

Chapter 2

Beyond the Blood–Brain Barrier: Intracranial Activity of HER2-Targeted ADC Therapy in HER2-Altered NSCLC with Brain Metastases

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Case Study

62-Year-Old Woman

Case Description:

- Metastatic NSCLC with *HER2* mutation
- Presented with new cough to her PCP
- Workup showed multiple lung nodules with mediastinal adenopathy, liver mets, and a right adrenal metastasis
- Biopsy demonstrated metastatic NSCLC
- Oncologist started carboplatin and pemetrexed while awaiting genomic testing due to worsening symptoms

Case Study

62-Year-Old Woman

- Genomic testing showed *HER2* mutation
- Given the initial response to carboplatin and pemetrexed, she continued on treatment
- After 8 months of therapy, scans showed progression
- Brain MRI for re-staging showed multiple brain mets up to 6 mm

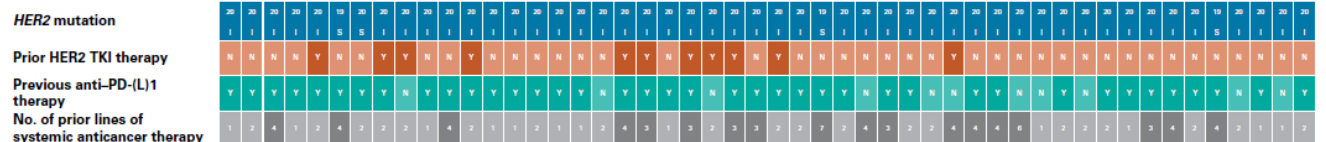
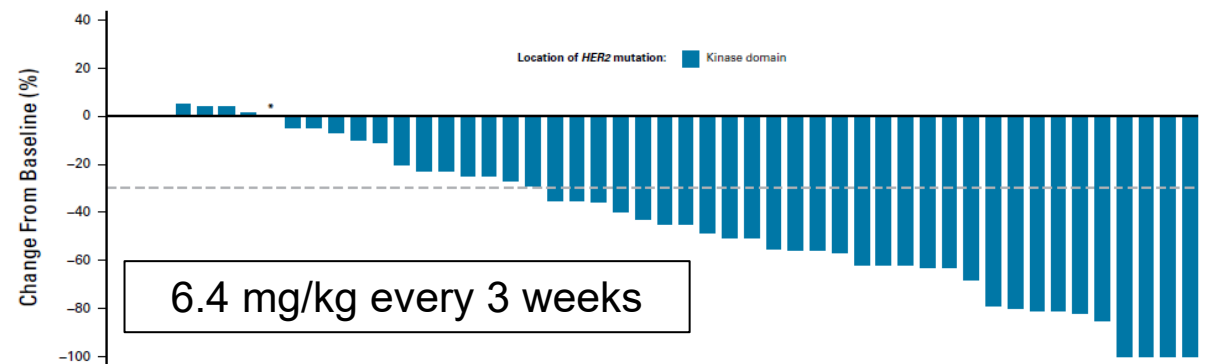
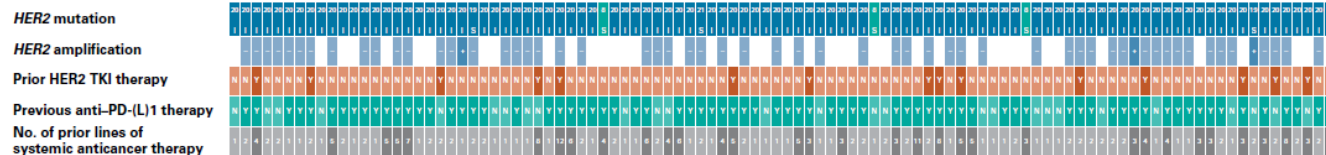
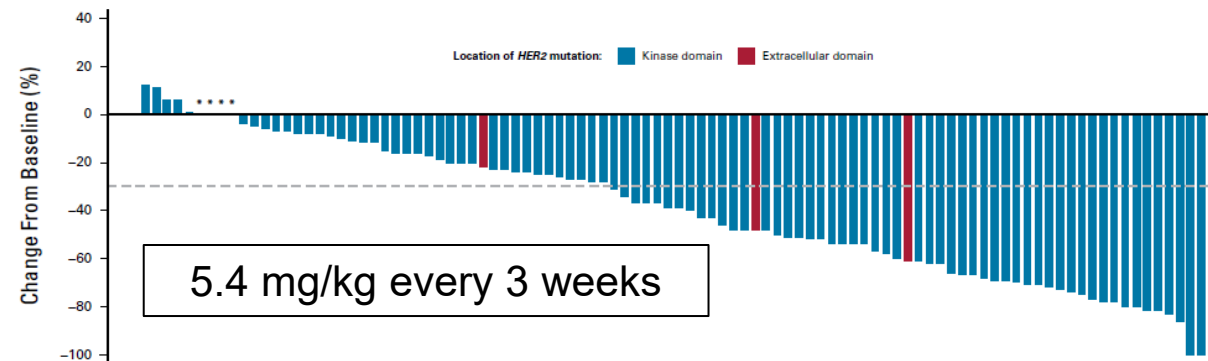
Brain Metastases

- Challenging scenario for solid tumor management
- Some targeted therapies are effective
- Most cytotoxic therapies have some limitations
- Destiny Lung-01 and 02: Trastuzumab deruxtecan for HER2+ NSCLC **allowed enrollment of asymptomatic untreated brain mets**

DESTINY-Lung02

- Similar efficacy with 5.4 mg/kg dosing for lung cancer relative to the higher dose
- Less toxicity (esp. ILD) with 5.4 mg/kg dosing

Adjudicated drug-related ILD	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101), No. (%)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50), No. (%)
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)
Total (95% CI)	13 (12.9) (7.0 to 21.0)	14 (28.0) (16.2 to 42.5)





For HER2-mutant non-small cell lung cancer, the dose [of trastuzumab deruxtecan] is 5.4 mg/kg.



DESTINY-Lung-01

- 33 patients with CNS metastases at baseline were included
 - 14 had previous treatment with radiation to brain mets
 - 19 presumably had no prior therapy to brain mets
- Of the 19 patients with untreated brain mets, there were a reported 10 that that achieved partial response (53%)
- Among all 33 patients, mPFS: 7.1 months, mOS : 13.8 months
- Overall numbers of trial, mPFS 8.2 months, mOS: 17.8 months

DESTINY-Lung01 and DESTINY-Lung02 Pooled Analysis, Patients ± Brain Mets

	Destiny-Lung02 T-DXd 5.4 mg/kg		Destiny-Lung01 T-DXd 6.4 mg/kg	
	BM (n = 32)	Non-BM (n = 70)	BM (n = 54)	Non-BM (n = 87)
Confirmed systemic ORR, n (%)	15 (46.9)	35 (50.0)	27 (50.0)	51 (58.6)
DCR, n (%)	29 (90.6)	66 (94.3)	50 (92.6)	80 (92.0)
mDoR, mos	4.6	16.8	7.2	14.1
!C-ORR, n (%)	8 (25.0)	--	10 (18.5)	--
CR	4 (12.5)	--	1 (1.9)	--
PR	4 (12.5)	00	9 (16.7)	--
SD	18 (56.3)	--	31 (57.4)	--
PD	3 (9.4)	--	4 (7.4)	--
IC-DCR, n (%)	26 (81.3)	--	4 (7.4)	--
m!C-DoR, mos	9.2	--	4.4	--

Pooled Analysis from Destiny-Breast01, 02, and 03

- Treated/Stable BMs:**

- Received prior CNS-directed therapy for the BMs, and their CNS disease is stable

- Untreated/active BMs:**

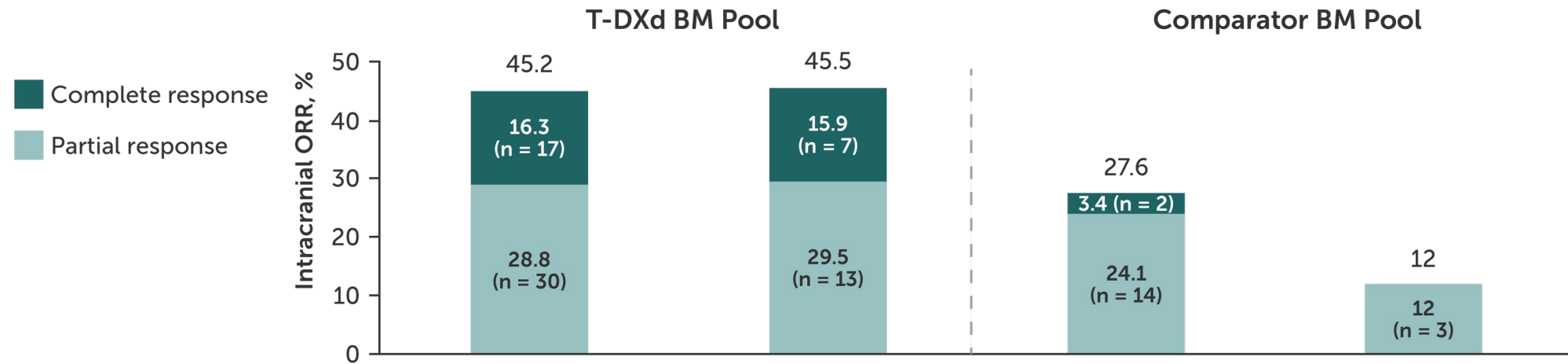
- New or progressive BMs that have not been subjected to CNS-directed therapy since documented progression

	T-DXd Pool (N = 851)		Comparator Pool (N = 465)	
	BM Pool (n = 148)	Non-BM Pool (n = 703)	BM Pool (n = 83)	Non-BM Pool (n = 382)
Prior regimens in the metastatic setting, Median, (range), n (%)	3.0 (1.0-14.0)	3.0 (0-27.0)	3.0 (1.0-15.0)	2.0 (0-12.0)
0	0	2 (0.3)	0	1 (0.3)
1	16 (10.8)	108 (15.4)	14 (16.9)	99 (25.9)
2	41 (27.7)	192 (27.3)	27 (32.5)	110 (28.8)
3	35 (23.6)	156 (22.2)	22 (26.5)	89 (23.3)
4	18 (12.2)	71 (10.1)	9 (10.8)	39 (10.2)
≥5	38 (25.7)	174 (24.8)	11 (13.3)	44 (11.5)
Prior anti-HER2 therapy, n (%)				
Trastuzumab	142 (95.9)	643 (91.5)	83 (100)	381 (99.7)
Pertuzumab	104 (70.3)	497 (70.7)	59 (71.1)	255 (66.8)
T-DM1	102 (68.9)	487 (69.3)	41 (49.4)	161 (42.1)
HER2 TKI	17 (11.5)	51 (7.3)	14 (16.9)	39 (10.2)
Prior treatment for brain metastasis, n (%)				
None (untreated/active)	44 (29.7)	642 (91.3)	25 (30.1)	359 (94.0)
Any prior treatment for BMs (treated/stable)	104 (70.3)	61 (8.7) ^a	58 (69.9)	23 (6.0) ^a
RT alone	80 (54.1)	45 (6.4) ^a	44 (53.0)	15 (3.9) ^a
Surgery alone	5 (3.4)	6 (0.9) ^a	5 (6.0)	5 (1.3) ^a
RT and surgery	19 (12.8)	10 (1.4) ^a	9 (10.8)	3 (0.8) ^a

Pooled Analysis from Destiny-Breast01, 02, and 03

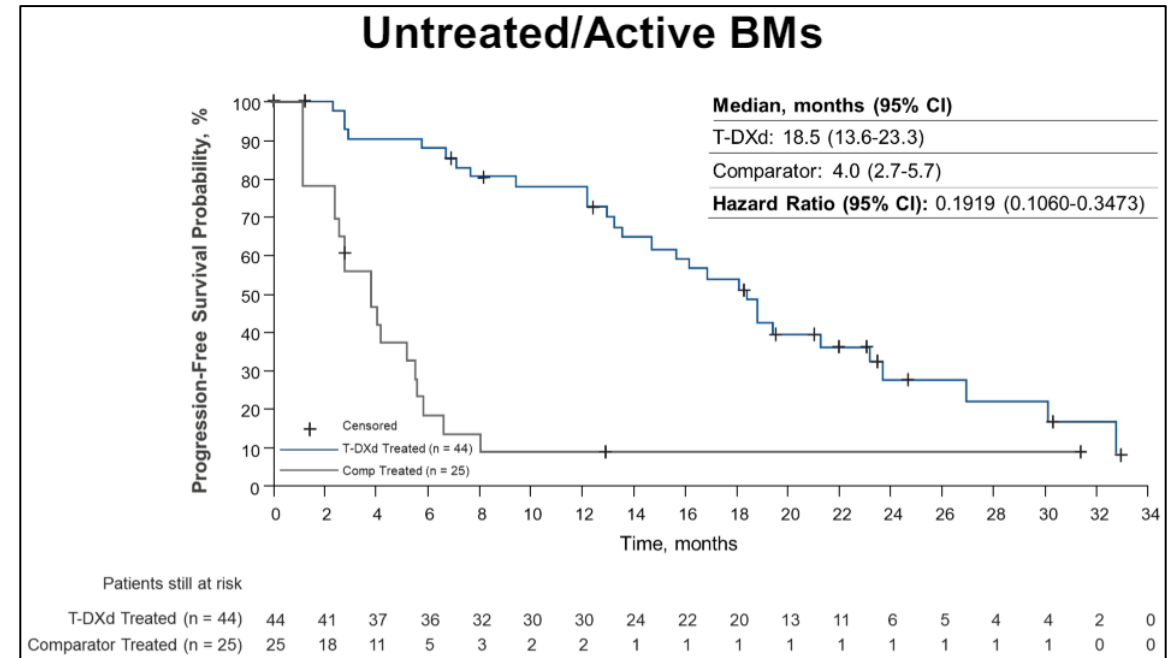
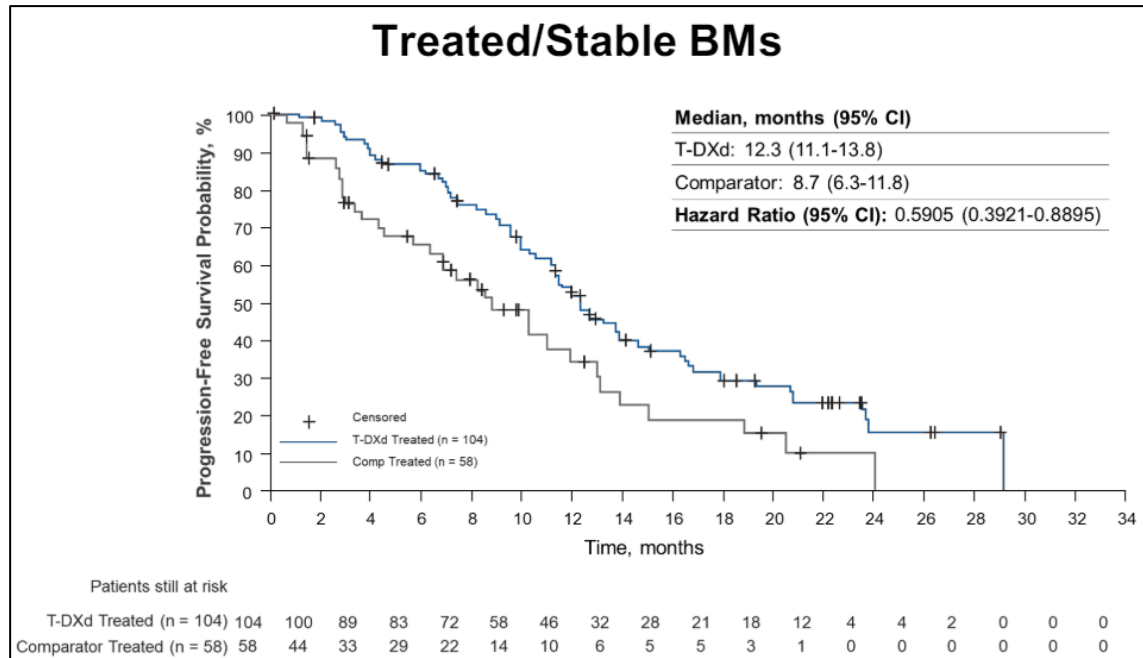
Exploratory Best IC Response, ORR, and DoR per BICR

Intracranial ORR



	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)	Treated/stable BMs (n = 58)	Untreated/active BMs (n = 25)
Best overall IC response, n (%)				
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
Not evaluable/Missing	6 (5.8)	8 (18.2)	7 (12.1)	2 (8.0)
IC-DoR, median, months (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)	11.0 (5.6-16.0)	NA

Pooled Analysis from Destiny-Breast01, 02, and 03



Hurvitz SA, et al. ESMO 2023. Abstract 3770.

62-Year-Old Woman With *HER2*-Mutated, Metastatic NSCLC

- Multiple asymptomatic, untreated brain mets
- Can monitor closely on trastuzumab deruxtecan in this case given the small size of brain mets
- If symptomatic or larger size brain mets, consider treatment with radiation (or resection if indicated)