MCM Tampa Bay Edition Jan 11, 2025

ADCs in NSCLC: Too Much Hope?

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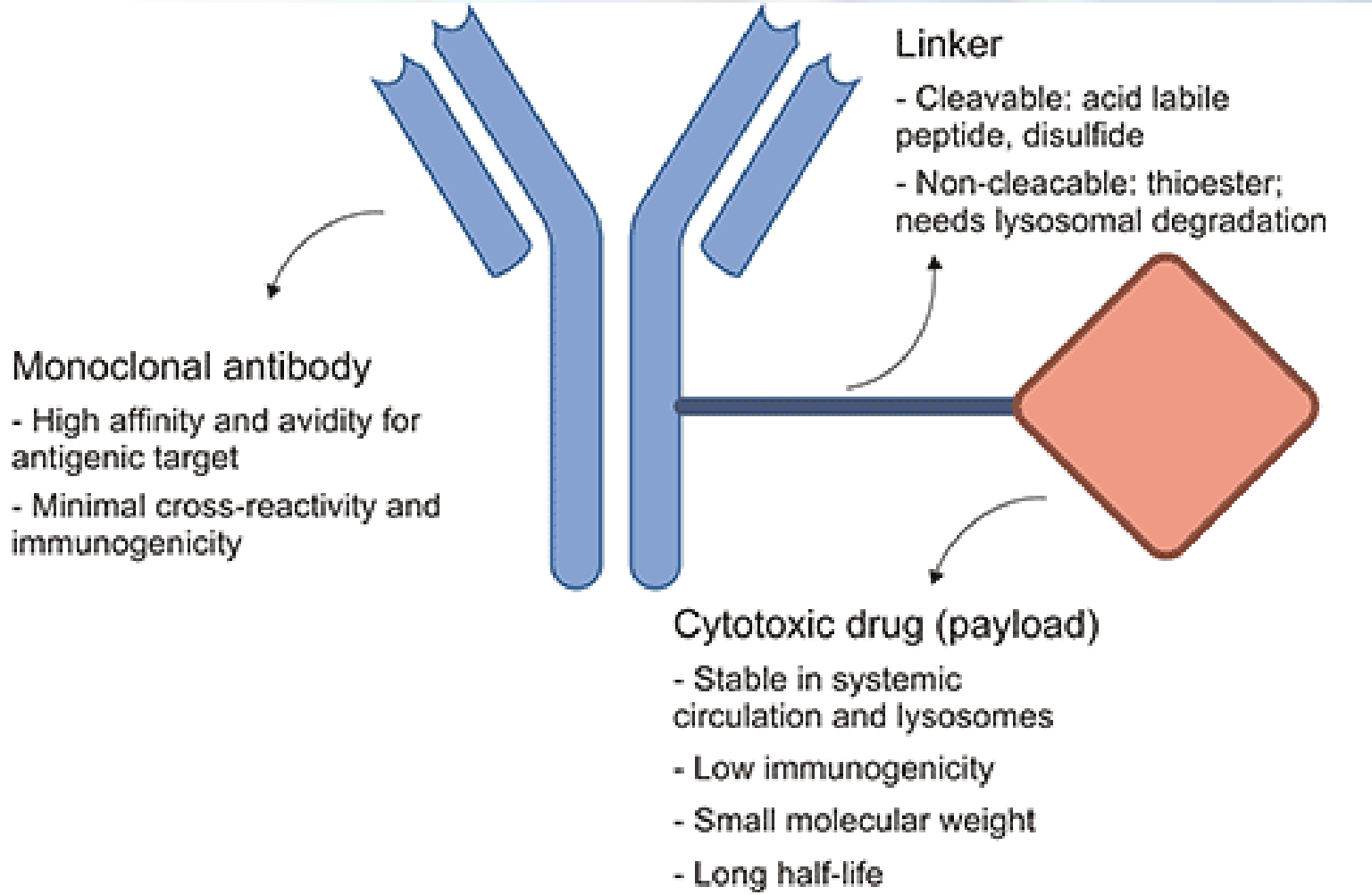
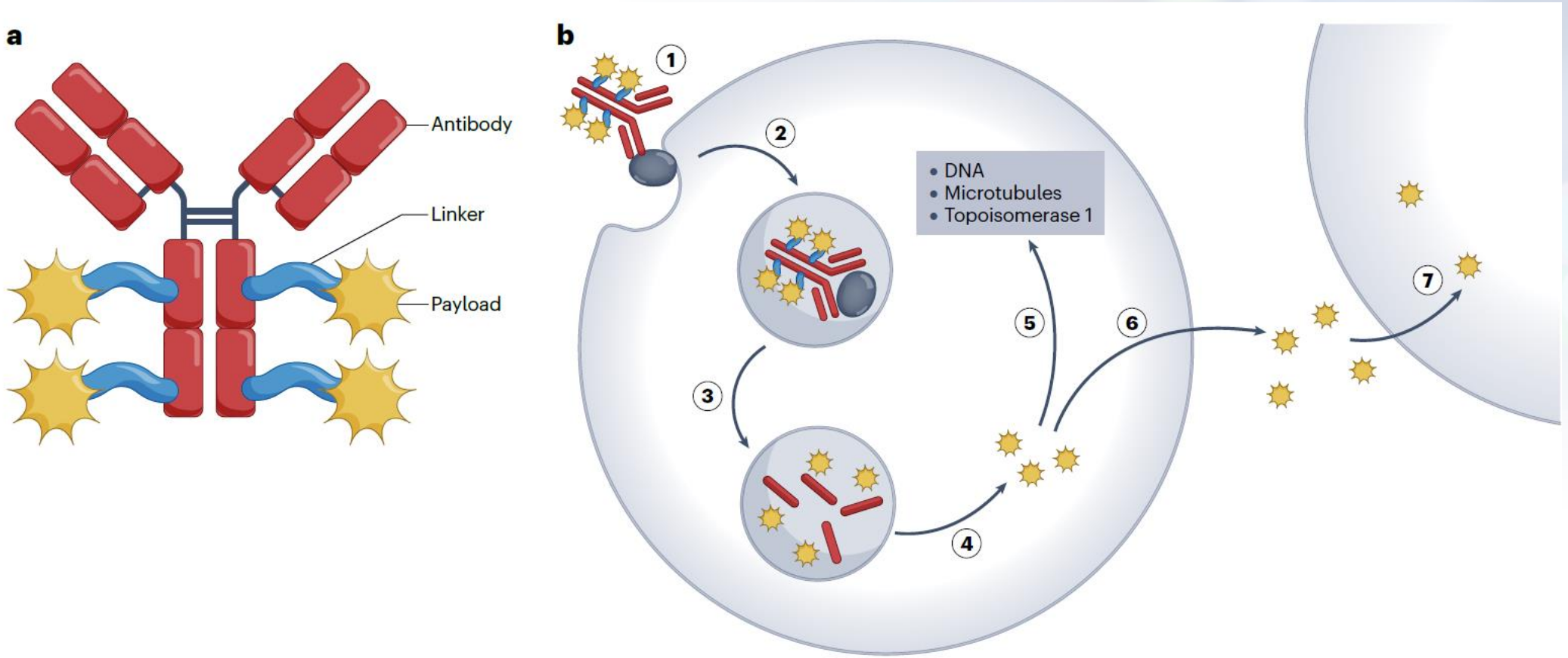
ABCs of ADCs - Structure

A. Monoclonal Antibody
B. Linker
C. Payload (cytotoxic)



Cancer Treat Rev. 2022 May;106:102393

Mechanism of action



Nat Rev Drug Discov. 2023 Aug;22(8):641-661.

Trophoblast cell surface antigen-2 (TROP 2) in NSCLC

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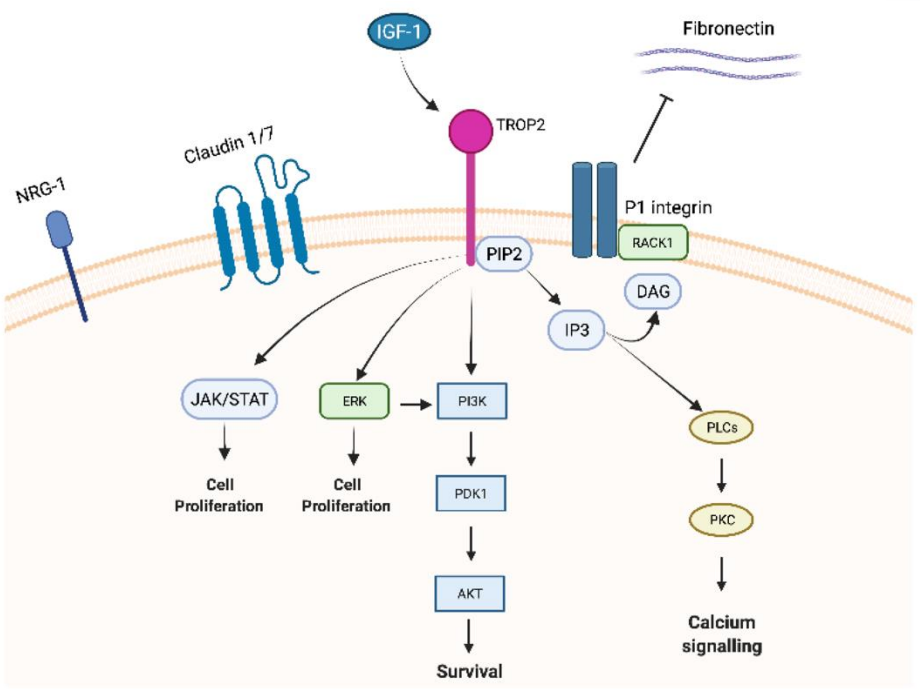
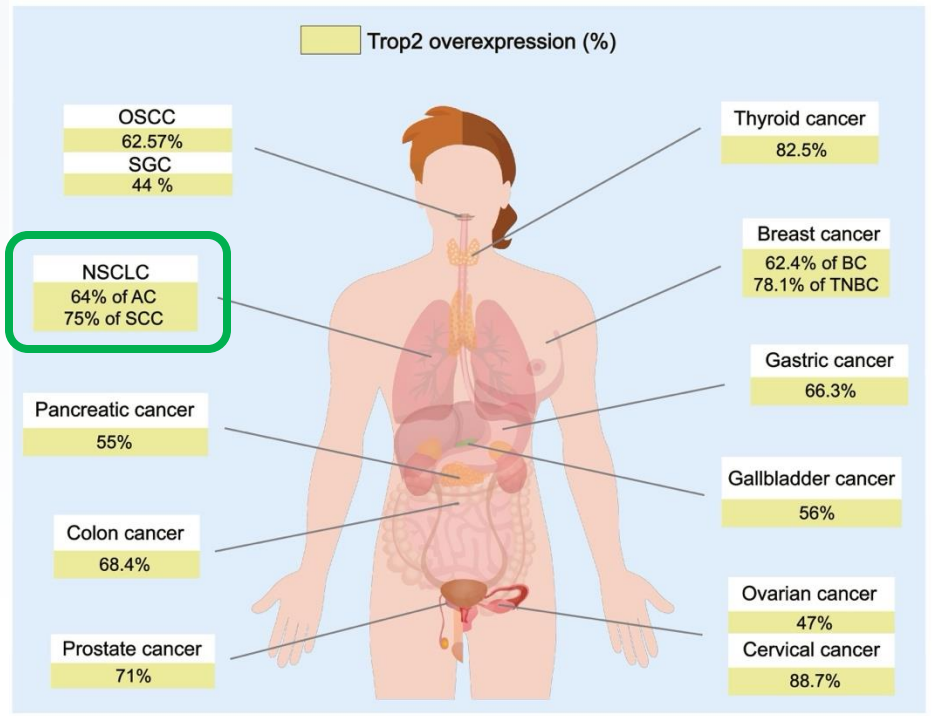
TROP-2 in NSCLC





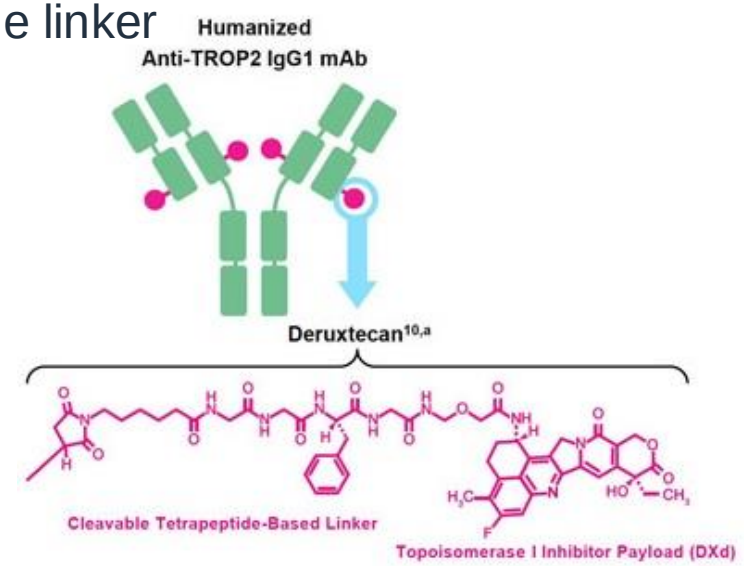
- *Cancers (Basel). 2023 Mar 13;15(6):1744.*

**Pharmacol Ther. 2022 Nov;239:108296*

TROP-2 ADCs in NSCLC

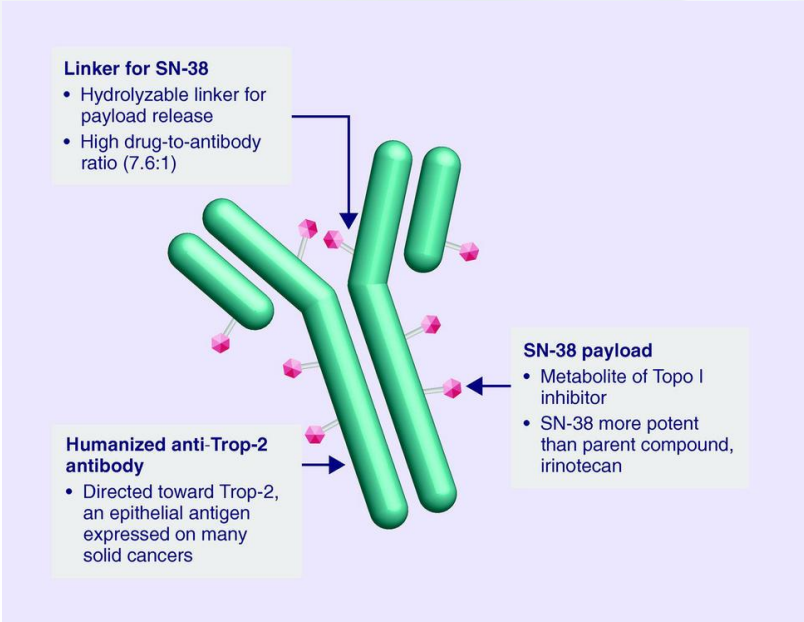
Datopotomab deruxtecan (Dato-DXd)

- Humanized anti-TROP2 IgG1 mAb
- Topoisomerase 1 inhibitor
- Tetrapeptide cleavable linker



Sacituzumab govitecan(SG)

- Anti-TROP2 IgG1 mAb
- Topoisomerase 1 inhibitor – SN38



- *ELCC Mar 20-24, 2024 Prague, Czech Republic*

EVOKE-01 – Study Design (SG)

- Global, multicenter, randomized, open-label phase III trial

Stratified by histology (sq vs nonsq), response to last anti–PD-1/PD-L1 regimen (PD/SD vs CR/PR), receipt of prior targeted therapy for AGA (yes vs no)

- Stage IV NSCLC with PD after
- platinum-based CT and anti–PD-1/PD-L1 regimen
- ≥1 approved targeted tx for AGAs; testing for *EGFR, ALK,*
- ECOG PS 0/1
- no active CNS metastases
- (N = 603)

Sacituzumab Govitecan (n = 299)

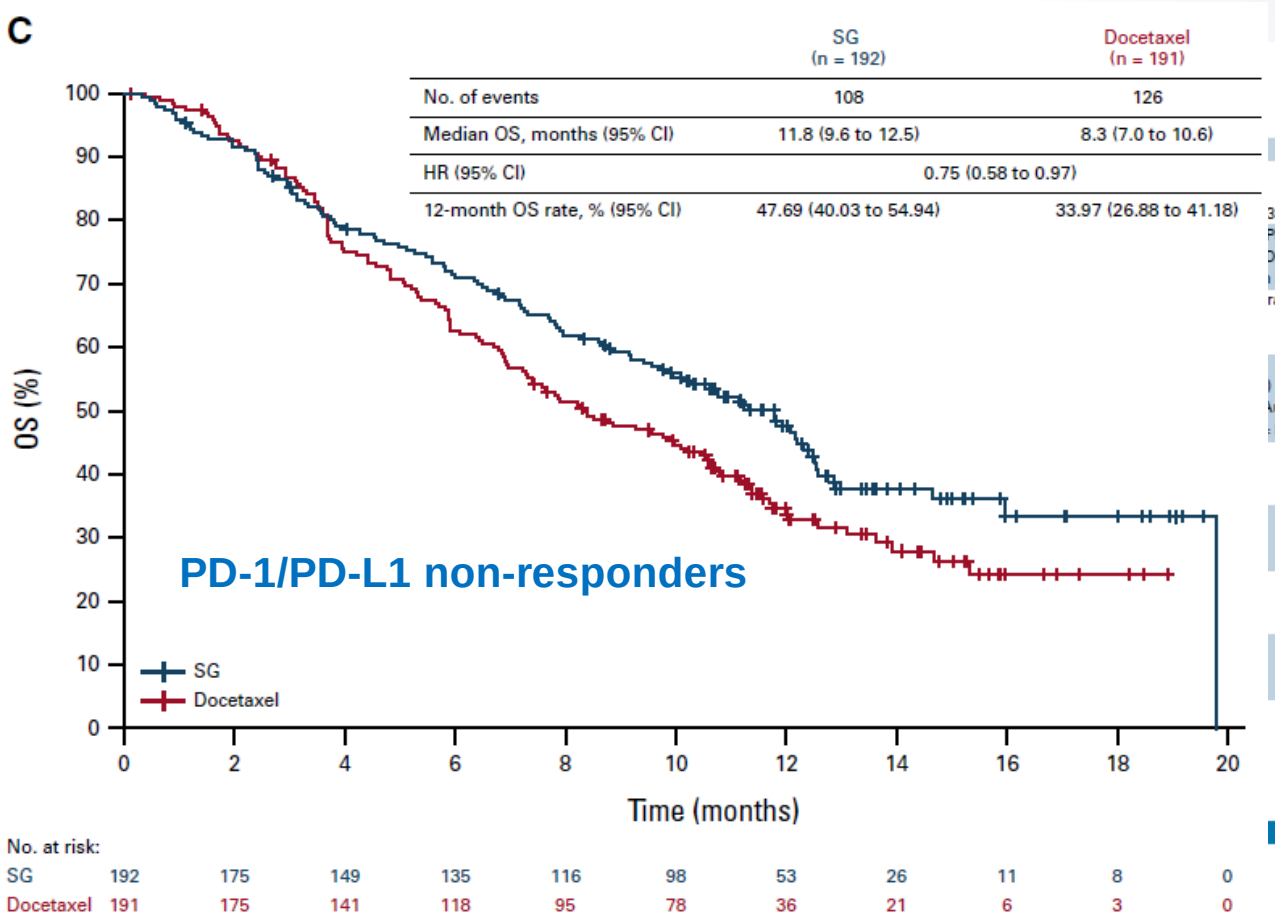
Docetaxel (n = 304)

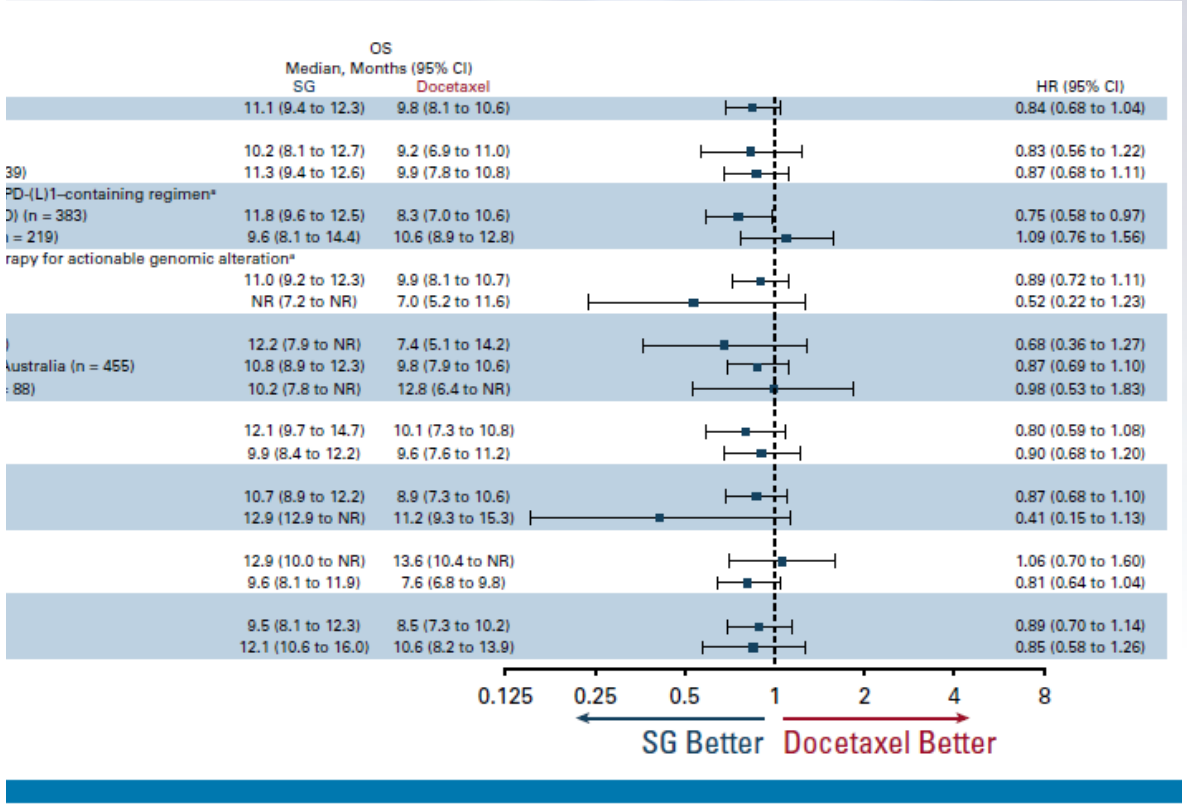
Tx continued until PD or unacceptable toxicity

- **Primary endpoints:** OS
- **Secondary endpoints:** PFS, ORR, DoR, DCR by inv per RECIST v1.1, safety, QoL

Paz-Ares. ASCO 2024. Abstr LBA8500. Paz-Ares. JCO. 2024;[Epub].

EVOKE-01 –Efficacy





The Randomized, Open-Label Phase III EVOKE-01 Study. J Clin Oncol. 2024 Aug 20;42(24):2860-2872

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EVOKE-01 – Safety

TEAEs Occurring in ≥20% in Either Arm, %	SG (n = 296)		Docetaxel (n = 288)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Overall	100	67	98	76
Fatigue	57	13	56	10
Diarrhea	53	10	34	4
Alopecia	43	1	30	1
Nausea	42	2	26	1
Anemia	40	6	31	6
Neutropenia	38	25	43	37
Constipation	29	0	17	0
Decreased appetite	26	2	24	2
Vomiting	21	2	15	2
Stomatitis	13	1	20	2
Leukopenia	13	5	22	17

- Additional safety outcomes for SG vs docetaxel
  - Serious TEAEs: 46.3% vs 43.1%
  - TEAEs leading to d/c: 9.8% vs 16.7%
  - TEAEs leading to dose reduction: 29.4% vs 38.9%
  - TEAEs leading to death: 3.4% vs 4.5%

The Randomized, Open-Label Phase III EVOKE-01 Study. J Clin Oncol. 2024 Aug 20;42(24):2860-2872

TROPION-Lung01 – Study Design (Dato-Dxd)

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

Key eligibility criteria

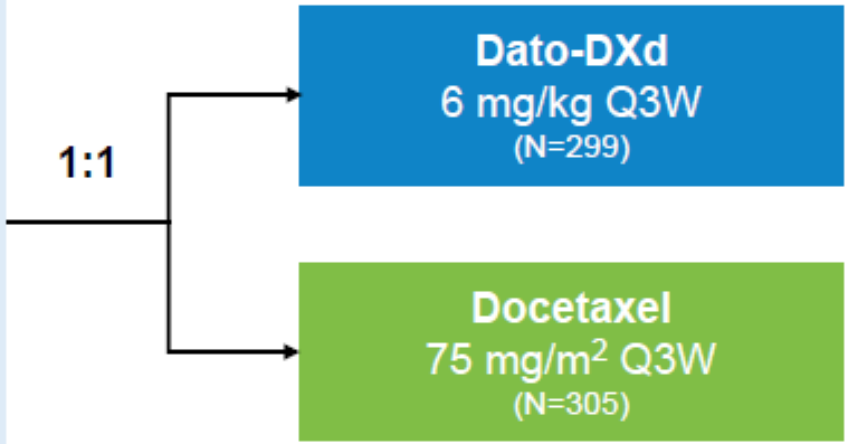
- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0–1
- No prior docetaxel

Without actionable genomic alterations

- One to two prior lines, including platinum-based 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*
- One to two prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb



Dual primary endpoints

- PFS by BICR[a]
- OS

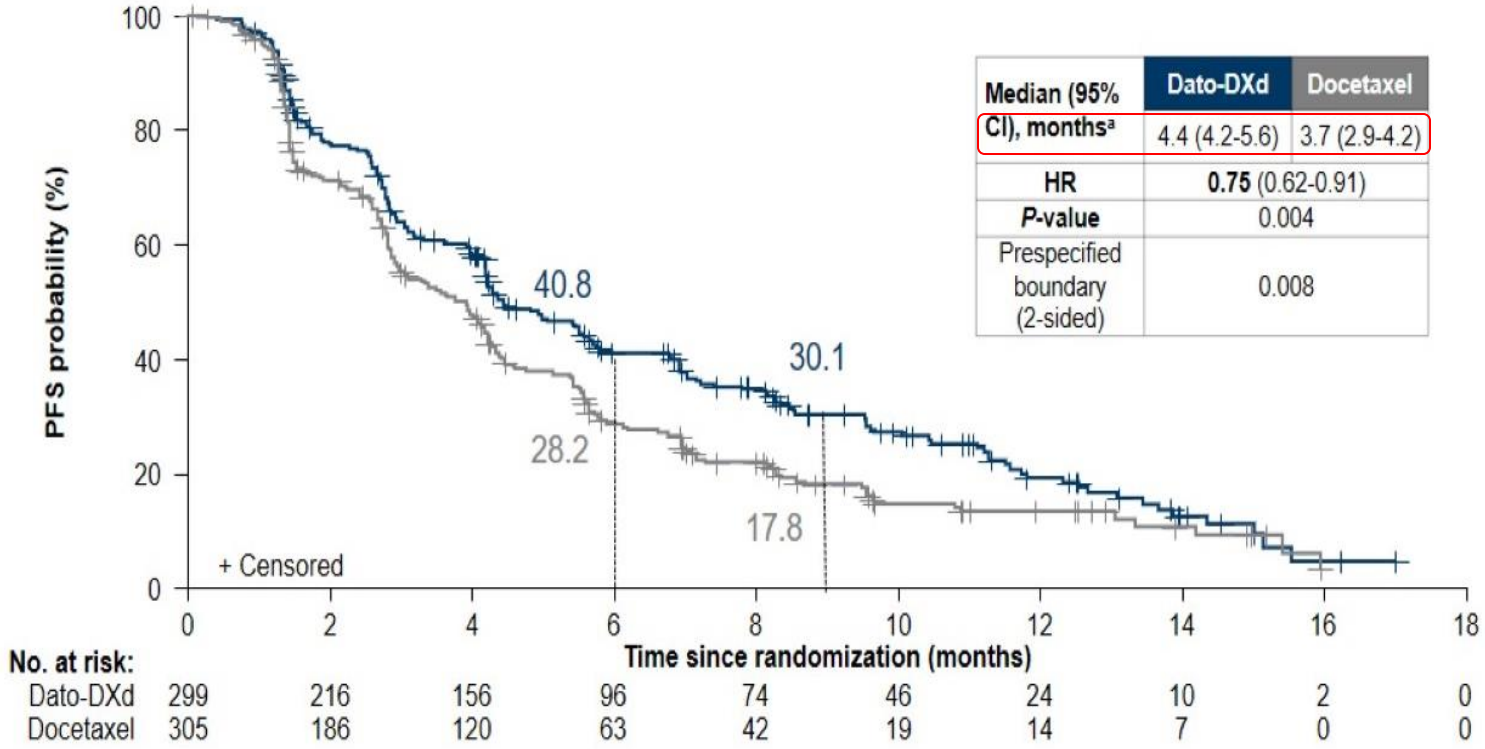
Secondary endpoints

- ORR[a]
- DOR[a]
- Safety and tolerability

Stratified by histology (nonsquamous vs squamous), actionable genomic alteration status,[b] anti–PD-(L)1 mAb included in most recent prior therapy, and geography[c]

- *J Clin Oncol. 2024 Sep 9:JCO2401544*

TROPION-Lung01 – PFS ITT



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	

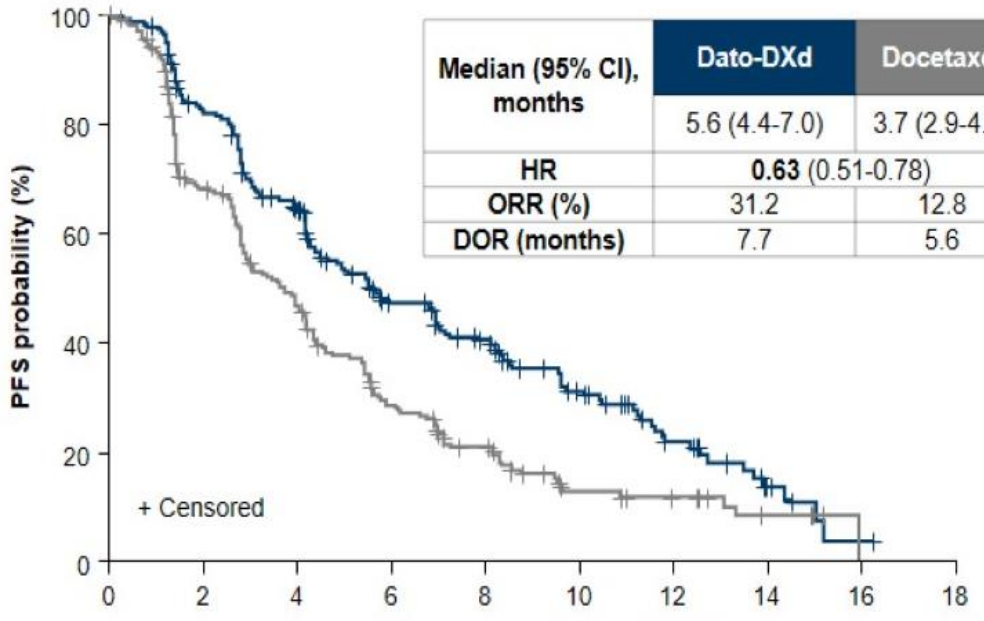
	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR, months (95% CI)	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

ESMO 2023 - Oct 20-24, 2023 Madrid, Spain

TROPION-Lung01 – PFS by histology

Non-squamous

(With and without actionable genomic alterations)



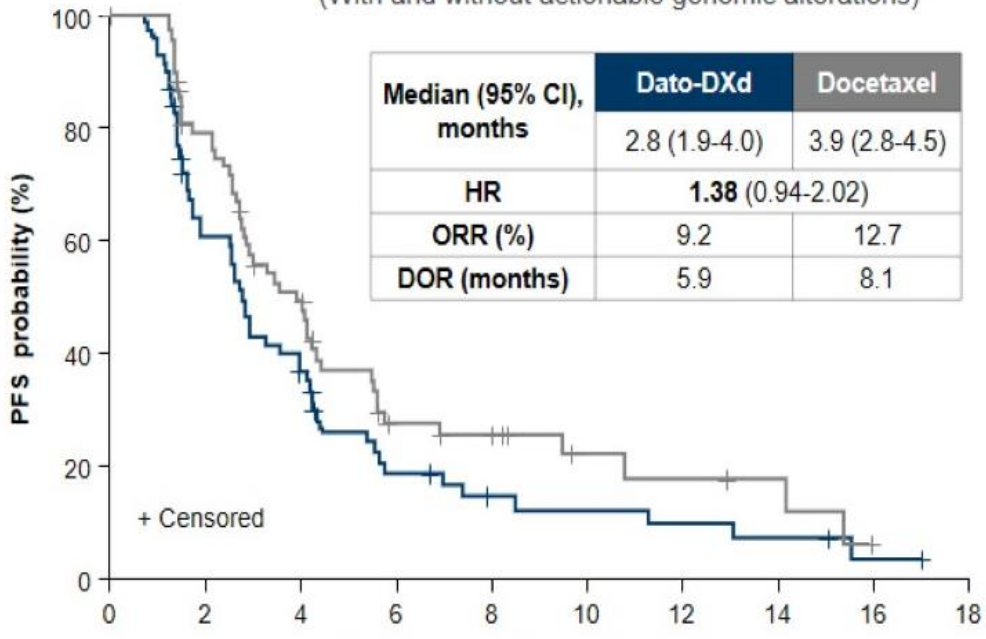
Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR (%)	31.2	12.8
DOR (months)	7.7	5.6

No. at risk:										
Dato-DXd	229	178	134	86	68	41	20	7	1	0
Docetaxel	232	135	90	50	32	14	10	4	0	0

PFS HR for non-squamous patients without actionable genomic alterations: 0.71 (0.56, 0.91)

Squamous[a]

(With and without actionable genomic alterations)

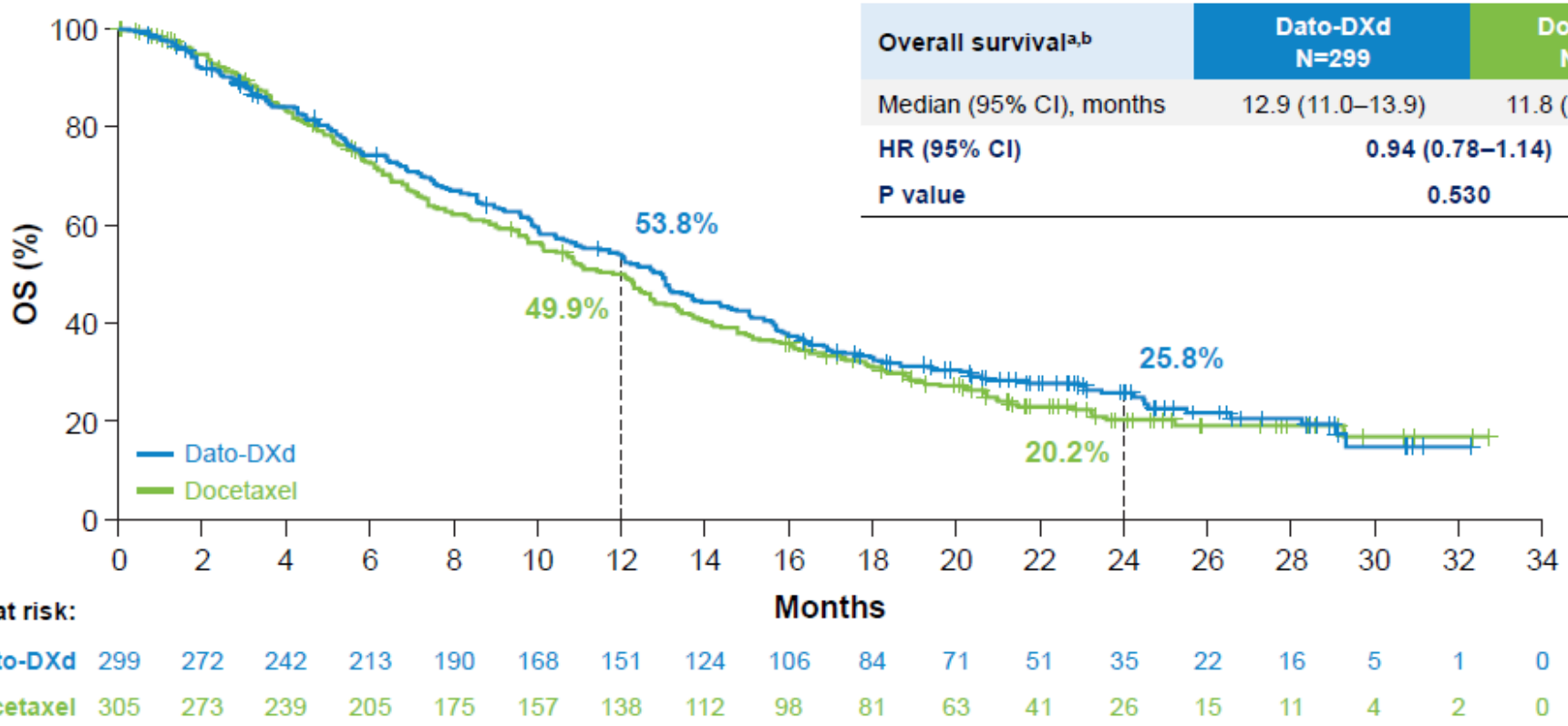


Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR (%)	9.2	12.7
DOR (months)	5.9	8.1

No. at risk:										
Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

ESMO 2023 - Oct 20-24, 2023 Madrid, Spain

TROPION-Lung01 – OS ITT



Overall survival[a,b]	Dato-DXd N=299	Docetaxel N=305
Median (95% CI), months	12.9 (11.0–13.9)	11.8 (10.0–12.8)
HR (95% CI)	0.94 (0.78–1.14)	
P value	0.530	

WCLC24 Sep 7-11, 2024 San Diego, CA

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TROPION-Lung01 – Safety

TRAEs ≥15% and Adjudicated Drug-Related ILD

TRAEs,[a] n (%)	Dato-DXd (N=297)		Docetaxel (N=290)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Stomatitis	141 (47)[b]	20 (7)	45 (16)	3 (1)
Nausea	101 (34)	7 (2)	48 (17)	3 (1)
Alopecia	95 (32)	0	101 (35)	1 (<1)[c]
Decreased appetite	68 (23)	1 (<1)	46 (16)	1 (<1)
Asthenia	56 (19)	8 (3)	56 (19)	5 (2)
Anemia[d]	44 (15)	12 (4)	60 (21)	12 (4)
Diarrhea	30 (10)	1 (<1)	55 (19)	4 (1)
Neutropenia[e]	14 (5)	2 (1)	76 (26)	68 (23)
Leukopenia[f]	9 (3)	0	45 (16)	38 (13)
Adjudicated drug-related ILD or pneumonitis	26 (9)[g]	11 (4)	12 (4)	4 (1)

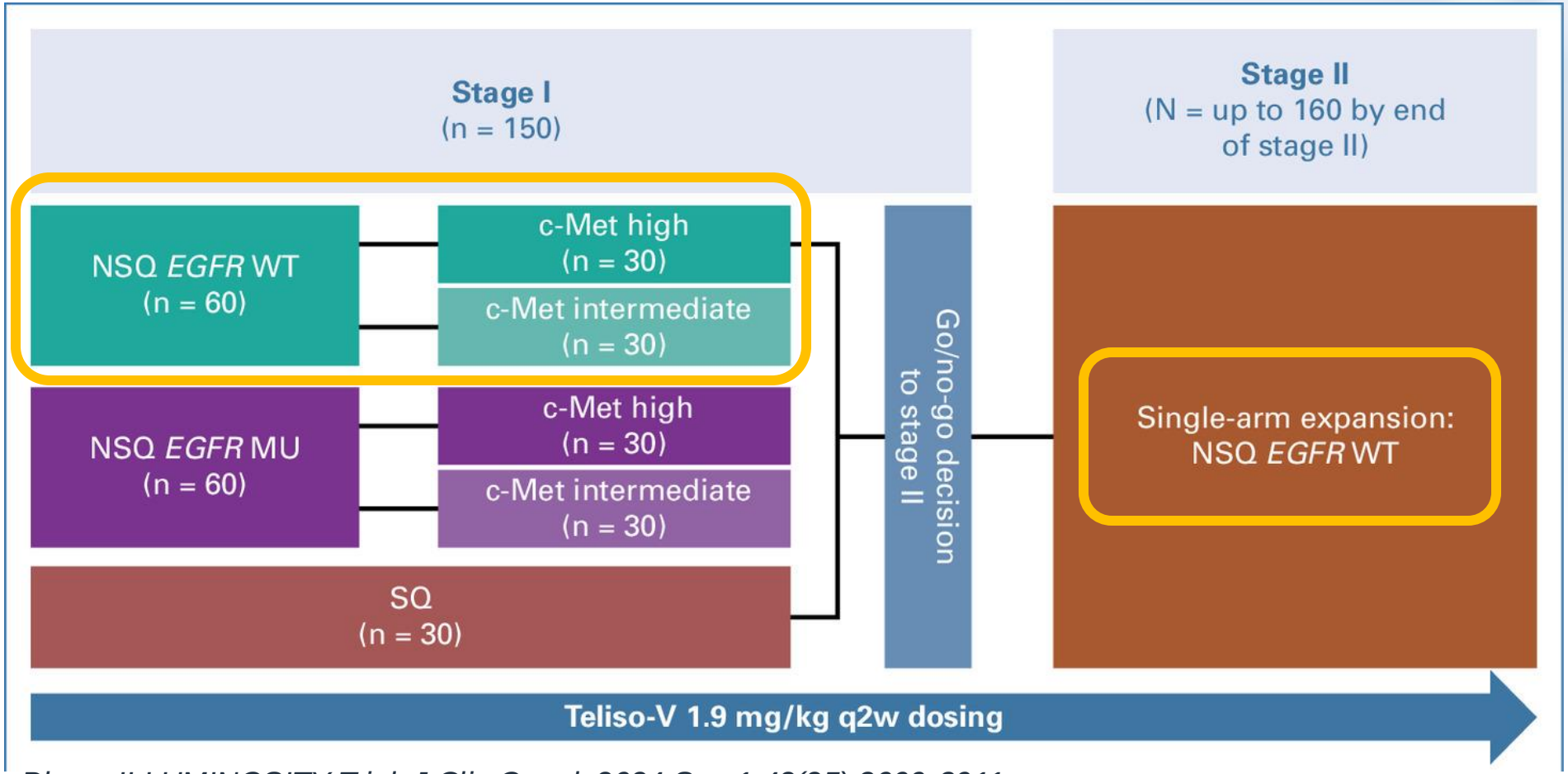
- Stomatitis events, the most common TRAE with Dato-DXd, were primarily grade 1 (23%) or grade 2 (18%)
- Hematologic toxicities, including neutropenia and febrile neutropenia[h], were more common with docetaxel
- No new adjudicated drug-related ILD events or deaths occurred since the PFS database lock
- Similar safety profiles were seen for the full safety analysis set and the NSQ subgroup

WCLC24 Sep 7-11, 2024 San Diego, CA

c-Met (Hepatocyte growth factor receptor) in NSCLC

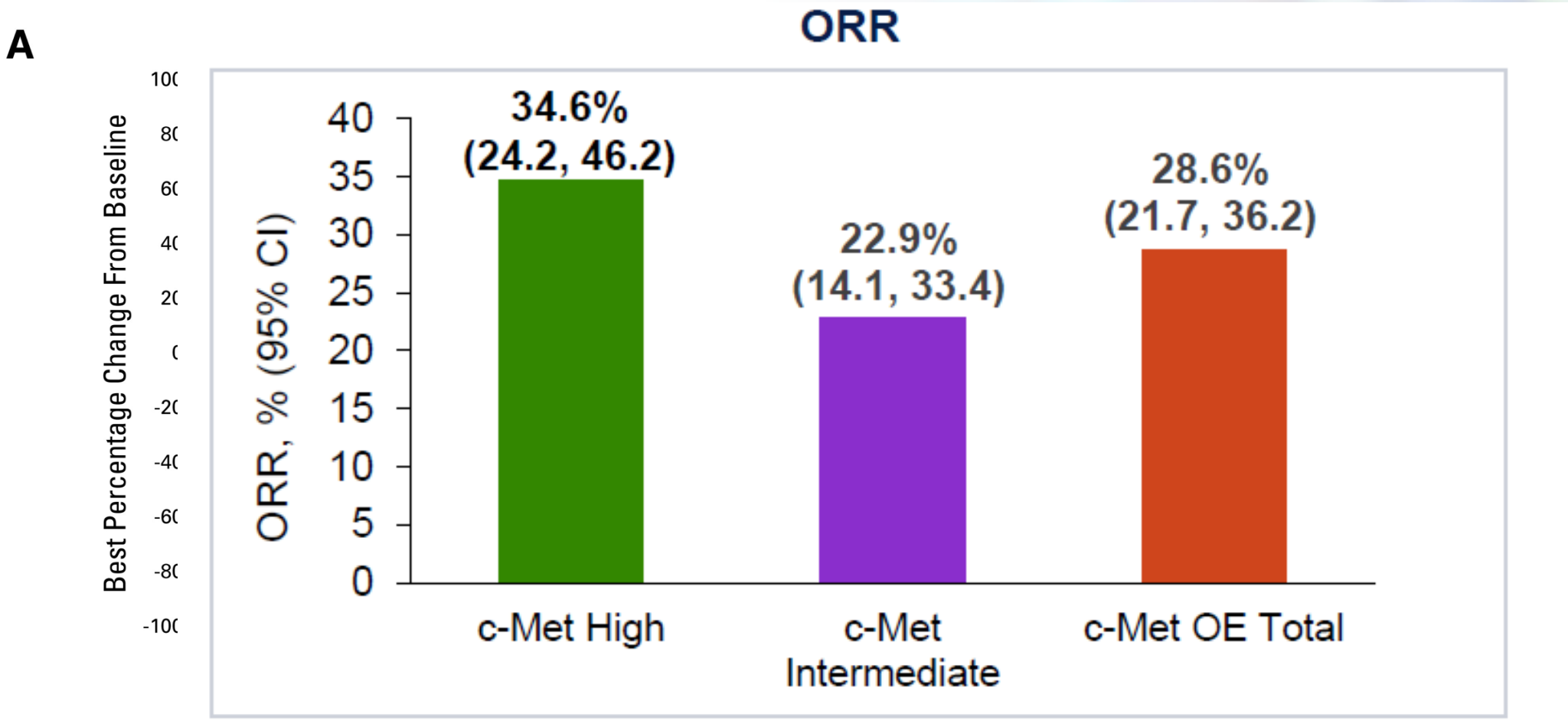
TGH Tampa General Hospital | USF Health Morsani College of Medicine

LUMINOSITY Trial – Study Design (Telisotuzumab Vedotin – Teliso-V)



Phase II LUMINOSITY Trial. J Clin Oncol. 2024 Sep 1;42(25):3000-3011

LUMINOSITY Trial – Efficacy (NSQ EGFR WT)



Phase II LUMINOSITY Trial. J Clin Oncol. 2024 Sep 1;42(25):3000-3011

LUMINOSITY Trial – Safety (select AEs)

	Total N= 172	
	Any Grade	**Grade ≥ 3**
Any TRAE, n(%)	140 (81.4)	48 (27.9)
TRAEs occurring in ≥ 5% of patients, n (%)		
*Peripheral sensory neuropathy**	52 (30)	12 (7)
Peripheral edema	28 (16.3)	3 (1.7)
ALT increase	19 (11)	6 (3.5)
Pneumonitis	18 (10.5)	4(2.9) **– 3 deaths**
Hypoalbuminemia	18 (10.5)	0
Blurred vision	16 (9.3)	2 (1.2)

*18 (10%) patients had an AE of peripheral neuropathy leading to discontinuation

Phase II LUMINOSITY Trial. J Clin Oncol. 2024 Sep 1;42(25):3000-3011

Human Epidermal growth factor Receptor 3 (HER3) in EGFR mutated NSCLC

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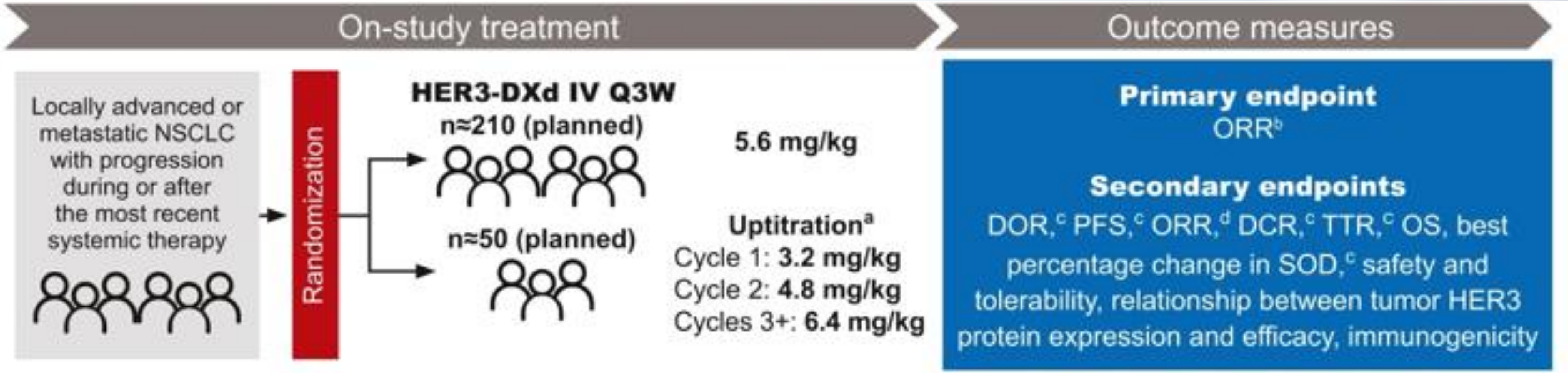
HERTHENA-Lung01 – Study Design (Patritumab Deruxtecan)



EGFR mutated

J Clin Oncol. 2023 Dec 10;41(35):5363-5375

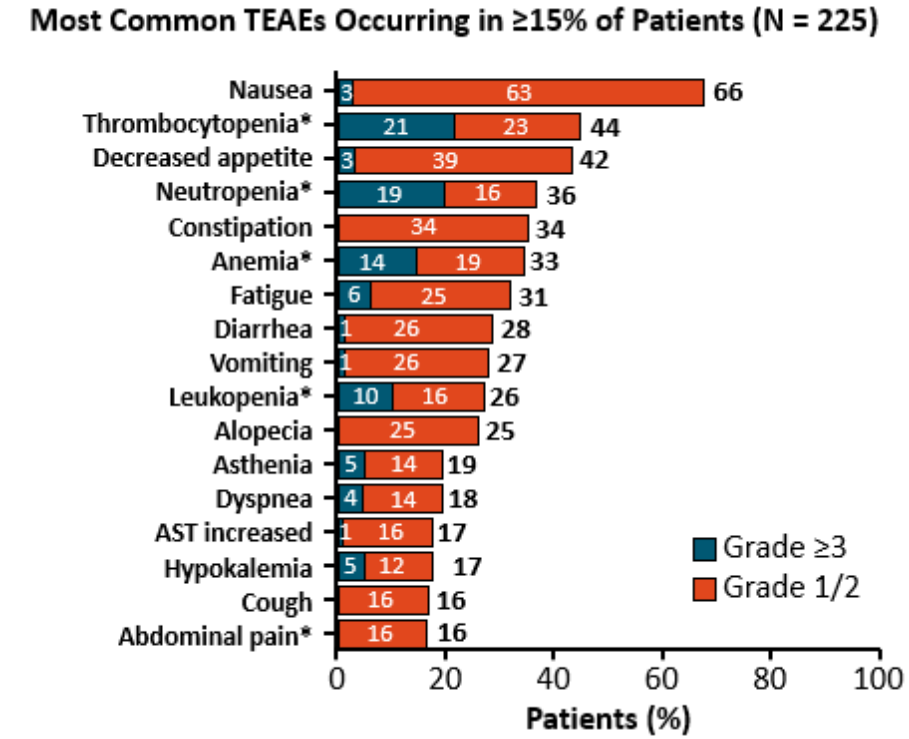
HERTHENA-Lung01 – Efficacy (P-Dxd)

	N = 225
ORR by BICR	29.8%
median duration of response (mDOR)	6.4 months
median overall survival (mOS)	11.9 months

J Clin Oncol. 2023 Dec 10;41(35):5363-5375

HERTHENA-Lung01 – Safety (P-Dxd)

Safety Outcome, n (%)	HER3-DXd 5.6 mg/kg (N = 225)
Any TEAE	224 (99.6)
▪ **Associated with treatment d/c**	**16 (7.1)**
▪ Associated with dose reduction	48 (21.3)
▪ Associated with dose interruption	91 (40.4)
TEAE grade ≥3	146 (64.9)
Treatment-related TEAE	215 (95.6)
▪ Grade ≥3	102 (45.3)
▪ Serious TEAE	34 (15.1)
▪ Associated with death	4 (1.8)
Adjudicated ILD (as treatment related)	**12 (5.3)**
▪ Grade 1	1 (0.4)
▪ Grade 2	8 (3.6)
▪ Grade 3	2 (0.9)
▪ Grade 4	0
▪ Grade 5	1 (0.4)



*Grouped preferred terms.

Sep 17, 2024 Press release:

Patritumab Deruxtecan Demonstrated Statistically Significant Improvement in Progression-Free Survival Versus Doublet Chemotherapy in Patients with Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer in HERTHENA-Lung02 Phase 3 Trial

J Clin Oncol. 2023 Dec 10;41(35):5363-5375

Human Epidermal growth factor Receptor 2 (HER2) in NSCLC

TGH Tampa General Hospital | USF Health Morsani College of Medicine

HER2 in NSCLC (Non-Squamous)

HER2 Overexpression (HER-OE)	HER2 Amplification	HER2 Mutation (HER2m)
2-30%	2-4%	2-4%
IHC	FISH/NGS	rt-PCR/ NGS

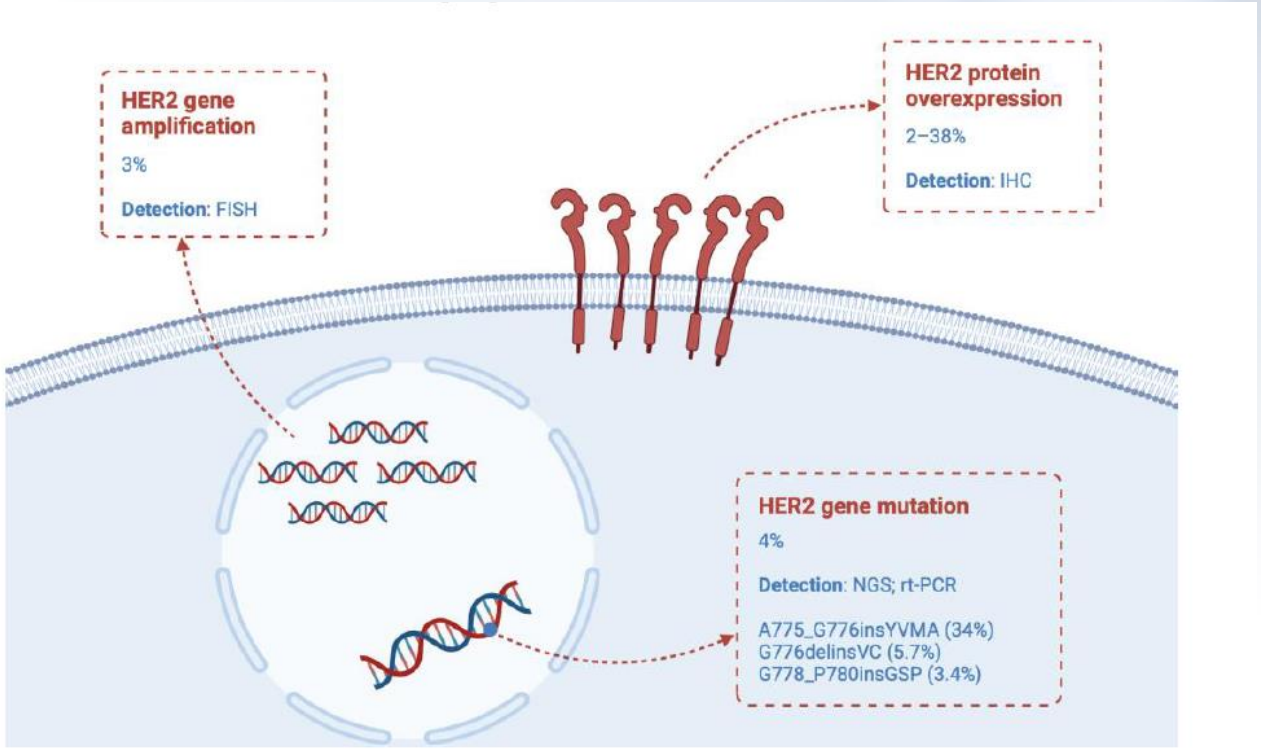
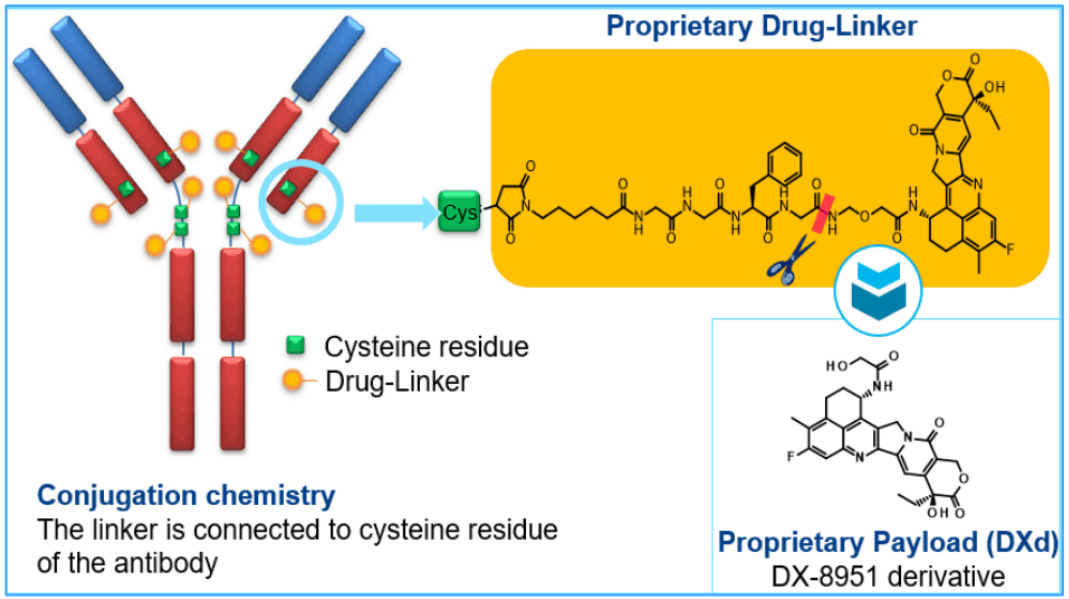


Figure 1. HER2 alterations in advanced non-small cell lung cancer.

Cancers (Basel). May 26;16(11):2018.

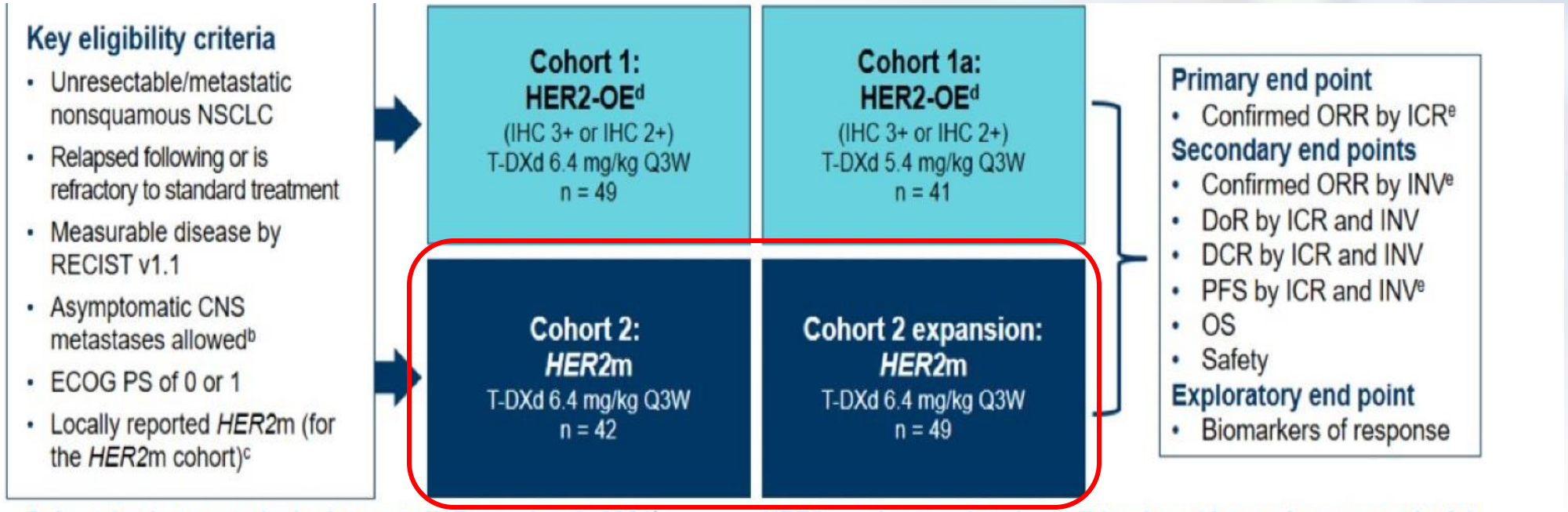
ADCs in HER2 altered NSCLC (Non-Squamous)

- **Ado-trastuzumab emtansine (T-DM1)**
  - **Phase II Study (N=15)**[1]
    - HER2m 47%, HER2 OE 53%
    - ORR 6.7%
  - **Phase II Study – Li et al. (N=18)** [2]
    - HER2 mutated
    - ORR 44%
- **Trastuzumab deruxtecan (T-Dxd)**



1. *J Thorac Oncol. 2018 Feb;13(2):273-279*
2. *J Clin Oncol. 2018 Aug 20;36(24):2532-2537*

DESTINY-Lung01 – Study Design



Cohort 1 primary analysis data cutoff: December 3, 2021[1]

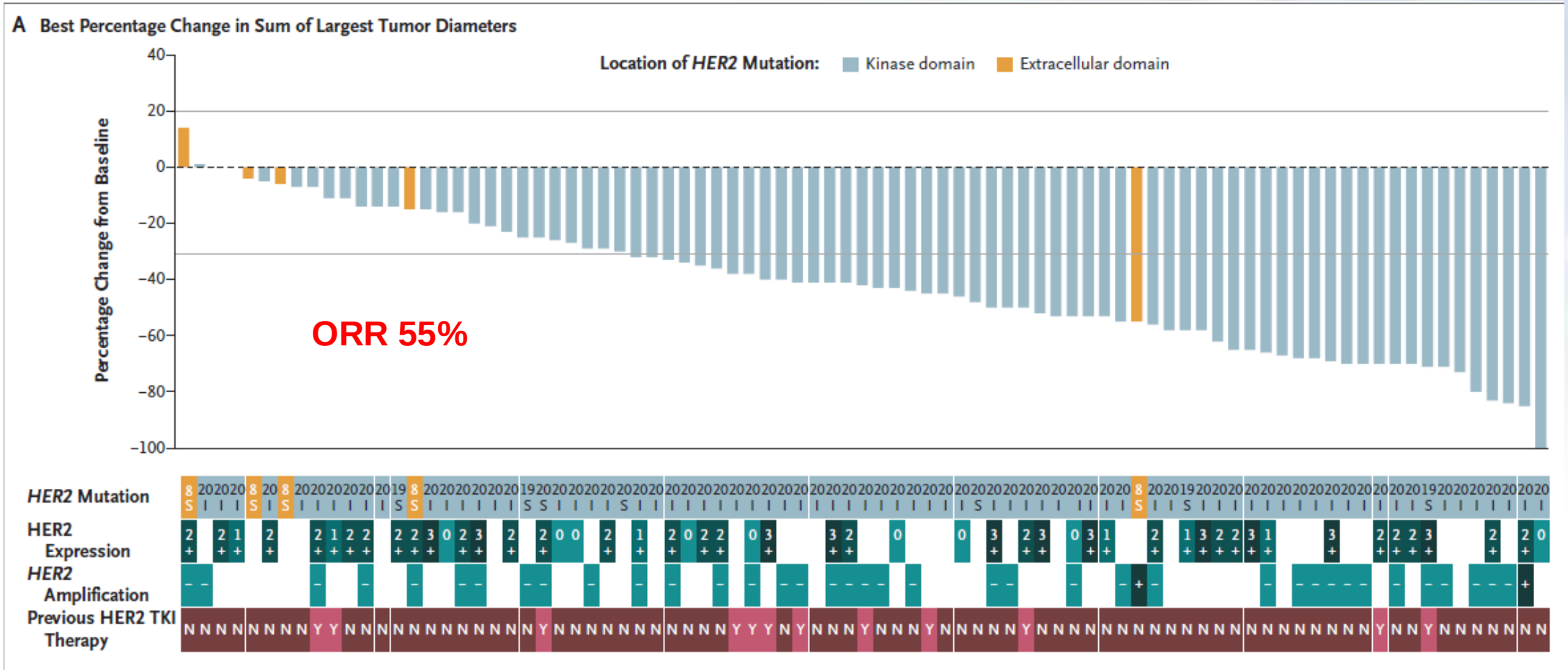
- 2 (4%) and 5 (12%) patients were receiving ongoing treatment in Cohorts 1 and 1a, respectively

***HER2*m cohort updated cutoff (and post hoc subgroup analysis): December 3, 2021[2]**

- 11 out of 91 patients (12.1%) remain on treatment
- 80 patients (87.9%) discontinued, primarily for progressive disease (40.7%) and adverse events (30.8%)

N Engl J Med. 2022 Jan 20;386(3):241-251
Lancet Oncol. 2024 Apr;25(4):439-454

DESTINY-Lung01 – Efficacy (HER2m)



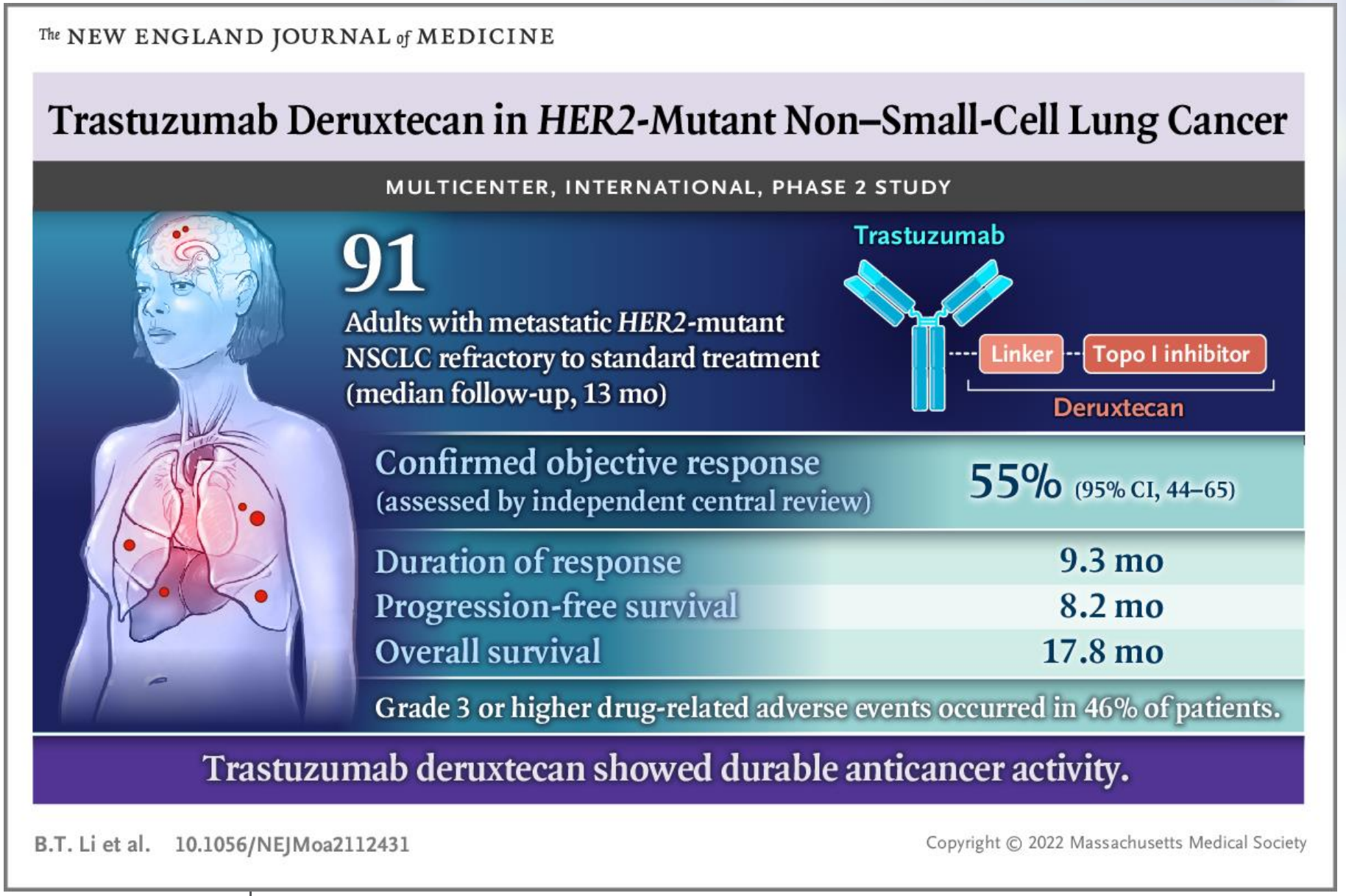
N Engl J Med. 2022 Jan 20;386(3):241-251

DESTINY-Lung01 – Safety (HER2m)

n (%)	*HER2*m Cohort (T-DXd 6.4 mg/kg) Overall population N = 91
Any grade TEAEs	91 (100)
Drug-related TEAEs	88 (96.7)
Drug-related grade ≥3 TEAEs	42 (46.2)
Serious drug-related TEAEs	18 (19.8)
Drug-related TEAEs associated with:	
Drug discontinuation[a]	24 (26.4)
Dose reduction	33 (36.3)
Drug interruption	31 (34.1)
Drug-related TEAEs associated with an outcome of death	2 (2.2)[b]

- GI
- Alopecia
- Cytopenias

N Engl J Med. 2022 Jan 20;386(3):241-251



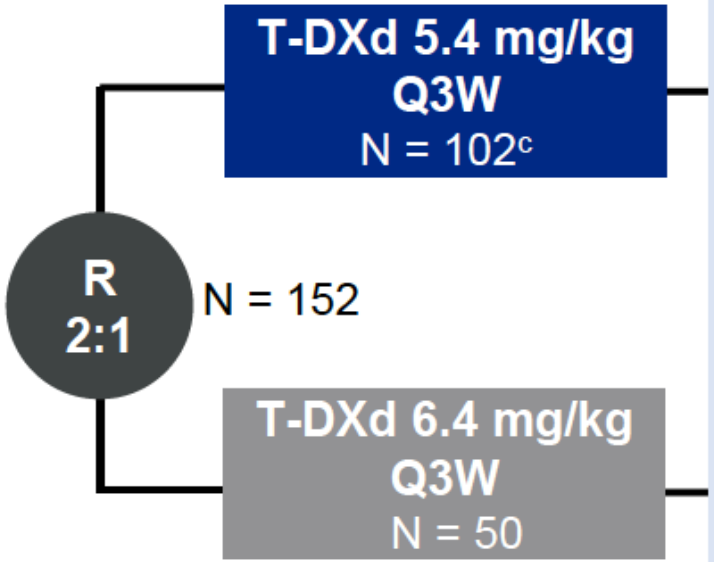
August 11, 2022

FDA - accelerated approval to trastuzumab NSCLC with HER2 mutations in ≥1L prior

DESTINY-Lung02 – Study Design

Key Eligibility Criteria[a]
- Metastatic *HER2*m[b] 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

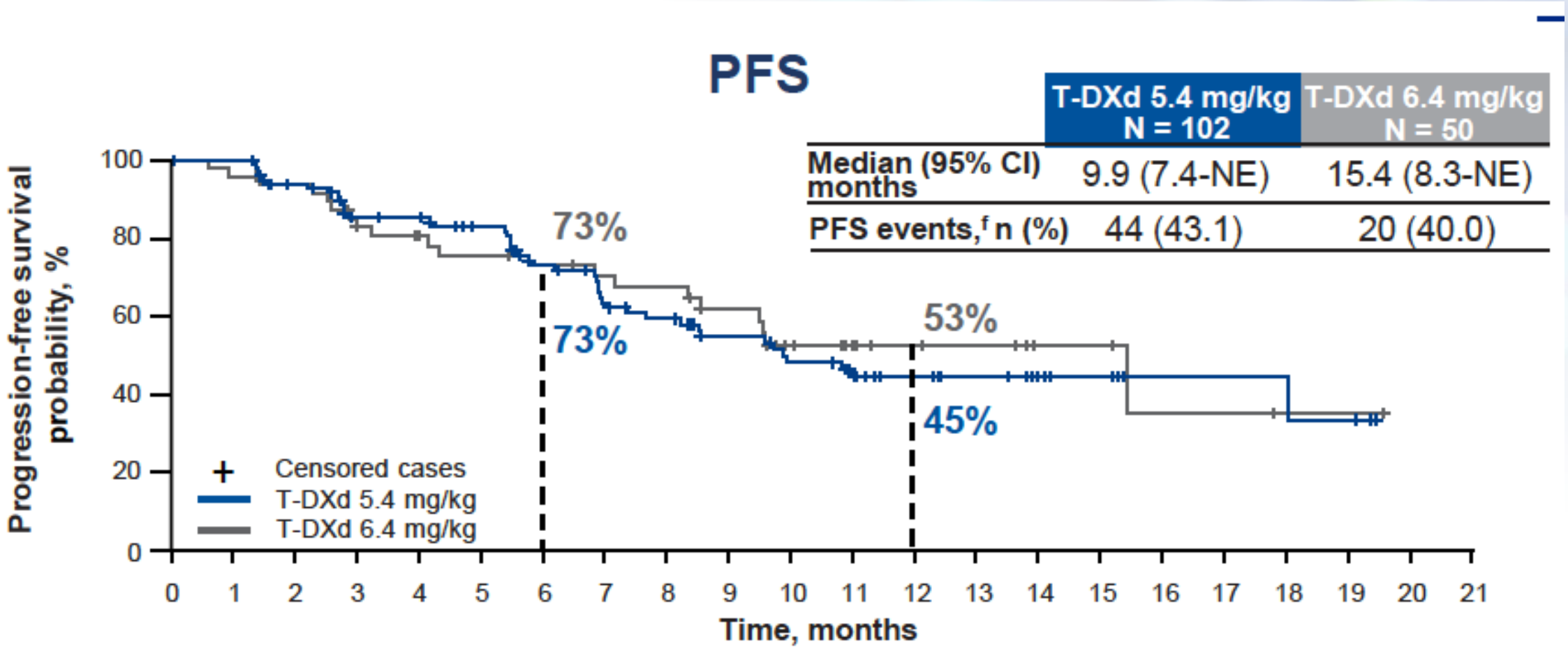
Secondary Endpoints
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Primary analysis data cutoff: 23 December 2022

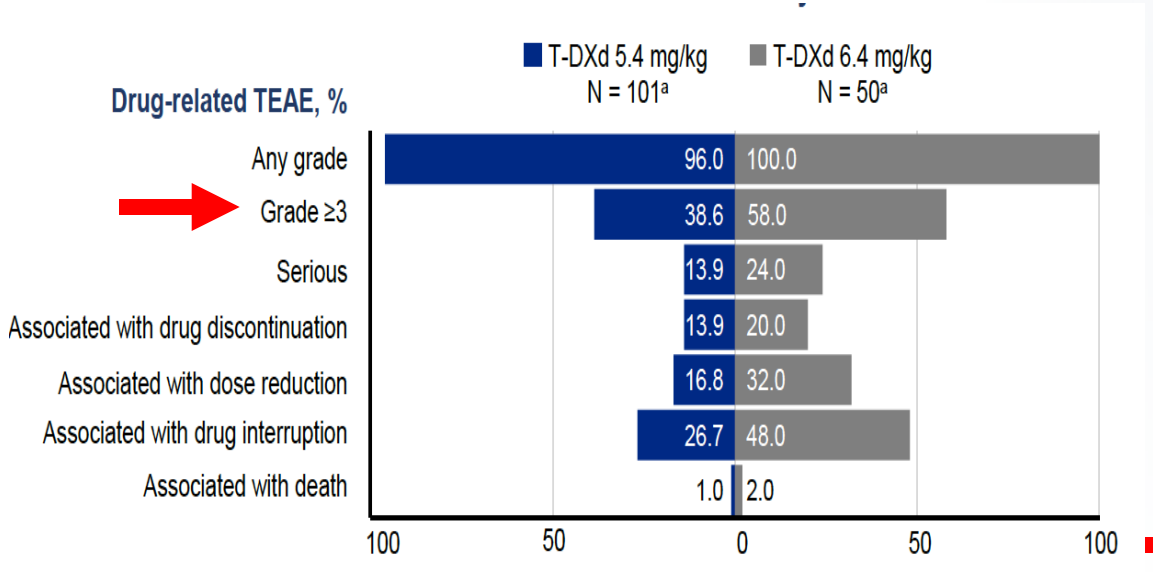
Janne P, WCLC 2023, Abstract MA13.20

DESTINY-Lung02 – Efficacy



Janne P, WCLC 2023, Abstract MA13.20

DESTINY-Lung02 – Safety

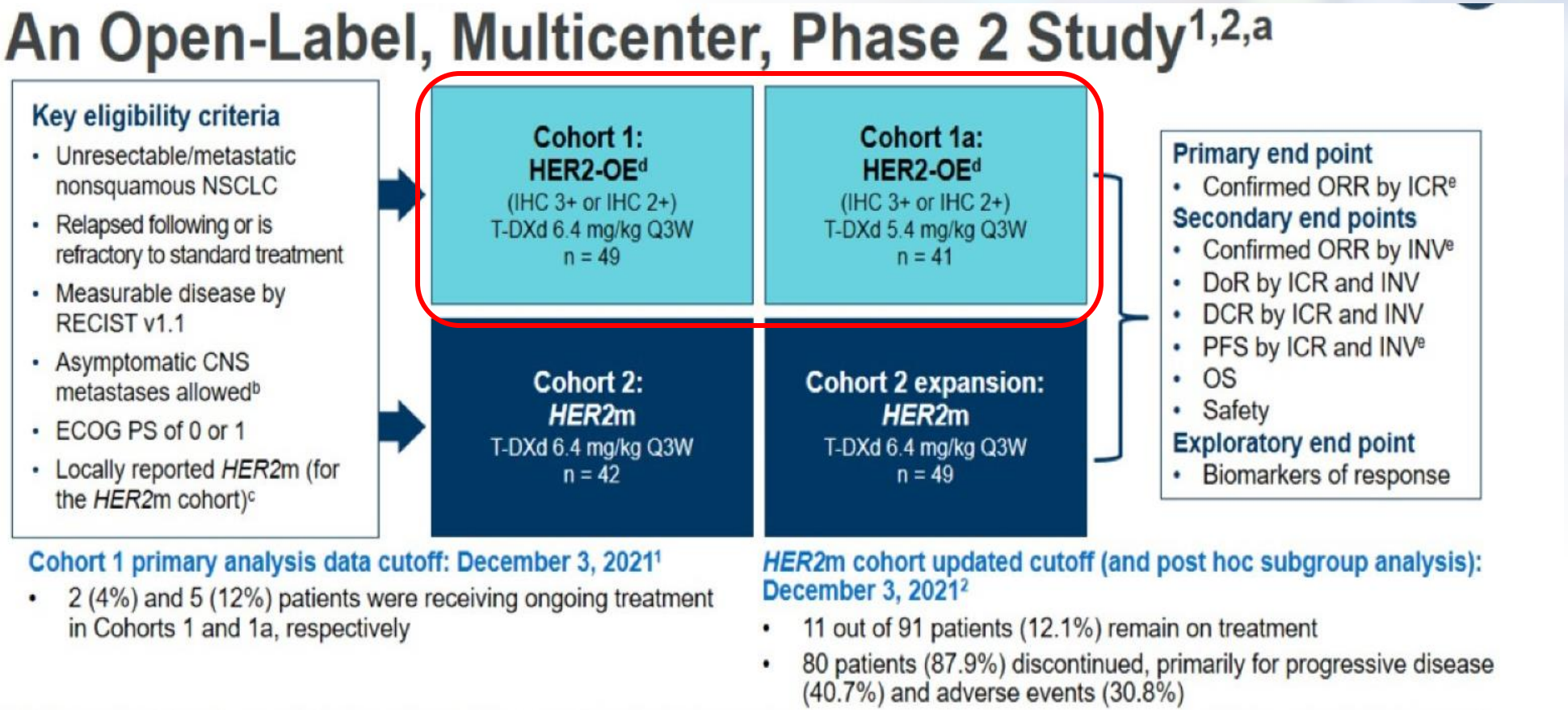


Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
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)

Janne P, WCLC 2023, Abstract MA13.20

DESTINY-Lung01 – Study Design



Lancet Oncol. 2024 Apr;25(4):439-454

DESTINY-Lung01 – Efficacy (HER2-OE)

Efficacy by ICR	Cohort 1 (6.4 mg/kg) n = 49	Cohort 1a (5.4 mg/kg) n = 41
Confirmed ORR, n (%; 95% CI)	13 (26.5; 15.0-41.1)	14 (34.1; 20.1-50.6)
Response outcomes, n (%)		
CR	0	2 (5)
PR	13 (27)	12 (29)
SD	21 (43)	18 (44)
PD	11 (22)	4 (10)
NE	4 (8)	5 (12)
DCR, n (%; 95% CI)	34 (69.4; 54.6-81.8)	32 (78.0; 62.4-89.4)
DoR, months, median (95% CI)	5.8 (4.3-NE)	6.2 (4.2-9.8)

- Primary endpoint of ORR by ICR was achieved by 26.5% (95% CI, 15.0%-41.1%) of patients in Cohort 1 and 34.1% (95% CI, 20.1%-50.6%) of patients in Cohort 1a
- The median duration of follow-up was 12.0 months (IQR, 5.4-22.4 months) and 10.6 months (IQR, 4.5-13.5 months) in Cohorts 1 and 1a, respectively
- Both T-DXd doses had encouraging and consistent antitumor activity in heavily pretreated patients with HER2-OE NSCLC

April 5, 2024

FDA – granted accelerated approval to trastuzumab deruxtecan-nxki for metastatic HER2-positive (IHC3+) solid tumors ≥ 1L prior

Lancet Oncol. 2024 Apr;25(4):439-454

Challenges – ADCs in NSCLC

- Patient selection
  - Biomarkers of response – antigen expression ≠ response
  - Identification of patients likely to respond – NSQ, mEGFR, localized
- Rationale combinations
  - IO, VEGF, others
- More specific ADCs
- Improved safety/therapeutic index
  - Prodrugs
- Overcome resistance
  - Dual payloads
  - Alternative payloads – immunotoxins (pseduotox A), bcl2 inhibitors, immunomodulators (TLR8 agonists)

Select ongoing trials of ADCs in NSCLC

Trial / Drug	Patient population / target	Line of therapy	Design
DESTINY-Lung03	HER2-OE	1st and ≥2L	Phase 1b – multicohort, single & combination
DESTINY-Lung04	HER2m	1st	Phase 3 – T-DXd vs. SOC
TROPION-Lung02	TROP2	1st	Phase 1b – Dato-DXd + Pembro +/- Platinum chemo (Presented at ASCO 2024, combo is safe)
TROPION-Lung05	AGA/TROP2	> 2L	Phase 2 - Dato-DXd
NEOCOAST-2	TROP2	Neoadj	Multicohort Dato-DXD + Durva + Platinum chemo
Sacituzumab tirumotecan	mEGFR NSQ/TROP2	> 2L	Phase 2 - after 3rd Gen EGFR TKI & chemo
HERTHENA Lung-02	mEGFR/Her3	2L	Phase 3 – P-Dxd vs. Chemo after 3rd Gen EGFR TKI
TeliMET NSCLC-01	C-Met OE NSQ WGFR WT	≥2L	Phase 3 – Teliso-V vs. Docetaxel
Tusamitanib-Ravtansine	CEACAM5		
Mirvetuximab-Soravtansine	FRα	≥2L	
Tisotumab vedotin	TF		

Conclusions

- ADCs are just entering the arena of NSCLC
  - Currently, only one ADC is FDA-approved for NSCLC – T-Dxd
- Several promising ADCs
  - Patritumab Dxd
  - Telisotuzumab vedotin
  - Dato-Dxd (mEGFR)
- Further studies
  - Identify patients likely to respond
  - Biomarkers of response
  - Novel mechanisms of action

“Hope is being able to see that there is light despite all of the darkness.”

Desmond Tutu

THANK YOU