Chapter 1

Progressive HER2-Altered NSCLC After Standard Frontline Therapies

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TOTAL CME

Case Study

76-Year-Old Female

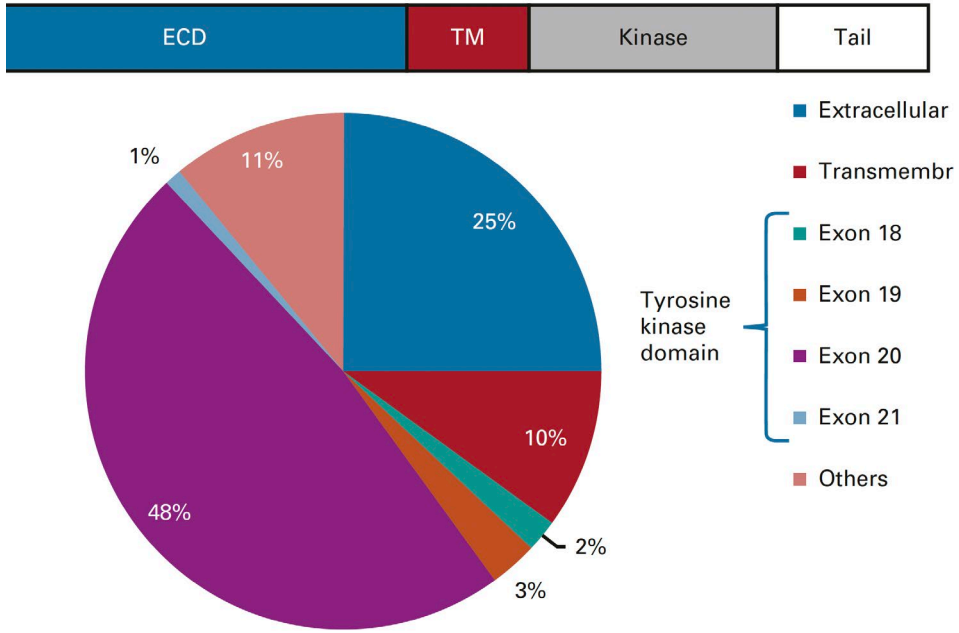
Case Description:

- Never smoker with history of HTN
- Presents with fevers and cough
- CXR – L hilar mass
- Chest CT – 6.4 cm L hilar mass occluding the LLL segmental bronchus; multi-station mediastinal adenopathy; multiple hypodense liver lesions
- Liver biopsy – adenocarcinoma consistent with lung origin (TTF1+), PD-L1 20%
- Tissue and liquid NGS – HER2 G776delinsVC
- Initiates first-line therapy with carboplatin/pemetrexed/pembrolizumab
- Repeat imaging after 2 cycles shows evidence of tumor shrinkage in L lung mass but interval progression of liver metastases

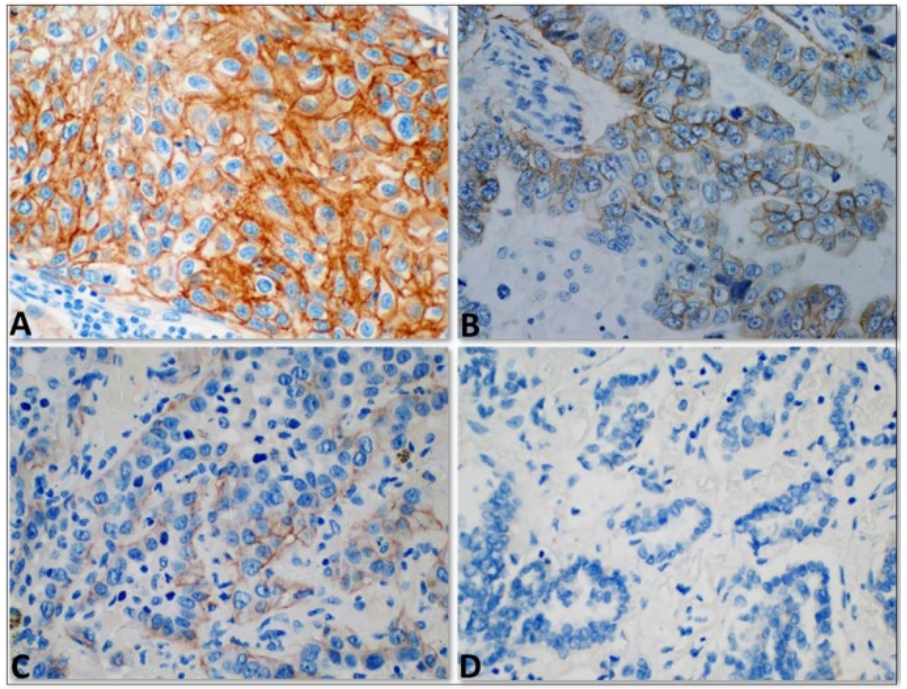
What is the optimal management for this patient?

HER2 Alterations

HER2 Mutations

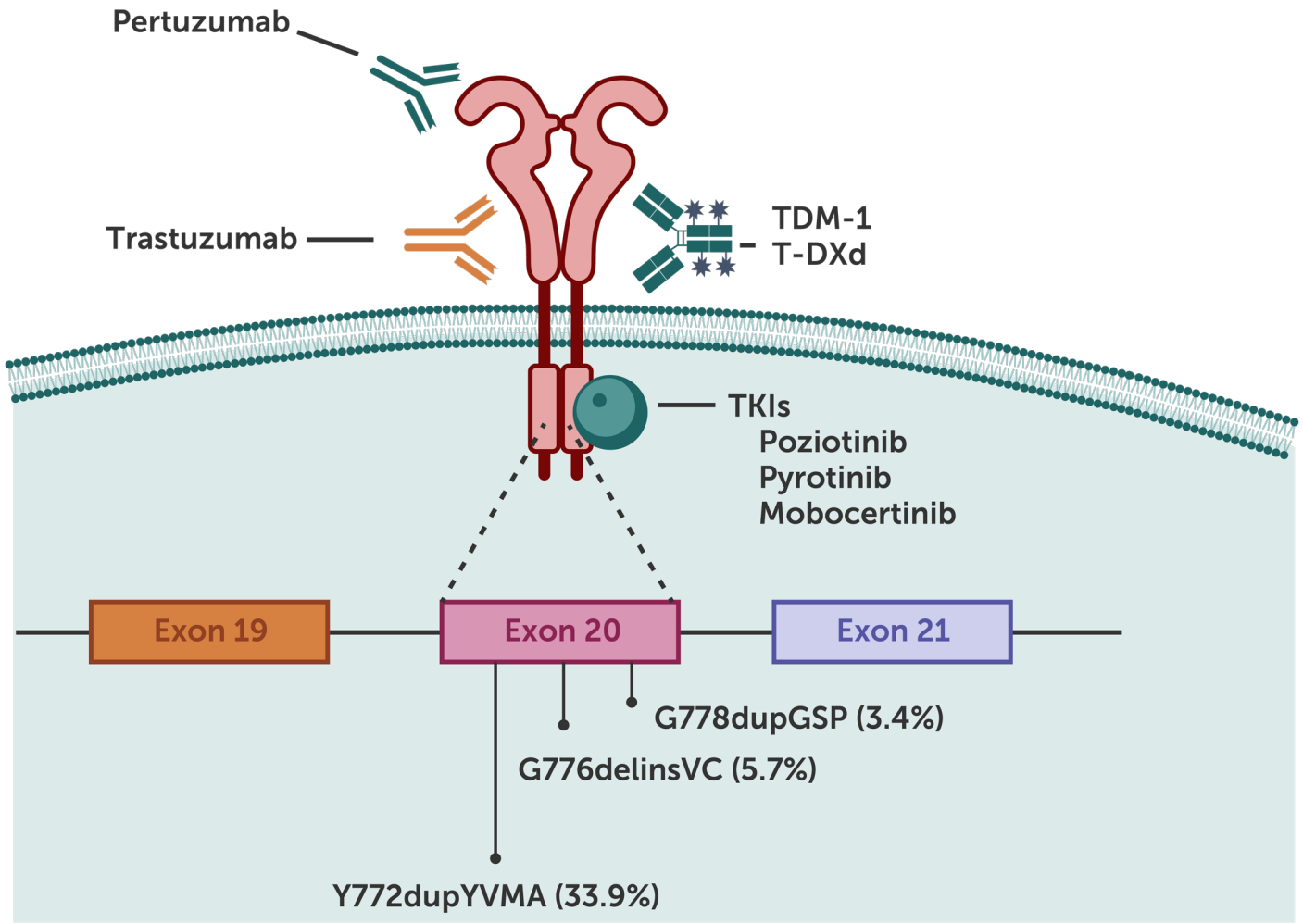


HER2 Expression



Cooper A, Gainor J. *J Clin Oncol.* 2022;40(7):693-697. Al Karsaneh OA, et al. *Diag Pathol.* 2023;18(1):75.

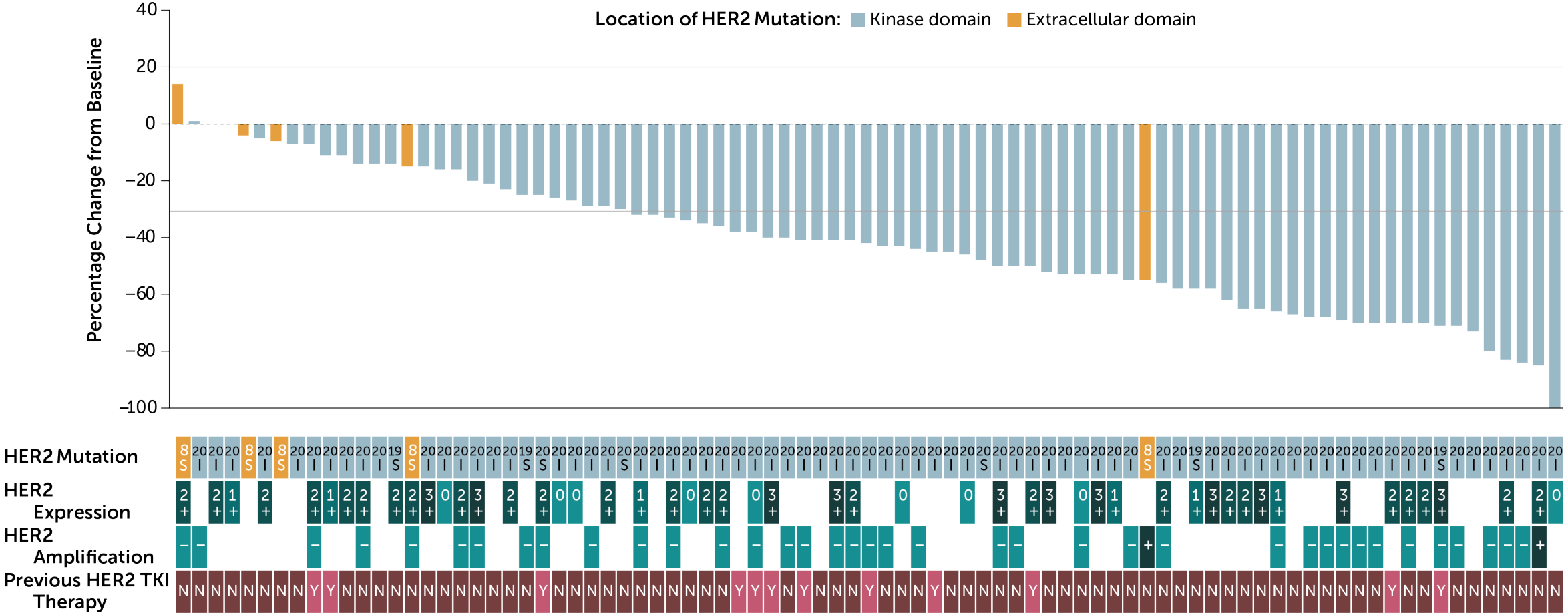
HER2-Targeting Strategies



Cooper A, Gainor J. *J Clin Oncol.* 2022;40(7):693-697.

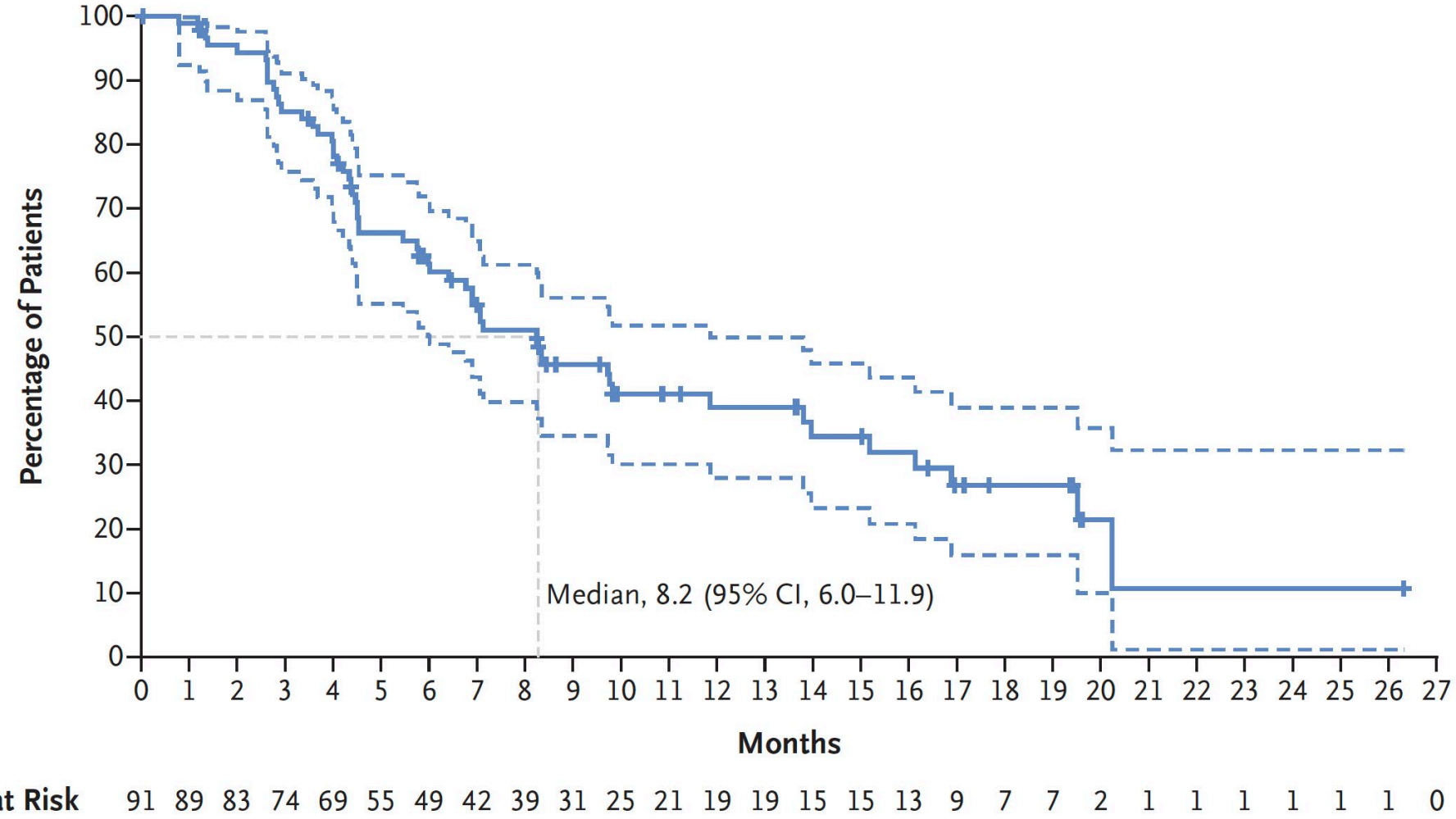
DESTINY-Lung01

Best Percentage Change in Sum of Largest Tumor Diameters



Li BT, at al. *N Engl J Med.* 2022;386(3):241-251.

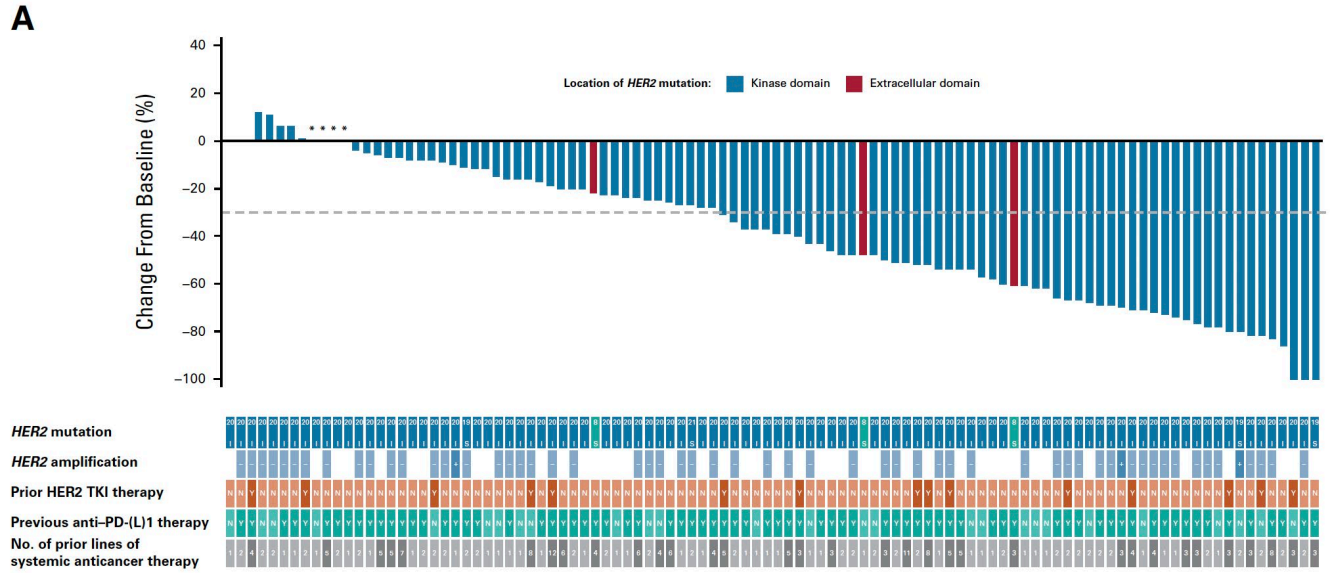
DESTINY-Lung01: PFS



Li BT, at al. *N Engl J Med.* 2022;386(3):241-251.

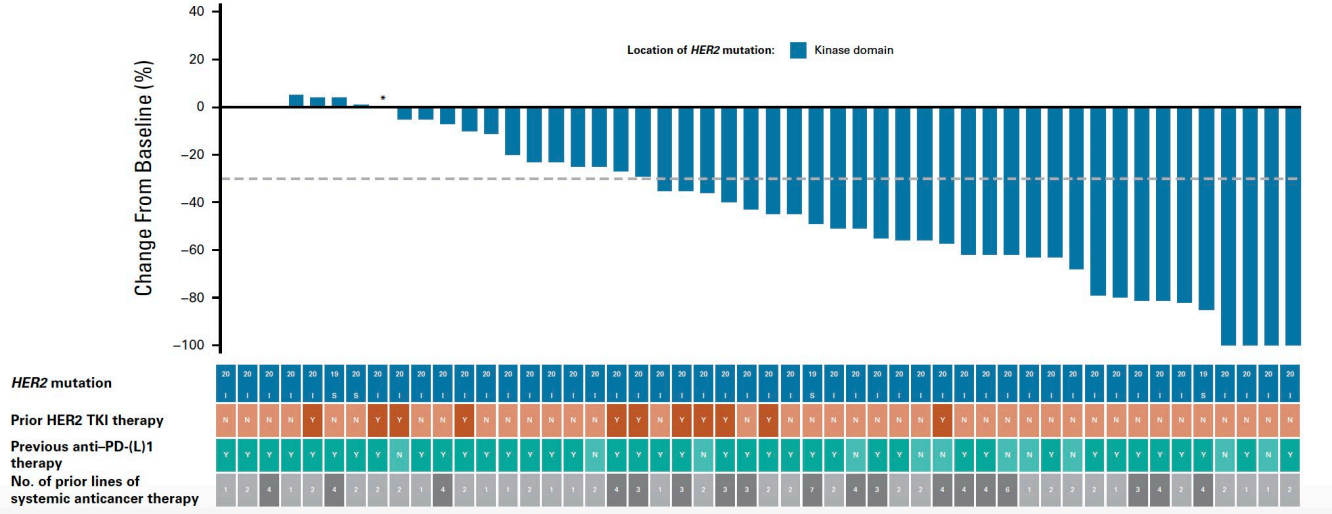
HER2 Mutations

A



5.4 mg/kg Dose	
ORR	49%
mPFS	9.9 mo
DOR	16.8

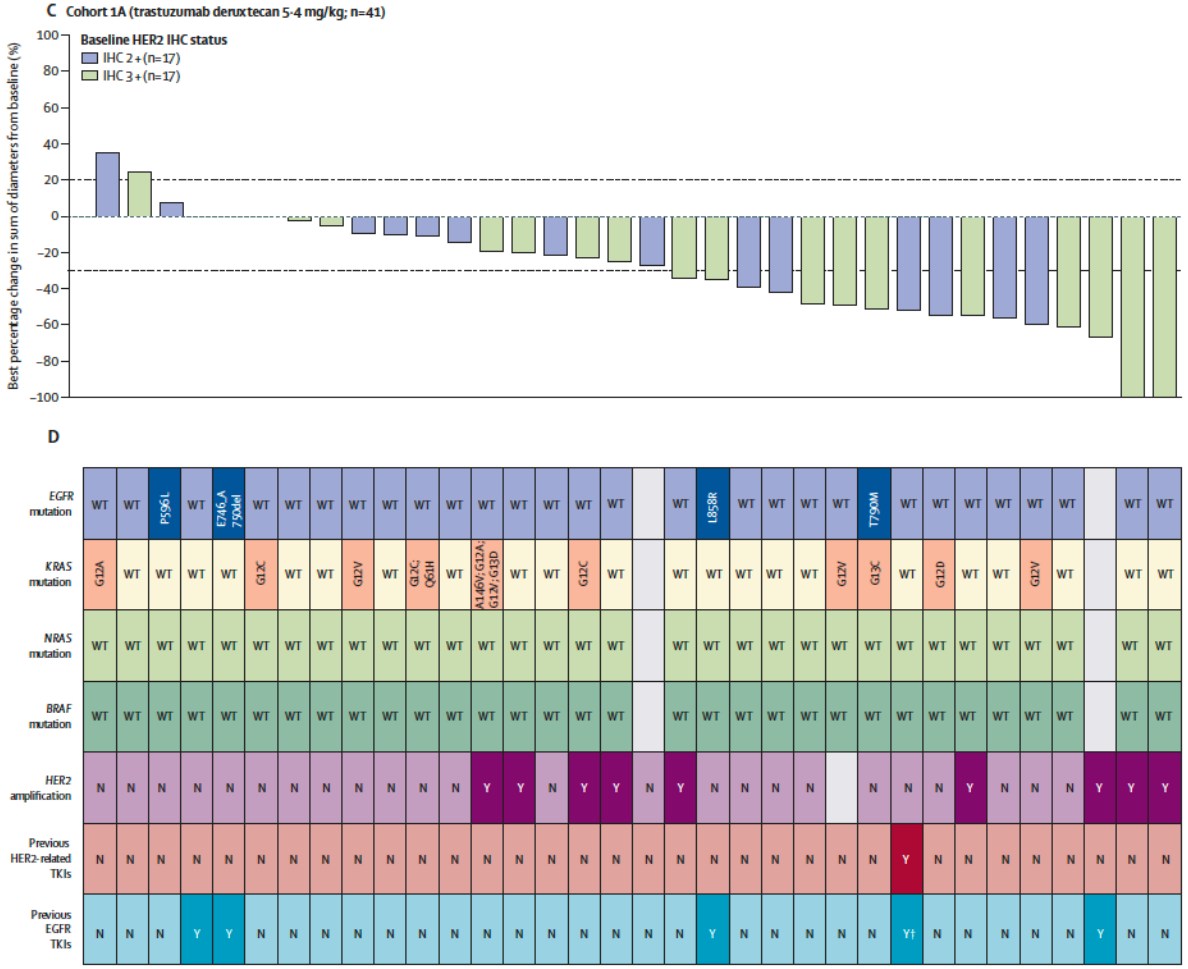
B

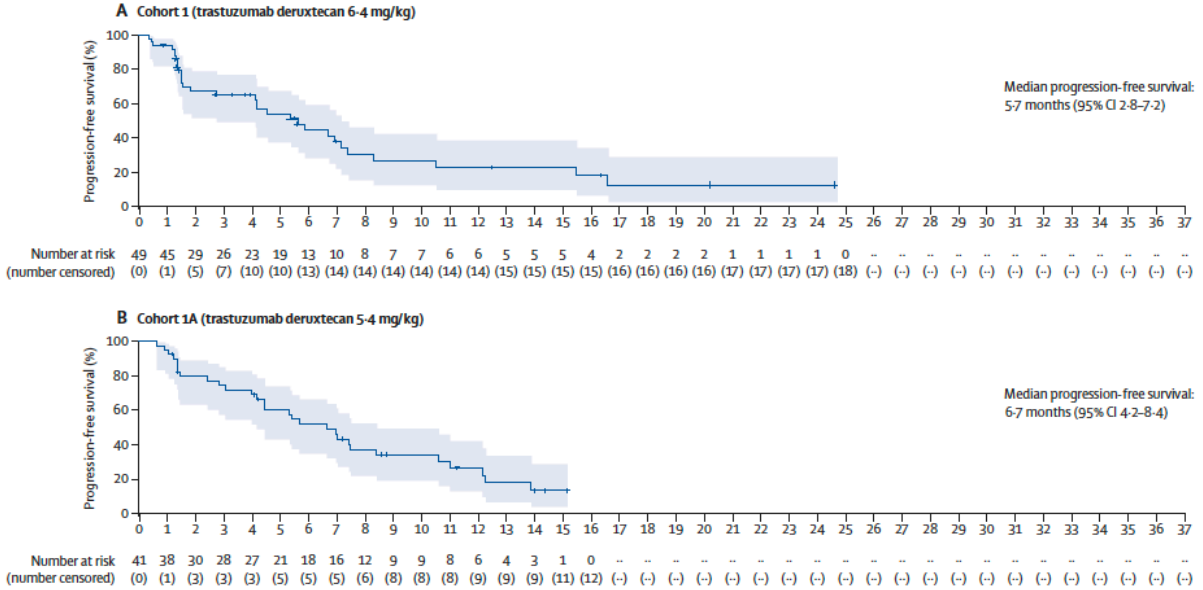


6.4 mg/kg Dose	
ORR	56%
mPFS	15.4 mo
DOR	NE

Goto K, et al. *J Clin Oncol.* 2023;41(31):4852-4863.

HER2 Overexpression





HER2 IHC 3+
ORR 52.9%; mDOR 6.9 months

Smit EF, et al. *Lancet Oncol.* 2024;25(4):439-454.

Most Common AEs: Trastuzumab Deruxtecan

Preferred Term, n (%)	T-DXd 5.4 mg/kg Q3W (n = 101)		T-DXd 6.4 mg/kg Q3W (n = 50)	
	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 (7.0)	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.)
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)	1 (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

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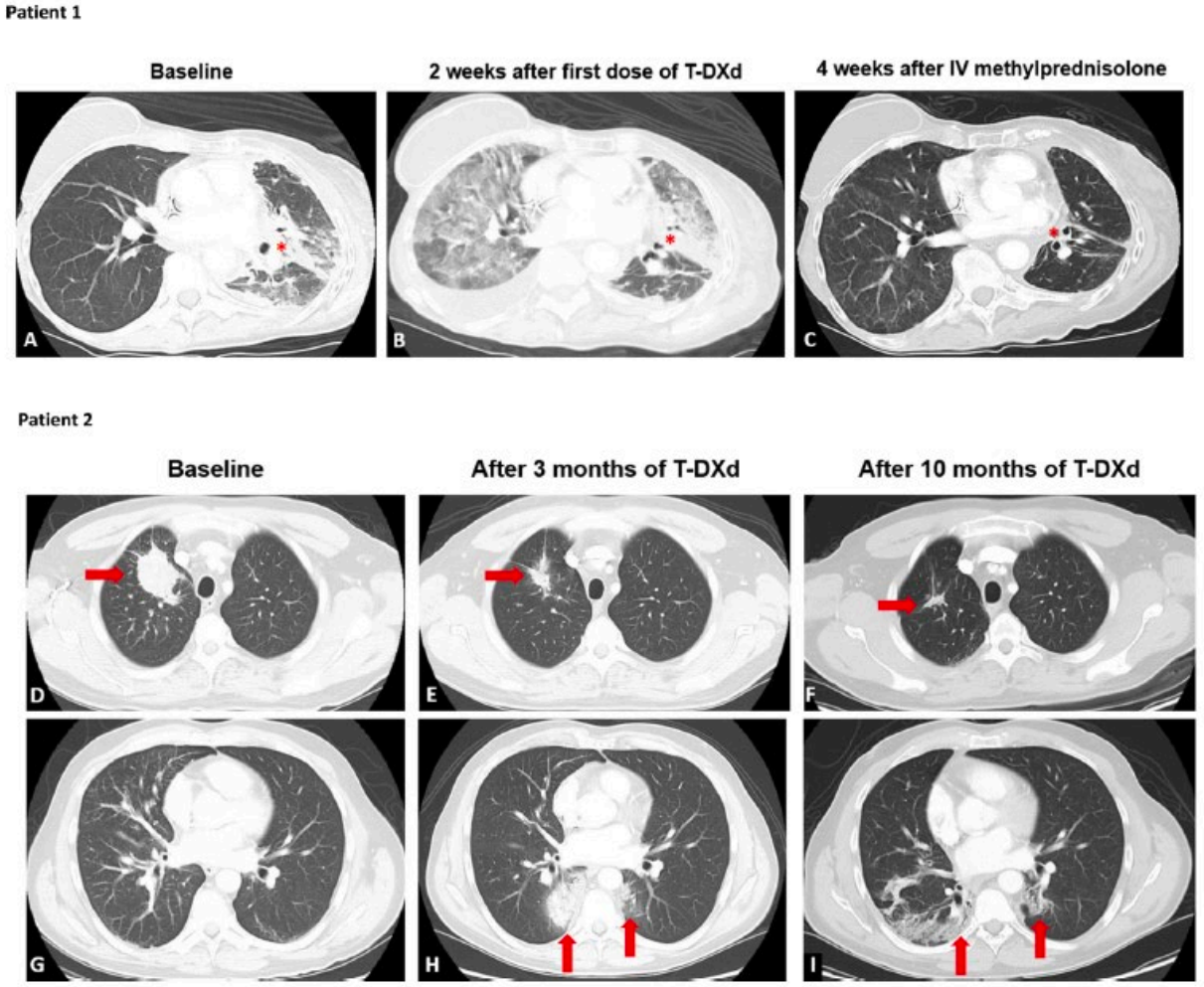
Pneumonitis Risk



Goto K, et al. *J Clin Oncol.* 2023;41(31):4852-4863. Swain SM, et al. *Cancer Treat Rev.* 2022:106:102378.

Pneumonitis Risk

Adjudicated Drug-Related ILD in Patients With Prior Anti-PD(L)1 Therapy, n (%)	T-DXd 5.4 mg/kg Q3W (n = 74)	T-DXd 6.4 mg/kg Q3W (n = 39)
Grade 1	4 (5.4)	2 (5.1)
Grade 2	5 (6.8)	9 (23.1)
Grade 3	1 (1.4)	0
Grade 4	0	0
Grade 5	1 (1.4)	0
Total	11 (14.9)	11 (28.2
Adjudicated Drug-Related ILD in Patients Without Prior Anti-PD(L)1 Therapy, n (%)	**T-DXd 5.4 mg/kg Q3W (n = 27)**	**T-DXd 6.4 mg/kg Q3W (n = 11)**
Grade 1	0	2 (18.2)
Grade 2	2 (7.4)	0
Grade 3	0	0
Grade 4	0	0
Grade 5	0	1 (9.1)
Total	2 (7.4)	3 (27.3)

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Summary

- Testing for *HER2* mutations and overexpression is now a standard of care in advanced NSCLC
- Trastuzumab deruxtecan is now approved for previously-treated, *HER2*-mutant NSCLC and HER2 (3+ overexpressing) solid tumors
- Dose optimization studies established 5.4 mg/kg as preferred T-DXd dose
- Drug-induced ILD is a critical AE that clinicians should be aware of for any patients on T-DXd