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CHALLENGING CASES

Lung Cancer

Combined results from 2 programs
November 17th and November 18th, 2023
Live Program in Nashville, TN

Challenging Cases in Lung Cancer

Presented by Dr. Lee Schwartzberg

Program Disclosures

COIs: Consultant for Daiichi Sankyo, AstraZeneca, Seagen, Novartis, Foundation Medicine, Spectrum. Speaker for Daiichi Sankyo, Seagen, AstraZeneca, Merck

The information presented is consistent with FDA Guidelines and includes the latest clinical trial data

This program has been provided as an opportunity for discussion and learning, with insights from key opinion leaders

Lee Schwartzberg, MD

Renown Oncology/Hematology

Reno, Nevada

Challenging Cases in… Lung Cancer

NSCLC with HER2 alteration

- 2-4% of NSCLC
- Adenocarcinomas
- Female, never smokers
- Poor prognosis
- Lower TMB

- *What is the optimal first line therapy? Second line therapy?*
- *Challenges with biopsy and testing?*
- *Sequencing considerations to provide the best outcomes for patients?*

NSCLC Patient

- *65-year-old woman*
- 30 pack-year smoker
- Developed back pain and worsening cough
- CT scan chest showed 3x4 cm mass in left upper lung, mediastinal LN enlargement, lytic lesion in T8 without soft tissue component
- PET scan: All above hypermetabolic
- Lesion in T12 and sacrum

Initial Diagnosis

- Tissue biopsy
- T8: NSCLC, adenocarcinoma
- TFF+
- PD-L1: CPS 30
- EGFR negative
- Not enough tissue for NGS
- ECOG PS 1

What first-line treatment do you initially recommend?

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CPS=combined positive score

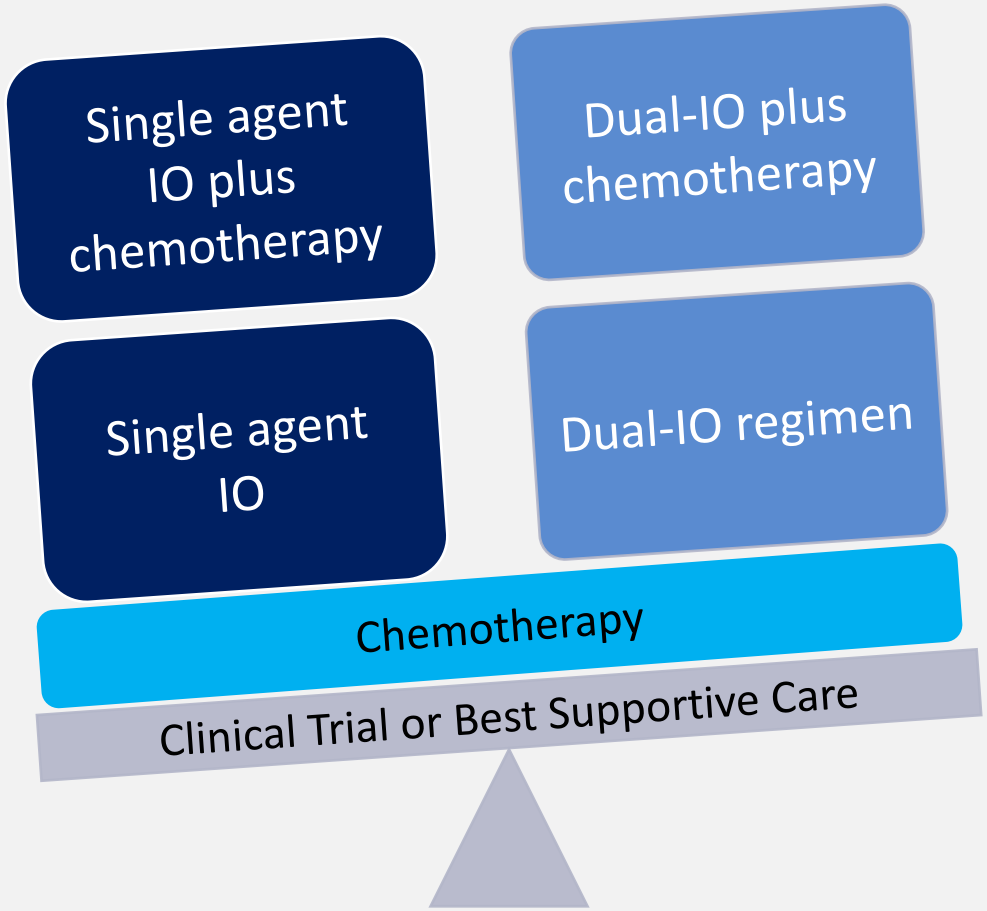
Open-text Response Results from HCP Participants

What first-line treatment do you initially recommend?

- ***Chemotherapy plus immunotherapy***
- ***Pembrolizumab + Platinum doublet***
- ***Carbo pemetrexed pembrolizumab***
- ***Liquid biopsy***
- ***Carbo pemetrexed cemiplimab***
- ***Chemo plus cemiplimab***
- ***Get peripheral blood for NGS, then if negative treat***

Text size indicates frequency of response

1L Metastatic Treatment Options



Choice of treatment

- No head-to-head comparisons between the IO agents
- Differences in the study populations
- Differences in measurements of PD-L1

1L metastatic treatment

- Carbo/Alimta/Pembro
- 4 cycles, then maintenance Pembro/Alimta
- Partial response to therapy
- Decreased tumor size and reduced hypermetabolic after 3 cycles
- Stable for 6 more months; well tolerated except for fatigue

Progression

- CT scan shows enlargement in primary tumor and new liver mets
- MRI head - negative
- ECOG PS 1
- Some increase in fatigue
- No pulmonary symptoms
- Tissue biopsy of liver lesion
- Liquid biopsy

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Open-text Response Results from HCP Participants

How often do you test new metastatic lesions on first tumor recurrence (progression)?

- ***Always***
- *I would at least get liquid NGS, whether a previous NGS was done or not, and if a biopsy is repeated, then I will get NGS on tissue*
- *At each progression*
- *Most of the time*
- *In this case I would definitely do it now. And I usually repeat at each progression to evaluate for new anomalies*
- *100% liquid and tissue for first recurrence*
- *Liquid Bx and then decide treatment*
- *Send for liquid biopsy*
- *With liquid biopsy - or if in a trial*
- *Most of the time if candidate for 2nd line*
- *At time of each progression with liquid; will repeat tissue if >1 year*
- *Tissue biopsy if patient is amenable*
- *100%*

Text size indicates frequency of response

Open-text Response Results from HCP Participants

How often do you perform liquid biopsy and tissue biopsy?

- *Tissue biopsy as first choice. Liquid biopsy if can't get tissue*
- *At diagnosis, most likely I'd get tissue + liquid; at fist progression it depends if a biopsy is repeated; at 2nd progression not always*
- *If the tissue Bx is easy to do.*
- *At initial diagnosis. Would also consider both if patient on treatment for close to a year and then progresses*
- *My preference is to do both*
- *When I see disease progression – I do liquid biopsy Tissue biopsy - depends case by case*
- *The NGS company that I use Tempus requires both*
- *Liquid biopsy at every progression Tissue biopsy for new site of disease if amenable and at least one year*
- *For all metastatic patients. Sometimes tissue is qns to do tissue testing*
- *At time of first diagnosis; then if tissue >1y or tumor not behaving as expected*
- *Tissue + liquid.*
- *At diagnosis of metastatic disease*
- *Often*

Text size indicates frequency of response

Open-text Response Results from HCP Participants

How often do you perform a tissue biopsy if liquid biopsy is uninformative?

- ***100%***
- ***Most of the time***
- ***Always***
- ***Yes, at diagnosis, but not always at progression***
- ***75%. Sometimes patient choice or technical issues***
- ***Frequently depending on pt PS & ease of target.***
- ***Start second line treatment***
- ***If locations is accessible and patient willing 100%***

Text size indicates frequency of response

Open-text Response Results from HCP Participants

How often do you test new metastatic lesions on subsequent progression?

- ***Liquid***
- ***Liquid at every progression***
- ***Test with liquid on each progression if PFS is >6 months***
- ***After 2nd and 3rd***
- ***If it's been over a year, I repeat it***
- ***Depends on timing. Would if greater than 12 months***
- ***Depending on timeline and if new area of spread***
- ***Unless significant period between progressions would not test***
- ***Sometimes liquid but rarely sequential tissue***
- ***Think about it depending on clinical status***
- ***Always***
- ***Usually***
- ***50/50***
- ***Often***
- ***Not normally / not really***
- ***Only for EGFR and ALK patients***

Text size indicates frequency of response

Site of Metastases:

- Bone
- Liver

➢ Liver, undergoes tissue biopsy

Testing Results:

HER2 exon 20 mutation

TMB 6/Mb

MSI-S

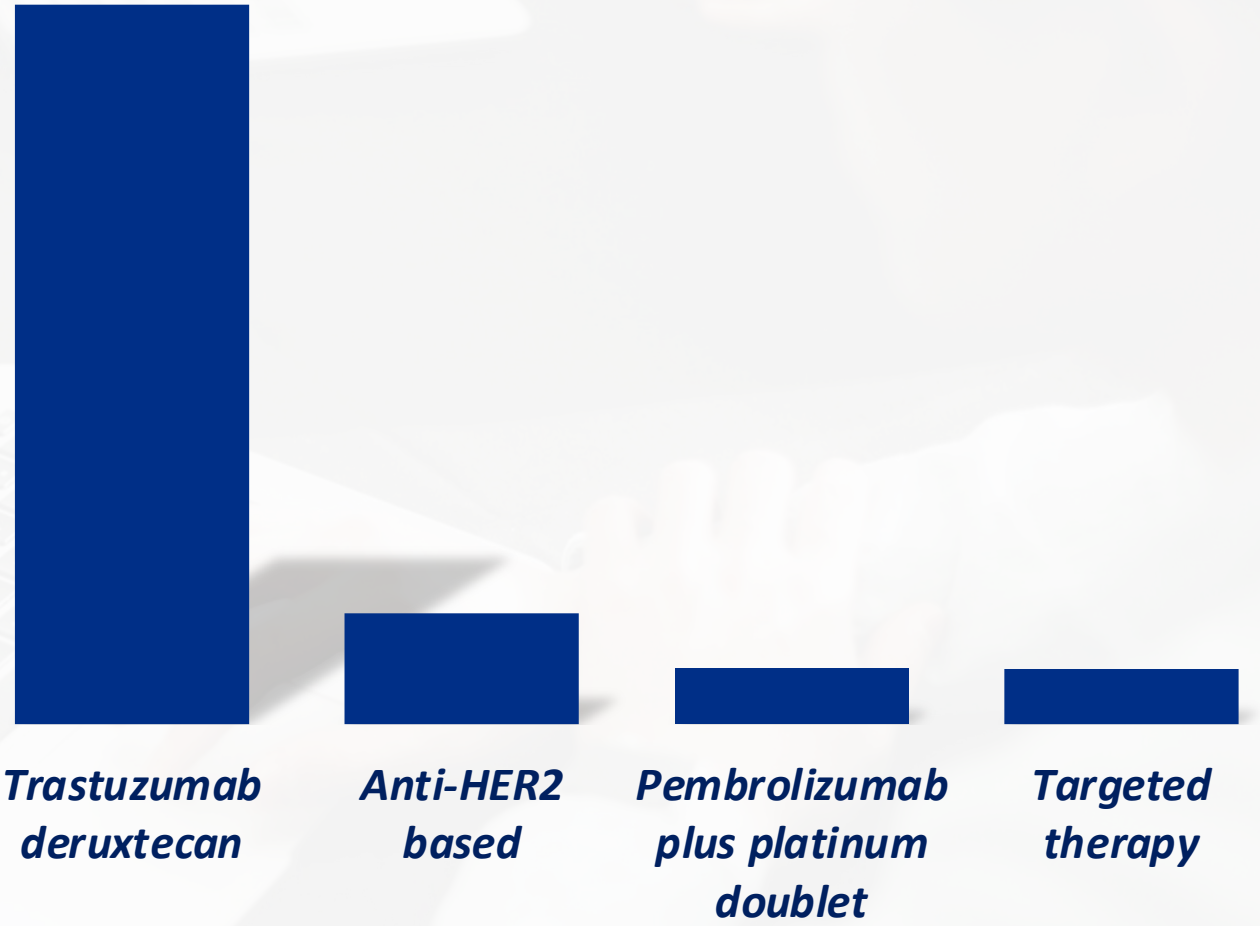
TP53 mutation

PD-L1 20%

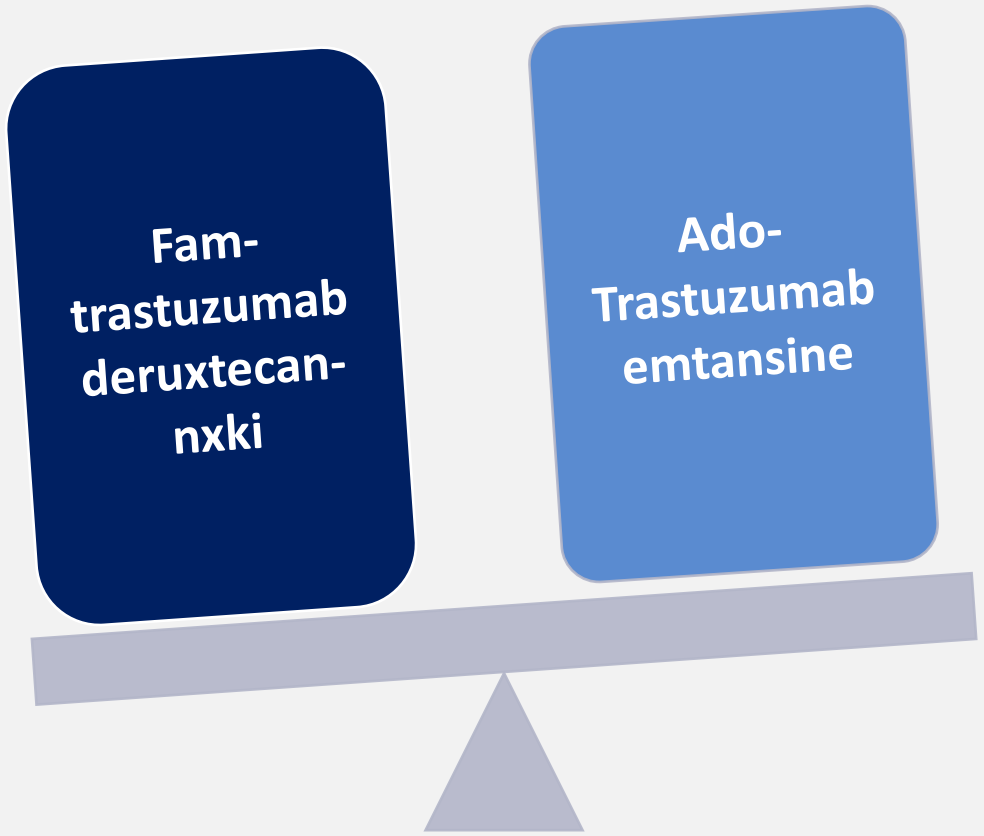
What treatment do you recommend?

Open-text Response Results from HCP Participants

What treatment do you recommend?



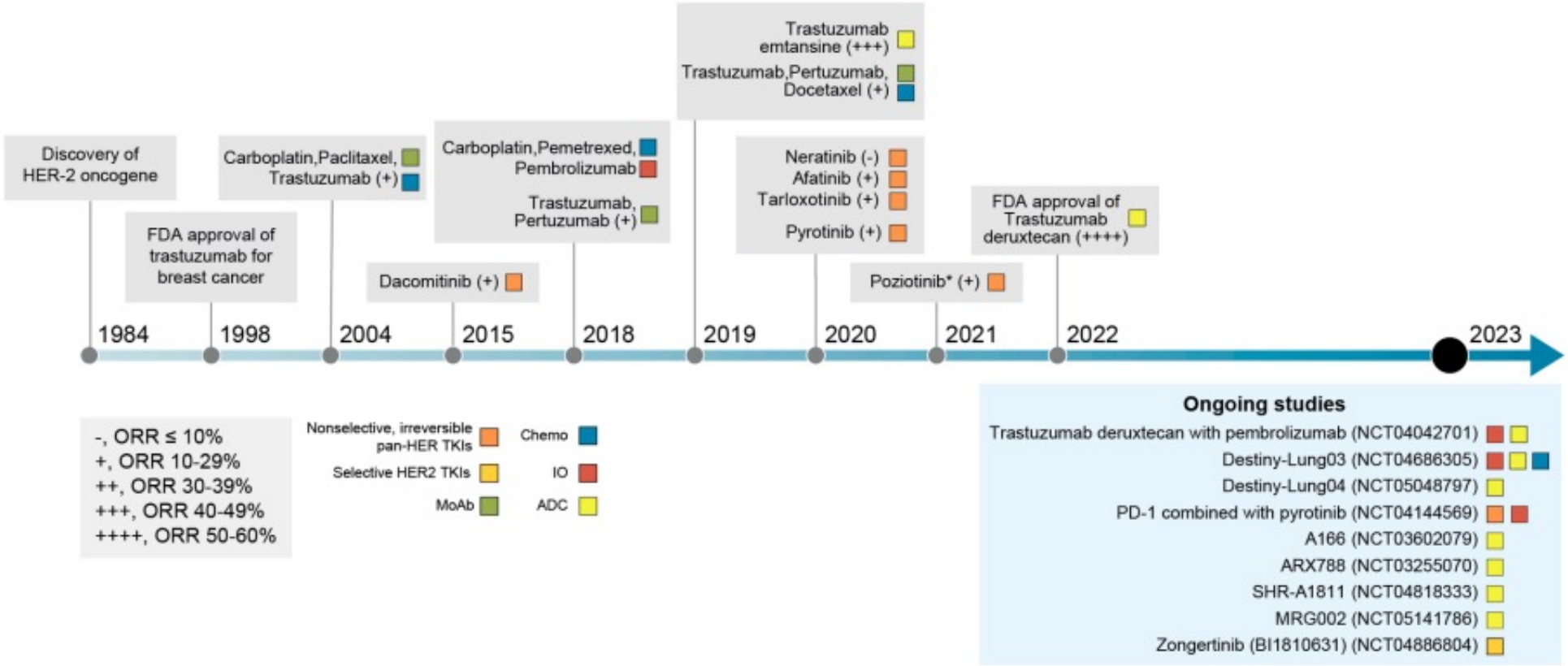
2L Metastatic Treatment Options



Choice of treatment

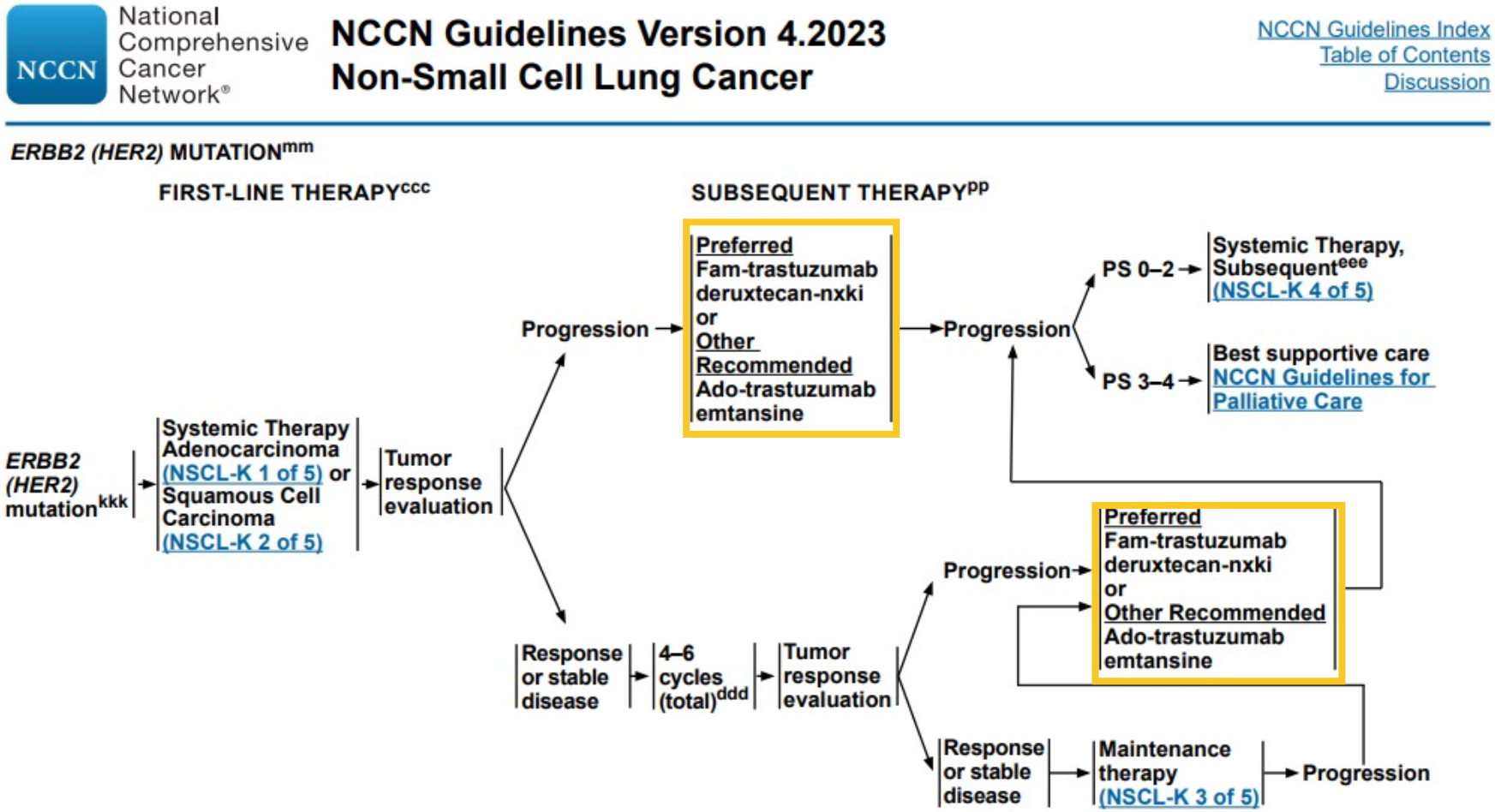
- No head-to-head comparisons between the agents
- NCCN Guidelines versus FDA approved indication
- Limited data to support sequencing of therapies

Anti-HER2 agents in HER2-mutated NSCLC



Nützinger et al., Lung Cancer 186 (2023) 107385

NCCN Guidelines for ERBB2 (HER2) Mutated NSCLC



STUDY DESIGN

Fam-Trastuzumab Deruxtecan in HER2-mutated NSCLC

DESTINY-Lung01: Multicenter, international, 2-cohort phase 2 trial

Key eligibility criteria

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation (for Cohort 2)[b]

Cohort 2: *HER2*-mutated T-DXd 6.4 mg/kg q3w

N = 42

Cohort 2 expansion: *HER2*-mutated T-DXd 6.4 mg/kg q3w

N = 49

Primary end point

- Confirmed ORR by ICR[d]

Secondary end points

- DOR
- PFS
- OS
- DCR
- Safety

Exploratory end point

- Biomarkers of response

Data cutoff: May 3, 2021

- 91 patients with *HER2*m NSCLC were enrolled and treated with T-DXd
- 15 patients (16.5%) remain on treatment to date
- 76 patients (83.5%) discontinued, primarily for progressive disease (37.4%) and adverse events (29.7%)

[a]Patients with asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy were allowed to enroll [b]*HER2* mutation documented solely from a liquid biopsy could not be used for enrolment [c]HER2 overexpression without known *HER2* mutation was assessed by local assessment of archival tissue and centrally confirmed [d]Per RECIST v1.1

DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

ESMO Congress 2021; Abstract LBA45; NEJM 2022; 386:241-251

KEY DATA

DESTINY-Lung01, HER2 Mutation

Confirmed ORR, Best Overall Response and DoR

	Patients (N = 91)
Confirmed ORR[a], n (%)	**50 (54.9)** (95% CI, 44.2-65.4)
Best overall response, n (%)	
CR	**1 (1.1)**
PR	**49 (53.8)**
SD	34 (37.4)
PD	3 (3.3)
Not evaluable	4 (4.4)
DCR, n (%)	**84 (92.3)** (95% CI, 84.8-96.9)
Median DoR, months	**9.3** (95% CI, 5.7-14.7)
Median follow up, months	13.1 (range, 0.7-29.1)

[a]Primary endpoint

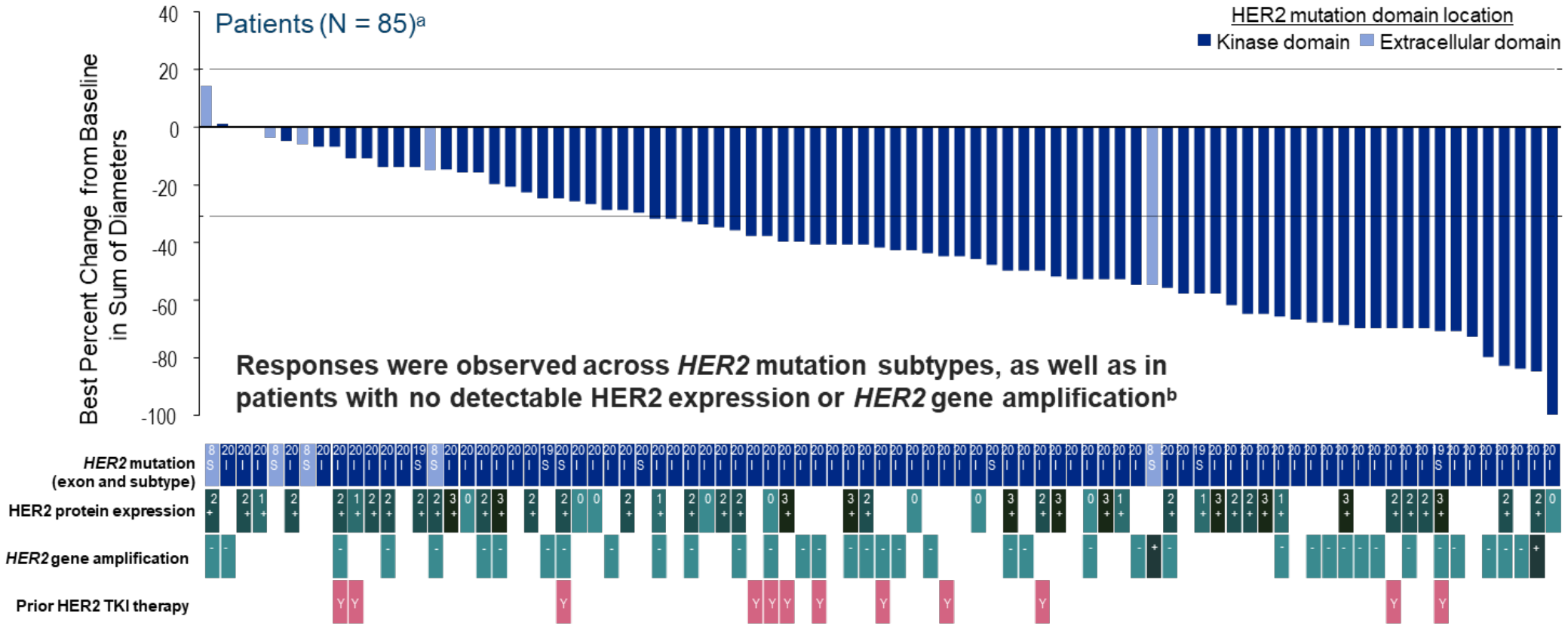
CR, complete response; DoR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

ESMO Congress 2021; Abstract LBA45; NEJM 2022; 386:241-251

KEY DATA

DESTINY-Lung01, HER2 Mutation

Best Percentage Change of Tumor Size From Baseline



[a]Best change in tumor size by ICR for 85 of 91 patients for whom baseline and postbaseline data were available. Baseline is last measurement taken before enrollment. [b]The Oncomine™ Dx Target Test (Thermo Fisher Scientific) was used to confirm local HER2 mutation status and to determine HER2 amplification status. HER2 protein expression status was determined by immunohistochemistry using a modified PATHWAY anti-HER2 (4B5) (Ventana Medical Systems, Inc.) assay. Shown is best (minimum) percentage change from baseline in the sum of diameters for all target lesions; (-), negative; (+), positive; I, insertion; N, no; S, substitution; Y, yes. Blank cells (except for the prior HER2 TKI therapy row) indicate pati ents whose tumor samples were not evaluable or assessed. The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression and the lower dashed line indicates a 30% decrease in tumor size (partial response).

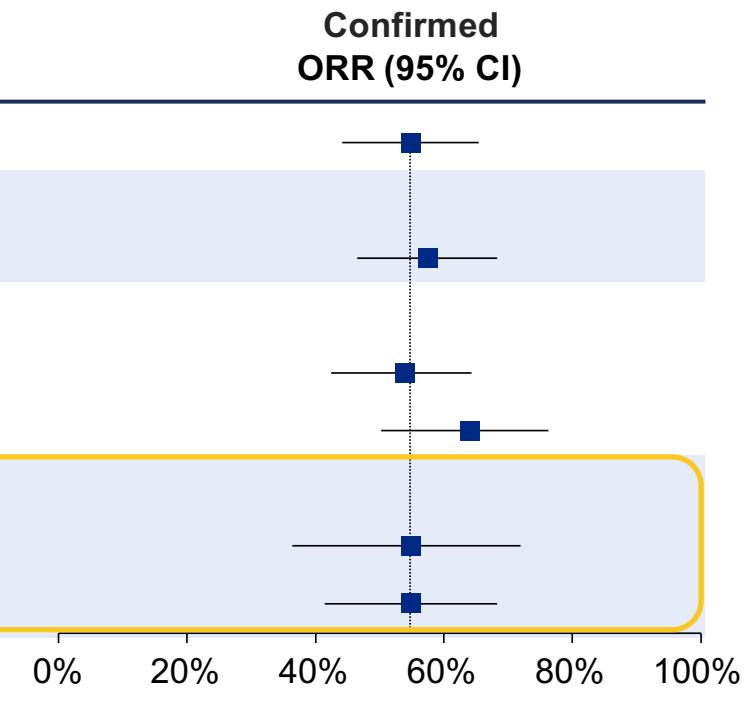
ESMO Congress 2021; Abstract LBA45; NEJM 2022; 386:241-251

KEY DATA

DESTINY-Lung01, HER2 Mutation

Response to T-DXd in Subgroups

	No. of Responders	Confirmed ORR (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-PD-(L)1 therapy[a]	**37/57**	**64.9 (51.1-77.1)**
Asymptomatic CNS metastasis at baseline[b]		
Yes	18/33	54.5 (36.4-71.9)
No	32/58	55.2 (41.5-68.3)



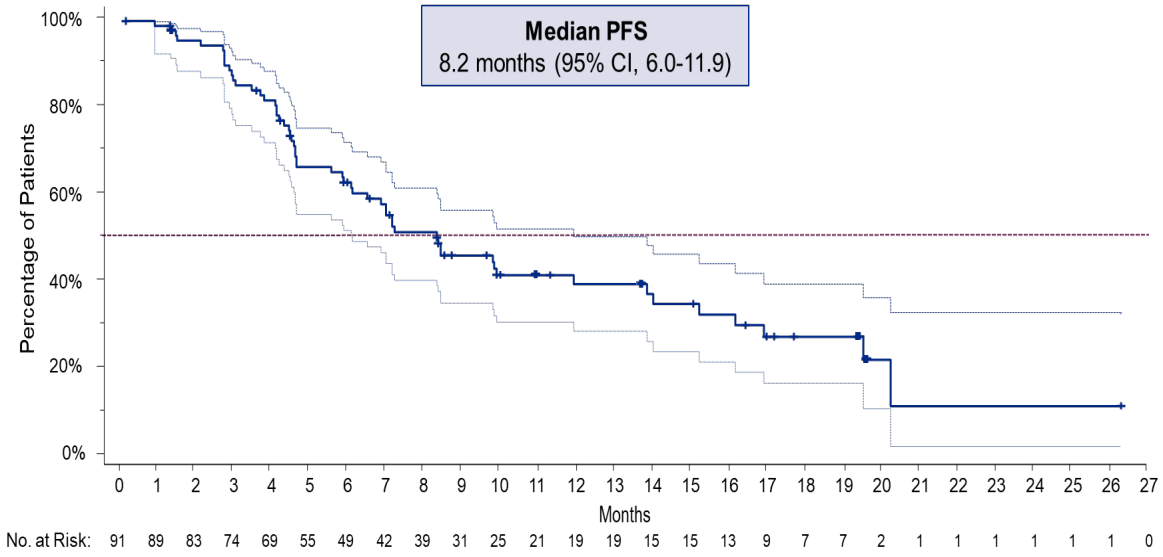
[a]Given separately or in combination
[b]Patients had asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy

ESMO Congress 2021; Abstract LBA45; NEJM 2022; 386:241-251

KEY DATA

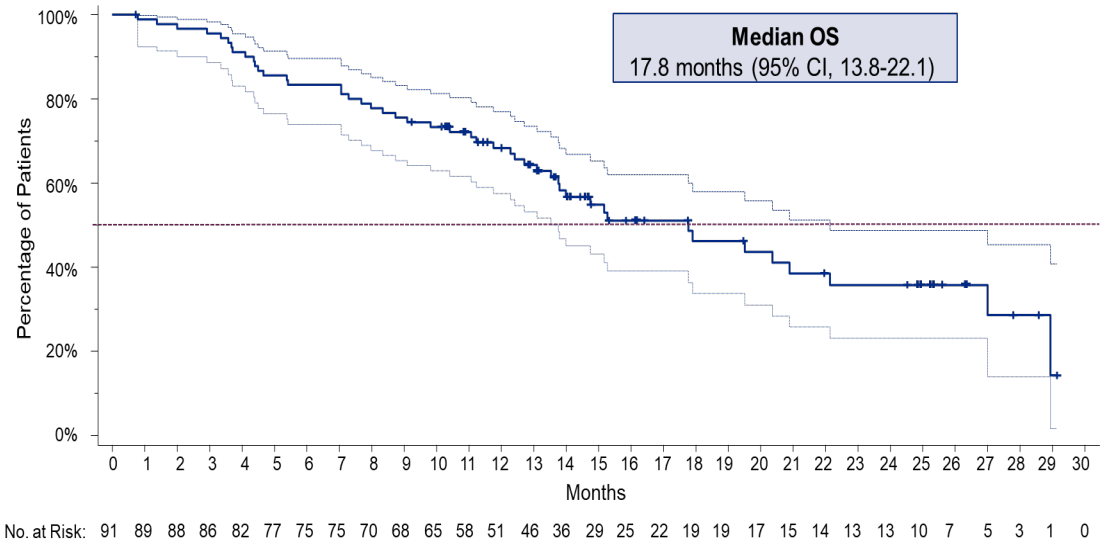
DESTINY-Lung01, HER2 Mutation

Progression-free Survival



Median follow-up was 13.1 months (range, 0.7-29.1)
PFS assessed by ICR using RECIST v1.1., the median was based on Kaplan-Meier estimate, and 95% CI for median was computed using the Brookmeyer-Crowley method, and dashed lines indicate the 95% CI. Of 91 patients, 41 had progressive disease and 15 had died by the data cutoff date. Data for 35 patients were censored as indicated by tick marks; patients were censored if they discontinued treatment.

Overall Survival



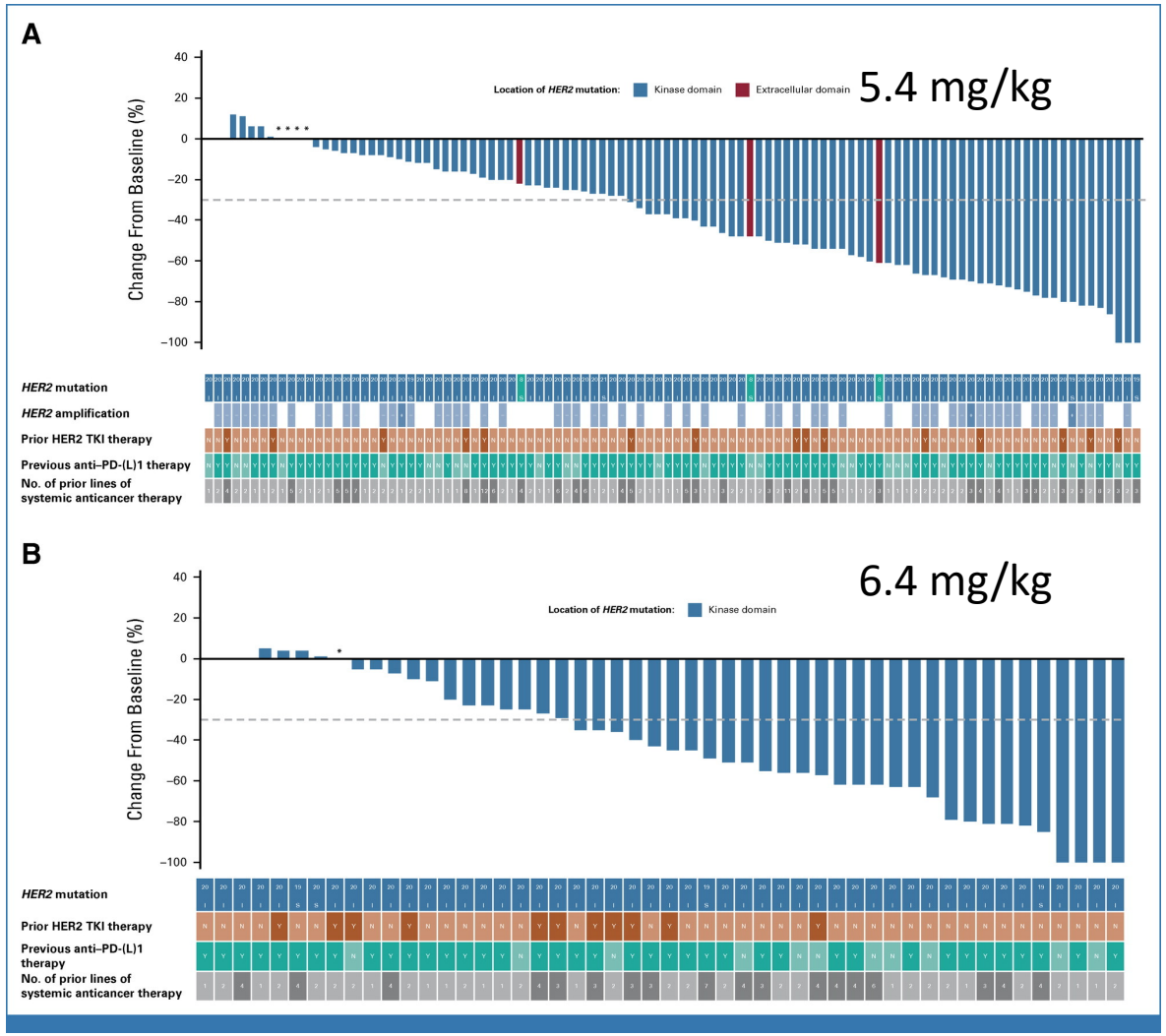
Median follow-up was 13.1 months (range, 0.7-29.1 months)
Dashed lines indicate the 95% CI. Of 91 patients, 47 had died by the data cutoff date. Data for 44 patients were censored as indicated by tick marks; patients were censored if they discontinued treatment.

ESMO Congress 2021; Abstract LBA45; NEJM 2022; 386:241-251

KEY DATA

DESTINY-Lung02, HER2 Mutation

Best Percentage Change of Tumor Size From Baseline



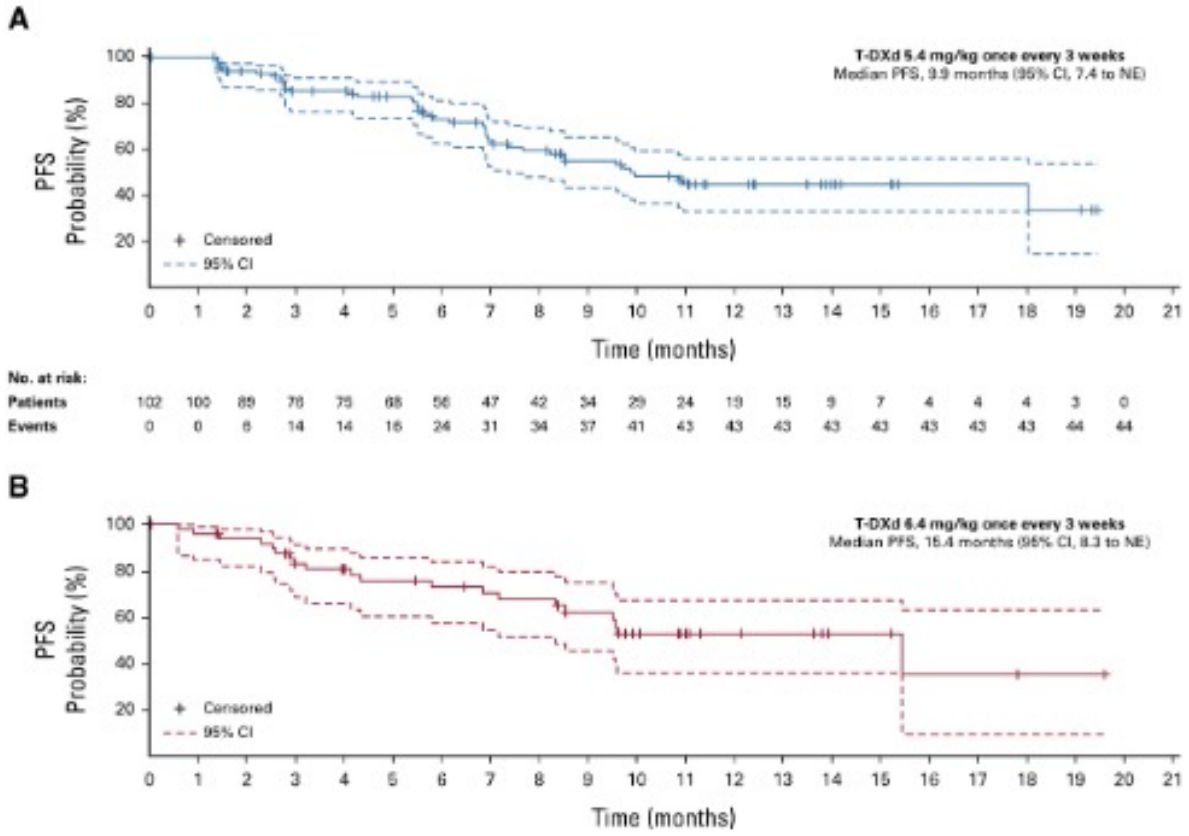
5.4 mg/kg T-DXd		6.4 mg/kg
ORR: 49%		ORR 56%
DCR: 93%		DCR: 92%
DOR: 16.8 m		DOR NE
ILD		
Gr 1/2:	10.9%	26%
Gr 3:	1%	-
Gr 5:	1%	2%

Goto K, et. al JCO 2023

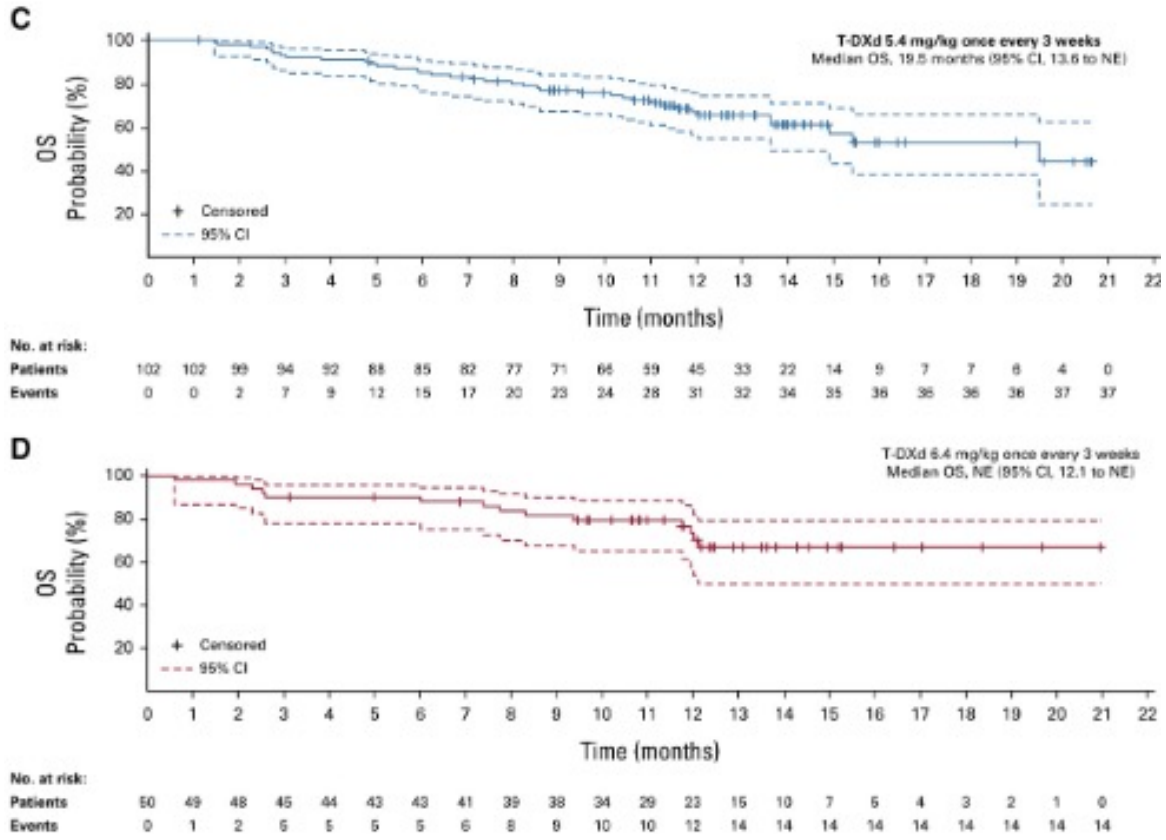
KEY DATA

DESTINY-Lung02, HER2 Mutation

Progression-free Survival



Overall Survival



Goto K, et. al JCO 2023

Site of Metastases:

- Bone
- Liver

- HER2 mutation in Exon 20

Treated with fam-trastuzumab deruxtecan

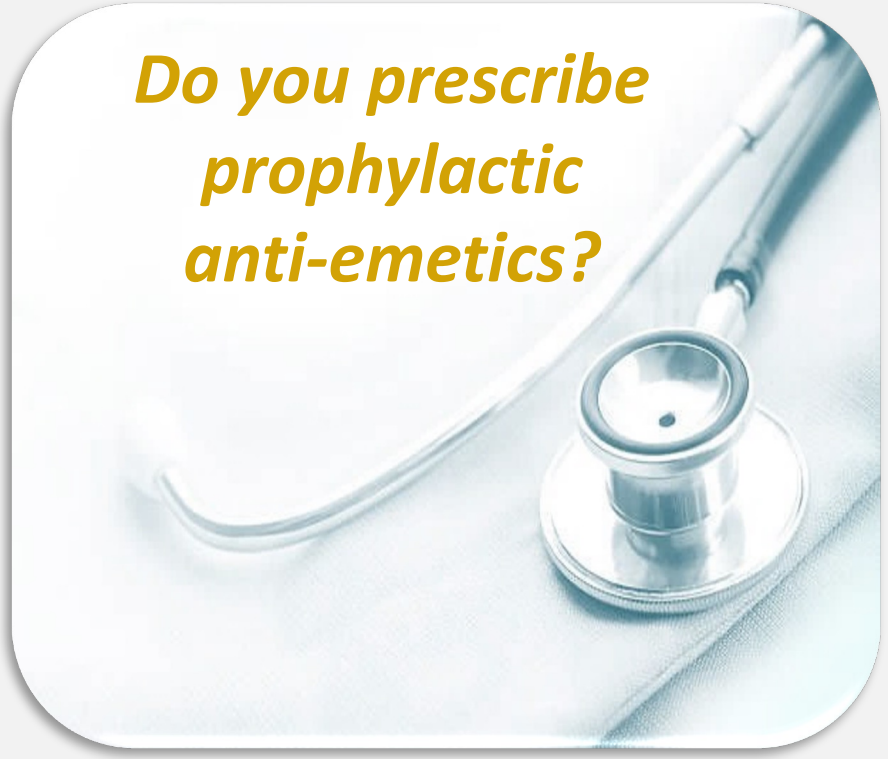
5.4 mg/kg Q 3 wk

Partial response (50% reduction in liver mets on CT) after 2 cycles

Grade 1 Nausea

Grade 2 Neutropenia

Do you prescribe prophylactic anti-emetics?



Open-text Response Results from HCP Participants

Do you prescribe prophylactic anti-emetics?

- *3 drugs*
- *High emetogenic regimen*
- *5-HT3*
- *Emend zofran compazine*
- *5HT3 plus dex*
- *Emend aloxi steroids*
- *Zofran, compazine alternating. If intractable, I add olanzapine*
- *NK-1, 5-HT3, dexamethasone*
- *H2b and NK-1*

Text size indicates frequency of response

NCCN Guidelines Version 2.2023
Antiemesis

NCCN Guidelines Index
Table of Contents
Discussion

EMETOGENIC POTENTIAL OF PARENTERAL ANTICANCER AGENTS

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[a]	• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4 • Carmustine >250 mg/m²	• Cisplatin • Cyclophosphamide >1500 mg/m² • Dacarbazine • Doxorubicin ≥60 mg/m² • Epirubicin >90 mg/m² • Fam-trastuzumab deruxtecan-nxki	• Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Melphalan ≥140 mg/m² • Sacituzumab govitecan-hziy • Streptozocin

High Emetic Risk

Treatment option A	Treatment option B	Treatment option C
• Olanzapine • NK1 receptor antagonist (RA) • 5-HT3 RA • Dexamethasone	• Olanzapine • Palonosetron • Dexamethasone	• NK1 RA • 5-HT3 RA • Dexamethasone

Moderate Emetic Risk

Treatment option D	Treatment option E	Treatment option F
• 5HT3-RA • Dexamethasone	• Olanzapine • Palonosetron • Dexamethasone	• NK1 RA • 5-HT3 RA • Dexamethasone

All treatment options are category 1 and should be started before anticancer therapy

ENHERTU PI: *moderately emetogenic* – nausea occurred in 76% all grades, Grade 3-4 in 7% of patients

Metastatic Progression:

On T-DXd, has partial response to therapy for 11 months

Progression in the liver: enlarging mets and new mets

2 new bone mets on PET

ECOG remains PS 1

Some weight loss

What treatment would you recommend next?

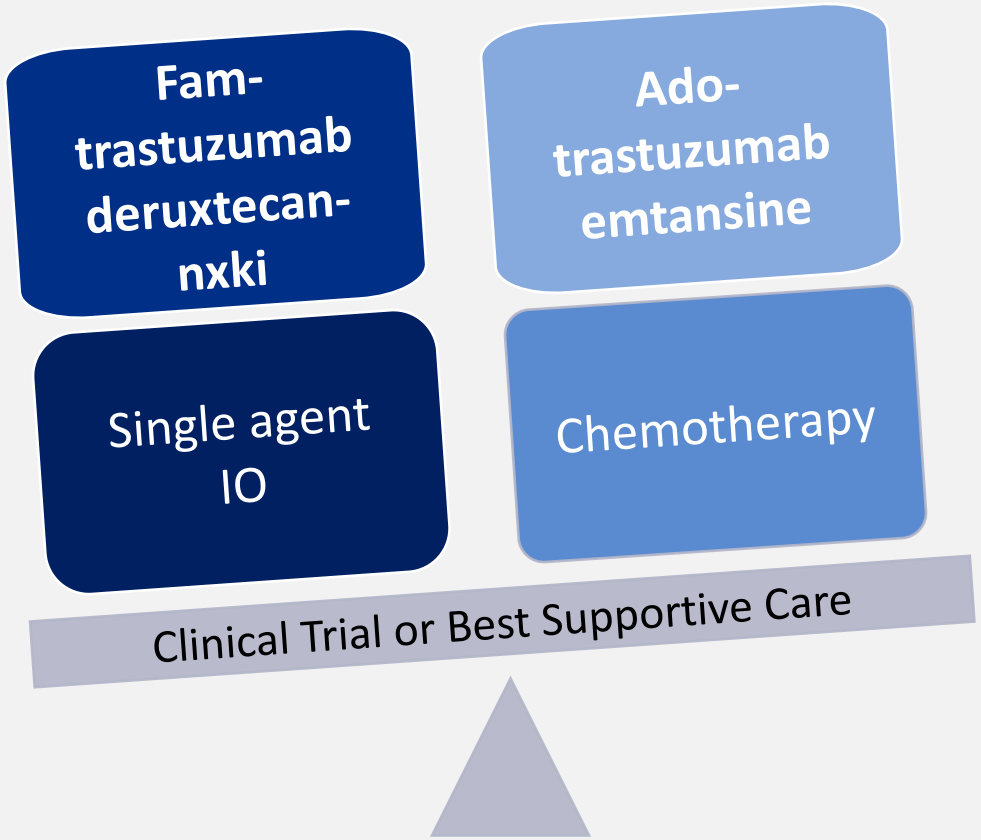
Open-text Response Results from HCP Participants

What treatment would you recommend next?

- ***Docetaxel / ramucirumab***
- ***TDM-1***
- ***Chemotherapy***
- ***Liquid Bx, then Taxotere / ramucirumab***
- ***Doublet vs single agent, to include a taxane***
- ***Taxotere***
- ***Docetaxel***
- ***Tucatinib perhaps***
- ***Clinical trial & antiresorptive agent***
- ***Clinical trial or docetaxel***
- ***Clinical trial after testing liquid Bx***
- ***Clinical trial***

Text size indicates frequency of response

3L Metastatic Treatment Options



Choice of treatment

- No head-to-head comparisons between the agents
- Differences in the study populations
- Limited data to support sequencing of anti-HER2 therapies

Program Sponsor