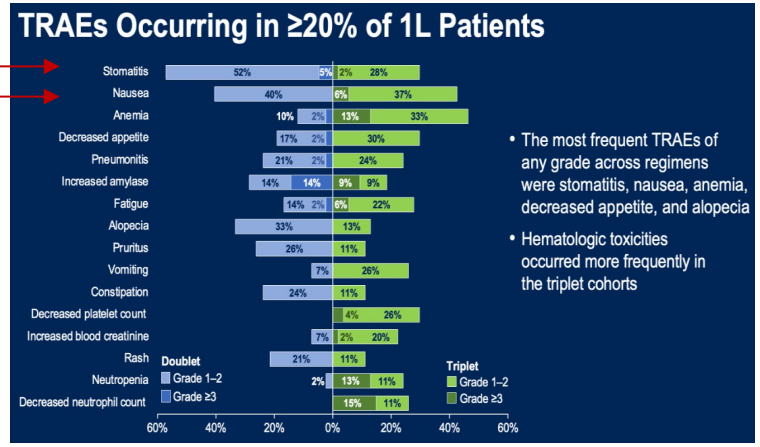


Levy ASCO 2024; Kalinka ESMO TAT 2023; Waqar ASCO 2025

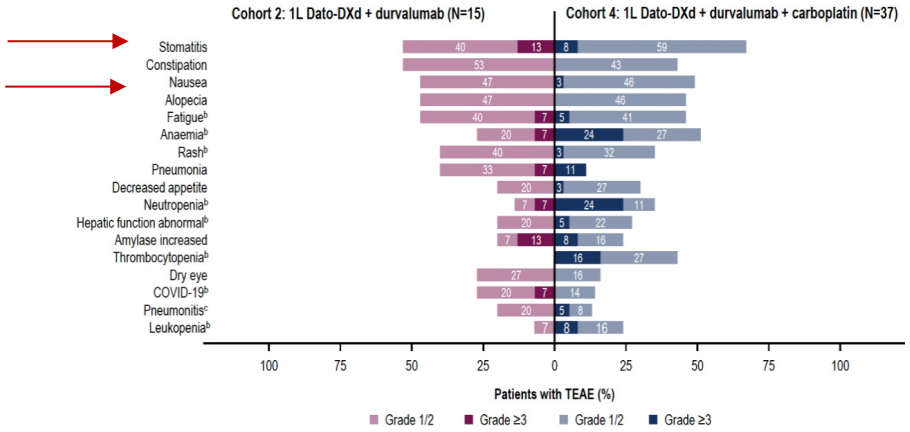
Anti-TROP2 ADC - Ready for the first LINE?

Toxicity

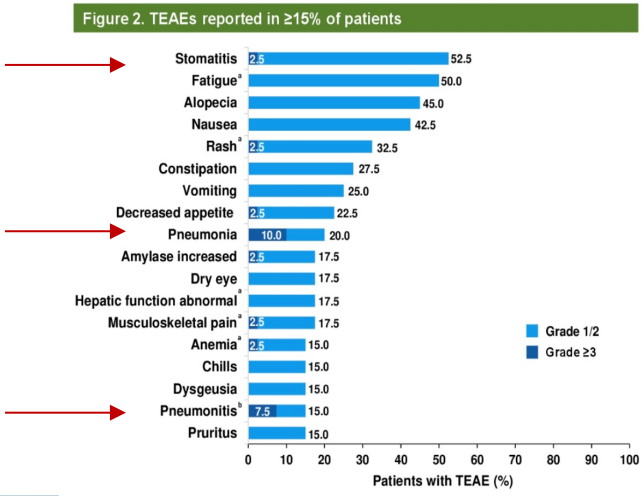
TROPION-Lung02: First-line Dato-DXd + pembro +/- chemo



TROPION-Lung04: First-line Dato-DXd + durva +/- chemo



TROPION-Lung04: First-line Cohort 5 Dato-DXd + Rilvegostomig



n (%)	Cohort 2 (Dato-DXd + durvalumab) N=15	Cohort 4 (Dato-DXd + durvalumab + carboplatin) N=37
TEAEs	15 (100)	37 (100)
Treatment-related	15 (100)	37 (100)
Grade ≥3 TEAEs	9 (60.0)	26 (70.3)
Treatment-related	7 (46.7)	23 (62.2)
Serious TEAEs	7 (46.7)	19 (51.4)
Treatment-related	6 (40.0)	10 (27.0)
TEAEs leading to discontinuation of any study drug	4 (26.7)	9 (24.3)
Related to Dato-DXd	4 (26.7)	8 (21.6)
Related to durvalumab	2 (13.3)	7 (18.9)
Related to carboplatin	0	3 (8.1)
TEAEs associated with death of any study drug	0	2 (5.4)[a]
Related to Dato-DXd	0	2 (5.4)
Related to durvalumab	0	2 (5.4)
Related to carboplatin	0	0
Stomatitis	8 (53.3)	25 (67.6)
Grade ≥3	2 (13.3)	3 (8.1)
Ocular surface events	4 (26.7)	14 (37.8)
Grade ≥3	0	1 (2.7)
Adjudicated drug-related ILD/pneumonitis[b]	3 (20.0)	6 (16.2)
Grade ≥3	1 (6.7)[c]	1 (2.7)[d]

Levy ASCO 2025; Kalinka ESMO TAT 2023; Waqar ASCO 2025

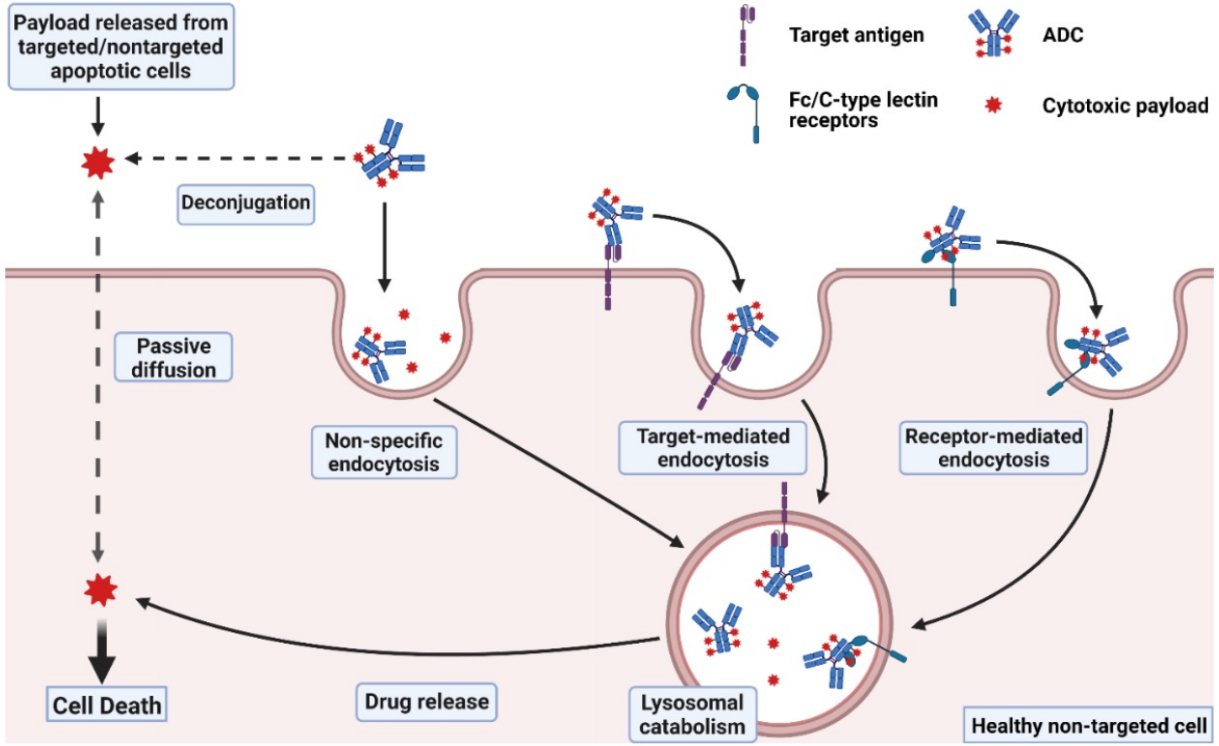
If ADCs are so specific, why do they have toxicity?

On target, off tumour toxicity

- Presence of the target in normal cells

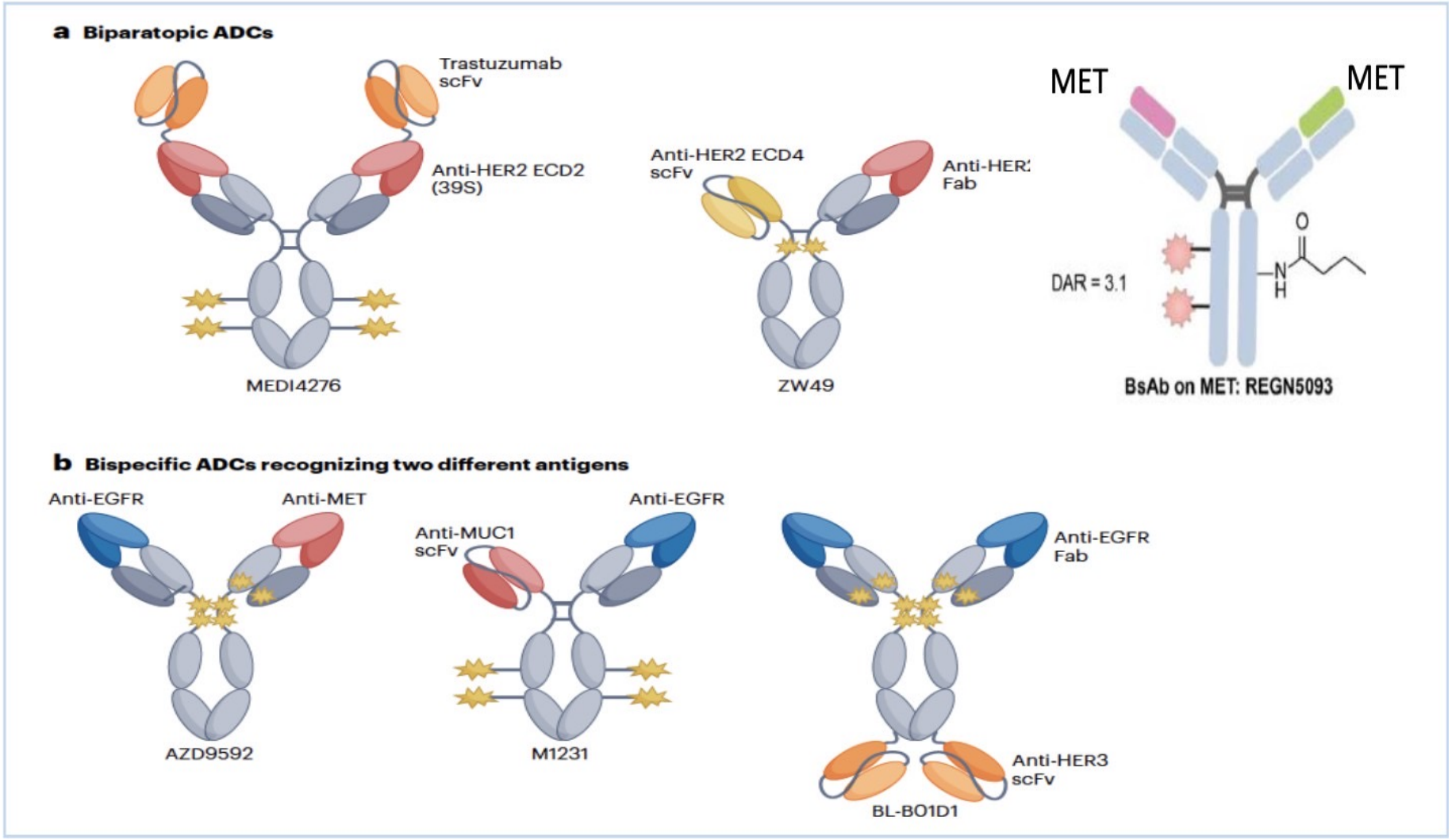
Off target, off tumour toxicity

- Related to the payload and the linker



Nguyen et al., Cancers 2023

Improving ADCs efficacy: New agents



Conclusions

✓ ADCs are effective in oncogene-addicted NSCLC

- The best sequence in the therapeutic strategy remains undefined

For non oncogene-addicted NSCLC, no long term OS benefit has been shown to date

- Define optimal biomarkers
- Define the optimal population for treatment intensification

Safety could be critical

- Second-line: AEs are an issue in a frail population
- First-line: Risk of toxicity when combined with other agents
- Neoadjuvant or adjuvant: Safe agents are needed

New generation ADCs are under investigation

Thank you for your attention!

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

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GECP lung cancer research