HER2 Tx in Advanced NSCLC
From TKIs to ADCs
MATOS 11.23

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HER2 Modification in NSCLC

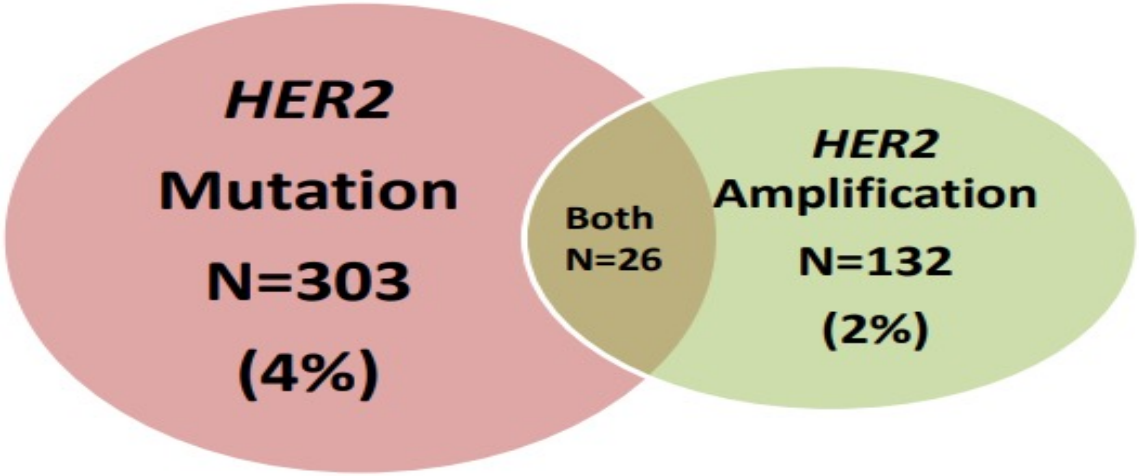
- HER2 can be both amplified and mutated in NSCLC
  - Overexpression 59% NSCLC
    - 2-3+ up to 30%
  - Amplifications: 2-2.5%
  - Mutation 3% of adenocarcinomas
    - Mostly Exon 20 In-frame insertions
      - YMVA most common insertion variant ~ 80%
    - Mostly never smokers
    - Worse survival than others in LCMC
    - Marginal overlap with HER2 gene amplification or protein expression

Characteristic	*HER2* Cohort, No. of Patients (%) N = 24	Non-*HER2* Cohort, No. of Patients (%) N = 896
Sex		
Female	14 (58.3%)	532 (59.4%)
Male	10 (41.7%)	364 (40.6%)
Median age (range), y	62 (37-73)	61 (18-88)
Stage of disease at time of diagnosis (TNM Staging for Lung Cancer, 7th edition)		
I-IIIA	4 (16.7%)	230 (25.7%)
IIIB	3 (12.5%)	66 (7.4%)
IV	17 (70.8%)	578 (64.5%)
Unknown stage		21 (2.3%)
Tobacco use		
Never	17 (70.8%)	288 (32.1%)
Former	6 (25%)	539 (60.2%)
Current	1 (4.2%)	65 (7.3%)
Smoking status unknown		4 (0.4%)

Pillai et al Cancer 2017

MSK IMPACT 2014-2022
HER2 Aberrations in Persons with Lung Cancers

- 5% with *HER2* Mutation or Amplification (409/7993)



- 26/329 (8%) of patients with mutations have amplification
- *26/132* (20%) of patients with amplification have mutations
- *HER2* mutation mutually exclusive with other oncogenic drivers

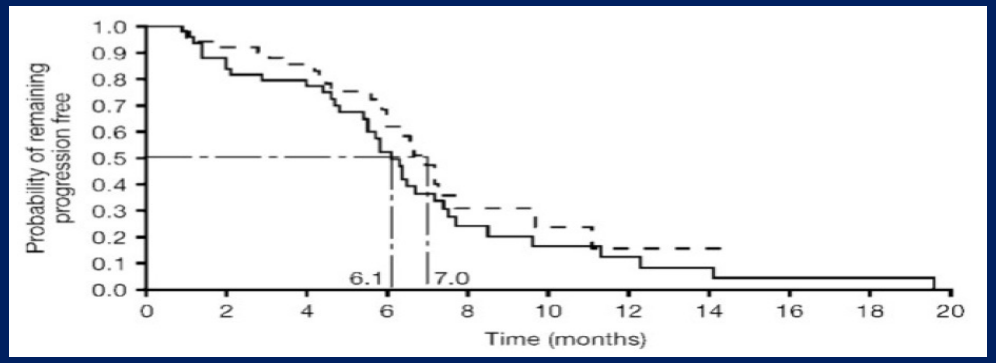
Most strategies in HER2 (+) NSCLC adapted from work in MBC

- HER2 directed therapies are central in the treatment of HER2 amplified breast cancer
  - Lapatinib
  - Afatinib
  - Dacomitinib
  - Pyrotinib
  - Poziotinib
  - Trastuzumab
  - Pertuzumab
  - Ado-trastuzumab emtansine
  - Trastuzumab Deruxtecan

MBC → mNSCLC

Turn of the Century Trials Based on IHC/FISH

- Cis-gem +/- trastuzumab in HER2 amplified or overexpressing NSCLC
  - RPhII of 101 pts: ORR 41 vs 36%, PFS 7 vs 6.1 mo
  - ORR 83%, PFS 8.5 mo in 12 pts with IHC3+/FISH+
  - No unexpected toxicity



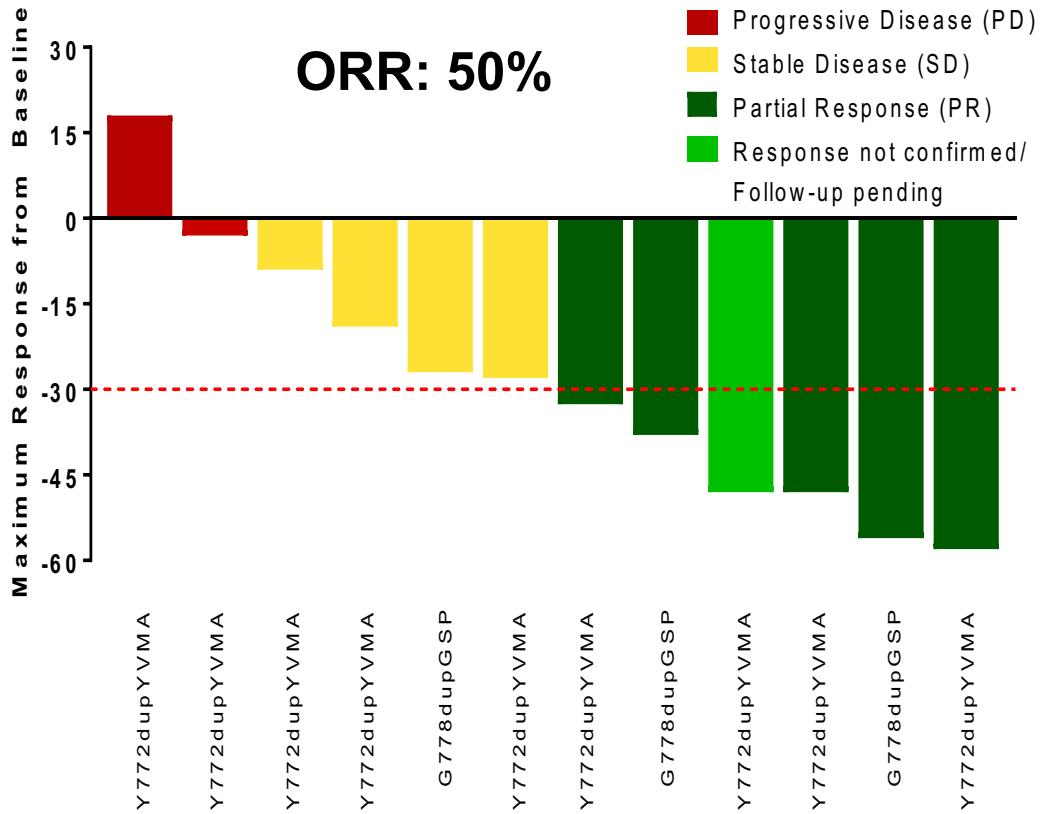
- Carbo/pac/trastuzumab in HER2+ NSCLC – ECOG 2598
  - 139 pts screened; 82 expressed HER2 (13 3+; 31 2+; 38 1+)
  - 56 pts enrolled; 53 eligible
  - ORR 13/52 (24.5%) PFS 3.3 months OS 10.1 months 1-year OS 42%
    - 35% pts went on to maintenance trastuzumab
  - Suggestion of better outcomes in small subset of 3+ patients
  - Toxicity as expected for chemo except 7% asymptomatic decrease LVEF

ORR = overall response rate; LVEF: left venticular ejection fraction.

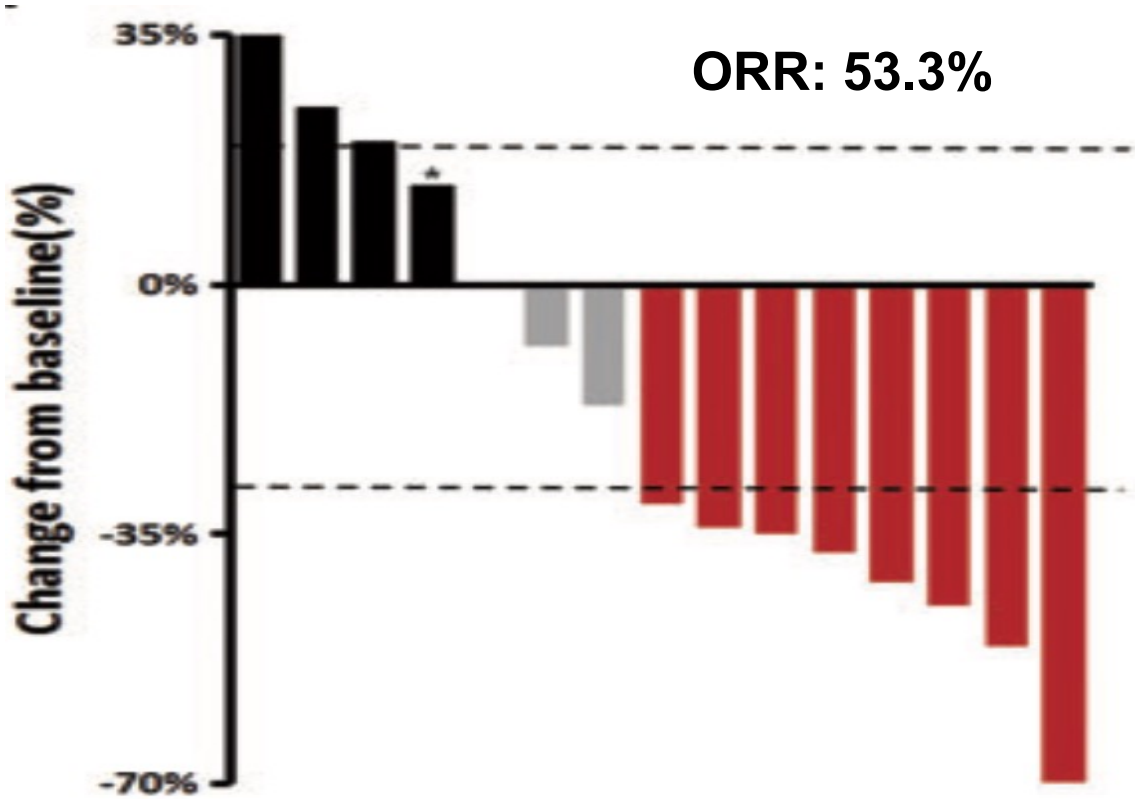
Gatzemeier U, et al. *Ann Oncol.* 2004;15(1):19-27
Langer CJ, et al. *J Clin Oncol.* 2004;22(7):1180-7.

Are newer TKI's likely to improve outcomes?

Poziotinib



Pyrotinib



Heymach et al WCLC 2018
Wang et al Annals of Oncology 2019

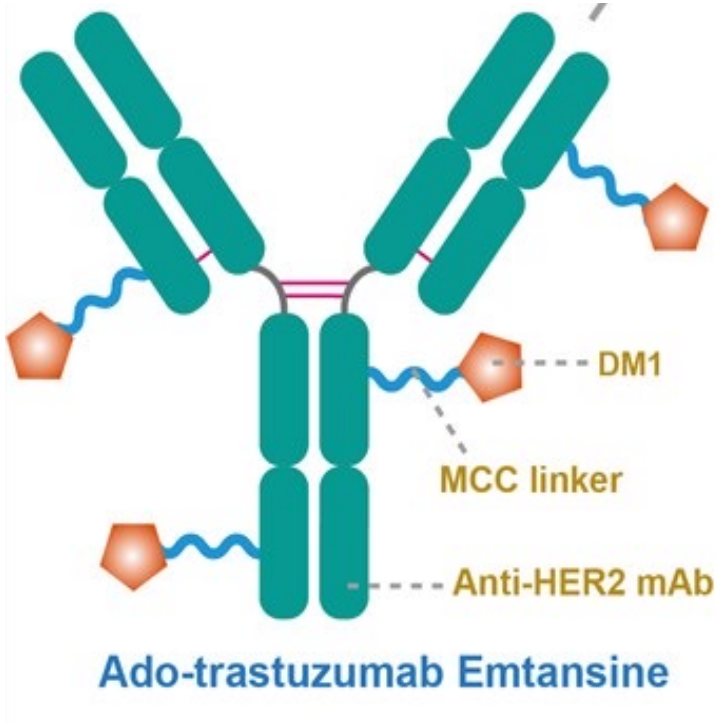
EGFR/HER2 TKIs for HER2-mutant NSCLC

Drug	Target Pop	N	ORR	mPFS	Toxicities
Afatinib[1]	HER2^{mt}	13	8%	16 weeks	Diarrhea, vomiting, rash, paronychia, fatigue, mucositis
Afatinib[2]	HER2^{mt}	27	13%	3 mo	Diarrhea/GI toxicity, skin rash.
Neratinib[3]	HER2^{mt}	26	4%	5.5 mo	Diarrhea (74%), Nausea (43%), Vomiting (41%)
Dacomitinib[4]	HER2^{mt}	26	12%	3 mo	Diarrhea (90%), rash (73%)
Mobocertinib[5]	HER2^{mt}	5	1/5 (20%)		83% Diarrhea, 50% Anorexia
Pyrotinib[6]	HER2^{mt}	60	30%	6.9 mo	92% Diarrhea; 30% Creatinine increase
Poziotinib[7]	HER2^{mt}, Pretreated	90	28%	5.5 mo	49% Gr 3 Rash; 25.6 % Gr 3 Diarrhea
Poziotinib[8]	HER2^{mt}, First-line	48	44%	5.6 mo	49% Gr 3 Rash; 25.6 % Gr 3 Diarrhea

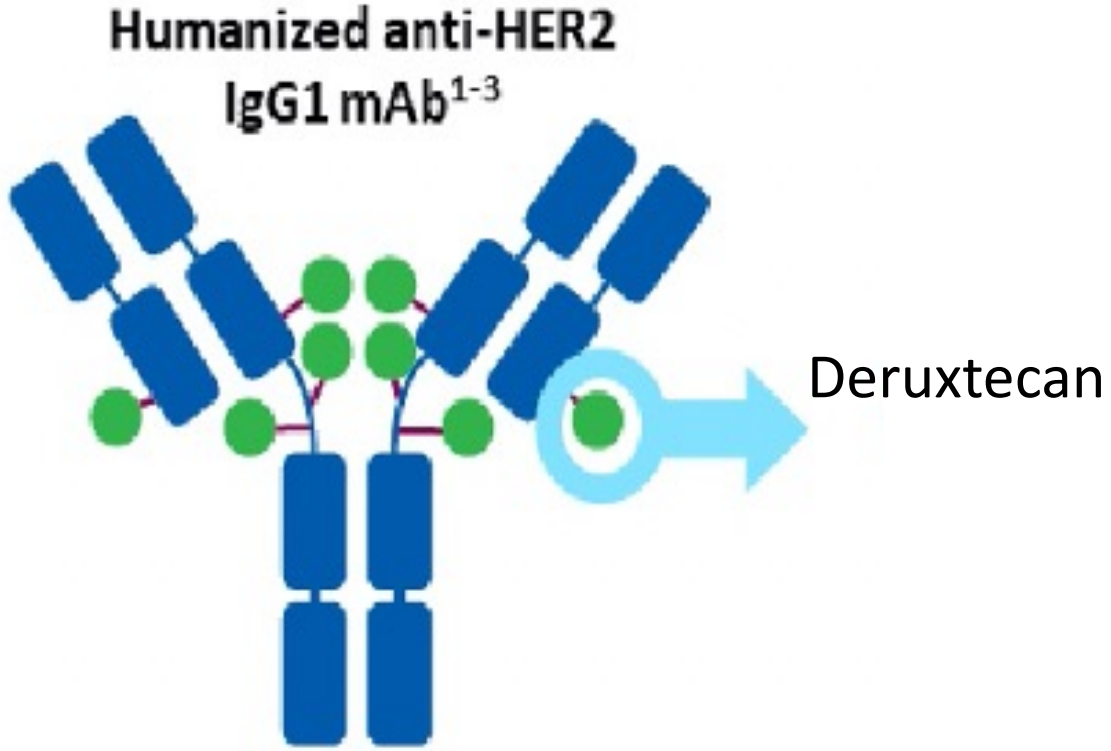
1. Dziadziuszko R, JTO 2019; 2. Lai WCV et al, European Journal of Cancer 2018; 3. Hyman DM, Nature 2018; 4. Kris MG et al. Ann Onc. 2015; 5. Zhou C et al. J Clin Oncol. 2020; 6. Neal JW et al. WCLC 2018. Abstract P1.13-44, 7. Zhou C, JCO 2020, 7. Le X, JCO 2022; 8. Cornelisson R, ESMO 2021

Slide kindly shared by Zofia Piotrowska, MD, MHS

A Tale of Two ADC's

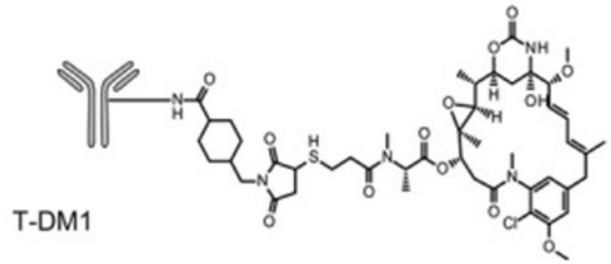


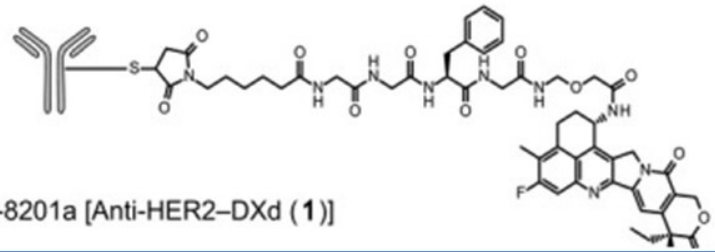
Ado-trastuzumab Emtansine: T-DM1



Trastuzumab Deruxtecan: T-DXd

Comparison of T-DM1 and T-DXd

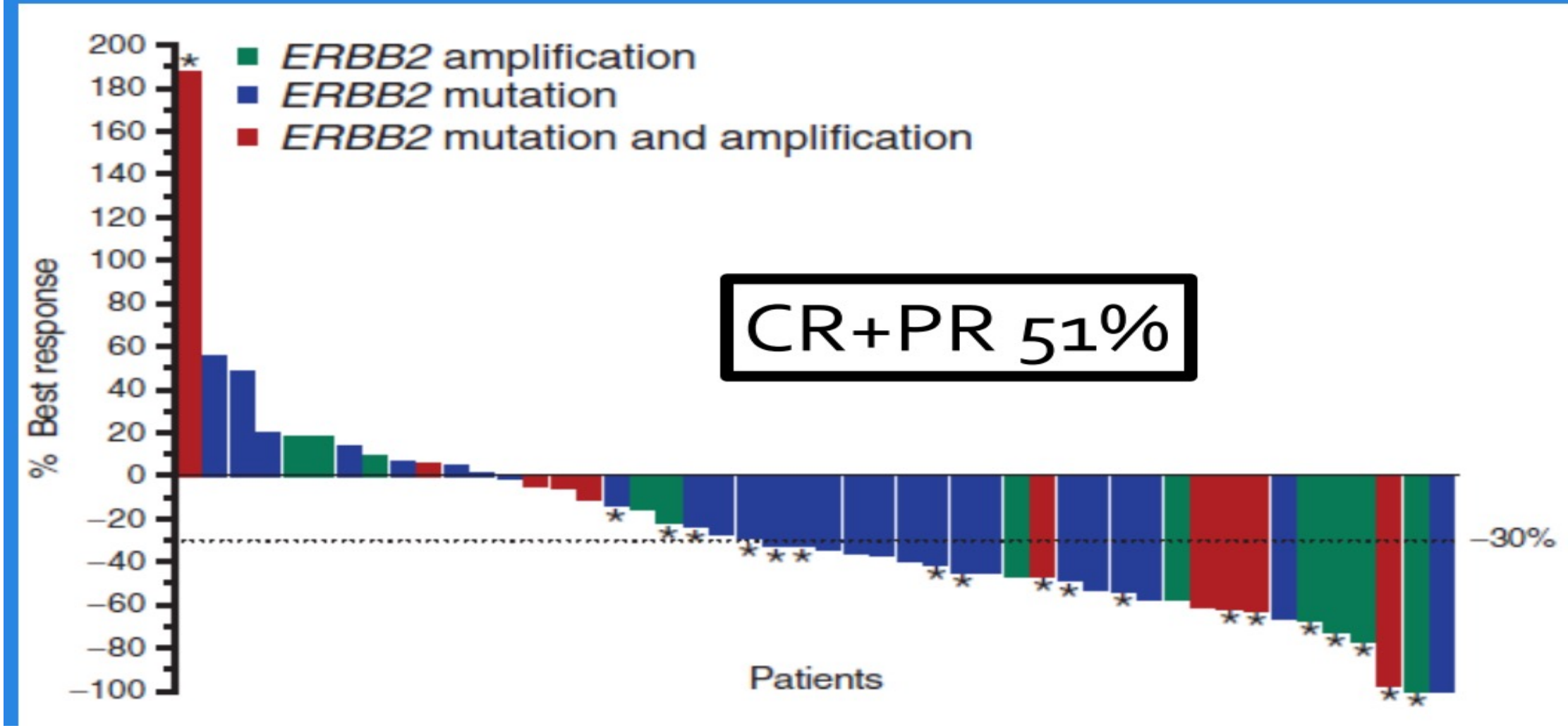




	Trastuzumab Emtansine (TDM-1)	Trastuzumab Deruxtecan (T-DXd)
HER2 targeting Ab	Trastuzumab	Trastuzumab
Linker	Non-Cleavable	Cleavable (in tumor, stable in plasma)
Drug-Antibody Ratio (DAR)	3.5:1	8:1
Payload	Mytansine derivative	Extecan derivative
Mechanism of action	Antimicrotubule agent	Topoisomerase inhibitor
Bystander Effect	No	Yes

Ogitani Cancer Sci 2016; Eiger Cancer 2021

Best Overall Response to T-DM1 Treatment



Li et al, Cancer Discovery 2020

ADCs for HER2-Mutant Lung Cancers
Ado-Trastuzumab Emtansine

VOLUME 36 · NUMBER 24 · AUGUST 20, 2018

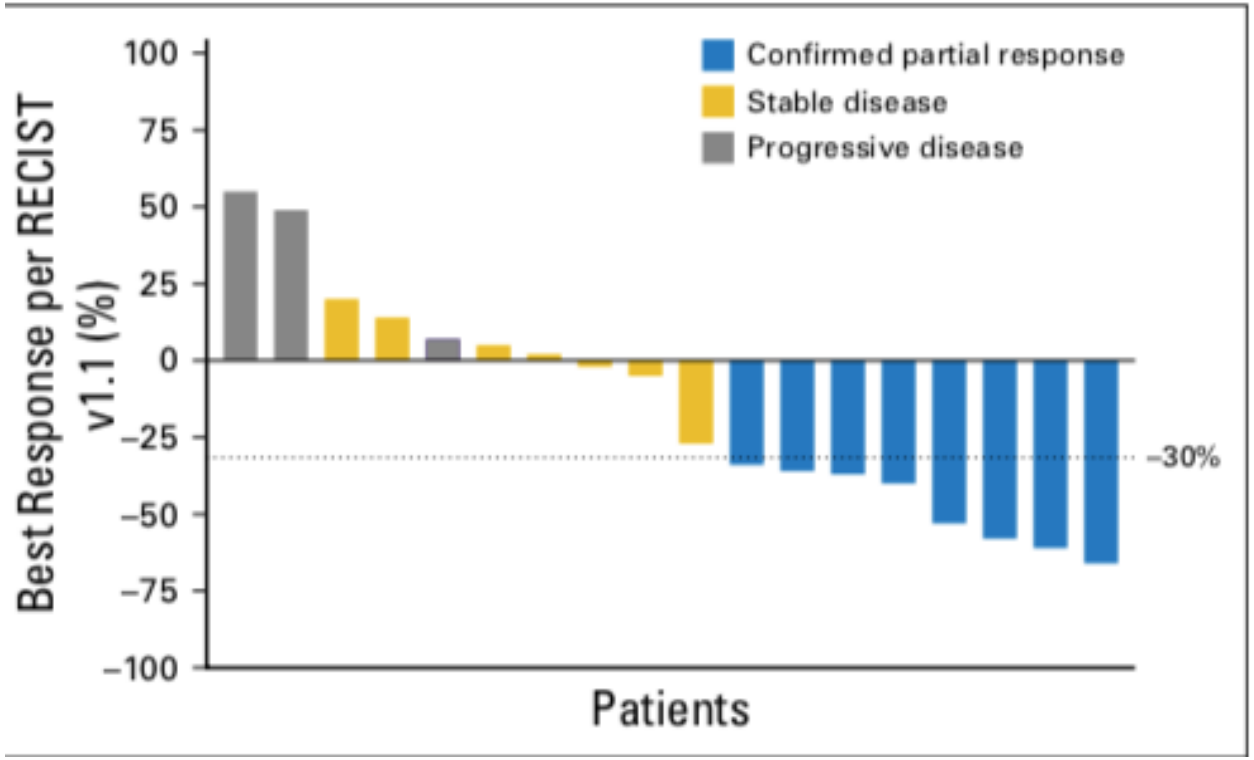
JOURNAL OF CLINICAL ONCOLOGY

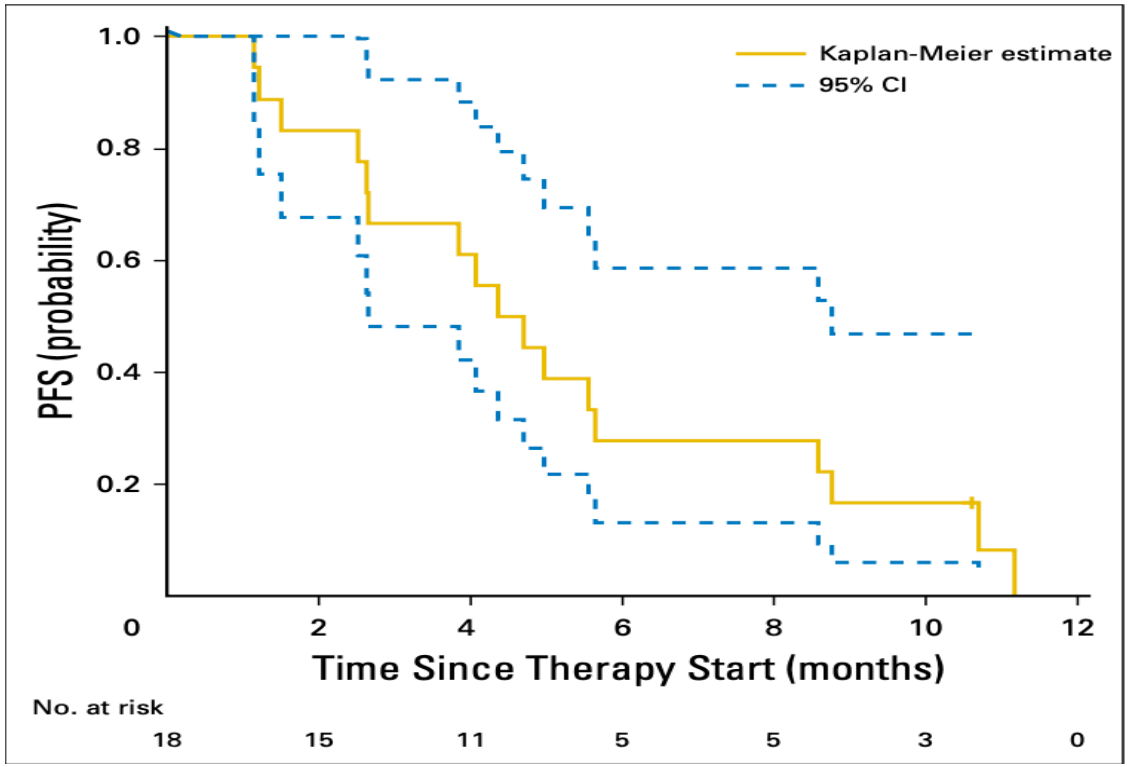
ORIGINAL REPORT

Ado-Trastuzumab Emtansine for Patients With *HER2*-Mutant Lung Cancers: Results From a Phase II Basket Trial

Bob T. Li, Ronglai Shen, Darren Buonocore, Zachary T. Olah, Ai Ni, Michelle S. Ginsberg, Gary A. Ulaner, Michael Offin, Daniel Feldman, Todd Hembrough, Fabiola Cecchi, Sarit Schwartz, Nick Pavlakis, Stephen Clarke, Helen H. Won, Edyta B. Brzostowski, Gregory J. Riely, David B. Solit, David M. Hyman, Alexander Drilon, Charles M. Rudin, Michael F. Berger, José Baselga, Maurizio Scaltriti, Maria E. Arcila, and Mark G. Kris

Ado-Trastuzumab Emtansine in HER2 Mutant NSCLC





ORR 44%
Median DOR 4 months

Median PFS 5 months

Li et al JCO 2018

Ado-trastuzumab Toxicity

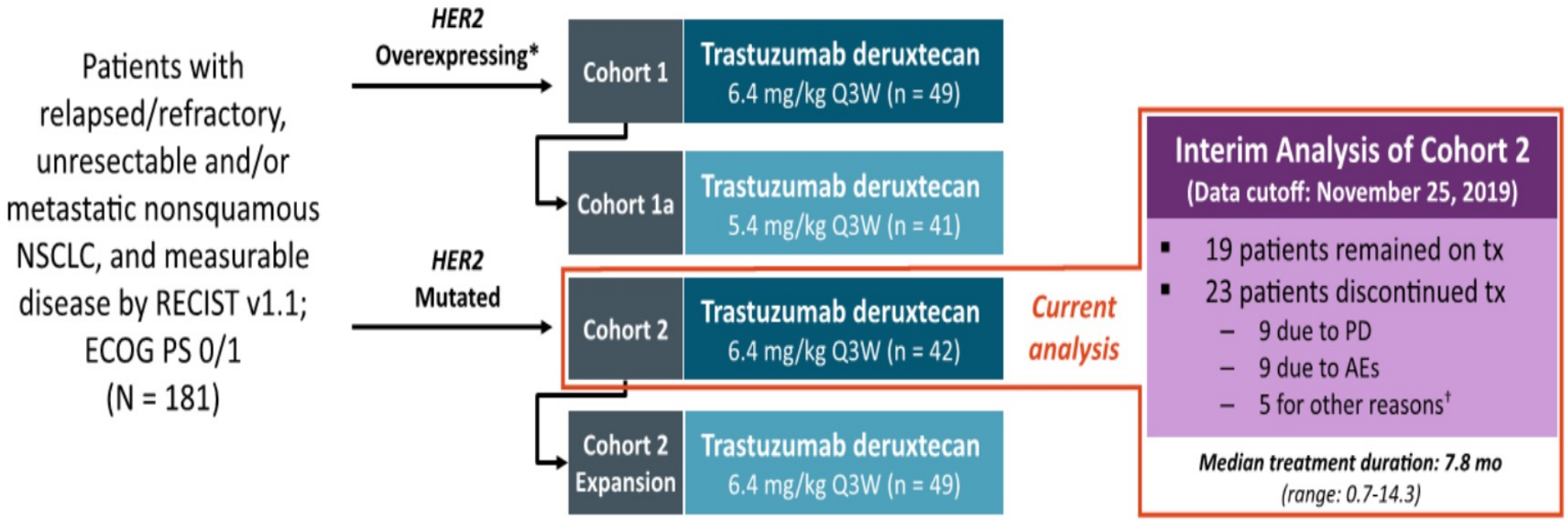
Adverse Event	No. of Patients (%)			
	Grade 1	Grade 2	Grade 3	Total
Elevated AST or ALT	7 (39)	1 (6)	—	8 (44)
Thrombocytopenia	6 (33)	—	—	6 (33)
Fatigue	5 (28)	1 (6)	—	6 (33)
Infusion reaction	2 (11)	3 (17)	—	5 (28)
Nausea	6 (33)	—	—	6 (33)
Weight loss	1 (6)	2 (11)	—	3 (17)
Rash, maculopapular	3 (17)	—	—	3 (17)
Anorexia	1 (6)	1 (6)	—	2 (11)
Epistaxis	2 (11)	—	—	2 (11)
Anemia	—	1 (6)	1 (6)	2 (11)

NOTE. There were no grade 4 or 5 adverse events.

Li et al JCO 2018

DESTINY Lung-01 - Trastuzumab Deruxtecan (T-DXd)

- Multicenter, open-label phase II study



HER2 overexpression (IHC3+ or IHC2+; without known *HER2* mutation) using locally archived tissue and confirmed centrally.
†Other reasons included death (n = 3; treatment unrelated), withdrawal of consent (n = 1), investigator decision (n = 1).

N=42

ORR 61.9%
DCR 90.5%
DOR NR
PFS 14 mo
MS: NR

Median f/u 8 mo

Smit et al ASCO 2020

ADCs for HER2-Mutant Lung Cancers
Trastuzumab Deruxtecan

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

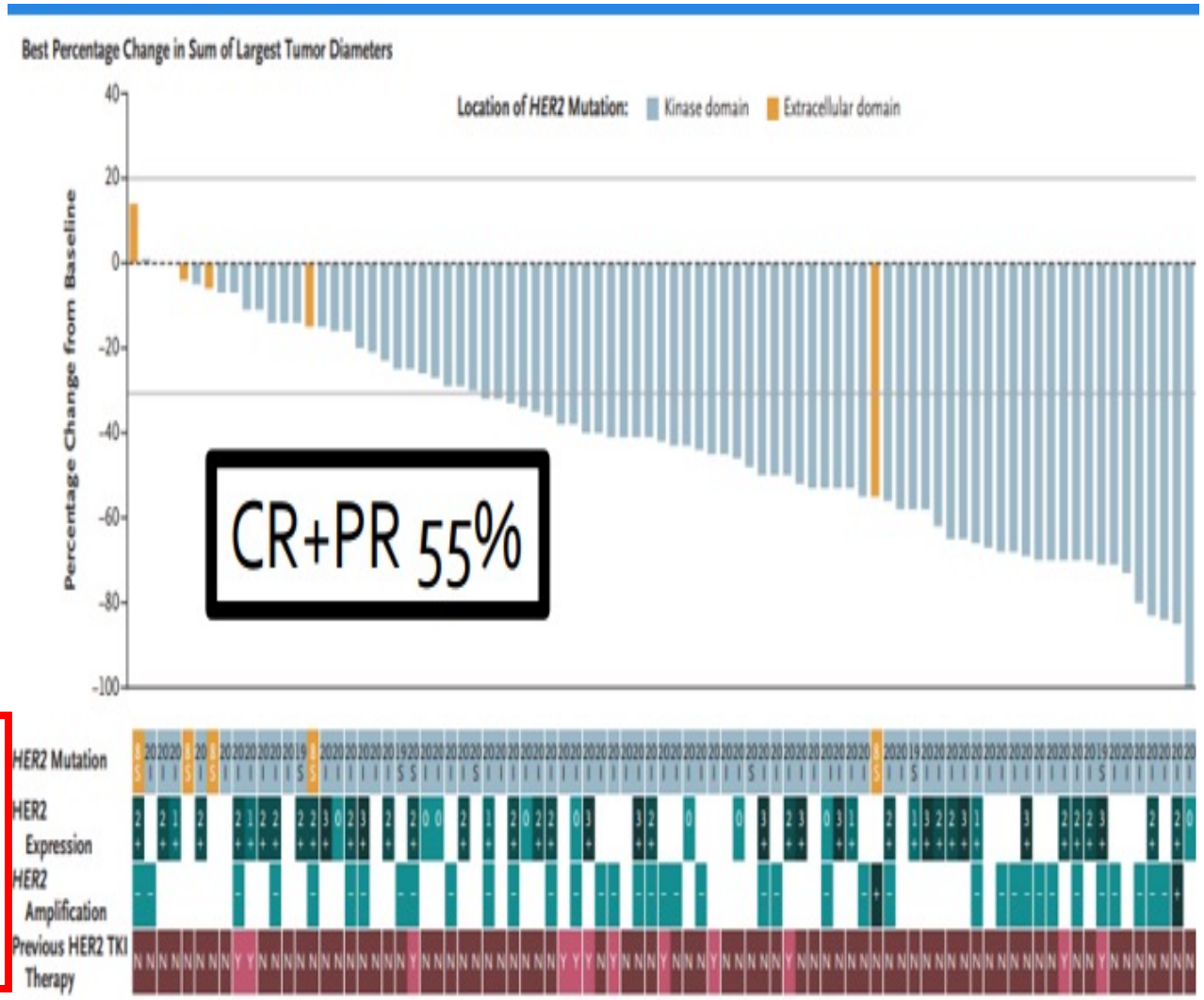
Bob T. Li, M.D., Ph.D., M.P.H., Egbert F. Smit, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Hibiki Udagawa, M.D., Julien Mazières, M.D., Misako Nagasaka, M.D., Ph.D., Lyudmila Bazhenova, M.D., Andreas N. Saltos, M.D., Enriqueta Felip, M.D., Ph.D., Jose M. Pacheco, M.D., Maurice Pérol, M.D., Luis Paz-Ares, M.D., Kapil Saxena, M.D., Ryota Shiga, B.Sc., Yingkai Cheng, M.D., Ph.D., Suddhasatta Acharyya, Ph.D., Patrik Vitazka, M.D., Ph.D., Javad Shahidi, M.D., David Planchard, M.D., Ph.D., and Pasi A. Jänne, M.D., Ph.D., for the DESTINY-Lung01 Trial Investigators*

This article was published on September 18, 2021, at NEJM.org.

Trastuzumab deruxtecan in HER2 Mutant NSCLC

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)



Li B et al, NEJM 2021

Trastuzumab deruxtecan in HER2 Mutant NSCLC

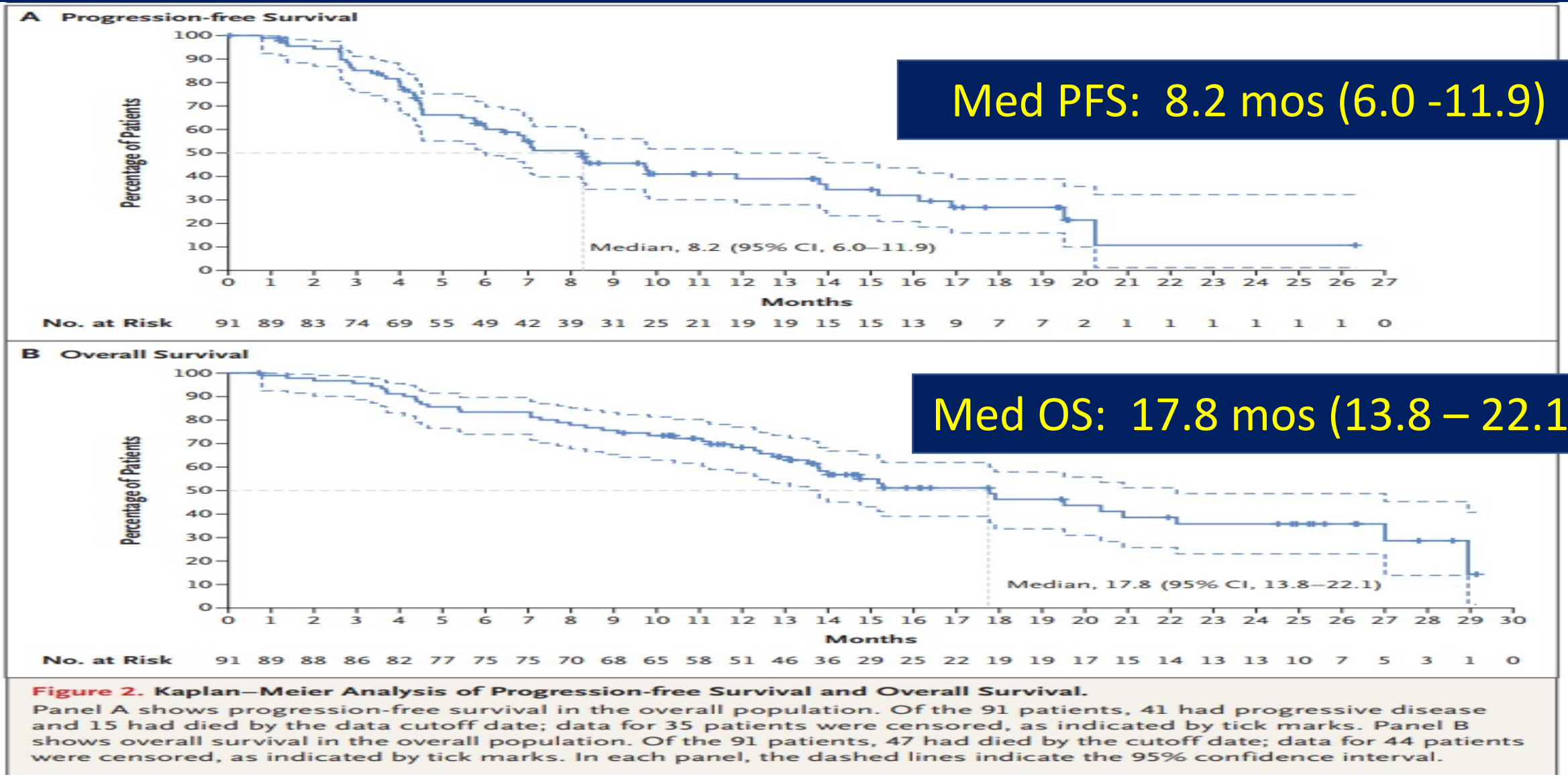


Figure 2. **Kaplan–Meier Analysis of Progression-free Survival and Overall Survival.**
Panel A shows progression-free survival in the overall population. Of the 91 patients, 41 had progressive disease and 15 had died by the data cutoff date; data for 35 patients were censored, as indicated by tick marks. Panel B shows overall survival in the overall population. Of the 91 patients, 47 had died by the cutoff date; data for 44 patients were censored, as indicated by tick marks. In each panel, the dashed lines indicate the 95% confidence interval.

Med PFS: 8.2 mos (6.0 -11.9)

Med OS: 17.8 mos (13.8 – 22.1)

Li B et al, NEJM 2021

Trastuzumab Deruxtecan (T-DXd) in HER2-mutant NSCLC

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)

- **Most commone AEs: Nausea and Fatigue**
- **Most common dose reductions: ANC and ILD**
- **Pneumonitis (ILD)**
  - **Adjudicated drug-related ILD occurred in 24/91 patients (26%)**
    - Grade 1: 3 patients
    - Grade 2: 15 patients
    - Grade 3: 4 patients
    - Grade 5: 2 patients
  - Median duration of onset of ILD – 141 days (range, 14-462)

How do the HER2 ADC's Compare?

	Ado-Trastuzumab Emtansine	Trastuzumab Deruxtecan
Objective Response Rate	44%	55%
Median PFS	5 mos	8.2 mos
Median OS	Not reported	17.8 mos
Grade 3-4 AE's	6%	64.3%

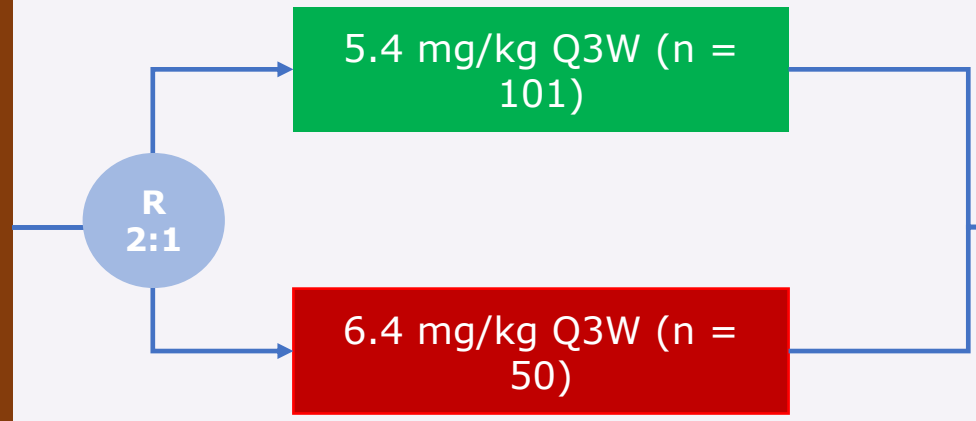
Smit et al ASCO 2020, Li NEJM 2022
Li et al JCO 2018

Trastuzumab Deruxtecan (T-DXd;DS-8201): DESTINY 2

- **DESTINY-Lung02**: Phase 2, randomized, double-blind study of safety and efficacy of T-DXd in patients with *HER2*-mutated metastatic NSCLC

Key inclusion criteria

- Unresectable or metastatic NSCLC
- *HER2*-mutation
- Age ≥18 years
- ECOG PS 0 or 1
- Received ≥1 line of therapy including platinum therapy
- Clinically inactive brain metastases allowed



Primary objectives

- ORR

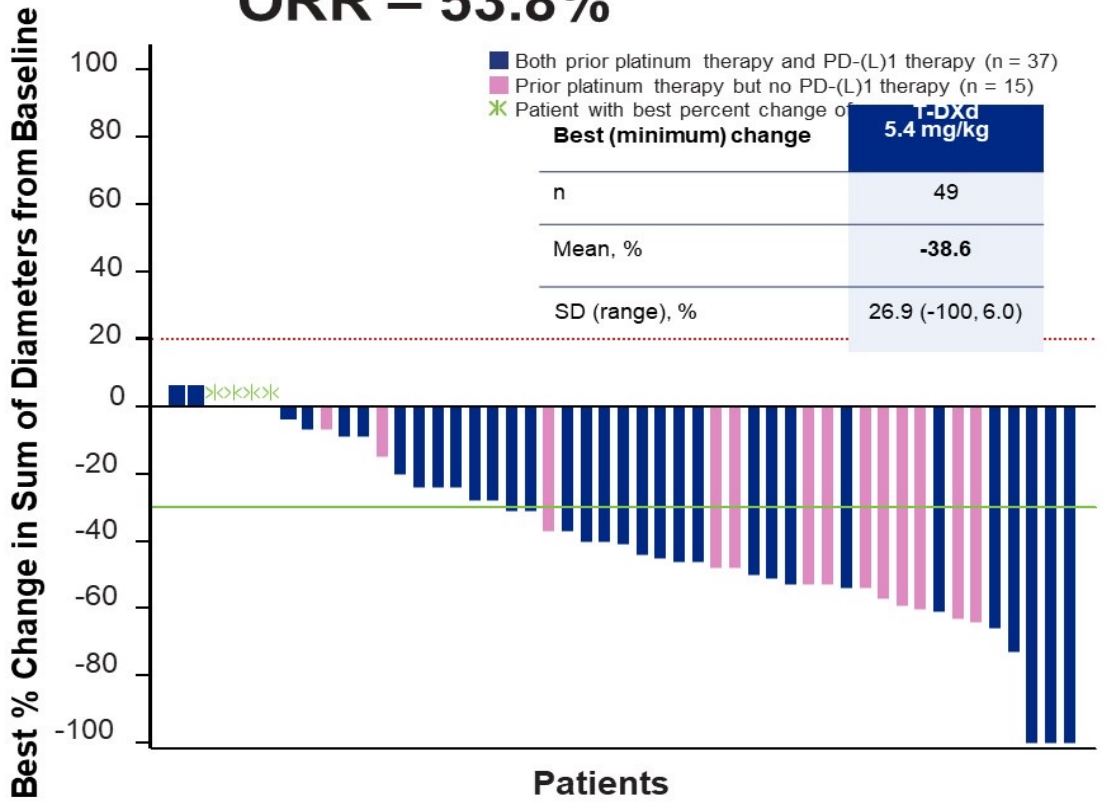
Secondary objectives

- DoR, DCR, PFS, OS
- Safety and PK

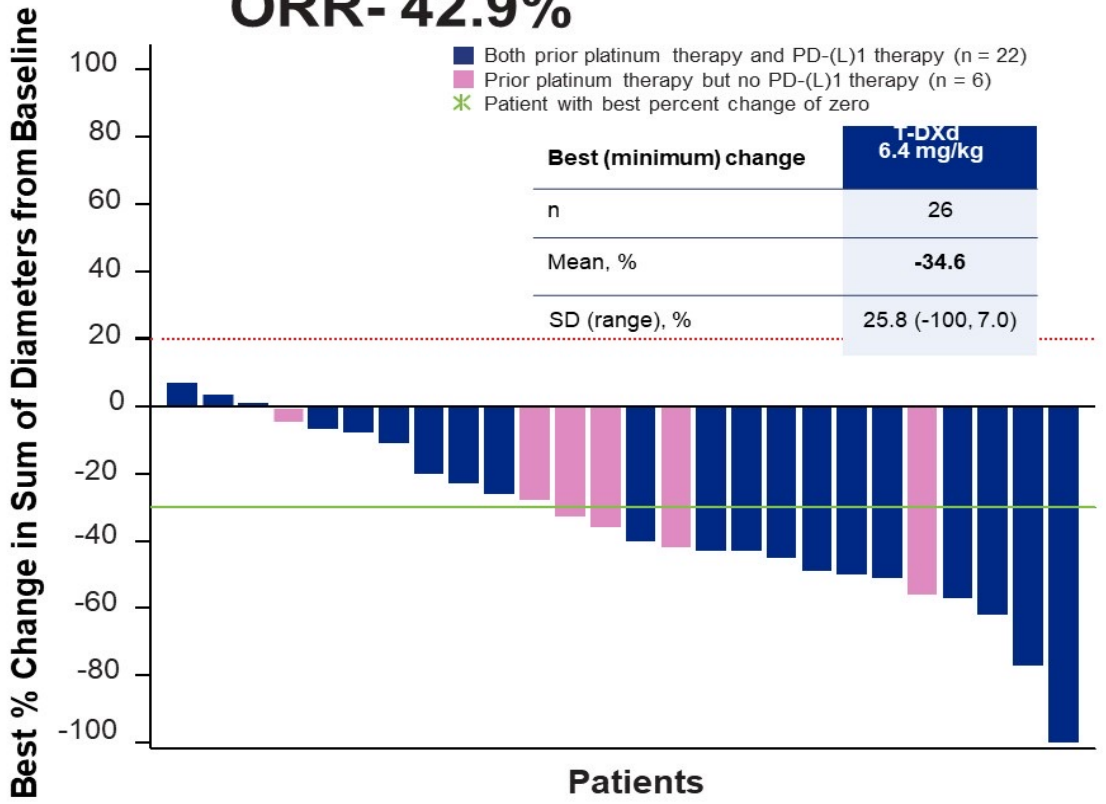
- DCR, disease control rate; DoR, duration of response; DS-8201, trastuzumab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; R, randomized; T-DXd, trastuzumab deruxtecan.
- clinicaltrials.gov. Accessed June 28, 2023.; Goto K, et al. *Ann Oncol*. 2022;33(Supp 7):S1422.

DESTINY-Lung02

T-DXd 5.4 mg/kg (n = 52)
ORR – 53.8%



T-DXd 6.4 mg/kg (n = 28)
ORR- 42.9%

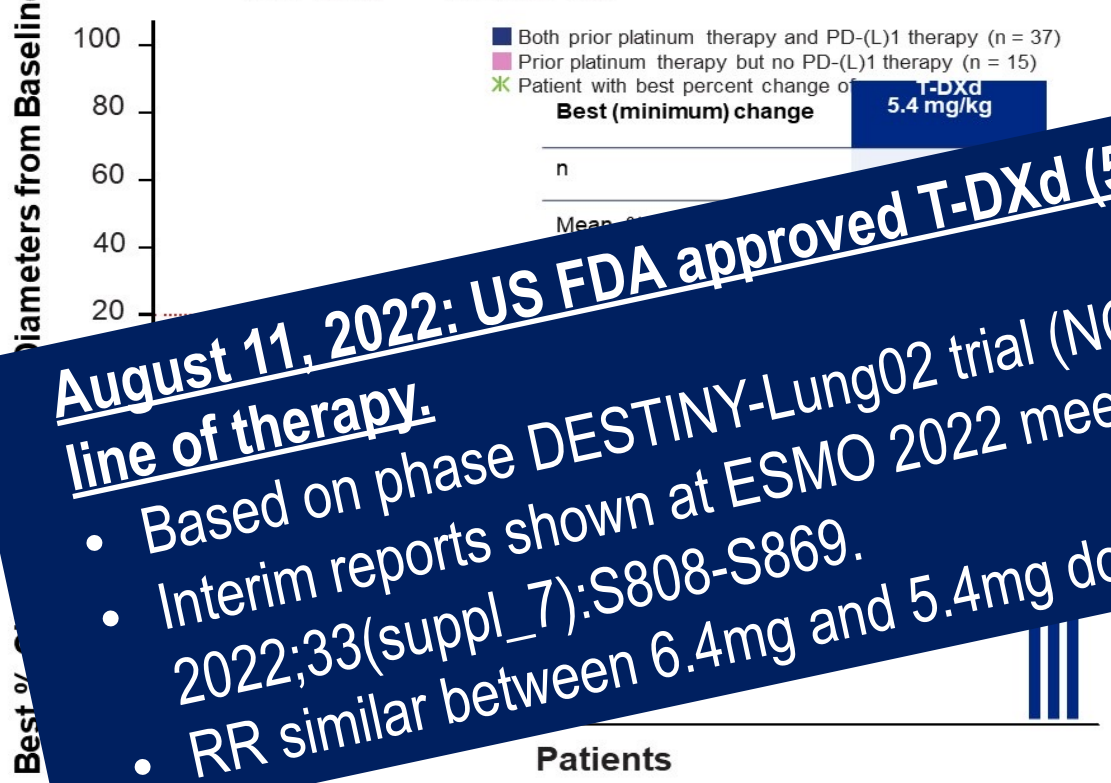


Goto ESMO 2022 NCT04644237

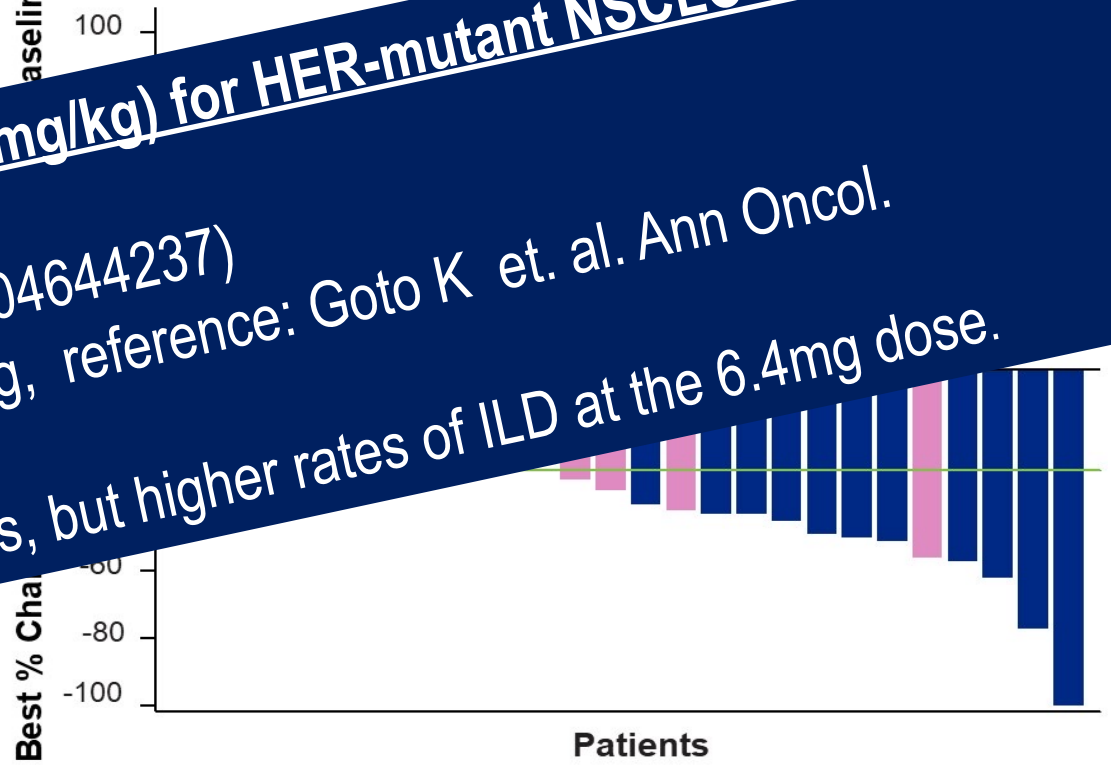
PRESENTED BY: Benjamin J. Solomon MBBS, PhD

DESTINY-Lung02

T-DXd 5.4 mg/kg (n = 52)
ORR – 53.8%



T-DXd 6.4 mg/kg (n = 28)
ORR- 42.9%



August 11, 2022: US FDA approved T-DXd (5.4mg/kg) for HER-mutant NSCLC after one prior line of therapy.

- Based on phase DESTINY-Lung02 trial (NCT04644237)
- Interim reports shown at ESMO 2022 meeting, reference: Goto K et. al. Ann Oncol. 2022;33(suppl_7):S808-S869.
- RR similar between 6.4mg and 5.4mg doses, but higher rates of ILD at the 6.4mg dose.

Goto ESMO 2022 NCT04644237

PRESENTED BY: Benjamin J. Solomon MBBS, PhD

Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small-Cell Lung Cancer: Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial

Koichi Goto, MD, PhD[1]; Yasushi Goto, MD, PhD[2]; Toshio Kubo, MD, PhD[3]; Kiichiro Ninomiya, MD, PhD[4]; Sang-We Kim, MD, PhD[5]; David Planchard, MD, PhD[6]; Myung-Ju Ahn, MD, PhD[7]; Egbert F. Smit, MD, PhD[8]; Adrianus Johannes de Langen, MD, PhD[9]; Maurice Pérol, MD[10]; Elvire Pons-Tostivint, MD, PhD[11]; Silvia Novello, MD, PhD[12]; Hidetoshi Hayashi, MD, PhD[13]; Junichi Shimizu, MD, PhD[14]; Dong-Wan Kim, MD, PhD[15]; Chih-Hsi Kuo, MD, PhD[16]; James Chih-Hsin Yang, MD, PhD[17]; Kaline Pereira, MD, PhD[18]; Fu-Chih Cheng, PhD[18]; Ayumi Taguchi, PharmD[19]; Yingkai Cheng, MD, PhD[18]; Wenqin Feng, PhD[18]; Zenta Tsuchihashi, PhD[18]; and Pasi A. Jänne, MD, PhD[20]

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ABSTRACT

PURPOSE Trastuzumab deruxtecan (T-DXd) 5.4 and 6.4 mg/kg showed robust antitumor activity in multiple cancer indications; however, T-DXd 5.4 mg/kg has not been evaluated in patients with previously treated human epidermal growth factor receptor 2–mutant (*HER2*m; defined as single-nucleotide variants and exon 20 insertions) metastatic non–small-cell lung cancer (mNSCLC).

METHODS DESTINY-Lung02, a blinded, multicenter, phase II study, investigated T-DXd 5.4 mg/kg once every 3 weeks for the first time in previously treated (platinum-containing therapy) patients with *HER2*m mNSCLC and further assessed T-DXd 6.4 mg/kg once every 3 weeks in this population. The primary end point was confirmed objective response rate (ORR) per RECIST v1.1 by blinded independent central review.

RESULTS One hundred fifty-two patients were randomly assigned 2:1 to T-DXd 5.4 or 6.4 mg/kg once every 3 weeks. As of December 23, 2022, the median duration of follow-up was 11.5 months (range, 1.1-20.6) with 5.4 mg/kg and 11.8 months (range, 0.6-21.0) with 6.4 mg/kg. Confirmed ORR was 49.0% (95% CI, 39.0 to 59.1) and 56.0% (95% CI, 41.3 to 70.0) and median duration of response was 16.8 months (95% CI, 6.4 to not estimable [NE]) and NE (95% CI, 8.3 to NE) with 5.4 and 6.4 mg/kg, respectively. Median treatment duration was 7.7 months (range, 0.7-20.8) with 5.4 mg/kg and 8.3 months (range, 0.7-20.3) with 6.4 mg/kg. Grade ≥ 3 drug-related treatment-emergent adverse events occurred in 39 of 101 (38.6%) and 29 of 50 (58.0%) patients with 5.4 and 6.4 mg/kg, respectively. 13 of 101 (12.9%) and 14 of 50 (28.0%) patients had adjudicated drug-related interstitial lung disease (2.0% grade ≥ 3 in each arm) with 5.4 and 6.4 mg/kg, respectively.

CONCLUSION T-DXd demonstrated clinically meaningful responses at both doses. Safety profile was acceptable and generally manageable, favoring T-DXd 5.4 mg/kg.

Goto, K et al J Clin Oncol 41:4852-4863, 2023

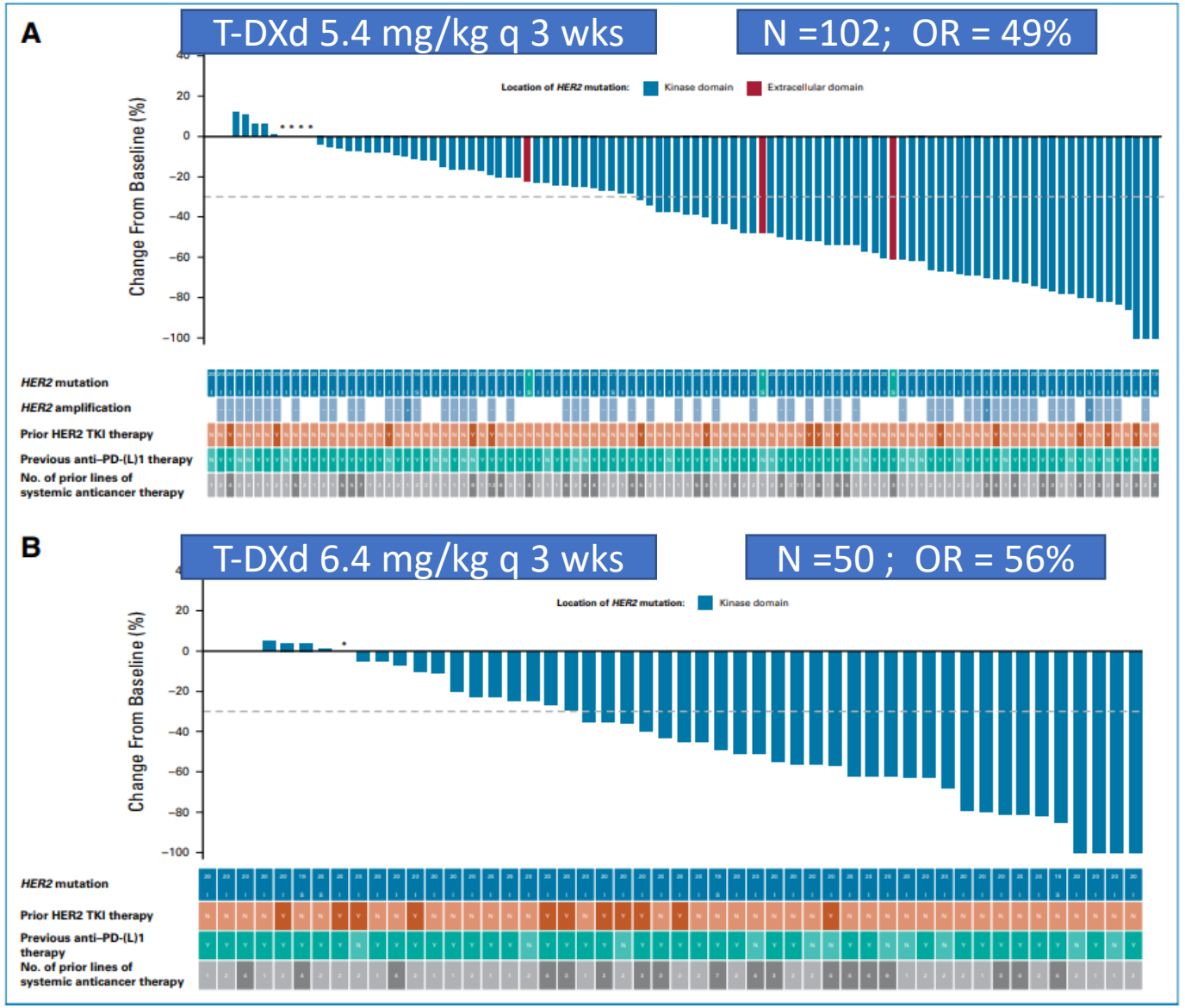
Trastuzumab Deruxtecan (T-DXd;DS-8201): DESTINY 2

TABLE 1. Patient Baseline Characteristics and Prior Therapies (continued)

Baseline Characteristic	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
Platinum-based therapy	102 (100.0)	50 (100.0)
Anti–PD-(L)1	75 (73.5)	39 (78.0)
Platinum and anti–PD-(L)1 (in combination)	51 (50.0)	29 (58.0)
Platinum and anti–PD-(L)1 (not in combination)	24 (23.5)	10 (20.0)
Docetaxel	30 (29.4)	17 (34.0)
Prior radiation therapy, No. (%)	58 (56.9)	25 (50.0)
Prior cancer surgery, No. (%)	25 (24.5)	13 (26.0)

TABLE 2. Response to T-DXd in Patients With *HER2*-Mutant mNSCLC

Response Assessment by BICR	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
Confirmed ORR, No. (%)	50 (49.0)	28 (56.0)
95% CI	39.0 to 59.1	41.3 to 70.0
Best confirmed overall response, No. (%)		
CR	1 (1.0)	2 (4.0)
PR	49 (48.0)	26 (52.0)
SD	45 (44.1)	18 (36.0)
PD	4 (3.9)	2 (4.0)
Nonevaluable[a]	3 (2.9)	2 (4.0)
DCR, No. (%)	95 (93.1)	46 (92.0)
95% CI	86.4 to 97.2	80.8 to 97.8
DoR, months, median (95% CI)	16.8 (6.4 to NE)	NE (8.3 to NE)
TTIR, months, median (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Follow-up, months, median (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)

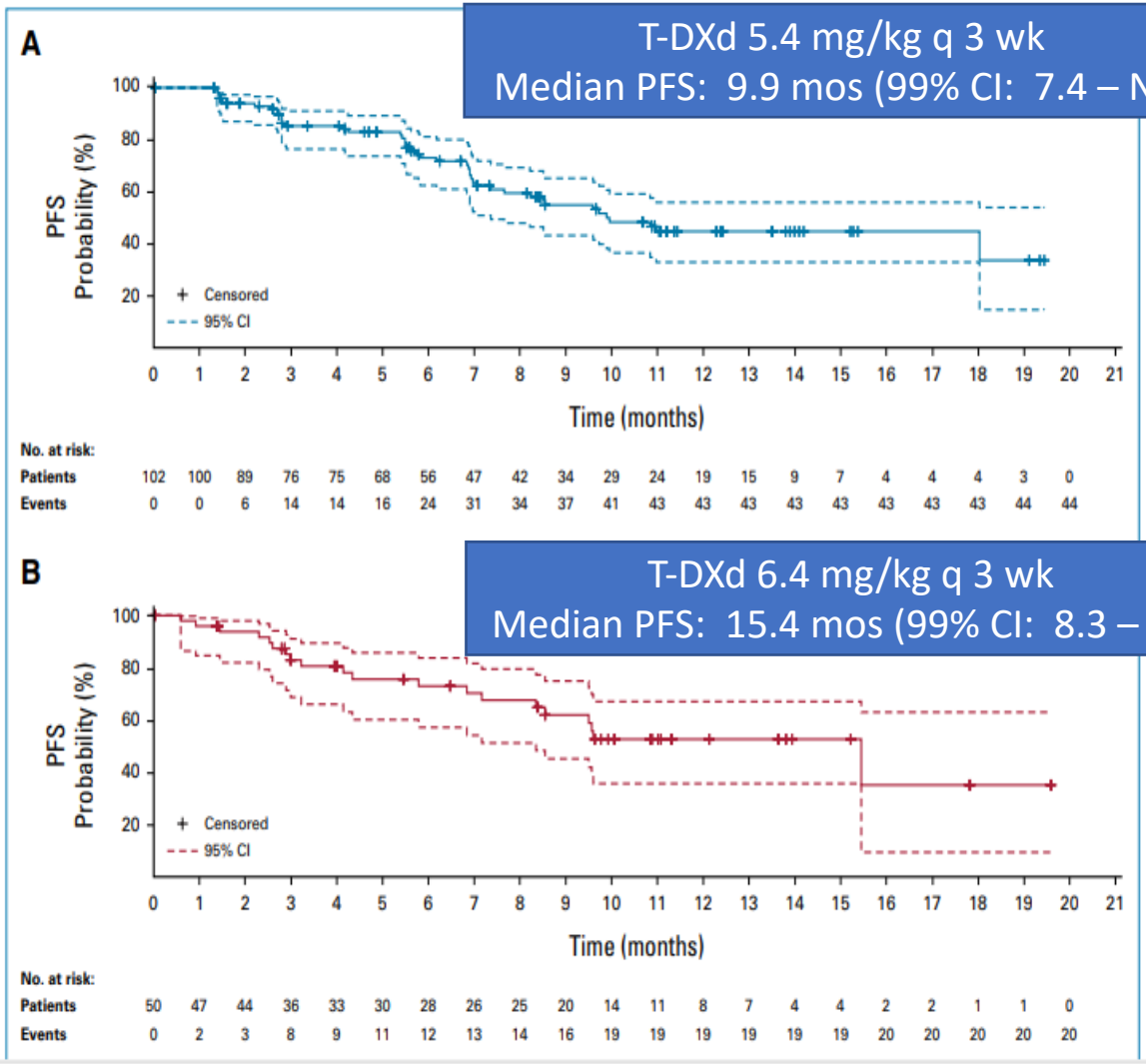


Goto, K et al J Clin Oncol 41:4852-4863, 2023

Trastuzumab Deruxtecan (T-DXd;DS-8201): DESTINY 2

PFS

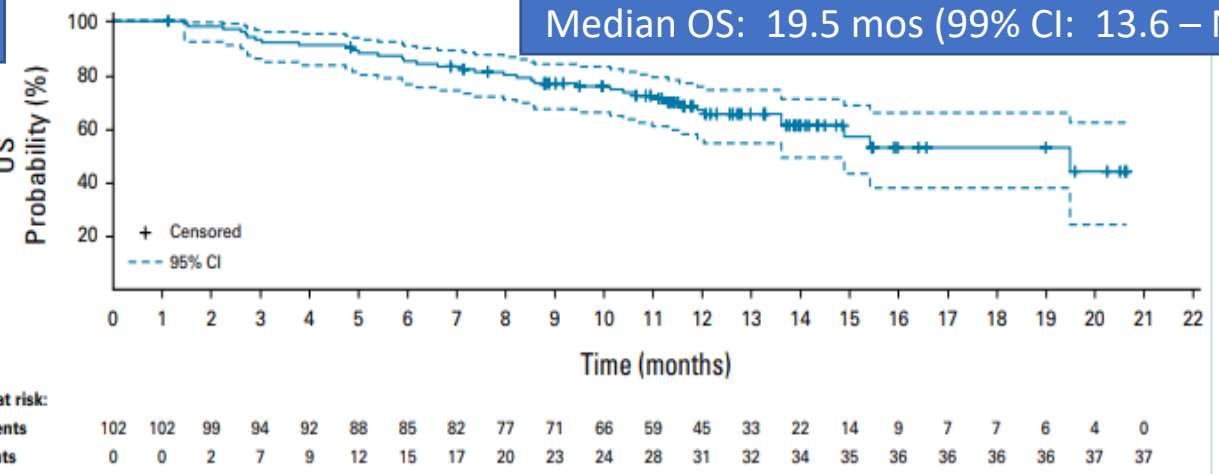
T-DXd 5.4 mg/kg q 3 wk
Median PFS: 9.9 mos (99% CI: 7.4 – NE)



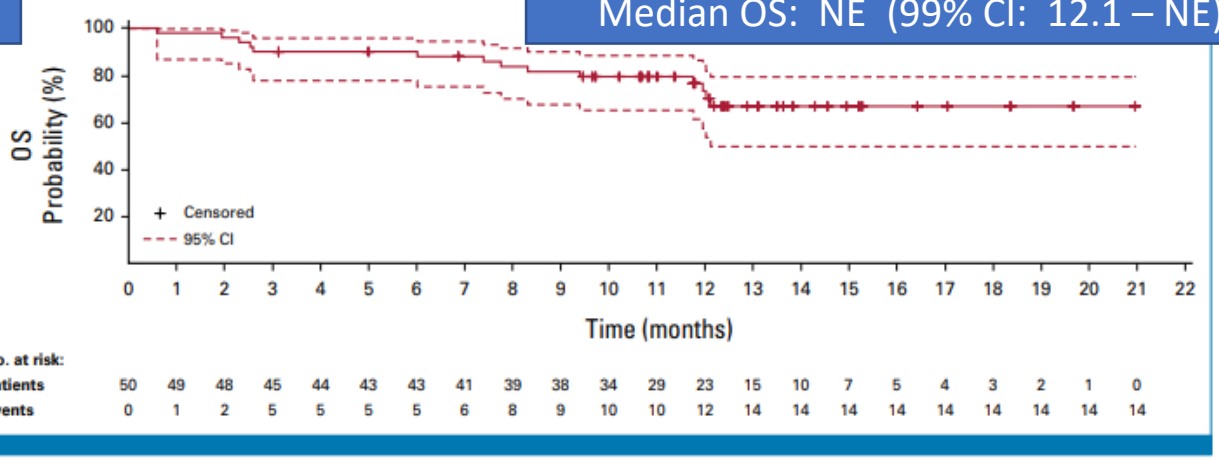
T-DXd 6.4 mg/kg q 3 wk
Median PFS: 15.4 mos (99% CI: 8.3 – NE)

OS

T-DXd 5.4 mg/kg q 3 wk
Median OS: 19.5 mos (99% CI: 13.6 – NE)



T-DXd 6.4 mg/kg q 3 wk
Median OS: NE (99% CI: 12.1 – NE)



Goto, K et al. J Clin Oncol 41:4852-4863, 2023

Trastuzumab Deruxtecan (T-DXd;DS-8201): ORR% and Toxicity

DESTINY-Lung02 Trial: PFS and OS in patients with *HER2*-mutant NSCLC

Response assessment by BICR	5.4 mg/kg (N = 102)	6.4 mg/kg (N = 50)
cORR*, n (%) 95% CI	50 (49) 39.0–59.18	28 (56) 41.3 –70.0
Best confirmed response, n (%)		
Complete response	1 (1.0)	2 (4.0)
Partial response	49 (48.0)	26 (52.03)
Stable disease	45 (44.1)	19 (36.0)
Progressive disease	4 (3.9)	2 (4.0)
Response could not be evaluated	3 (2.9)	2 (4.0)
Disease control†, n (%) 95% CI	95 (93.1) 86.4–97.2	46 (92.0) 80.8 –97.8
Median duration of response (95% CI), mos	16.8 (6.4–NE)	NE (8.3 –NE)
F/U mos , median (range)	11.5 (1.1-20.6)	11.9 (0.6-21.0)

*cORR was assessed by blinded independent central review.
†Disease control was defined as complete response, partial response, or stable disease at 6 weeks with no progression.

DESTINY-Lung02 Trial: Safety outcomes: updates based on Goto

Safety (SAS), %	5.4 mg/kg (N = 101)	6.4 mg/kg (N = 50)
Drug-related TEAEs		
All grade	92.1	100.0
Grade ≥3	**38.6**	**58.0**
Dose reduction	**16.8**	**32**
Discontinuation	**14.9**	**26**
Dose interruption	**26.7**	**48.0**

In the safety analysis set:

Any grade adjudicated drug-related ILD:

- **6.4mg/kg arm – 7 (28%); grade 5 in 1 (2%)**
- **5.4mg/kg arm – 6 (12.9%): grade 5 in 1 (1%)**

CI, confidence interval; cORR, confirmed objective response rate; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; NE, not evaluable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.
Goto K, et al. *Ann Oncol*. 2022;33(Supp 7):S1422.

Goto, K et al J Clin Oncol 41:4852-4863

Trastuzumab Deruxtecan (T-DXd;DS-8201): [illegible] Toxicity

DESTINY-Lung02 Trial: PFS and OS in patients with *HER2*-mutant NSCLC [illegible] **mes: updates**

Response assessment by BICR	6.4 mg/kg (N = 50)
cORR*, n (%) 95% CI	
Best confirmed resp	100.0
Complete response	**58.0**
Partial response	**32**
Stable disease	
Progressive disease	**26**
Response could not be e	**48.0**
Disease control†, n (%) 95% CI	
Median duration of response	
F/U mos , median (range)	

ug-related ILD:
[illegible] – 7 (28%); grade 5 in 1 (2%)
[illegible]mg/kg arm – 6 (12.9%): grade 5 in 1 (1%)

*cORR was assessed by blinded independent ce
†Disease control was defined as complete respo [illegible] ession.

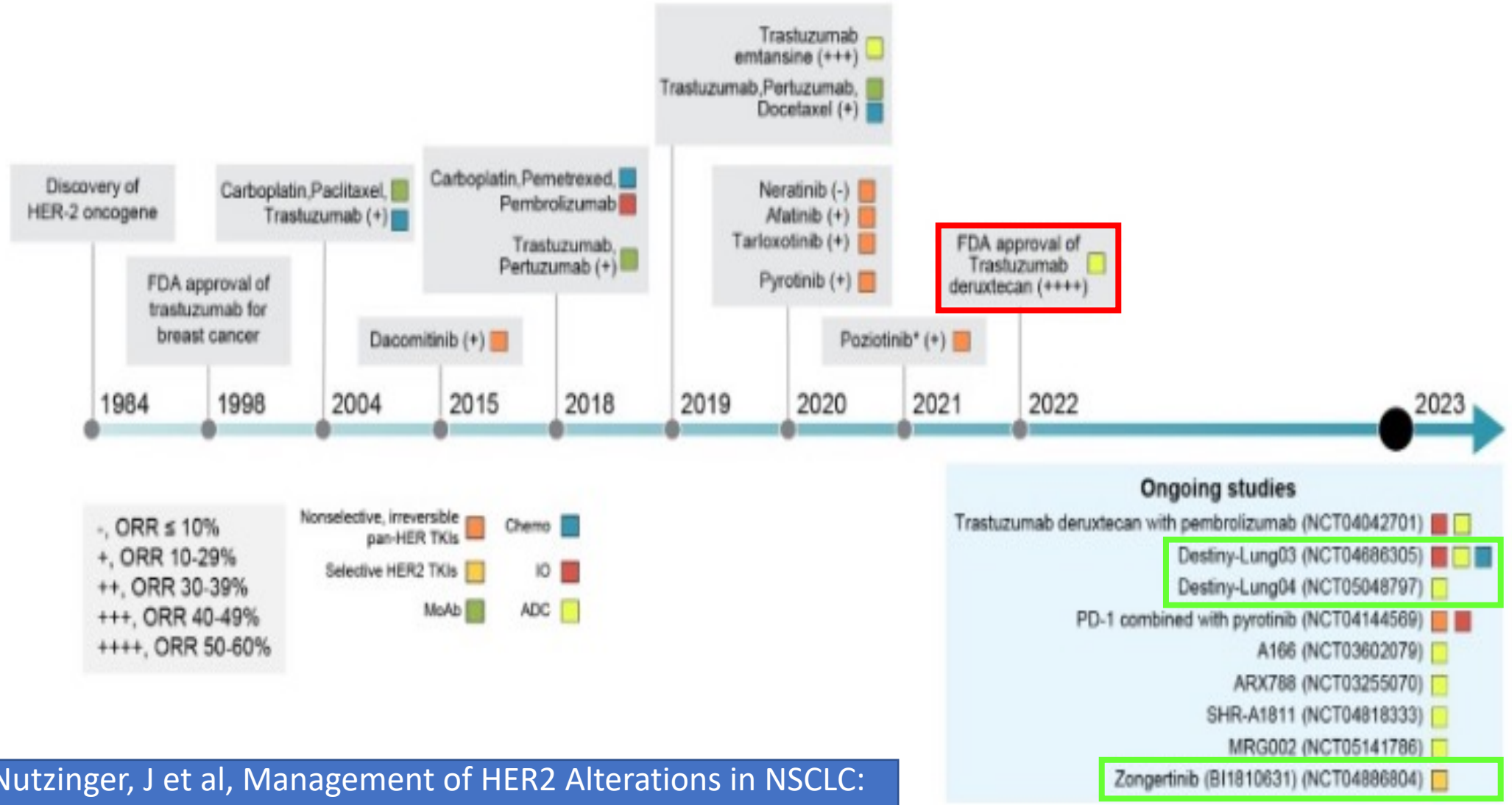
CI, confidence interval; cORR, confirmed objectiv [illegible] OR, duration of response; HER2, human epidermal growth factor receptor 2; NE, not evaluable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; T-
Goto K, et al. *Ann Oncol*. 2022;33(Supp 7):S1422.

T-DXd

- yielded deep, durable repsonses, matching or exceeding results seen in Phase I-II studies
- ORR% independent of CNS status or # prior lines of Tx
- Approved in 2L (not yet in 1L)
- 5.4 mg/kg IV q 3 wk dose chosen: similar efficacy, reduced toxicity

Goto, K et al J Clin Oncol 41:4852-4863

HER-2 mt (+) NSCLC Tx Landscape

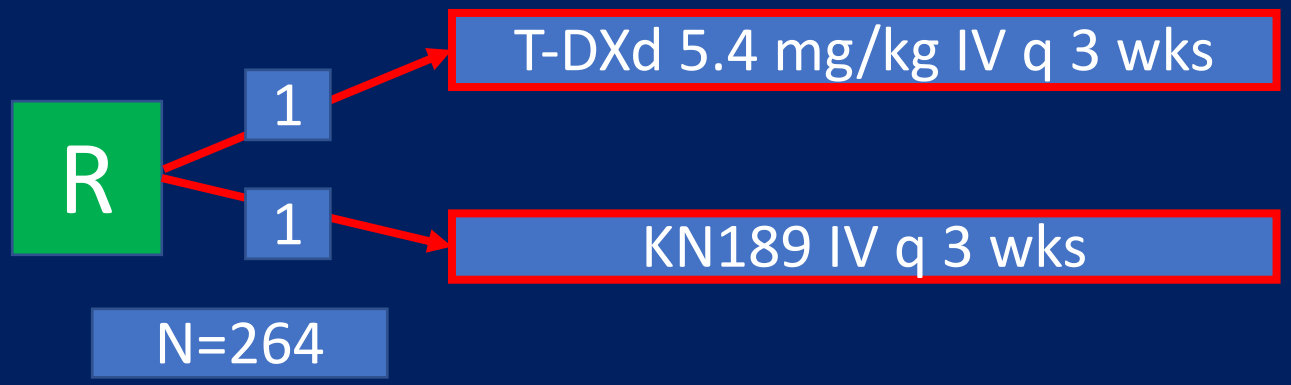


Nutzinger, J et al, Management of HER2 Alterations in NSCLC: the past, present and future, December 2023, 107385, Vol 189

DESTINY LUNG 03 and 04

- DESTINY-LUNG04 randomize Tx-naïve pts to T-DxD vs KN189 (NCT05048797)

Eligibility
- Tx-naïve, recurrent or mNSCLC
- HER2 mt (+) by either ctDNA or tissue
- "Controlled" CNS mets

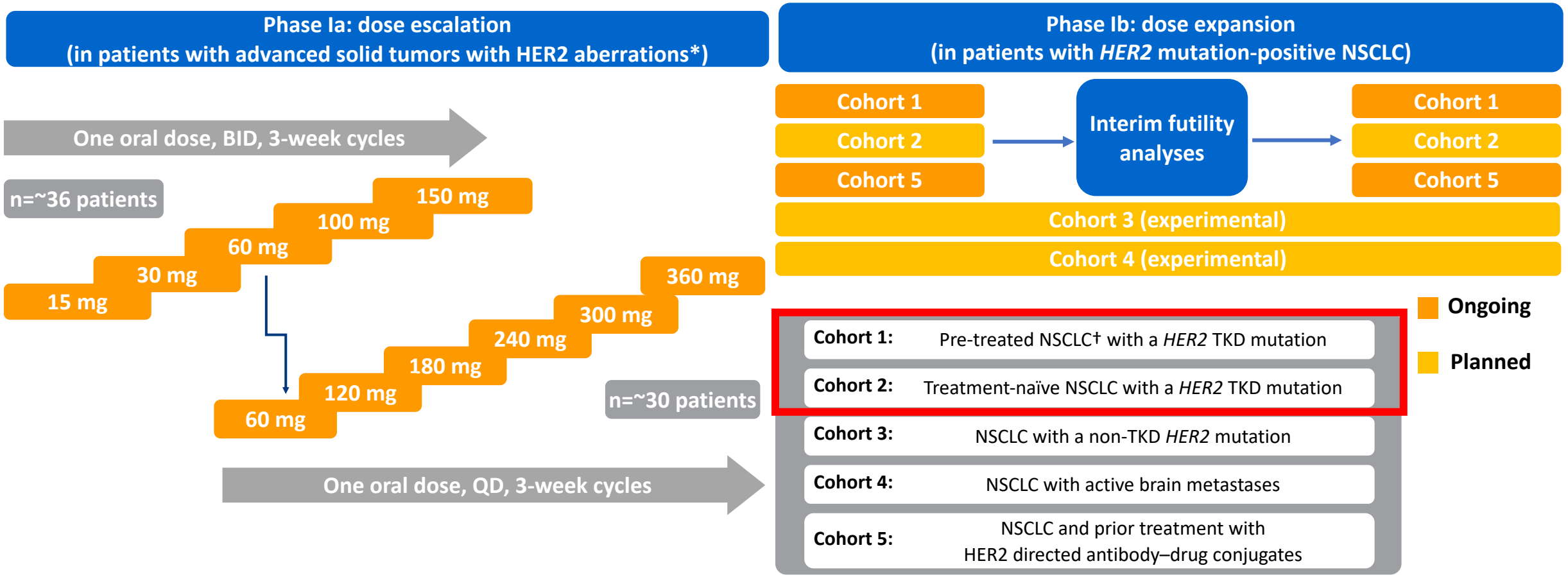


- Primary Endpoint: PFS by RECIST (BICR)
- Seondary Endpoints: OS, ORR, DOR, iPFS, PFS2, CNS PFS, landmark OS 24 mos, safety, tolerability, PKs, etc
- Estimated completion date: 2027

- DESTINY-LUNG03 Multi-arm P2 TDxD + Durvalumab + either Carbo, DDP, or PEM (NCT04686305)

Small molecule tki's: BI 1810631: Zongertinib

- Zongertinib (BI 1810631) is a novel TKI that covalently and selectively binds to the TKD of HER2, and is under investigation as an oral treatment for NSCLC tumors harboring HER2 TKD mutations, including ex20ins mutations



Opdam et al. WCLC 2023

Small molecule tki's: BI 1810631: Zongertinib

Phase Ib baseline characteristics and preliminary safety

Characteristic	Phase Ib (N=42)
Median age, years (range)	62.0 (34–80)
Female sex, n (%)	22 (52.4)

Phase Ib TRAEs (%*)	Any	Grade ≥3
Any TRAE	**66.7**	**9.5**
Diarrhea	28.6	-
Rash†	21.4	-
AST increased	9.5	2.4
Decreased appetite	9.5	-
Dysgeusia	9.5	-

- To date, 42 patients have been treated in Phase Ib in Cohort 1
- Three patients had DLTs (all 240 mg)
  - Two patients in MTD evaluation period: Grade 3 febrile neutropenia; Grade 4 immune thrombocytopenia
  - One patient in the on-treatment period: Grade 3 ALT and AST increased, and Grade 4 neutrophil count decreased
- One patient with dose reduction due to TRAEs (Grade 3 febrile neutropenia and neutrophil count decreased)
- No discontinuations due to adverse events
- Two patients with serious TRAEs (Grade 3 ALT and AST increased; Grade 4 immune thrombocytopenia and neutrophil count decreased)

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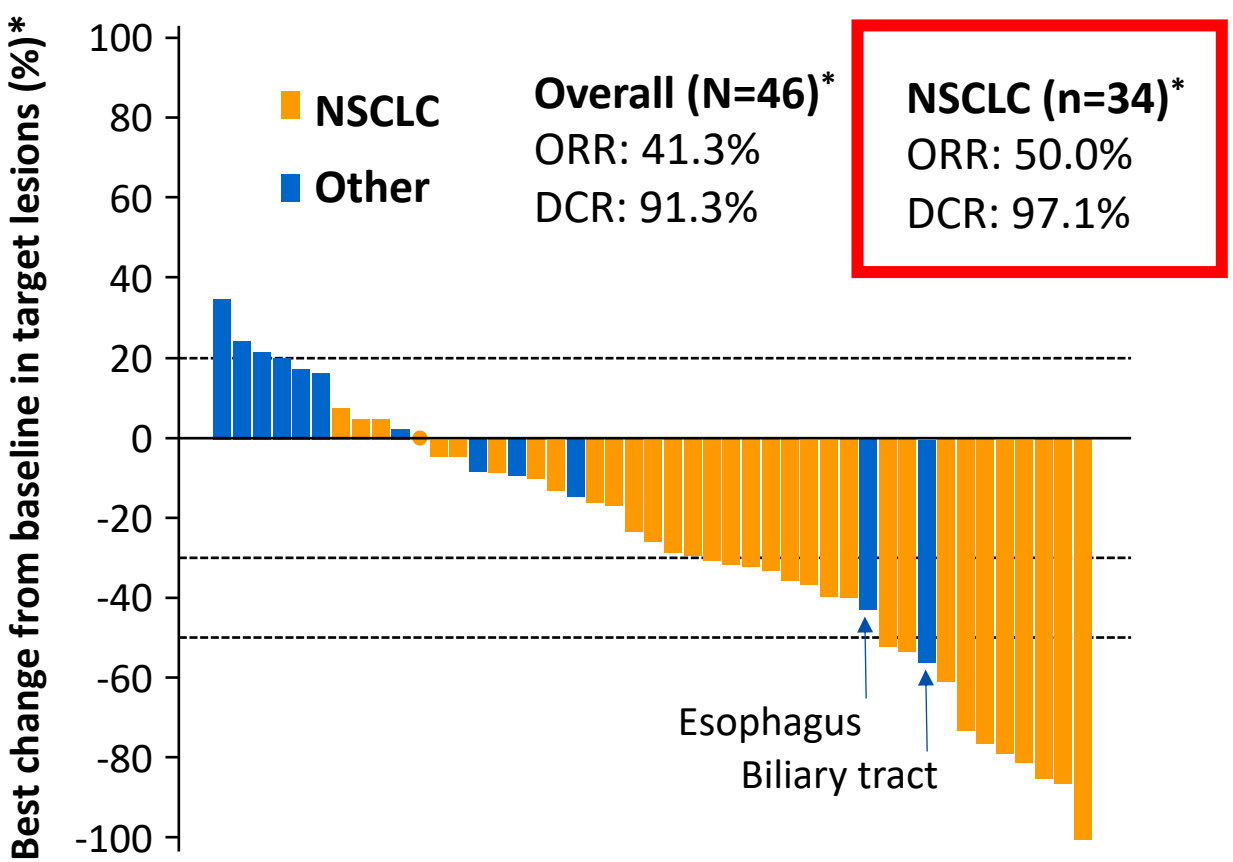
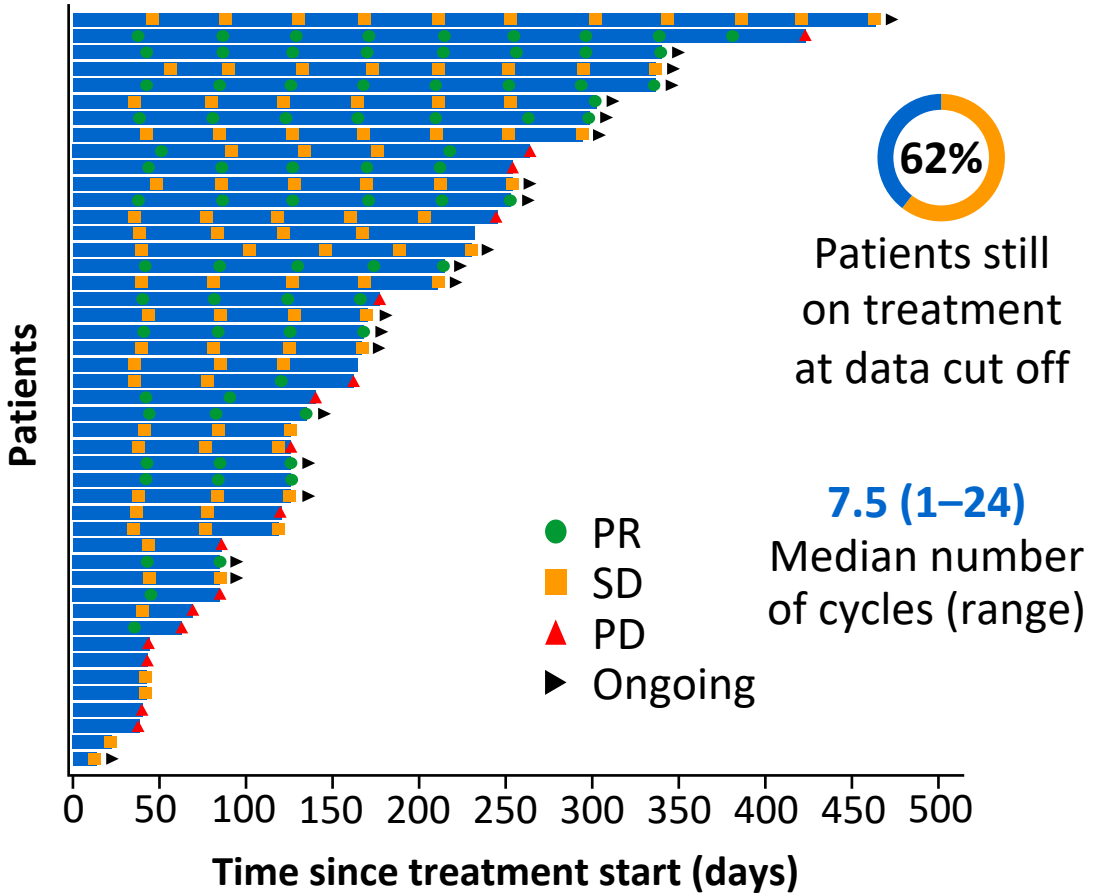
Small molecule tki's: BI 1810631: Zongertinib

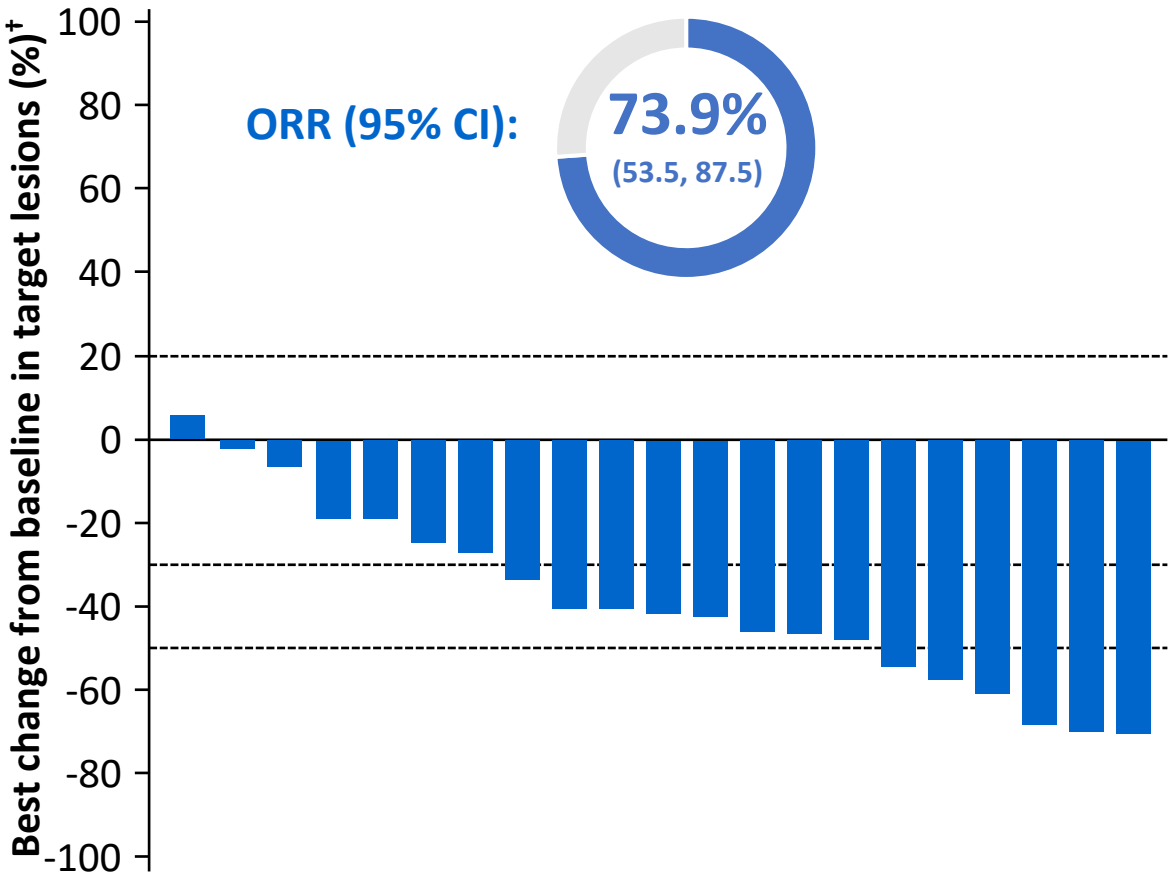
Antitumor response in Phase Ia





Opdam et al. WCLC 2023

Zongertinib: Antitumor activity in Phase Ib



Overall (N=23)*

- First interim analysis in Cohort 1 passed
- Patients included in efficacy analysis all had between 2–5 cycles of Tx at cut off
- DCR: 91.3%
- Median best percentage change from baseline in target lesions: -41.2%

HER2 Summary: NSCLC

- Mutation incidence: < 3-3.5%; amplification in ~ 2%; 3+ IHC expression: 5-10%
- No routine role for HER2 IHC or FISH (yet) in Tx decision-making
- Starting to see agents with substantial activity against HER2 mutant NSCLC
  - Trastuzumab Deruxtecan holds the greatest promise and is FDA approved in the 2L –
    - Best RR% and PFS to date
    - Unclear if it should be considered 1st line as well
  - Need more data on emerging agents – Zongertinib data "appear" promising
  - Need to balance toxicity against efficacy
- For available agents, HER2 amplification/overexpression does not seem to be a consistent driver
  - Somewhat surprising for ADC's given mechanism of action
- Salvage Tx or 1st Line Tx: Carbo/Pem +/- Bev; unclear if Chemo-IO is an advisable strategy
- Research underway to decipher HER2 signaling, HER2 targeted combinations, utility in the neoadjuvant and adjuvant setting, toxicity mitigation.

Thank you for your attention!!!

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