MAYO CLINIC

HER-2 in Non–Small–Cell Lung Cancer

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HER/erbB family

- HER/erbB family of growth factor receptors, which includes EGFR (HER1 or erbB1), HER2/neu (erbB2), HER3 (erbB3), and HER4 (erbB4)

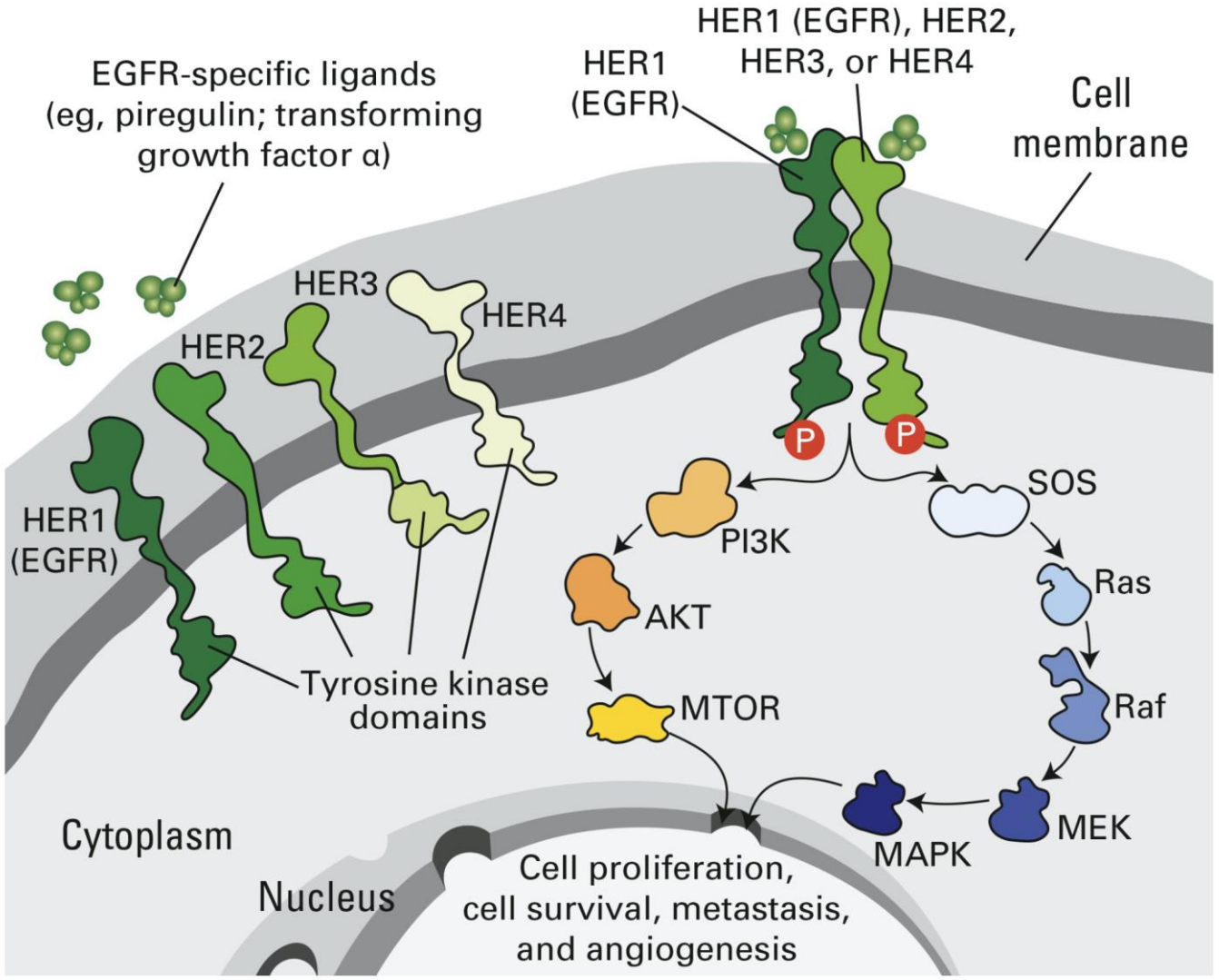
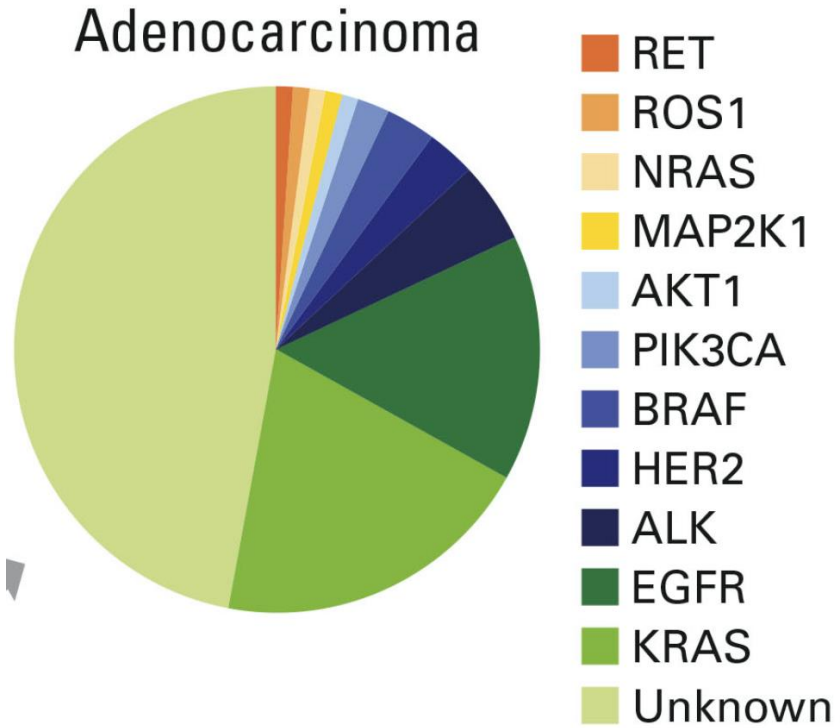


Fig. 11-2 **Epidermal growth factor receptor (EGFR) signaling pathways.**

HER-2 in NSCLC

- 3% of nonsquamous NSCLC
- Gene mutation (1%-4%), gene amplification (2%-5%), and protein over-expression (2%-30%)
- HER2 mutation and amplification: associated with females, never-smoking history, poor prognosis, slightly younger age, higher incidence of brain metastases
- Mutually exclusive to EGFR, KRAS, NRAS, ALK, PI3KCA, and BRAF
- In-frame exon 20 insertions occur in 83% of all HER2-mutant NSCLC
- Gain of HER2 protein expression in general, cannot serve as a surrogate marker for HER2 mutation



ASCO SEP 2021
ESMO Open. 2021 Oct;6(5):100260
Cancer Treat Rev . 2020 Jun;86:101996

Treatment of HER mutant NSCLC

- Limited and varied results have been reported for responses to immune-checkpoint inhibitors in this population, with 6 to 27% of patients having an objective response to treatment

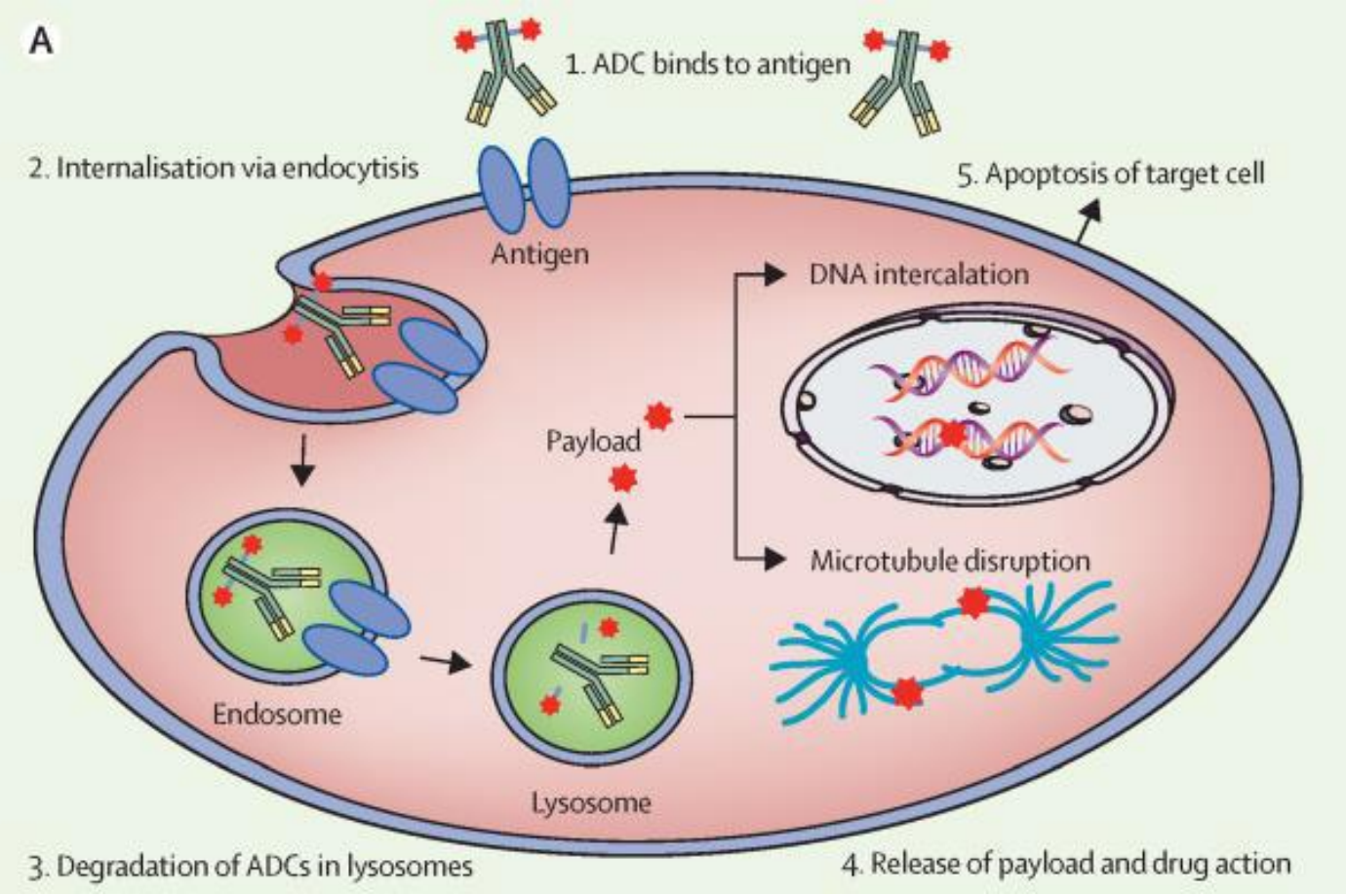
Table 5. Retrospective studies evaluating the efficacy of immune checkpoint inhibitors in NSCLC with *Her2* mutations

	Sample size, *n*	Type of ICIs and treatment line	PD-L1 expression ≥1%	ORR *n* (%)	DCR *n* (%)	Median PFS, months (95% CI)	Median OS, months (95% CI)	Reference
MSKCC	26	Not specified	23%	3/26 (12)		1.9 (1.5-4)	10.4 (5.9-NR)	Lai *et al.*[90] ASCO 2018
IMMUNOTARGET registry[a]	29	Nivolumab 89.6% ≥2 lines 94.5%	53.3%	2/29 (7.4)	9/29 (31)	2.5 (1.8-3.5)	20.3 (7.8-NR)	Mazieres *et al.*[91] *Ann Oncol*, 2019
MD Anderson	16	—	—	1/16 (6)	3/16 (18.8)	1.8	17.1	Negrao *et al.*[92] ASCO 2018
French Lung Cancer Group (GFPC)[b]	23	Nivolumab 83% ≥2 lines 100%	17%[c]	6/23 (27.3)	11/23 (50)	2.2 (1.7-15.2)	20.4 (9.3-NR)	Guisier *et al.*[93] *JTO*, 2020

First line ICI +/- chemo (21 pts): ORR is 52% (95% CI: 30%–74%), median PFS is 6 months

ESMO Open. 2021 Oct;6(5):100260
J Thorac Oncol . 2021 Nov;16(11):1952-1958

Antibody-drug conjugates (ADC) mechanism of action



Chau CH, et al, Lancet 2019

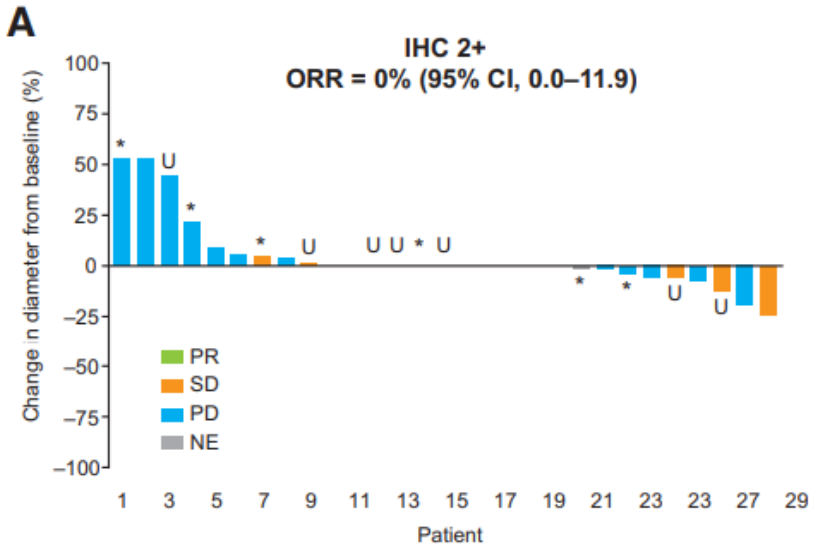
ADCs in development in NSCLC

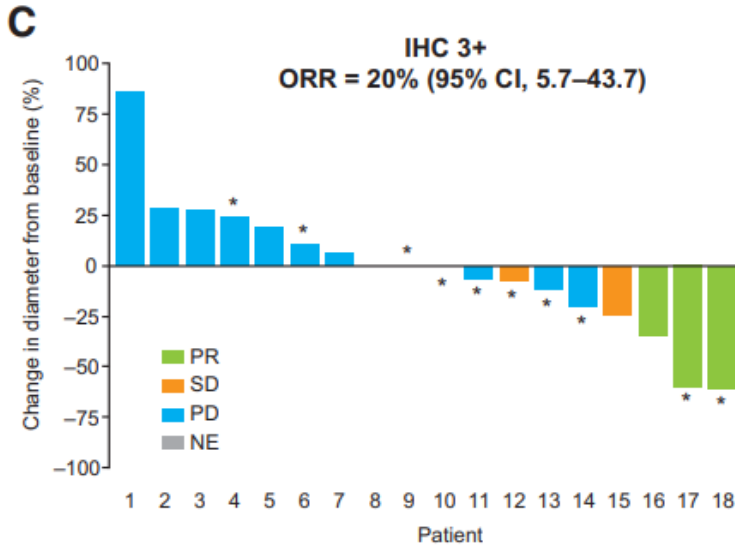
Drug	Antibody-Target	Linker	Payload (DAR)	RP2D and Schedule
Ado-trastuzumab emtansine (T-DM1)	HER2	Noncleavable	DM1 (3.5)	3.6 mg/kg every 3 wks
Trastuzumab deruxtecan (T-DXd)	HER2	Cleavable	DXd (8)	6.4 mg/kg every 3 wks
A166	HER2	Cleavable	Duostatin-5 (-)	TBD
XMT-1522	HER2	Cleavable	Auristatin F-hydroxypropylamide (12)	Development discontinued
Sacituzumab govitecan (SG)	Trop 2	Cleavable	SN-38 (7.6)	10 mg/kg on d 1 and 8 of 21 d cycle
Datopotamab-deruxtecan (Dato-DXd)	Trop 2	Cleavable	DXd (4)	6 mg/kg every 3 wks
Telisotuzumab vedotin (Teliso-V)	MET	Cleavable	MMAE (3.1)	2.7 mg/kg every 3 wks
Glembatumumab vedotin	gpNMB	Cleavable	MMAE (-)	Development discontinued
Cofetuzumab pelidotin	PTK7	Cleavable	Aur0101 (4)	TBD
Anetumab ravtansine	Mesothelin	Cleavable	DM4 (3.2)	6.5 mg/kg every 3 wks
MGC018	B7-H3	Cleavable	Duocarmycin (2.7)	TBD
Tisotumab vedotin	Tissue Factor	Cleavable	MMAE (4.1)	2.0 mg/kg every 3 wks
Enapotamab vedotin (EnaV)	AXL	Cleavable	MMAE (4)	2.2 mg/kg every 3 wks
MRG003	EGFR	Cleavable	MMAE (-)	2.0 mg/kg every 3 wks
Patritumab deruxtecan (HER3-DXd)	HER3	Cleavable	DXd (8)	TBD
XMT-1536	NaPi2B	Cleavable	AF-HPA (10-15)	TBD
Rovalpituzumab teserine (Rova-T)	DLL3	Cleavable	SC-DR002 (2)	Development discontinued
SC-002	DLL3	Cleavable	SC-DR002 (2)	Development discontinued

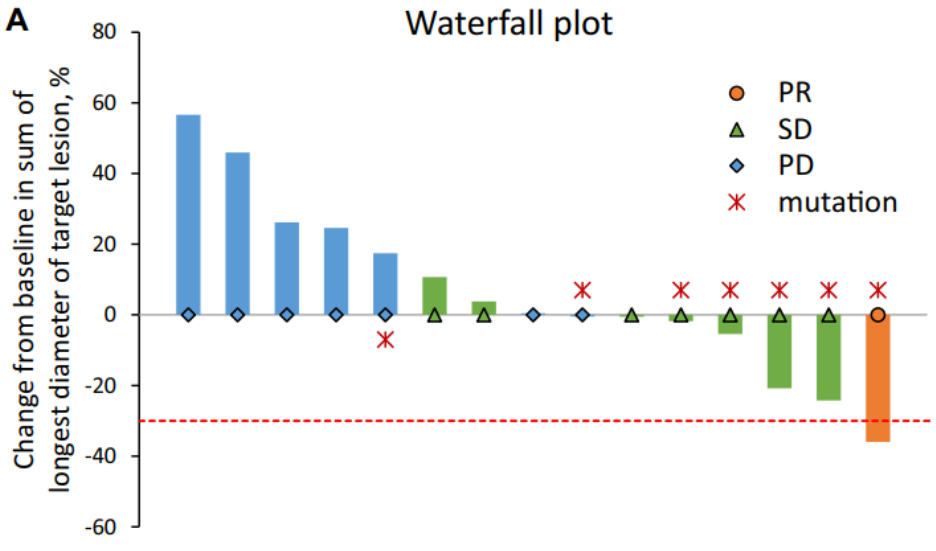
Abbreviations: AF-HPA = auristatin F - hydroxypropylamide; d, day; DAR = drug-antibody ratio; MMAE = monomethyl auristaitn E; RP2D = recommended phase 2 dose; TBD = to be determined; wks, weeks.

Reuss et al. Clin Lung Cancer 2021

ADCs targeting HER-2 overexpression

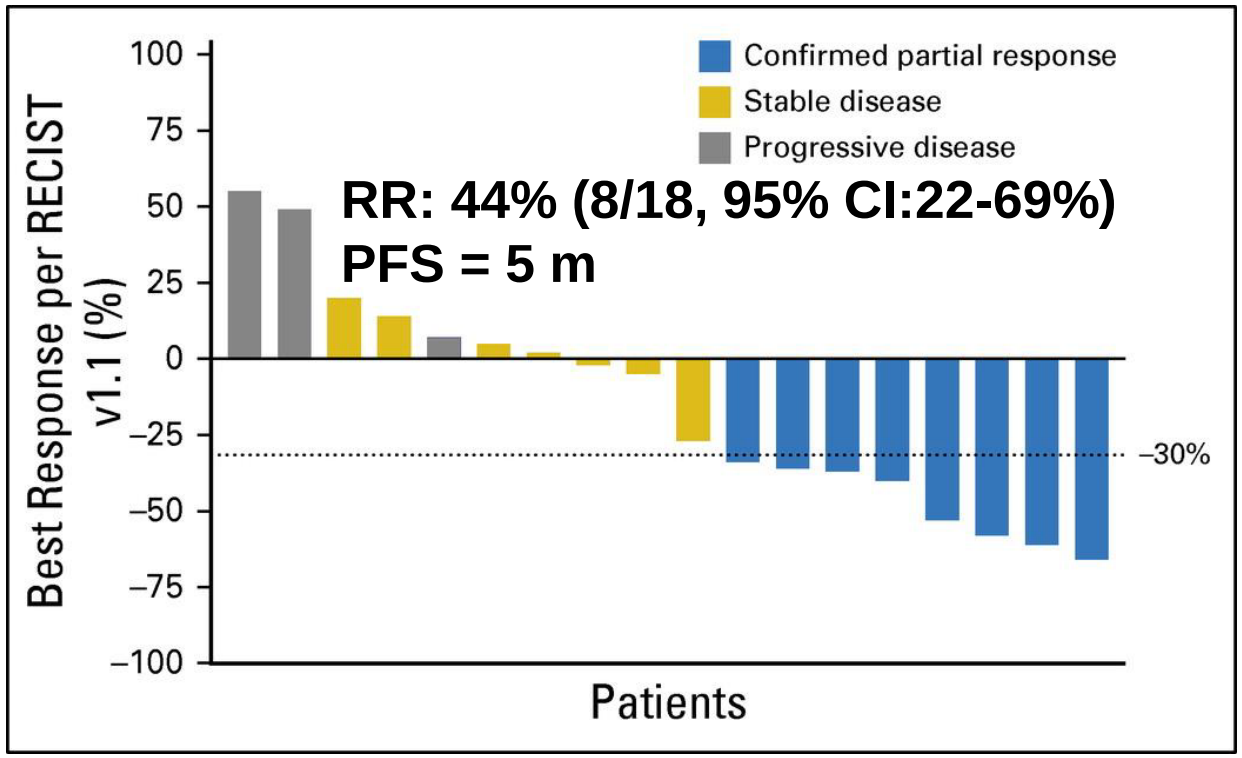


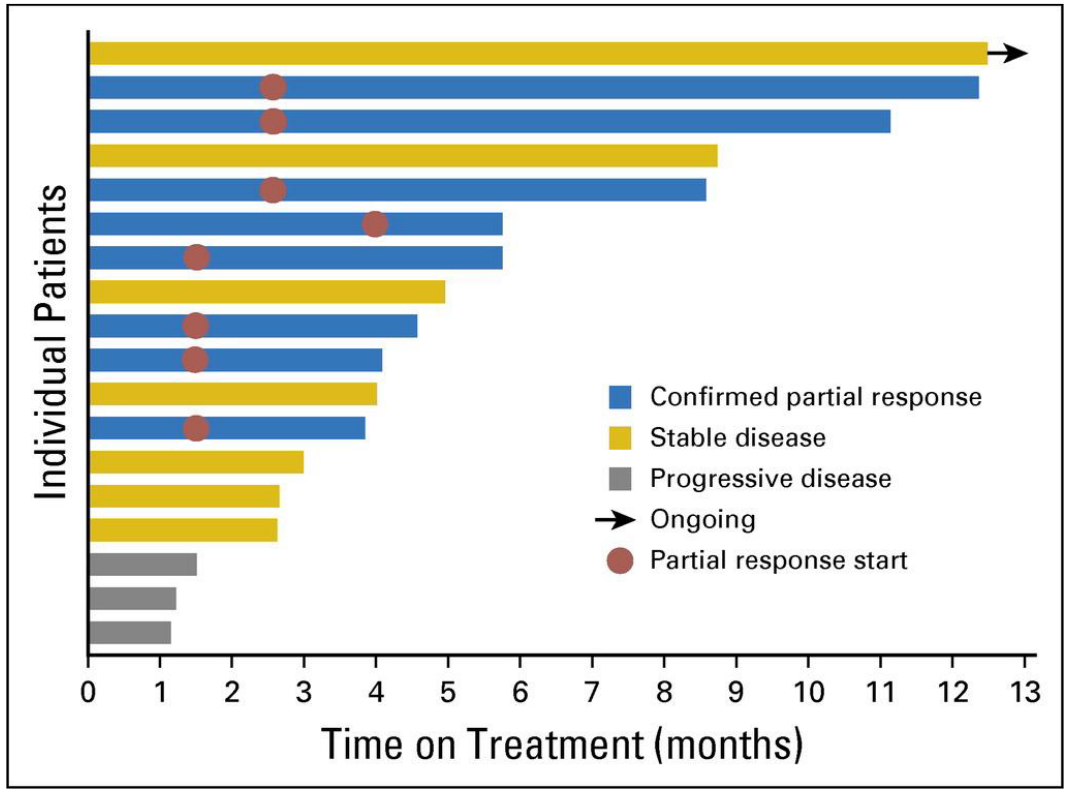




Peters et al. Clin Cancer Res 2019
Hotta et al, J Thorac Oncol 2018
Li, IASLC 2022

Trastuzumab emtansine (TDM1) targeting HER-2 mutation





Li et al. J Clin Oncol 2018

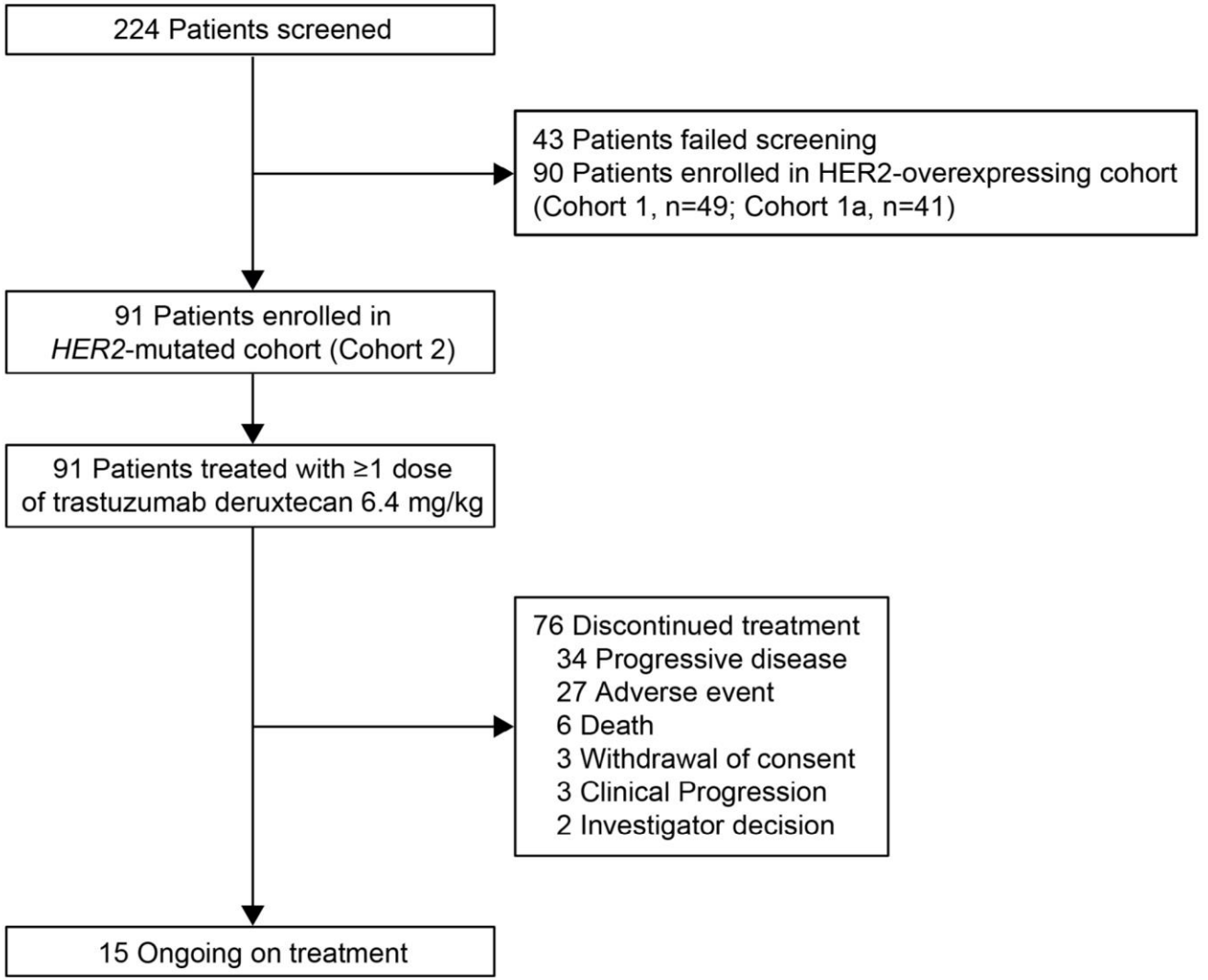
Trastuzumab emtansine (TDM1) targeting HER-2 mutation

NGS Result	FISH Result (HER2/CEP17 ratio)	IHC Result	Mass spectrometry (amol/μg)	Partial Response
Exon 20 p.A775_G776insYVMA	1.1 (2.7/2.5)	0	NA	Yes
Exon 20 p.A775_G776insYVMA	1.8 (8.1/4.5)	2+	642	No
Exon 20 p.A775_G776insYVMA	NA	NA	NA	No
Exon 20 p.A775_G776insYVMA	1.4 (4.5/3.3)	1+	586	Yes
Exon 20 p.A775_G776insYVMA	1.9 (5.6/2.9)	1+	548	Yes
Exon 20 p.G778_P780dup	1.6 (7.6/4.8)	1+	0	No
Exon 20 p.G778_P780dup	1.8 (4.6/2.5)	2+	507	Yes
Exon 20 p.G778_P780dup	1.4 (5.8/4.2)	2+	NA	No
Exon 20 p.G778-779 insCPG	1.6 (4.3/2.7)	0	NA	No
Exon 20 p.G776_V777>VCV	NA	NA	NA	Yes
Exon 20 p.G776delinsVC	1.6 (5.7/3.6)	0	205	Yes
Exon 19 p.L755P	1.5 (3.2/2.1)	2+	434	No
Exon 19 p.L755P	NA	0	NA	No
Exon 17 p.V659E	1.2 (2.4/2.0)	2+	NA	No
Exon 17 p.V659E	1.1 (2.3/2.0)	2+	688	Yes
Exon 8 p.S310F, amplification fold change 2.8	4.1 (8.4/2.5)	2+	1,495	Yes
Exon 8 p.S310F	1.8 (3.2/1.8)	0	0	No
Exon 8 p.S335C	2.4 (4.8/2.0)	2+	902	No

Abbreviations: FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NA, not available; NGS, next-generation sequencing.

Li et al. J Clin Oncol 2018

Trastuzumab Deruxtecan in HER2-Mutant NSCLC (DESTINY-Lung 01)



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Demographic and Clinical Characteristics

Characteristic	Patients (N = 91)
Median age (range) — yr	60 (29–88)
Female sex — no. (%)	60 (66)
Race — no. (%)†	
Asian	31 (34)
White	40 (44)
Black	1 (1)
Other	19 (21)
Geographic region — no. (%)	
Asia	23 (25)
North America	35 (38)
Europe	33 (36)
ECOG performance-status score — no. (%)‡	
0	23 (25)
1	68 (75)
Location of *HER2* mutations — no. (%)	
Kinase domain	85 (93)
Extracellular domain	6 (7)
Previous cancer therapy — no. (%)	90 (99)§
Platinum-based therapy	86 (95)
Docetaxel	18 (20)
Anti–PD-1 or anti–PD-L1 treatment	60 (66)
HER2 TKI	13 (14)
Reason for discontinuation of previous cancer therapy — no./total no. (%)	
Disease progression	63/90 (70)
Completed therapy	6/90 (7)
Adverse event	8/90 (9)
Investigator decision	3/90 (3)
Patient choice	1/90 (1)
Unknown	5/90 (6)
Other	4/90 (4)
CNS metastases at baseline — no. (%)	33 (36)
Smoking history — no. (%)	
Current	2 (2)
Former	37 (41)
Never	52 (57)
Previous lung resection — no. (%)	20 (22)

Response to trastuzumab Deruxtecan

Table 2. Response to Trastuzumab Deruxtecan as Assessed by Independent Central Review.

Response Assessment	Patients (N=91)
Confirmed objective response*	
No. of patients	50
Percentage of patients (95% CI)	55 (44–65)
Best response — no. (%)	
Complete response	1 (1)
Partial response	49 (54)
Stable disease	34 (37)
Progressive disease	3 (3)
Response could not be evaluated	4 (4)
Disease control†	
No. of patients	84
Percentage of patients (95% CI)	92 (85–97)
Median time to response (range) — mo‡	1.5 (1.2–9.3)
Median duration of response (95% CI) — mo‡	9.3 (5.7–14.7)

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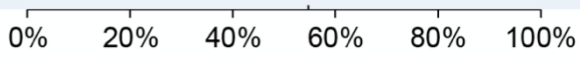
Response to trastuzumab Deruxtecan

	No. of Events/ Total No. of Patients	Objective Response Rate (95% CI)
All patients	50/91	54.9 (44.2-65.4)
HER2 mutation domain		
Kinase domain	49/85	57.6 (46.5-68.3)
Prior treatment received		
Platinum-based therapy	46/86	53.5 (42.4-64.3)
Platinum-based therapy and anti-PD1/PD-L1 therapy	37/57	64.9 (51.1-77.1)
Central nervous system metastasis at baseline		
Yes	18/33	54.5 (36.4-71.9)
No	32/58	55.2 (41.5-68.3)



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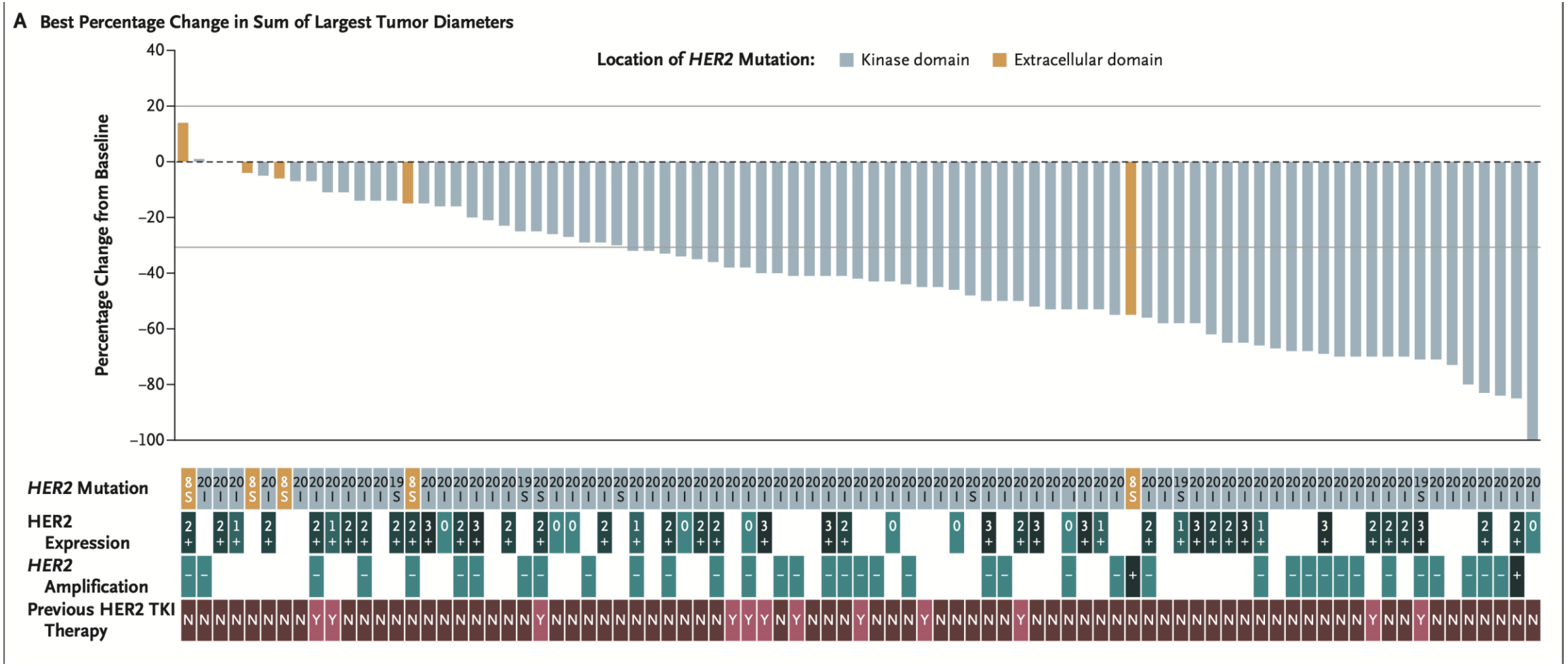
Response by biomarkers



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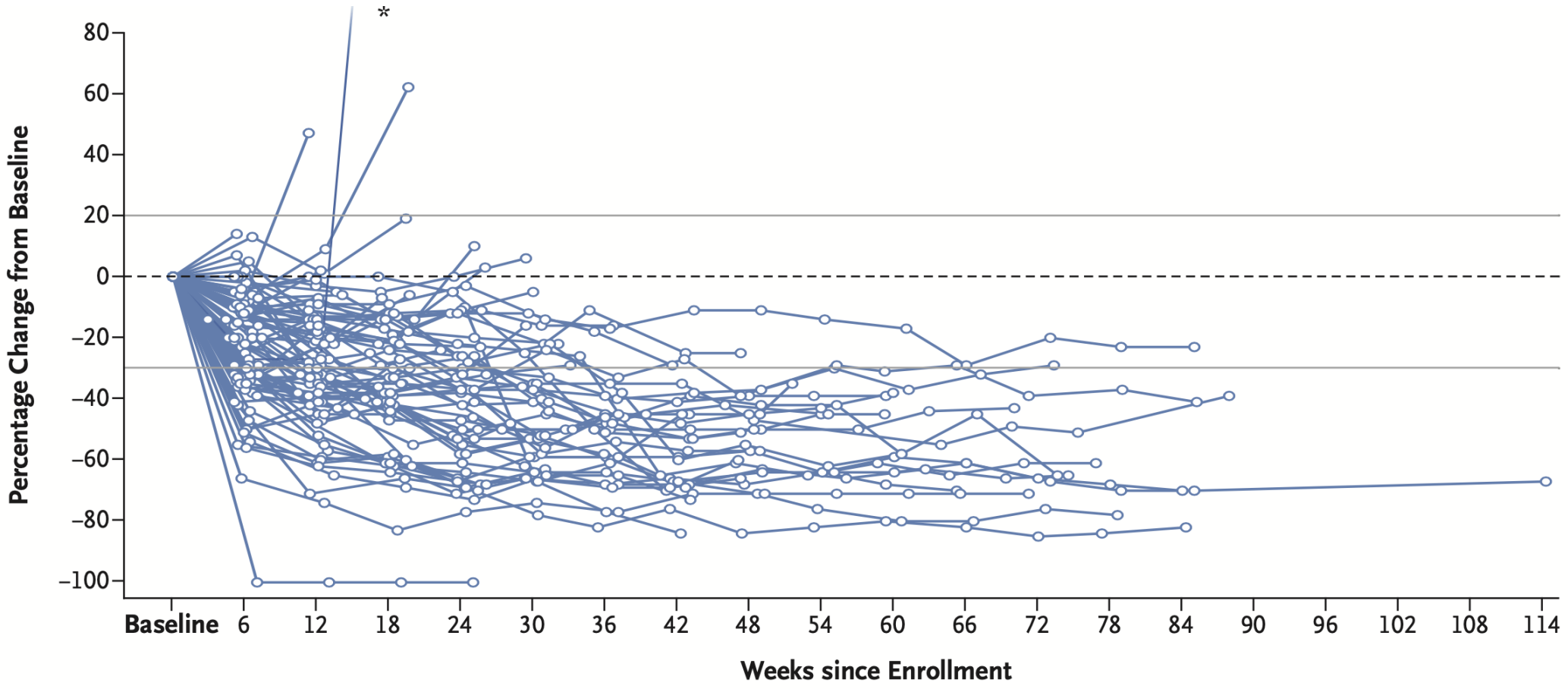
Response to trastuzumab Deruxtecan



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Safety

Table 3. Most Common Investigator-Reported Drug-Related Adverse Events in the Study Population (91 Patients).

Event	Grade 1–2	Grade 3	Grade 4	Grade 5	Overall
			number of patients (percent)		
Drug-related adverse event	46 (51)	37 (41)	4 (4)	1 (1)*	88 (97)
Drug-related adverse events with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue†	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia‡	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia§	21 (23)	9 (10)	0	0	30 (33)
Diarrhea	26 (29)	2 (2)	1 (1)	0	29 (32)
Decreased appetite	27 (30)	0	0	0	27 (30)
Leukopenia¶	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

Table S5. Adjudicated Drug-related Interstitial Lung Disease.

	Patients (N = 91)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Adjudicated drug-related interstitial lung disease, n (%)*	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)†	24 (26.4)

- Trastuzumab deruxtecan was withdrawn in 16 patients and interrupted in 8 patients

Li B, et al, N Engl J Med. 2022 Jan

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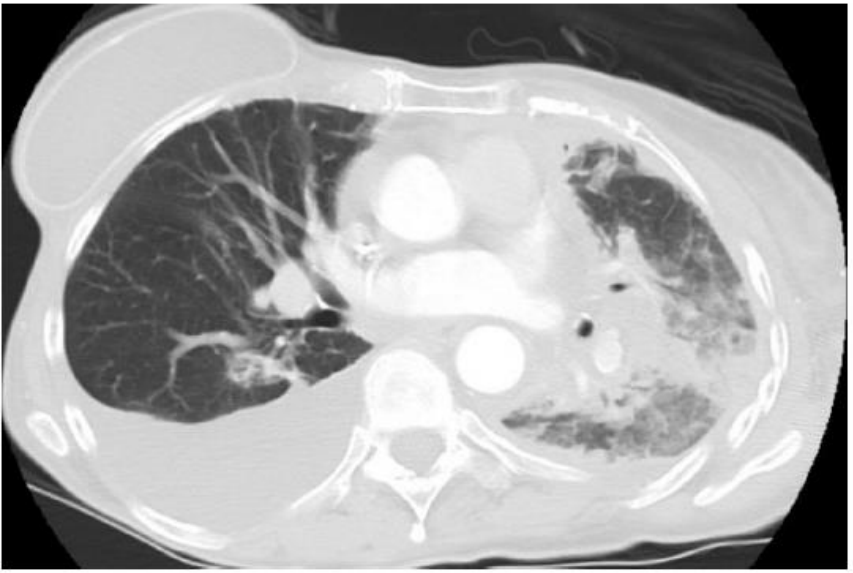
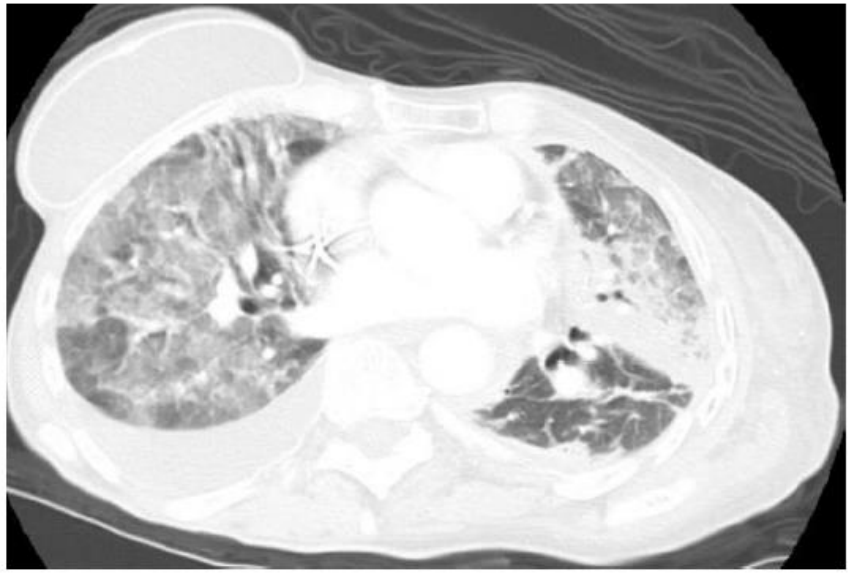
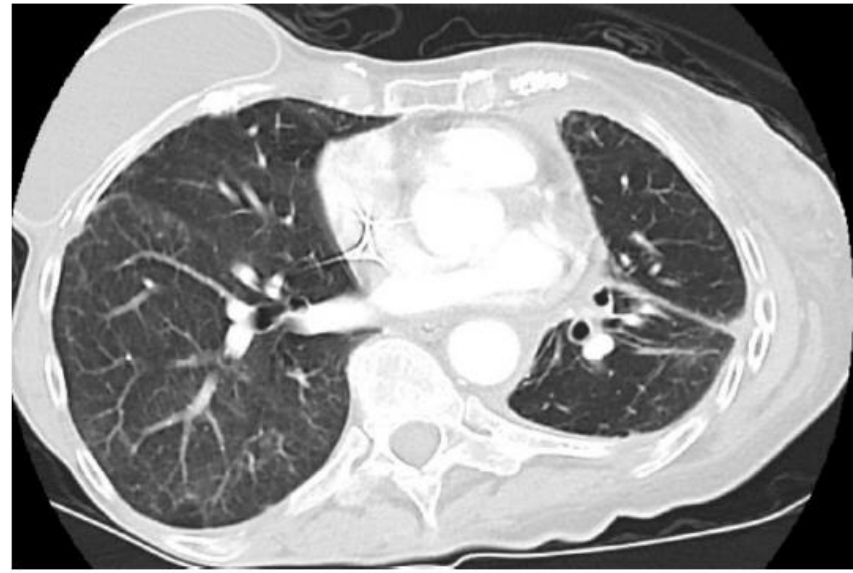
Drug-induced pneumonitis



Baseline refractory progressive stage 4 lung adenocarcinoma



After 1 dose of T-DXd



4 weeks after IV methylprednisolone Partial response

Swain et al. Cancer Treat Rev 2022
Bob Li, IASLC 2022

Discussion

- Efficacy was consistently observed across different subgroups, including those who had previously been treated with a HER2 TKI and those with CNS metastasis
- Excluded patients previously treated with HER2 Ab or ADC
- CNS surveillance was not performed systematically in all patients, which makes it impossible to assess anti-CNS tumor activity comprehensively
- Response % were similar between pts +/- CNS metastasis
- Responses were seen in patients with different mutation subtypes located across the extracellular and kinase domains of the HER2 protein
- Responses were observed in the majority of the small number of patients with no detectable HER2 expression as assessed by IHC analysis or gene amplification

Discussion

- HER targeted therapy in NSCLC:
  - HER2 tyrosine kinase inhibitors and antibodies - ORR 0 to 30%
  - Trastuzumab emtansine - ORR 44%, median PFS 5 months, small size
- Preclinical studies: the internalization and ubiquitination of an ADC are mostly dependent on the presence of an HER2 mutation or amplification rather than that of a simple HER2 over-expression (cohort1 vs. cohort2)

Ongoing Trials

- **DESTINY-Lung02**: lower dose of 5.4mg/kg
- **DESTINY-Lung03**: phase Ib trial, T-Dxd + durvalumab + chemotherapy as a first-line treatment
- **DESTINY-Lung04:** open-label, randomized, multicenter, phase III, T-Dxd vs. SoC as a first-line treatment
- **NCT04042701**: phase Ib, T-Dxd + pembrolizumab
- **HUDSON umbrella study**: phase II, T-Dxd + durvalumab in HER2-altered NSCLC its who progressed on anti-PD-1/PD-L1 containing therapy

Thank you

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