ANTIBODY-DRUG CONJUGATES (ADCs) IN LUNG CANCER: A TRANSFORMATIVE THERAPEUTIC CLASS?

Joshua E. Reuss, MD

Georgetown University

@Joshua_Reuss

April 20, 2024

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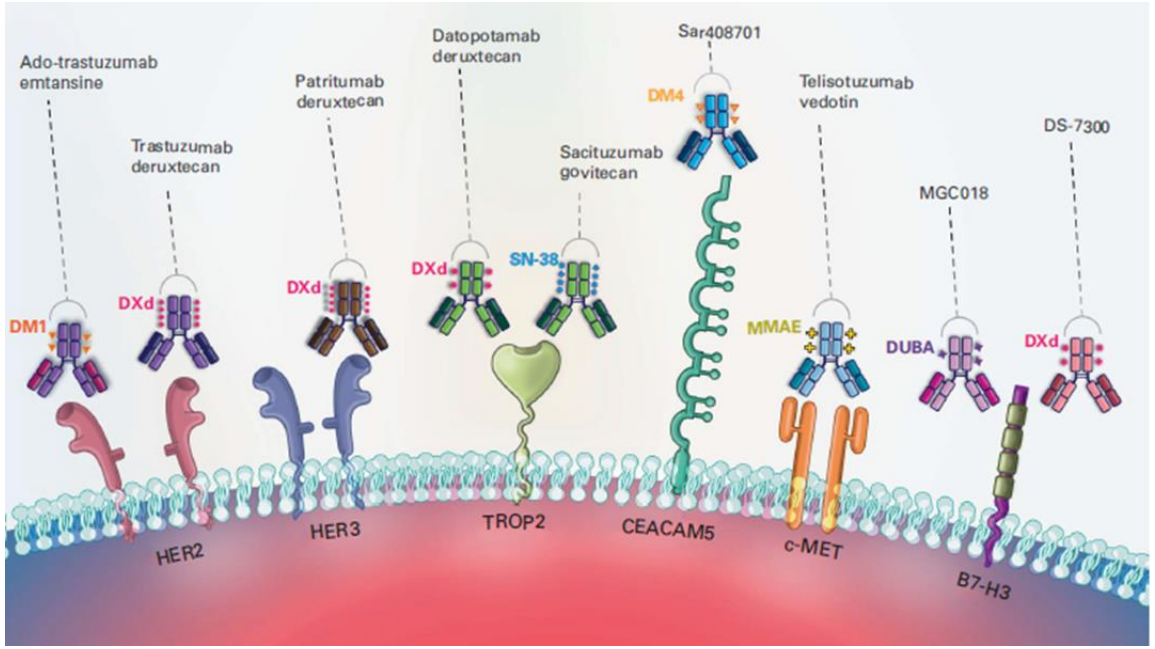
ADCs in Lung Cancer – superheroes we need?



Passaro et al. *J Clin Oncol* 2023

ADCs ASSEMBLE!

Antibody-Target

- Target - selectively expressed or over-expressed on tumor cells.
- Antibody - Human or humanized immunoglobulin, IgG1 most common.
- High internalization capacity.

Linker

- Non-cleavable.
  - Traffic to mature lysosomes for degradation.
  - Limited “bystander effect”.
- Cleavable.
  - Cell physiology key to payload-linker uncoupling.
  - Prominent “bystander effect”.

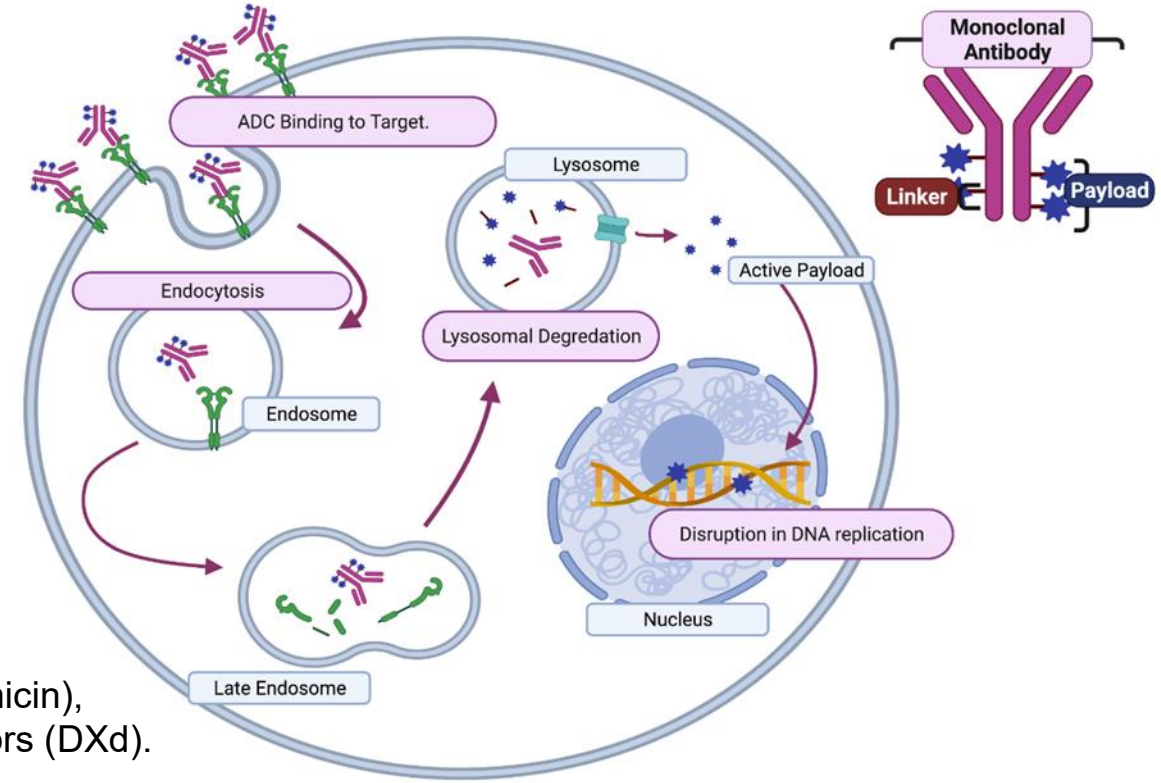
Payload

- Highly potency cytotoxin including DNA damaging agents (PBD, calicheamicin), tubulin polymerization inhibitors (MMAE, DM1), and topoisomerase inhibitors (DXd).
- Drug-antibody ratio: number of payloads attached to an antibody.

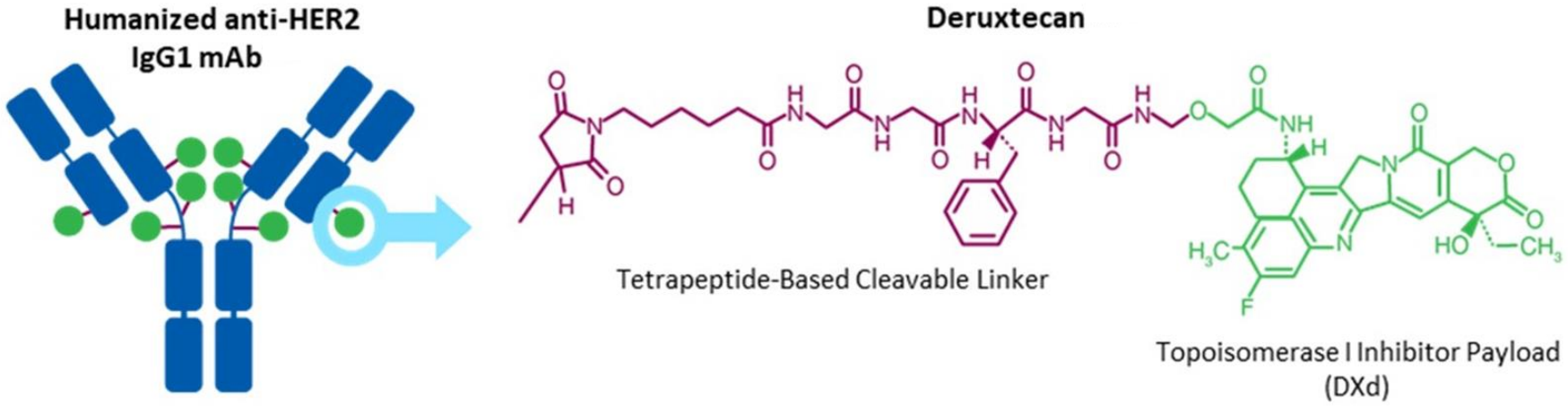
Mechanism of Action

- Payload delivery, ADCC, complement-mediated cytotoxicity, inhibition of oncogenic drivers.

Marks et al. *Curr Oncol Rep* 2023



HER2: Trastuzumab Deruxtecan (T-DXd)



- T-DXd: HER2-targeted ADC of trastuzumab (anti-HER2 mAb) conjugated to deruxtecan (DXd) via cleavable linker with DAR of 8.
- Elicits significant bystander effect, supporting use in tumors with heterogeneous HER2-expression.

DESTINY-Lung01

- *HER2-mutated:* ORR 55%, mOS 17.8mo, mPFS 8.2mo, mDOR 9.3mo.
- HER2 overexpression: ORR 34%, mOS 11.2mo, mPFS 6.7mo, mDOR 6.2mo.

Smith et al. *ASCO* 2020; Li *et al.* NEJM 2021; Smit *et al.* ESMO 2022

T-DXd in advanced *HER2*-mutated NSCLC – Phase 2 DESTINY-Lung02 Trial

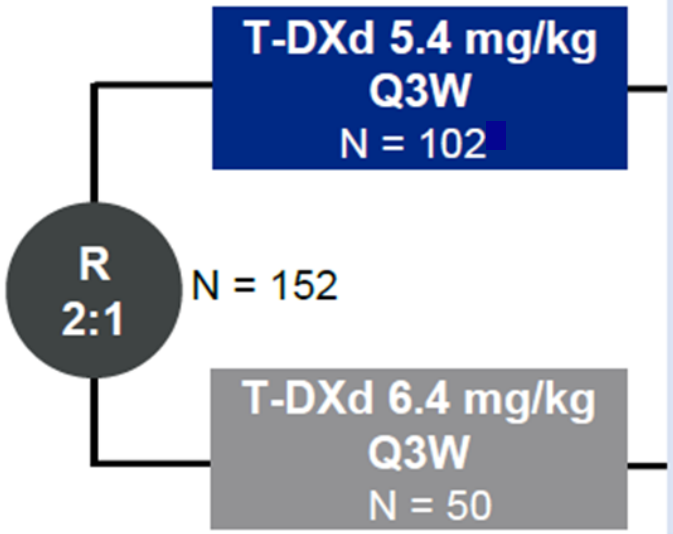
Study Design

Key Eligibility Criteria

- Metastatic *HER2*m NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:

- Prior anti–PD-(L)1 treatment



Primary Endpoint

- Confirmed ORR by BICR

Secondary Endpoints

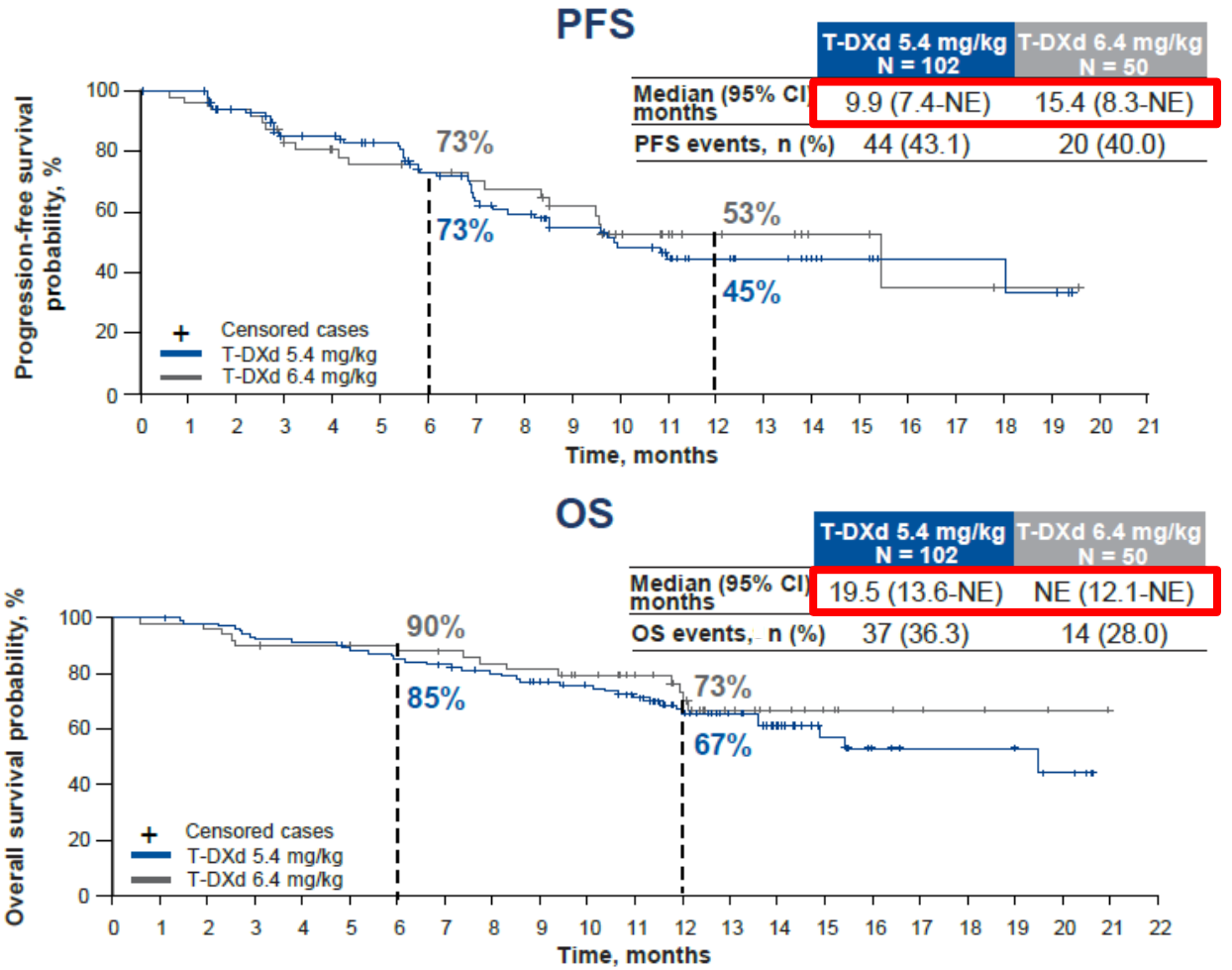
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Janne et al. *WCLC* 2020

Comparable efficacy observed at both T-DXd doses in DESTINY-Lung02

Response Assessment by BICR	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
Confirmed ORR, No. (%)	50 (49.0)	28 (56.0)
95% CI	39.0 to 59.1	41.3 to 70.0
Best confirmed overall response, No. (%)		
CR	1 (1.0)	2 (4.0)
PR	49 (48.0)	26 (52.0)
SD	45 (44.1)	18 (36.0)
PD	4 (3.9)	2 (4.0)
Nonevaluable[a]	3 (2.9)	2 (4.0)
DCR, No. (%)	95 (93.1)	46 (92.0)
95% CI	86.4 to 97.2	80.8 to 97.8
DoR, months, median (95% CI)	16.8 (6.4 to NE)	NE (8.3 to NE)
TTIR, months, median (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Follow-up, months, median (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)



Goto et al *J Clin Oncol* 2023; Janne et al. *WCLC* 2023

Favorable toxicity **of T-DXd at 5.4 mg/kg compared to 6.4 mg/kg dose in DESTINY-Lung02**

	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101), No. (%)		T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50), No. (%)	
Preferred Term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Nausea	68 (67.3)	4 (4.0)	41 (82.0)	3 (6.0)
Neutropenia	43 (42.6)	19 (18.8)	28 (56.0)	18 (36.0)
Fatigue	45 (44.6)	8 (7.9)	25 (50.0)	5 (10.0)
Decreased appetite	40 (39.6)	2 (2.0)	25 (50.0)	2 (4.0)
Anemia	37 (36.6)	11 (10.9)	26 (52.0)	8 (16.0)
Vomiting	32 (31.7)	3 (3.0)	22 (44.0)	1 (2.0)
Constipation	37 (36.6)	1 (1.0)	16 (32.0)	0
Leukopenia	29 (28.7)	5 (5.0)	17 (34.0)	8 (16.0)
Thrombocytopenia	28 (27.7)	6 (5.9)	14 (28.0)	5 (10.0)
Diarrhea	23 (22.8)	1 (1.0)	18 (36.0)	2 (4.0)
Alopecia	22 (21.8)	0	17 (34.0)	0
Transaminases increased	22 (21.8)	3 (3.0)	10 (20.0)	0

Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101	T-DXd 6.4 mg/kg N = 50
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

- Based on these efficacy and safety data, T-DXd 5.4 mg/kg q3w was granted accelerated FDA approval in Aug 2022 for the treatment of advanced HER2-mutated NSCLC after progression on prior therapy.

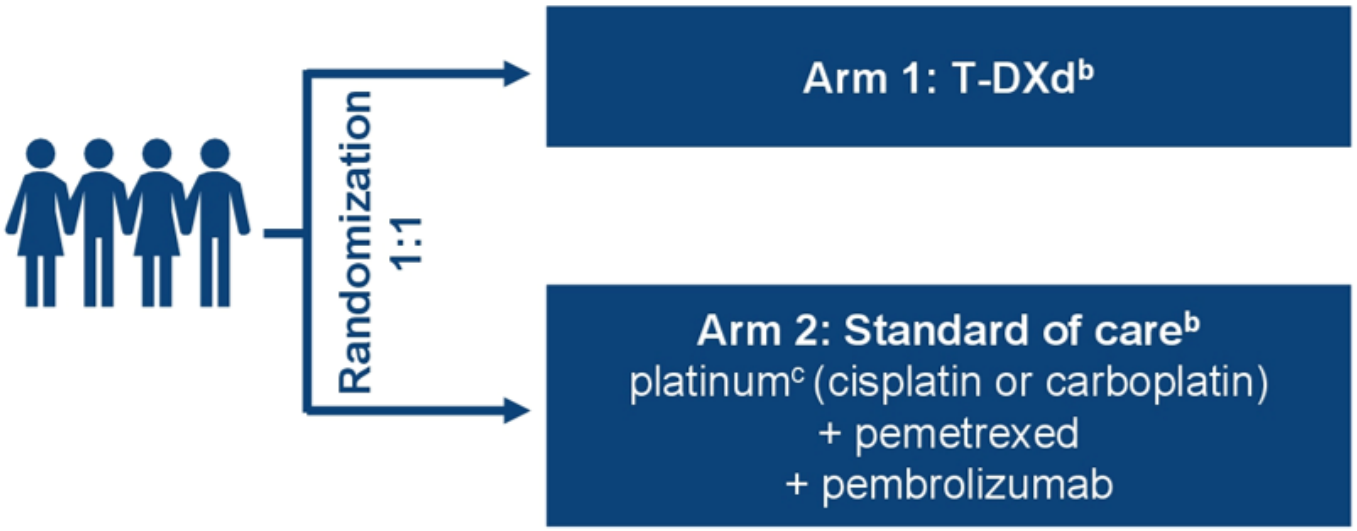
Goto et al *J Clin Oncol* 2023; Janne et al. *WCLC* 2023

Will T-DXd eclipse platinum-doublet chemotherapy (+/- immunotherapy) in the frontline?

Phase 3 DESTINY-Lung04 Trial (NCT05048797)

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



Primary Endpoint: PFS

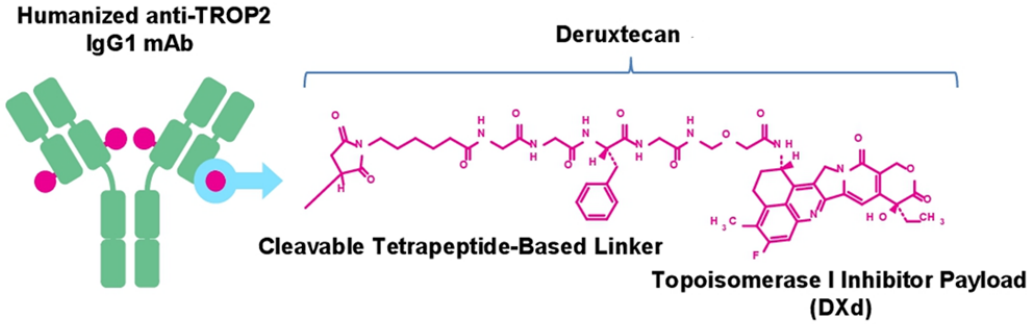
[a] *HER2* mutations may be detected in tissue or ctDNA.
[b] Crossover is not permitted.
[c] Investigator's choice of cisplatin or carboplatin.

Li et al. *ASCO* 2023

TROP2 & NSCLC

- Cell surface signal transducer expressed in >90% NSCLC.
- Associated with poor prognosis in multiple tumor types, including NSCLC.

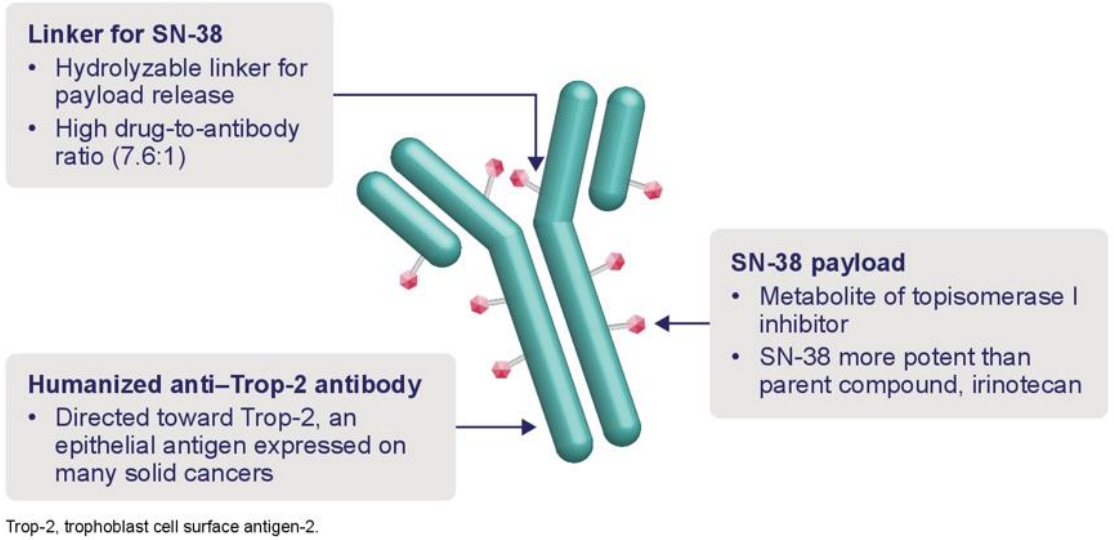
Datopotamab Deruxtecan (Dato-DXd)



Designed With 7 Key Attributes:

- Payload mechanism of action: topoisomerase I inhibitor
- High potency of payload
- Optimized DAR ≈4
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Bystander antitumor effect

Sacituzumab Govitecan



Trop-2, trophoblast cell surface antigen-2.

Meric-Bernstsein et al. *ASCO* 2021; Saxena et al. *ASCO* 2020

Dato-DXd in previously treated advanced NSCLC – Phase 3 TROPION-Lung01 Trial

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/m^2 Q3W
(N=305)

Dual Primary Endpoints

- PFS by BICR
- OS

Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

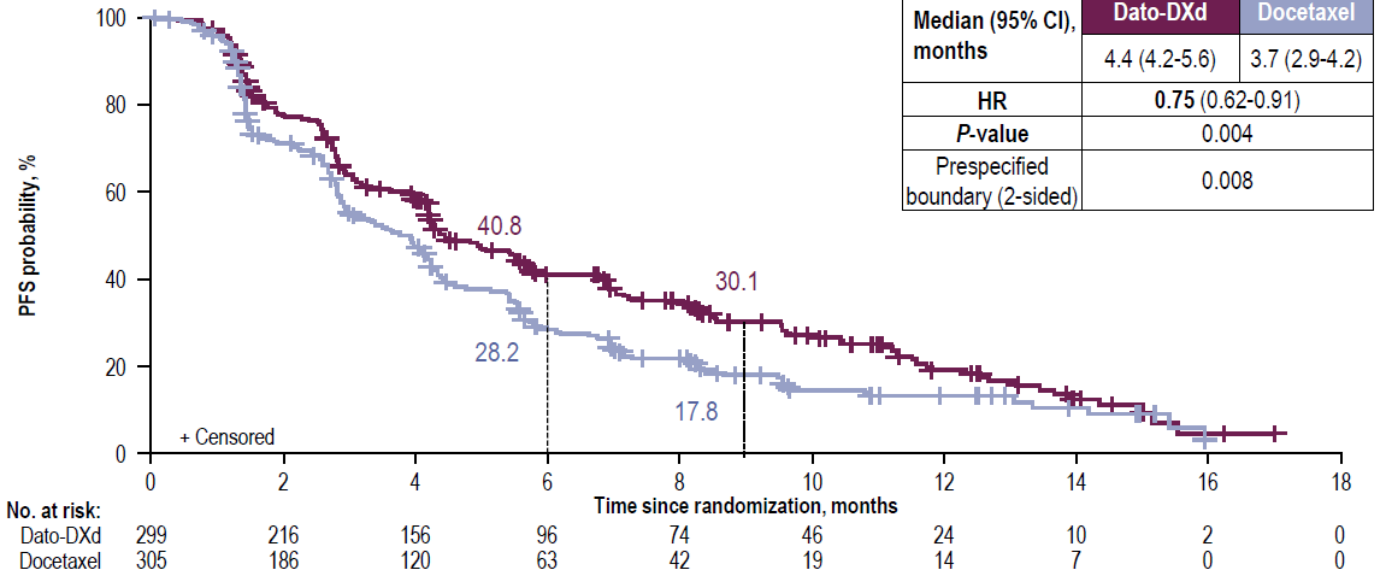
Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

Enrollment period: 19 February 2021 to 7 November 2022.
BICR, blinded independent central review; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.
[a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. [b]Squamous vs non-squamous.
[c]Presence vs absence. [d]United States/Japan/Western Europe vs rest of world.

Ahn et al. *ESMO* 2023

Phase 3 TROPION-Lung01 – significant improvement in PFS, but will it be clinically meaningful?

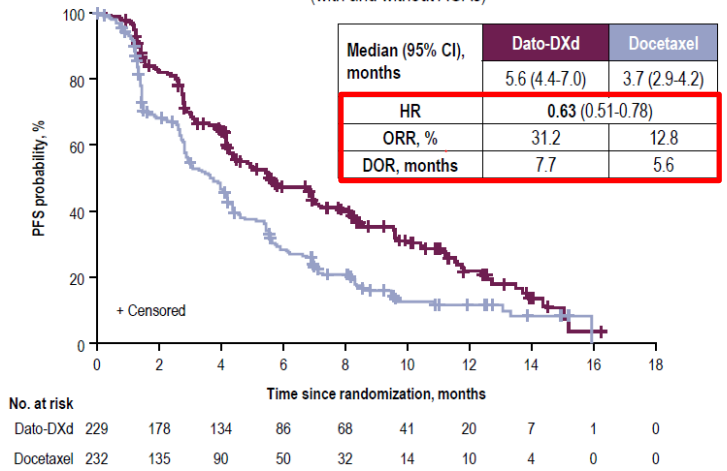
Progression-Free Survival: ITT



Median (95% CI), months	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	

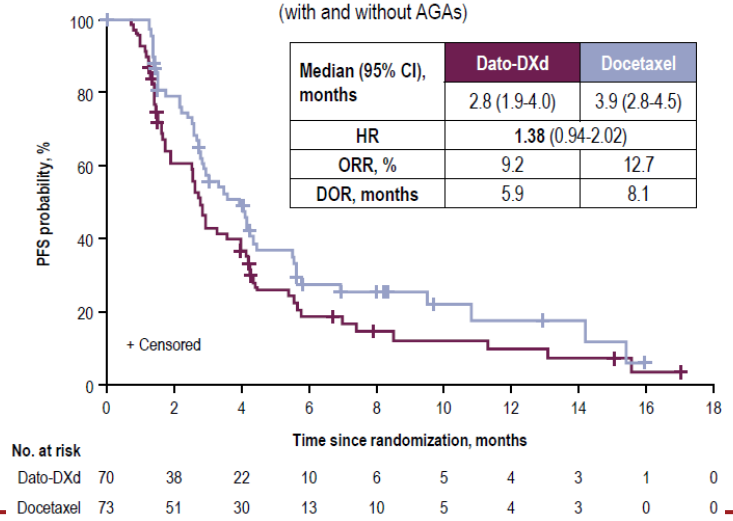
	Dato-DXd	Docetaxel
ORR (95% CI), %	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

Non-squamous
(with and without AGAs)



Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6

Squamous
(with and without AGAs)



Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1

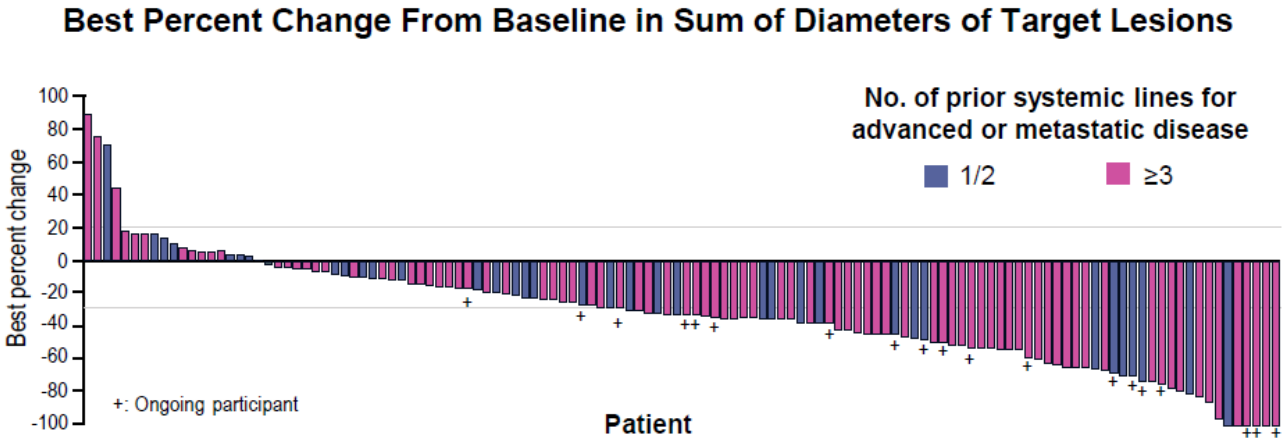
Ahn et al. *ESMO* 2023

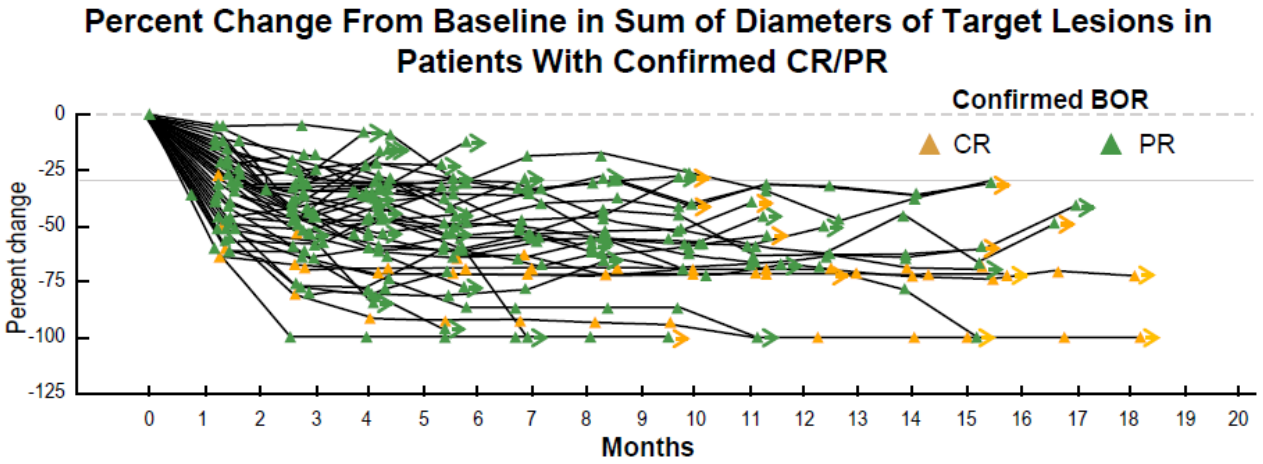
Benefit of Dato-DXd in patients with genomic driver alterations – Phase 2 TROPION-Lung05 study

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

BOR: In the overall population (N=137), 4 patients (3%) achieved a CR and 45 (33%) achieved a PR

***EGFR* subset:** Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib

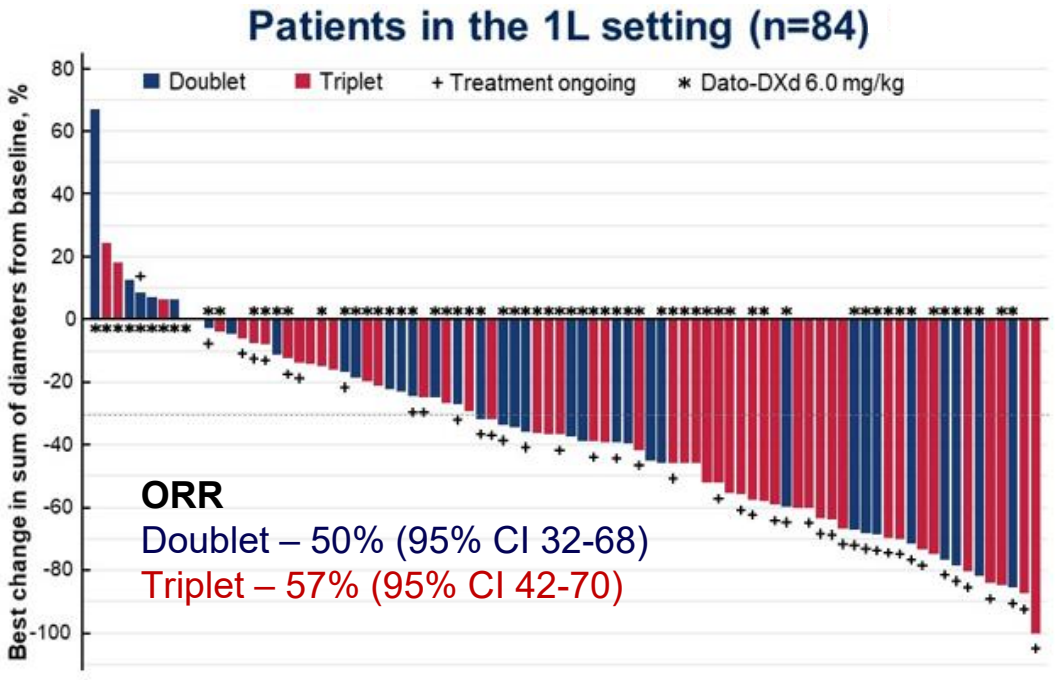




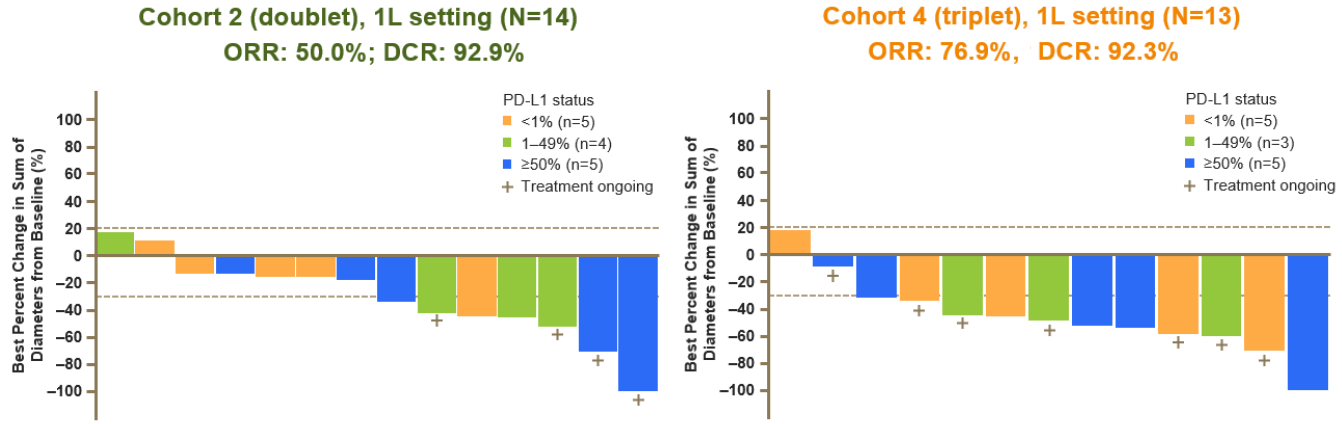
Paz-Ares et al. *ESMO* 2023

First-line efficacy of TROP2-targeted ADCs

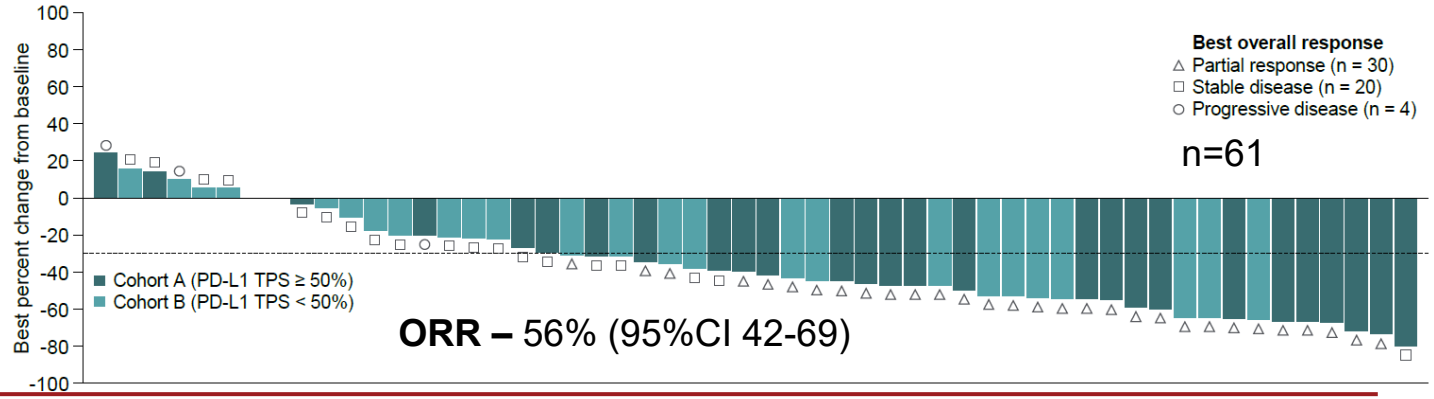
TROPION-Lung02: Dato-DXd + pembrolizumab +/- platinum



TROPION-Lung02: Dato-DXd + durvalumab +/- carboplatin



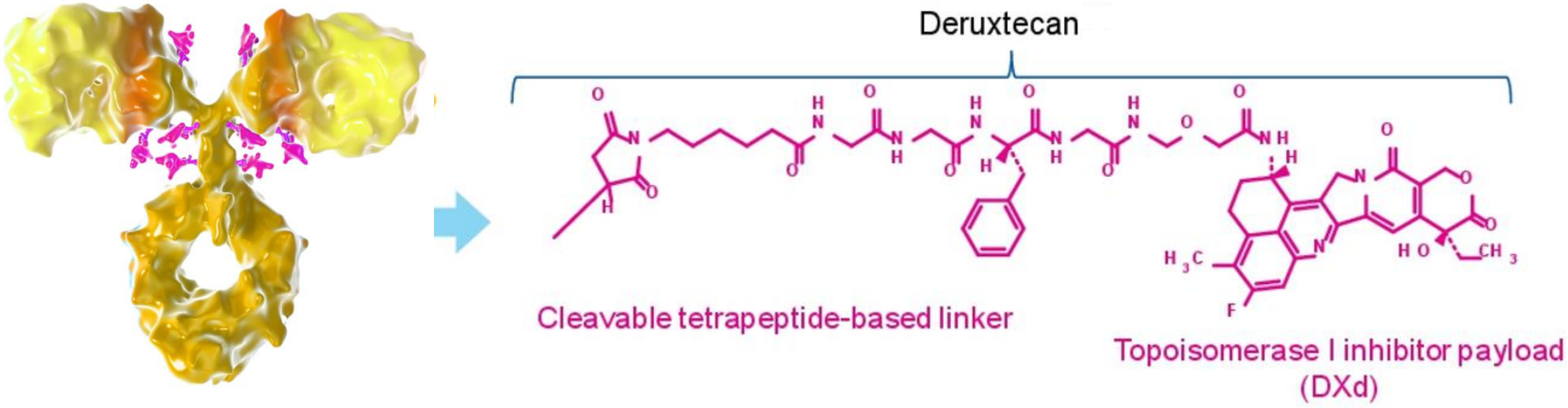
EVOKE-02: 1L Sacituzumab Govitecan + pembrolizumab



Goto et al. *ASCO* 2023; Cho et al. *WCLC* 2023; Cho et al. *WCLC* 2023

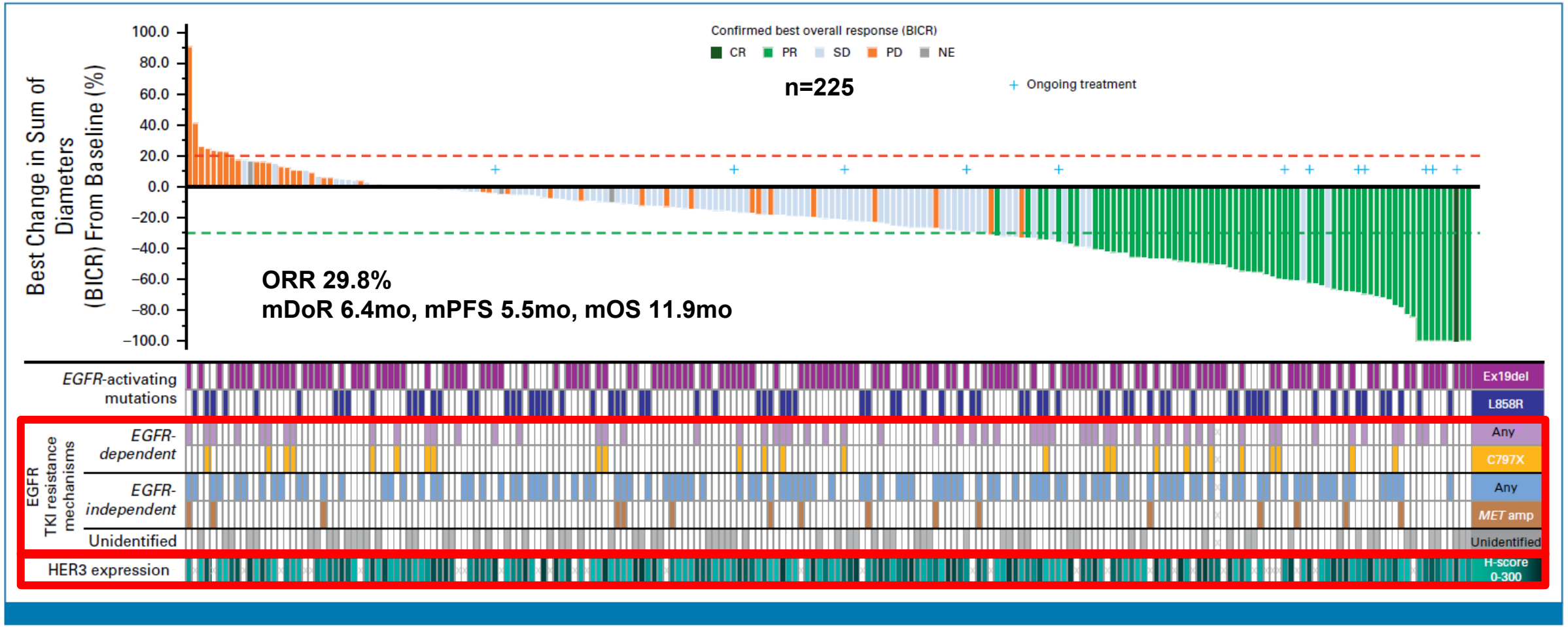
HER3 & NSCLC

- HER3 is a partner with HER2 hetero-dimerization and subsequent PI3K/AKT signalling.
- Expressed in ~83% NSCLC, associated with poor prognosis.
- Upregulated expression observed in *EGFR*-mutated NSCLC.
- HER3-DXd: anti-HER3 mAb conjugated to DXd via cleavable linker with DAR 8.



Jänne et al. *ASCO* 2021; Yu et al. *WCLC* 2023

Phase 2 HERTHENA-Lung01 Trial: Efficacy of subsequent line HER3-DXd in *EGFR*m NSCLC across mechanisms of resistance

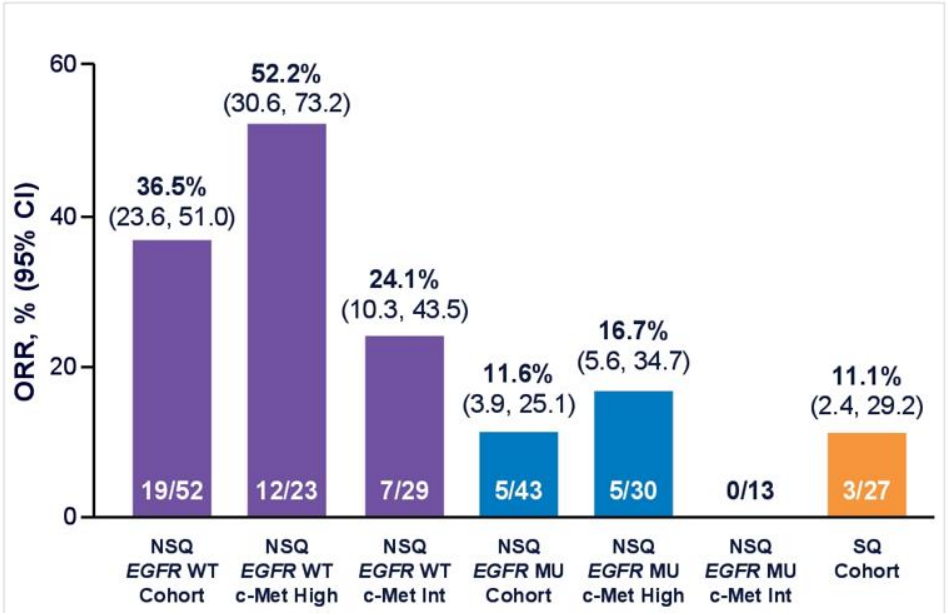


Yu et al. *J Clin Oncol* 2023

Telisotuzumab vedotin (Teliso-V) in advanced NSCLC w/ MET overexpression

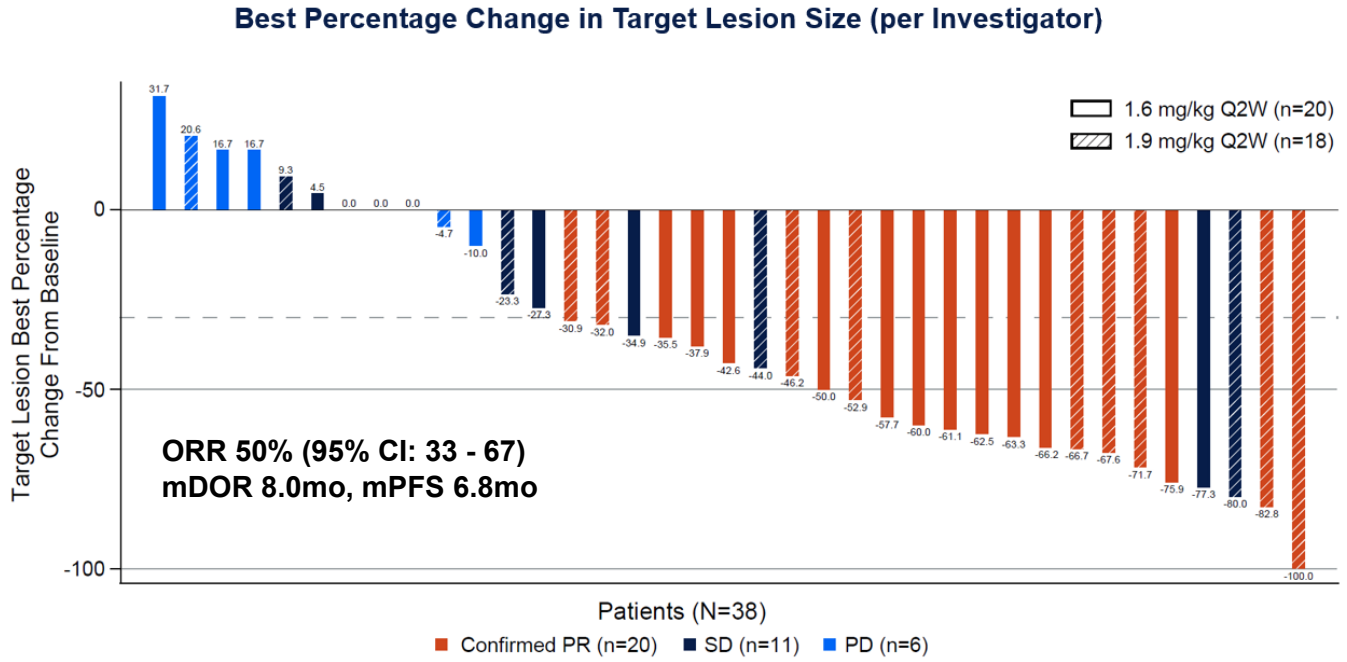
- MET alterations are seen *de novo* and as acquired mechanisms of resistance in driver+ NSCLC.
- Teliso-V: anti-cMET mAb conjugated to MMAE payload via cleavable linker w/ DAR ~3.1.

Teliso-V in *EGFR* wt NSCLC w/ c-MET overexpression (Phase II LUMINOSITY Trial)



Camidge et al. *ASCO* 2023; Horinouchi et al. *ESMO Asia* 2023

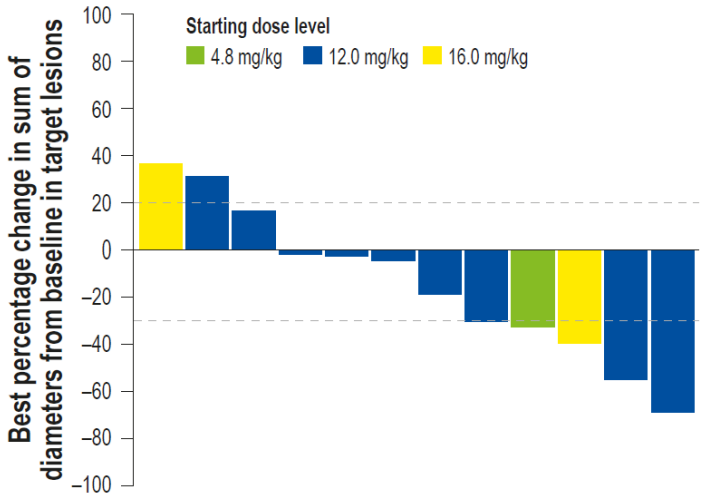
Teliso-V + osimertinib after osimertinib failure in *EGFR*m NSCLC w/ c-MET overexpression



Not just adenocarcinoma! Early efficacy of B7-H3-directed Ifinatamab Deruxtecan (I-DXd) in small-cell and squamous lung cancer

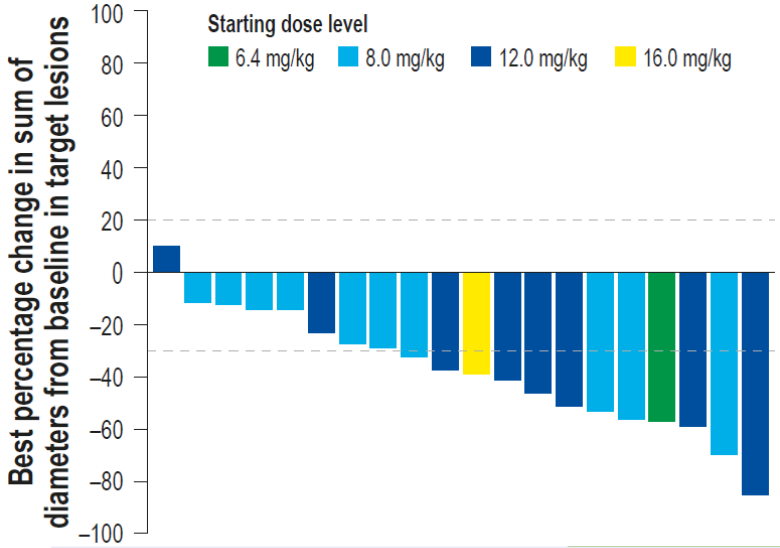
- B7-H3 – transmembrane protein overexpressed in solid tumors.
- I-DXd: anti-B7-H3 mAb conjugated to DXd payload via cleavable linker w/ DAR 4.

Sq-NSCLC



Efficacy population (≥4.8 mg/kg)	n=13
Confirmed ORR, n (%; 95% CI)	4 (30.8, 9.1–61.4)
Confirmed PR, n (%)	4 (30.8)
TTR, median (95% CI), months	1.3 (0.7–NE)
DOR, median (95% CI), months	4.1 (2.8–NE)
Follow-up, median (95% CI), months	5.2 (1.7–NE)

SCLC

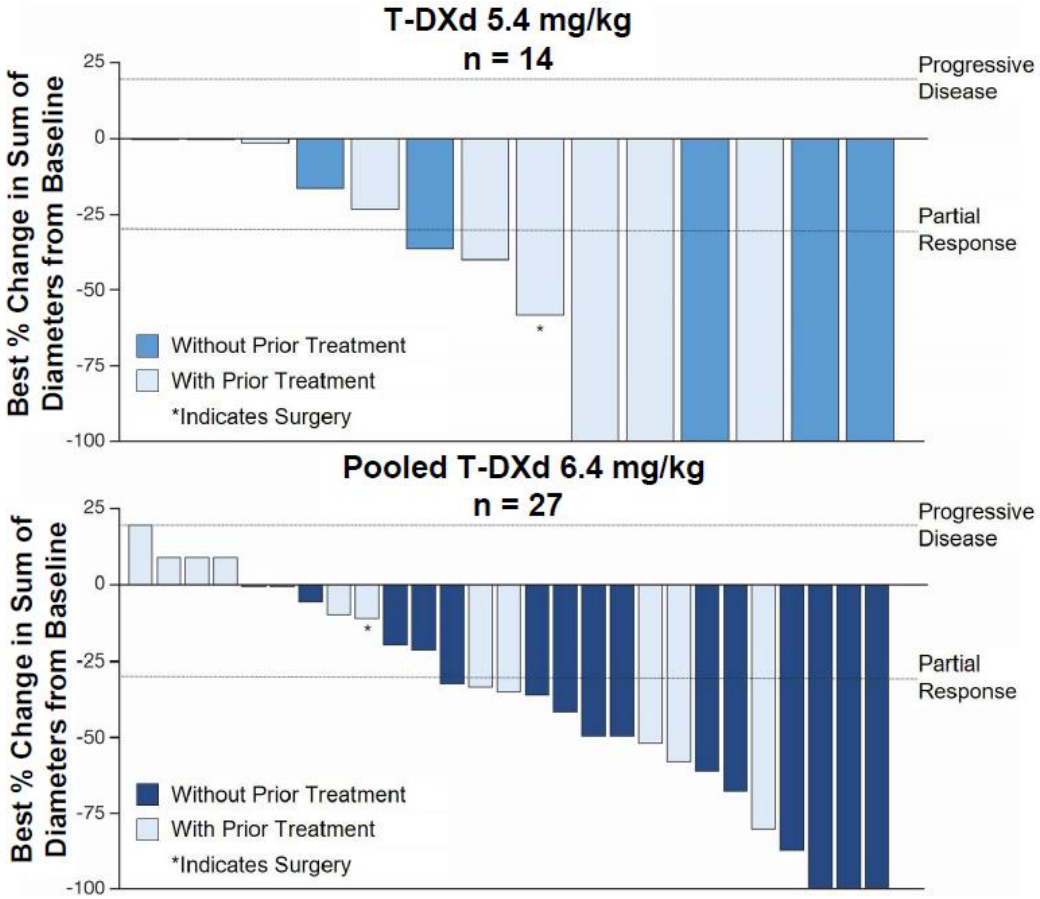


Efficacy population (≥4.8 mg/kg)	n=21
Confirmed ORR, n (%; 95% CI)	11 (52.4; 29.8–74.3)
Confirmed CR, n (%)	1 (4.8)
Confirmed PR, n (%)	10 (47.6)
TTR, median (95% CI), months	1.2 (1.2–1.4)
DOR, median (95% CI), months	5.9 (2.8–7.5)
Median PFS, months (95% CI)	5.6 (3.9–8.1)
Median OS, months (95% CI)	12.2 (6.4–NE)
Follow-up, median (95% CI), months	11.7 (4.6–12.9)

Patel et al. *ESMO* 2023

Intracranial efficacy observed for select ADCs in NSCLC

T-DXd – pooled DESTINY-Lung01, -Lung02



HER3-DXd – HERTHENA-Lung01

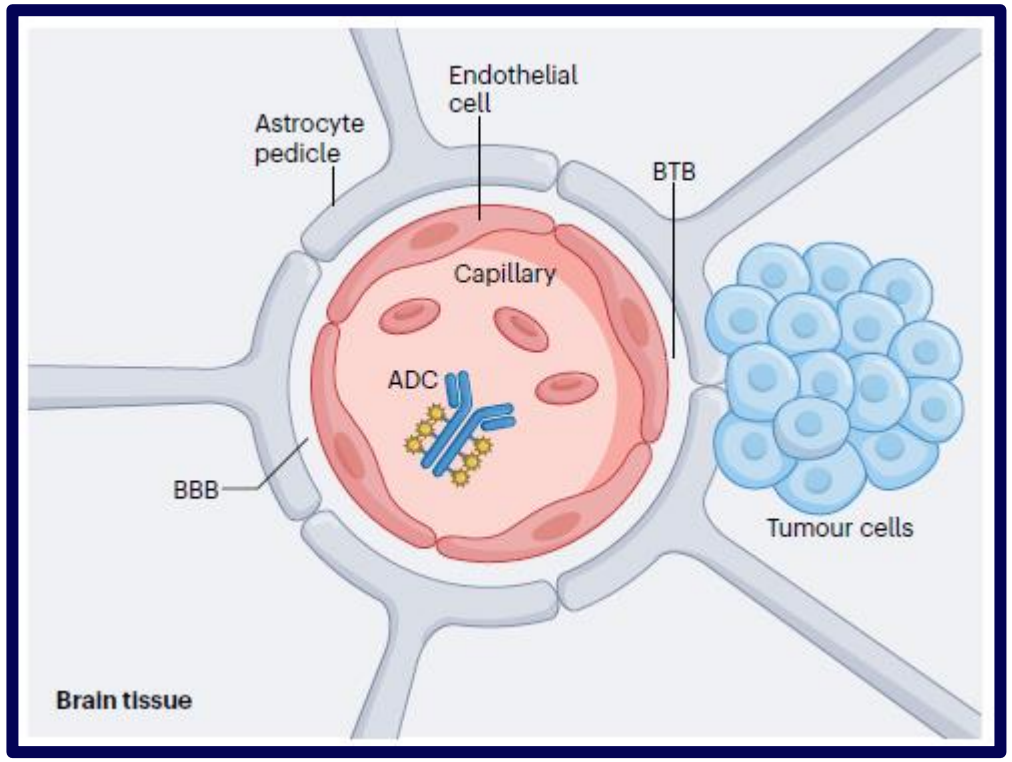
Responses by CNS BICR	All patients with baseline BM by CNS BICR (n=95)	Patients whose baseline BM had not been irradiated (n=30)
CNS cORR, n (%) [95% CI]	19 (20.0) [12.5, 29.5]	10 (33.3) [17.3-52.8]
CR, n (%)	15 (15.8)	9 (30.0)
PR, n (%)	4 (4.2)	1 (3.3)
SD/non-CR/non-PD, n (%)	57 (60.0)	13 (43.3)
PD, n (%)	13 (13.7)	4 (13.3)
NE, n (%)	6 (6.3)	3 (10.0)
CNS DCR (95% CI), %	80.0 (70.5, 87.5)	76.7 (57.7-90.1)
CNS DOR, median (95% CI), mo	9.2 (8.1-11.1)	8.4 (5.8-9.2)

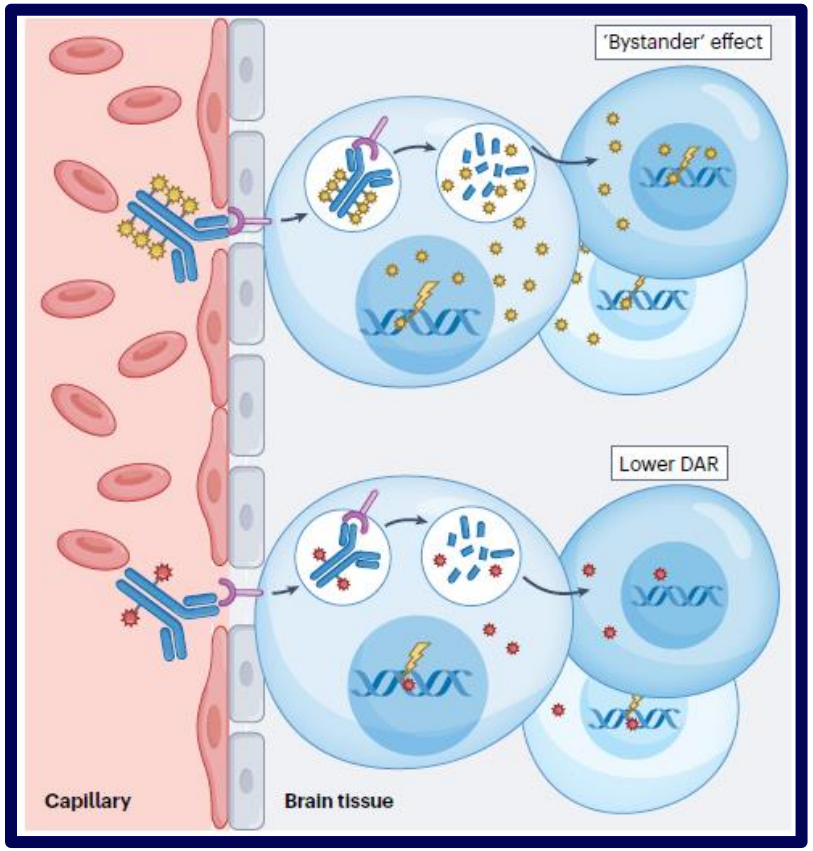
Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

Li et al. *ESMO* 2023; Johnson et al. *ESMO* 2023

Intracranial efficacy observed for select ADCs in NSCLC

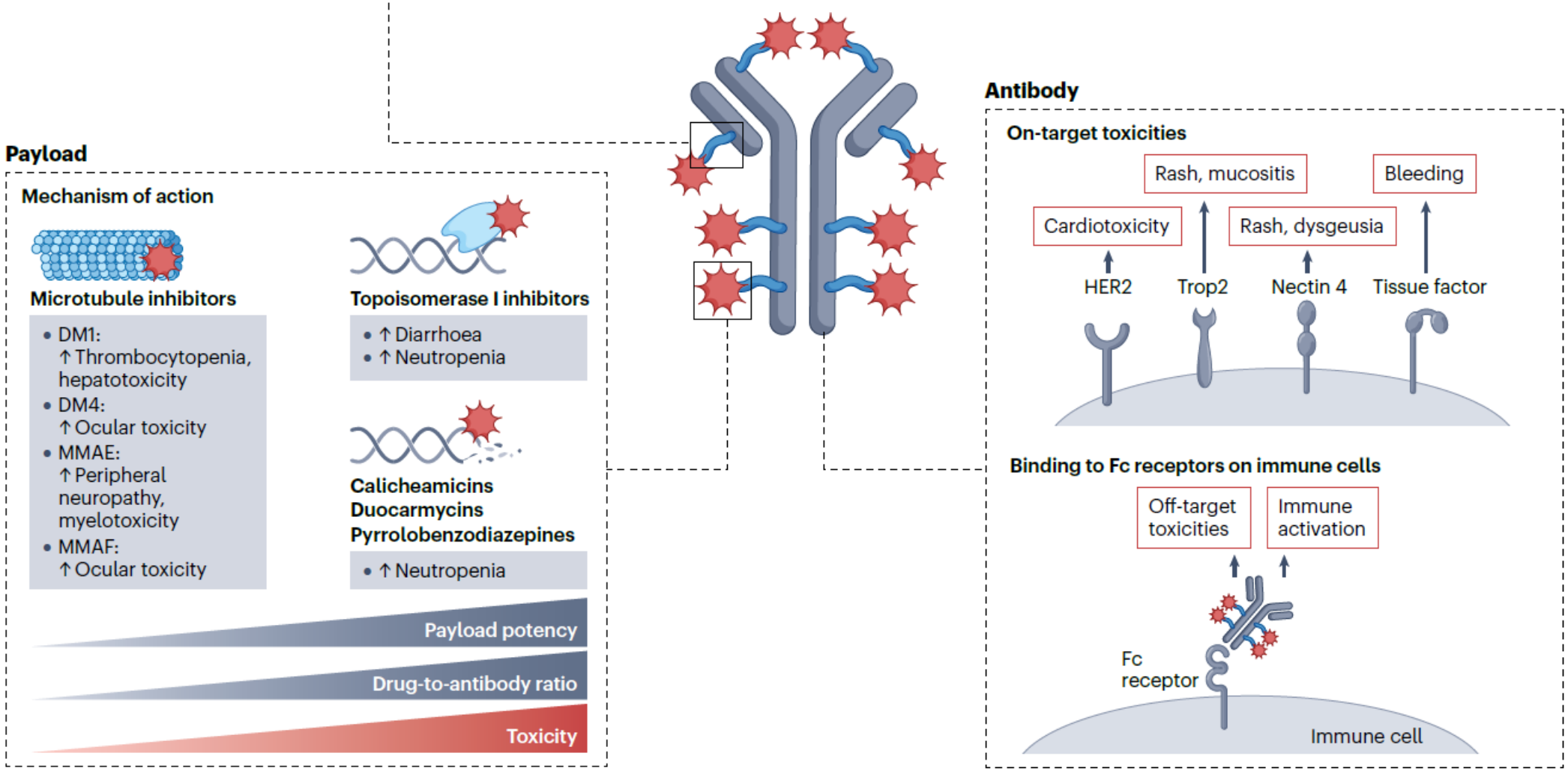
Blood Brain Barrier ≠ Blood Tumor Barrier





Mair et al. *Nat Rev Clin Oncol* 2023

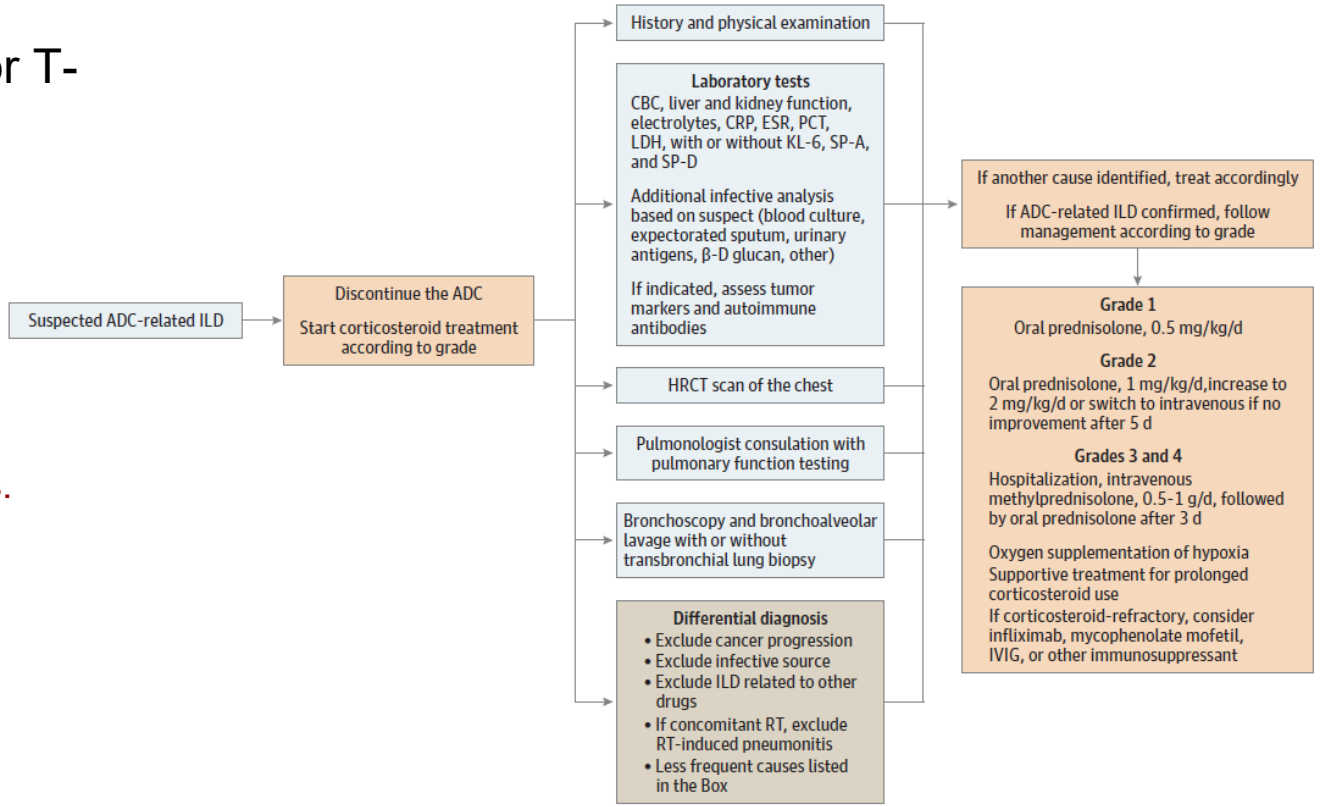
Management of unique ADC-related toxicities



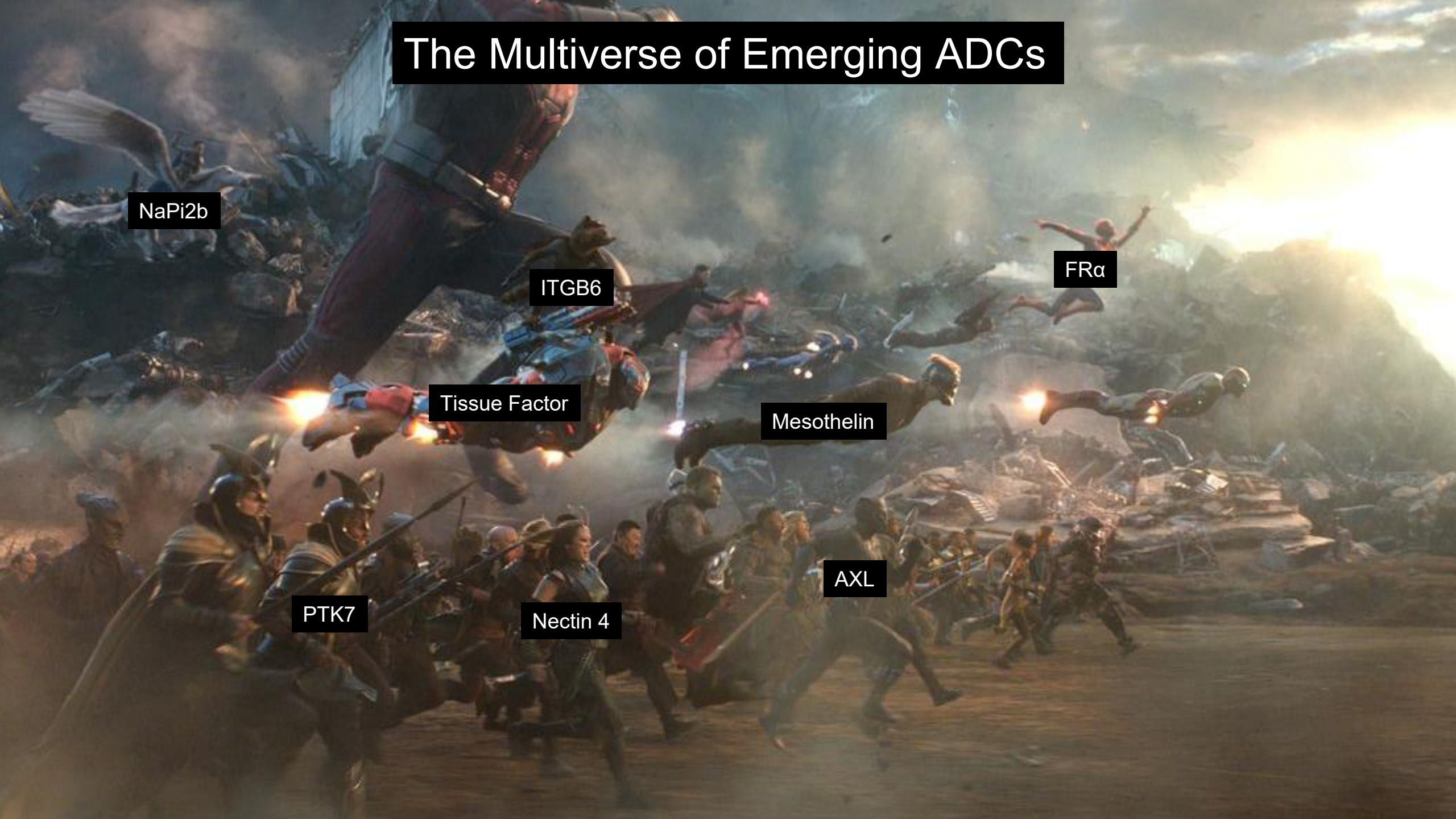
Tarantino et al. *Nat Rev Clin Oncol* 2023

Clinical Management of T-DXd-related ILD

- Observed across studies of ADCs with DXd-containing payloads.
- Incidence of all-grade ILD ~15% in pooled data for T-DXd in solid tumors.
  - ≥G3 Incidence: ~3.5%.
  - Median time to onset: 5.4mo.
- Management pearls:
  - If suspected, **STOP** T-DXd and promptly initiate prednisone ~1mg/kg/d.
  - Differential Dx: infection, progression, other ILD/pneumonitis.
  - Work-up: High res Chest CT, pulm consult, bronch.
- Can I re-initiate T-DXd?
  - Data limited.
  - Can consider for case of grade 1 (asymptomatic) ILD.
  - Generally not recommended if grade 2+.



Tarantino et al. *JAMA Onc* 2021


The Multiverse of Emerging ADCs
NaPi2b
ITGB6
FRα
Tissue Factor
Mesothelin
AXL
PTK7
Nectin 4

Notable disappointments

Tusamitamab ravtansine (TUSA)

Press Release

sanofi

Sanofi announces end of program evaluating tusamitamab ravtansine after a 2L NSCLC Phase 3 trial did not meet a primary endpoint

- CARMEN-LC03 trial did not meet dual primary endpoint of improving progression-free survival; tusamitamab ravtansine clinical development program will be discontinued
- Sanofi reinforces commitment to broader oncology development program including CEACAM5-directed antibody drug conjugates (ADC) with additional anticipated trials

Ph3 EVOKE-01: sacituzumab govitecan vs docetaxel in previously treated adv NSCLC

Press Releases

January 22, 2024

Gilead Provides Update on Phase 3 EVOKE-01 Study

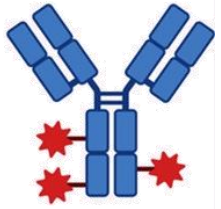
FOSTER CITY, Calif.--(BUSINESS WIRE)-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced that the Phase 3 EVOKE-01 study did not meet its primary endpoint of overall survival (OS) in previously treated metastatic non-small cell lung cancer (NSCLC). EVOKE-01 is evaluating Trodelvy® (sacituzumab govitecan-hziy; SG) vs. docetaxel in patients with metastatic or advanced NSCLC that had progressed on or after platinum-based chemotherapy and checkpoint inhibitor therapy.

Biomarker selection to guide ADC development and identify target population **is critical!**

The Next Frontier of ADCs…

First generation ADCs

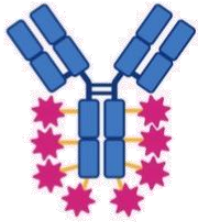
e.g. T-DM1



-New linker technologies (↑DAR);
-improved conjugation chemistry;
-membrane-permeable payloads

Current ~~Next~~-generation ADCs

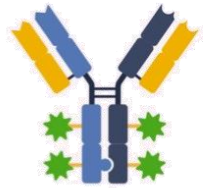
- ↑therapeutic index
- bystander effect;
- ↑tissue agnostic profile.



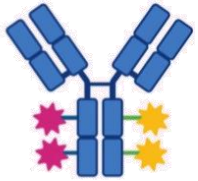
e.g. T-DXd

Future Perspectives

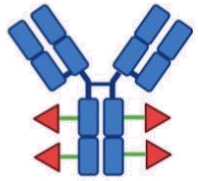
1) Bispecific ADCs



2) Dual-payload ADCs



3) ADCs with immune-stimulating payloads
(e.g. TLR8 agonist)



4) Radionuclide ADCs

Tarantino et al. *CA Cancer J Clin* 2022 (adapted from Levy ASCO 2023)

Concluding Remarks

- ADCs are an emerging class of anti-cancer therapeutic in the treatment of advanced lung cancer, with T-DXd carrying an accelerated approval for subsequent line therapy in advanced *HER2*-mutated NSCLC.
- Several agents carry FDA breakthrough designation, among which multiple phase 3 registrational studies are ongoing.
- Are ADCs the superhero we need? Time will tell. Important to address biomarker selection and identification of synergistic combinations.
- The ADC construct has the potential to unlock mechanistically novel therapeutic strategies.

THANK YOU!

GEORGETOWN UNIVERSITY

Lombardi Comprehensive Cancer Center