15th CONGRESS on Lung CANCER

MADRID

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#15CongressGECP

Fundación GECP lung cancer research

HER2 role in lung cancer

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DISCLOSURE

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OUTLINE

- *HER2* BIOLOGY
- *HER2* ALTERATIONS IN NSCLC
- CLINICAL AND BIOLOGIC CHARACTERISTICS *HER2*-MUTANT NSCLC
- TIMELINE OF DEVELOPMENT OF HER2 TARGETED THERAPIES IN *HER2*-MUTANT NSCLC
- MECHANISM OF ACTION FOR HER2 TARGETED THERAPIES IN *HER2*-MUTANT NSCLC
- HER2 THERAPY
    - CHEMOTHERAPY
    - IMMUNOTHERAPY
    - HER2 TARGETED TYROSINE KINASE INHIBITORS (TKIs)
    - HER2 TARGETED MONOCLONAL ANTIBODIES (mAb)
    - HER2 TARGETED ANTIBODY-DRUG CONJUGATES (ADCs)
- MECHANISM OF RESISTANCE
- FUTURE PERSPECTIVES
- CONCLUSION

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HER2 BIOLOGY

- Discovery in the mid 1980´s
- *HER2* proto-oncogene is located on the long arm of human chromosome 17 (17q11.2-q12)
- The *HER2* transcript encodes a transmembrane glycoprotein belonging to the ErbB-family of type 1 transmembrane growth factor receptors: HER1 (ErbB1, EGFR), HER2 (ErbB2, HER2/neu), HER3 (ErbB3) and HER4 (ErbB4)
- Each receptor is composed of three main components: an extracellular ligand binding domain, an α-helical transmembrane segment and an intracellular tyrosine kinase domain

Bargmann CI, et al. Nature. 1986;319(6050):226-30

HER2 BIOLOGY

- HER2 is a common oncogenic driver in multiple tumor types, including breast, gastroesophageal and colorectal cancers
- HER2 has no known ligand-binding capacity and can be activated in a ligand-independent manner through homodimerization or heterodimerization with other HER proteins
- Deregulation of HER2 signalling can be caused by HER2 amplification, overexpression or mutations, including exon 20 insertions
- These different alterations do not confer equal sensitivity to HER2-targeted therapies

Li Z, et al EBioMedicine. 2020;62:103074; Bang Y-J, et al. Lancet. 2010;376:687-97; Swain SM, et al. N Engl J Med. 2015;372:724-34

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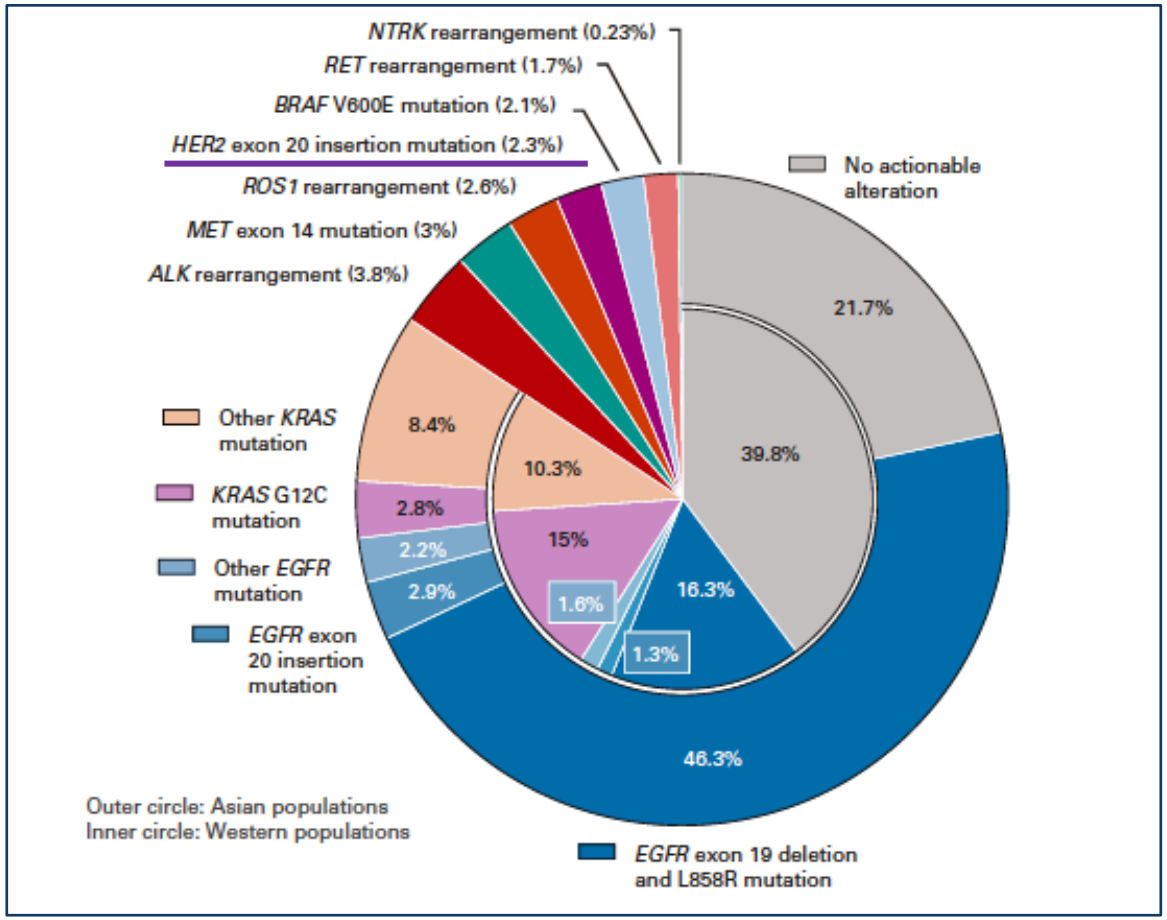
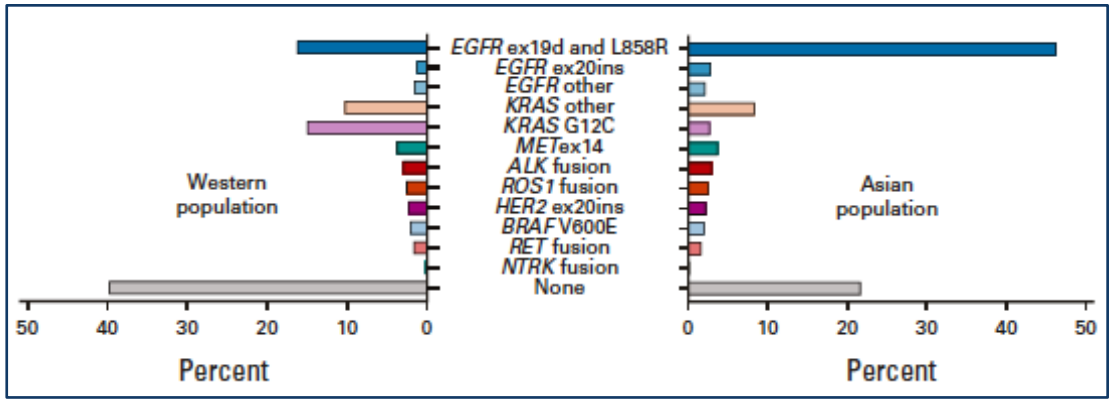
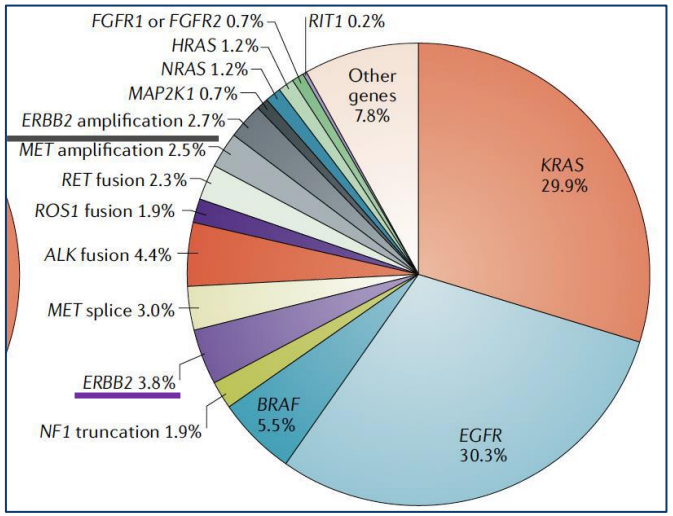
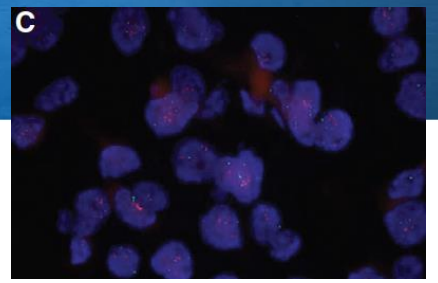
HER2 ALTERATIONS IN NSCLC







Tan AC, Tan DSW. J Clin Oncol 2022;40(6):611-25



HER2 ALTERATIONS IN NSCLC

HER2 Mutations

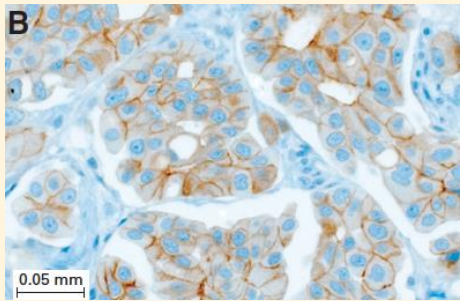
- Driver mutation in 2% to 4%
- The majority are exon 20 insertions that occur within the kinase domain
- Detectable by **NGS**

HER2 Gene Amplification

- 3% to 13%
- Described as mutually exclusive from *HER2* mutations
- Known resistance mechanism in *EGFR*+ disease, but not necessarily driver mutation
- Detectable by **FISH** and **NGS**

HER2 Protein Overexpression

- 2.4% to 38%
- IHC 3+ in 3-6% of cases
- Not considered actionable
- Easily identifiable by **IHC**



IHC: score 2+

HER2 mutations are generally mutually exclusive of other actionable oncogenic drivers (such as EGFR, KRAS, and ALK alterations) and are associated with a poor prognosis

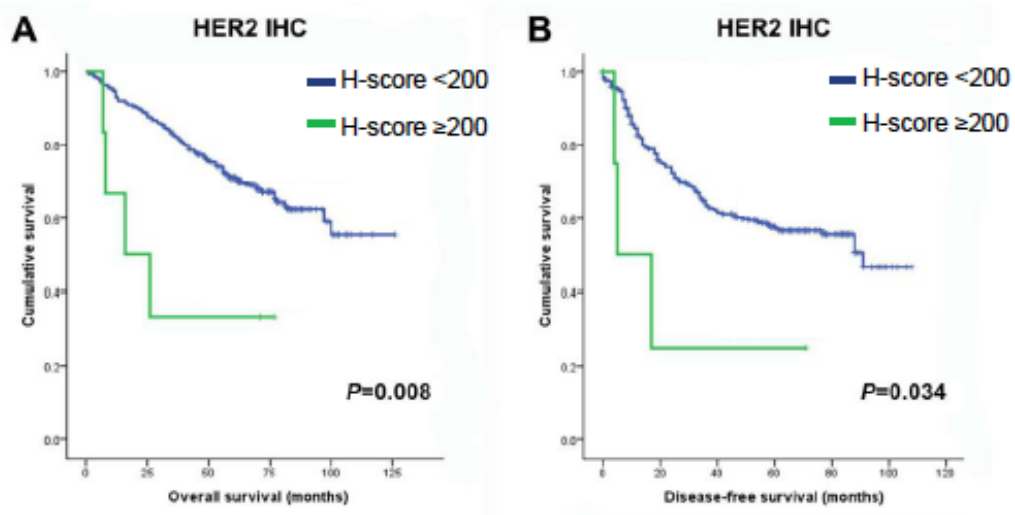
Mazieres J, et al. J Clin Oncol. 2013; Pillai RN, et al. Cancer. 2017;123(21):4099-4105; Takeda M, et al. Oncotarget. 2018; Zhou J, et al. Ther Avd Med Oncol. 2020

HER2 ALTERATIONS IN NSCLC

MARKER OF POOR PROGNOSIS

- *HER2* mutant NSCLC patient have worse prognosis
- The prognostic significance of *HER2* amplification is unclear
- HER2 overexpressing NSCLC is associated with lower survival rates

High HER2 Overexpression Was Associated With Significantly Shorter OS and DFS Than Lower HER2 Expression (N=321)[4]



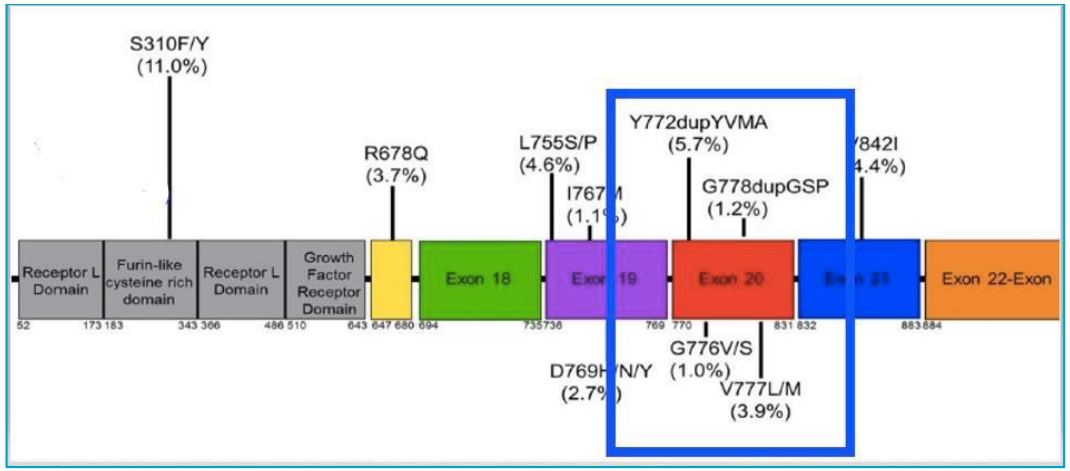
OS (A) and DFS (B) Kaplan-Meier curves according to the HER2 IHC H-score. Patients with overexpression of HER2 showed significantly shorter OS and DFS rates compared to patients without HER2 overexpression according to the H-scoring method.

Liu L, et al. J Thorac Oncol. 2010;5(12):1922-32; Zhao J, Xia Y. JCO Precision Oncology. 2020;4:411-25; Pillai RN, et al. Cancer. 2017;123(21):4099-4105; Kim EK, et al. PLoS One. 2017;12(2):e0171280

HER2 ALTERATIONS IN NSCLC

HER2 EXON 20 INSERTIONS

- *HER2* exon 20 insertions occur in 1.5% of NSCLC patients
- Account for 90% of all *HER2* mutations
- *HER2* mutations encompass heterogeneous alterations clustered in the extracellular, transmembrane and kinase domains
- Kinase domains alterations predominate in NSCLC, the most common of which is: Y772_A775dupYVMA variants (p.Y772dupYVMA or p.A775_G776insYVMA); 34-83% of *HER2* mutations in NSCLC



Arcilla ME, et al. Clin Cancer Res. 2012;18:4910-8; Robichaux J, et al. Cancer Cell. 2019;36:444-57; Zhao S, et al. J Thorac Oncol. 2020;15:962-72

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CLINICAL AND BIOLOGIC CHARACTERISTICS *HER2*-MUTANT NSCLC

- Clinical phenotype presentation:
  - Women
  - Younger patients
  - Non-smokers
  - Adenocarcinoma
  - Poor prognosis
  - Increased incidence of brain metastasis

Table 1. Clinical and Biologic Characteristics of Patients With *HER2*-Mutated Disease (n = 65)

Characteristic	No. of Patients	%
Age at diagnosis, years	65	100
Mean	61.1	
SD	11.6	
Median	60.4	
Sex		
Women	45	69
Men	20	31
Tobacco		
Never	34	52.3
Former	11	16.9
Current	12	18.5
Unknown	8	12.3
Tumor stage		
I	11	16.9
II	3	4.6
III	15	23.1
IV	33	50.8
Unknown	3	4.6
Metastasis sites for stage IV	33	
Lung	8	24.2
Brain	3	9.1
Bone	2	6.1
Multiples organs	13	39.4
Other or unknown	7	21.3

Abbreviation: SD, standard deviation.

Mazieres J , et al. J Clin Oncol. 2013;31:1997-2003

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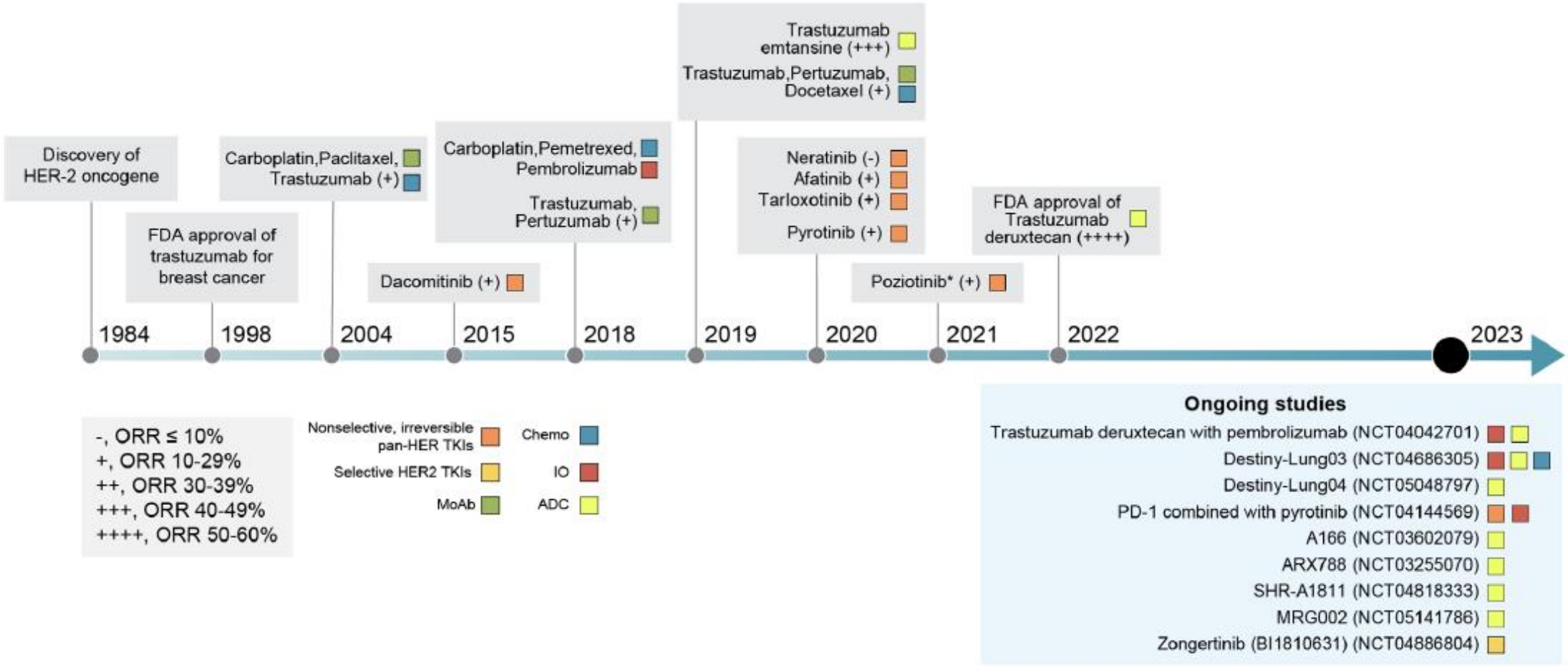
TIMELINE OF DEVELOPMENT OF HER2 TARGETED THERAPIES IN *HER2*-MUTANT NSCLC



Nützinger J, et al. Lung Cancer. 2023;186:107385

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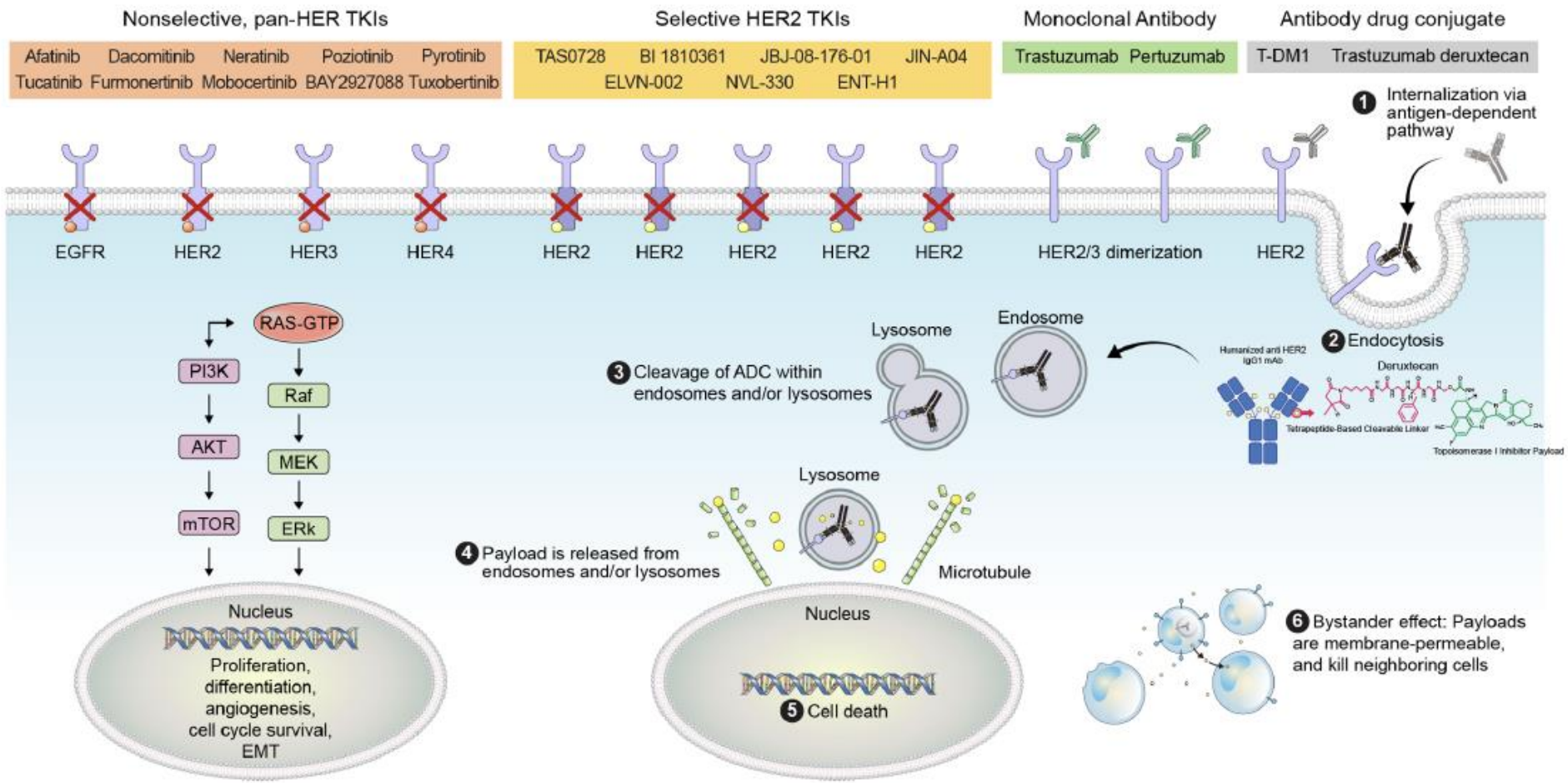
MECHANISM OF ACTION FOR HER2 TARGETED THERAPIES IN *HER2*-MUTANT NSCLC



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CHEMOTHERAPY

- First-line: Pemetrexed based chemotherapy:
  - ORR: 36%
  - PFS: 5.1 months
  - Among the HER2 mutation variants, there was a trend towards inferior PFS in A775_G776insYVMA group compared with other variants (4.2 vs 7.2 months, p=0.085)

- Several phase II studies have reported the efficacy of chemotherapy in combination with HER2 targeting agents

Study	Phase	Patient population	N	Agents	ORR (%)	PFS	G3 + TRAE
ECOG 2598[1]	II	Untreated HER2 1-3+	56	Carboplatin, paclitaxel, trastuzumab	24.5%	3.25 months	35.8% G4
MSKCC[2]	II	Untreated HER2 0-3+	64	Trastuzumab + docetaxel/paclitaxel	28%	2.4 months /3.9 months	G3 diarrhea (10% docetaxel)
Gatzemeier U, et al.[3]	II	Untreated HER2 1-3+	101	Cisplatin, gemcitabine +/- trastuzumab	36% (vs 41% in control arm)	6.3 months (vs 7.2 months)	Not reported

1. Langer CJ, et al. J Clin Oncol. 2004;22(7):1180-7; 2. Krug LM, et al. Cancer. 2005;104(19):2149-55; 3. Gatzemeier U, et al. Ann Oncol. 2004;15(1):19-27

IMMUNOTHERAPY

- ICI monotherapy:
  - ORR: 0% to 27.3%
  - PFS: 1.88 to 2.5 months
- The current evidence does not support the use of ICIs as a single agent in the treatment of HER2-altered NSCLC
- Immuno-chemotherapy combinations, with limited supporting evidence, remain a viable first-line treatment option

Study	Phase	Patient population	N	Agents	ORR (%)	PFS
IMMUNOTARGET[1]	Retrospective	HER2mt (ex20ins)	29	ICI monotherapy	7.4%	2.5 months
Guisier F, et al.[2]	Retrospective	HER2mt (ex20ins)	23	ICI monotherapy	27.3%	2.2 months
Saalfeld FC, et al.[3]	Retrospective	HER2mt (ex 8, 19, 20)	22	Immuno-chemotherapy combination	52%	6 months
Yang G, et al.[4]	Retrospective	HER2 alterated (mutant or amplification)	46	Immuno-chemotherapy combination	28.9%	5.2months

1.Mazieres J, et al. Ann Oncol. 2019;30(8):1321-8; 2.Guisier F, et al. J Thorac Oncol. 2020;15(4):628-36; 3.Saalfeld FC, et al. J Thorac Oncol. 2021;16(11):1952-8; 4.Yang G, et al. Ther Adv Med Oncol 2022;14

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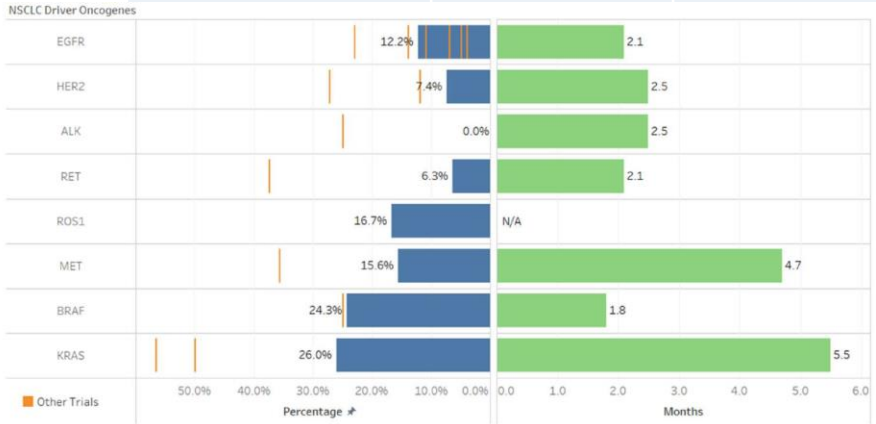

*bars reflect overall ORR (blue) and mPFS (green) demonstrated in retrospective IMMUNOTARGET study
**vertical orange lines depict ORRs shown in other individual ICI monotherapy trials

1.Mazieres J, et al. Ann Oncol. 2019;30(8):1321-8; 2.Guisier F, et al. J Thorac Oncol. 2020;15(4):628-36; 3.Saalfeld FC, et al. J Thorac Oncol. 2021;16(11):1952-8; 4.Yang G, et al. Ther Adv Med Oncol 2022;14

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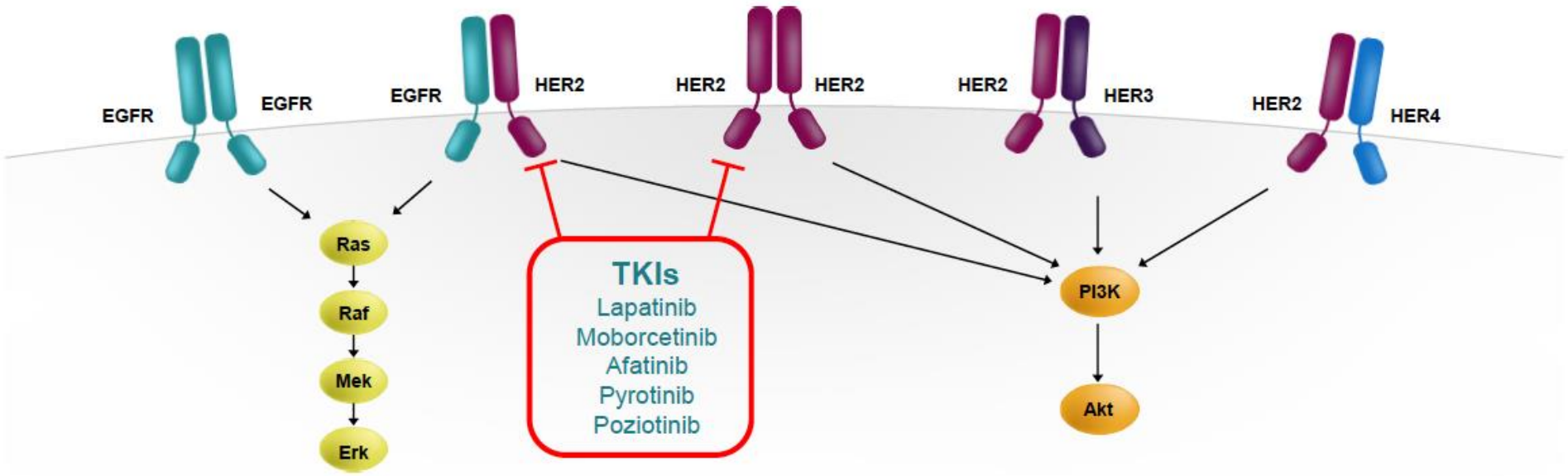
OVERVIEW OF HER2 TARGETING APPROACHES IN NSCLC



Modified from A Passaro

HER2 TKIs

- TKIs with activity against HER2 have shown limited efficacy in targeting *HER2* exon 20 insertions

- Non-selective HER2 inhibitors:
  - Include the pan-HER TKIs:
    - **Afatinib, dacomitinib, neratinib, poziotinib, pyrotinib,** tucatinib, furmonertinib, mobocertinib, BAY2927088, tarloxotinib and tuxobertinib

- Selective HER2 inhibitors:
  - Include novel HER2 TKIs that are highly selective with EGFR sparing activity:
    - TAS0728, **BI 1810631**, JBJ-08-176-01, JIN-A04, ELVN-002, NVL-330 and ENT-H1

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- Selective HER2 inhibitors:
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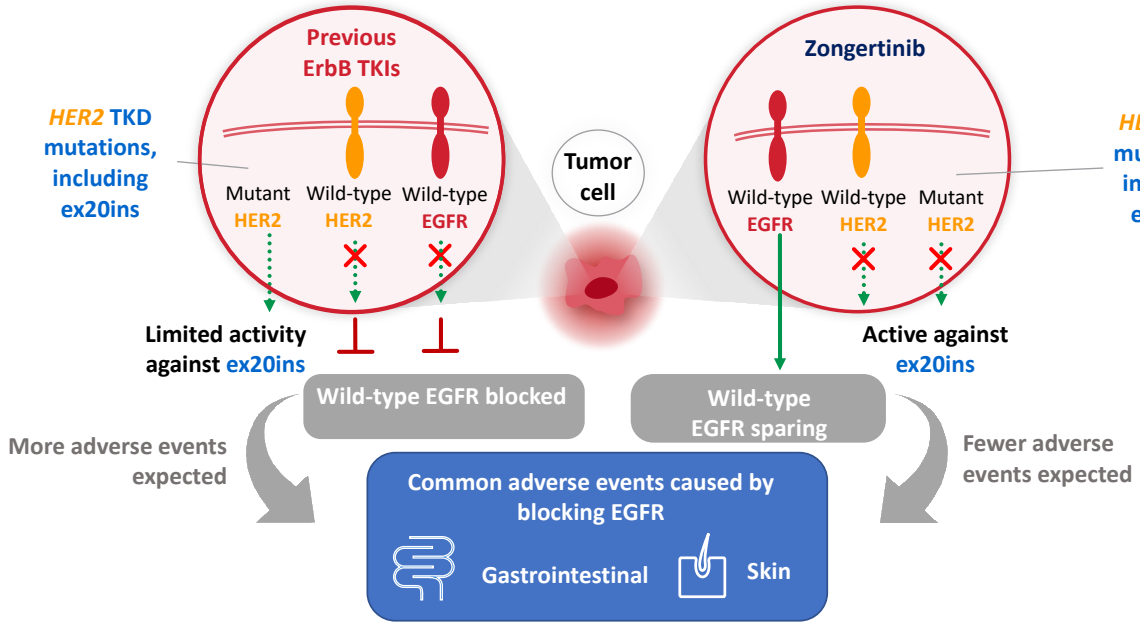
    - TAS0728, **BI 1810631**, JBJ-08-176-01, JIN-A(



HER2 TKIs

Study	Phase	Patient population	N	Agents	ORR (%)	PFS	Toxicities
Dziadziuszko R, et al.[1]	Prospective, phase II NICHE trial (ETOP)	HER2mt (ex20ins)	13	Afatinib	53.8%	15.9 weeks	Diarrhea, vomiting, rash, paronychia, fatigue, mucositis G3 + TRAE <10%
Lai WV, et al.[2]	Retrospective international	HER2mt (ex20ins)	27	Afatinib	13% (3/23)	3 months	Diarrhea/GI toxicity, skin rash
Kris MG, et al.[3]	Phase II	HER2mt (ex20ins) and amplification	30 (26/4)	Dacomitinib	12% (3/26) 0% (0/4)	3 months	Diarrhea (90%; grade 3/4: 20%/3%), dermatitis (73%; grade 3/4: 3%/0%), and fatigue (57%; grade 3/4: 3%/0%)
Negrao MV, et al.[4]	Phase II, SUMMIT	HER2/3mt	26	Neratinib	4% (1/26)	5.5 months	Diarrhea (74%; grade 3: 22%), nausea (43%), vomiting (41%)

1.Dziadziuszko R, et al. J Thorac Oncol. 2019;14(6):1086-1094; 2.Lai WV, et al. Eur J Cancer. 2019;109:28-35; 3.Kris MG, et al. Ann Oncol. 2015;26(7):1421-1427; 4. Negrao MV, et al. J Immunother Cancer. 2021;9(8):e002891

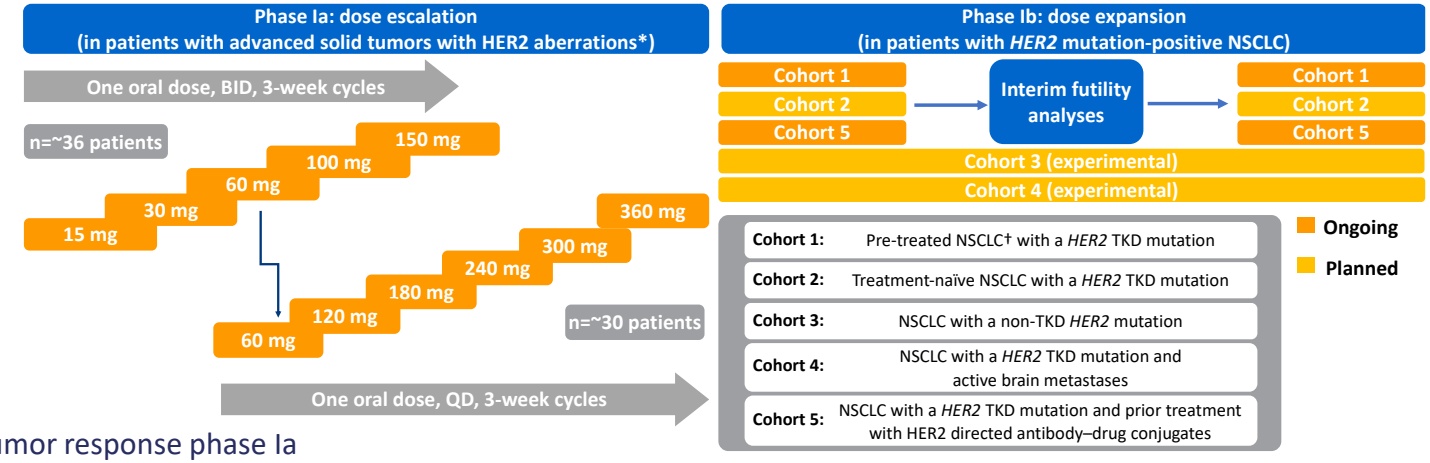
HER2 TKIs

Study	Phase	Patient population	N	Agents	ORR (%)	PFS	Toxicities
Le X, et al.[1]	Phase II, ZENITH-20 (cohort 2)	Previously treated HER2mt (ex20ins)	90	Poziotinib	27.8%	5.5 months	G3 rash (49%), G3 diarrhea (25.6%), G3 stomatitis (24.4%)
Cornelissen R, et al.[2]	Phase II, ZENITH-20 (cohort 4)	Treatment naïve HER2mt (ex20ins)	80	Poziotinib	39%	5.6 months	Rash (43%; 45% in the 16mg QD, 39% in the 8mg BID), stomatitis (19%; QD:21%, BID:15%), diarrhea(18%; QD:15%, BID:21%)
Zhou C, et al[3]	Phase II	Previously treated HER2mt	60	Pyrotinib	30%	6.9 months	Diarrhea (92%; G3 20%), creatinine increase (30%)
Song Z, et al[4]	Phase II	Treatment naïve HER2mt	78	Pyrotinib	19.2%	5.6 months	G3 diarrhea 16.7%

1.Le X, et al. J Clin Oncol. 2022;40(7):710-8; 2.Cornelissen R, et al. J Thorac Oncol 2023;
3. Zhou C, et al. J Clin Oncol 2020;38(24):2753-61; 4.Song Z, et al. BMC Med. 2022;20(1):42

HER2 TKIs

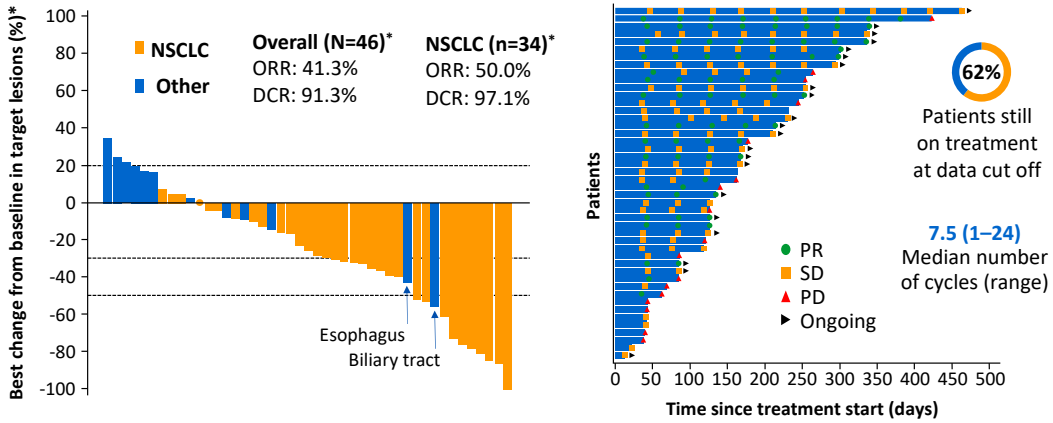
- BI 1810361 (zongertinib) is an orally active, potent, covalent, and highly selective HER2 inhibitor
- Phase I Beamion Lung 1 (NCT04886804)
- *HER2*-mutant NSCLC refractory to platinum-based chemotherapy



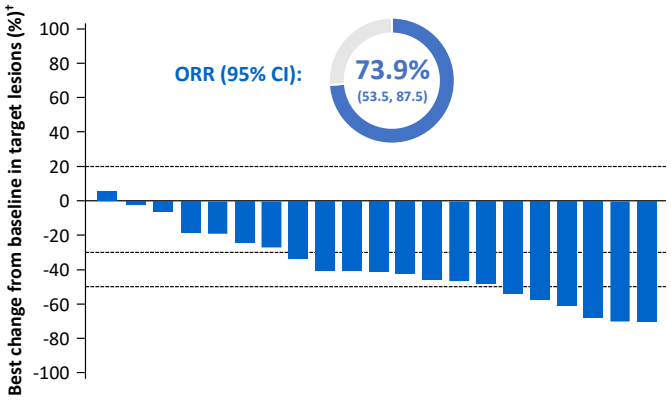
Phase Ia: dose escalation and safety

Phase Ia TRAEs (%*)	Zongertinib BID (n=17)		Zongertinib QD (n=33)		Total (N=50)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Any TRAE	**76.5**	**5.9**	**84.8**	**12.1**	**82.0**	**10.0**
Diarrhea	47.1	—	36.4	—	40.0	—
AST increased	5.9	—	18.2	3.0	14.0	2.0
Rash†	11.8	—	15.2	—	14.0	—
ALT increased	5.9	5.9	15.2	6.1	12.0	6.0
Paronychia	5.9	—	12.1	—	10.0	—
Dry skin	11.8	—	6.1	—	8.0	—
Anaemia	11.8	—	6.1	—	8.0	—

Antitumor response phase Ia

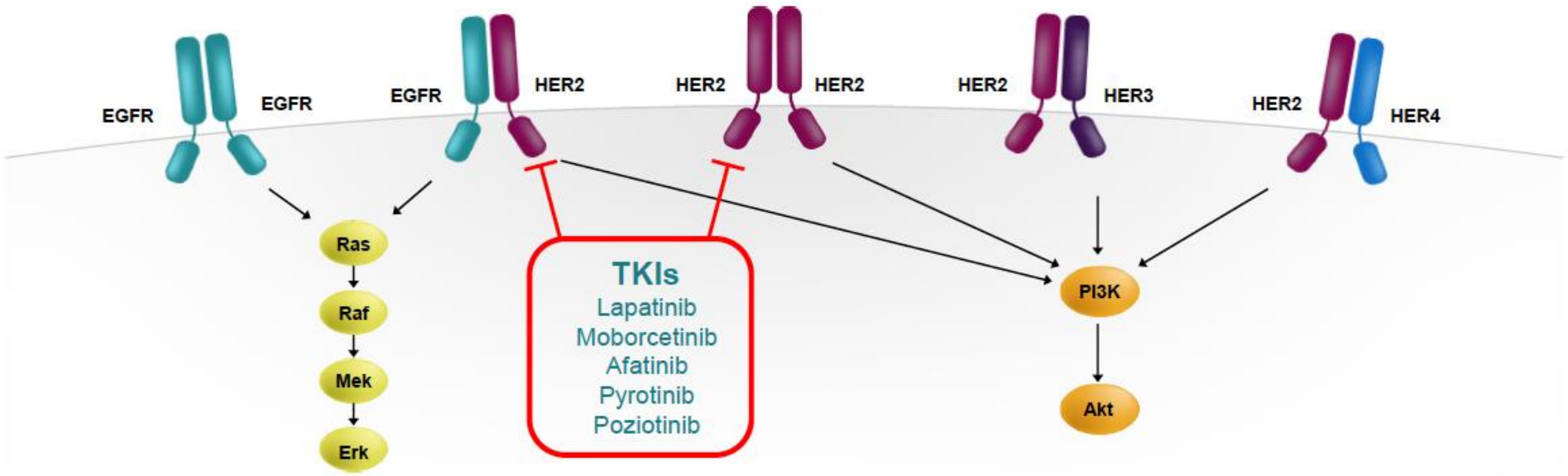


Antitumor response phase Ib



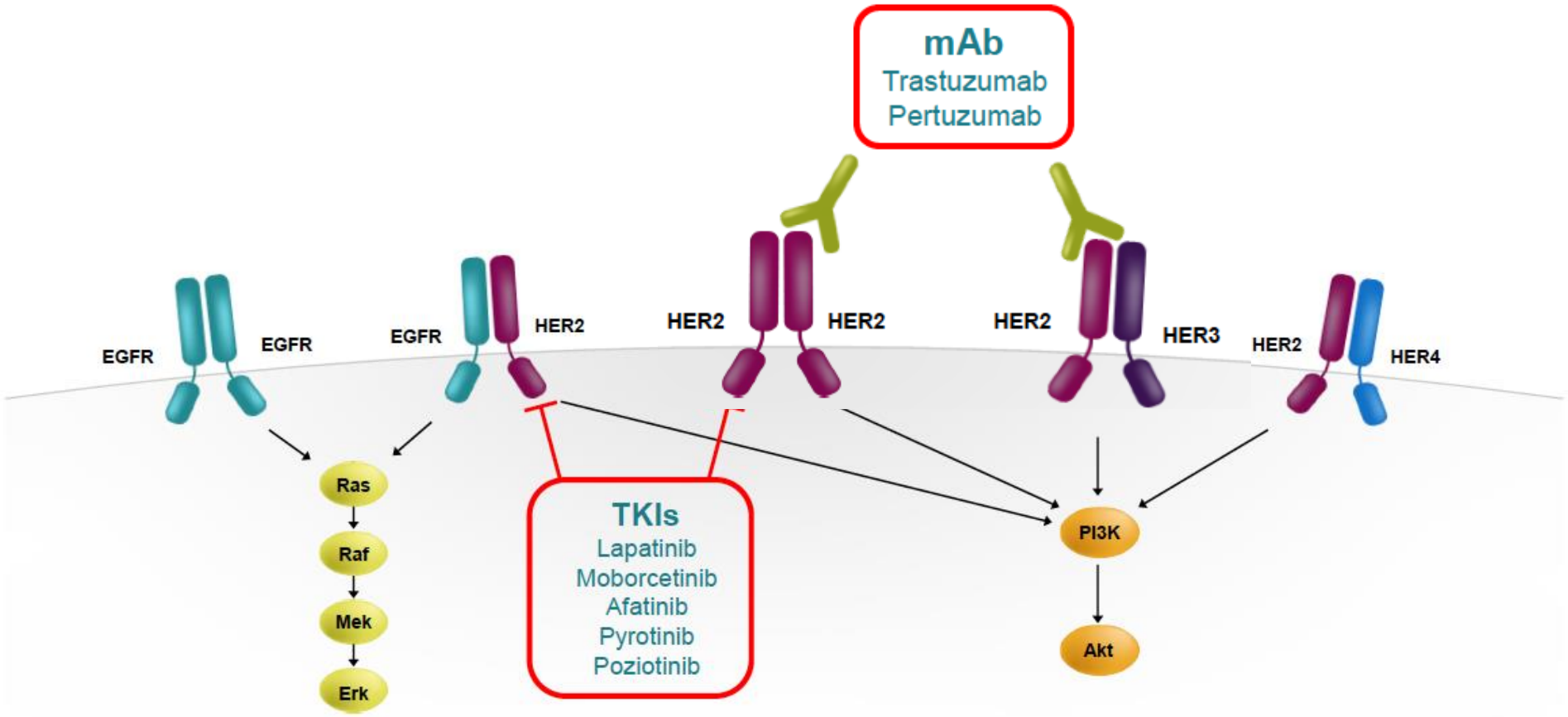
Opdam F, et al. J Clin Oncol 2023;41(16_suppl):8545. ASCO 2023; Yamamoto N, et al. IASLC 2023

OVERVIEW OF HER2 TARGETING APPROACHES IN NSCLC



Modified from A Passaro

OVERVIEW OF HER2 TARGETING APPROACHES IN NSCLC



Modified from A Passaro

Anti-*HER2* monoclonal antibodies (mAb)

- Early efforts to target NSCLC with *HER2* amplification have been unsuccessful with modest responses

- TRASTUZUMAB (a humanized monoclonal antibody directly targeting *HER2*)
  - Monotherapy: HOT1303 trial
    - ORR: 0%
    - Median PFS: 5.2 months

  - Combinations: phase II studies, HER2-overexpressed NSCLC, chemotherapy combination (gemcitabine and cisplatin; paclitaxel and carboplatin; docetaxel
    - ORR: 24.5-38%
    - Median PFS: 3.3-8.5 months

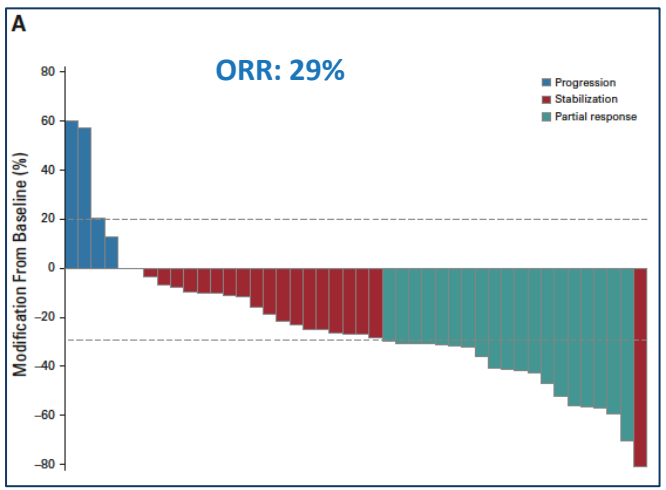
Study	Phase	Patient population	N	Agents	ORR (%)	PFS	G3 + TRAE
ECOG 2598[1]	II	Untreated HER2 1-3+	56	Carboplatin, paclitaxel, trastuzumab	24.5%	3.25 months	35.8% G4
MSKCC[2]	II	Untreated HER2 0-3+	64	Trastuzumab + docetaxel/paclitaxel	28%	2.4 months /3.9 months	G3 diarrhea (10% docetaxel)
Gatzemeier U, et al.[3]	II	Untreated HER2 1-3+	101	Cisplatin, gemcitabine +/- trastuzumab	36% (vs 41% in control arm)	6.3 months (vs 7.2 months)	Not reported

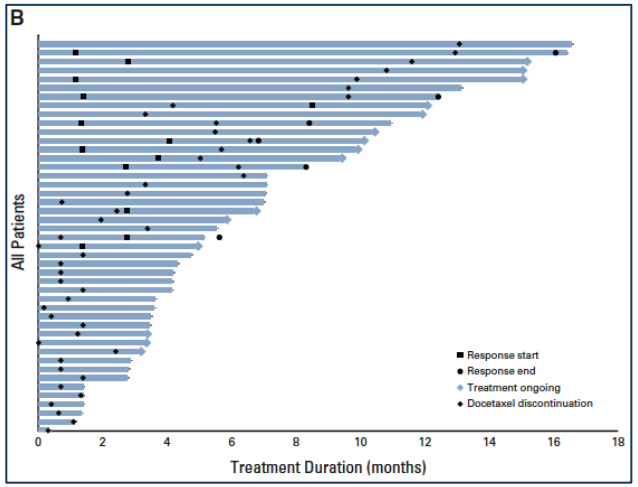
Lara PN, et al. Clin Lung Cancer 2004;5(4):231-236; Kinosita I, et al. Ann Oncol. 2018;29:viii540; Zinner RG, et al. Lung Cancer 2004;44(1):99-110; Gatzemeier U, et al. Ann Oncol. 2004;15(1):19-27; Langer Cj, et al. J Clin Oncol. 2004;22(7):1180-1187

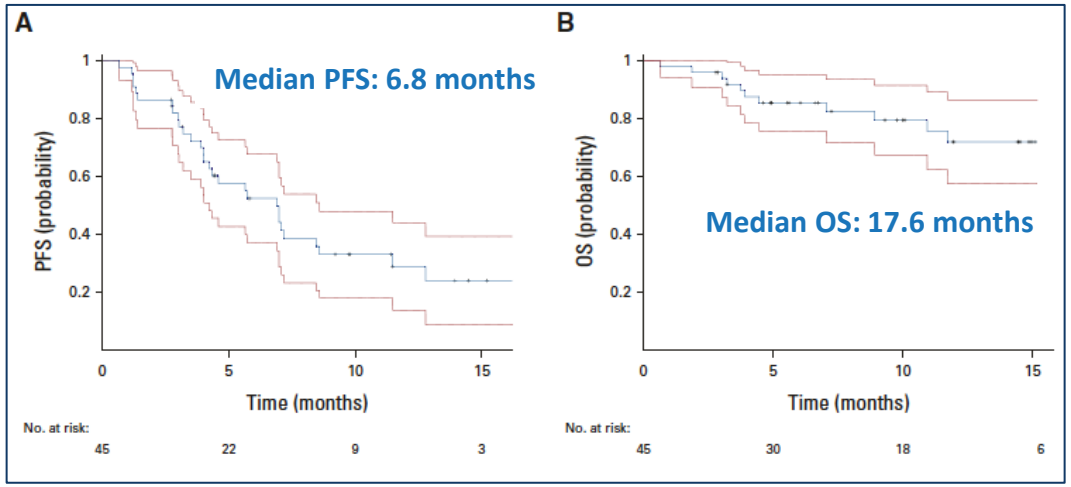
Anti-*HER2* monoclonal antibodies (mAb)

- PERTUZUMAB (a *HER2* humanized mAb) combined with TRASTUZUMAB in *HER2* mutation and amplification
  - ORR: 11% (heavily pretreated patients)
  - Median PFS: 5.2 months

- IFCT-1703 (PERTUZUMAB-TRASTUZUMAB-DOCETAXEL): phase II study of patients with HER2-mutated, advanced NSCLC after ≧ one platinum-based treatment

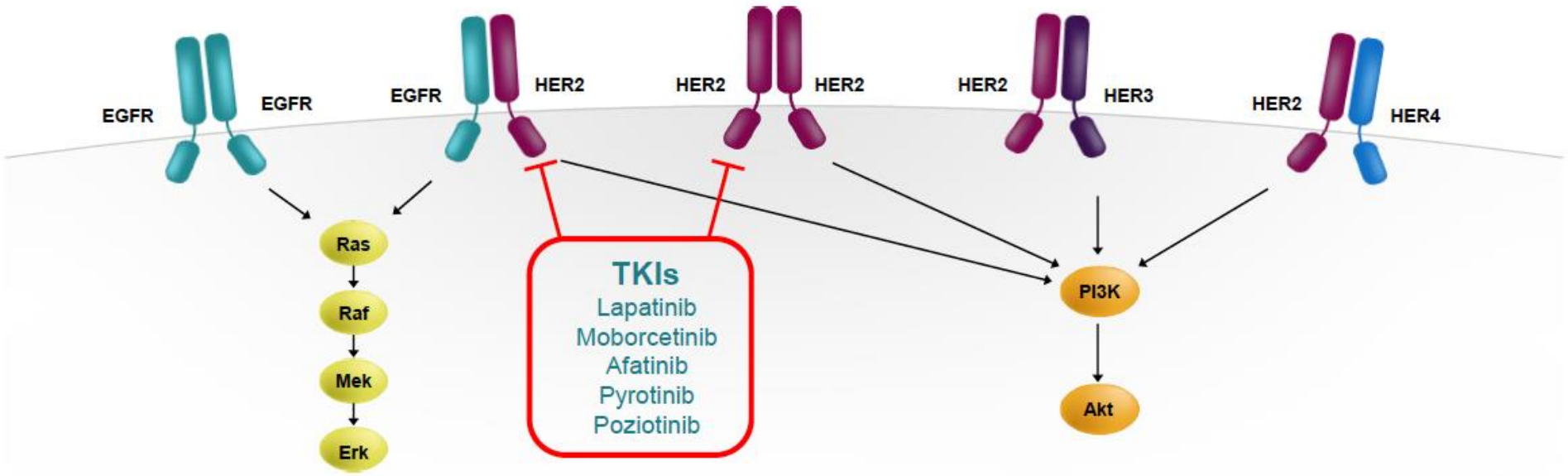






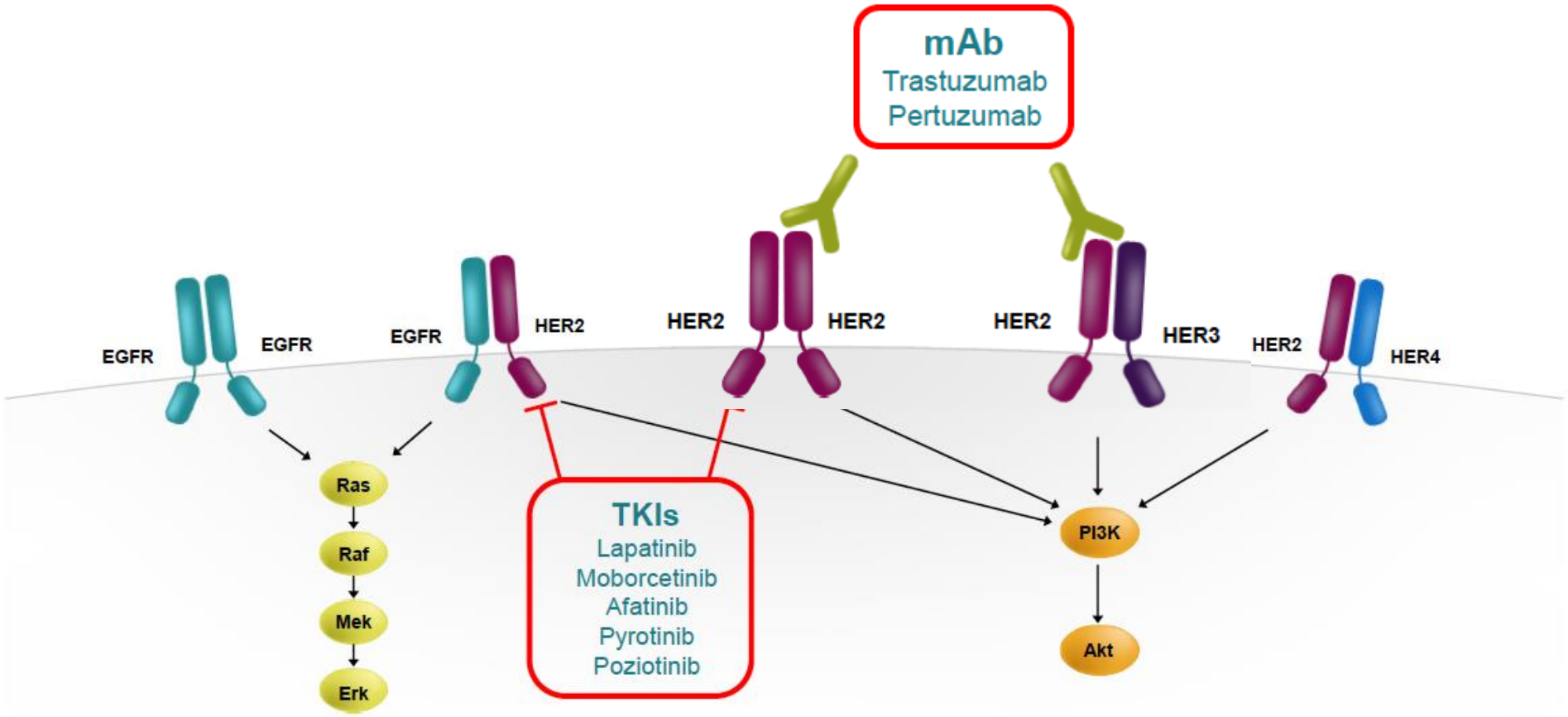
Ganti AK, et al. JCO Precis Oncol. 2023;7:e2300041; Kuyama S, et al. J Thorac Oncol. 2008;3(5):477-482; Mazieres J, et al. J Clin Oncol. 2022;40(7):719-28

OVERVIEW OF HER2 TARGETING APPROACHES IN NSCLC



Modified from A Passaro

OVERVIEW OF HER2 TARGETING APPROACHES IN NSCLC



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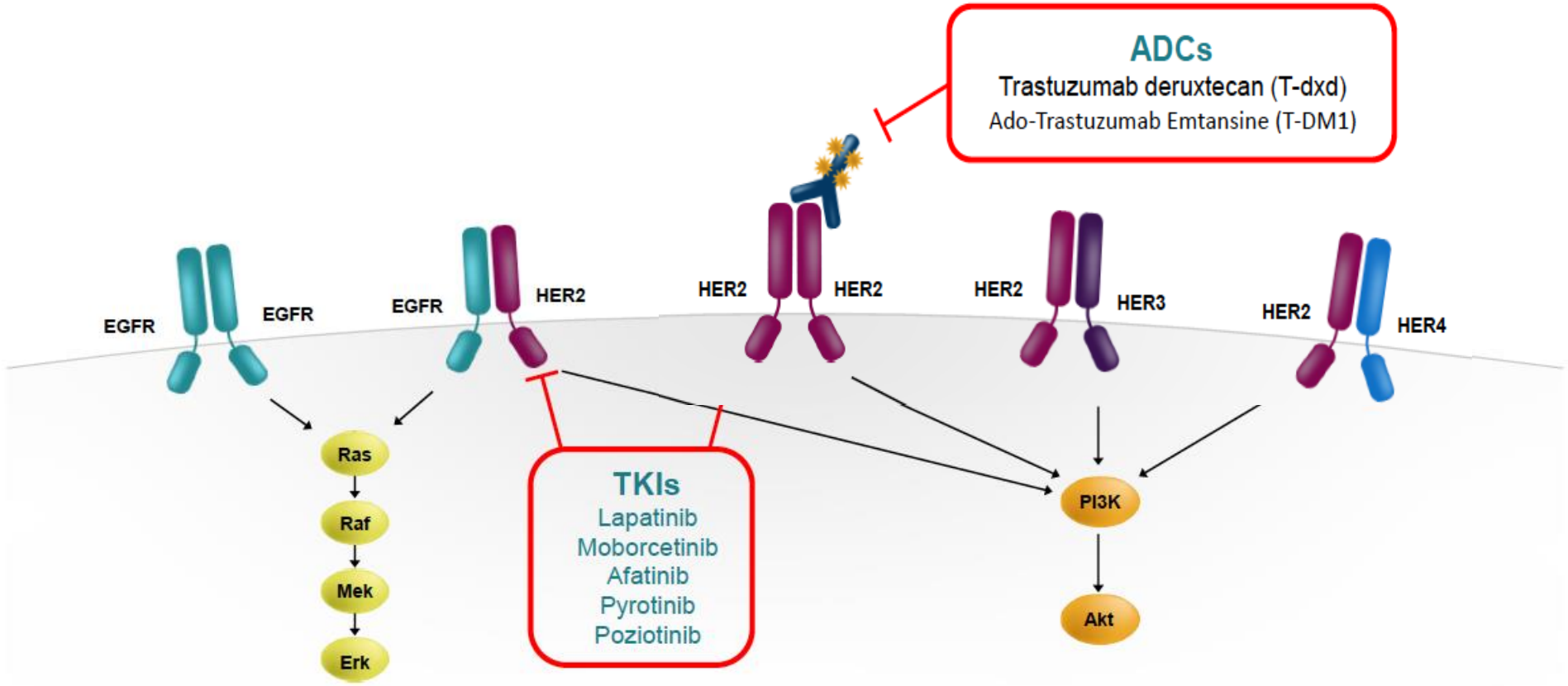
OVERVIEW OF HER2 TARGETING APPROACHES IN NSCLC



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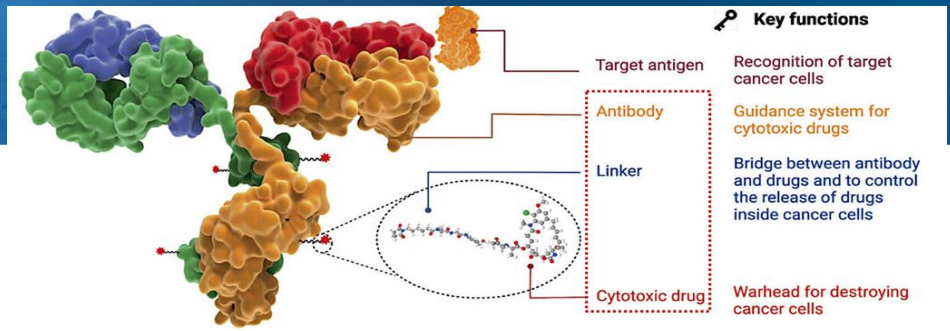
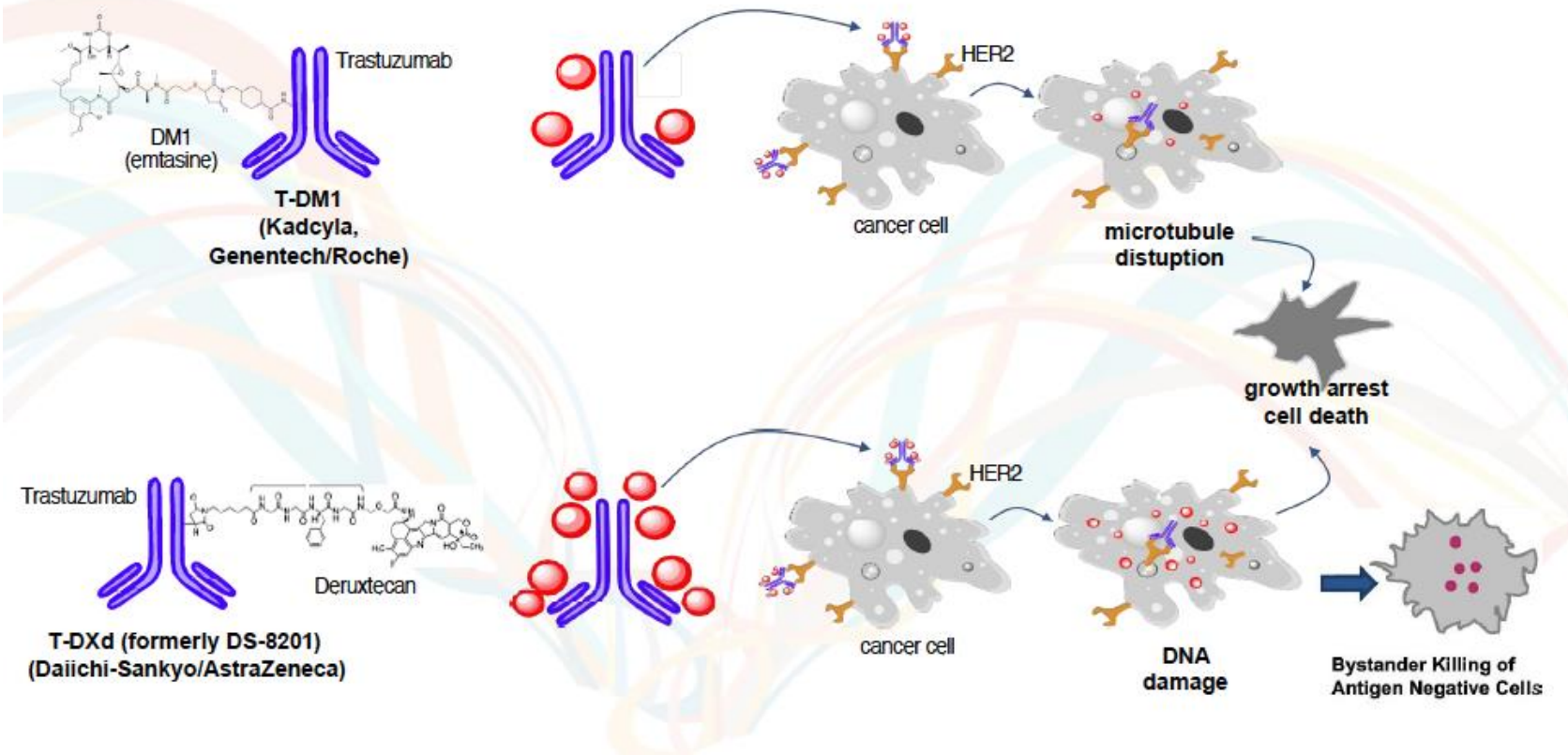
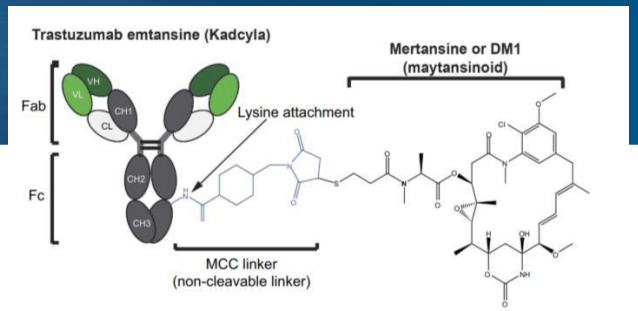


HER2 antibody drug conjugates (ADCs)

- ADCs: composed of a monoclonal antibody, payload and chemical linker designed to selectively target cancer cells

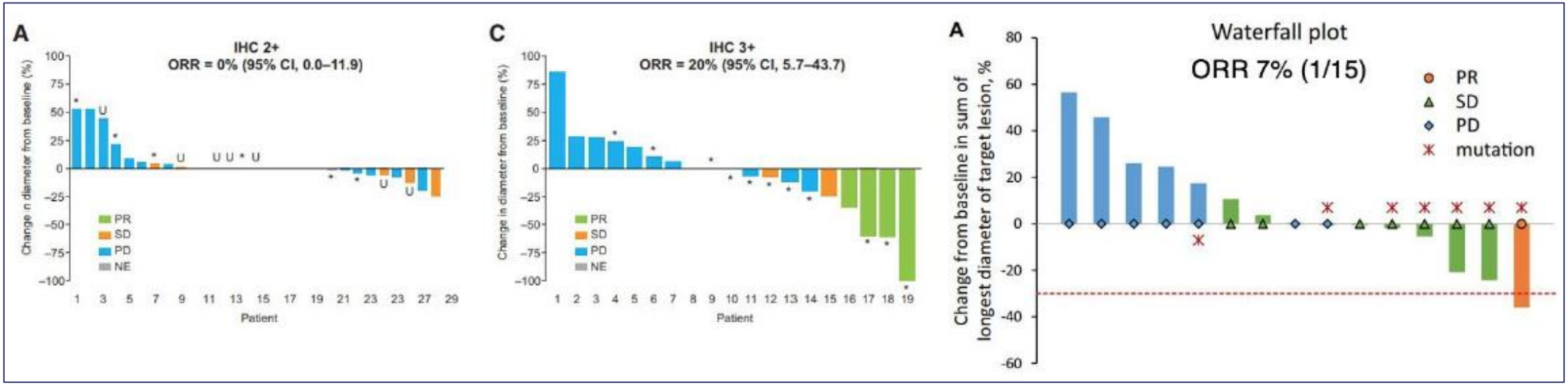




HER2 antibody drug conjugates (ADCs): T-DM1

- T-DM1 (ado-trastuzumab emtasine) is a HER2-targeted ADCs linking trastuzumab with emtasine, an antimicrotubule agent with a drug-to-antibody-ratio (DAR) of 3 to 4

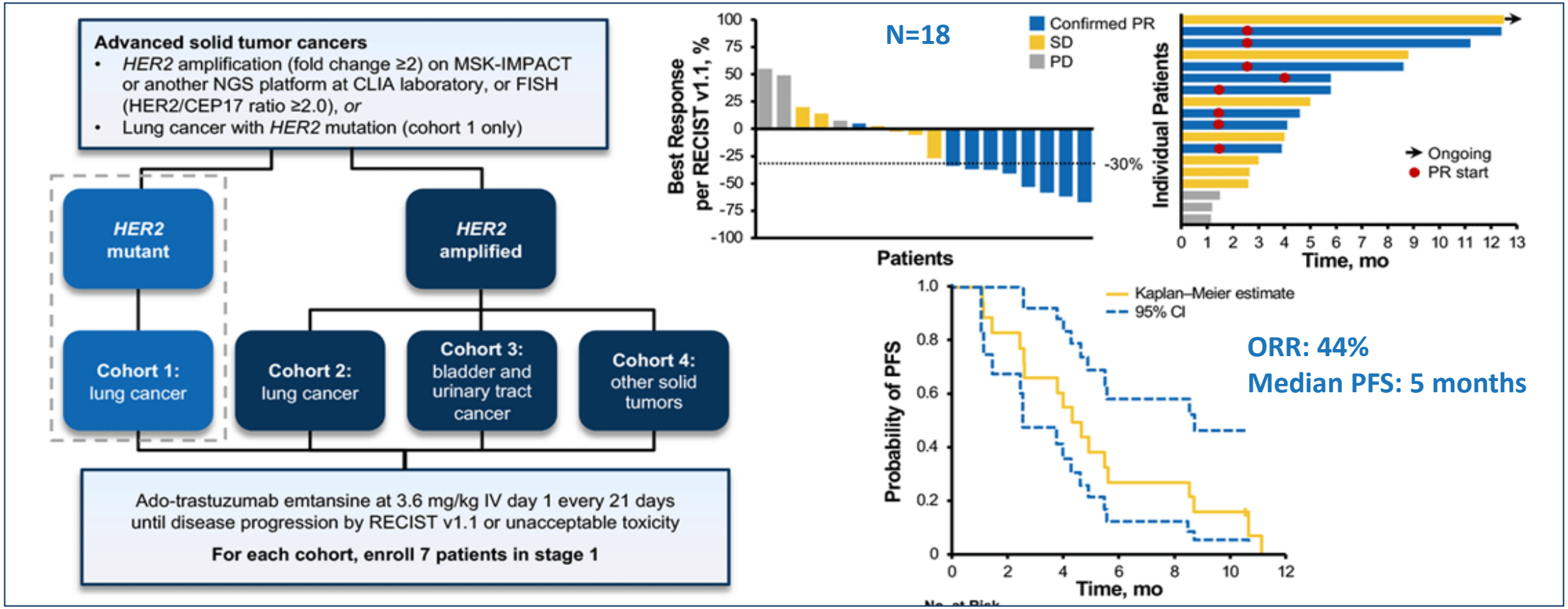
- Negative trials targeting HER2 protein overexpression in NSCLC



Hotta K, et al. J Thorac Oncol. 2018;13(2):273-279; Peters S, et al. Clin Cancer Res. 2019;25(1):64-72

HER2 antibody drug conjugates (ADCs): T-DM1

- Positive trial targeting HER2 mutant or amplified. Phase II basket trial in heavily pre-treated patients

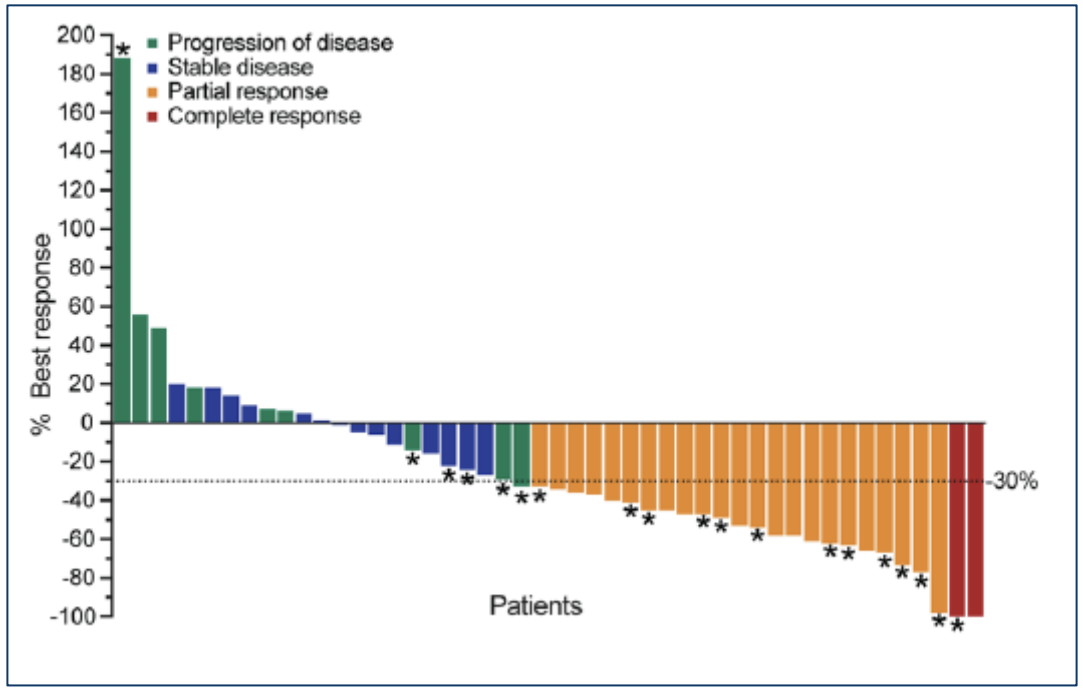


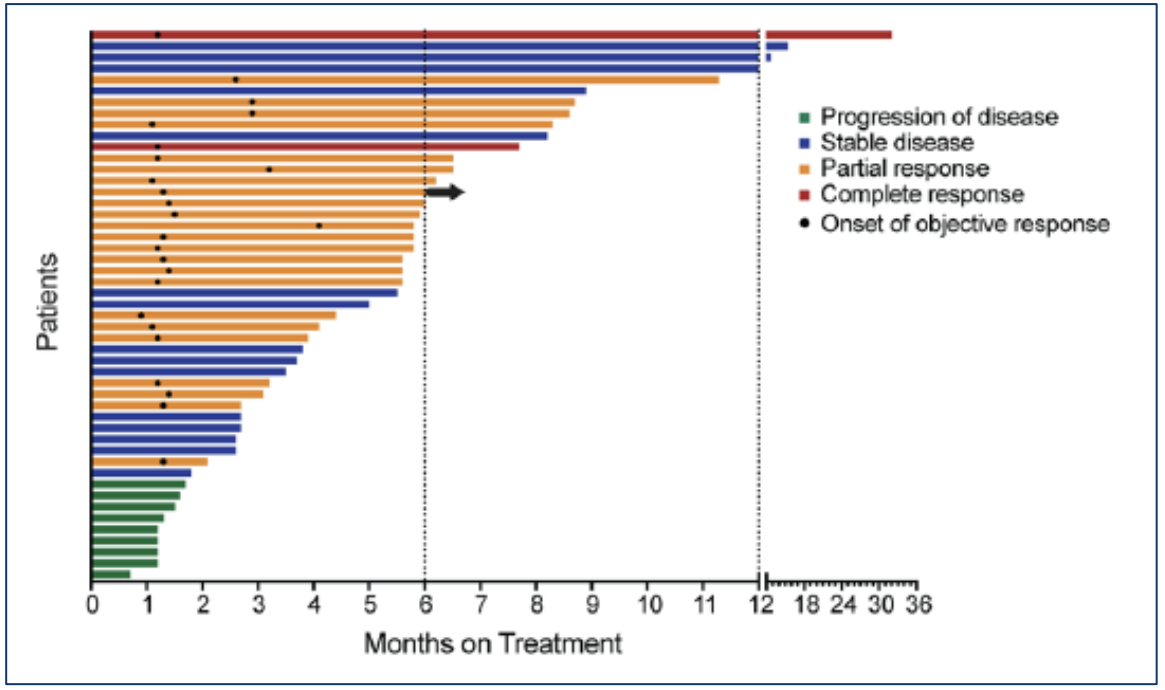
Li BT, et al. J Clin Oncol 2018;36(24):2532-2537

HER2 antibody drug conjugates (ADCs): T-DM1

- Phase II basket trial (NCT02675829)

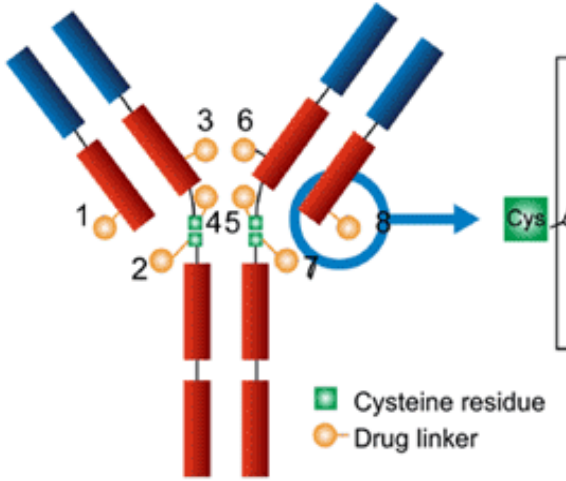
ORR: 51% (24/49)
Median DoR: 4 months
Median PFS: 5 months



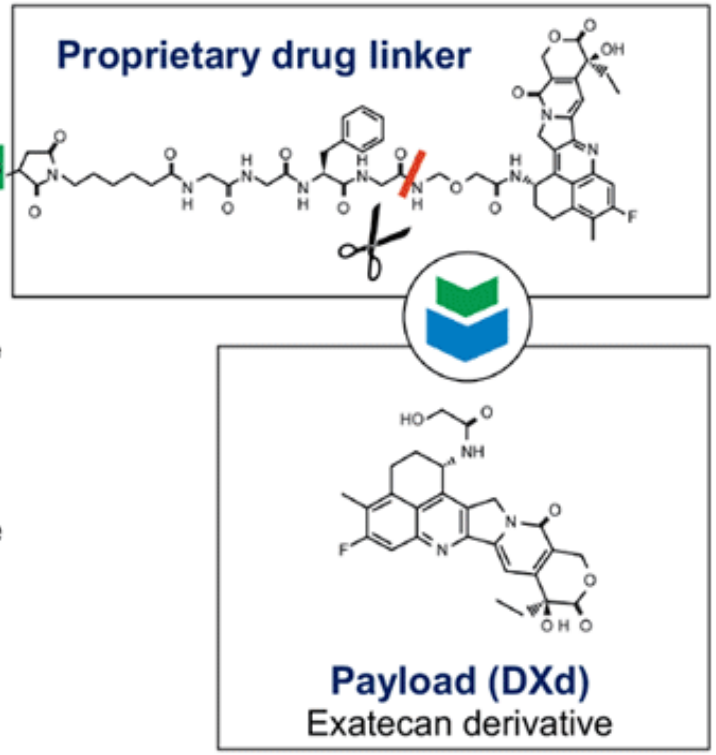


Li BT, et al. Cancer Discov. 2020;10(5):674-687

HER2 antibody drug conjugates (ADCs): TRASTUZUMAB DERUXTECAN (T-DXd)



Conjugation Chemistry
The linker is connected to cysteine residue of the antibody



- ADC composed of three components
  - Humanized HER2-targeted mAb
  - Topoisomerase I inhibitor "payload"
  - Tetrapeptide-based cleavable linker

- High drug-to-antibody ratio (≈8:1)
- High potency payload that is membrane-permeable → nearby cells in tumor targeted regardless of HER2 expression ("bystander antitumor effect")

HER2 antibody drug conjugates (ADCs): TRASTUZUMAB DERUXTECAN (T-DXd)

- DESTINY-Lung01: phase II study of T-DXd in patients with HER2-overexpressing or HER2-mutated 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

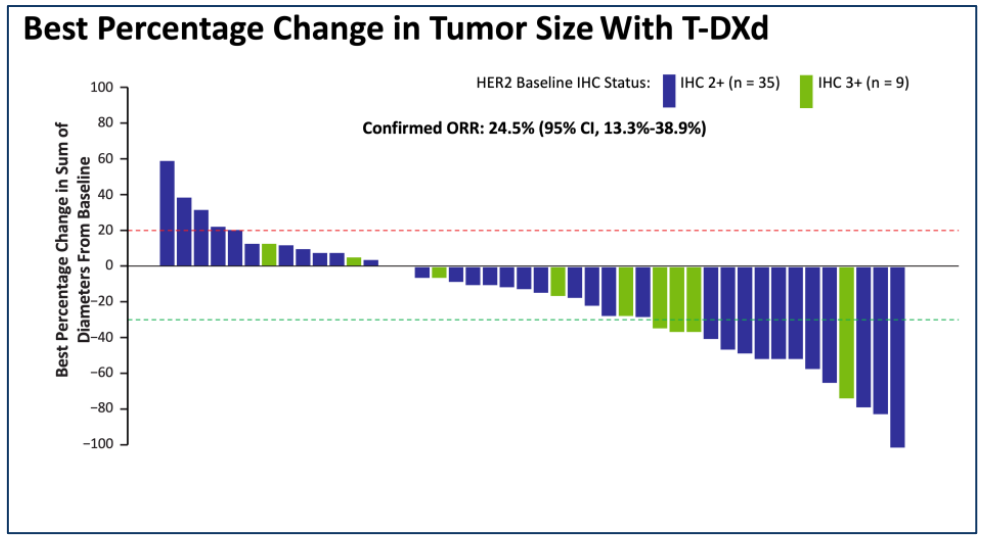
- **Primary endpoint:** confirmed ORR by ICR[d]
- **Secondary endpoints:** DOR, PFS, OS, DCR, and safety
- **Exploratory endpoint:** biomarkers of response

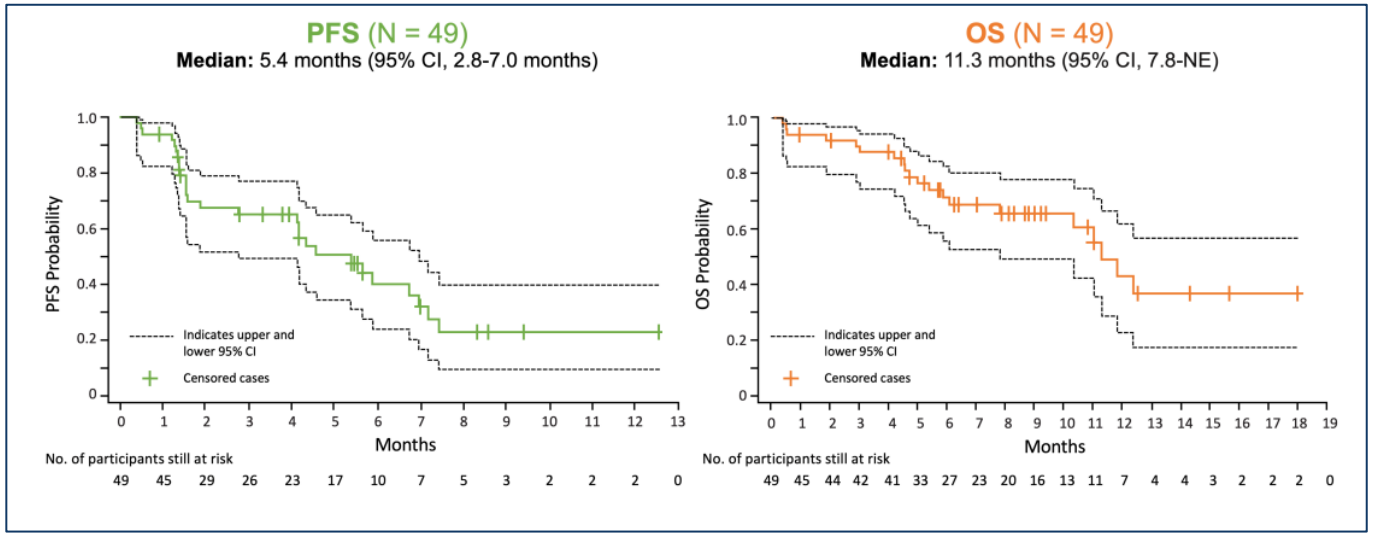
Data cutoff: May 3, 2021
- 91 pts with *HER2*-mutated NSCLC
- 15 pts (16.5%) remain on treatment
- 76 pts (83.5%) discontinued, primarily for PD and AEs

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

HER2 antibody drug conjugates (ADCs): TRASTUZUMAB DERUXTECAN (T-DXd)

- DESTINY-Lung01: cohort HER2-overexpressing (heavily pre-treated patients)
  - ORR: 24.5% and 20.0%, with no apparent difference by HER2 expression (IHC 2+ vs 3+)
  - DCR: 69.4%
  - Median PFS: 5.4 months
  - Median OS: 11.3 months
  - ILD: 16.3%

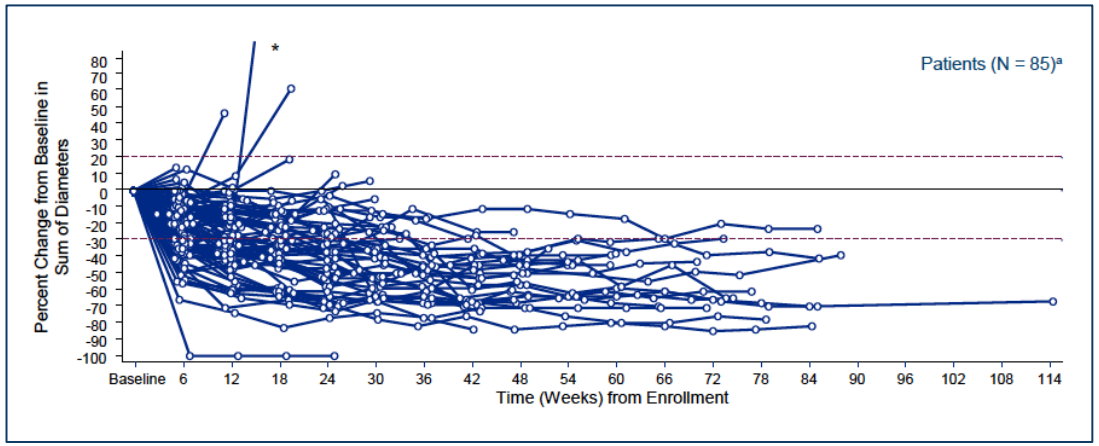


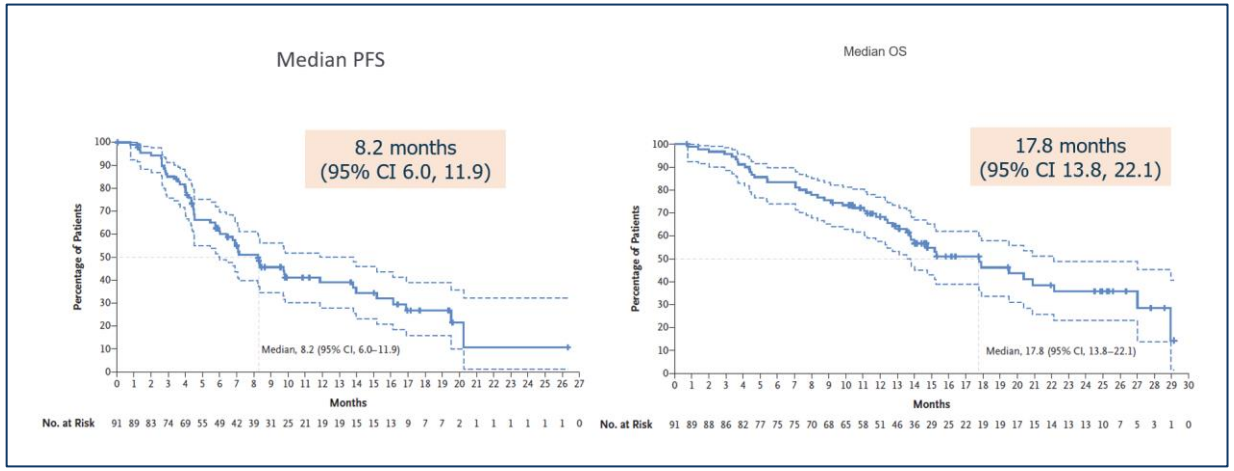


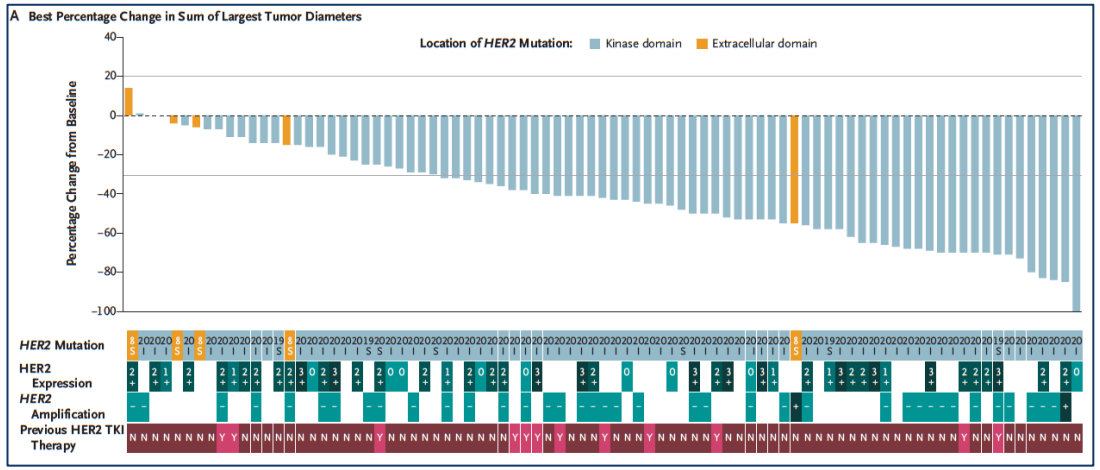
Nakagawa K, et al. J Thorac Oncol 2021;16(3):S109-S110. IASLC 2020

HER2 antibody drug conjugates (ADCs): TRASTUZUMAB DERUXTECAN (T-DXd)

- DESTINY-Lung01: cohort HER2-mutated
  - ORR: 55% (50/91). DoR: 9.3 months
  - DCR: 92%
  - Median PFS: 8.2 months
  - Median OS: 17.8 months
  - ILD: 26.4% (any grade)





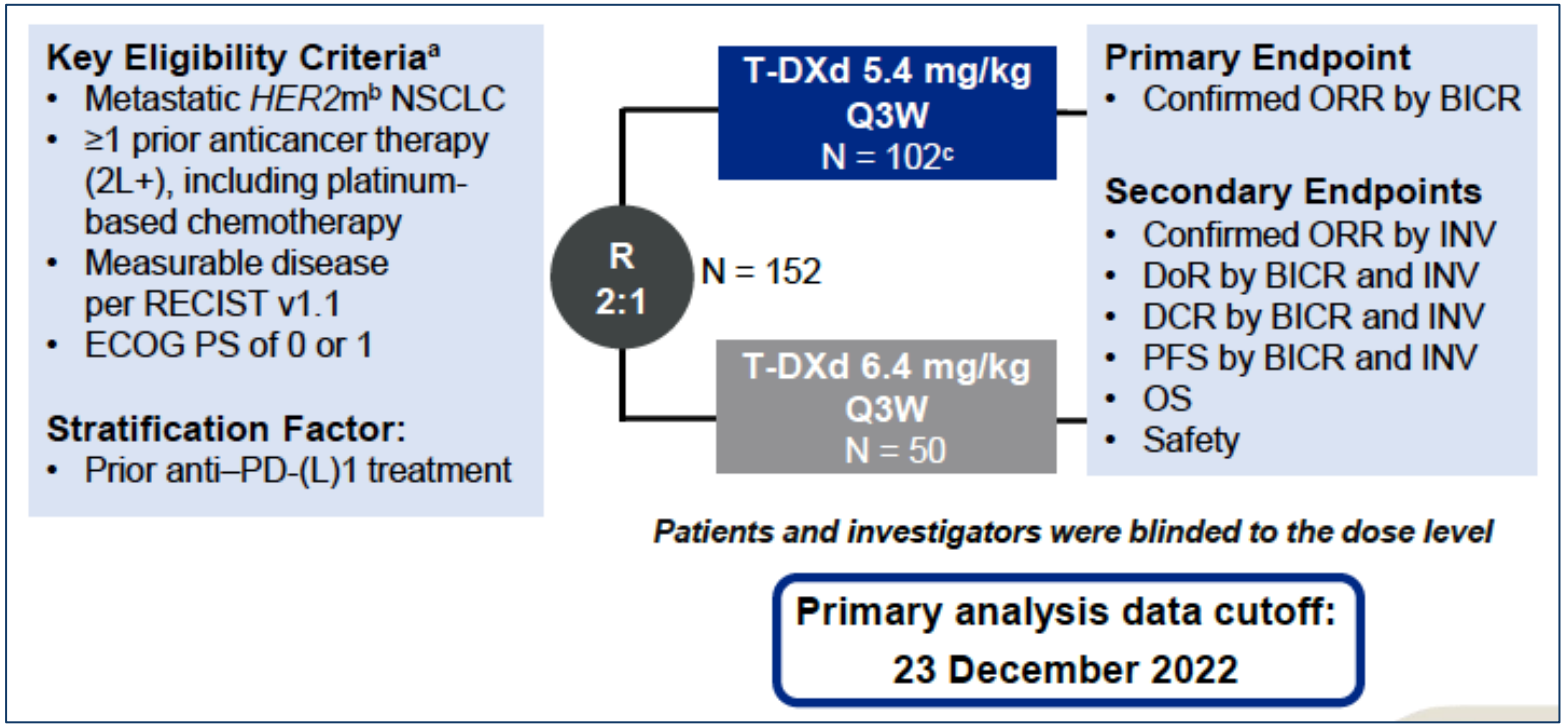


Li BT, et al. N Engl J Med 2022;386:241-251

HER2 antibody drug conjugates (ADCs): TRASTUZUMAB DERUXTECAN (T-DXd)

- DESTINY-Lung02: a non-comparative, randomized, blinded phase II trial of T-DXd 5.4 or 6.4 mg/kg every 3 weeks in patients with HER2-mutated metastatic NSCLC

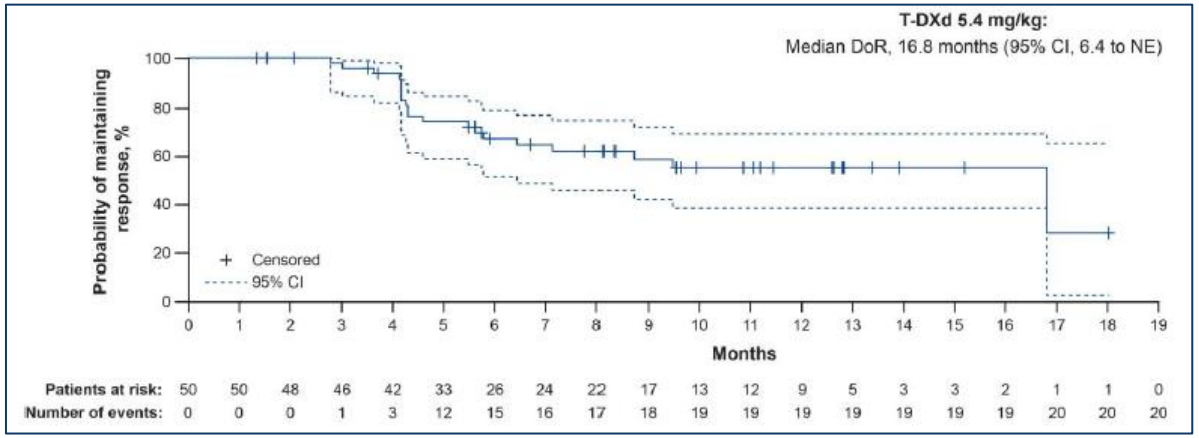
In the interim analysis, T-DXd showed deep and durable responses and an acceptable and generally manageable safety profile → accelerated approval of T-DXd 5.4mg/kg in the United States (FDA approval)



Goto K, et al. Ann Oncol 2022;33:S1422 (abstr LBA55). ESMO 2022; Goto K, et al. J Clin Oncol 2023 Sep 11:JCO2301361; Jänne PA, et al. IASLC 2023

HER2 antibody drug conjugates (ADCs): TRASTUZUMAB DERUXTECAN (T-DXd)

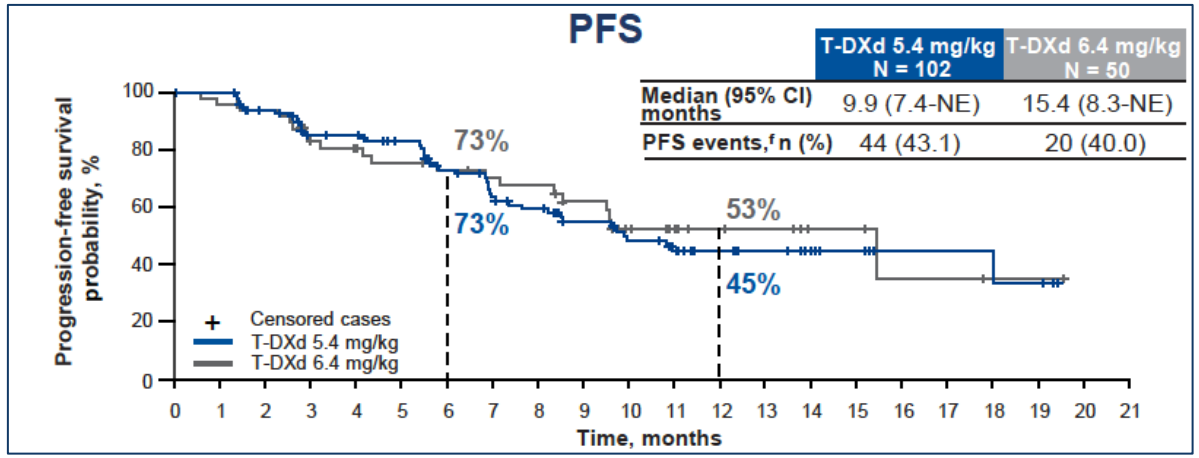
- DESTINY-Lung02
  - ORR: 49% vs 56% (regardless of number or type of prior systemic anticancer therapy and baseline metastasis
  - DCR: 93.1% vs 92%
  - DoR: 16.8 months vs NE

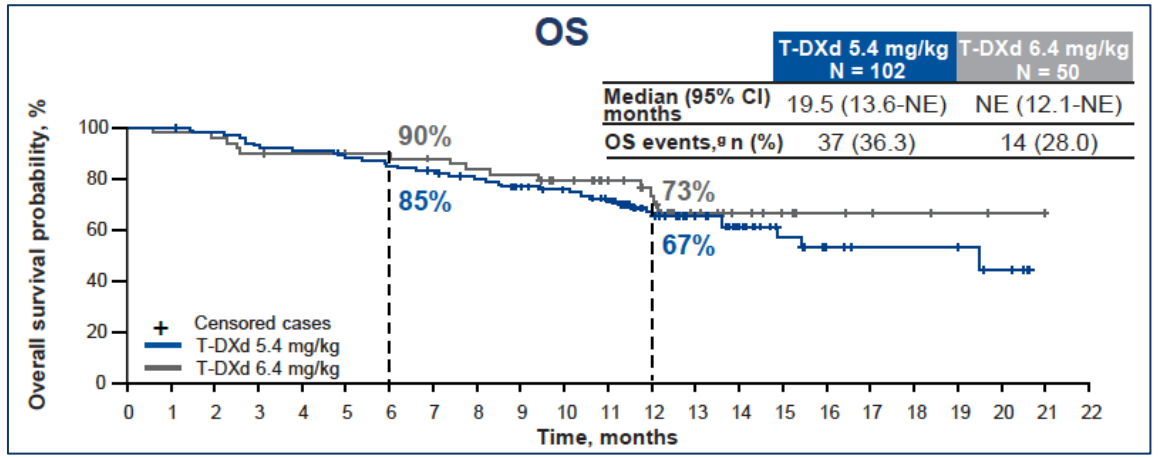


Response Assessment by BICR	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
Confirmed ORR, No. (%)	50 (49.0)	28 (56.0)
95% CI	39.0 to 59.1	41.3 to 70.0
Best confirmed overall response, No. (%)		
CR	1 (1.0)	2 (4.0)
PR	49 (48.0)	26 (52.0)
SD	45 (44.1)	18 (36.0)
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 2023 Sep 11:JCO2301361; Jänne PA, et al. IASLC 2023

HER2 antibody drug conjugates (ADCs): TRASTUZUMAB DERUXTECAN (T-DXd)





Median duration of follow-up was 11.5 months in the T-DXd 5.4mg/kg and 11.8 months in the T-DXd 6.4mg/kg

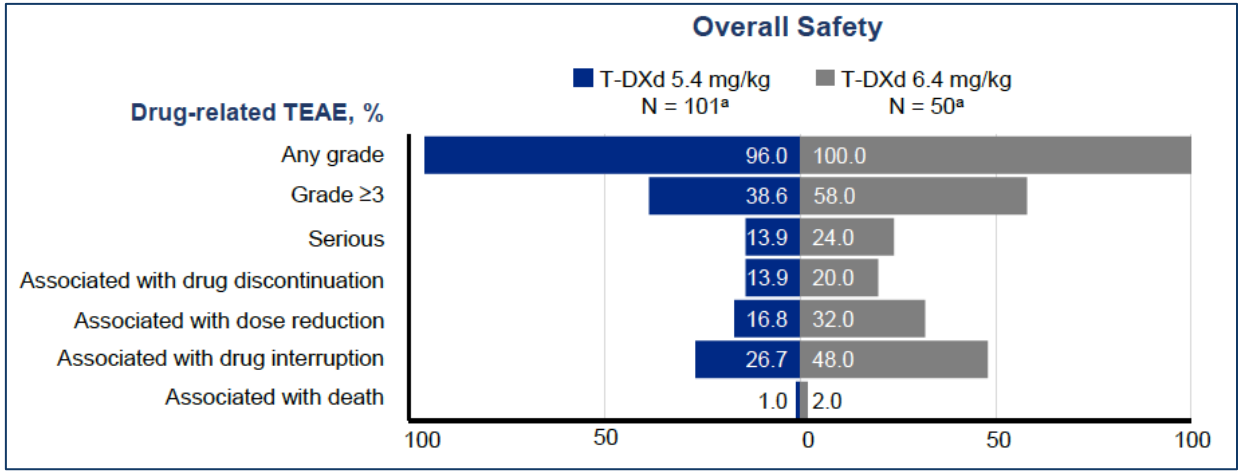
- Median PFS by BICR: 9.9 months vs 15.4 months
- Median OS: 19.5 months vs NE

Goto K, et al. J Clin Oncol 2023 Sep 11:JCO2301361; Jänne PA, et al. IASLC 2023

HER2 antibody drug conjugates (ADCs): TRASTUZUMAB DERUXTECAN (T-DXd)

- Median treatment duration: 7.7 months with T-DXd 5.4 mg/Kg and 8.3 months with T-DXd 6.4 mg/kg

- Most common any-grade TEAEs:
  - Nausea (67.3% and 82.0%)
  - Neutropenia (42.6% and 56%)
  - Fatigue (44.6% and 50.0%)
  - Decreased appetite (39.6% and 50.0%)



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)

- 14.9% and 28.2% of patients who received prior anti-PD-(L)1 treatment had adjudicated drug-related ILD, whereas in patients who did not receive prior anti-PD-(L)1 treatment, rates were 7.4% and 27.3%

Goto K, et al. J Clin Oncol 2023 Sep 11:JCO2301361; Jänne PA, et al. IASLC 2023

OUTLINE

- *HER2* BIOLOGY
- *HER2* ALTERATIONS IN NSCLC
- CLINICAL AND BIOLOGIC CHARACTERISTICS *HER2*-MUTANT NSCLC
- TIMELINE OF DEVELOPMENT OF HER2 TARGETED THERAPIES IN *HER2*-MUTANT NSCLC
- MECHANISM OF ACTION FOR HER2 TARGETED THERAPIES IN *HER2*-MUTANT NSCLC
- HER2 THERAPY
  - CHEMOTHERAPY
  - IMMUNOTHERAPY
  - HER2 TARGETED TYROSINE KINASE INHIBITORS (TKIs)
  - HER2 TARGETED MONOCLONAL ANTIBODIES (mAb)
  - HER2 TARGETED ANTIBODY-DRUG CONJUGATES (ADCs)
- MECHANISM OF RESISTANCE
- FUTURE PERSPECTIVES
- CONCLUSION

MECHANISM OF RESISTANCE

- Acquired resistance to HER2-targeted therapy is inevitable
  - HER2-dependent: *HER2* secondary mutations
  - HER2-independent: bypass activation such as RAS/MAPK signaling pathway or PI3K/AKT

- Data insufficient

- Further investigations are needed

Neel DS, et al. Precis Oncol. 2017;1

OUTLINE

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- MECHANISM OF RESISTANCE
- FUTURE PERSPECTIVES
- CONCLUSION

FUTURE

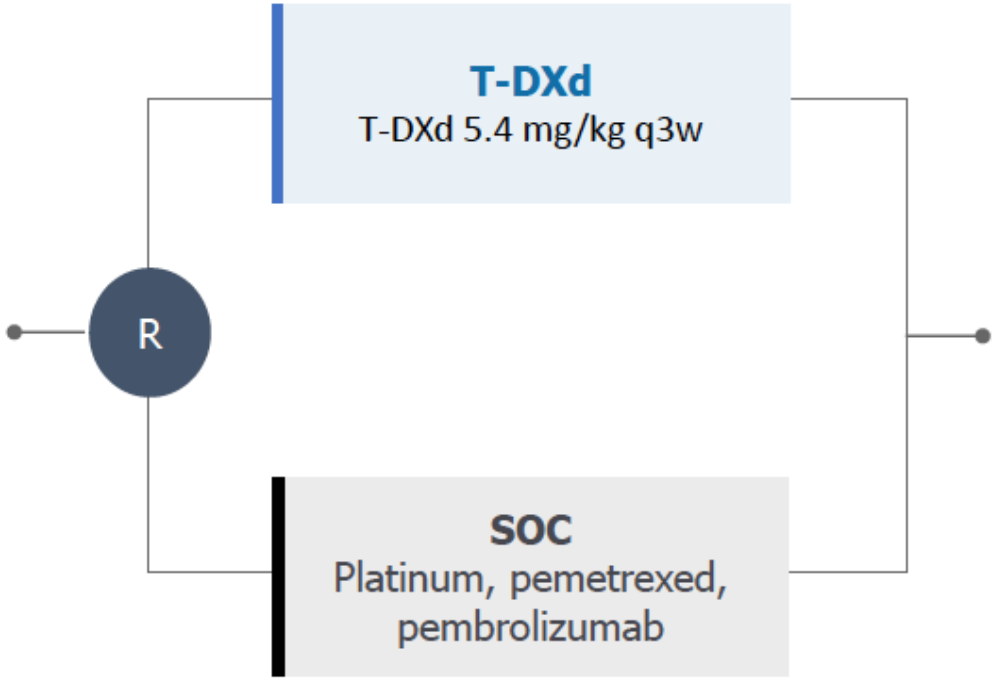
- The optimal sequencing strategy and exploration of the best combination treatment
- Currently, only NSCLC patients with HER2 mutations are indicated for the use of HER directed targets because overexpression and amplifications of HER2 do not have the same benefits
- The intracranial efficacy for the HER2 ADCs is not fully established

FUTURE

DESTINY-Lung04 is a randomized phase 3 study investigating the safety and efficacy of T-DXd vs SOC for 1L treatment of unresectable, locally advanced/metastatic NSCLC with *HER2* mutations

Eligibility Criteria

- Unresectable, locally advanced, or metastatic histologically documented non-squamous NSCLC with *HER2* exons 19 or 20 mutations by tissue NGS or ctDNA
- Measurable based on RECIST 1.1
- ECOG PS 0 or 1
- Having tumor tissue available for central testing
- ~N = 264

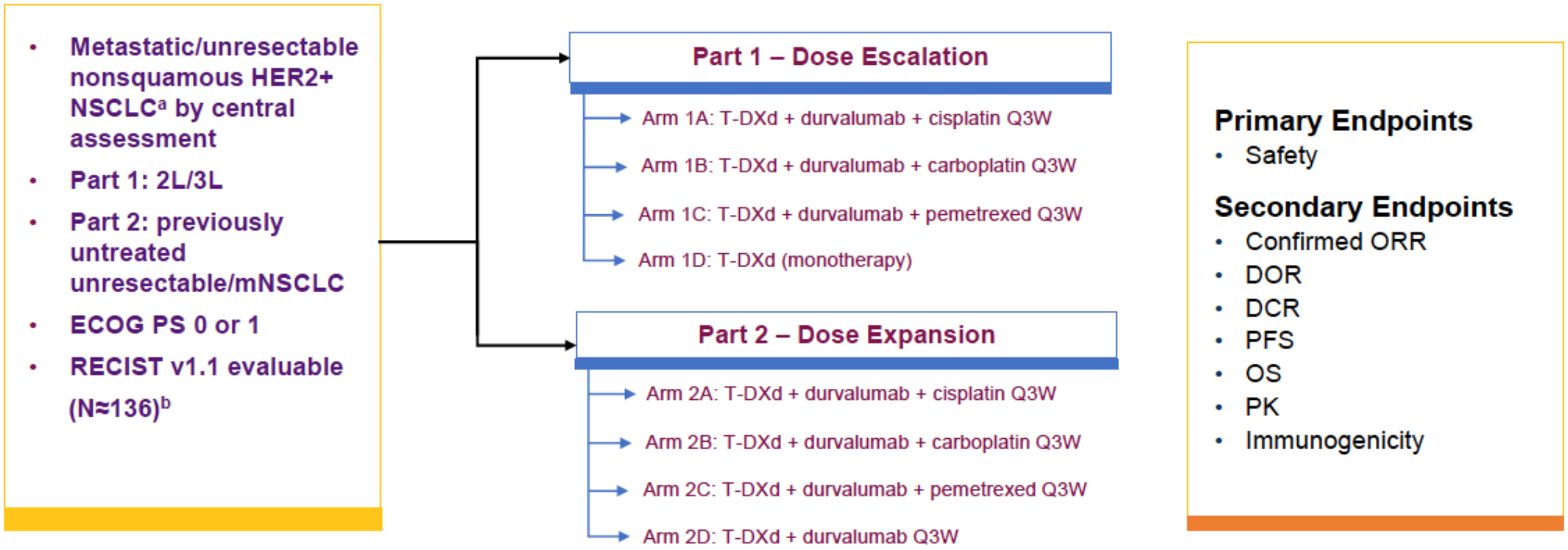


Primary Endpoint:
- PFS by BICR

Secondary Endpoints:
- OS
- PFS (IA)
- ORR
- DOR
- CNS PFS
- Safety, tolerability
- PK
- PROs

FUTURE

- DESTINY-Lung03: phase Ib, open-label, dose-escalation



FUTURE

- Others:
  - HUDSON study phase II basket trial: T-DXd + durvalumab (2L)
  - NCT04042701: T-DXd + pembrolizumab
  - NCT04144569: Pyrotinib + PD-1 inhibitors
  - Zenocutuzumab (MCLA-128): bi-specific antibody
  - NCT03602079, NCT03255070, NCT04818333, NCT05141786: several other HER2 ADCs

OUTLINE

- *HER2* BIOLOGY
- *HER2* ALTERATIONS IN NSCLC
- CLINICAL AND BIOLOGIC CHARACTERISTICS *HER2*-MUTANT NSCLC
- TIMELINE OF DEVELOPMENT OF HER2 TARGETED THERAPIES IN *HER2*-MUTANT NSCLC
- MECHANISM OF ACTION FOR HER2 TARGETED THERAPIES IN *HER2*-MUTANT NSCLC
- HER2 THERAPY
    - CHEMOTHERAPY
    - IMMUNOTHERAPY
    - HER2 TARGETED TYROSINE KINASE INHIBITORS (TKIs)
    - HER2 TARGETED MONOCLONAL ANTIBODIES (mAb)
    - HER2 TARGETED ANTIBODY-DRUG CONJUGATES (ADCs)
- MECHANISM OF RESISTANCE
- FUTURE PERSPECTIVES
- CONCLUSION

CONCLUSIONS

- HER2 alterations, including mutations, protein overexpression and gene amplification, represent three distinct molecular entities
- *HER2* mutations, are a confirmed therapeutic target in NSCLC
- Identifying *HER2* mutations is very important for NSCLC patients to benefit from these new therapies
- Platinum based chemotherapy currently remains the preferred first line treatment for patients with *HER2*-mutant NSCLC
- Trastuzumab-deruxtecan remains the new line treatment for patients with previously treated
- The management of ILD requires a specific evaluation and expertise
- For *HER2*-mutant disease, the role of selective or irreversible TKIs, showed a modest activity and relevant rate of toxicities, due to the inhibition of EGFR pathway
- Novel HER2-selective TKIs (without activity against other HER/ERBB family members) may lead to enhanced activity and improved safety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