Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer

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Presentation Structure

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1. Introduction
2. Study design
3. Results – Efficacy
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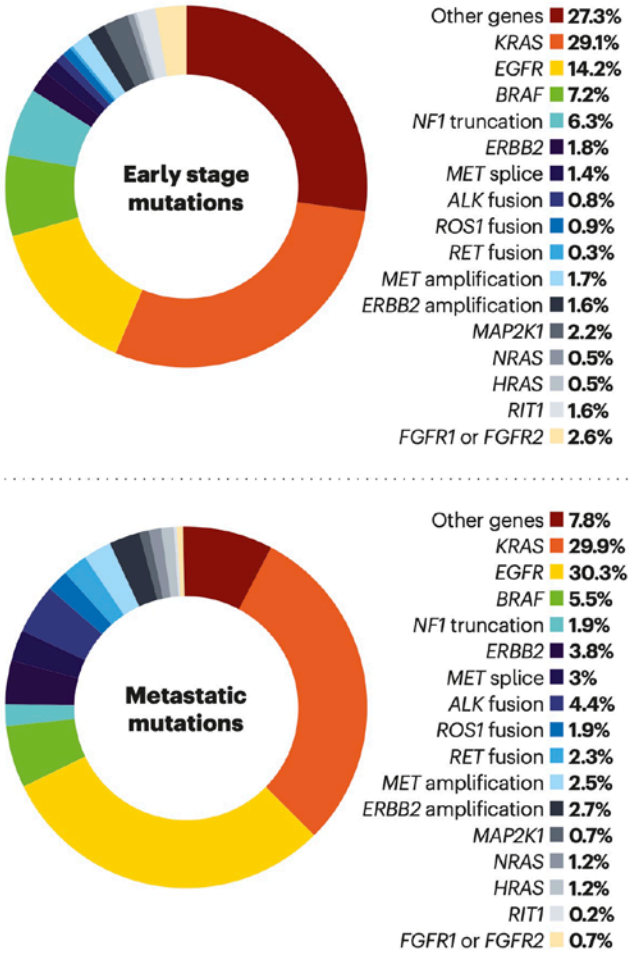
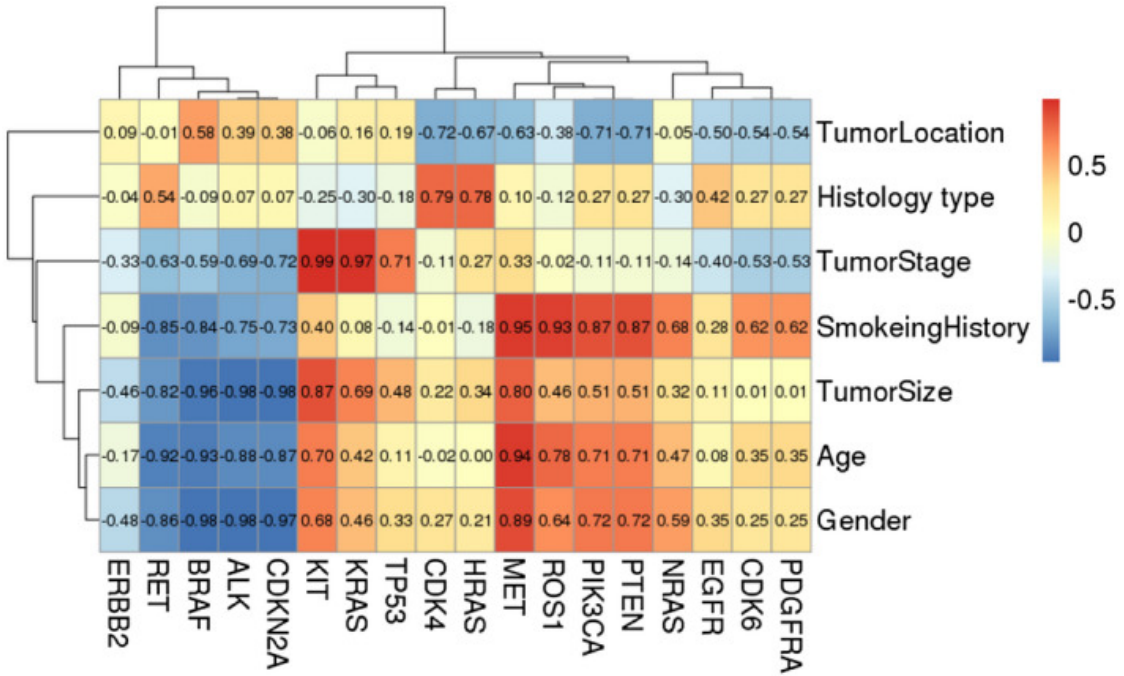
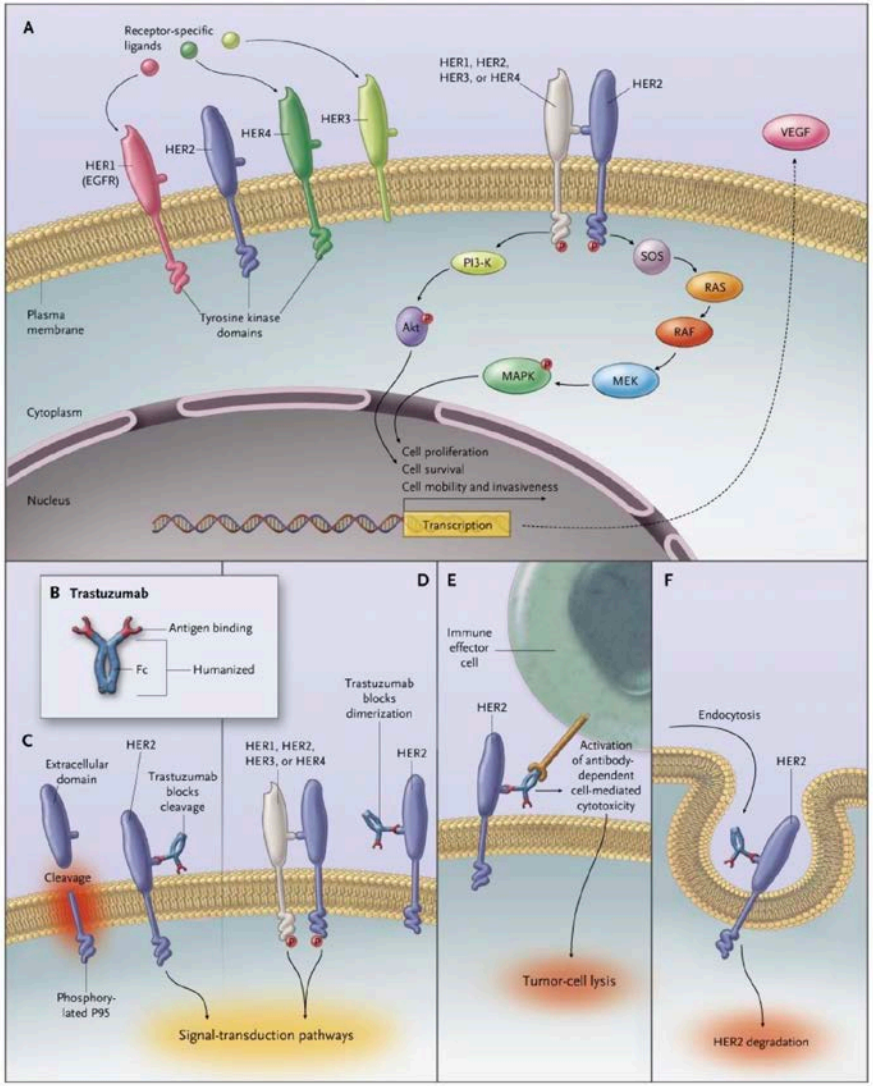




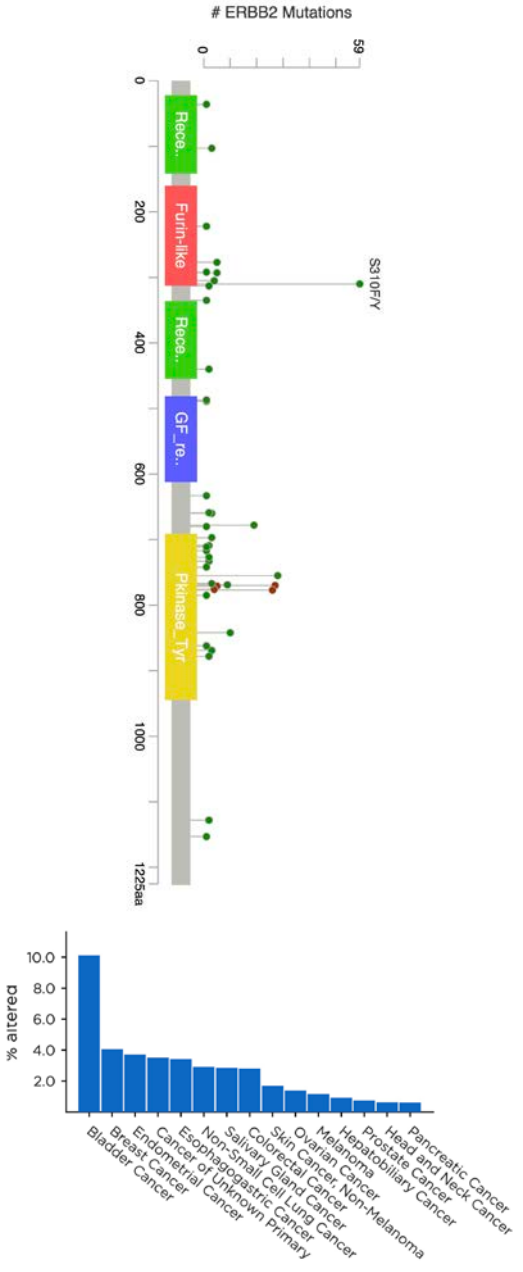
- ERBB2 is altered in 3.8%
of non-small cell lung carcinoma patients
- ERBB2 Amplification present in 2.7% of all non-small cell lung carcinoma patients

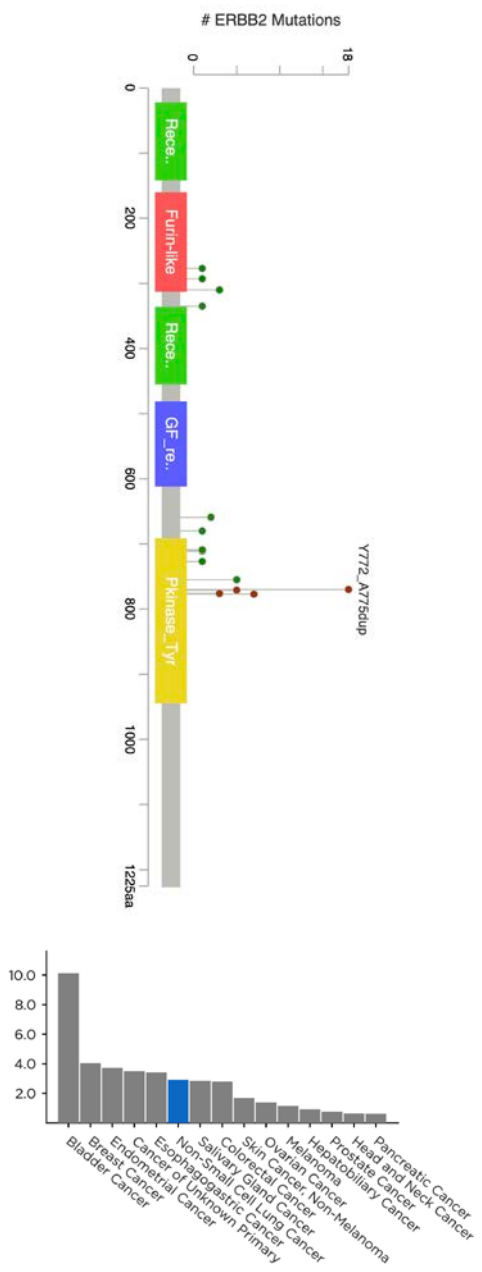
NSCLCs with ErbB2 mutations are associated with:

- female sex,
- never-smoking history,
- a slightly younger age and
- higher incidence of brain metastases than NSCLC without *HER2* mutations or with other mutations.

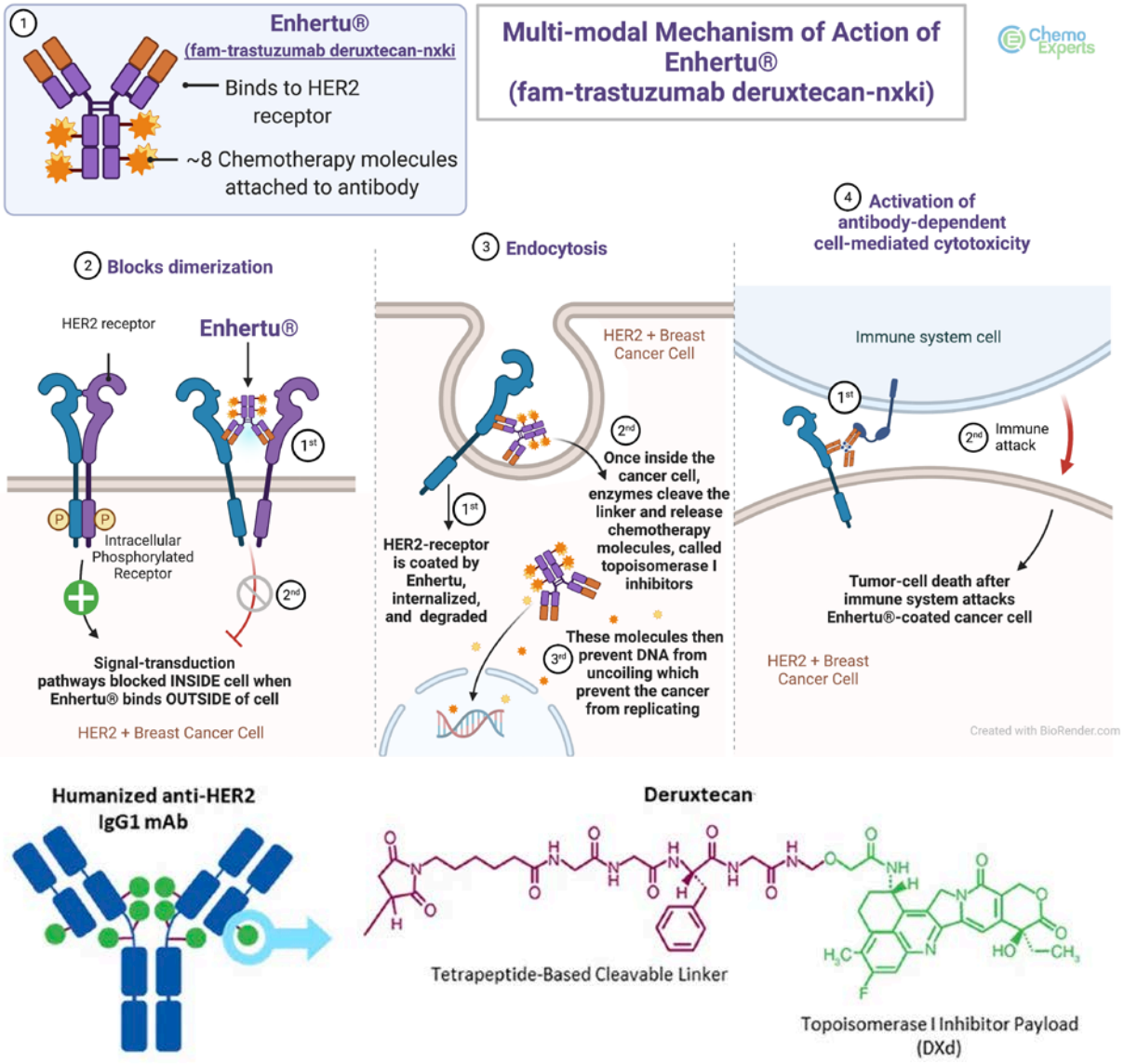


HER2/ErbB2 signaling promotes cell proliferation through the RAS–MAPK pathway and inhibits cell death through the phosphatidylinositol 3'-kinase–AKT–mammalian target of rapamycin (mTOR) pathway.





Trastuzumab-Deruxtecan



- humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab

- topoisomerase I inhibitor payload (an exatecan derivative)

- tetrapeptide-based cleavable link

Ad 3) HER2 mutationsin Exon 20 (Protein tyrosine kinase 691 - 945) seem to force receptor internalization and intracellular uptake of the HER2 receptor antibody–drug conjugate complex.

FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for HER2-mutant non-small cell lung cancer

„Although HER2 targeting has transformed the treatment of patients with breast and gastric cancers, HER2-targeted therapies have not been approved for patients with NSCLC. Therefore, patients with HER2-mutant NSCLC are currently treated with standard chemotherapy or immuno- therapy, which have limited activity as second- or later-line treatment.“

→ On August 11 – accelerated approval to trastuzumab deruxtecan (Enhertu®) by Food and Drug Administration (FDA)

→ Eligible for treatment are adults with NSCLC and:
- activating mutation in the HER2 gene
- unresectable and metastatic cancer

→ Efficacy for accelerated approval based on DESTINY-Lung02 (multicenter, multi-cohort, randomized, blinded, dose-optimization trial)

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

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)§
No. of lines of previous cancer therapy — median (range)	2 (0–7)
Previous cancer therapy — no. (%)	
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)

N=91 Patients were eligible for participation:

- confirmed HER2-overexpressing or *HER2*- mutant NSCLC
- unresectable or metastatic nonsquamous NSCLC, at least one measurable lesion
- relapsed during standard treatment / refractory to standard treatment

Could also be enrolled:

- while receiving an earlier line of treatment.
- previously had received a HER2 tyrosine kinase inhibitor such as afatinib, pyrotinib, or poziotinib

Following patients were excluded:

- previously been treated with a HER2 antibody or an antibody–drug conjugate
- history of noninfectious interstitial lung disease treated with glucocorticoids or current or suspected interstitial lung disease

Intervention:
→ Trastuzumab deruxtecan (i.v) every 3 weeks at a dose of 6.4 mg per kilogram of body weight.

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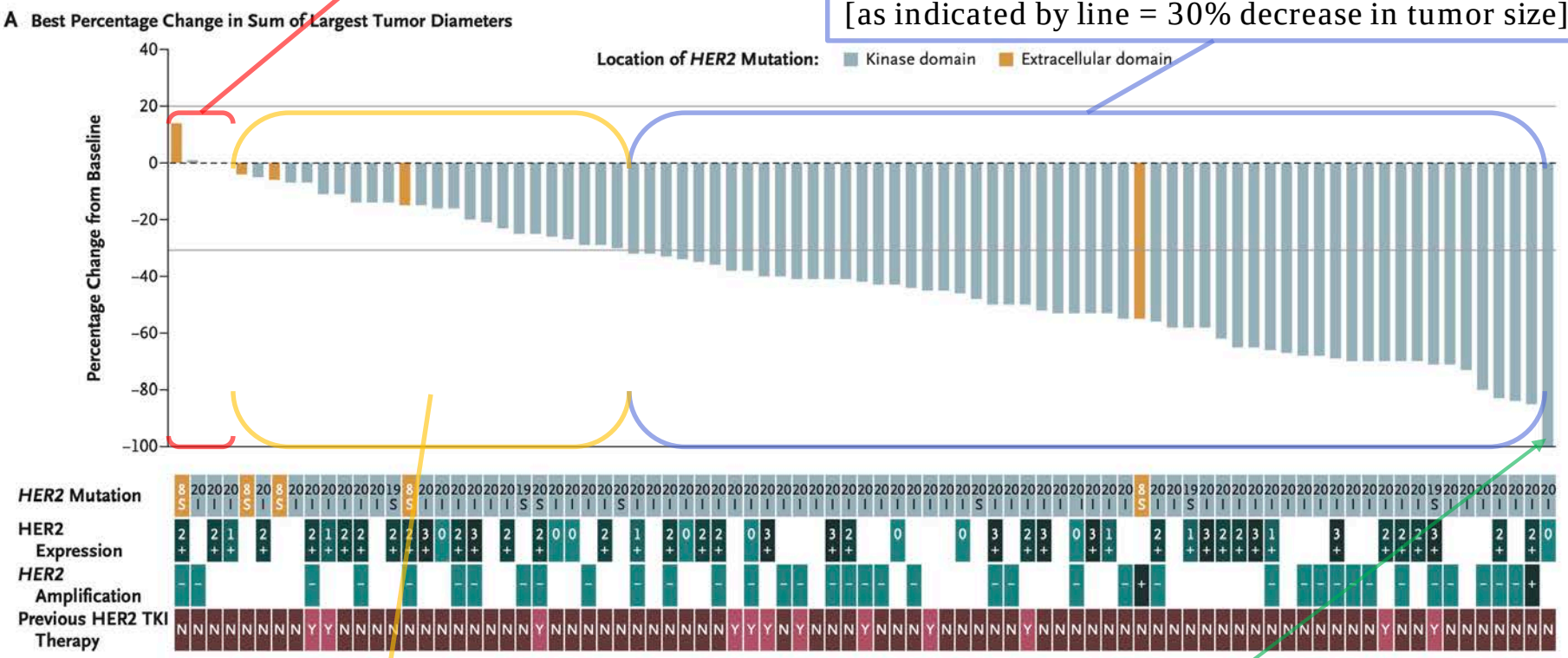
Best percentage change from baseline -> largest diameters of measurable tumors in 85 of 91 patients
(for whom data from both baseline and postbaseline assessments of target lesions - by independent central review - were available)

Progressive disease in 3 patients

49 patients had partial response
[as indicated by line = 30% decrease in tumor size]



In 34 patients the disease was stable

One patient had a confirmed complete response

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

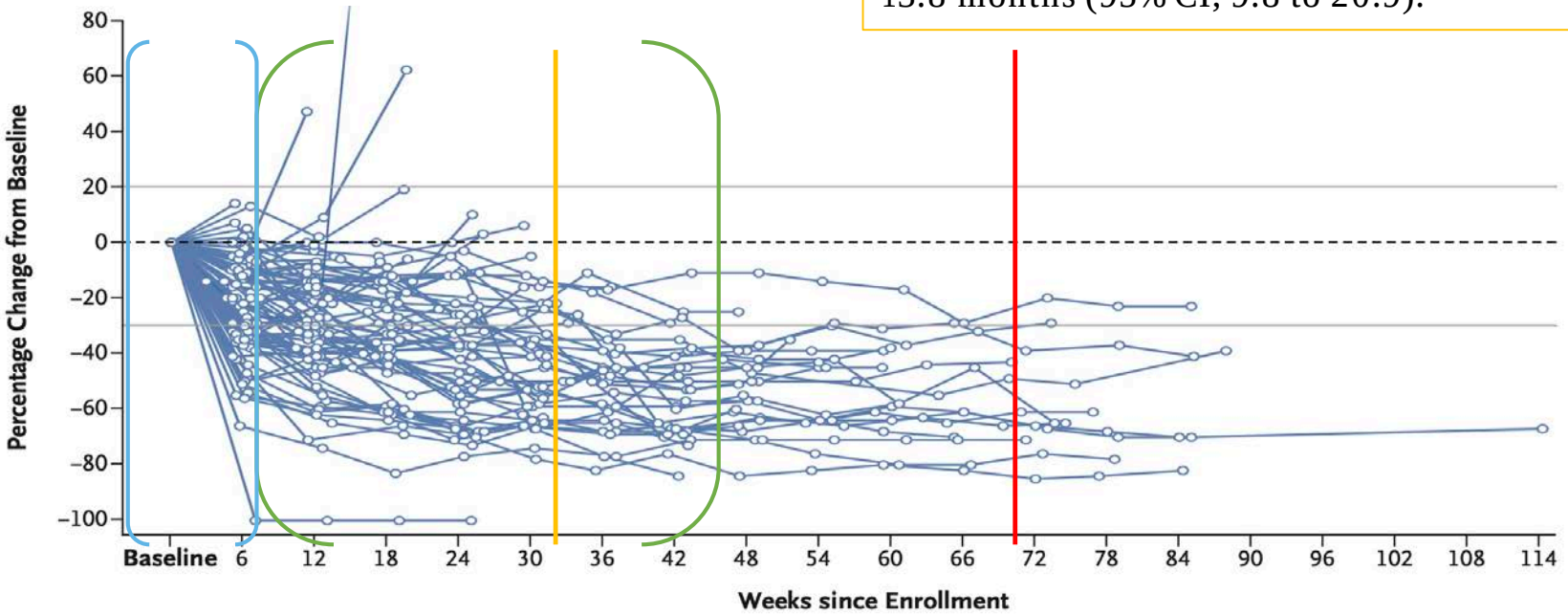
Response Assessment	Patients (N=91)
Confirmed objective response*	
No. of patients	50
Percentage of patients (95% CI)	55 (44–65)
Best response — no. (%)	
Complete response	1 (1)
Partial response	49 (54)
Stable disease	34 (37)
Progressive disease	3 (3)
Response could not be evaluated	4 (4)
Disease control†	
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)

median duration of response:
9.3 months (95% CI, 5.7 to 14.7),

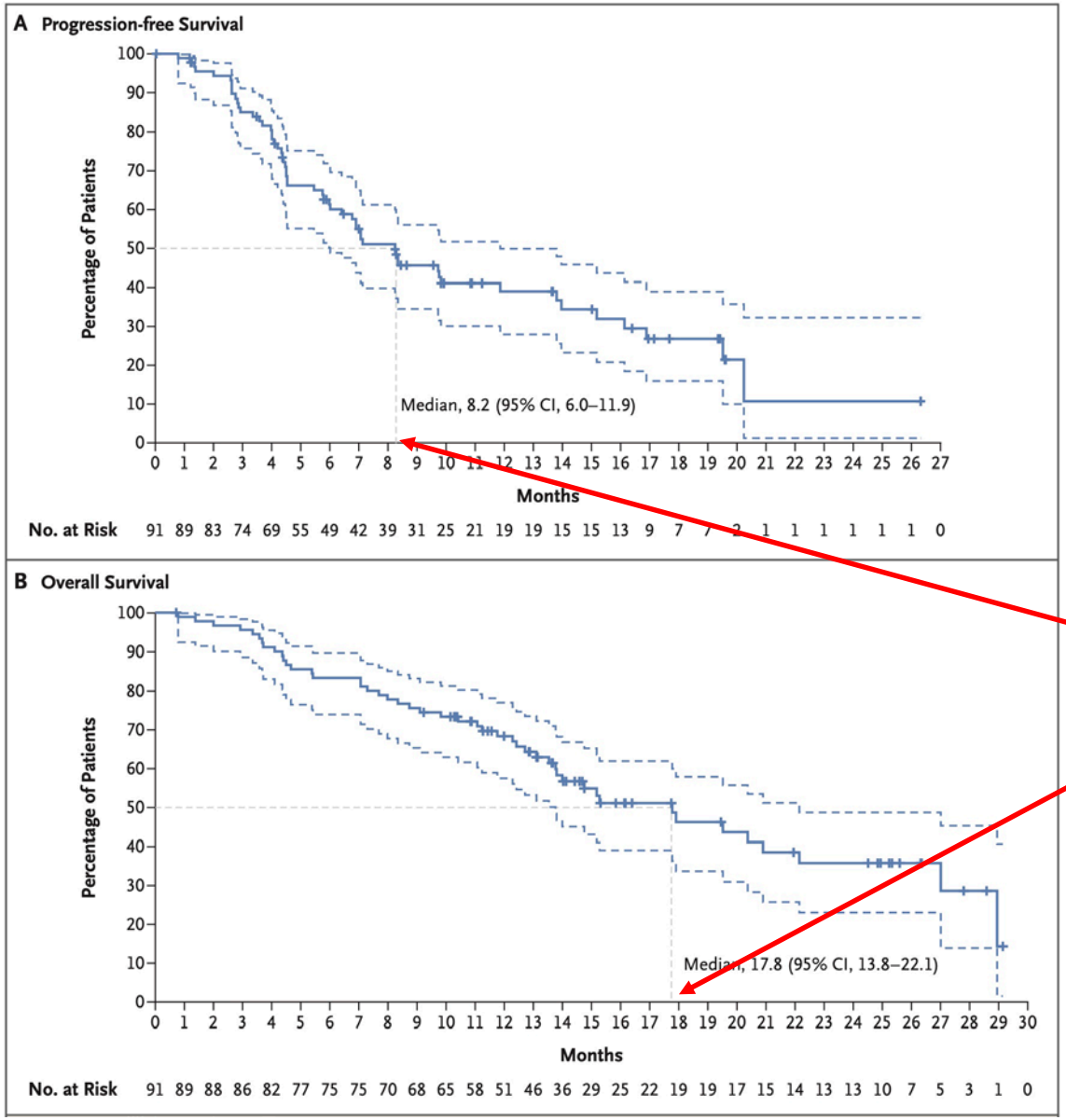
median progression- free survival:
8.2 months (95% CI, 6.0 to 11.9)

median overall survival:
17.8 months (95% CI, 13.8 to 22.1)

Among the 33 patients with CNS metastases:
median progression-free survival:
7.1 months (95% CI, 5.5 to 9.8)
median overall survival:
13.8 months (95% CI, 9.8 to 20.9).



A total of 47 patients (52%) had died as of the data cutoff



A) 91 patients, 41 had progressive disease and 15 had died by the data cutoff date; data for 35 patients were censored *(tick marks)*

B) 91 patients, 47 had died by the cutoff date; data for 44 patients were censored

median duration of response:
9.3 months (95% CI, 5.7 to 14.7),

median progression- free survival:
8.2 months (95% CI, 6.0 to 11.9)

median overall survival:
17.8 months (95% CI, 13.8 to 22.1)

Among the 33 patients with CNS metastases:
median progression-free survival: 7.1 months (95% CI, 5.5 to 9.8)
median overall survival was 13.8 months (95% CI, 9.8 to 20.9).

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Table S4. Most Common Adverse Events Reported by Investigators.

Incidence — no. (%)	Patients (N = 91)				
	Grade 1-2	Grade 3	Grade 4	Grade 5	All Grades
Patients with ≥1 adverse event	28 (30.8)	46 (50.5)	4 (4.4)	13 (14.3)	91 (100)
Adverse events with ≥20% incidence in all patients					
Nausea	61 (67.1)	8 (8.8)	0	0	69 (75.8)
Fatigue*	49 (53.9)	6 (6.6)	0	0	55 (60.4)
Vomiting	37 (40.7)	5 (5.5)	0	0	42 (46.2)
Alopecia	42 (46.2)	0	0	0	42 (46.2)
Diarrhea	34 (37.4)	2 (2.2)	1 (1.1)	0	37 (40.7)
Constipation	34 (37.4)	0	0	0	34 (37.4)
Anemia†	23 (25.3)	10 (11.0)	0	0	33 (36.3)
Decreased appetite	32 (35.2)	0	0	0	32 (35.2)
Neutropenia‡	15 (16.5)	14 (15.4)	3 (3.3)	0	32 (35.2)
Leukopenia§	17 (18.7)	4 (4.4)	0	0	21 (23.1)
Weight decreased	19 (20.9)	2 (2.2)	0	0	21 (23.1)
Pneumonitis	14 (15.4)	4 (4.4)	0	1 (1.1)	19 (20.9)

* This category includes fatigue, asthenia, and malaise.
† This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased.
‡ This category includes the preferred terms neutrophil count decreased and neutropenia.
§ Thus category includes the preferred terms white blood cell count decrease and leukopenia.

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)

* One patient had grade 5 (i.e., fatal) pneumonitis that was assessed as drug-related by the investigator (subsequently adjudicated as interstitial lung disease). Another patient had grade 3 interstitial lung disease, as reported by the investigator, and died; the reported interstitial lung disease was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee. All adjudicated events of drug-related interstitial lung disease are reported in Table S5.
† This category includes the preferred terms fatigue, asthenia, and malaise.
‡ This category includes the preferred terms neutrophil count decreased and neutropenia.
§ This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased.
¶ This category includes the preferred terms white-cell count decreased and leukopenia.

Type of adverse events — no. (%)	Patients (N = 91)
Any adverse event	91 (100)
Drug-related	88 (96.7)
Adverse event grade 3 or higher	63 (69.2)
Drug-related	42 (46.2)
Serious adverse event	39 (42.9)
Drug-related	18 (19.8)
Adverse event associated with discontinuation	34 (37.4)
Drug-related	23 (25.3)
Adverse event associated with dose reduction	32 (35.2)
Drug-related	31 (34.1)
Adverse event associated with dose interruption	44 (48.4)
Drug-related	29 (31.9)
Adverse event associated with an outcome of death	13 (14.3)
Drug-related	2 (2.2)[a]

[a]One patient experienced grade 3 interstitial lung disease as reported by investigator and died. The reported interstitial lung disease was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee.

Serious drug-related adverse events:
18 patients (20%).

Treatment discontinued:
23 patients (25%) i.e. pneumonitis in 12 patients (13%) interstitial lung disease in 5 patients (5%)

Dose redution:
31 patients (34%)
mostly nausea (in 10 patients) and fatigue (in 8 patients).

Dose interruption:
29 patients (32%)
Most common - decreased neutrophil count (in 13 patients) and pneumonitis (in 5 patients).

Table S5. Adjudicated Drug-related Interstitial Lung Disease.

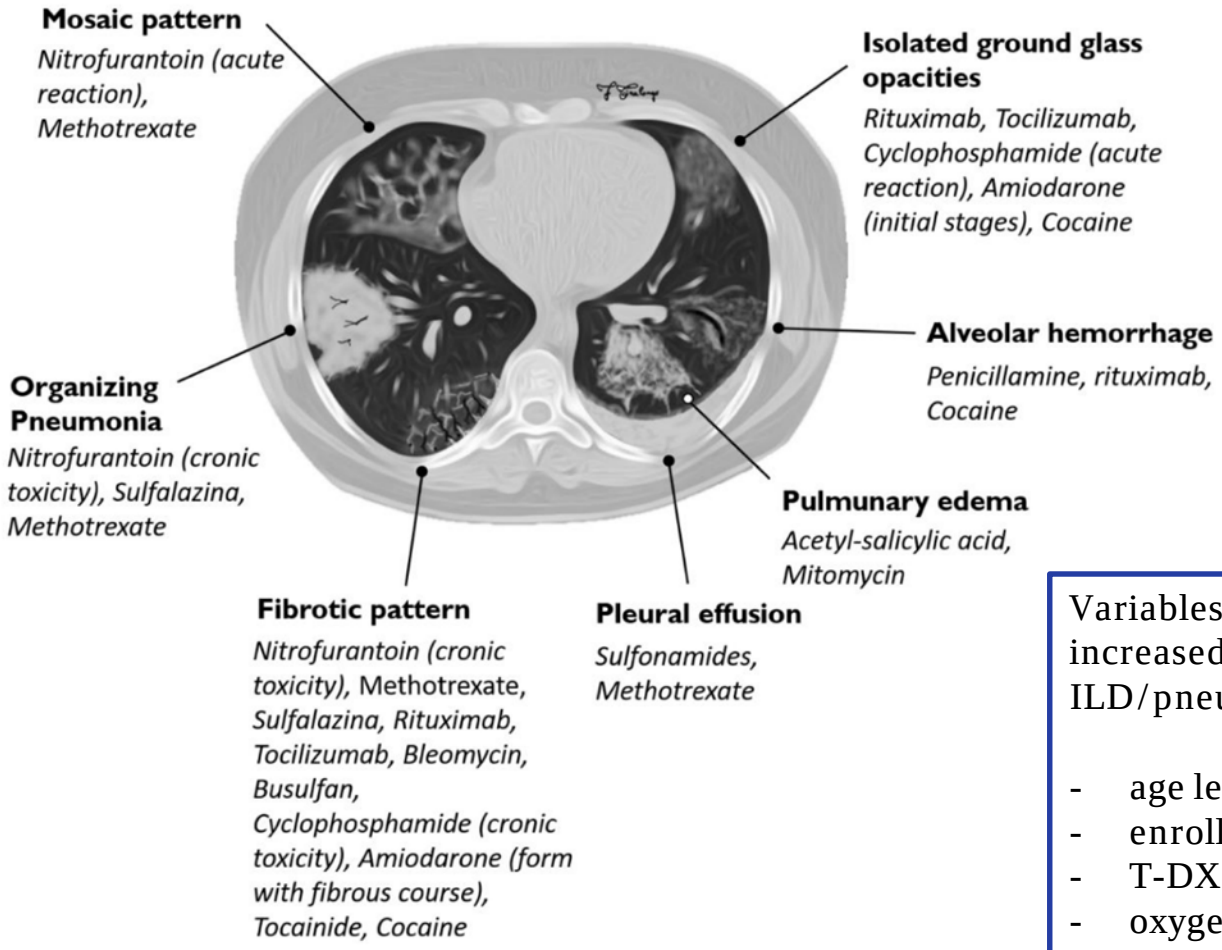
	Patients (N = 91)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Adjudicated drug-related interstitial lung disease, n (%)*	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)†	24 (26.4)

Drug-related interstitial lung disease occurred in 24 patients (26%);

- grade 1 in 3 patients, grade 2 in 15 patients, grade 3 in 4 patients, and grade 5 in 2 patients
- occured in 8 of the 20 patients who had previously undergone lung resection.
- Trastuzumab deruxtecan was withdrawn in 16 patients and interrupted in 8 patients because of adjudicated interstitial lung disease.

https://www.pneumotox.com/drug/view/1629/trastuzumab-deruxtecan

Drug-related interstitial lung disease associated with Trastuzumab deruxtecan



Association between HRCT patterns and the drugs most frequently responsible for lung toxicity.

Variables significantly associated with increased risk for drug-related ILD/pneumonitis:

- age less than 65 years;
- enrollment in Japan;
- T-DXd dose greater than 6.4 mg/kg;
- oxygen saturation less than 95%;
- moderate or severe renal impairment;
- presence of lung comorbidities (not including lung cancer)
- time since initial cancer diagnosis of more than 4 years.

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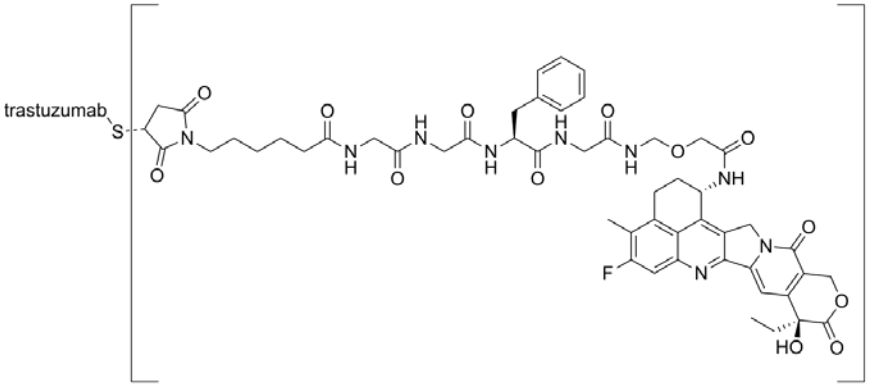
Comparison

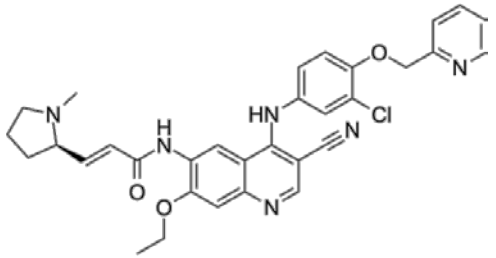
Trastuzumab Deruxtecan:

response occurred in 55% of the patients
median duration of response = 9.3 months,
median progression-free survival = 8.2 months
and median overall survival = 17.8 months.



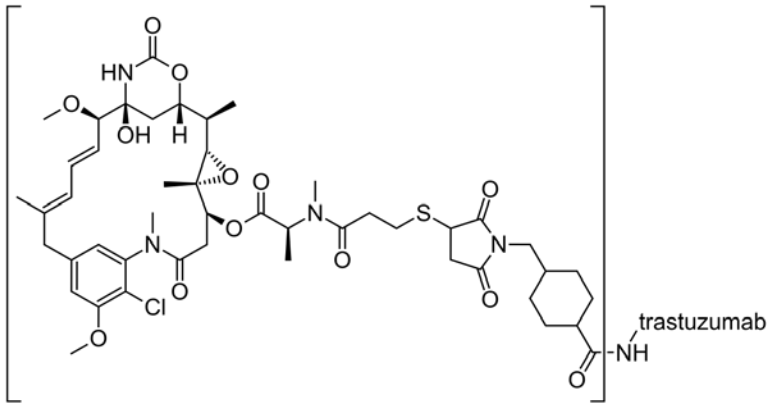
Pyrotinib and Poziotinib:

response in 30% and 28%
median duration of response = 4.6 to 6.9 months
median progression-free survival = 5.5 to 6.9 months



Trastuzumab Emtansine:

response occurring in 44%
median duration of response = 4 months



Limitations

- CNS surveillance (for patients with CNS metastasis) was not performed systematically in all patients, which makes it impossible to assess anti-CNS tumor activity comprehensively.
- The lack of a comparator group in this study necessitates further clinical research
- Patients who had previously been treated with HER2-directed antibodies or antibody–drug conjugates were excluded from the current study.
- „A randomized phase 2 trial is under way to further evaluate the efficacy and safety of trastuzumab deruxtecan, including a lower dose of 5.4 mg per kilogram“*
  → DESTINY-Lung02

*the recommended and approved dosage in HER2- positive breast cancer, in patients with *HER2*- mutant NSCLC)

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