Safety profile and side effect management of ADCs treatment

柯皓文醫師

林口長庚 胸腔內科系 肺腫瘤科

How-Wen Ko, MD, PhD*

Div. Pulmonary Oncology & bronchoscopy, Dept. Thoracic Medicine

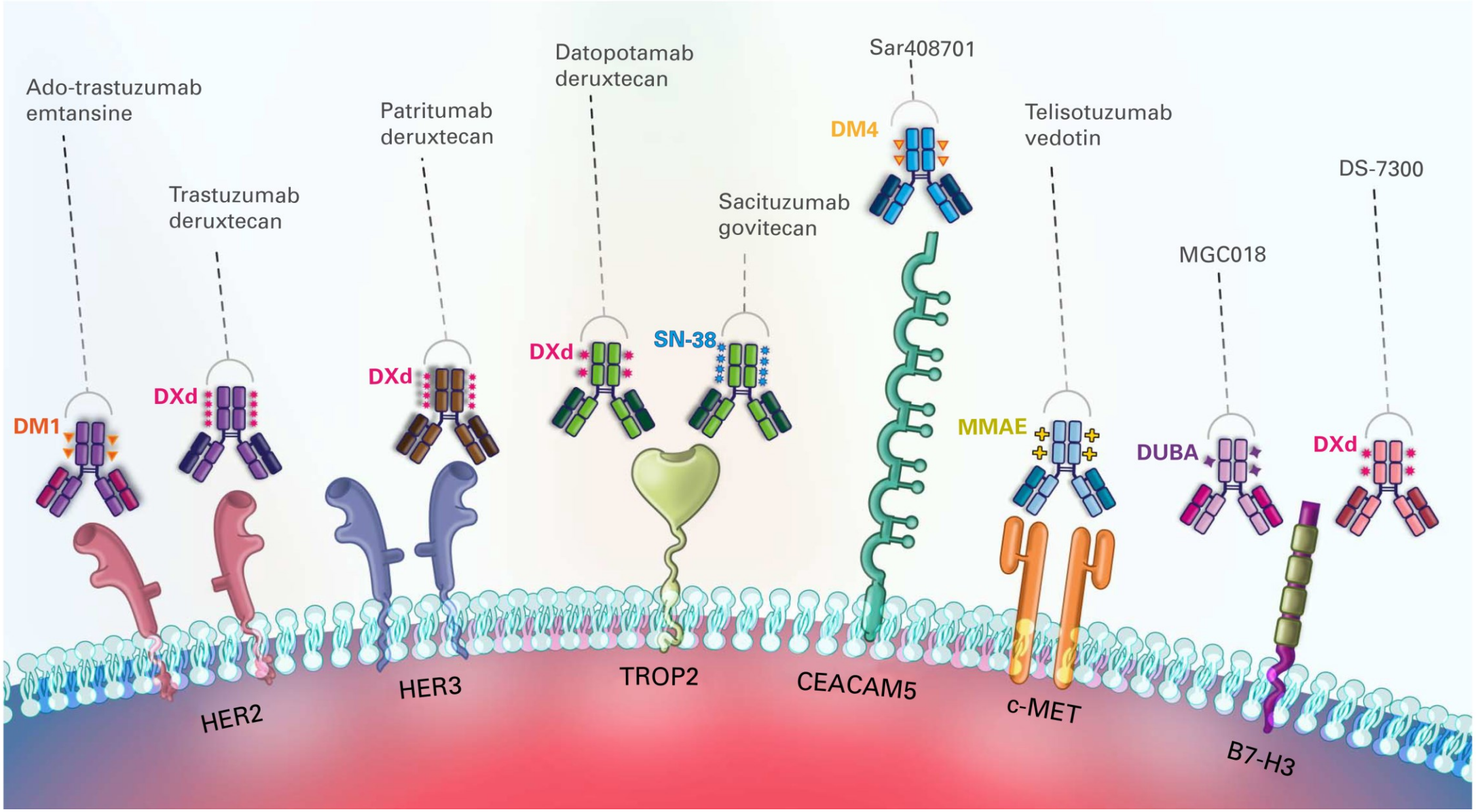
Chang-Gung Memorial Hospital, Linkou Medical Center

*University of Texas M.D. Anderson Cancer Center

Outline

- Brief overview of ADCs in lung cancer treatment:
  - ADCs in HER2m-mNSCLC
- Safety profile and side effect management of ADCs treatment
  - ILD/pneumonitis management
- Case experience

Overview of ADCs for lung cancer

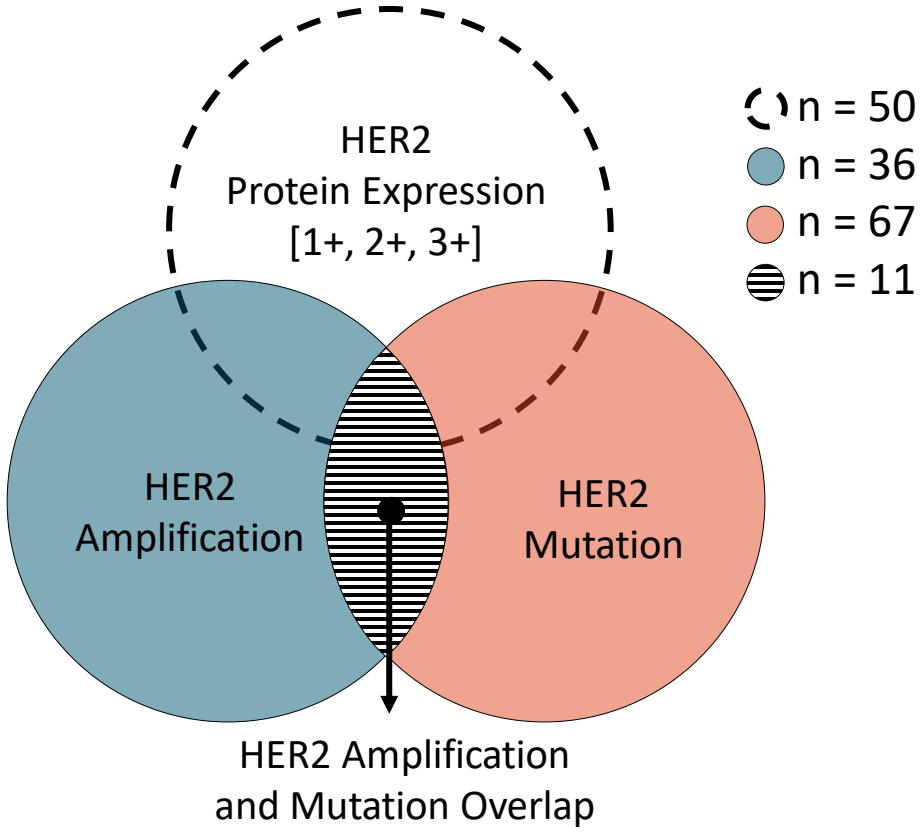


Passaro et al. J Clin Oncol. 2023 May 24

Overview of ADCs for lung cancer

- ADC application in lung cancer treatment:
  - **HER2**
  - TROP2
  - cMET
  - HER3

HER2 alteration in NSCLC



- Not all tumors with HER2 protein expression have *HER2* gene amplification.
- *HER2* mutation and *HER2* amplification are distinct entities with only ~10% overlap.

	Frequency
Overexpression (IHC 2+ and 3+)	15%-30%
Overexpression (IHC 3+)	2%-6%
Amplification	2%-6%
Mutations	1%-5%

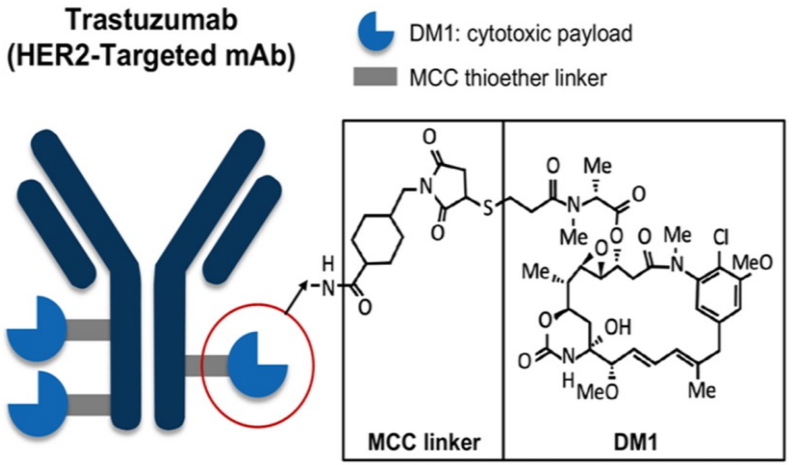
Nakamura. Int J Cancer. 2003;103:61; Mazières. JCO. 2013;31:1997; Li. J Thorac Oncol. 2016;11:414.

HER2m-mNSCLC

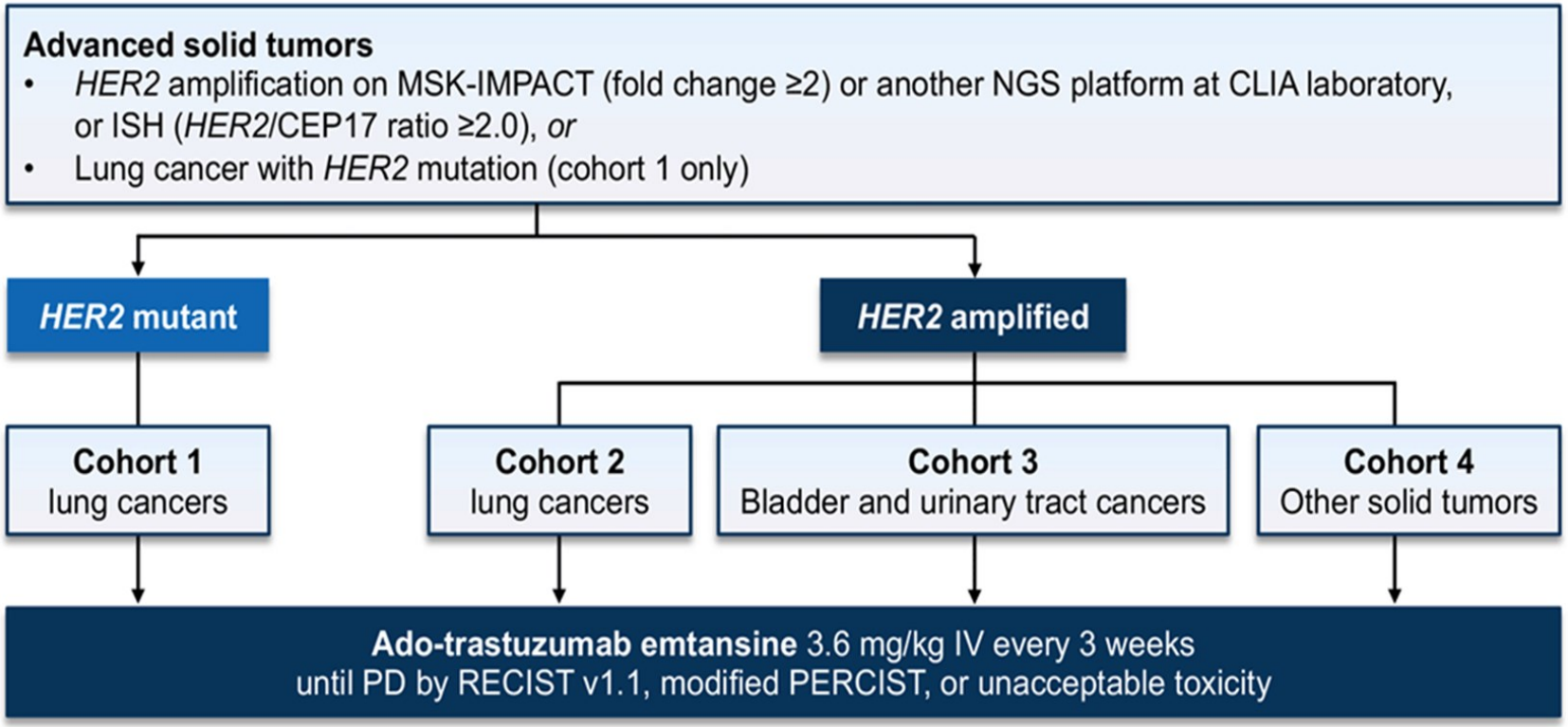
- ADCs:
  - T-DM1 (Ado-Trastuzumab Emtansine)
  - T-Dxd (Trastuzumab Deruxtecan)

T-DM1

Ado-Trastuzumab Emtansine (T-DM1) for Patients With HER2-Amplified or Mutant Cancer



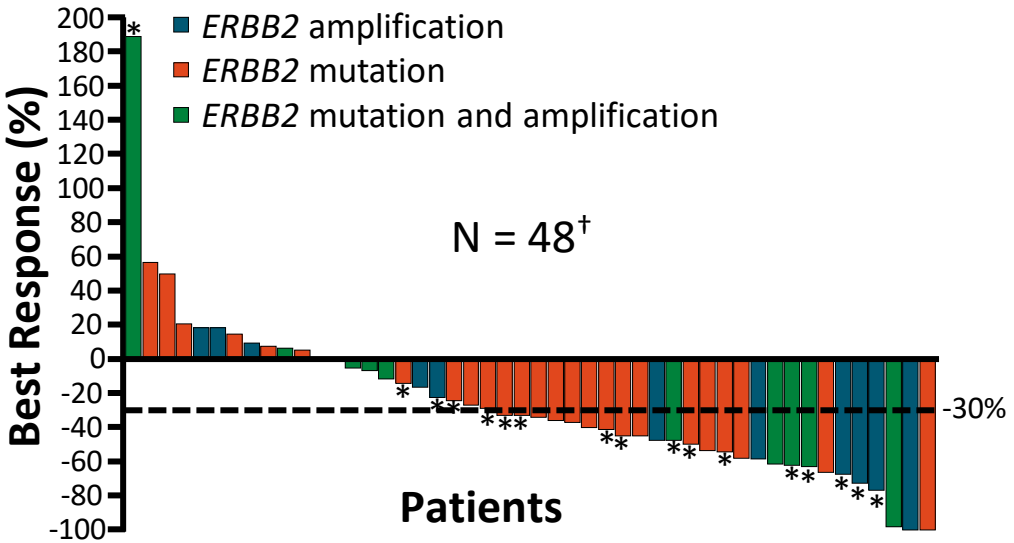
mAb: trastuzumab
Linker: non-cleavable
Payload: DM1 (anti-microtubule)
DAR: 3

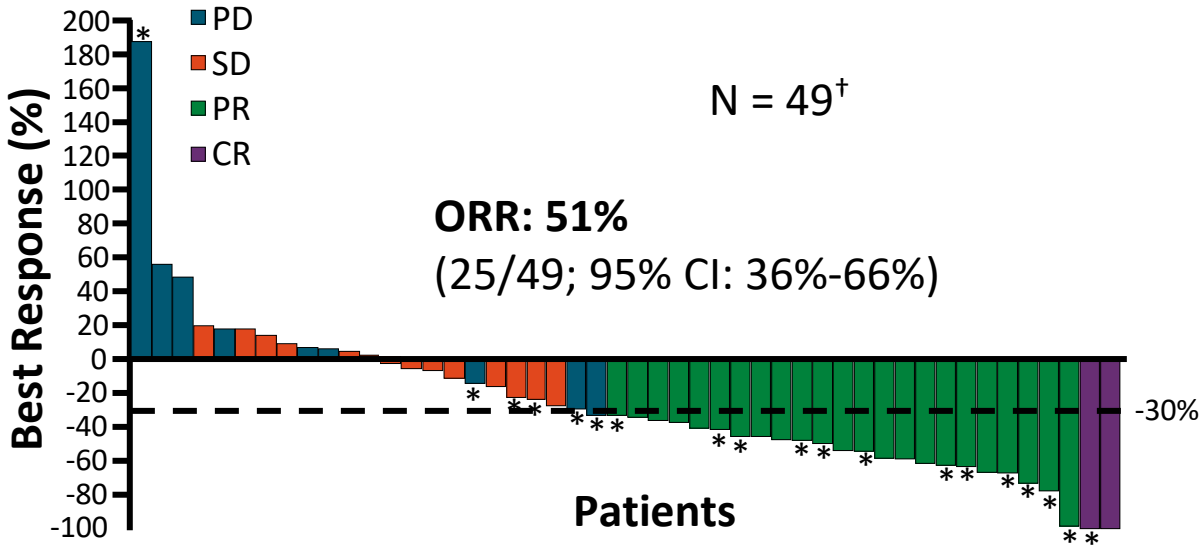


Ado-trastuzumab emtansine PI. Li. JCO. 2018;36:2532. Li. Cancer Discov. 2020;10:674.

T-DM1

Clinical Activity of T-DM1: HER2-Mutated or HER2-Amplified NSCLC





ORR:

- **50%** (14/28; 95% CI: 31%-69%) for *ERBB2*-mutant patients
- **50%** (5/10; 95% CI: 19%-81%) for concurrently *ERBB2*-mutant and *ERBB2*-amplified patients
- **55%** (6/11; 95% CI: 23%-83%) for *ERBB2*-amplified patients

Overall RR: 51%

Median DoR: 4.4 mo

Median PFS: 5.0 mo

*Indicates response per modified PET Response Criteria in Solid Tumors (PERCIST). †Excludes n = 1 without measurable disease.

Li. Cancer Discov. 2020;10:674.

T-DM1

Treatment-Related Adverse Events of T-DM1 in NSCLC

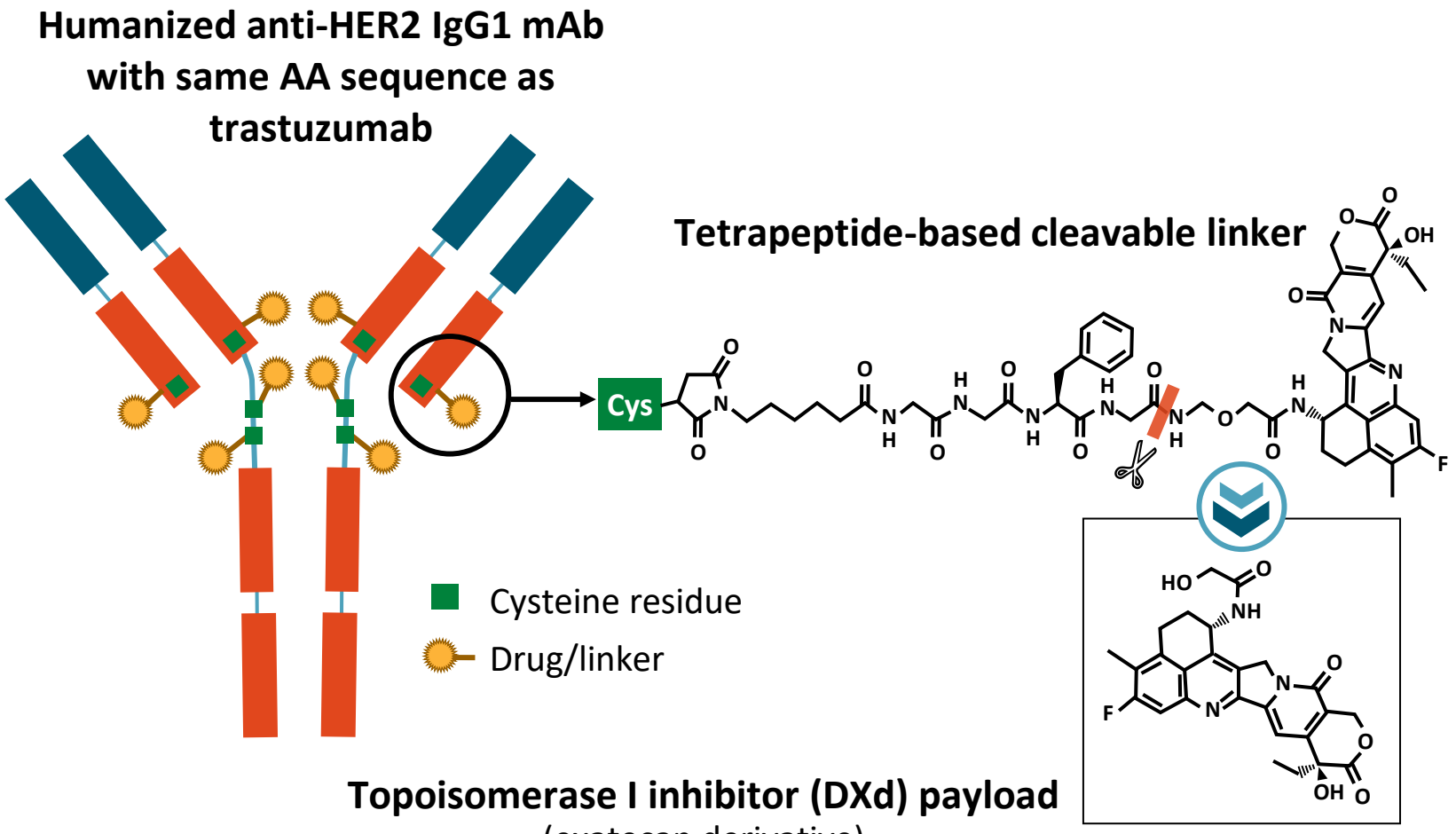
AE, n (%)*†	Patients			
	Grade 1	Grade 2	Grade 3	Total
Elevated AST or ALT	28 (57)	3 (6)	--	31 (63)
Thrombocytopenia	13 (27)	1 (2)	1 (2)	15 (31)
Fatigue	6 (12)	2 (4)	--	8 (16)
Nausea	14 (29)	--	--	14 (29)
Infusion reaction	2 (4)	5 (10)	--	7 (14)
Anorexia	3 (6)	2 (4)	--	5 (10)
Anemia	1 (1)	3 (6)	1 (2)	5 (10)

*According to Common Terminology Criteria for Adverse Events Version 4.1. †No grade 4 or 5 AEs.

Li. Cancer Discov. 2020;10:674.

T-DXd

HER2-Targeted ADC: Trastuzumab Deruxtecan (T-DXd)



- mAb: trastuzumab
- Linker: cleavable
- Payload: Deruxtecan (T-DXd), Topo I inhibitor
- DAR: ~8
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

T-DXd

DESTINY-Lung01: in *HER2*-Mutated/Overexpressing Metastatic NSCLC

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

→ **Cohort 1[c]** (n = 49)
HER2 overexpressing
(IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg Q3W

Cohort 1a[c] (n = 41)
HER2 overexpressing
(IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg Q3W

→ **Cohort 2** (n = 42)
***HER2* mutated**
T-DXd 6.4 mg/kg Q3W

Cohort 2 (n = 49)
***HER2* mutated**
T-DXd 6.4 mg/kg Q3W

- **Primary endpoint:** confirmed ORR by ICR[d]
- **Secondary endpoints:** DOR, PFS, OS, DCR, and safety
- **Exploratory endpoint:** biomarkers of response

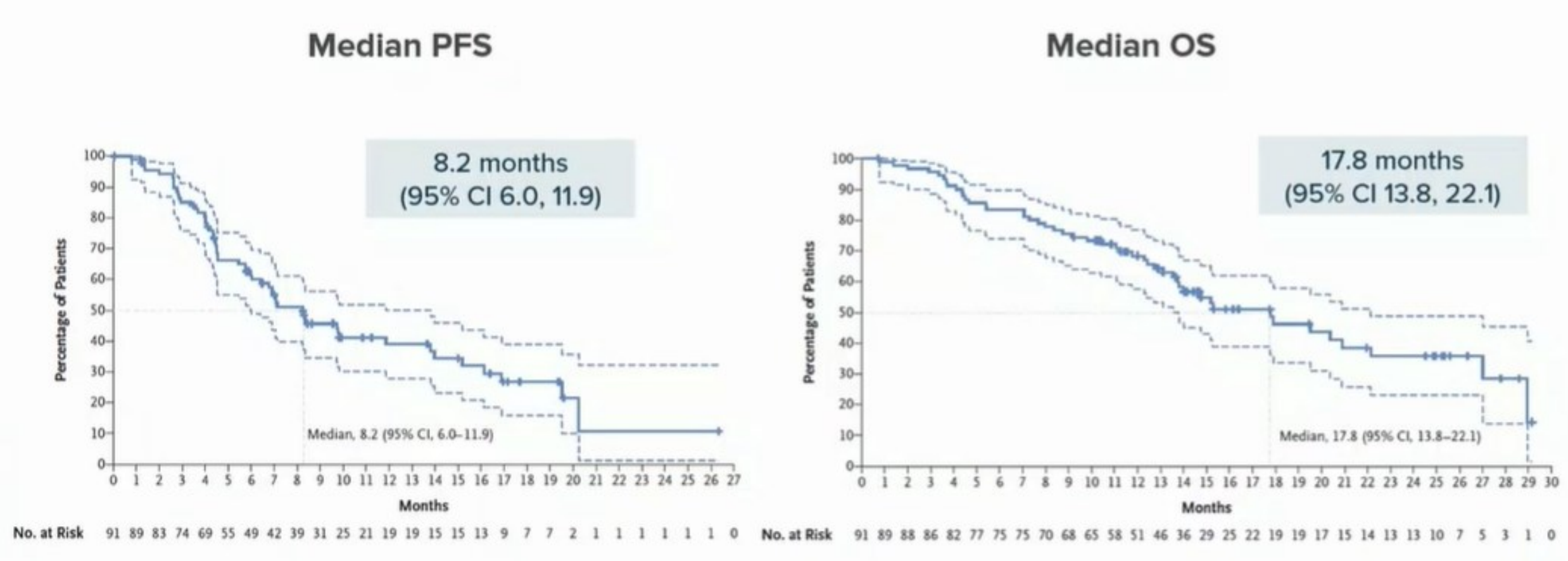
Data cutoff: May 3, 2021
- 91 pts with *HER2*-mutated NSCLC
- 15 pts (16.5%) remain on treatment
- 76 pts (83.5%) discontinued, primarily for PD and AEs

[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 enrollment. [c] HER2 overexpression without known *HER2* mutation was assessed by local assessment of archival tissue and centrally confirmed.
[d] Per RECIST v1.1.

1.Smit E et al. J Clin Oncol. 2020;38(15_suppl):9504; 2.Li BT et al. N Engl J Med. 2022;386:241-251

T-DXd

DESTINY-Lung01: in *HER2*-Mutated Metastatic NSCLC



LI BT et al. N Engl J Med. 2022;386:241-251

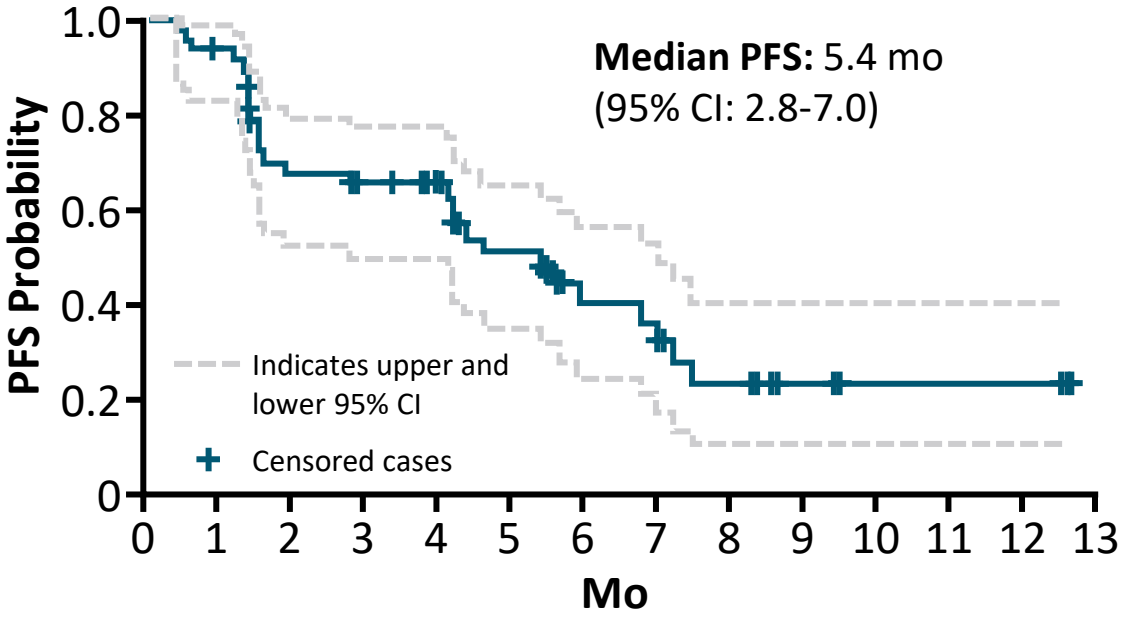
T-DXd

DESTINY-Lung01: in *HER2*-Overexpressing Metastatic NSCLC

- **Confirmed ORR: 24.5% (95% CI: 13.3% to 38.9%)**

HER2 mutant (cohort 2):
- ORR: 54.9%
- mPFS: 8.2 mo
- mOS: 17.8 mo

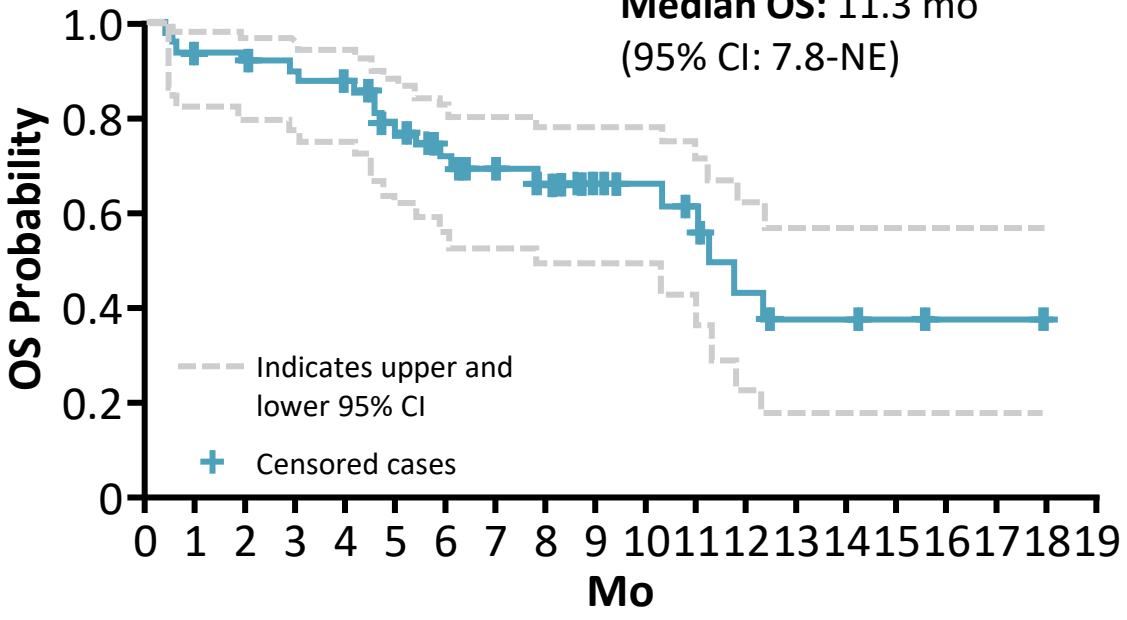
PFS (n = 49)



Patients at Risk, n

49	45	29	26	23	17	10	7	5	3	2	2	2	0

OS (n = 49)



Patients at Risk, n

49	45	44	42	41	33	27	23	20	16	13	11	7	4	4	3	2	2	2	0

Nakagawa. WCLC 2020. Abstr OA04.05.

T-DXd

DESTINY-Lung01: in *HER2*-Overexpressing Metastatic NSCLC

Event, %	Cohort 1 (6.4 mg/kg) n = 49	Cohort 1a (5.4 mg/kg) n = 41
Any-grade TEAEs	100	100
Drug related	89.8	92.7
Grade ≥3 TEAEs	81.6	51.2
Drug related	53.1	22
TEAEs associated with drug discontinuation	26.5	17.1
Drug related	16.3	7.3
TEAEs associated with dose reduction	36.7	17.1
Drug related	34.7	17.1
TEAEs associated with drug interruption	49	24.4
Drug related	34.4	9.8
TEAEs associated with death	20.4	17.1
Drug related	2	0

- Independently adjudicated drug-related ILD of any grade occurred in 20.4% and 4.9% of patients in cohorts 1 and 1a, respectively

Smit E et al. ESMO 2022 Abstract 975P

T-DXd

DESTINY-Lung01: in *HER2*-Mutated Metastatic NSCLC

Safety Outcome	T-DXd (N = 91)
Drug-related TEAE, n (%)	88 (97)
▪ Grade ≥ 3	42 (46)
▪ Serious	18 (20)
Drug-related TEAE outcomes, n (%)	
▪ Discontinuation	23 (25)
▪ Dose reduction	31 (34)
▪ Death	2 (2)
Median treatment duration, mo (range)	6.9 (0.7-26.4)

- Grade 5 events deemed therapy related: n = 1 pneumonitis/ILD; n =1 ILD

Drug-Related TEAEs Reported in ≥20% of Patients, n (%)	T-DXd (N = 91)	
	Any Grade	Grade ≥3
Nausea	66 (73)	8 (9)
Fatigue	48 (53)	6 (7)
Alopecia	42 (46)	0
Vomiting	36 (40)	3 (3)
Neutropenia	32 (35)	17 (19)
Anemia	30 (33)	9 (10)
Diarrhea	29 (32)	3 (3)
Deceased appetite	27 (30)	0
Leukopenia	21 (23)	4 (4)
Constipation	20 (22)	0

Li. ESMO 2021. Abstr LBA45. Li. NEJM. 2022;386:241.

Slide credit: clinicaloptions.com

DESTINY-Lung02

Blinded, randomized, multicenter, international, noncomparative, phase 2 trial (NCT04644237)

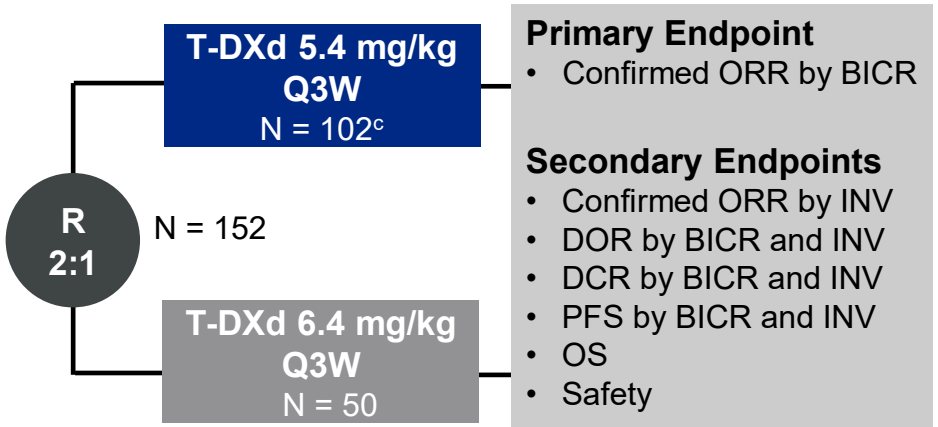
Key Eligibility Criteria[a]

- Metastatic *HER2*-mutant[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:

- Prior anti–PD-(L)1 treatment

Study Design



Primary Endpoint

- Confirmed ORR by BICR

Secondary Endpoints

- Confirmed ORR by INV
- DOR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and staff were blinded to the dose level

Primary analysis data cutoff: 23 December 2022

Statistical Considerations

- Statistical hypothesis testing for the primary analysis was performed by comparing the lower limit of the 95% Clopper-Pearson CI of confirmed ORR with the benchmark ORR of 26.4% (upper limit of the ORR 95% CI in the ramucirumab-plus-docetaxel arm of the REVEL trial)
- The study was not powered to statistically compare between arms

[a]Patients with stable baseline brain metastases (asymptomatic; not requiring corticosteroid or anticonvulsant treatment) were eligible. [b]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment. [c]1 patient randomly assigned to the T-DXd 5.4 mg/kg arm did not receive treatment as the patient discontinued due to COVID-19 before cycle 1 day 1.
2L+, second line or later; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *HER2*m, human epidermal growth factor receptor 2-mutant; INV, investigator assessment; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; T-DXd, trastuzumab deruxtecan.

DESTINY-Lung02: Systemic Efficacy, brain met vs not

Efficacy/safety outcome	T-DXd 5.4 mg/kg DL-02		Pooled T-DXd 6.4 mg/kg DL-01 *HER2*m/DL-02	
	BM n = 32	Non-BM n = 70	BM n = 54	Non-BM n = 87
Systemic cORR, n (%)[a]	15 (46.9)	35 (50.0)	27 (50.0)	51 (58.6)
95% CI[b]	29.1-65.3	37.8-62.2	36.1-63.9	47.6-69.1
DCR, n (%)[a]	29 (90.6)	66 (94.3)	50 (92.6)	80 (92.0)
95% CI[b]	75.0-98.0	86.0-98.4	82.1-97.9	84.1-96.7
DoR, median, months[c]	4.6	16.8	7.2	14.1
95% CI	4.2-9.5	8.7-NE	5.3-NE	9.3-NE
Sites of progression, n (%)				
Intracranial only	3 (9.4)	0	8 (14.8)	0
Extracranial only	6 (18.8)	14 (20.0)	9 (16.7)	23 (26.4)
Both	3 (9.4)	0	0	2 (2.3)
Missing	1 (3.1)	1 (1.4)	5 (9.3)	10 (11.5)
Median PFS, months	7.1	18.0	7.1	11.9
95% CI	5.5-9.7	8.5-NE	4.5-9.6	7.2-16.1
Median OS, months	13.6	19.5	13.8	27.9
95% CI	9.4-NE	14.9-NE	11.1-19.5	17.8-NE
Grade ≥3 TEAE, n (%)	20 (64.5)[d]	33 (47.1)	41 (75.9)	55 (63.2)
Drug related	12 (38.7)[d]	27 (38.6)	32 (59.3)	39 (44.8)

<u>T-DXd 5.4 mg/kg Arm</u>:

mDOR: 16.8 mo

mPFS: 9.9 mo

mOS: 19.5 mo

Daiichi-Sankyo | AstraZeneca

DESTINY-Lung02

Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
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)

Most adjudicated drug-related ILD events were low grade

All potential ILD/pneumonitis cases by DCO have been adjudicated. [a]The safety analysis set included all randomly assigned patients who received ≥1 dose of study drug.
DCO, data cut off; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

Safety profile and side effect management of ADCs treatment

Overview of the Studied Doses for T-DXd in Lung Cancer and Colorectal Cancer

Lung[1]

5.4 and ~~6.4 mg/kg*~~

- T-DXd is currently under investigation for the treatment of patients with non-small cell lung cancer

Colorectal[2]

5.4 and 6.4 mg/kg*

- T-DXd is currently under investigation for the treatment of patients with colorectal cancer

***This is an investigational dose for investigational tumors.**
It has currently not been evaluated by any global regulatory authorities.

HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.

1. Li BT, et al. *N Engl J Med.* 2021. 2. Siena S, et al. *Lancet Oncol.* 2021;22:779-789.

Daiichi-Sankyo | AstraZeneca

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Overview of the Recommended Dose for T-DXd

Breast[1,2]

5.4 mg/kg

T-DXd is indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting*

Gastric[3]

6.4 mg/kg

T-DXd is indicated for the treatment of adult patients with:

- Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen*

***Please check local regulations for approval status and exact indication per region**

HER2, human 2; T-DXd, trastuzumab deruxtecan.

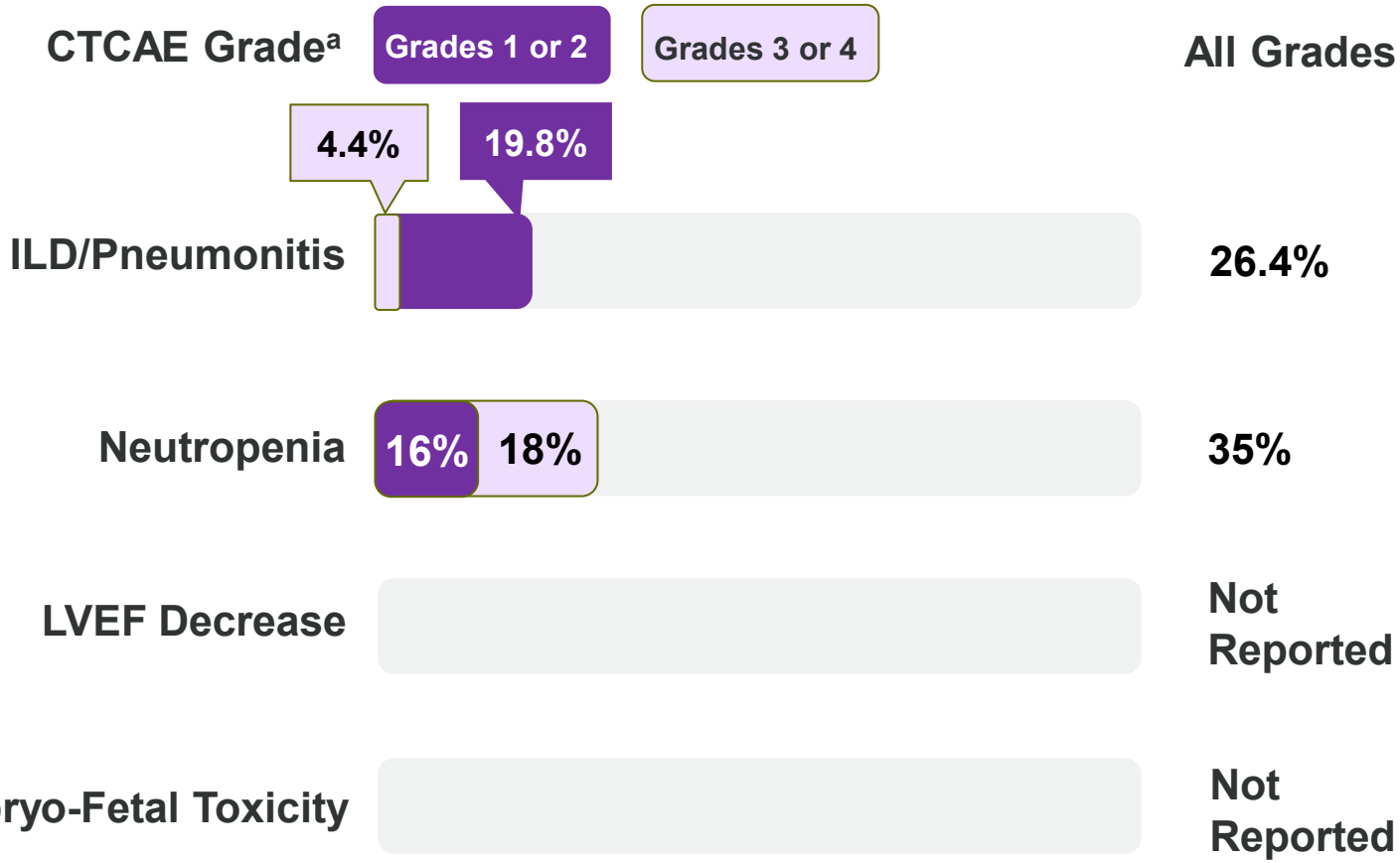
1. Modi S, et al. *N Engl J Med*. 2020;382(7epidermal growth factor receptor):610-621. 2. Tamura K et al. *Lancet Oncol*. 2019; 20:816-26. 3. Shitara K, et al. *N Engl J Med*. 2020;382(25):2419-2430.

Daiichi-Sankyo | AstraZeneca

TW-20504 ENH 7/13/2022, DSTW-MA-TDXd-08/2022, AE

Warnings & Precautions: ILD/Pneumonitis

Adverse Reactions of Special Interest Reported Among Patients With *HER2* Mutated NSCLC (Cohort 2) Receiving T-DXd 6.4 mg/kg in DESTINY-Lung01 (n = 91)[1]



All Grades:

26.4%

35%

Not Reported

Not Reported

This is an investigational dose for an investigational tumor.

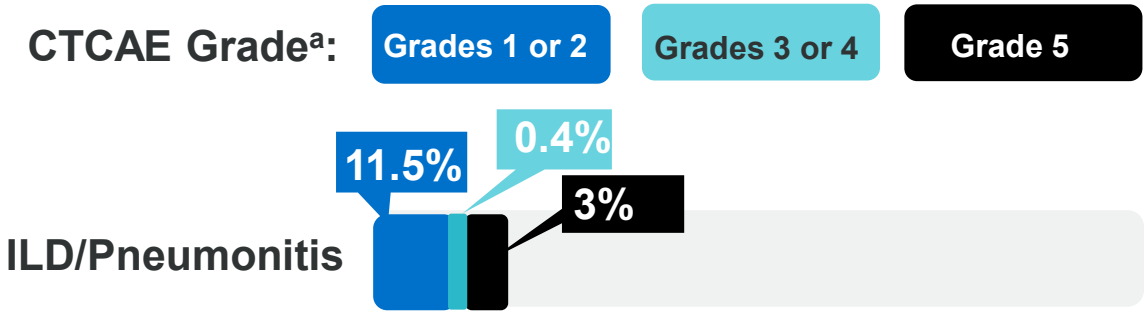
[a] NCI-CTCAE v.4.03.

CTCAE, Common Terminology Criteria for Adverse Events; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

1. Li BT, et al. *NEJM*. 2021.

Data cutoff: May 3, 2021

Adverse Reactions of Special Interest and Time to Onset Reported Among Patients With mBC Receiving T-DXd 5.4 mg/kg in a Pooled Analysis (N=234)



	All Grades:	Median Time to Onset in Patients Treated with T-DXd
ILD/Pneumonitis	15%	5.5 Months (Range: 1.2-20.8 Months)
Neutropenia[b]	32.5%	1.8 Months (Range: 0.3-18 Months)
LVEF Decrease	1.3%	Not Available
Embryo-Fetal Toxicity	Not Reported	Not Available

[a] NCI-CTCAE v.4.03. [b] Grouped term of neutropenia includes preferred terms of decreased neutrophil count and neutrophil count decreased.

AR, adverse reaction; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

1. Trastuzumab Deruxtecan Summary of Product Characteristics

Data cutoff: August 1, 2019

Adverse Reactions of Special Interest Reported Among Patients With mBC Receiving T-DXd 5.4 mg/kg in DESTINY-Breast03

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF decrease, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

LVEF, left-ventricular ejection fraction.
[a]Patients with prior history of ILD/pneumonitis requiring steroids were excluded. [b]Left ventricular dysfunction. [c]Decreased ejection fraction
Cortes J, et al. Presented at ESMO Virtual Congress 2021; September 16-20, 2021.

Data cutoff: May 21, 2021

An ILD/Pneumonitis Management Program for T-DXd Clinical Studies Has Been Established

Updated Guidelines (2019)

STEP 1: Monitor

Suspected ILD/pneumonitis

Interrupt drug

Rule out ILD/pneumonitis if a patient develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms, such as dyspnea, cough, or fever.

STEP 2: Confirm

Evaluations should include:

- **High-resolution CT**
- **Pulmonologist** consultation (infectious disease consultation as clinically indicated)
- Blood culture and CBC. Other blood tests could be considered as needed
- Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- PFTs and pulse oximetry
- Arterial blood gasses, if clinically indicated
- One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible

All events of ILD/pneumonitis, regardless of severity or seriousness, should be followed until resolution including after drug discontinuation.

STEP 3: Manage

Drug must be interrupted for any ILD/pneumonitis events regardless of grade

- **Grade 1: Interrupt until fully resolved, then:**
  - if resolved in 28 days or less from date of onset, maintain dose
  - if resolved in greater than 28 days from date of onset, reduce dose one level
  - however, if the event Grade 1 ILD/pneumonitis occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued
- **Grades 2-4: Permanently discontinue treatment**. Refer to toxicity management guidelines for trastuzumab deruxtecan

Li BT, et al. Article and supplementary appendix. *N Engl J Med*. 2021.

Daiichi-Sankyo | AstraZeneca

ILD/Pneumonitis Management Guidelines for T-DXd

Updated Guidelines (2019)

	Grade 1	Grade 2	Grade 3/4

Toxicity Management	• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry
	• Consider follow-up imaging in 1-2 weeks (or as clinically indicated)
	• **Consider starting systemic steroids** (e.g. at least **0.5 mg/kg/day prednisone** or equivalent) until improvement, followed by **gradual taper over at least 4 weeks**
	• If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines
	  • **If patient is asymptomatic, then patient should still be considered as grade 1 even if steroid treatment is given**
		• Promptly start and **treat with systemic steroids** (e.g., at least **1mg/kg/day prednisone** or equivalent) for **at least 14 days** or until complete resolution of clinical symptoms and chest CT findings, then followed by a **gradual taper over at least 4 weeks**
		• Monitor symptoms closely
		• Re-image as clinically indicated
		• If worsening or no improvement in clinical or diagnostic observations in 5 days,
		  • **Consider increasing dose of steroids** (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone)
		  • Re-consider additional work-up for alternative etiologies as described above
		  • Escalate care as clinically indicated
			• Hospitalization required
			• Promptly **initiate empiric high-dose methylprednisolone IV treatment** (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) **for at least 14 days** followed by a gradual taper over at least 4 weeks
			• Re-image as clinically indicated
			• If still no improvement within 3 to 5 days,
			  • Re-consider additional work-up for alternative etiologies as described above
			  • Consider other immuno-suppressants and/or treat per local practice

Li BT, et al. Article and supplementary appendix. *N Engl J Med*. 2021.

Nausea and Vomiting

Nausea and Vomiting

Potential Management Strategies & NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Patient Counseling[1]

- Eat small meals throughout the day
- Avoid foods with strong smells
- Eat food at room temperature
- Sip only small amounts of liquid during meals
- Keep a record of nausea and why
- Wear loose and comfortable clothing
- Sit up or lie with your head raised for one hour after eating

Rx Options[2-4]

Prophylaxis

- Serotonin (5-HT_3) receptor antagonists
- Neurokinin-1 receptor (NK1R) antagonists
- Corticosteroids
- Oral antipsychotics

Breakthrough

- Atypical antipsychotics
- Benzodiazepines
- Cannabinoids
- Phenothiazines
- 5-HT_3 receptor antagonists
- Corticosteroids

Permitted Therapies in Clinical Trials[5]

Prophylactic Antiemetics:
Patients are recommended to receive prophylactic anti-emetic combination regimens prior to infusion of T-DXd and on subsequent days

Persistent AR

T-DXd clinical trial protocol guidance

Do not re-escalate the T-DXd dose after a dose reduction[6]

Dose Modification[5,6]

	mBC	GC, NSCLC, CRC*
Starting Dose	5.4 mg/kg	6.4 mg/kg
Initial dose reduction	4.4 mg/kg	5.4 mg/kg
Final dose reduction	3.2 mg/kg	4.4 mg/kg
Further dose reduction required	Discontinue Treatment	

Resume Therapy[5]

- If resolved in ≤ 7 days, maintain dose
- If resolved in > 7 days, reduce dose 1 level

Dose Interruption[5]

For grade ≥ 3 nausea:
Delay dose until resolved to grade ≤ 1 or baseline values

*6.4 mg/kg starting dose is an investigational dose for investigational tumors.

5-HT_3, 5-hydroxytryptamine (serotonin); CRC, colorectal cancer; GC, gastric cancer; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

1. National Cancer Institute. Nutrition in Cancer Care (PDQ®)–Patient Version. Updated March 16, 2018. www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss/nutrition-pdq. Accessed January 15, 2020. 2. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.1.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed May 17, 2021. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 3. Navari RM, et al. *N Engl J Med* 2016; 374:1356-1367. 4. Navari RM. *Biomed Res Int* 2015;2015:595894. 5. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020. 6. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021.

NCCN Guidelines® for Antiemesis: Acute and Delayed Nausea and Vomiting

National Comprehensive Cancer Network® (NCCN®) Recommended

NCCN Guidelines for Antiemesis, lists fam-trastuzumab deruxtecan-nxki (ENHERTU) as a parenteral anticancer agent with *moderate emetic risk* and recommends several prophylactic antiemetic regimens to decrease potential vomiting

中致吐性藥物

Moderate Emetic Risk Parenteral Anticancer Agents—
Acute and Delayed Emesis Prevention[a,b,c]

DAY 1:	Select treatment option D, E, or F	DAYS 2, 3
	All treatment options are category 1 and should be started before chemotherapy[d]	
	Treatment option D, use the following combination: • 5-HT3 RA • Dexamethasone[e,f]	Treatment option D: • Dexamethasone[e,f] OR • 5-HT3 RA monotherapy[k]: – Granisetron – Ondansetron – Dolasetron
	Treatment option E, use the following combination[e]: • **Olanzapine**[h] • Palonosetron • Dexamethasone[e,f]	Treatment option E: • **Olanzapine**[h]
	Treatment option F, use the following combination[g]: • NK1 RA • 5-HT3 RA[i,j] • Dexamethasone[e,f]	Treatment option F: • Aprepitant • +/-Dexamethasone[e,f]

[a] For details regarding recommendations and specific dosing information, please refer to the NCCN Guidelines for Antiemesis. [b] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors. [c] With or without lorazepam 0.5–2 mg PO or IV or sublingual every 6 hours as needed days 1–4. With or without H2 blocker or proton pump inhibitor. For olanzapine-containing regimens, only use PO lorazepam if needed. [d] Category 1 recommendations indicate uniform NCCN consensus that the intervention is appropriate based on high-level evidence. [e] Emerging data and clinical practice suggest dexamethasone doses may be individualized. Higher doses may be considered, especially when an NK1 RA is not given concomitantly. Lower doses, given for shorter durations, or even elimination of dexamethasone on subsequent days (for delayed nausea and emesis prevention) may be acceptable for non-cisplatin regimens based on patient characteristics. If dexamethasone eliminated on subsequent days for delayed nausea and emesis prevention, consider other alternative antiemetics (eg, olanzapine). [f] Use of corticosteroid premedications should be avoided with cellular therapies. [g] A 3-drug prophylactic regimen (E or F) is recommended for select patients with additional patient-related risk factors or previous treatment failure with a corticosteroid + 5-HT3 RA alone. [h] Data suggest that a 5-mg dose of olanzapine is efficacious. Consider this dose especially for elderly or over sedated patients. Hashimoto H, et al. Lancet Oncol 2020;21:242-249. Mukhopadhyay S, et al. Future Oncol 2021;17:2041-2056. [i] If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product used, no further 5-HT3 RA is required. [j] When used in combination with an NK1 RA, there is no preferred 5-HT3 RA. [k] No further 5-HT3 therapy required if palonosetron or granisetron extended-release injection administered, or if granisetron transdermal patch applied, on day 1.

ASCO, American Society of Clinical Oncology; 5-HT_3, 5-hydroxytryptamine (serotonin); NCCN, National Comprehensive Cancer Network; NK1, neurokinin 1; RA, receptor antagonist.

Anemia & Neutropenia

Anemia

Potential Management Strategies & NCCN Guidelines

Patient Counseling[1]

- Plan ahead and save your energy for the most important activities
- Balance rest and activities
- Eat a balanced diet that includes protein (meat, fish, eggs, cheese, milk, nuts, peas, and beans)
- Drink plenty of nonalcoholic liquids
- When to call health care provider
  - Severe weakness
  - Dizziness or lightheadedness
  - Palpitation
  - Shortness of breathe or difficulty breathing
- Regular blood tests are necessary to monitor for ARs such as treatment-related anemia

Clinical Evaluation/Rx Options[2,3]

Clinical Evaluation of Anemia

Consider use of treatment such as:

- **Iron Supplement**
- Multivitamin
- **Red blood cell transfusion**
- **Consider ESAs as an alternative to RBC transfusions in select patients[4]**

Persistent AR

T-DXd clinical trial protocol guidance

Do not re-escalate the T-DXd dose after a dose reduction is made[5]

Dose Modification[4,5]

	mBC	GC, NSCLC, CRC
Starting Dose	5.4 mg/kg	6.4 mg/kg*
Initial dose reduction	4.4 mg/kg	5.4 mg/kg
Final dose reduction	3.2 mg/kg	4.4 mg/kg
Further dose reduction required	Discontinue Treatment	

Resume Therapy[4]

For grade 3 (Hgb < 8.0 g/dL);
Maintain dose

For grade 4 (life-threatening);
Reduce dose 1 level

Dose Interruption[4]

For grade 3 (Hgb < 8.0 g/dL);
Transfuse
Delay dose until resolved to grade ≤2

For grade 4 (life-threatening);
Transfuse
Delay dose until resolved to grade ≤2

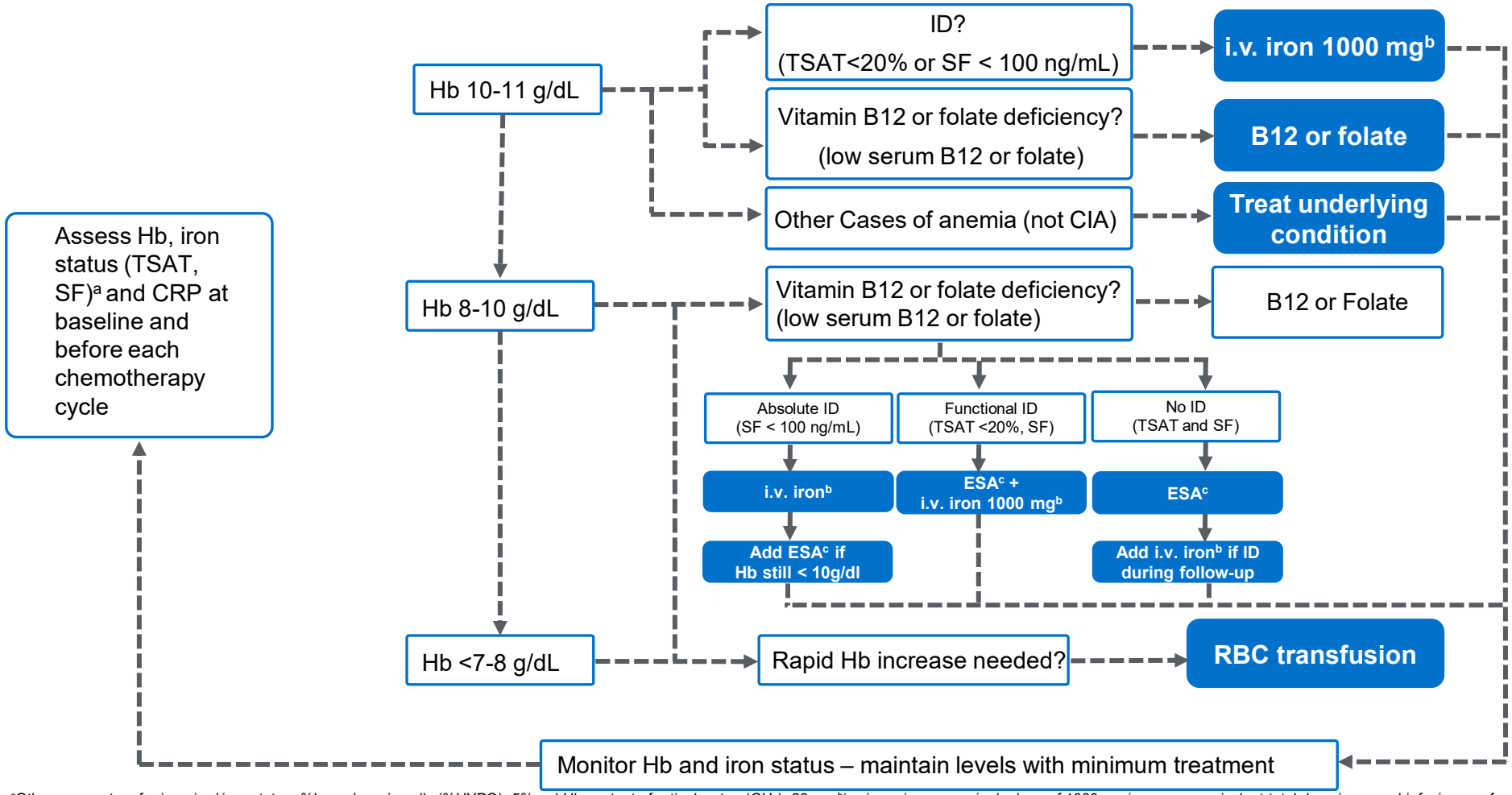
*6.4 mg/kg starting dose is an investigational dose for investigational tumors.

AR, adverse reaction; CRC, colorectal cancer; ESA, erythropoiesis-stimulating agent; GC, gastric cancer; Hgb, hemoglobin; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; RBC, red blood cell; T-DXd, trastuzumab deruxtecan.

1. American Cancer Society website. Managing Anemia at Home. www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/managing-anemia-at-home.html. Accessed January 15, 2020. 2. Chemocare.com website. Low Blood Counts. chemocare.com/chemotherapy/side-effects/low-blood-counts.aspx. Accessed January 15, 2020. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 17, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 4. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020. 5. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021

Daiichi-Sankyo | AstraZeneca

ESMO Clinical Practice Guidelines: Management of Chemotherapy-Induced Anemia in Patient with Solid or Hematological Malignancies



[a]Other parameters for impaired iron status: %hypochromic cells (%HYPO)>5%and Hb content of reticulocytes (CHr)<28 pg. [b]i.v. iron given as a single dose of 1000 mg iron or an equivalent total dose in several infusions as feasible with available i.v. iron formulations.Oral iron to be considered only for patients with ferritin<30 ng/mL and non-inflammatory conditions [CRP<5 mg/L]. [c]ESA dosing should follow approved labels (i.e.450 IU/week/kg body weight for epoetins alpha, beta and zeta; 6.75mg/kg body weightevery 3 weeks or 2.25mg/kg body weight weekly for darbepoetin alpha; 20 000 IU once weekly for epoetin theta which may be doubledafter 4 weeks upon insufficient response). ESA dose escalations or a change to another ESA in patients who do not respond within 4–8 weeksare not recommended; ESA should be stopped in this case.

CIA, chemotherapy-induced anemia. CRP, C-reactive protein. ESA, erythropoiesis-stimulating agent. Hb, hemoglobin. ID, iron-deficiency. i.v., intravenous. RBC, red blood cell; SF, serum ferritin. TSAT, transferrin saturation.

Apro M et al. *Ann Oncol*. 2018; 29(4):iv96-iv110.

Daiichi-Sankyo | AstraZeneca

NCCN Guidelines for Management of (Febrile) Neutropenia

Potential Management Strategies & NCCN Guidelines

If Fever Is Present[1]

- Administer empirical therapy ≤1 hour after triage
- Patients with febrile neutropenia should receive an intravenous dose of therapy while undergoing evaluation

Clinical Evaluation[1]

- Complete history and physical examination; complete blood count with leukocyte differential count, hemoglobin, and platelet count
- ≥2 blood cultures from different sites and cultures from other sites (eg, urine or wounds)
- Chest imaging for patients with symptoms of lower respiratory tract infection; nasopharyngeal swab for patients with an influenza-like illness

Empiric Therapy[1]

- An antipseudomonal β-lactam agent is recommended, but other antibacterials may be added for management of complications or if resistance is suspected
- If patients are appropriate for outpatient management, observe for ≥4 hours before discharge
- G-CSFs may be given to prevent febrile neutropenia in select patients based on chemotherapy regimen, patient risk factors and treatment intent.[2,a]

T-DXd clinical trial protocol guidance

Dose Interruption[3]

In the event of febrile neutropenia:

Delay dose until resolved

Resume Therapy[3]

↓ Reduce dose 1 level

Dose Modification[4,5]

	mBC	GC, NSCLC, CRC
Starting Dose	5.4 mg/kg	6.4 mg/kg*
Initial dose reduction	4.4 mg/kg	5.4 mg/kg
Final dose reduction	3.2 mg/kg	4.4 mg/kg
Further dose reduction required	Discontinue Treatment	

*6.4 mg/kg starting dose is an investigational dose for investigational tumors.

Do not re-escalate the T-DXd dose after a dose reduction is made[4,5]

[a] All recommendations are category 2A unless otherwise indicated. Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

CRC, colorectal cancer; FDA, United States Food and Drug Administration; G-CSF, Granulocyte-colony stimulating factor; GC, gastric cancer; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

1.Taplitz RA, et al. *J Clin Oncol*. 2018;36(14):1443-1453. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed August 17, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 3. Investigator's brochure for trastuzumab deruxtecan. Version 6.0. Basking Ridge, NJ: Daiichi Sankyo, Inc. Effective September 9, 2019. 4. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021. 5. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020.

Daiichi-Sankyo | AstraZeneca

Other Warnings & Precautions:
LV Dysfunction & Embryo-Fetal Toxicity

優赫得®凍晶注射劑 100 毫克

ENHERTU® 100 mg powder for concentrate for solution for infusion

衛部菌疫輸字第 001179 號　　本藥限由醫師使用

特殊警語:

1. ENHERTU®不可與 trastuzumab 或 trastuzumab emtansine 相互替代。
2. 肺毒性:ENHERTU®使用經驗中曾通報間質性肺病(ILD)及肺炎(pneumonitis)案例(含致命案例),應監測並立即調查徵兆及症狀如咳嗽、呼吸困難、發燒及其他新發生或惡化的呼吸道症狀。如有發生第 2 級以上 ILD/肺炎,請永久停藥。告知病人此項風險並須立即通報症狀。
3. 左心室功能不全: 在抗 HER2 療法中,曾觀察到左心室射出分率(LVEF)降低的案例。應在初次施用 ENHERTU®之前,及在治療期間視臨床需求定期評估 LVEF。若發生 LVEF 降低應以中斷治療進行處理。若確認 LVEF 低於 40%,或相較於基期的絕對下降量大於 20%,應永久停用 ENHERTU®。發生症狀性鬱血性心臟衰竭(CHF)的病人,應永久停用 ENHERTU®。
4. 胚胎-胎兒毒性: 懷孕期間暴露於 ENHERTU®可能導致胚胎-胎兒傷害。告知病人此項風險並須採取有效的避孕措施。

Left Ventricular Dysfunction Management

Specific Dose Modifications

LV Dysfunction Severity		Dose or schedule modification for T-DXd
LVEF > 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with T-DXd
LVEF 40% to 45%	And absolute decrease from baseline is < 10%	• Continue treatment with T-DXd • Repeat LVEF assessment within 3 weeks
	And absolute decrease from baseline is 10% to 20%	• Interrupt T-DXd • Repeat LVEF assessment within 3 weeks • If LVEF has not recovered to within 10% from baseline, permanently discontinue T-DXd • If LVEF recovers to within 10% from baseline, resume treatment with T-DXd at the same dose
LVEF < 40% or absolute decrease from baseline is > 20%		• Interrupt T-DXd • Repeat LVEF assessment within 3 weeks • If LVEF of < 40% or absolute decrease from baseline of > 20% is confirmed, permanently discontinue T-DXd
Symptomatic congestive heart failure		• Permanently discontinue T-DXd

LV, left ventricular; LVEF, left ventricle ejection fraction; T-DXd, trastuzumab deruxtecan.

Trastuzumab deruxtecan Summary of Product Characteristics. January 2021.

Daiichi-Sankyo | AstraZeneca

Embryo-Fetal Toxicity

Specific Patient Counseling Information

Inform female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider of a known or suspected pregnancy

Advise females of reproductive potential to use effective contraception during treatment with T-DXd and for at least 7 months after the last dose

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with T-DXd and for at least 4 months after the last dose

T-DXd, trastuzumab deruxtecan.

Trastuzumab deruxtecan Summary of Product Characteristics. January 2021.

Summary

- ADCs in HER2m-mNSCLC
  - T-DM1 (Ado-Trastuzumab Emtansine)
  - T-Dxd (Lung-02, 5.4mg/kg): mPFS: 9.9 mo; DoR: 16.8 mo; mOS: 19.5mo

- ILD/pneumonitis management of ADCs treatment:
  - Early diagnosis and intervention are important to averting serious outcome

Thanks for your attention