2025 DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center
Where Science Becomes Hope

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Are ADCs Highly Promising for the Treatment of NSCLC…or… ADCs are the Futures of NSCLC?
Yes!

Conor Steuer, MD

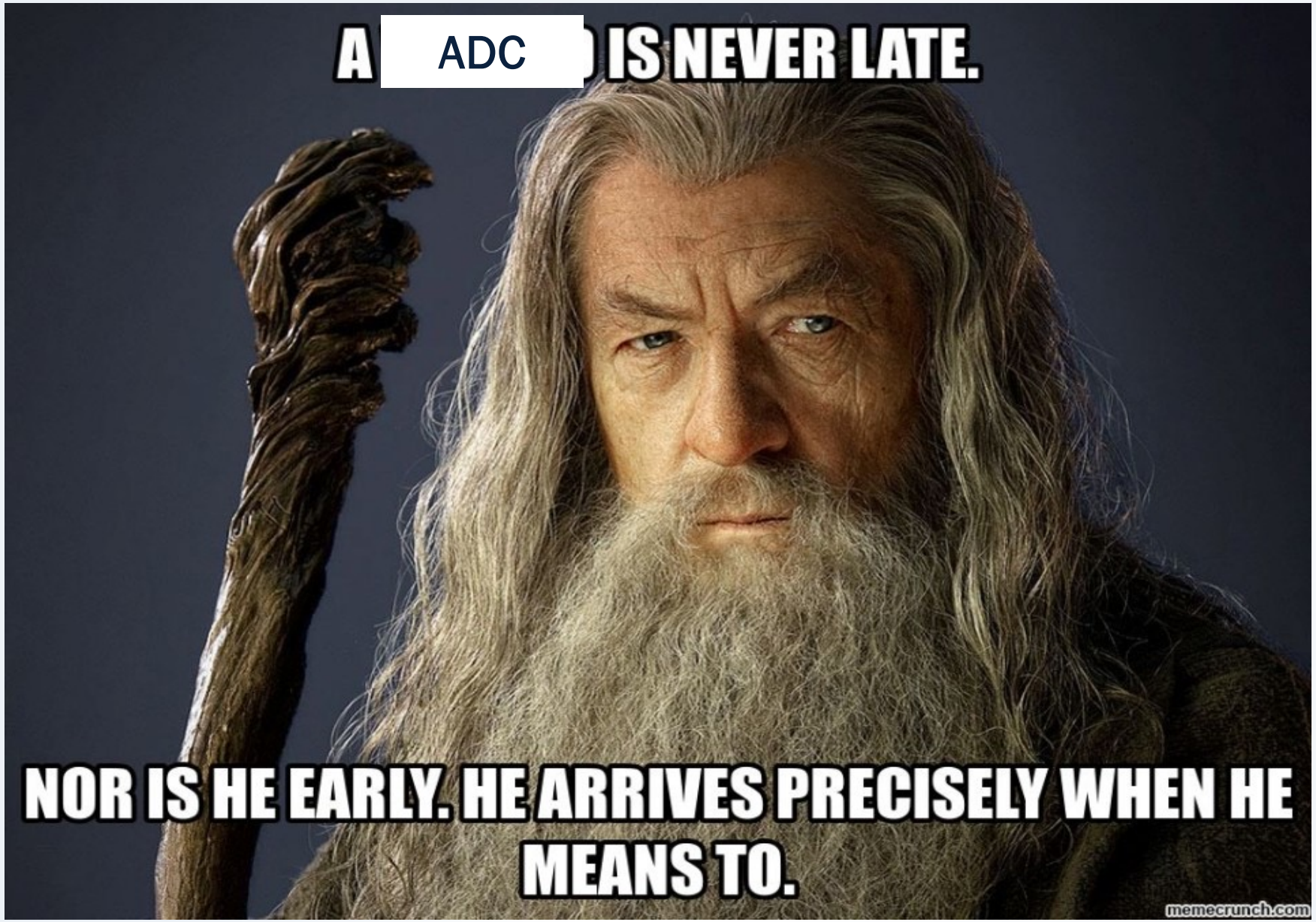
Associate Professor

Interim Associate Division Director of Medical Oncology

Winship Cancer Institute of Emory University

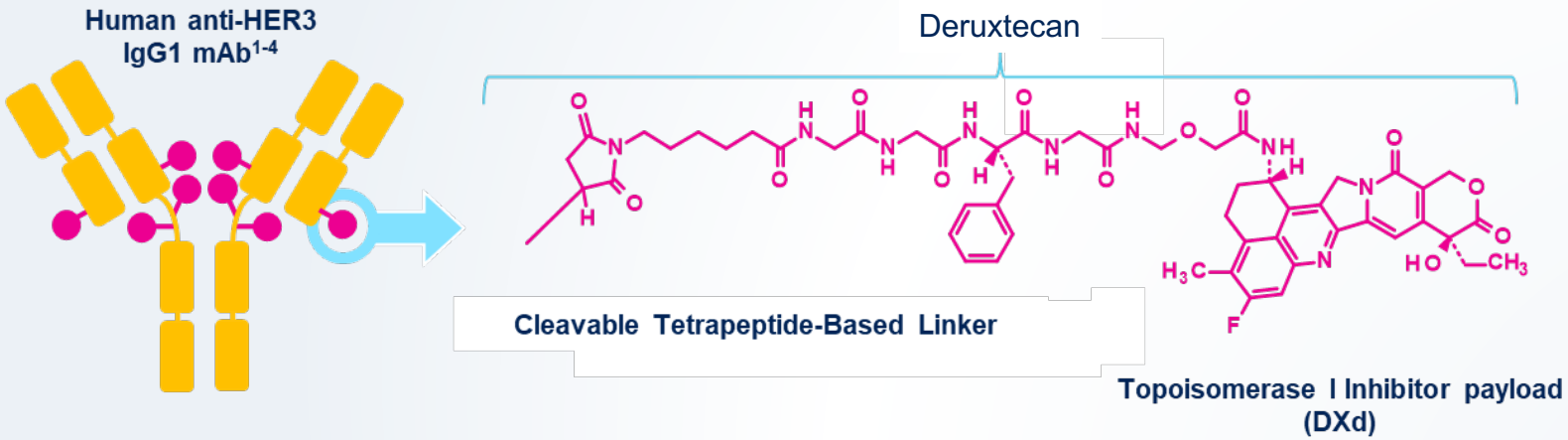
Disclosures

Consultant/Advisor/Speaker (Received honoraria for):Merck, Daiichi, Novocure, Boehringer Ingelheim


A ADC IS NEVER LATE.
NOR IS HE EARLY. HE ARRIVES PRECISELY WHEN HE MEANS TO.
memecrunch.com

So what is an Antibody Drug Conjugate? Patritumab Deruxtecan

- HER3-DXd is an ADC with 3 components[1-4]:
  - A fully human anti-HER3 IgG1 mAb (patritumab)
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components

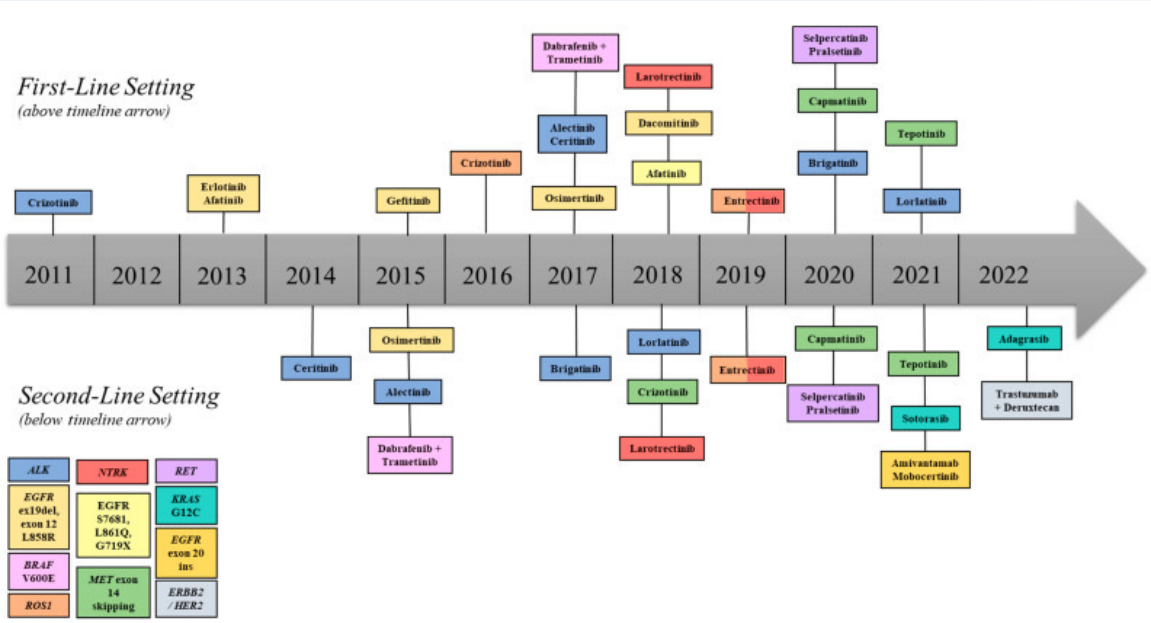


Even in theory it is exciting, combining the best of targeted therapy and cytoxic chemotherapy! “Biologic homing missles”

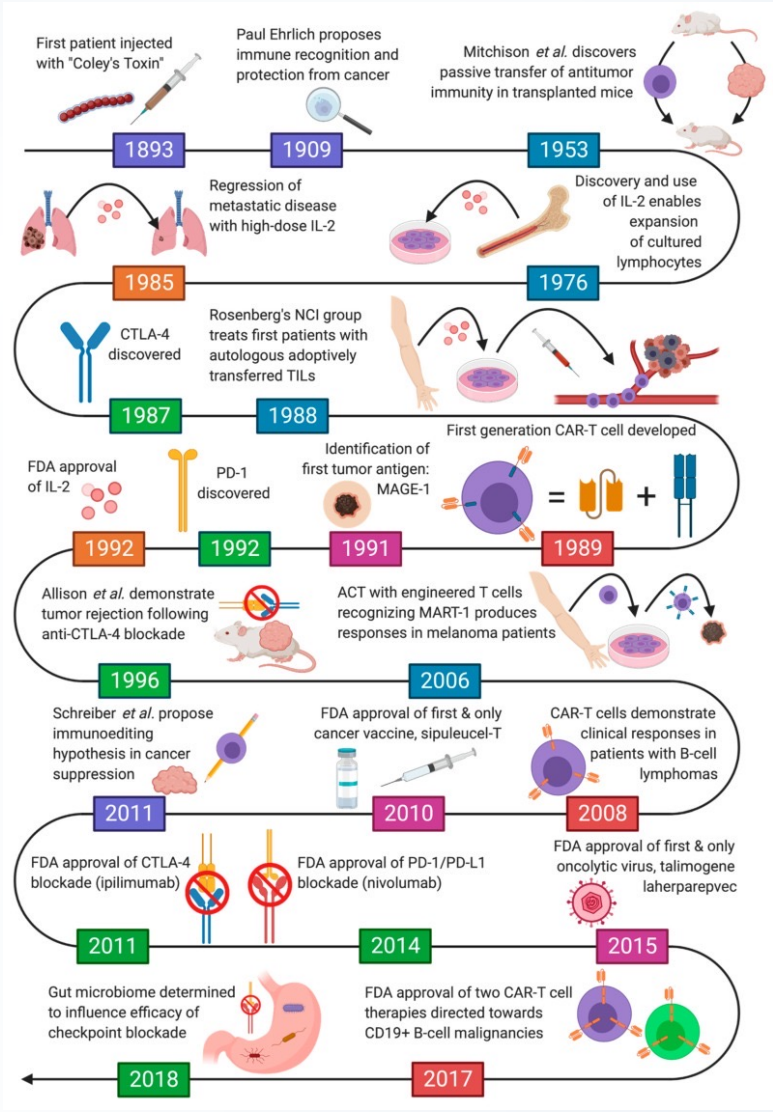
Hashimoto Y, et al. *Clin Cancer Res.* 2019

“But I’ve seen some data, and not sure about ADCs…”

Targeted therapy



Immunotherapy



-KRAS, first discovered in 1982 in NSCLC

-EGFR mutations 2004 in NSCLC

Mitchell et al. Diagnostics 2023
Carlsen et al. Toxins 2023

The Future is now: Current ADC approvals (as of 2023)

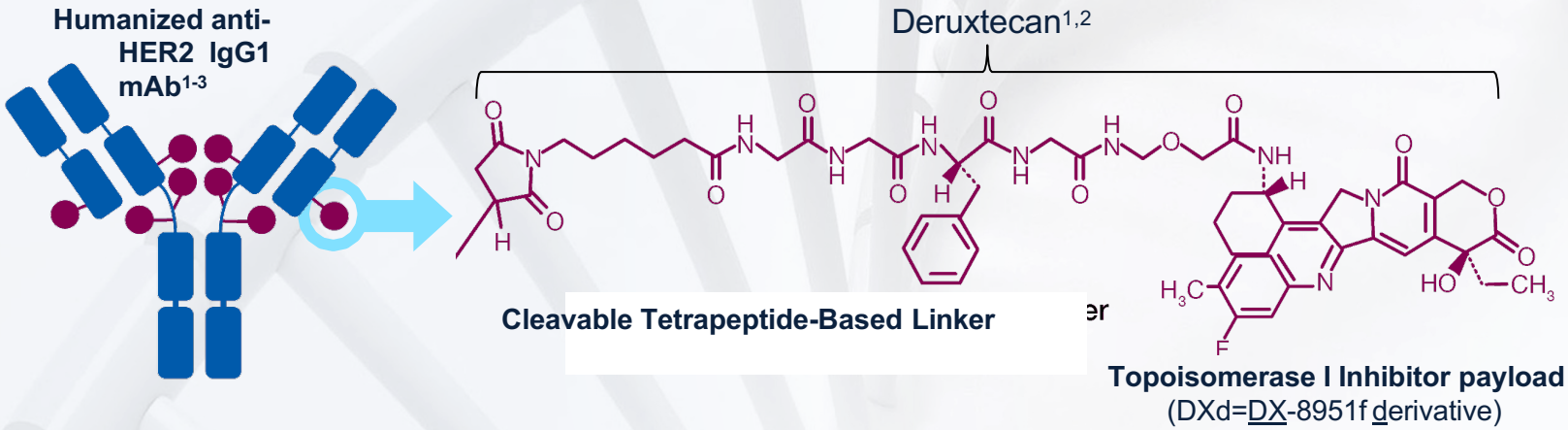
ADC	TargetmAb antigen isotype	Linker type	Payload	Payload class	Payload action	Disease indication	Year of Approval
Gemtuzumab ozogamicin	CD33IgG4	Cleavable	Ozogamicin	Calicheamicin	DNA cleavage	Relapsed or refractory CD33+AML**	2000
Brentuximab Vedotin	CD30IgG1	Cleavable	MMAE	Auristatin	Microtubule inhibitor	Relapsed or refractory systemic ALCL or classical HL Relapsed and/or refractory primary cutaneous ALCL or CD30+MF (2017) classical HL, systemic ALCL or CD30+PTCL#	2011 2018
Ado-Trastuzumab emtansine	HER2IgG1	Non-cleavable	DM1	Maytansinoid	Microtubule inhibitor	Advanced-stage HER2+breast cancer previously treated with trastuzumab and a taxane; early-stage HER2+breast cancer in patients with residual disease following neoadjuvant trastuzumab–taxane-based treatment	2013 2019
Inotuzumab ozogamicin	CD22IgG4	Cleavable	Ozogamicin	Calicheamicin	DNA cleavage	Relapsed or refractory B-ALL	2017
Fam-trastuzumab deruxtecan	HER2IgG1	Cleavable	DXd	Camptothecin	TOP1 inhibitor	Advanced-stage HER2+breast cancer after two or more anti-HER2-based regimens: locally advanced or metastatic gastric cancer who have received a prior trastuzumab-based regimen; locally advanced or metastatic NSCLC patients who have progressed on platinum-based chemotherapy	2019 2021
Polatuzumab Vedotin	CD79bIgG1	Cleavable	MMAE	Auristatin	Microtubule inhibitor	Relapsed or refractory DLBCL¶	2019
Sacituzumab govitecan	TROP2IgG1	Cleavable	SN-38 (active metabolite of irinotecan)	Camptothecin	TOP1 inhibitor	Metastatic triple-negative breast cancer in the third-line setting or beyond; metastatic urothelial cancer following progression on platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor	2020 2021
Enfortumab vedotin	Nectin 4 IgG1	Cleavable	MMAE	Auristatin	Microtubule inhibitor	Advanced-stage urothelial carcinoma, following progression on a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy	2020
Belantamab Mafodotin	BCMAIgG1	Non-cleavable	MMAF	Auristatin	Microtubule inhibitor	Relapsed and/or refractory multiple myeloma in the fifth-line setting or beyond	2020
Tisotumab vedotin	Tissue IgG1 Factor	Cleavable	MMAE	Auristatin	Microtubule inhibitor	Recurrent or metastatic cervical cancer, no more than two prior systemic regimens in the recurrent or metastatic setting	2021
Loncastuximab tesirine	CD20 IgG1	Cleavable	SG3199	PBD DIMER	DNA cleavage	Relapsed and/or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma	2021
Moxetumomab pasudotox	CD22 IgG1	Cleavable	PE38	Pseudomonas exotoxin	Immunotoxin	Relapsed and/ or refractory hairy cell leukemia	2018

Coleman et al. NPJ Precision Medicine 2023

Trastuzumab Deruxtecan (T-DXd)

T-DXd is an ADC composed of 3 components[1,2]:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker

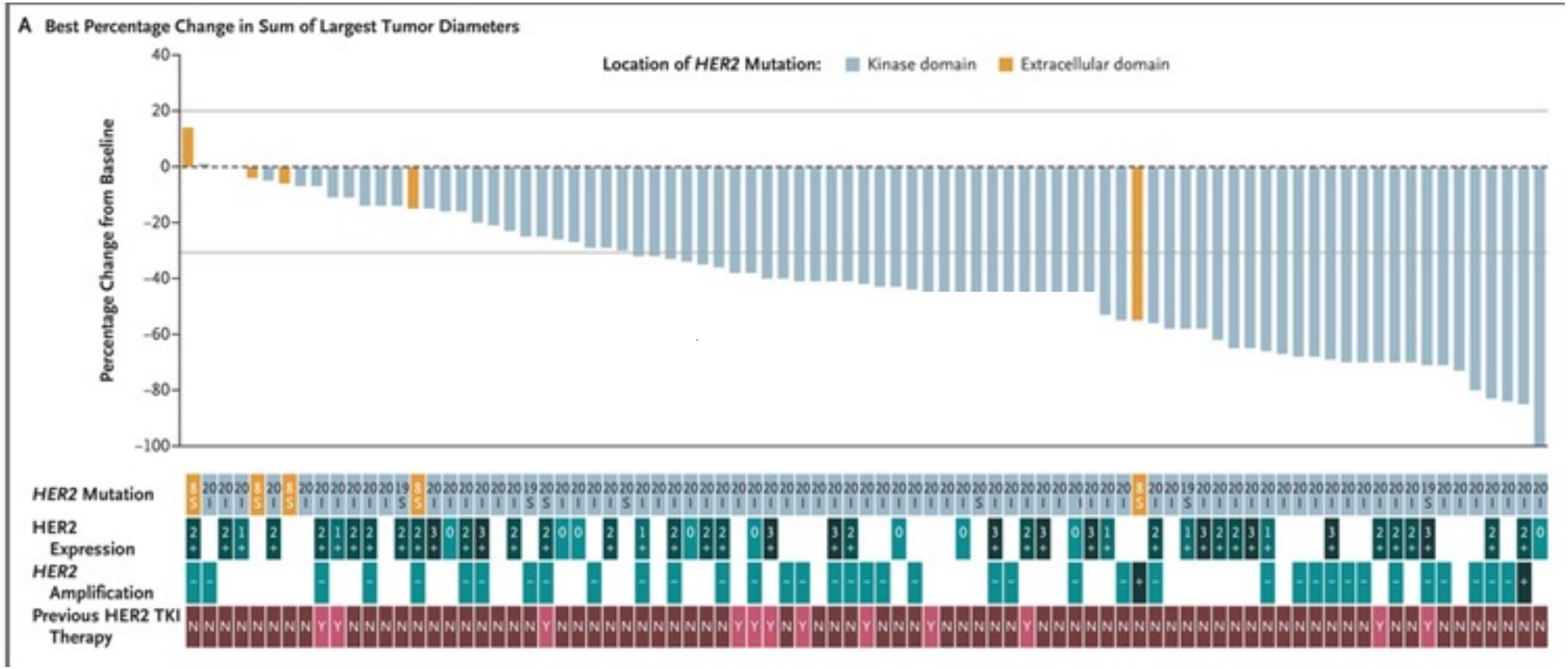


Payload mechanism of action: topoisomerase I inhibitor [a,1,2]
High potency of payload [a,1,2]
High drug to antibody ratio ≈ 8 [a,1,2]
Payload with short systemic half-life [a,1,2]
Stable linker-payload [a,1,2]
Tumor-selective cleavable linker [a,1,2,]
Bystander antitumor effect [a,1,4]

[a]Based on in vitro and in vivo non-clinical studies. The clinical relevance of these features is under investigation.

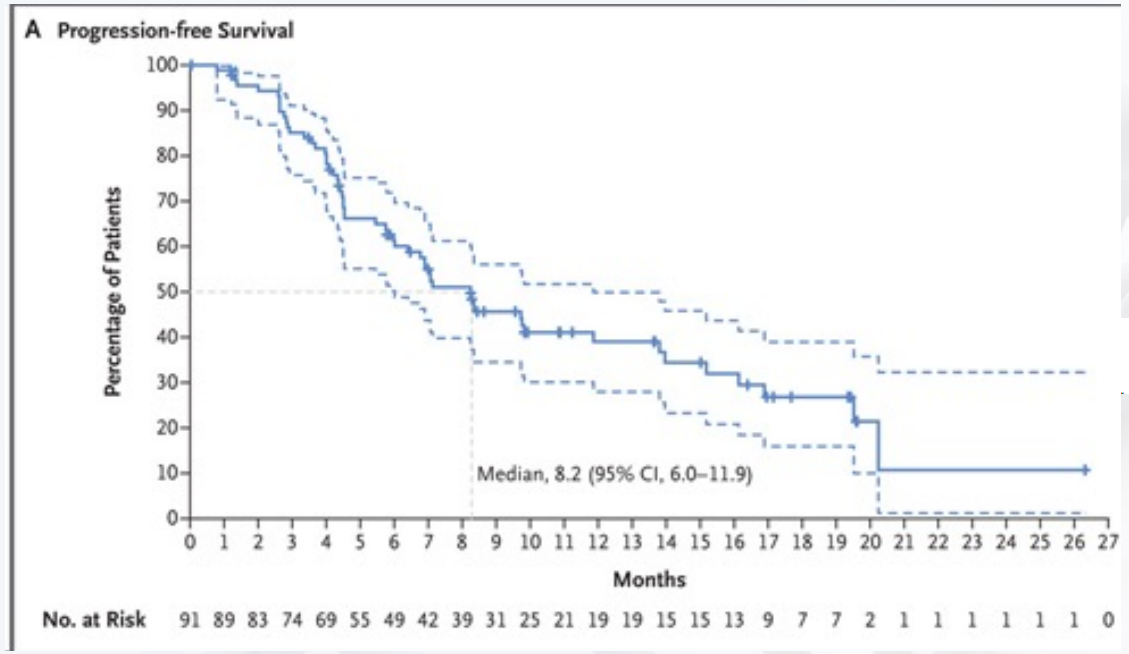
1. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. **2.** Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. **3.** Trail PA, et al. *Pharmacol Ther.* 2018;181:126-142. **4.** Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046.

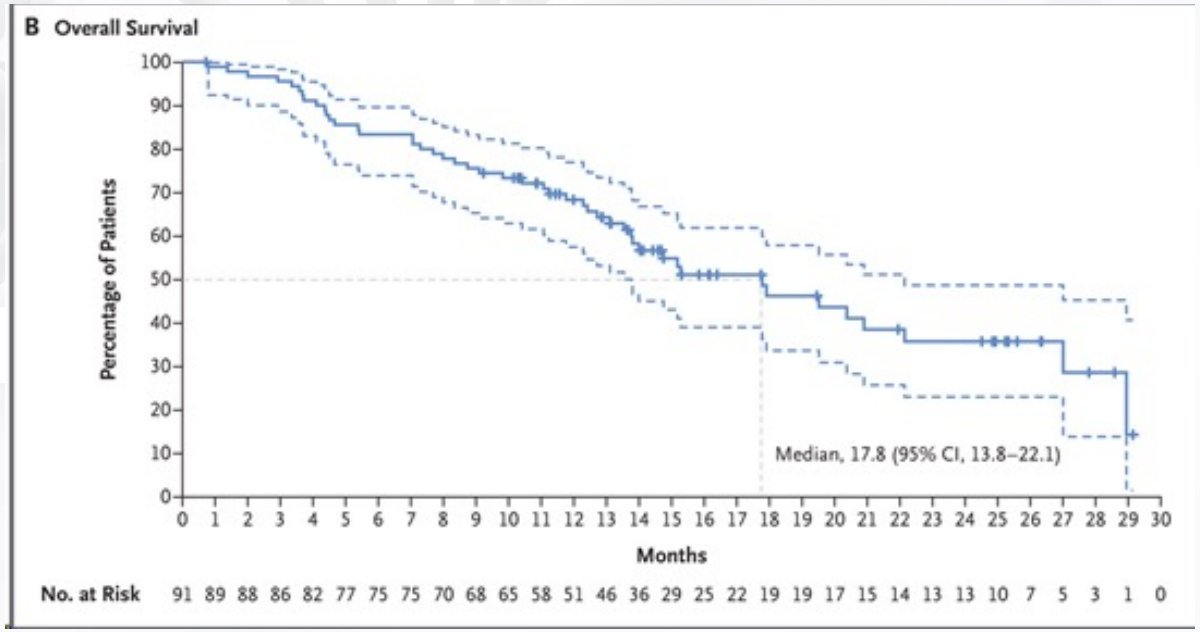
Efficacy of T-DXd- DESTINY Lung-1



BT Li et al. N Engl J Med 2021.

Efficacy of T-DXd





ORR: 55% (95% CI 44-65) n=91
Median PFS: 8.2 months
Median DOR: 9.3 months

BT Li et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2112431

Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD[a]	Safety Analysis Set[b]		Prespecified Early Cohort[c]	
	T-DXd 5.4 mg/kg n = 101	T-DXd 6.4 mg/kg n = 50	T-DXd 5.4 mg/kg n = 51	T-DXd 6.4 mg/kg n = 28
Any grade, n (%)	**6 (5.9)**	**7 (14.0)**	**4 (7.8)**	**5 (17.9)**
Grade 1	3 (3.0)	1 (2.0)	3 (5.9)	1 (3.6)
Grade 2	2 (2.0)	6 (12.0)	1 (2.0)	4 (14.3)
Grade 3	1 (1.0)	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Cases resolved, n (%)	3 (50.0)	1 (14.3)	1 (25.0)	1 (20.0)
Median time to onset of first adjudicated ILD, days (range)	67.5 (40-207)	41.0 (36-208)	104.5 (40-207)	43.0 (36-208)

- The rate of adjudicated drug-related ILD was lower in the T-DXd 5.4 mg/kg arm compared with the 6.4 mg/kg arm
- Most cases of adjudicated drug-related ILD were low grade (grade 1/2)

[a]Cases of potential ILD or pneumonitis were evaluated by an independent adjudication committee. Data shown here are for cases that were deemed drug related by the adjudication committee.
[b]In the safety analysis set, 1 investigator-reported grade 3 ILD event in the 5.4 mg/kg arm and 1 investigator-reported grade 5 ILD event in the 6.4 mg/kg arm pending adjudication at the data cutoff were subsequently adjudicated as drug-related grade 2 and grade 5 ILD, respectively.
[c]In the prespecified early cohort, 1 investigator-reported grade 3 event in the 5.4 mg/kg arm pending adjudication was subsequently adjudicated as drug-related grade 2 ILD. Goto K et al. ESMO 2022 [Supplement]. Presentation LBA#55.

New Kid on the Block: Telisotuzumab Vedotin-tllv

LUMINOSITY Trial

-Multicohort study: 84 patients with non-squamous NSCLC treated with c-met overexpression (3+ IHC)

-Stable brain metastasis allowed

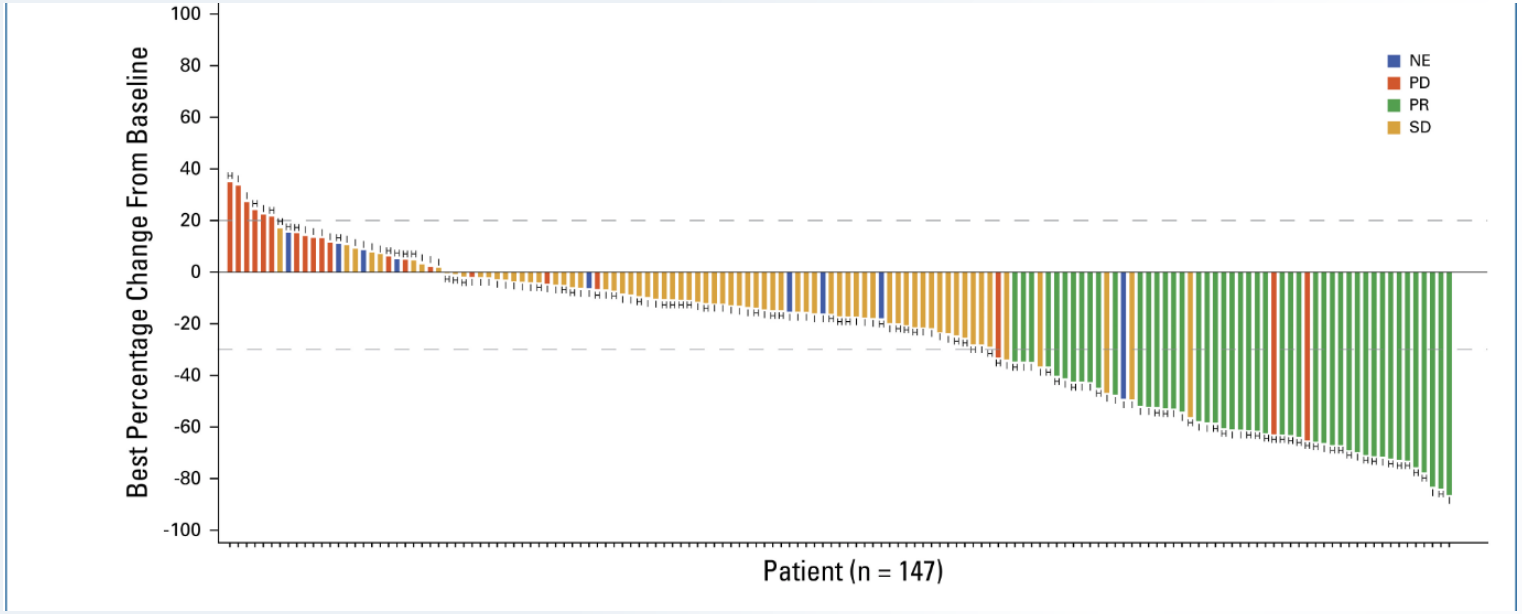
-1-3 lines prior therapy allowed.

-5% of patients received prior targeted therapy

-Other cohorts of squamous and EGFRm non-sq deemed futile

Camidge et al. JCO 2024

Telisotuzumab Vedotin-tllv



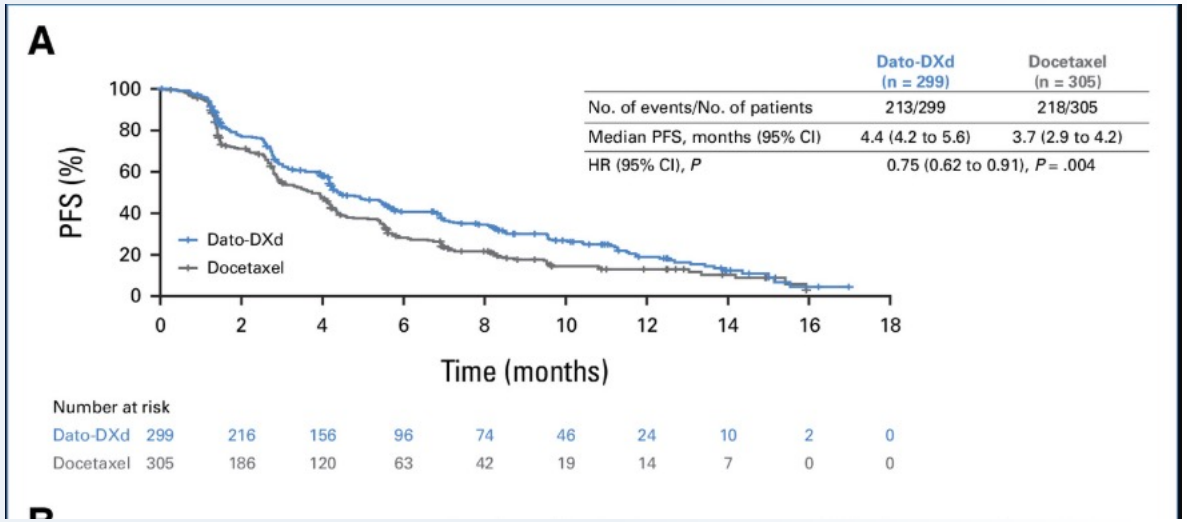
Outcome	c-Met High (n = 78)
ORR,[a] % (95% CI)	34.6 (24.2 to 46.2)
DCR,[a] % (95% CI)	60.3 (48.5 to 71.2)
DOR,[a] months, median (95% CI)	9.0 (4.2 to 13.0)
DOR ≥6 months,[a] n/no. of responders (%)	17/27 (63.0)
PFS,[a] median, months (95% CI)	5.5 (4.1 to 8.3)
6-month PFS,[a,b] % (95% CI)	45.8 (33.8 to 57.1)
OS, months, median (95% CI)	14.6 (9.2 to 25.6)
12-month OS,[b] % (95% CI)	57.0 (45.0 to 67.4)

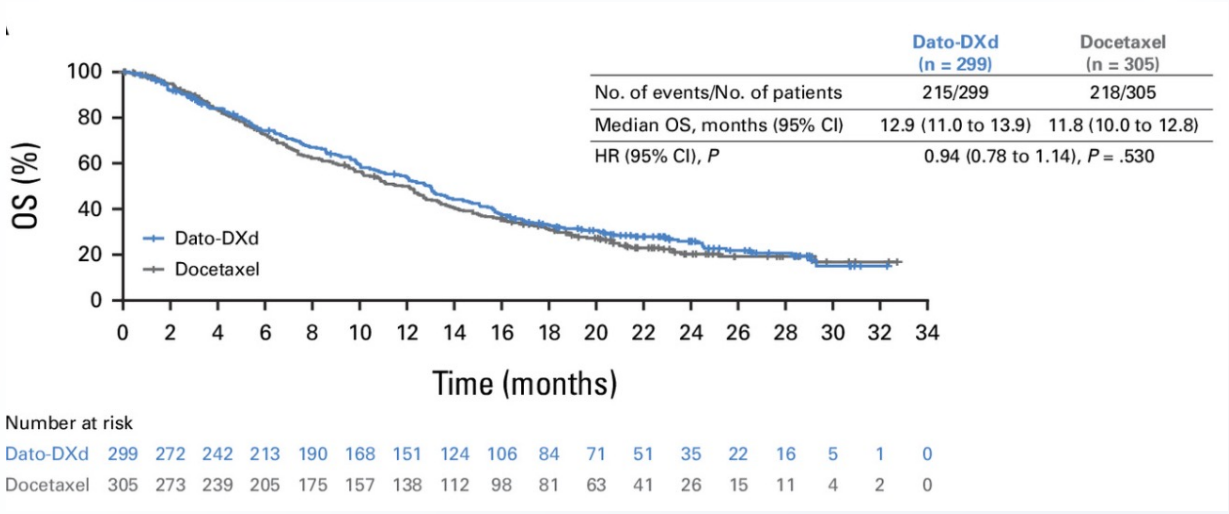
Camidge et al. JCO 2024

Not everything is a homerun, and that's OK!

Datopotamab Deruxtecan Versus Docetaxel TROPION Lung01

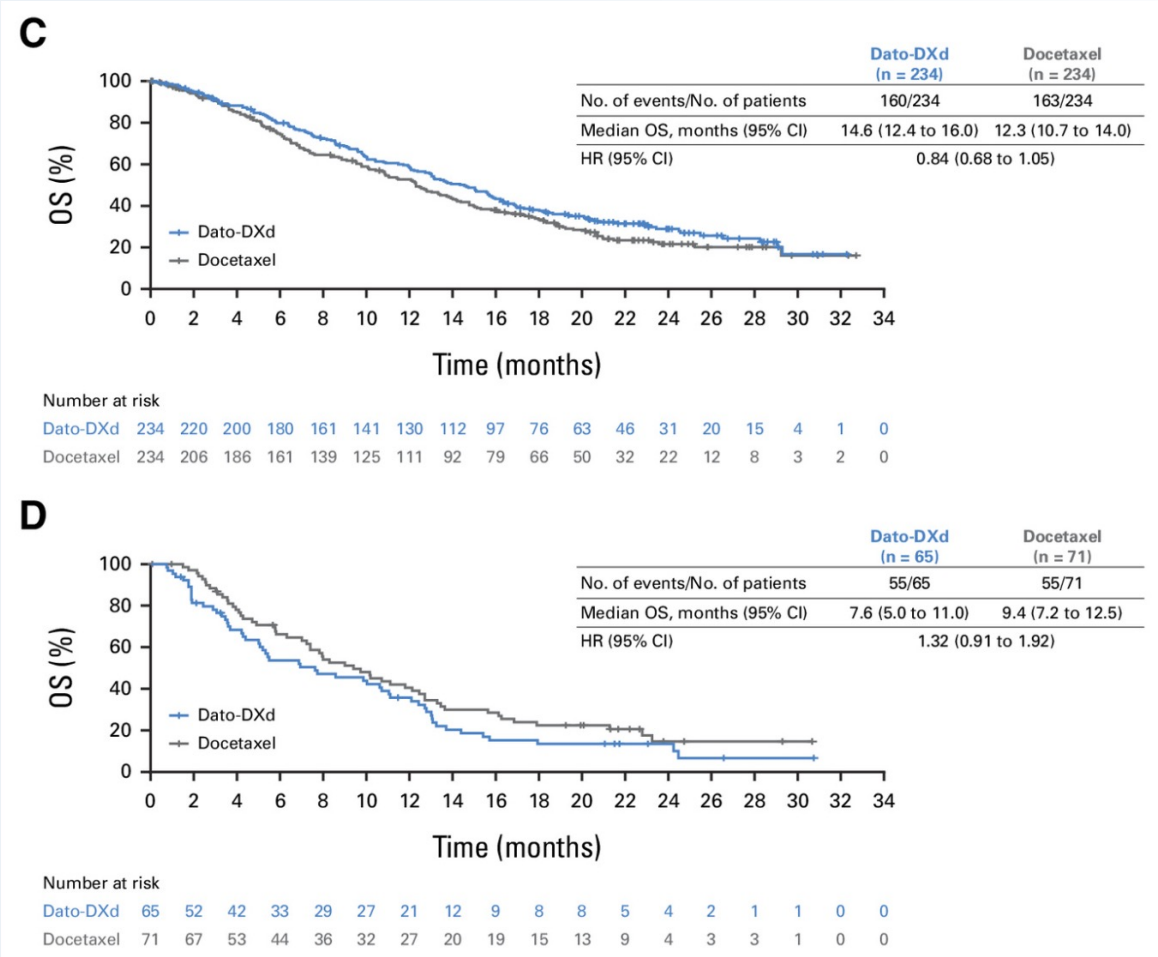
- Phase 3 randomized trial comparing Dato-DXd vs Docetaxel in second line metastatic NSCLC





Ahn et al. JCO 2024

Better by histology



Ahn et al. JCO 2024

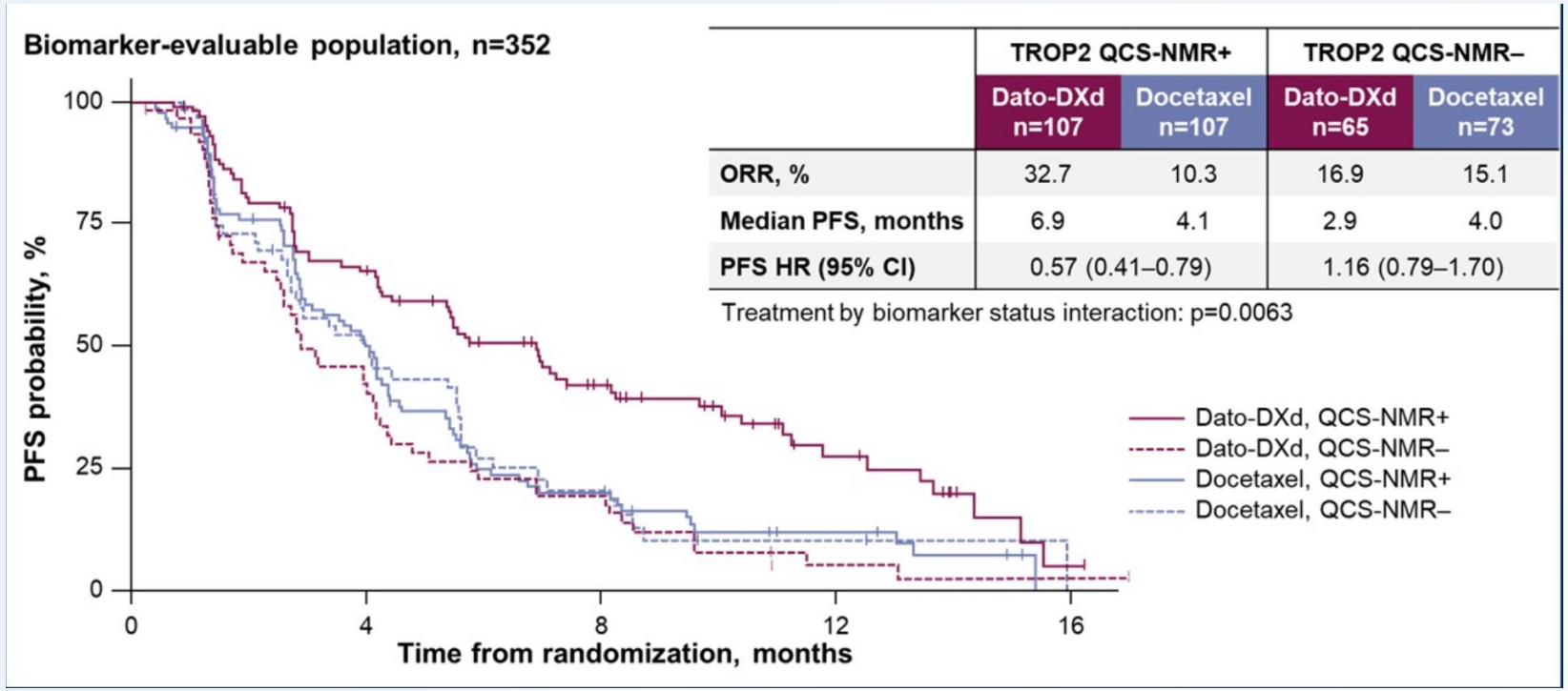
But the secret sauce is…Better Biomarkers!

Recent data presented at ASCO showed promise for a novel biomarker known as TROP2 quantitative continuous scoring (QCS) normalized membrane ratio (NMR)

The TROPION-Lung02 study included a 96 patients who received Dato-DXd along with pembrolizumab or pembrolizumab plus carboplatin or cisplatin

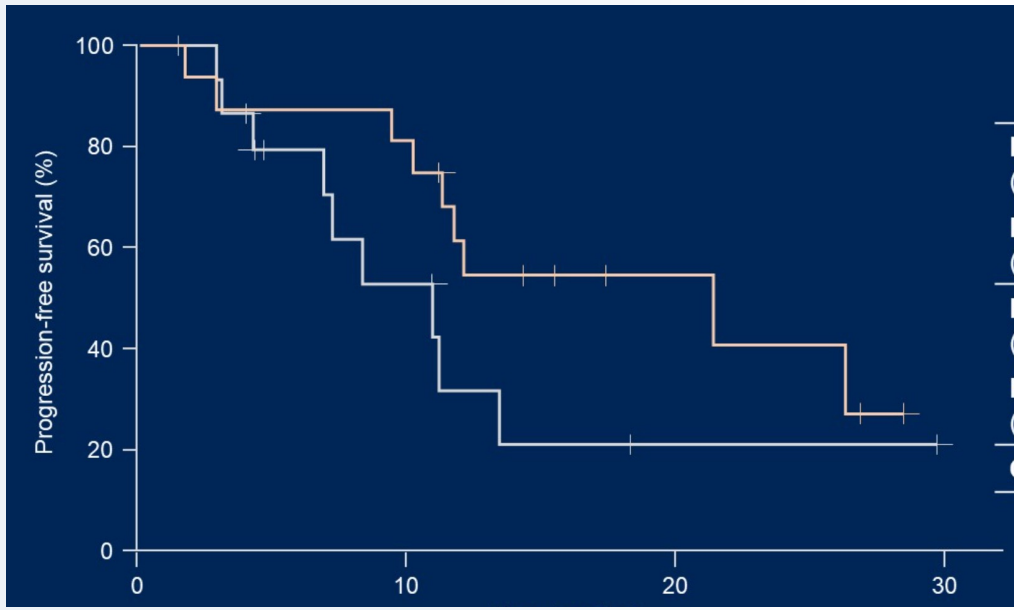
Significant adverse events with triplet therapy

Levy et al. ASCO 2025



	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

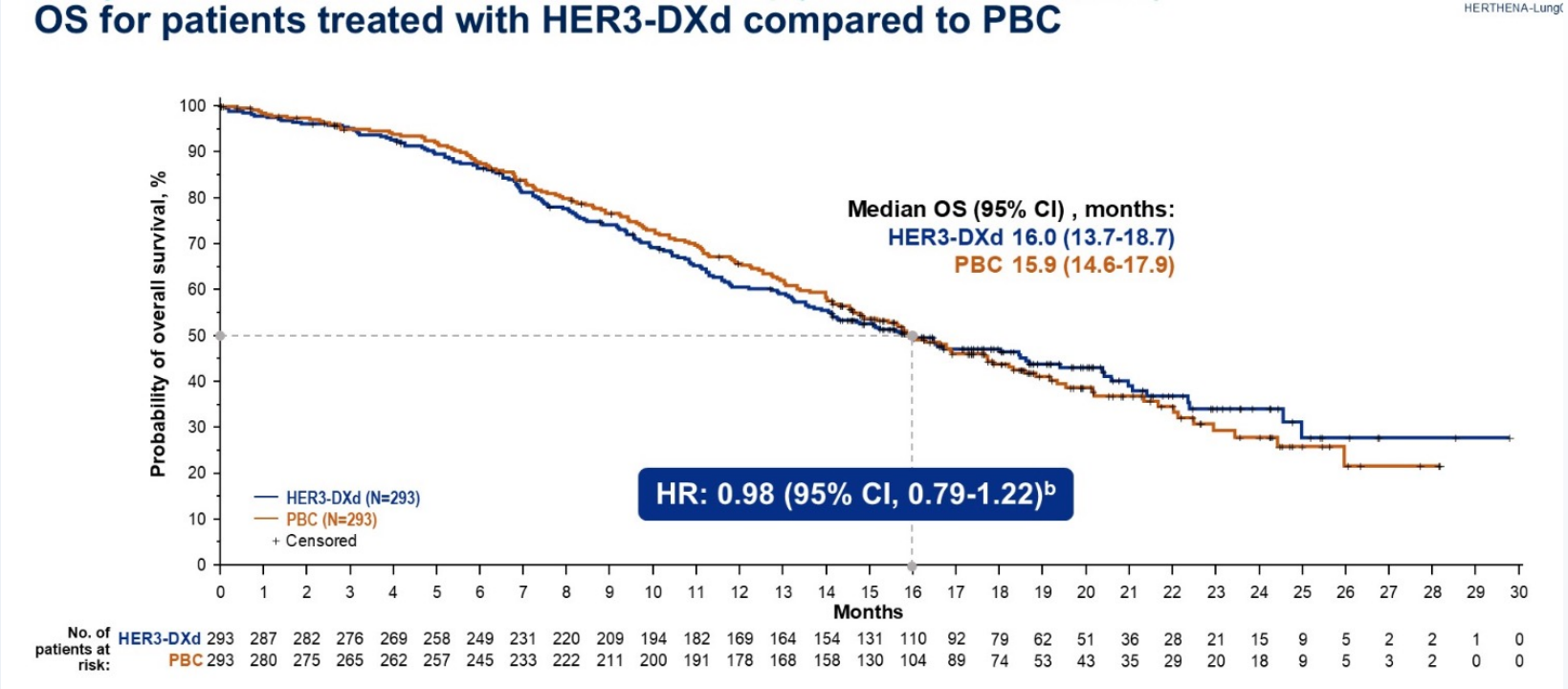


	TROP2 NMR+ (n=16)	TROP2 NMR– (n=16)
Median PFS (95% CI)	21.3 mo (10.2–NE)	10.9 mo (4.2–13.4)
HR (95% CI)	0.50 (0.19–1.29)	
Median OS (95% CI)	NE (26.2–NE)	NE (14.3–NE)
HR (95% CI)	0.35 (0.07–1.72)	
ORR	68.8%	62.5%

Levy et al. ASCO 2025

Patritumab Deruxtecan

Phase 3 study of Patritumab Deruxtecan vs Chemotherapy post EGFR TKI in EGFRm NSCLC



Maybe a Biomarker would help. Also not worse than chemotherapy!

Mok et al. ASCO 2025

Up and coming

BL-B01D1: ADC targeting both EGFR and HER3

BL-B01D1 is a first-in-class novel ADC consisting of an EGFRxHER3 bispecific antibody linked to a novel TOP-I inhibitor payload via a cleavable linker.

Zang et al. ASCO 2024

ADCs at ASCO 2025 in Lung Cancer - Updated

Study Name	Abs No	Population	Regimen	Target	Payload	Data Release
TROPION-Lung04	Abs: 8521	1L a/m NSCLC	Dato-DXd +Rilve	TROP2	TOPOIi	P1 - Data from cohort 5
NCT05194982	Abs: 3001	Ia/m NSCLC (outside EGFRm)	Iza-bren	EGFR, HER3	TOPOIi	P1 - Clinical data
NCT05194982	Abs: 3002	Ia/m SCLC	Iza-bren	EGFR, HER3	TOPOIi	P1 - Clinical data
TROPION-Lung02	Abs: 8501	1L aNSCLC	Dato-DXd + Pembro +/- Chemo	TROP2	TOPOIi	P1 - Clinical data
M21-404	Abs: 8512	EGFRmut adv nsqNSCLC	Telisotuzumab adizutecan	c-MET	TOPOIi	P1 - Clinical data
OptiTROP-Lung01	Abs: 8529	1L aNSCLC	Sac-TMT + Tagitanlimab	TROP2	TOPOIi	P1 - Data from non-squamous cohort
NCT05208762	Abs: 8611	NSCLC	PF-08046054	PD-L1	TUBi	P1 - Interim data
ZL-1310-001	Abs: 3041	2L+ ES-SCLC	ZL-1310	DLL3	TOPOIi	P1 - Updated data
KisMET-01	Abs: 8613	2L aNSCLC	MYTX-011	c-MET	TUBi	P1 - Updated dose escalation data
NCT06008379	Abs: 3036	Lung cancer	7MW3711 (ODD by FDA for SCLC)	B7-H3	TOPOIi	P1/2 - Clinical data
OptiTROP-Lung03	Abs: 8507	2L EGFRmut aNSCLC	Sac-TMT	TROP2	TOPOIi	P2 - Clinical data
RESOLUTION	Abs: e20515	HER2 alt Ia/m NSCLC	DV + Tisle + Bev	HER2	TUBi	P2 - Primary analysis data
LUMINOSITY	Abs: 8618	c-MET overexp EGFRwt adv nsqNSCLC	Teliso-V	c-MET	TUBi	P2 - Efficacy data by prior therapy
OptiTROP-Lung03	Abs: 8615	2L Ia/m NSCLC (with uncommon EGFRmut)	Sac-TMT	TROP2	TOPOIi	P2 - Preliminary data
TUXEDO-3	Abs: 2005	adv solid tumors (including NSCLC, mBC)	Patritumab deruxtecan	HER3	TOPOIi	P2 - Clinical data in BM from NSCLC, other solid tumors
HERTHENA-Lung02	Abs: 8506	2L EGFRmut aNSCLC	Patritumab deruxtecan	HER3	TOPOIi	P3 - Clinical data

https://www.linkedin.com/posts/larvol_adcs-at-asco-2025-in-lung-cancer-updated-activity-7332089652532707328-uu_Q/

Conclusion

- Not only are ADCs promising for the future of NSCLC, but they are already making a difference
- More “established” recent therapies, such as TKIs and immunotherapy took awhile to fine tune and become standard of care. Now looking at 4th generation EGFR TkIs
- Very adaptable drug delivery system
- Even the less exciting data has interesting info, good biomarkers are key.
- So many new agents, I can barely keep! The Future is ADCs!


“not all those
who wander
are lost”
J.R.R. Tolkien

Q&A