# HER2 IN NSCLC

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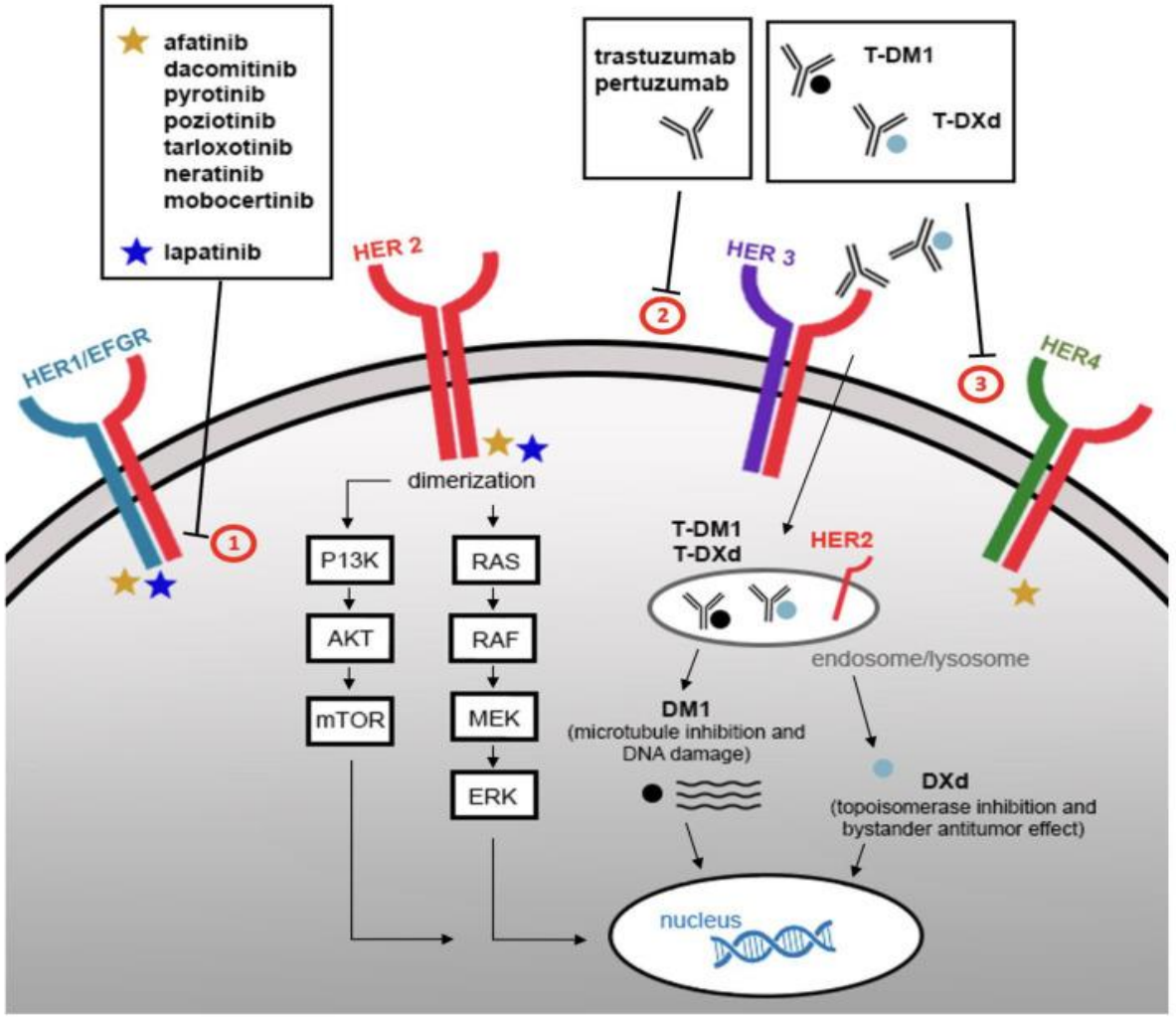
# HER2 in NSCLC

- HER alterations include –
  - Overexpression – IHC (2-20%)
  - Amplification – FISH (~3%)
  - **Mutations – NGS (2-4%)**





1. Uy NF et al. Cancers 14:4155, 2022
2. Brazel D et al.BioDrugs 36:777, 2022

**Table 3.** Studies Examining the Association of *HER2* Amplification and Mutation in Lung Cancers

| | *HER2* Amplification | | | *HER2* Mutation | | | Overall Overlap |
|---|---|---|---|---|---|---|---|
| Study | Method (Definition of Amplification) | Frequency (%) | Coexisting Mutation in Cases of *HER2* Amplification (%) | Method | Frequency (%) | Coexisting Amplification in Cases of *HER2* Mutation (%) | Frequency of Coexisting *HER2* Amplification and Mutation in Cases Tested for Both |
| Li et al. (this study) | FISH (HER2-to-CEP17 ratio ≥2) | 5 of 175 (3%) | 0 of 5 (0%) | Fragment analysis, mass spectrometry and Sanger sequencing | 4 of 148 (3%) | 0 of 4 (0%) | 0 of 148 (0%) |
| TCGA[3] | NGS, whole exome (significant copy number gain, computational algorithm) | 2 of 230 (1%) | 0 of 2 (0%) | NGS, whole exome | 5 of 230 (2%) | 0 of 5 (0%) | 0 of 230 (0%) |
| Arcila et al.[1] | FISH (HER2-to-CEP17 ≥2) | 1 of 50 (2%) | 0 of 1 (0%) | Fragment analysis, mass spectrometry, and Sanger sequencing | 25 of 1478 (2%) | 0 of 11 (0%) | 0 of 50 (0%) |
| Li et al.[6] | FISH (HER2-to-CEP17≥2 or homogeneous staining regions with ≥15 copies in ≥10% of cells) | Unknown | Unknown | Direct sequencing | 8 of 224 (4%) | 4 of 8 (50%) | 4 of 8 (50%) |
| Mazieres et al.[13] | FISH (HER2-to-CEP17 >2 or homogeneous staining regions with >15 copies in >10% of cells) | Unknown | Unknown | Direct sequencing | 65 of 3800 (2%) | 3 of 34 (9%) | 3 of 34 (9%) |
| Yoshizawa et al.[7] | FISH and DISH (HER2-to-CEP17 >2) | By FISH: 5 of 243 (2%) DISH: 9 of 243 (4%) | By FISH: 2 of 5 (40%) DISH: 2 of 9 (22%) | Direct sequencing | 6 of 220 (3%) | 2 of 6 (33%) | 2 of 220 (1%) |
| Suzuki et al.[14] | Brightfield ISH (HER2-to-CEP17 ≥2) | 222 of 1170 (19%) | 25 of 222 (11%) | Direct sequencing | 46 of 1275 (4%) | 25 of 44 (57%) | 25 of 1170 (2%) |

*HER2*, human epidermal growth factor receptor 2 gene; CEP17, chromosome enumeration probe 17; FISH, fluorescence in situ hybridization; TCGA, The Cancer Genome Atlas Research Network; NGS, next-generation sequencing; DISH, dual in situ hybridization; ISH, in situ hybridization (brightfield).

**159/7375 (2.1%)**

Li B et al. J Thoracic Oncol 11:414-419, 2016

# HER2 Mutations in NSCLC

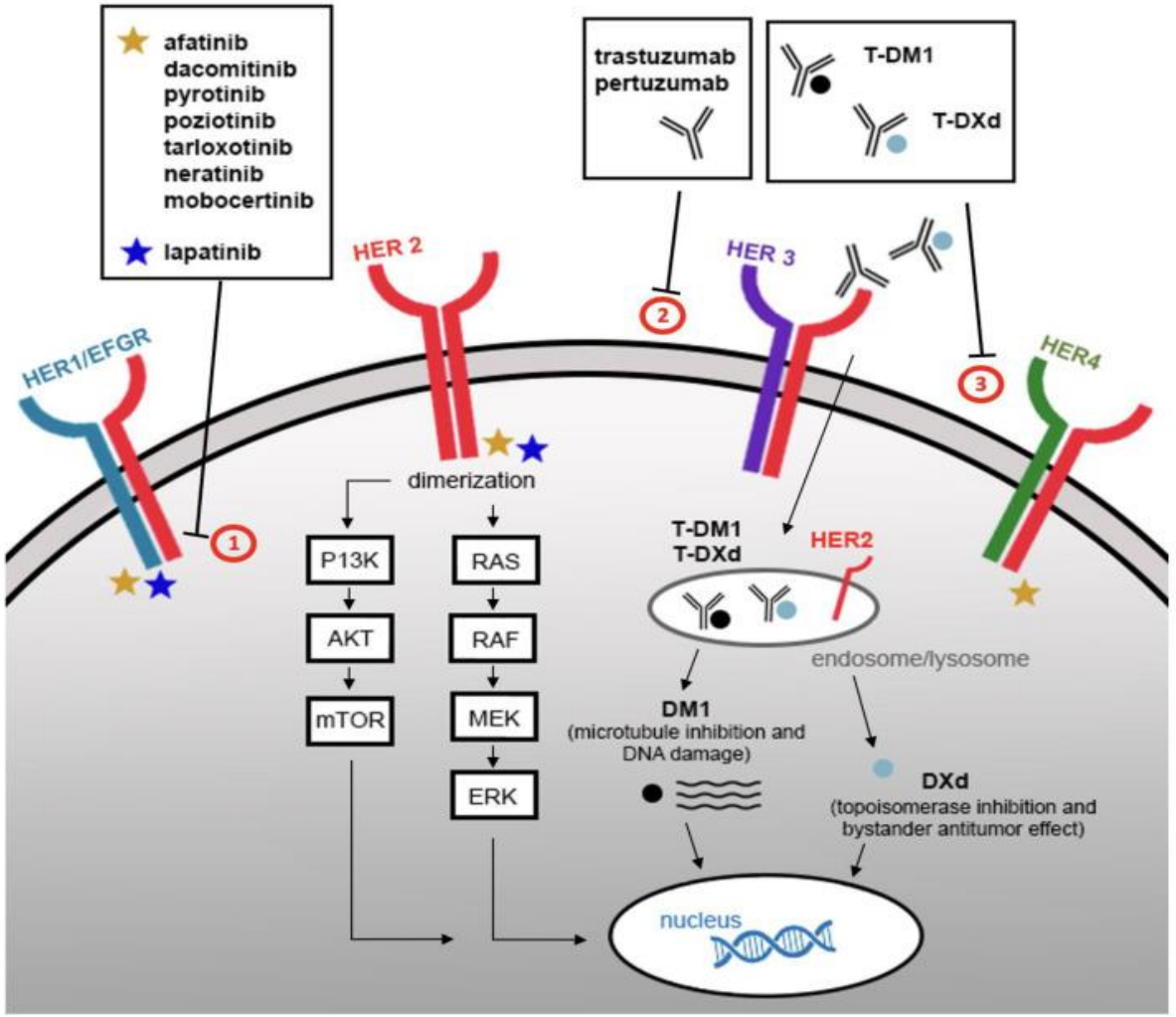
- HER2 mutations seen in 2-4% of advanced NSCLC
- Most common – A775_G776insYVMA
- Mutations lead to constitutive activation of the receptor which is ligand independent (true oncogenic driver mutation)
- Associated with female sex and never smokers
- Can be a mechanism of resistance to TKIs
- OS with “standard therapies” – 19-24 months – ORR to CPI 7%, PFS 2.1 mos

Brazel D et al. Biodrugs 36:717-29, 2022

# HER2 in NSCLC

- HER alterations include –
  - Overexpression – IHC (2-20%)
  - Amplification – FISH (~3%)
  - **Mutations – NGS (2-4%)**

- Therapeutic approaches
  - TKIs
  - Monoclonal antibodies
  - ADCs





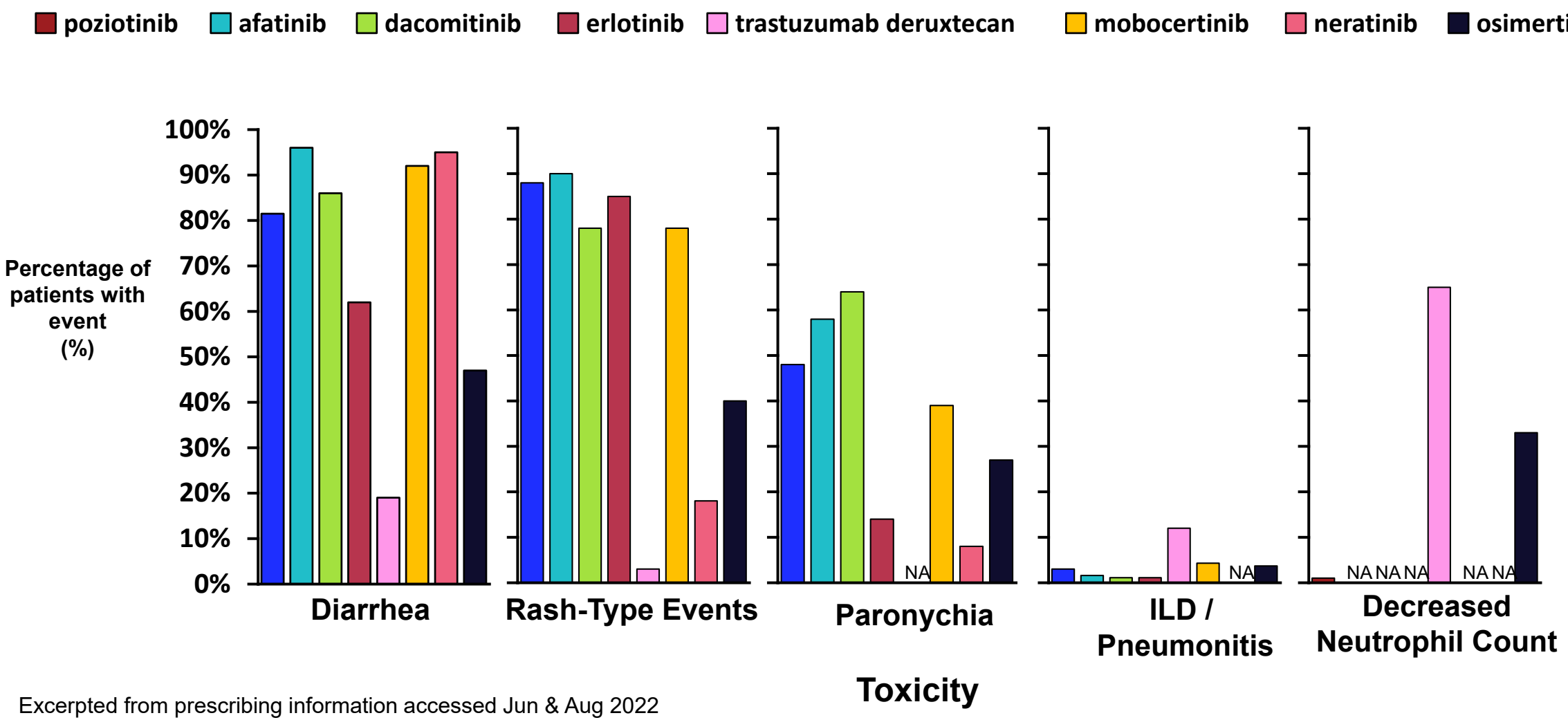
1. Uy NF et al. Cancers 14:4155, 2022
2. Brazel D et al.BioDrugs 36:777, 2022

# TKIs in HER2 exon 20 Mutations in NSCLC

| | ORR (%) | Median PFS (mos) |
|---|---|---|
| Pyrotinib[1,2,3] | 19-53 | 5.6-6.9 |
| Poziotinib[4,5] | 27-28 | 5.5 |
| Tarloxotinib[6] | 22 | n/a |
| Afatinib[7] | 8 | 4.0 |
| Dacomitinib[8] | 12 | 3.0 |
| Neratinib[9] | 0 | 3.0 |
| Neratinib + temsirolimus[9] | 19 | 4.1 |


1. Wang Y et al. Ann Oncol 30:447-55, 2019
2. Zhou C et al. J Clin Oncol 38:2753-61, 2020
3. Song Z et al BMC Med 20:42, 2022
4. Elamin YY et al. J Clin Oncol 40:702-9, 2022
5. Le X et al. J Clin Oncol 40:710-8, 2022
6. Liu SV et al. Ann Oncol 31:S1189, 2020
7. Dziadziuszko R et al J Thorac Oncol 14:1086-94, 2019
8. Kris MG et al Ann Oncol 26:1421-27, 2015
9. Gandhi L et al. J Thorac Oncol 12:S358, 2017

# Comparison of Toxicities with TKIs and HER2 Targeting ADC (Any Grade)




Excerpted from prescribing information accessed Jun & Aug 2022

# Monoclonal Abs in HER2-altered NSCLC

- **Traztuzumab – two studies including HER2 overexpressors or mutations – 0% ORR**
- **Traztuzumab – chemo combinations in HER2 overexpressing NSCLC including a RPhII – "negative"**
- **Pertuzumab – single study as single agent – 0% ORR**
- **2nd line pertuzumab, traztuzumab and docetaxel in HER2 mutated NSCLC – ORR 29%, median PFS 6.8 months**

- **Patient selection an issue in all of these studies**


1. Kinoshita I et al. Ann Oncol 29:viii540, 2018
2. Lara PN et al. Clin Lung Cancer 5;231-6, 2004
3. Langer C et al. Lung Cancer 22:1180-7, 2004
4. Zinner RG et al. Lung Cancer 44:99-110, 2004
5. Gatzemeier U et al. Ann Oncol 15:19-27, 2004
6. Herbst RS et al. Clin Cancer Res 13:6175-81, 2007
7. Mazieres J et al. J Clin Oncol 39:9015, 2021

# ADCs in HER2-altered NSCLC

- T-DM1 – ado-trastuzumab emtansine
  - ph II basket trial – 18 HER2 mutant pts – ORR 44%, PFS 5 mos
  - ph II trial – HER2 altered pts – ORR 7-20%
  - ph II trial – HER2 mutant pts only – ORR 38%, PFS 2.8 mos

- T-DXd – fam-trastuzumab deruxtecan


1. Li BT et al. J Clin Oncol 36:2532-37, 2018
2. Hotta K et al. J Thorac Oncol 13:273-9, 2018
3. Peters S et al. Clin Cancer Res 25:64-72, 2019
4. Iwana E et al. Eur J Cancer 162:99-106, 2022

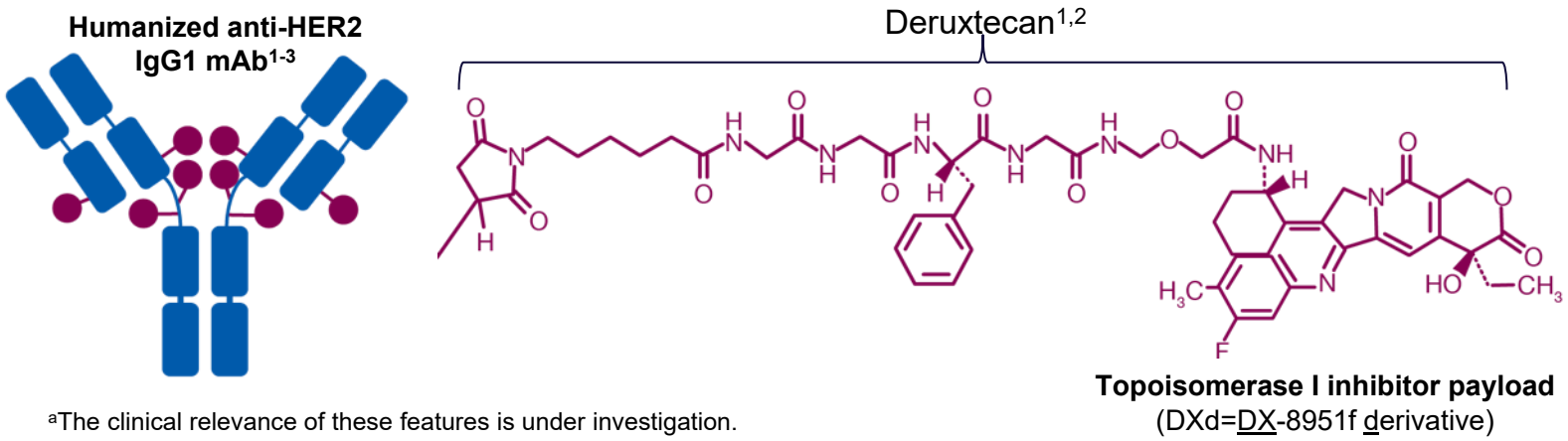
# Trastuzumab Deruxtecan (T-DXd) Is an ADC Designed to Deliver an Optimal Antitumor Effect

**T-DXd is an ADC with 3 components:**

**A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab**

**A topoisomerase I inhibitor payload, an exatecan derivative**

**A tetrapeptide-based cleavable linker**




[a]The clinical relevance of these features is under investigation.

- Payload mechanism of action: topoisomerase I inhibitor [a,1,2]
- High potency of payload [a,1,2]
- High drug to antibody ratio ≈ 8 [a,1,2]
- Payload with short systemic half-life [a,1,2]
- Stable linker-payload [a,1,2]
- Tumor-selective cleavable linker [a,1,2]
- Bystander antitumor effect [a,1,4]

1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther.* 2018;181:126-142.
4. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046.

# DESTINY-Lung01: Interesting observation

- **Study objective**
  - To evaluate the efficacy and safety of trastuzumab deruxtecan in patients with HER2-mutated NSCLC in the DESTINY-Lung01 study

**Key patient inclusion criteria**

- Unresectable/metastatic non-squamous NSCLC
- Relapsed/refectory to standard treatment
- HER2 expressing or HER2-activating mutation
- No prior HER2-targeted therapy
- CNS metastasis allowed

Cohort 1:
HER2-expressing (IHC3+ or IHC2+)
trastuzumab deruxtecan 6.4 mg/kg q3w
(n=90)

**RR: 24%**

Cohort 2:
HER2-mutated
trastuzumab deruxtecan 6.4 mg/kg q3w
(n=91)

**RR: 50%**

**Primary endpoint**

- ORR (ICR)

**Secondary endpoints**

- DCR, DoR, PFS, OS, safety

Li BT, et al. Ann Oncol 2021

# DESTINY-Lung02

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

## Background

- T-DXd 5.4 mg/kg and 6.4 mg/kg showed robust antitumor activity in multiple cancer types; however, T-DXd 5.4 mg/kg has not been evaluated in patients with previously treated *HER2*-mutant (*HER2*m) mNSCLC
- DESTINY-Lung02 assessed the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg in patients with *HER2*m mNSCLC
  - In the interim analysis, T-DXd showed deep and durable responses and an acceptable and generally manageable safety profile[1]
- Herein, we report the **primary analysis results** of DESTINY-Lung02

## 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 of a T-DXd dose with the benchmark ORR of 26.4% (upper limit of the ORR 95% CI in the ramucirumab plus docetaxel arm of the REVEL trial)[2]
- The study was not powered to statistically compare between arms

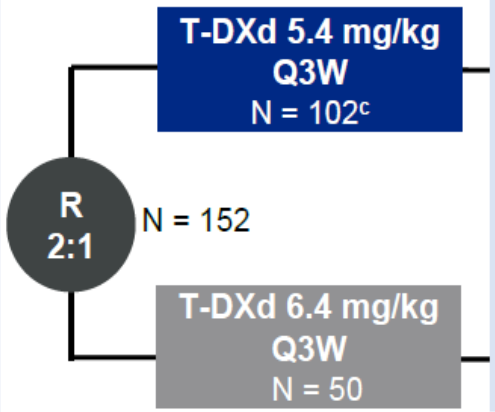
### Key Eligibility Criteria[a]

- Metastatic *HER2*m[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 investigators were blinded to the dose level***

**Primary analysis data cutoff: 23 December 2022**

BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; 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 Tumours version 1.1; T-DXd, trastuzumab deruxtecan.
[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.

1. Goto K et al. *Annals of Oncol*. 2022;33 (suppl_7): S808-S869 2. Garon EB et al. *Lancet*. 2014;384:665-73.

# DESTINY-Lung02: Baseline Characteristics and Efficacy Summary

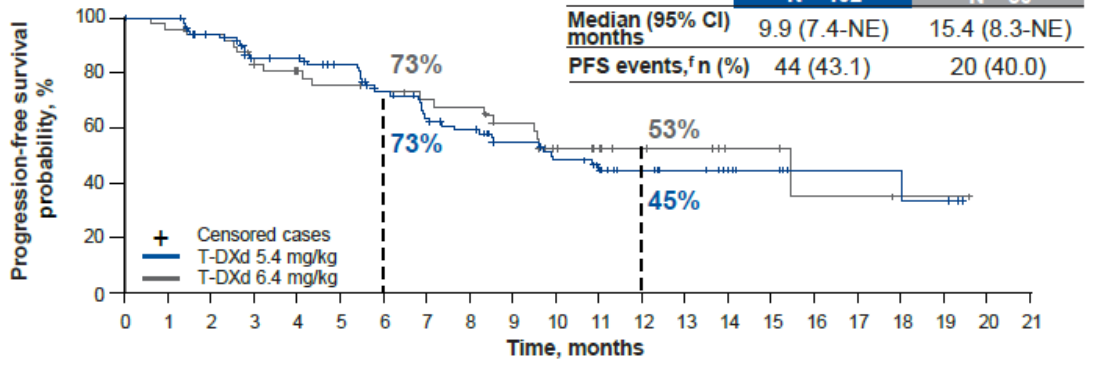
## Baseline Characteristics

In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively:

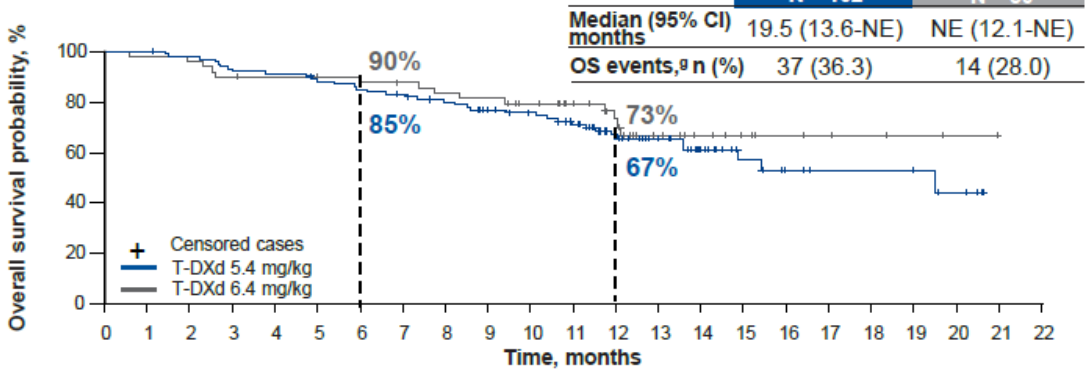
- **Median age** was 59.4 years (range, 31-84) and 61.3 years (range, 28-86)
- Most patients were **female** (63.7% and 68.0%), **from Asia** (61.8% and 60.0%), had **never smoked** (53.9% and 58.0%), and **received prior anti–PD-(L)1 therapy** (73.5% and 78.0%)
- *HER2* mutations were primarily in the **kinase domain** (97.1% and 100%)
- **Baseline CNS metastasis** was present in 34.3% and 44.0% of patients
- **Median prior lines of treatment** was 2 (range, 1-12) and 2 (range, 1-7)

| Efficacy summary | T-DXd 5.4 mg/kg N = 102 | T-DXd 6.4 mg/kg N = 50 |
|---|---|---|
| **Confirmed ORR,[a] n (%)** [95% CI] | **50 (49.0)** [39.0-59.1] | **28 (56.0)** [41.3-70.0] |
| CR \| PR | 1 (1.0) \| 49 (48.0) | 2 (4.0) \| 26 (52.0) |
| SD \| PD | 45 (44.1) \| 4 (3.9) | 18 (36.0) \| 2 (4.0) |
| Non-evaluable[b] | 3 (2.9) | 2 (4.0) |
| **DCR,[c] n (%)** [95% CI] | 95 (93.1) [86.4-97.2] | 46 (92.0) [80.8-97.8] |
| **Median DoR,[d,e] months (95% CI)** | 16.8 (6.4-NE) | NE (8.3-NE) |
| **Median TTIR,[d] months (range)** | 1.8 (1.2-7.0) | 1.6 (1.2-11.2) |
| **Median follow-up, months (range)** | 11.5 (1.1-20.6) | 11.8 (0.6-21.0) |

**PFS**

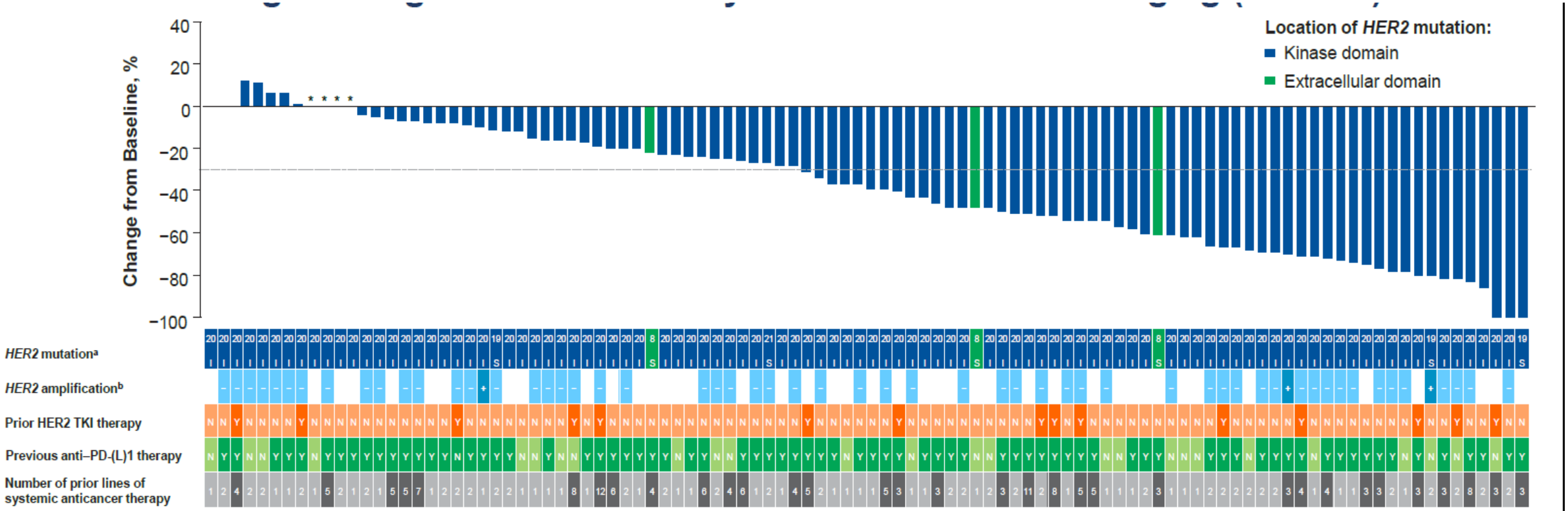



**OS**




BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTIR, time to initial response. [a]Proportion of patients with confirmed CR or PR assessed by BICR per RECIST v1.1. [b]3 patients were non-evaluable at 5.4 mg/kg (1 patient never received treatment due to COVID-19; 2 patients discontinued before first tumor assessment); 2 patients were non-evaluable at 6.4 mg/kg (discontinued due to adverse event before first tumor assessment). [c]Proportion of patients with confirmed CR, PR, or SD assessed by BICR. [d]Assessed by BICR. [e]60.0% and 75.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored. [f]56.9% and 60.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored. [g]63.7% and 72.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored.

# DESTINY-Lung02: Best Percent Change in Tumor Size by BICR with T-DXd 5.4 mg/kg (N=102)

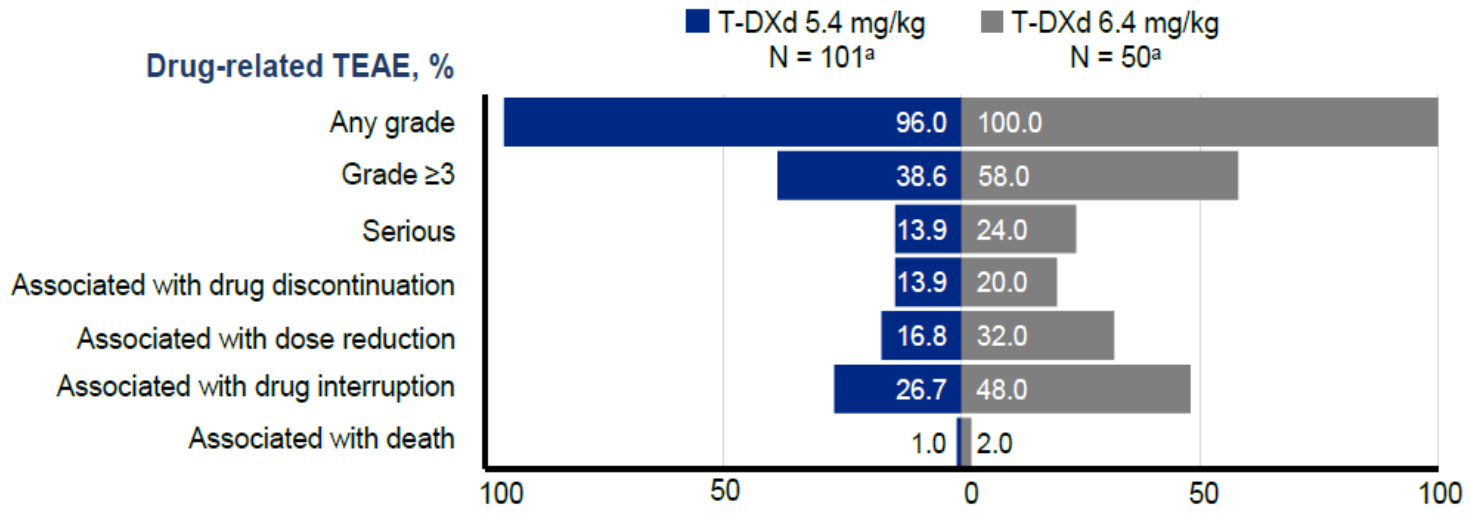



Responses were observed regardless of *HER2* mutation type, *HER2* amplification status, and number or type of prior therapies

BICR, blinded independent central review; I, insertion; HER2, human epidermal growth factor receptor 2; N, no; PD-(L)1, programmed death (ligand)1; S, substitution; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Y, yes. The line at −30% indicates a partial response. *Indicates the patient had 0 best percentage change from baseline in the sum of diameters for all target lesions. Numbers in the *HER2* mutation row indicate in which exon the mutation occurred (8, 19, or 20). *HER2* amplification was only assessed in patients who received T-DXd 5.4 mg/kg. [a]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment. [b]*HER2* amplification status was evaluated using an exploratory Oncomine DX Target test copy number algorithm on NSCLC formalin-fixed paraffin-embedded tissue samples. Thermo Fisher Scientific and its affiliates are not endorsing, recommending, or promoting any use or application of Thermo Fisher Scientific products presented by third parties during this seminar. Information and materials presented or provided by third parties are provided as-is and without warranty of any kind, including regarding intellectual property rights and reported results. Parties presenting images, text and material represent they have the rights to do so.

# DESTINY-Lung02: Overall Safety Summary

## Overall Safety



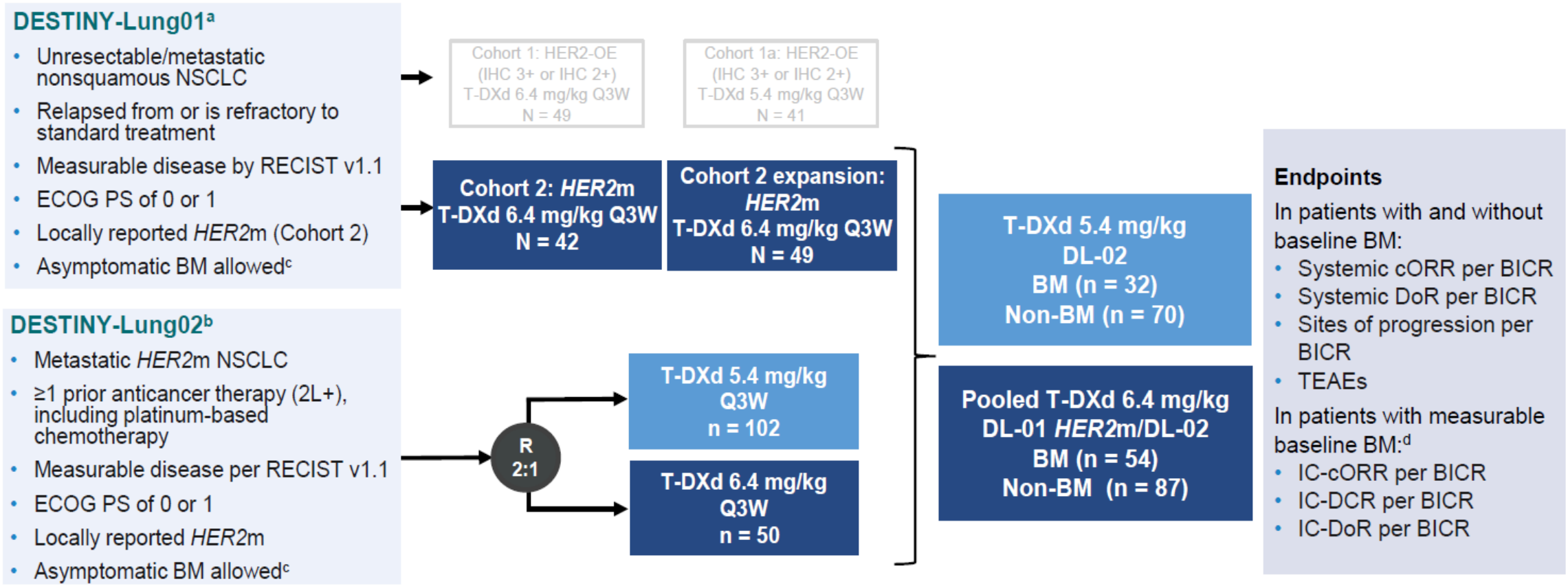

## Adjudicated Drug-Related ILD

| 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) |

- **Median treatment duration** was 7.7 months (range, 0.7-20.8) with T-DXd 5.4 mg/kg and 8.3 months (range, 0.7-20.3) with T-DXd 6.4 mg/kg
- The **most common any-grade TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **nausea** (67.3% and 82.0%), **neutropenia** (42.6% and 56.0%), and **fatigue** (44.6% and 50.0%)
- The **most common grade ≥3 TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **neutropenia** (18.8% and 36.0%) and **anemia** (10.9% and 16.0%)

ILD, interstitial lung disease; TEAE, treatment emergent adverse event; T-DXd, trastuzumab deruxtecan.
[a]The safety analysis set included all randomly assigned patients who received ≥1 dose of study drug.

# DESTINY-Lung01 and -02: Exploratory Pooled Brain Metastases Analyses




BICR, blinded independent central review; BM, brain metastases, cORR, confirmed objective response rate; CR, complete response; CT, computed tomography; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *HER2*, human epidermal growth factor receptor 2; *HER2*m, human epidermal growth factor receptor 2-mutant; IC-cORR, intracranial confirmed objective response rate; IC-DCR, intracranial disease control rate; IC-DoR, intracranial duration of response; IHC, immunohistochemistry; MRI, magnetic resonance imaging; NE, not evaluable; NSCLC, non–small cell lung cancer; OE, overexpressing; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events; WBRT, whole-brain radiotherapy.
[a]Data cutoff: December 3, 2021. [b]Data cutoff: December 23, 2022. [c]CT or MRI of the brain was required at screening; patients with asymptomatic BM at baseline were eligible if they did not need ongoing corticosteroid or anticonvulsant treatments, had recovered from acute radiotherapy toxicity, and ≥2 weeks had passed since WBRT. [d]BM were considered measurable if they were ≥10 mm in 1 dimension on CT or MRI. 14/32 patients with baseline BM in DL-01 and 30/54 in DL-02 had BM that were measurable. IC responses were evaluated in measurable baseline BM per RECIST v1.1 based on CT or MRI scans every 6 weeks from Cycle 1 Day 1; no additional scans were required for those without baseline BM unless clinically indicated.
1. Li BT et al. *N Engl J Med*. 2022;386:241-51. 2. Li BT et al. Poster presented European Society for Medical Oncology Annual Meeting; September 9-13, 2022, Paris, France. 3. Goto K et al. *J Clin Oncol*. 2023;JCO2301361

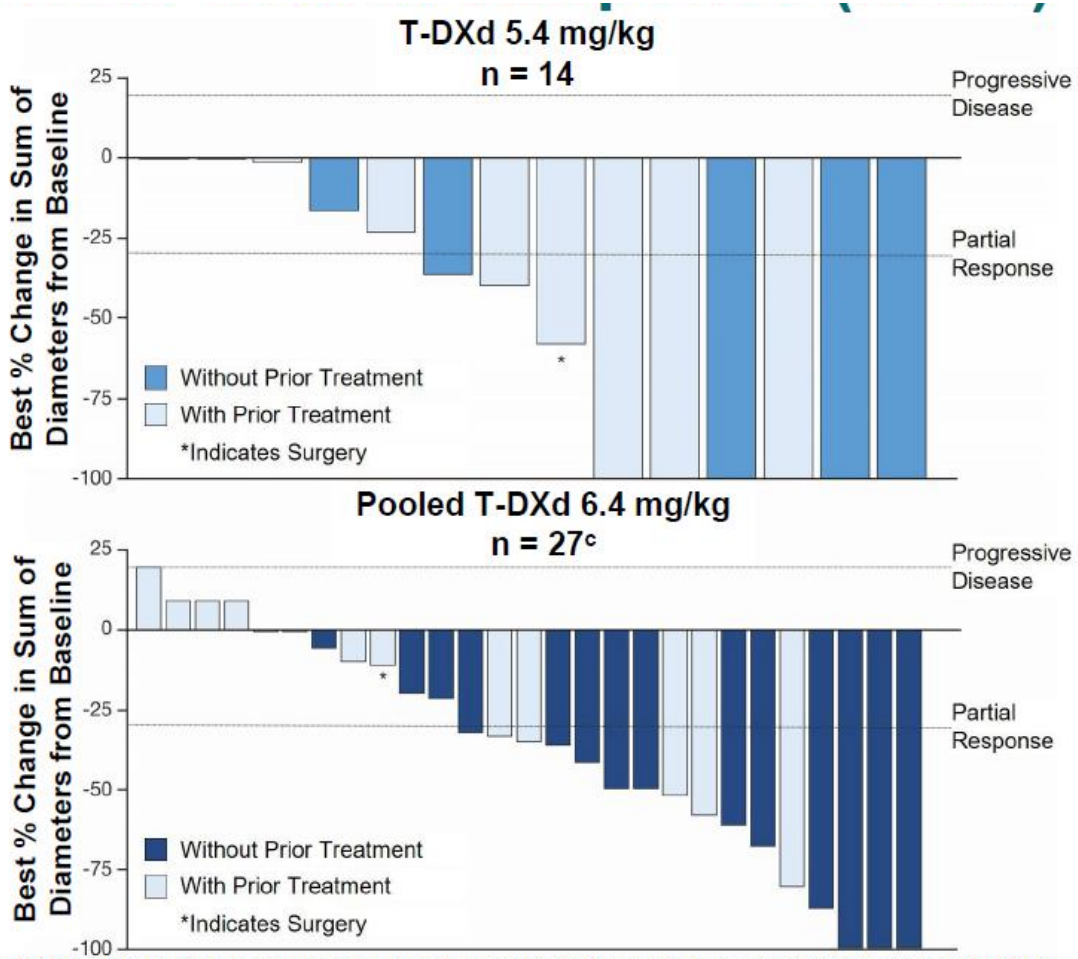
Planchard, D et al. ESMO 2023

# DESTINY-Lung01 and -02: IC Objective Response Rates & Best Overall Response (BICR)

## Measurable BM at Baseline

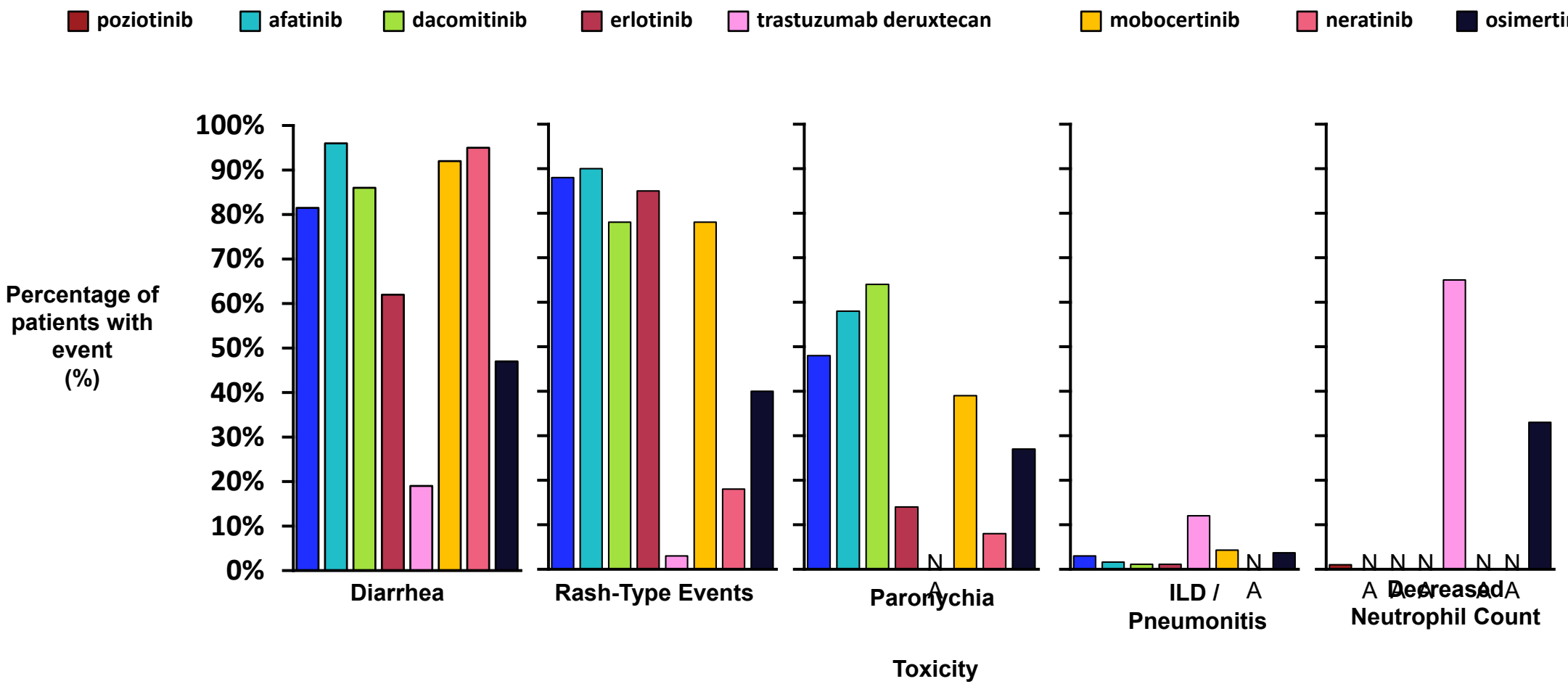
| | T-DXd 5.4 mg/kg DL-02 BM n = 14 | Pooled T-DXd 6.4 mg/kg DL-01 *HER2m*/DL-02 BM n = 30 |
|---|---|---|
| **IC-cORR, n (%)[a]** | **7 (50.0)** | **9 (30.0)** |
| 95% CI[b] | 23.0-77.0 | 14.7-49.4 |
| CR | 3 (21.4) | 0 |
| PR | 4 (28.6) | 9 (30.0) |
| SD | 6 (42.9) | 13 (43.3) |
| PD | 1 (7.1) | 4 (13.3) |
| NE[c] | 0 | 2 (6.7) |
| Missing | 0 | 2 (6.7) |
| **IC-DCR, n (%)[a]** | **13 (92.9)** | **22 (73.3)** |
| 95% CI[b] | 66.1-99.8 | 54.1-87.7 |
| **IC-DoR, months[d]** | | |
| Median, (95% CI)[e] | 9.5 (3.6-NE) | 4.4 (2.9-10.2) |

12/14 (86%) patients with measurable BM receiving T-DXd 5.4 mg/kg and 21/27 (78%) in the pooled 6.4 mg/kg group experienced a reduction in brain lesion size from baseline as their best overall response




BICR, blinded independent central review; BM, brain metastases; CR, complete response; DCR, disease control rate; DL, DESTINY-Lung; DoR, duration of response; *HER2*m, human epidermal growth factor receptor 2-mutant; IC, intracranial; IC-cORR, intracranial confirmed objective response rate; IC-DCR, intracranial disease control rate; IC-DoR, intracranial duration of response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan. [a]Denominator for percentage is the number of patients in the full analysis set who have at least 1 target lesion at baseline, per BICR. [b]Based on Clopper-Pearson method for single proportion. [c]For one patient deemed NE in the 6.4 mg/kg group, it was not possible to derive objective response due to missing data of 1 target lesion; the patient's best overall response however was calculated from available target lesion assessments and included the waterfall plot. [d]Calculated as time from first response in brain until progression in brain. [e]Based on Kaplan-Meier analysis and computed with the Brookmeyer-Crowley method.

# Comparison of Toxicities with TKIs and HER2 Targeting ADC (Any Grade)

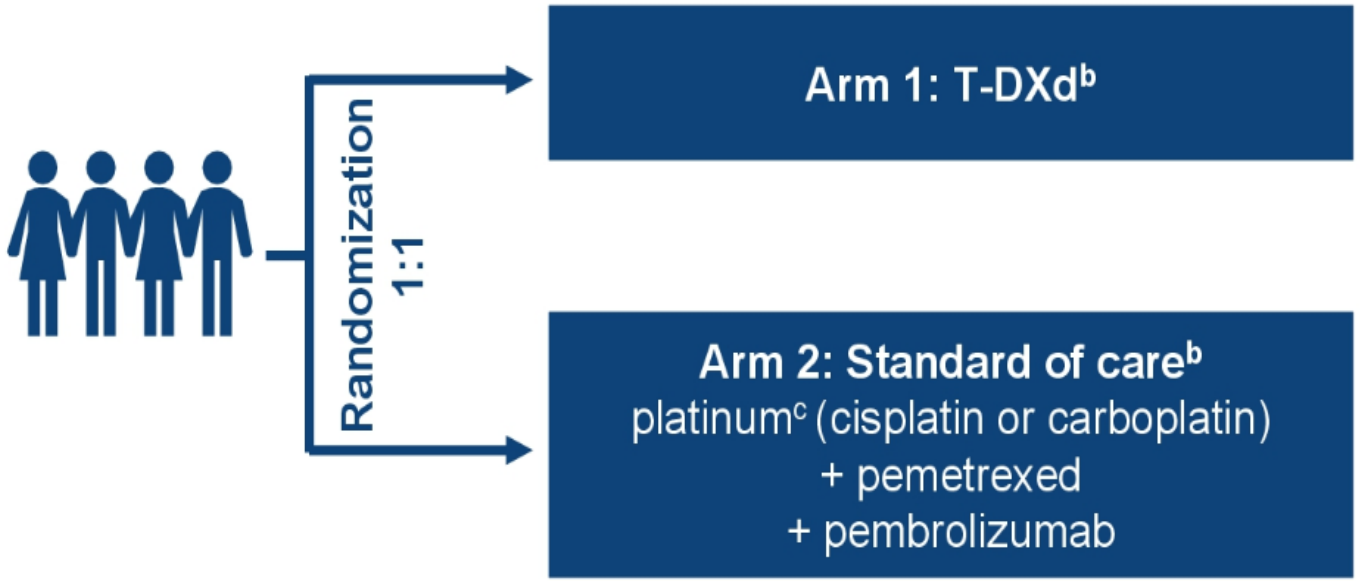



Excerpted from prescribing information accessed Jun & Aug 2022

# DESTINY-Lung04

## Patient population (N≈264)

- Unresectable, locally advanced (not amenable to curative therapy), or metastatic nonsquamous NSCLC with *HER2* exon 19 or 20 mutations[a]
- Naive to systemic therapy in the locally advanced or metastatic setting
- No known other targetable oncogenic mutations/alterations




[a] *HER2* mutations may be detected in tissue or ctDNA.
[b] Crossover is not permitted.
[c] Investigator's choice of cisplatin or carboplatin.

Li B et al. ASCO 2022. Abstract TPS9137.

# HER2 Overexpression in Advanced NSCLC

| HER2 in NSCLC | Frequency |
|---|---|
| Overexpression (IHC 2+ and 3+)[1,2,7-9] | 15–30% |
| Overexpression (IHC 3+ only)[2,8,9] | 2–6% |
| Amplification (ISH)[1,8,10] | 2–6% |
| Mutations[1,8,11-13] | 1–5% |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7. Bansal P, et al. *Front Oncol* 2016. 8. Heinmoller P, et al. *Clin Cancer Res* 2003. 9. Menard S, et al. *Ann Oncol* 2001.
10. Peters S, et al. *Transl Lung Cancer Res* 2014. 11. Rothschild SI. *Cancers* 2015. 12. Pellegrini C, et al. *Clin Cancer Res* 2003.
13. Buttitta F, et al. *Int J Cancer* 2006.

# April 5, 2024 - FDA grants accelerated approval for traztuzumab deruxtecan in HER2- positive (IHC 3+) solid tumors

- 192 HER2-positive (IHC 3+) previously treated, metastatic solid tumors enrolled in 3 multi-center trials
- DESTINY-PanTumor02 – ORR – 51.4%, DoR – 19.4 mos
- DESTINY-Lung01 – ORR – 52.9%, DoR – 6.9 mos
- DESTINY-CRC02 – ORR – 46.9%, DoR – 5.5 mos

# Agents currently under investigation in the HER2 space……

- ELVN-002
- ABT-101
- BAY2927088
- DB-1303
- Furmonertinib
- DS-8201a
- Inetetamab + pyrotinib
- DZD9008
- Zongertinib
- STX-721
- FWD1509
- HS-10376
- SHR-A1811

Clinicaltrials.gov accessed April 15, 2024

# Conclusions

- HER2 mutations should be assessed in all newly diagnosed mNSCLC pts
- NGS is optimal platform (consider IHC for overexpression)
- Currently available TKIs and MoAbs have limited activity
- Trastuzumab deruxtecan (T-DXd) is standard 2nd-line therapy for patients with *HER2*-mutated mNSCLC who have progressed on 1st-line chemotherapy (with or without immunotherapy)
- Monitor closely for ILD
- DESTINY-Lung04 will define role of T-DXd in the 1$^{st}$ line setting