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Compassion for Patients.™

Daiichi-Sankyo

ASCO 2025 Highlights

DAIICHI SANKYO CO., LTD.

June 2nd (US)/ 3rd (JP), 2025

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ASCO Highlights 2025: IR conference call

Hiroyuki Okuzawa
President and CEO

Mark Rutstein
Head of Therapeutic Area
Oncology Development

Agenda

1. Welcome message
2. R&D overview
3. Highlights from ASCO 2025
4. Q&A

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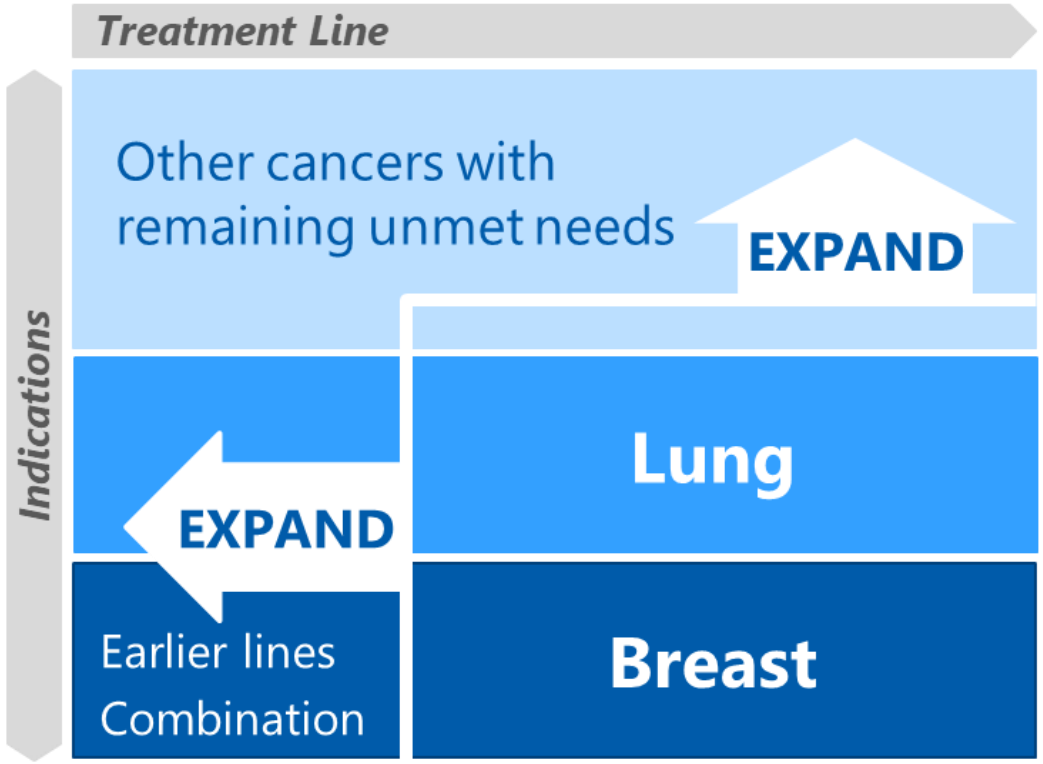
ASCO 2025

In our EXPAND strategy we showed ENHERTU footprint in earlier line



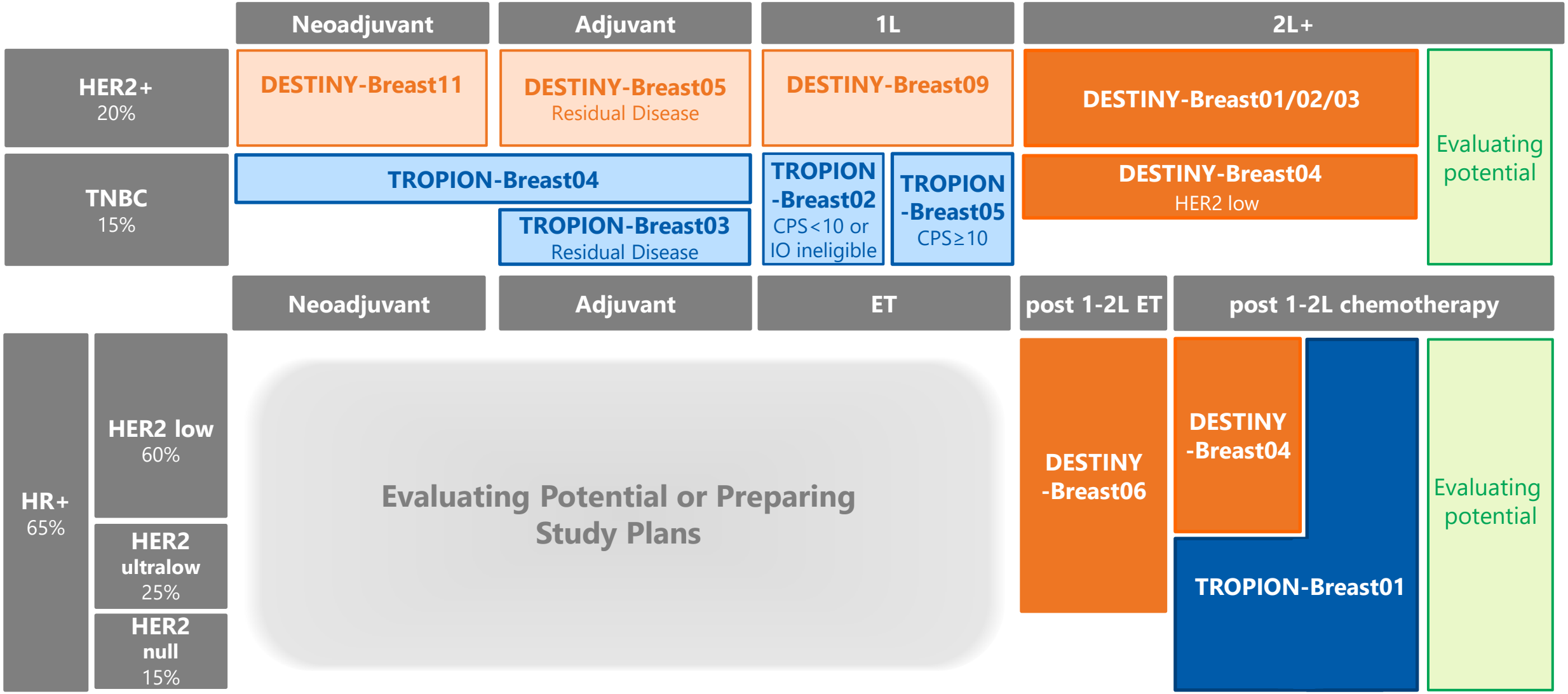
- Establish and expand DXd ADC therapies in **Breast** and **Lung** cancers
- **Go Earlier:** explore early lines of therapy/ stage of diseases; replace chemotherapy
- **Go Wider:** into new diseases beyond currently focusing areas to serve more patient needs

DESTINY Breast09

DESTINY Breast11

DESTINY-Breast05 to follow

Establish and expand DXd ADCs to address the broader spectrum of Breast Cancer

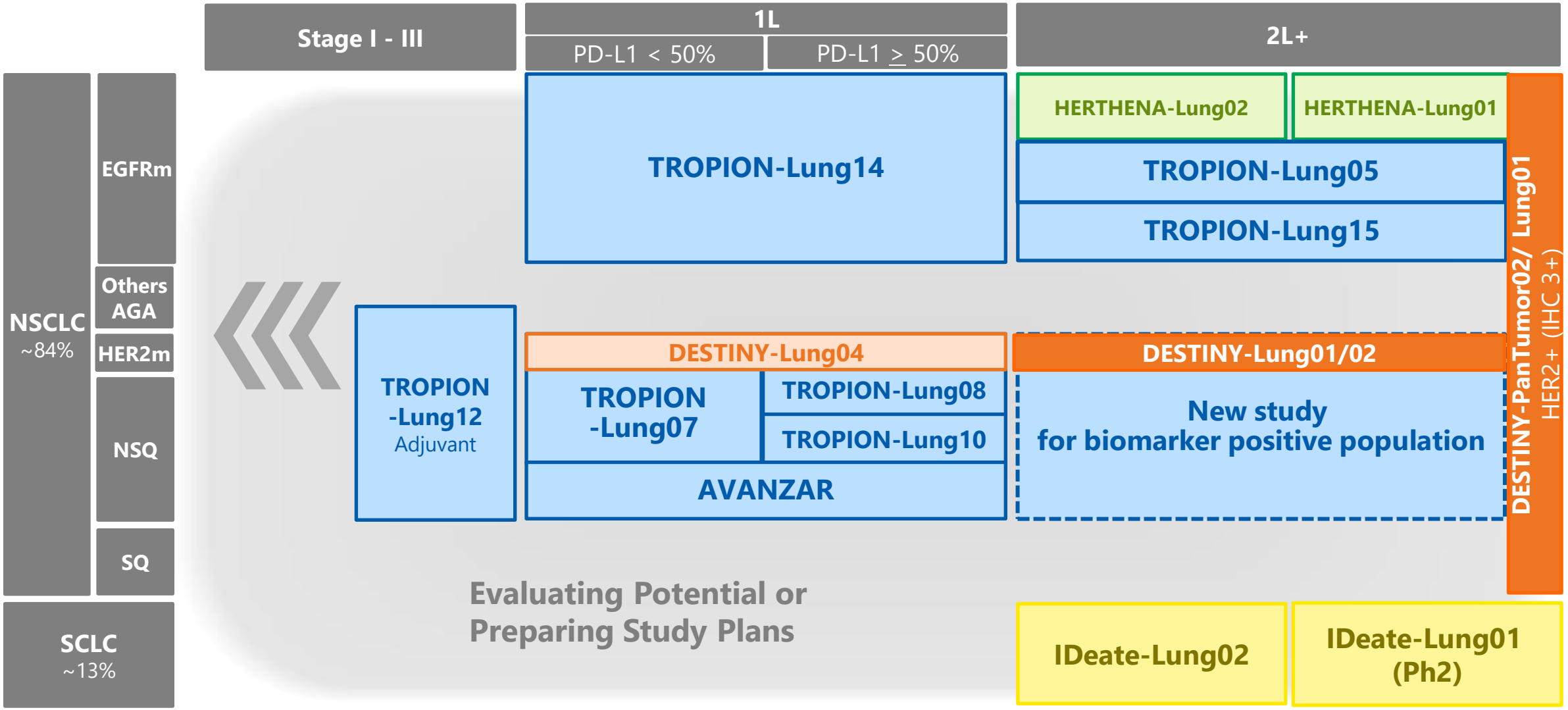


Launched | On-going | ENHERTU® | DATROWAY® | HER3-DXd

CPS: combined positive score; ET: endocrine therapy; HR: hormone receptor; IHC: immunohistochemistry, IO: immune oncology, TNBC: triple-negative breast cancer

- Pivotal studies only, not exhaustive
- Box size does not reflect the patient population
- Box indicates current potential target segment

Establish and expand DXd ADCs to address the broader spectrum of Lung Cancer



- Pivotal studies and major Ph2 only, not exhaustive
- Box size does not reflect the patient population
- Box indicates current potential target segment

AGA: actionable genomic alteration, IHC: immunohistochemistry, NSQ: non- squamous, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, SQ: squamous

Agenda

1. Welcome message
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3. **Highlights from ASCO 2025**
4. Q&A

Topics

ENHERTU®

- DESTINY-Breast09
- DESTINY-Gastric04

DATROWAY®

- TROPION-Lung02
- NeoCOAST-2

HER3-DXd

- HERTHENA-Lung02

Next Wave

- DS-2243

ENHERTU®

Trastuzumab deruxtecan (T-DXd) + pertuzumab vs taxane + trastuzumab + pertuzumab (THP) for first-line treatment of patients with human epidermal growth factor receptor 2–positive (HER2+) advanced/metastatic breast cancer: interim results from DESTINY-Breast09

Sara M Tolaney, MD, MPH
Dana-Farber Cancer Institute, Boston, MA, US

Monday, June 2, 2025

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On behalf of the DESTINY-Breast09 investigators

DESTINY-Breast09 study design

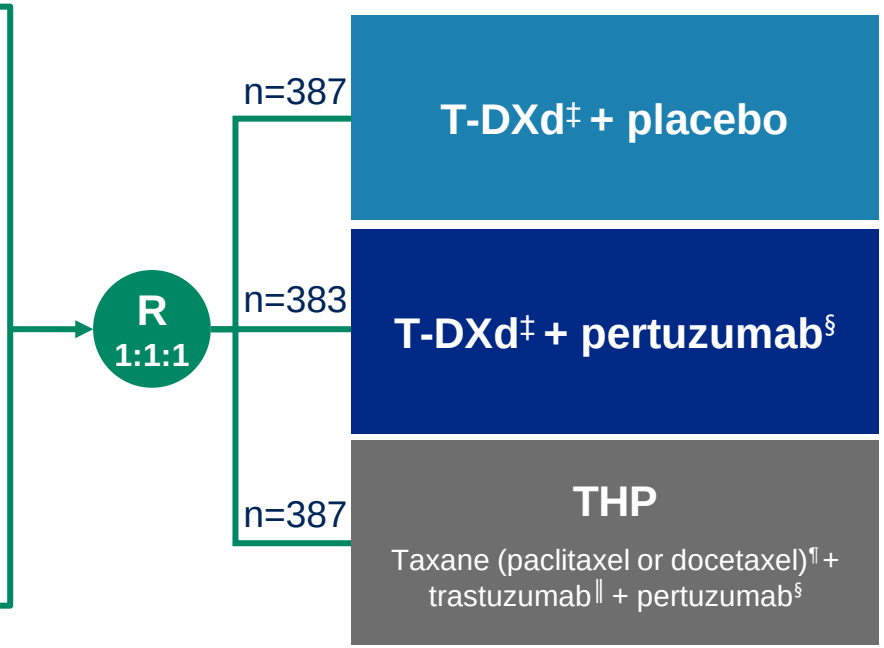
A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)

Eligibility criteria

- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/ adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC†**

Stratification factors

- De-novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA*m (detected vs non-detected)



Endpoints

Primary

- PFS (BICR)

Key secondary

- OS

Secondary

- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

- If T-DXd was discontinued due to AEs (except Grade >2 ILD), patients could switch to trastuzumab**
- Concurrent use of ET (AI or tamoxifen) was allowed for those with HR+ disease after six cycles of T-DXd or discontinuation of taxane in THP arm

*Open label for THP arm. Double blinded for pertuzumab in experimental arms; †HER2-targeted therapy or chemotherapy; ‡5.4 mg/kg Q3W; §840 mg loading dose, then 420 mg Q3W; ¶paclitaxel 80 mg/m^2 QW or 175 mg/m^2 Q3W, or docetaxel 75 mg/m^2 Q3W for a minimum of six cycles or until intolerable toxicity; ‖8 mg/kg loading dose, then 6 mg/kg Q3W; **without loading dose

AE, adverse event; AI, aromatase inhibitor; a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; DFI, disease-free interval; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR+/−, hormone receptor–positive/–negative; ILD, interstitial lung disease; INV, investigator; mets, metastases; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; *PIK3CA*m, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; Q3W, every 3 weeks; QW, once every week; R, randomization; T-DXd, trastuzumab deruxtecan

NCT04784715. Updated. May 6, 2025. Available from: https://clinicaltrials.gov/study/NCT04784715 (Accessed May 29, 2025)

DESTINY-Breast09 study design

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Stratification factors

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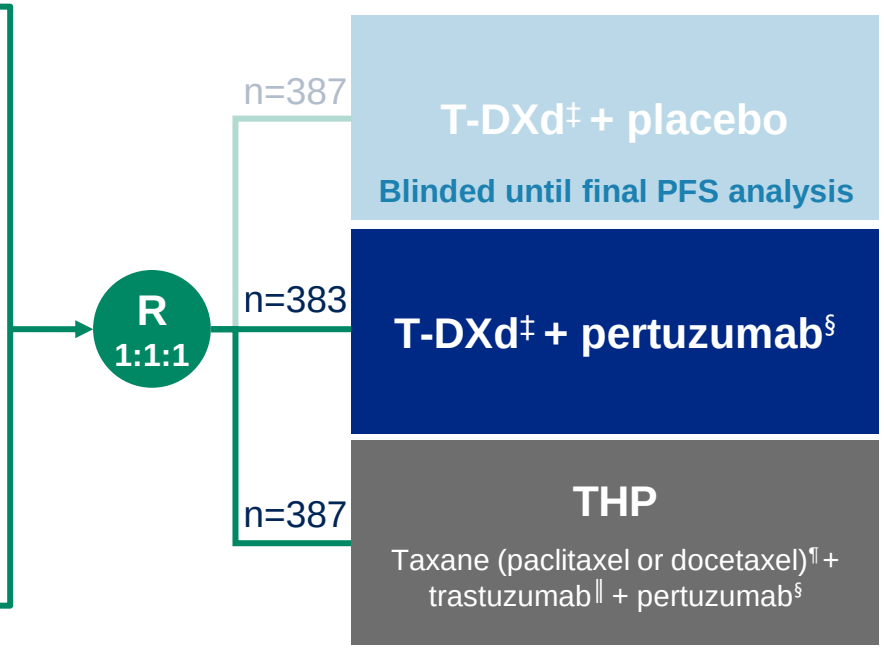


Endpoints

Primary

- PFS (BICR)

Key secondary

- OS

Secondary

- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

At this planned interim analysis (DCO Feb 26, 2025), results are reported for the T-DXd + P and THP arms

*Open label for THP arm. Double blinded for pertuzumab in experimental arms; †HER2-targeted therapy or chemotherapy; ‡5.4 mg/kg Q3W; §840 mg loading dose, then 420 mg Q3W; ¶paclitaxel 80 mg/m^2 QW or 175 mg/m^2 Q3W, or docetaxel 75 mg/m^2 Q3W for a minimum of six cycles or until intolerable toxicity; ‖8 mg/kg loading dose, then 6 mg/kg Q3W

a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; DCO, data cutoff; DFI, disease-free interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR+/−, hormone receptor–positive/–negative; INV, investigator; mBC, metastatic breast cancer; mets, metastases; mo, months; ORR, objective response rate; OS, overall survival; P, pertuzumab; PFS, progression-free survival; PFS2, second progression-free survival; *PIK3CA*m, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; Q3W, every 3 weeks; QW, once every week; R, randomization; T-DXd, trastuzumab deruxtecan

NCT04784715. Updated. May 6, 2025. Available from: https://clinicaltrials.gov/study/NCT04784715 (Accessed May 29, 2025)

Statistical analysis

Interim analysis for PFS by BICR

(planned after approximately 399 events across three arms, and at least 277 events per comparison)

- At this DCO (Feb 26, 2025), interim analysis criterion for superiority (P-value <0.00043) was already met for T-DXd + P vs THP (**maturity: ~38% of total N**)
- T-DXd + placebo remains blinded until final PFS analysis per protocol

First interim OS analysis

(prespecified)

- At DCO, 126 events had occurred (**maturity: ~16% of total N**)
- Final OS analysis will be conducted per protocol

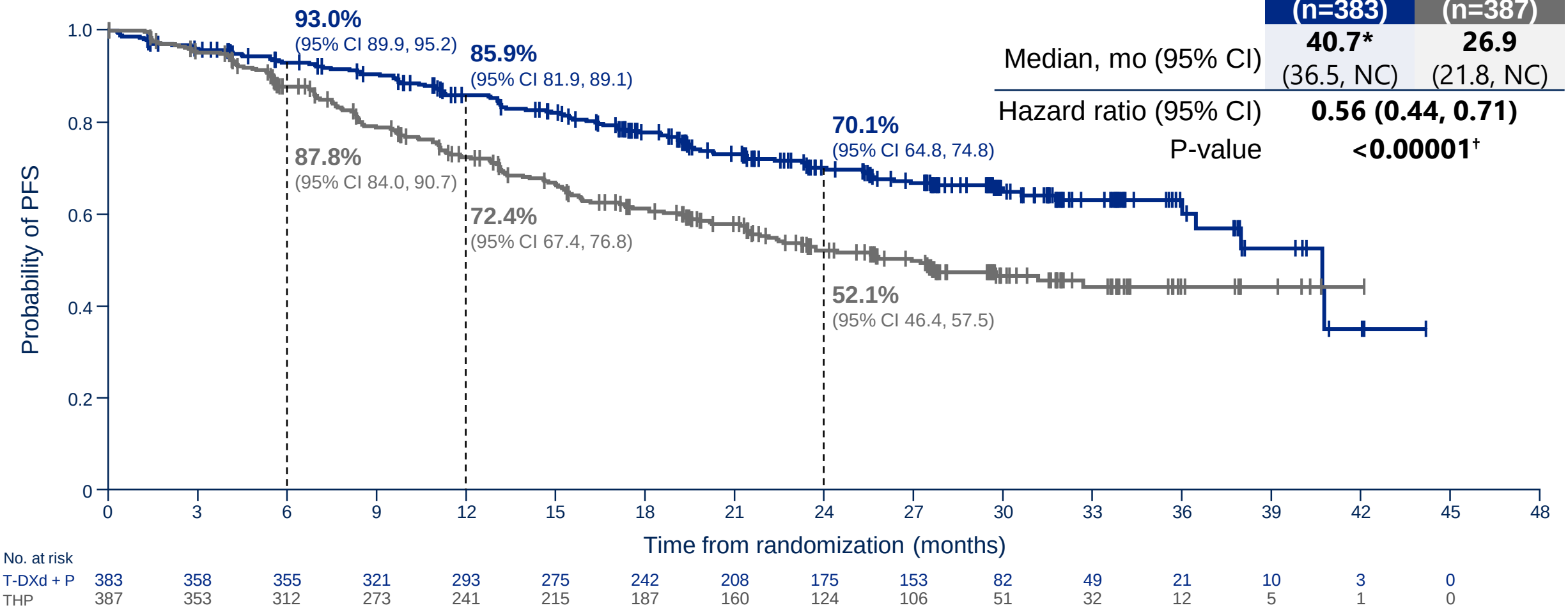
BICR, blinded independent central review; DCO, data cutoff; OS, overall survival; P, pertuzumab; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Patient demographics and key baseline characteristics

	T-DXd + P (n=383)	THP (n=387)
Age, median (range), years	54 (27–85)	54 (20–81)
Female, n (%)	383 (100)	387 (100)
Geographical region, n (%)		
Asia	188 (49.1)	191 (49.4)
Western Europe and North America	87 (22.7)	78 (20.2)
Rest of World	108 (28.2)	118 (30.5)
ECOG performance status, n (%)		
0 (normal activity)	256 (66.8)	246 (63.6)
1 (restricted activity)	127 (33.2)	141 (36.4)
HER2 score by central test, n (%)		
IHC 3+	318 (83.0)	315 (81.4)
IHC <3 / ISH+	62 (16.2)	71 (18.3)
IHC NR / ISH+	3 (0.8)	1 (0.3)
HR status, n (%)		
Positive*	207 (54.0)	209 (54.0)
Negative	176 (46.0)	178 (46.0)
De-novo disease at diagnosis, n (%)	200 (52.2)	200 (51.7)
***PIK3CA* mutations detected, n (%)**	116 (30.3)	121 (31.3)
Brain metastases, n (%)†	25 (6.5)	22 (5.7)
Visceral metastases, n (%)	281 (73.4)	268 (69.3)

*Defined as estrogen receptor–positive and/or progesterone receptor–positive (≥1%); †participants were eligible if they had brain metastases that were clinically inactive or treated/asymptomatic
ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; NR, not recorded; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

PFS (BICR): primary endpoint



	T-DXd + P (n=383)	THP (n=387)
Median, mo (95% CI)	**40.7*** (36.5, NC)	**26.9** (21.8, NC)
Hazard ratio (95% CI)	**0.56 (0.44, 0.71)**	
P-value	**<0.00001†**	

No. at risk

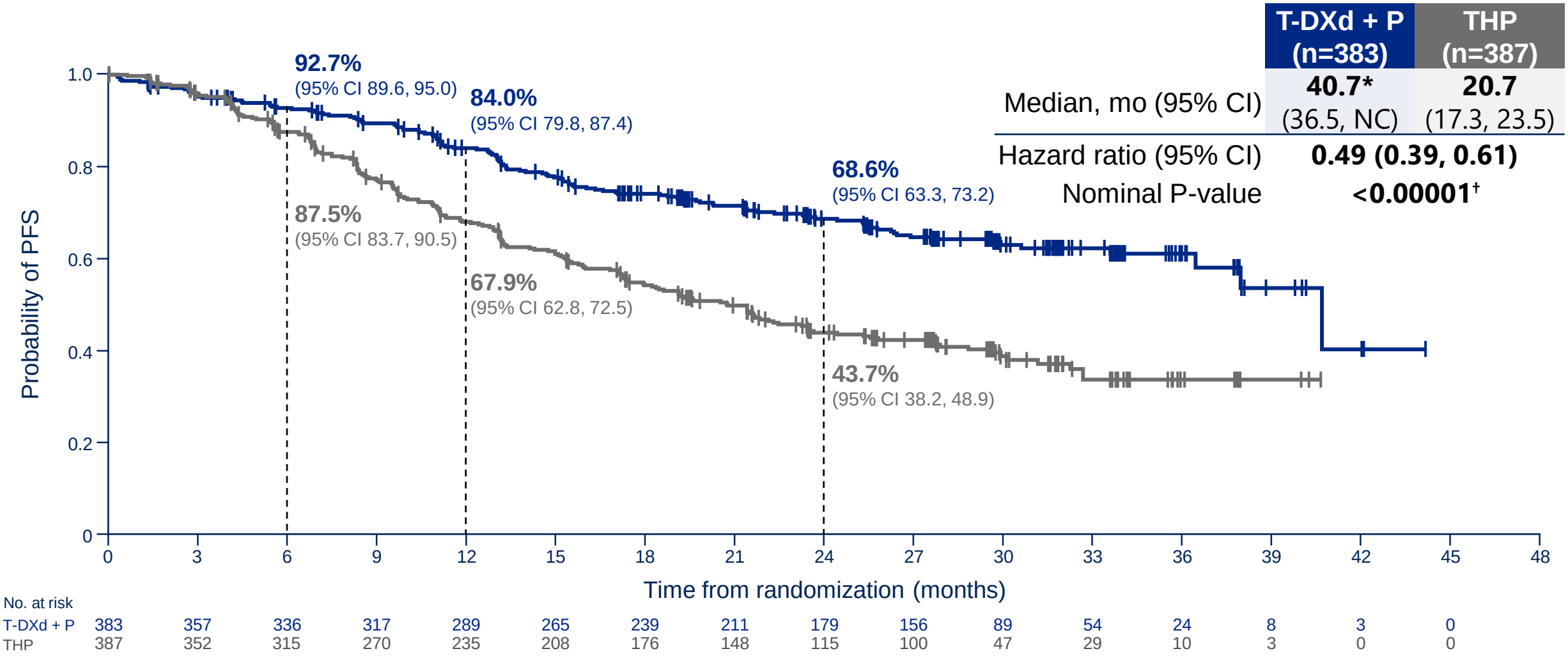
T-DXd + P	383	358	355	321	293	275	242	208	175	153	82	49	21	10	3	0
THP	387	353	312	273	241	215	187	160	124	106	51	32	12	5	1	0

Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

*Median PFS estimate for T-DXd + P is likely to change at updated analysis; †stratified log-rank test. A P-value of <0.00043 was required for interim analysis superiority

BICR, blinded independent central review; CI, confidence interval; mo, months; (m)PFS, (median) progression-free survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

PFS (investigator assessment)



	T-DXd + P (n=383)	THP (n=387)
Median, mo (95% CI)	**40.7*** (36.5, NC)	**20.7** (17.3, 23.5)
Hazard ratio (95% CI)	**0.49 (0.39, 0.61)**	
Nominal P-value	**<0.00001†**	

No. at risk

T-DXd + P	383	357	336	317	289	265	239	211	179	156	89	54	24	8	3	0
THP	387	352	315	270	235	208	176	148	115	100	47	29	10	3	0	0

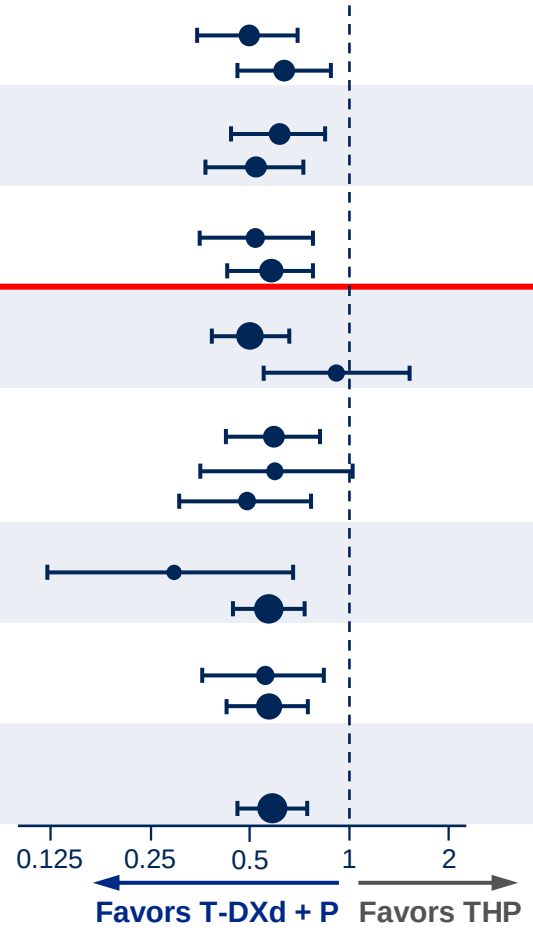
Clinically meaningful improvement in PFS with T-DXd + P over THP (median Δ 20.0 mo)

*Median PFS estimate for T-DXd + P is likely to change at updated analysis; †stratified log-rank test

CI, confidence interval; mo, months; (m)PFS, (median) progression-free survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

PFS (BICR): subgroup analyses

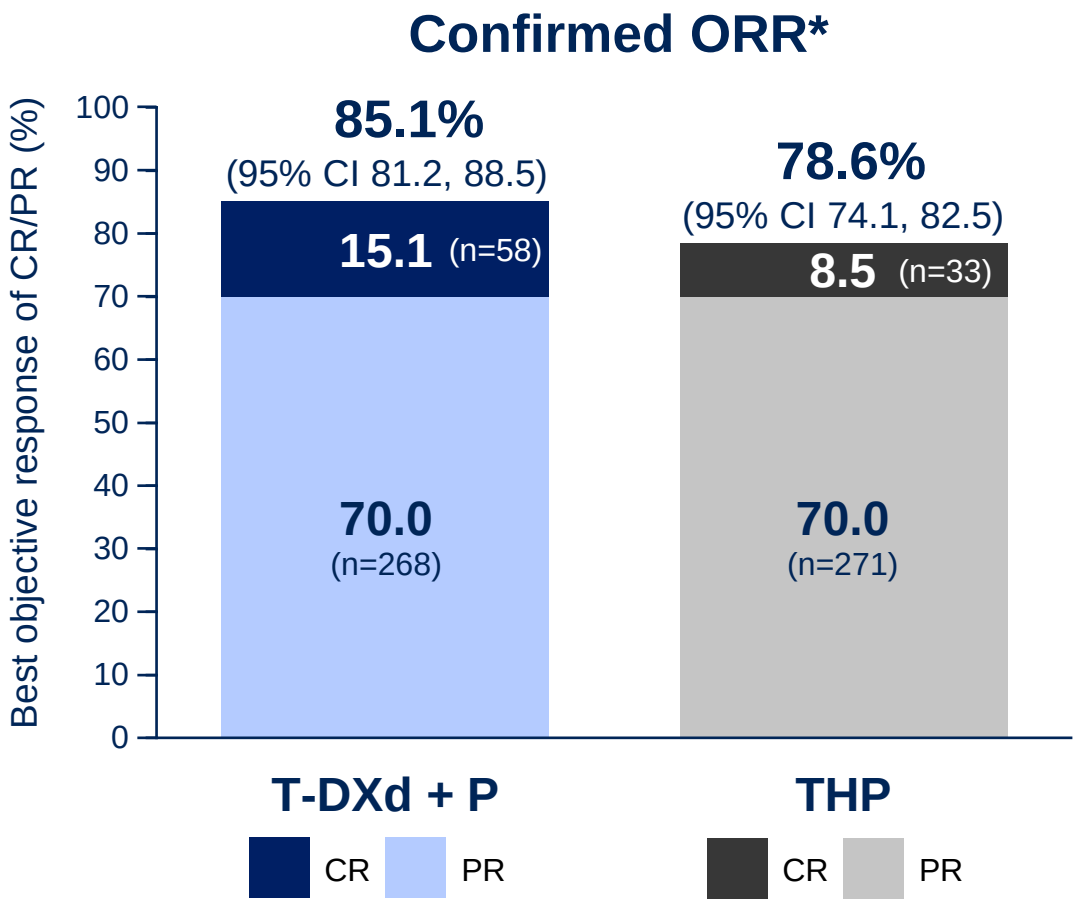
	No. of events / no. of patients		mPFS, months (95% CI)		Hazard ratio (95% CI)
	T-DXd + P	THP	T-DXd + P	THP	
Prior treatment status					
De novo	52/200	85/200	NC (36.5, NC)	31.2 (23.5, NC)	0.49 (0.35, 0.70)
Recurrent	66/183	87/187	38.0 (26.9, NC)	22.5 (18.1, NC)	0.63 (0.46, 0.87)
HR status					
Positive	65/207	87/209	38.0 (36.0, NC)	27.7 (22.4, NC)	0.61 (0.44, 0.84)
Negative	53/176	85/178	40.7 (40.7, NC)	22.6 (17.3, 32.7)	0.52 (0.37, 0.73)
***PIK3CA* mutation status**					
Detected	41/116	64/121	36.0 (29.7, NC)	18.1 (15.1, 25.6)	0.52 (0.35, 0.77)
Not detected	76/266	108/266	40.7 (38.0, NC)	32.7 (24.4, NC)	0.57 (0.43, 0.77)
Age at randomization					
<65 years	90/315	139/315	40.7 (36.5, NC)	27.4 (22.4, NC)	0.50 (0.38, 0.65)
≥65 years	28/68	33/72	27.6 (14.9, NC)	21.5 (13.9, NC)	0.92 (0.55, 1.51)
Geographical region					
Asia	62/188	87/191	40.7 (36.5, NC)	27.2 (21.5, NC)	0.60 (0.43, 0.83)
Western Europe and North America	27/87	31/78	36.0 (30.6, NC)	31.2 (15.8, NC)	0.60 (0.35, 1.01)
Rest of World	29/108	54/118	NC (38.0, NC)	24.4 (14.8, NC)	0.48 (0.30, 0.76)
Brain metastases at baseline					
Present	10/25	15/22	31.8 (18.5, NC)	9.5 (5.6, 13.3)	0.30 (0.12, 0.68)
Not present	108/358	157/365	40.7 (36.5, NC)	27.6 (22.6, NC)	0.58 (0.45, 0.74)
Prior exposure to anti-HER2 therapies					
Yes	39/115	51/112	38.0 (26.9, NC)	21.5 (15.3, NC)	0.55 (0.36, 0.83)
No	79/268	121/275	40.7 (36.5, NC)	27.6 (22.5, NC)	0.56 (0.42, 0.74)
Prior exposure to pertuzumab					
Yes	5/31	12/26	40.8 (25.4, NC)	19.8 (7.5, NC)	NC
No	113/352	160/361	40.7 (36.0, NC)	27.4 (22.4, NC)	0.61 (0.48, 0.77)



Size of circle is proportional to the number of events
BICR, blinded independent central review;
CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor;
NC, not calculable; P, pertuzumab;
(m)PFS, (median) progression-free survival;
T-DXd, trastuzumab deruxtecan;
THP, taxane + trastuzumab + pertuzumab

PFS benefit with T-DXd + P vs THP was consistently observed across prespecified subgroups, including stratification factors

ORR and DOR

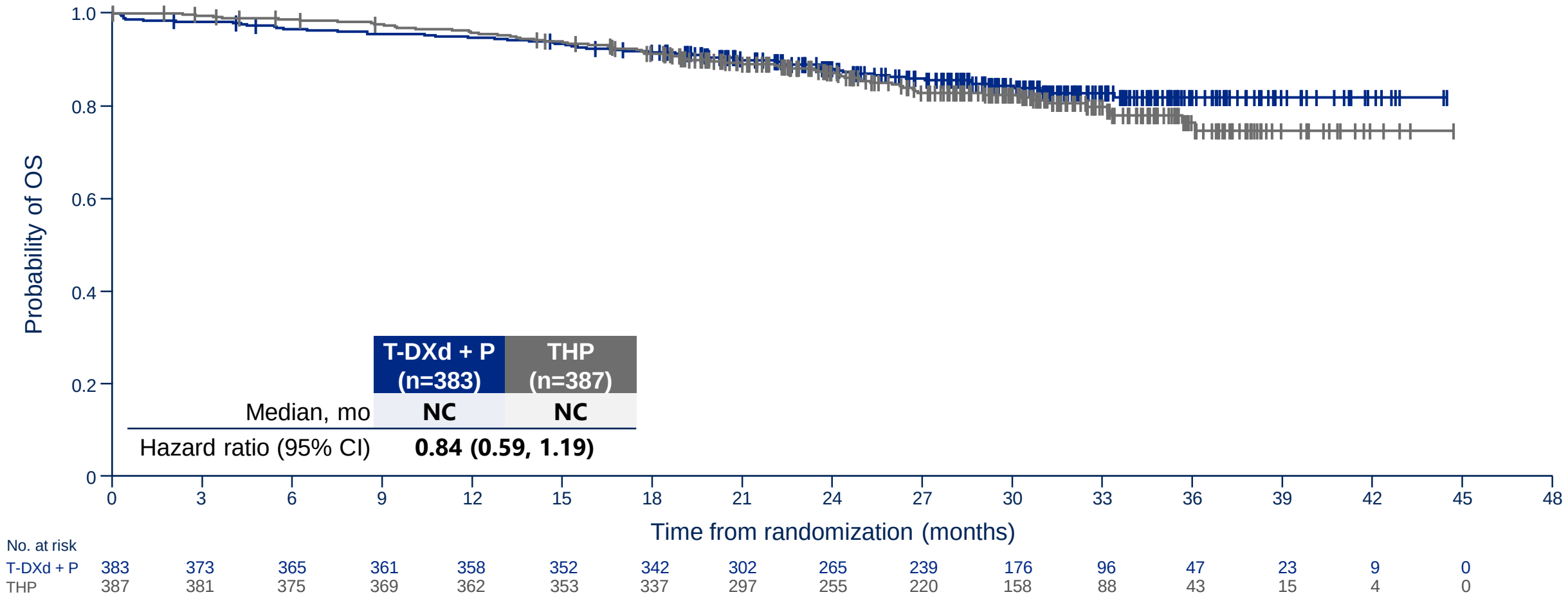


	T-DXd + P (n=383)	THP (n=387)
Median DOR, mo (95% CI)	39.2 (35.1, NC)	26.4 (22.3, NC)
Remaining in response at 24 mo (%)	73.3	54.9
Stable disease, n (%)	38 (9.9)	56 (14.5)

Response rates were greater with T-DXd + P vs THP and were durable

*Based on RECIST v1.1; response required confirmation after 4 weeks
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; mo, months; NC, not calculable; ORR, objective response rate; P, pertuzumab; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Overall survival (~16% maturity)



Early OS data suggest a positive trend favoring T-DXd + P over THP

CI, confidence interval; (m)OS, (median) overall survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Overall safety summary

	Safety analysis set*	
	T-DXd + P (n=381)	THP (n=382)
Total exposure, patient years	659.7	564.0
Any TEAE, n (%)	380 (99.7)	378 (99.0)
Possibly treatment-related TEAEs (investigator assessed), n (%) Grade ≥3	373 (97.9) 209 (54.9)	369 (96.6) 200 (52.4)
Serious TEAEs, n (%)	103 (27.0)	96 (25.1)
TEAEs associated with any treatment discontinuation,† n (%)	79 (20.7)	108 (28.3)
TEAEs associated with any dose interruptions,† n (%)	262 (68.8)	187 (49.0)
TEAEs associated with any dose reductions,† n (%)	175 (45.9)	76 (19.9)
TEAEs with outcome of death, n (%) Possibly treatment related (investigator assessed)‡	13 (3.4) 5 (1.3)	3 (0.8) 1 (0.3)

Median total treatment duration:

- **T-DXd + P: 21.7 mo (range 0.3–44.5)**
  - T-DXd: 20.0 mo§
- **THP: 16.9 mo (range 0.7–41.7)**

Median treatment duration for taxanes:

- Docetaxel: 5.5 mo (range 0.7–37.4)
- Paclitaxel: 4.4 mo (range 0.2–30.7)

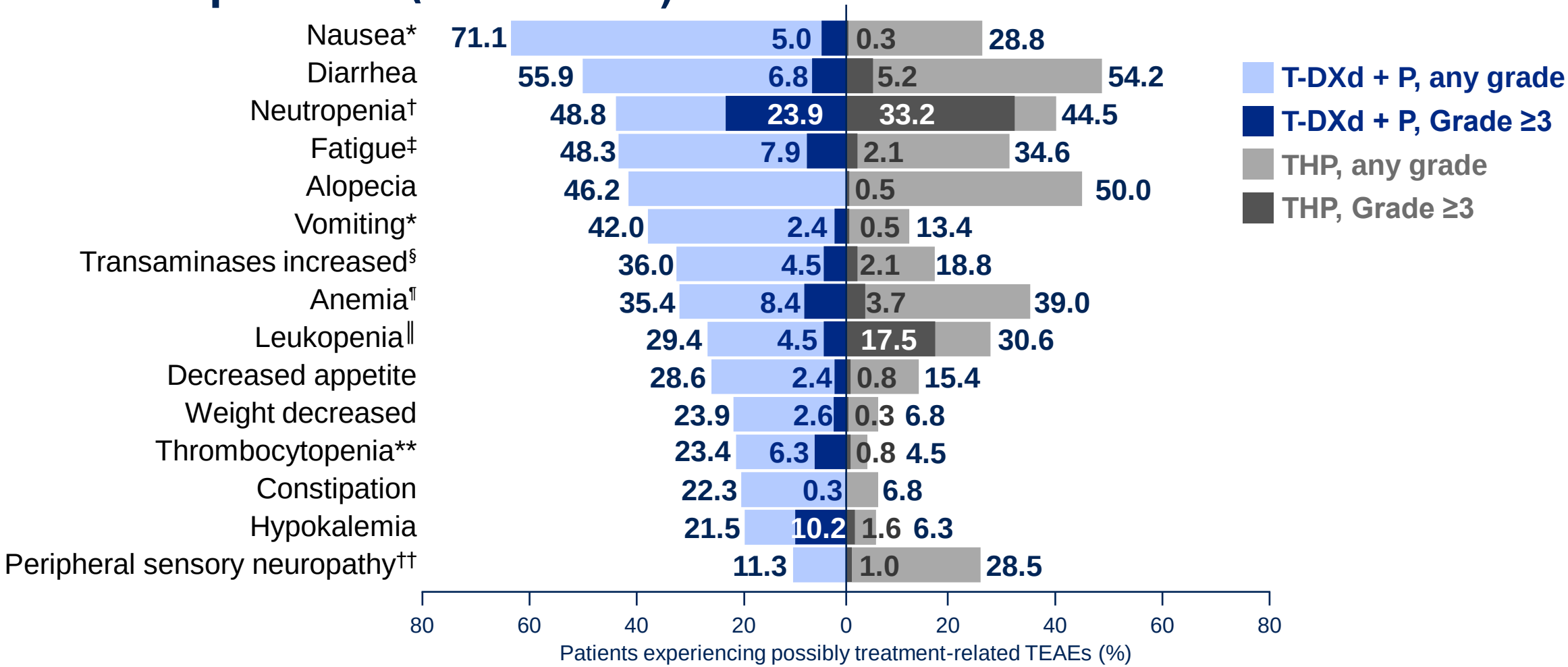
Median number of cycles for taxanes:

- Docetaxel: 8 (range 1–51)
- Paclitaxel: 6 (range 1–42)

*Safety analyses included all patients who received at least one dose of study treatment (at least one study drug); †dose modifications or discontinuations relate to any component of each arm; ‡treatment-related TEAEs with outcome of death were pneumonitis (n=1), sepsis (n=1), septic shock (n=1), febrile neutropenia (n=1), and dyspnea (n=1) in the T-DXd + P arm, and anemia (n=1) in the THP arm; §excludes data from the 8.7% (33/380) of treated patients who received trastuzumab after discontinuing T-DXd due to TEAEs

mo, months; P, pertuzumab; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; THP, taxane + trastuzumab + pertuzumab

Possibly treatment-related (investigator assessed) TEAEs in ≥20% of patients (either arm)



*Antiemetic prophylaxis was recommended but not mandated by protocol; †neutropenia (grouped term) includes: neutropenia and neutrophil count decreased; ‡fatigue (grouped term) includes: fatigue, asthenia, malaise, and lethargy; §transaminases increased (grouped term) includes: transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increase; ¶anemia (grouped term) includes: anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased; ‖leukopenia (grouped term) includes: leukopenia and white blood cell count decreased; **thrombocytopenia (grouped term) includes: platelet count decreased and thrombocytopenia; ††peripheral sensory neuropathy (grouped term) includes: neuropathy peripheral, peripheral sensory neuropathy, and polyneuropathy
P, pertuzumab; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; THP, taxane + trastuzumab + pertuzumab

Adverse events of special interest

Adjudicated drug-related ILD/pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd + P (n=381)	17 (4.5)	27 (7.1)	0	0	2 (0.5)	46 (12.1)
THP (n=382)	2 (0.5)	2 (0.5)	0	0	0	4 (1.0)

Left ventricular dysfunction†

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd + P (n=381)	4 (1.0)	30 (7.9)	7 (1.8)	1 (0.3)	0	42 (11.0)
THP (n=382)	1 (0.3)	19 (5.0)	7 (1.8)	0	0	27 (7.1)

Safety analysis set
*Adjudicated drug-related ILD/pneumonitis (grouped term) includes: chronic obstructive pulmonary disease, interstitial lung disease, organizing pneumonia, pneumonia, and pneumonitis, †left ventricular dysfunction (grouped term) includes: potential heart failure, cardiac failure, cardiac failure chronic, ejection fraction decreased, left ventricular dysfunction, and right ventricular failure
ILD, interstitial lung disease; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Conclusions

- T-DXd + P demonstrated a **statistically significant and clinically meaningful PFS benefit** by BICR vs THP, which was consistently observed across subgroups
  - Hazard ratio of **0.56** vs THP (**P<0.00001**)
  - Median PFS was **40.7 months (T-DXd + P)** vs **26.9 months (THP)**
- Median DOR of **>3 years with T-DXd + P**, with CRs in **15.1% (T-DXd + P)** vs **8.5% (THP)**
- Early OS data suggest a positive trend favoring T-DXd + P, with a supportive hazard ratio of **0.60** for PFS2
- T-DXd + P safety data were **consistent with known profiles of individual treatments**

PFS by BICR

44%

Reduction in risk of disease progression or death with T-DXd + P vs THP

T-DXd + P demonstrated a statistically significant and clinically meaningful PFS benefit vs THP and may represent a new first-line standard of care for patients with HER2+ a/mBC

a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; CR, complete response; DOR, duration of response; HER2+, human epidermal growth factor receptor 2–positive; OS, overall survival; P, pertuzumab; PFS, progression-free survival; PFS2, second progression-free survival; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Trastuzumab deruxtecan vs ramucirumab plus paclitaxel in second-line treatment of patients with human epidermal growth factor receptor 2–positive (HER2+) unresectable and/or metastatic gastric cancer or gastroesophageal junction adenocarcinoma: Primary analysis of the randomized, phase 3 DESTINY-Gastric04 study

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On behalf of the DESTINY-Gastric04 investigators

Current Treatment Landscape in HER2+ Metastatic GC/GEJA

- An estimated 5%-17% of GCs are HER2+ (IHC 3+ or IHC 2+/ISH+)[1-4]
- 1L therapy for patients with HER2+ metastatic GC/GEJA is chemotherapy plus trastuzumab, with pembrolizumab if PD-L1 is expressed (CPS ≥1)[5]
- Results from the phase 2 DESTINY-Gastric01/02/06 trials led to the approval of T-DXd in the 2L+ setting in patients with HER2+ metastatic GC/GEJA[6-8]
- The combination of RAM + PTX is the SOC in 2L GC/GEJA based on results from the phase 3 RAINBOW trial[9]

DESTINY-Gastric04 was conducted to evaluate T-DXd in a head-to-head phase 3 trial versus RAM + PTX in patients with HER2+ metastatic GC/GEJA

1L, first-line; 2L, second-line; CPS, combined positive score; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PD-L1, programmed death ligand 1; PTX, paclitaxel; RAM, ramucirumab; SOC, standard of care; T-DXd, trastuzumab deruxtecan.

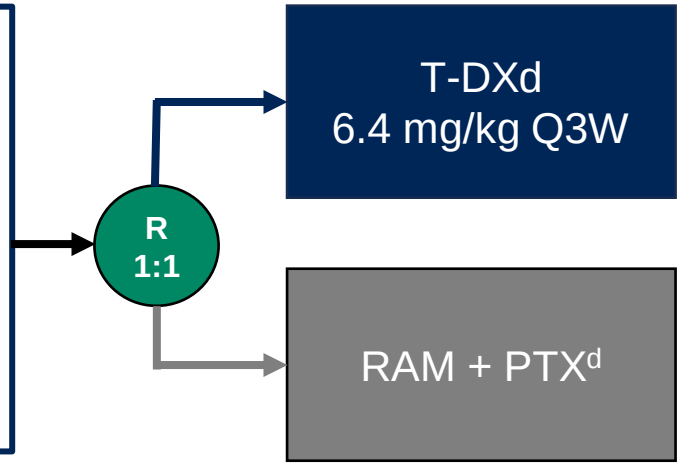
1. Uzunparmak B et al. *Ann Oncol.* 2023;34:1035-46. 2. Van Cutsem E et al. *Gastric Cancer.* 2015;18:476-84. 3. Subasinghe D et al. *J Int Med Res.* 2023;51:03000605231154403. 4. Bartley AN et al. *J Oncol Pract.* 2017;13:53-7. 5. ESMO Gastric Cancer Living Guideline v1.4 September 2024. European Society for Medical Oncology, 2024. (Accessed April 2, 2025, at https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline). 6. Shitara K et al. *N Engl J Med.* 2020;382:2419-30. 7. Van Cutsem E et al. *Lancet Oncol.* 2023;24:744-56. 8. Shen L et al. *Ann Oncol.* 2023;34:S1542-3. 9. Wilke H et al. *Lancet Oncol.* 2014;15:1224-35.

Study Design

DESTINY-Gastric04: A Global, Multicenter, Randomized, Phase 3 Trial (NCT04704934)

Patient Population

- HER2+ (IHC 3+ or IHC 2+/ISH+)[a] GC/GEJA
- HER2 status confirmed locally or centrally[b] on a recent biopsy obtained after progression on trastuzumab
- ECOG PS 0 or 1
- No clinically active CNS metastases[c]



Primary Endpoint

- OS

Secondary Endpoints

- PFS (INV)[e]
- Confirmed ORR (INV)[e]
- DCR (INV)[e]
- DOR (INV)[e]
- Safety

Exploratory Endpoints

- PROs[f]

Stratification factors

- HER2 status (IHC 3+ vs IHC 2+/ISH+)
- Geography (Asia [excluding mainland China] vs Western Europe vs mainland China/rest of world)
- Time to progression on 1L therapy (<6 months vs ≥6 months)

1L, first-line; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-Dimension, 5-Level; FACT-Ga, Functional Assessment of Cancer Therapy-gastric; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; PTX, paclitaxel; Q3W, every 3 weeks; R, randomization; RAM, ramucirumab; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale.

[a]As classified by the 2017 ASCO-CAP guidelines for HER2 testing in gastroesophageal adenocarcinoma. [b]Study protocol originally mandated HER2 status be determined centrally but was later amended to allow local determination. [c]Clinically active CNS metastases were defined as being untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants. Patients with clinically inactive CNS metastases could be enrolled. [d]RAM administered as 8 mg/kg on days 1 and 15 of each 28-day cycle and PTX administered as 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle. [e]Determined by investigator-based assessment on RECIST v1.1. [f]Based on EORTC EQ-5D-5L VAS and FACT-Ga subscales.

Statistical Analysis

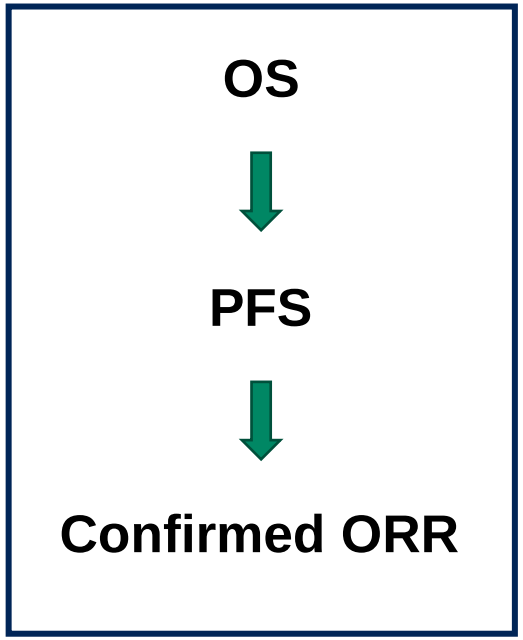
Planned sample size: 490

- 339 OS events were needed to ensure 90% power to detect an OS hazard ratio of 0.70 (overall 2-sided α error of 5%[a])

Interim OS analysis (planned after enrollment completion and 237 OS events [~70%[b]])

- OS, PFS, and confirmed ORR were tested hierarchically using a gatekeeping procedure to control for multiplicity[c]
- At DCO (October 24, 2024), there were 266 OS events and 322 investigator-assessed PFS events
- The superiority stopping boundary for OS was achieved at this interim analysis making this the primary analysis (2-sided $P < 0.0228$[d])

Hierarchical testing



DCO, data cutoff; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[a]1-sided error of 2.5%. [b]Information fraction. [c]Testing for these endpoints proceeded if the previous endpoint in the hierarchy was statistically significant. [d]Calculated based on the number of deaths by Lan-DeMets alpha-spending function, with an O'Brien-Fleming boundary.

Demographics and Baseline Characteristics

	T-DXd n = 246	RAM + PTX n = 248
Age, median (range), years	63.2 (21.1-84.1)	64.3 (31.9-87.0)
Male, n (%)	187 (76.0)	205 (82.7)
Geography,[a] n (%)		
Asia (excluding mainland China)	57 (23.2)	60 (24.2)
Western Europe	140 (56.9)	139 (56.0)
Mainland China/ROW	49 (19.9)	49 (19.8)
Race, n (%)		
White	116 (47.2)	130 (52.4)
Black/African American	0	2 (0.8)
Asian	101 (41.1)	97 (39.1)
Other	28 (11.4)	19 (7.7)
ECOG PS, n (%)		
0 | 1	97 (39.4) | 148 (60.2)	88 (35.5) | 158 (63.7)
2 | missing	1 (0.4) | 0	1 (0.4) | 1 (0.4)
Primary tumor location, n (%)		
Gastric	153 (62.2)	149 (60.1)
GEJ	93 (37.8)	99 (39.9)

	T-DXd n = 246	RAM + PTX n = 248
HER2 status,[a,b] n (%)		
IHC 2+/ISH+	39 (15.9)	40 (16.1)
IHC 3+	207 (84.1)	208 (83.9)
Time to progression on 1L therapy,[a] n (%)		
<6 months	61 (24.8)	61 (24.6)
≥6 months	185 (75.2)	187 (75.4)
Prior treatment with ICI, n (%)		
Yes	39 (15.9)	38 (15.3)
No	207 (84.1)	210 (84.7)
Metastatic sites, n (%)		
<2	73 (29.7)	75 (30.2)
≥2	173 (70.3)	173 (69.8)
Presence of liver metastases, n (%)	147 (59.8)	158 (63.7)
Presence of brain metastases, n (%)	16 (6.5)	18 (7.3)

1L, first-line; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; ISH, in situ hybridization; PTX, paclitaxel; RAM, ramucirumab; ROW, rest of world; T-DXd, trastuzumab deruxtecan.
[a]Stratification factor by interactive response technology. [b]Local or central HER2 status.

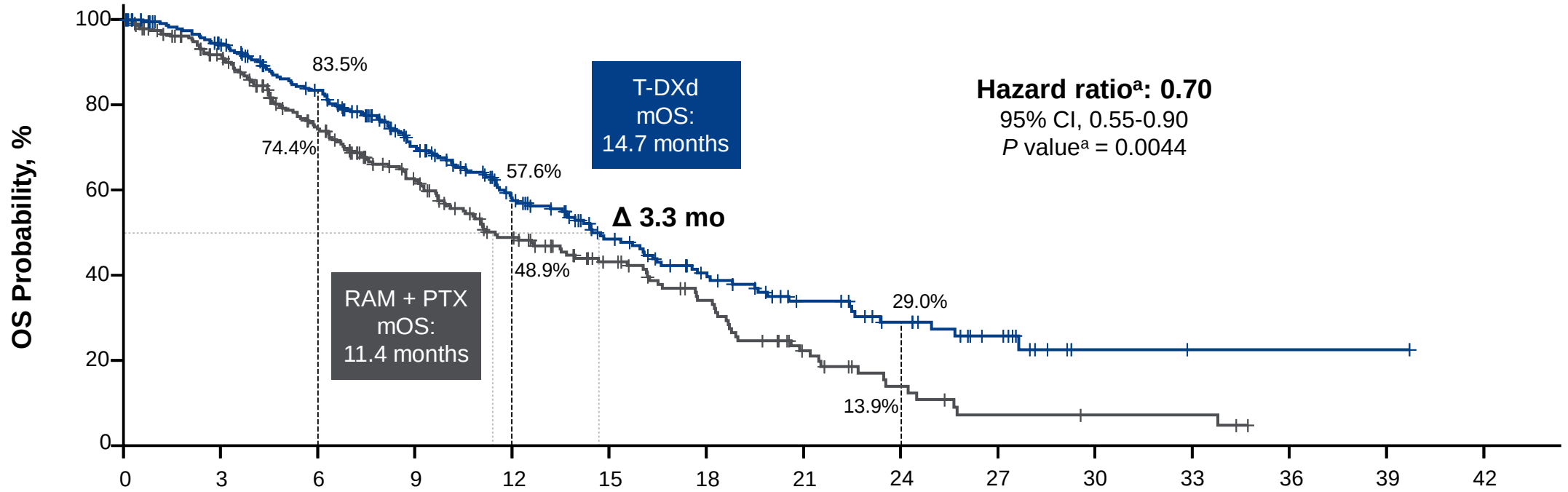
Subsequent Anticancer Therapy

	T-DXd n = 246	RAM + PTX n = 248
Patients receiving any subsequent systemic anticancer treatment,[a] n (%)	126 (51.2)	118 (47.6)
Paclitaxel	63 (25.6)	8 (3.2)
Ramucirumab	43 (17.5)	8 (3.2)
Irinotecan	16 (6.5)	16 (6.5)
Nivolumab	14 (5.7)	14 (5.6)
Paclitaxel nanoparticle albumin-bound	13 (5.3)	0
Paclitaxel; ramucirumab	13 (5.3)	3 (1.2)
Trastuzumab	12 (4.9)	8 (3.2)
Calcium folinate; fluorouracil; irinotecan hydrochloride	11 (4.5)	12 (4.8)
Tipiracil hydrochloride; trifluridine	11 (4.5)	11 (4.4)
Fluorouracil	10 (4.1)	11 (4.4)
Oxaliplatin	10 (4.1)	1 (0.4)
Disitamab vedotin	5 (2.0)	12 (4.8)
Trastuzumab deruxtecan	3 (1.2)	52 (21.0)

- Of patients who discontinued study treatment from the RAM + PTX arm, 52 (21.0%) received T-DXd and 12 (4.8%) received disitamab vedotin as subsequent systemic anticancer therapy

PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.
Received by ≥4% of patients in either arm, listed in descending order in the T-DXd arm.
[a]Patients may have received more than 1 type of subsequent anticancer therapy.

OS: Primary Endpoint



Patients still at risk

T-DXd	246	219	185	134	94	65	45	30	21	12	2	1	1	1	0
RAM + PTX	248	204	150	109	76	52	36	18	9	4	3	3	0		

T-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with RAM + PTX in HER2+ GC/GEJA, showing a 30% reduction in risk of death

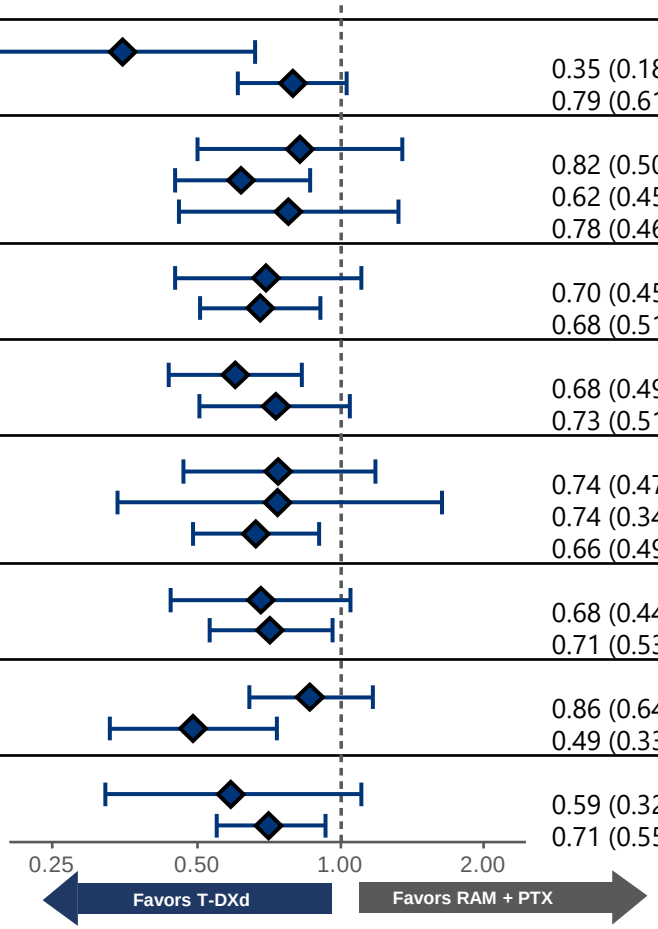
DCO, data cutoff; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; mOS, median overall survival; OS, overall survival; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.

At DCO (October 24, 2024), the median duration of OS follow-up was 16.8 months for T-DXd and 14.4 months for RAM + PTX. Boundary for superiority: 2-sided $P < 0.0228$.

[a]Two-sided *P* value from stratified log-rank test and stratified Cox proportional hazards model adjusted for stratification factor: HER2 status (IHC 3+ or IHC 2+/ISH+).

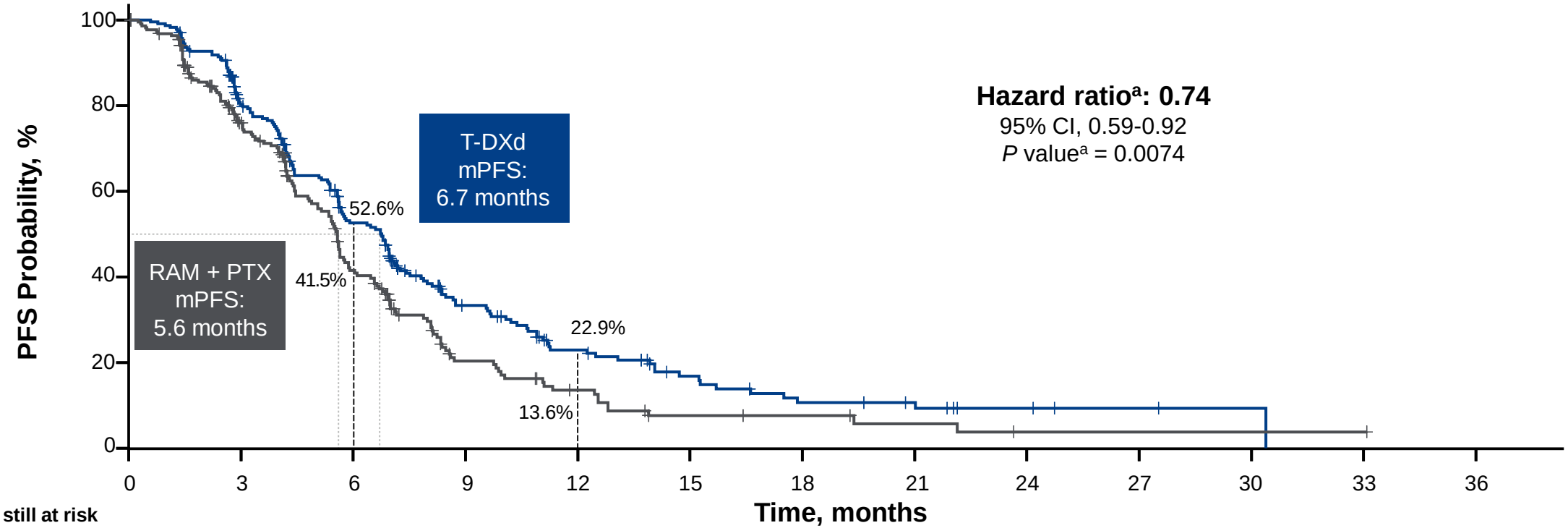
OS by Subgroups

	No. of Events/No. of Patients		OS, median (95% CI), months		Hazard Ratio (95% CI)
	T-DXd	RAM + PTX	T-DXd	RAM + PTX	
HER2 IHC status					
IHC 2+/ISH+	17/39	25/40	17.7 (9.1-NE)	7.4 (4.5-10.7)	0.35 (0.18-0.66)
IHC 3+	107/207	117/208	14.4 (11.9-16.4)	13.4 (10.8-16.5)	0.79 (0.61-1.03)
Geography					
Asia (excluding China)	31/57	34/60	14.4 (10.5-19.4)	16.1 (10.8-18.9)	0.82 (0.50-1.34)
Western Europe	67/140	79/139	15.7 (11.9-18.8)	11.1 (8.7-15.5)	0.62 (0.45-0.86)
Mainland China/ROW	26/49	29/49	14.8 (8.7-NE)	9.7 (7.4-16.0)	0.78 (0.46-1.33)
Time to progression on 1L					
<6 months	38/61	38/61	10.2 (8.1-14.4)	7.3 (5.0-10.1)	0.70 (0.45-1.10)
≥6 months	86/185	104/187	16.3 (13.7-19.4)	13.5 (11.0-17.6)	0.68 (0.51-0.91)
Age					
<65 years	69/140	75/130	15.7 (12.1-18.1)	11.1 (9.6-16.1)	0.68 (0.49-0.94)
≥65 years	55/106	67/118	13.7 (10.5-17.5)	11.5 (8.9-16.6)	0.73 (0.51-1.05)
Histologic subtype					
Intestinal	35/69	38/66	16.6 (11.5-20.5)	12.6 (9.9-18.3)	0.74 (0.47-1.18)
Diffuse	15/25	11/19	9.4 (7.9-16.0)	8.7 (4.6-16.1)	0.74 (0.34-1.64)
Others	74/152	93/163	14.7 (11.9-19.4)	11.1 (9.2-16.1)	0.66 (0.49-0.90)
ECOG PS					
0	38/97	45/88	18.1 (13.1-27.6)	17.6 (12.6-20.6)	0.68 (0.44-1.05)
1 or 2	86/149	96/159	13.9 (10.2-16.0)	9.9 (7.7-11.4)	0.71 (0.53-0.96)
Primary tumor location					
Gastric	83/153	83/149	11.9 (10.1-14.8)	11.4 (9.6-16.1)	0.86 (0.64-1.17)
GEJA	41/93	59/99	18.0 (14.7-22.5)	11.5 (9.2-16.2)	0.49 (0.33-0.74)
Prior treatment with ICI					
Yes	18/39	24/38	16.3 (10.2-NE)	10.1 (7.4-18.6)	0.59 (0.32-1.10)
No	106/207	118/210	14.4 (11.9-17.5)	12.6 (9.9-16.1)	0.71 (0.55-0.93)



1L, first-line; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; ISH, in situ hybridization; OS, overall survival; PTX, paclitaxel; RAM, ramucirumab; ROW, rest of world; T-DXd, trastuzumab deruxtecan.

PFS by Investigator: Key Secondary Endpoint



Hazard ratio[a]: 0.74
95% CI, 0.59-0.92
P value[a] = 0.0074

Patients still at risk

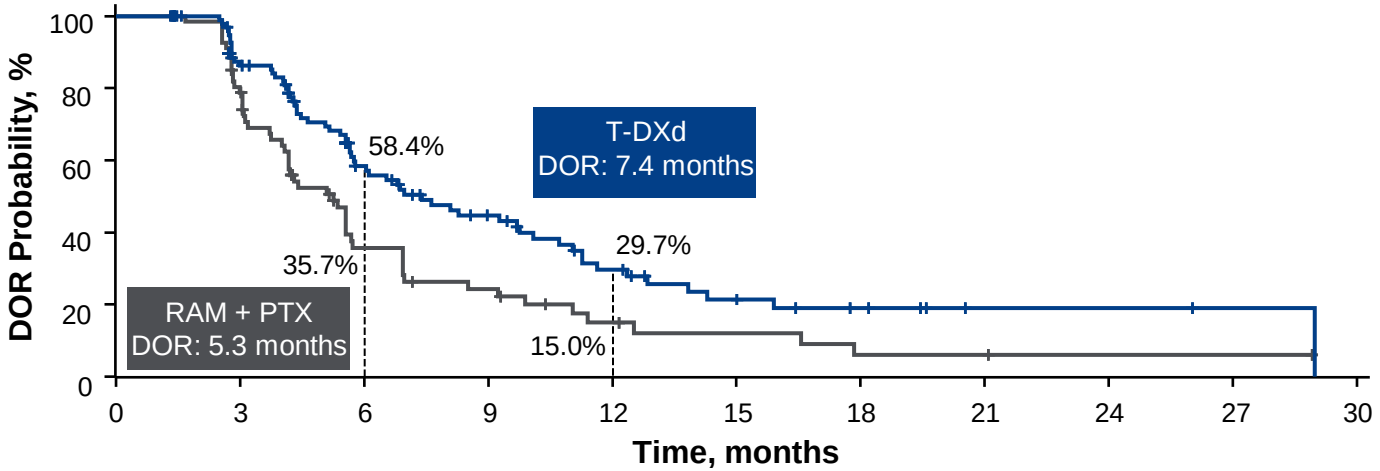
T-DXd	246	173	102	51	30	17	10	7	4	2	1	0	
RAM + PTX	248	144	68	25	14	6	5	3	1	1	1	1	0

T-DXd demonstrated a statistically significant improvement in PFS compared with RAM + PTX in HER2+ GC/GEJA, showing a 26% reduction in risk of progression or death

GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; mPFS, median progression-free survival; PFS, progression-free survival; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.
Boundary for superiority: 2-sided $P < 0.0185$.
[a]Two-sided *P* value from stratified log-rank test and stratified Cox proportional hazards model adjusted for stratification factor: HER2 status (IHC 3+ or IHC 2+/ISH+).

Confirmed ORR and DOR[a,b]

	T-DXd n = 246	RAM + PTX n = 248
Confirmed ORR (95% CI),[c] %	**44.3 (37.8-50.9)**	**29.1 (23.4-35.3)**
P value[d]	0.0006	
Difference (95% CI),[e] %	15.1 (6.1-24.2)	
DOR, median (95% CI), mo	**7.4 (5.7-10.1)**	**5.3 (4.1-5.7)**
DCR (95% CI), %	**91.9 (87.7-95.1)**	**75.9 (70.0-81.2)**
Confirmed BOR, n (%)		
CR[f]	7 (3.0)	3 (1.3)
PR	97 (41.3)	66 (27.8)
SD[g]	112 (47.7)	111 (46.8)
PD	13 (5.5)	22 (9.3)
NE	6 (2.6)	35 (14.8)



Patients still at risk

T-DXd	104	81	45	29	17	10	6	2	2	1	0
RAM + PTX	69	50	19	12	6	4	2	2	1	1	0

The confirmed ORR was 15.1% greater with T-DXd compared with RAM + PTX (*P* = 0.0006), with longer DOR

BOR, best overall response; CR, complete response; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NE, not evaluable; PD, progressive disease; PR, partial response; ORR, objective response rate; PTX, paclitaxel; RAM, ramucirumab; SD, stable disease; T-DXd, trastuzumab deruxtecan.
ORR eligible patients are those who were randomly assigned at least 77 days (ie, 2 × 6 weeks − 1 week) before DCO date of interim analyses. Confirmed BOR, ORR, and DCR are calculated using the eligible patients as the denominator.
[a]Based on investigator assessment. [b]Based on ORR eligible patients. [c]Based on Clopper-Pearson method for single proportion. [d]Stratified analysis using the Cochran-Mantel-Haenszel test adjusted for stratification factor: HER2 status (IHC 3+ or IHC 2+/ISH+). [e]2-sided 95% CI for the difference in ORR is based on Wald method using continuity correction. [f]CR patients without target lesions at baseline were included. [g]Non-CR/non-PD patients without target lesions at baseline were included.

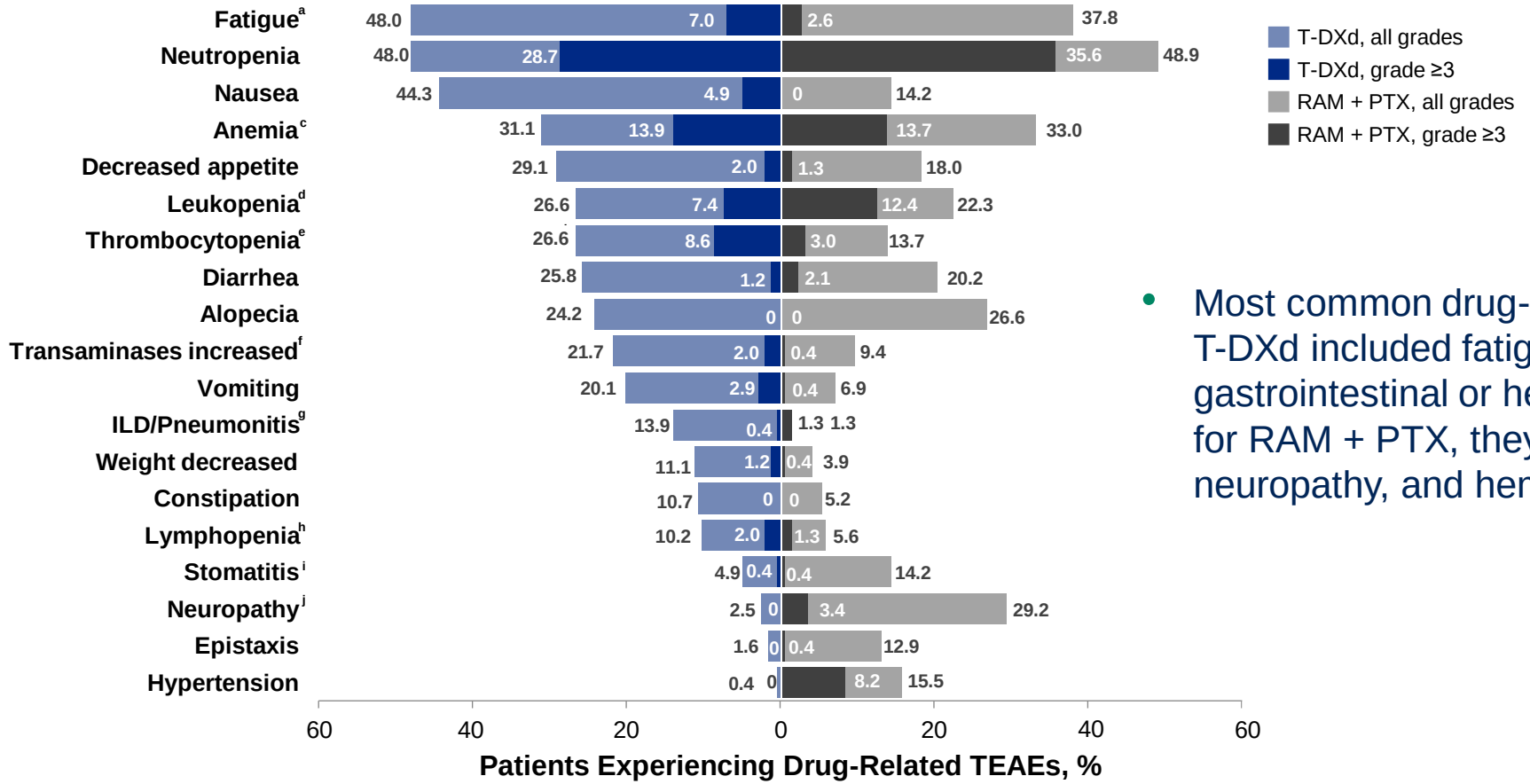
Overall Safety Summary

	Safety analysis set N = 477	
	T-DXd n = 244	RAM + PTX n = 233
Any TEAE, n (%)	244 (100)	228 (97.9)
Drug-related	227 (93.0)	213 (91.4)
Grade ≥3 TEAEs, n (%)	166 (68.0)	172 (73.8)
Drug-related	122 (50.0)	126 (54.1)
Serious TEAEs, n (%)	100 (41.0)	101 (43.3)
Drug-related	45 (18.4)	41 (17.6)
TEAEs associated with dose discontinuation, n (%)	35 (14.3)	40 (17.2)
Drug-related	28 (11.5)	31 (13.3)
TEAEs associated with dose interruption, n (%)	137 (56.1)	141 (60.5)
Drug-related	94 (38.5)	119 (51.1)
TEAEs associated with dose reduction, n (%)	77 (31.6)	87 (37.3)
Drug-related	76 (31.1)	84 (36.1)
TEAEs associated with death, n (%)	22 (9.0)	35 (15.0)
Drug-related[a]	4 (1.6)	2 (0.9)

- Median treatment duration:
  - **T-DXd:** 5.4 mo (range, 0.7-30.3 mo)
  - **RAM + PTX**: 4.6 mo (range, 0.9-34.9 mo)
- Similar incidence of drug-related grade ≥3 TEAEs, serious TEAEs, treatment discontinuations, and deaths were observed in the 2 arms

ILD, interstitial lung disease; mo, months; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]Drug-related adverse events that were associated with death occurred in 4 patients (1.6%) who received T-DXd (upper gastrointestinal hemorrhage, intestinal obstruction, sudden death, and death not otherwise specified in 1 patient each) and in 2 patients (0.9%) who received RAM + PTX (gastric perforation and ILD in 1 patient each).

Drug-Related TEAEs in ≥10% of Patients



- Most common drug-related TEAEs with T-DXd included fatigue or AEs of gastrointestinal or hematologic nature; for RAM + PTX, they included fatigue, neuropathy, and hematologic AEs

AE, adverse event; ILD, interstitial lung disease; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
By preferred or grouped term in ≥10% of patients with any-grade drug-related adverse event in either treatment arm.
[a]Includes fatigue, asthenia, malaise, and lethargy. [b]Includes neutrophil count decreased and neutropenia. [c]Includes hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [d]Includes white blood cell count decreased and leukopenia. [e]Includes platelet count decreased and thrombocytopenia. [f]Includes transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased. [g]Includes all adjudicated study drug–related events by the adjudication committee regardless of treatment-emergent events or not. [h]Includes lymphocyte count decreased and lymphopenia. [i]Includes stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, and oral mucosal eruption. [j]Includes peripheral sensory neuropathy, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, polyneuropathy.

AEs of Special Interest

Adjudicated drug-related ILD/pneumonitis

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 244)	7 (2.9)	26 (10.7)	1 (0.4)	0	0	34 (13.9)
RAM + PTX (n = 233)	0	0	2 (0.9)	0	1 (0.4)	3 (1.3)

Left ventricular dysfunction[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 244)	0	3 (1.2)	3 (1.2)	0	0	6 (2.5)
RAM + PTX (n = 233)	2 (0.9)	2 (0.9)	0	0	0	4 (1.7)

- ILD/pneumonitis events in the T-DXd arm were mainly low-grade, with no grade 4 or 5 events
  - Adjudicated drug-related ILD/pneumonitis occurred in 34 patients (13.9%) treated with T-DXd and 3 patients (1.3%) treated with RAM + PTX
- Incidence of left ventricular dysfunction was similar across both arms

AE, adverse event; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.
[a]Includes preferred terms of ejection fraction decreased, cardiac failure, cardiac failure acute, cardiac failure congestive, and left ventricular dysfunction.

Conclusions

- **T-DXd demonstrated a statistically significant and clinically meaningful improvement in OS** compared with RAM + PTX in patients with HER2+ metastatic GC/GEJA in the 2L setting (median, 14.7 vs 11.4 months, respectively, with 30% reduction in risk of death: **HR, 0.70 [*P* = 0.0044]**)
- **Improvement in PFS, confirmed ORR, DCR,** and **DOR** was also observed **with T-DXd**
- The toxicity profile of T-DXd 6.4 mg/kg was generally manageable and was consistent with its known safety profile, with **no new safety signals identified**
  - Patient-reported QOL was maintained with T-DXd; scores were comparable in the T-DXd versus RAM + PTX arm
- Results support further evaluation of T-DXd in an earlier line setting

DESTINY-Gastric04 confirms T-DXd as the global 2L standard-of-care therapy for patients with HER2+ metastatic GC/GEJA

2L, second-line; DCR, disease control rate; DOR, duration of response; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ORR, objective response rate; OS, overall survival, PFS, progression-free survival; PTX, paclitaxel; QOL, quality of life; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.

DATROWAY®

DATROWAY® : Combination Studies in NSCLC

Ph3
Ph2
Ph1

DATROWAY® + Immune checkpoint inhibitors

pembrolizumab	TROPION-Lung02 w/o AGA	
	TROPION-Lung08* w/o AGA PD-L1 ≥50%. 1L	TROPION-Lung07 NSQ w/o AGA PD-L1 <50%, 1L
durvalumab	NeoCOAST-2 early stage, neoadjuvant	AVANZAR* w/o AGA, 1L
rilvegostomig	TROPION-Lung04 w/o AGA	
	TROPION-Lung12 stage1 high risk, adjuvant	TROPION-Lung10 w/o AGA PD-L1 ≥50%, 1L

DATROWAY® + tyrosine kinase inhibitors

osimertinib	ORCHARD EGFRm, 2L	
	TROPION-Lung14 EGFRm, 1L	TROPION-Lung15 EGFRm, 2L+

* Due to the protocol revision, the inclusion criteria are limited to NSQ NSCLC

AGA: actionable genomic alteration, EGFRm: EGFR mutated, NSQ: non-squamous , NSCLC: non-small cell lung cancer

TROPION-Lung02: Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab (pembro) with or without platinum chemotherapy (Pt-CT) as first-line (1L) therapy for advanced non-small cell lung cancer (aNSCLC)

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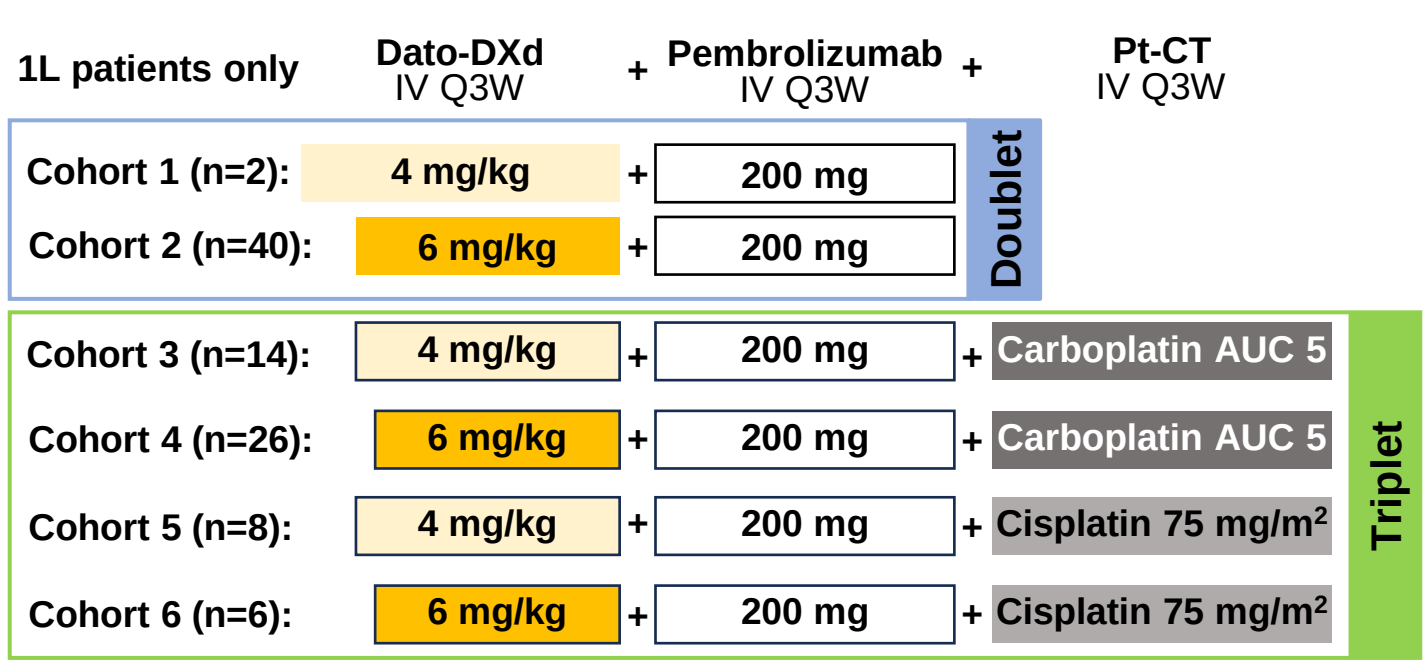
TROPION-Lung02

Phase 1b study of Dato-DXd + pembrolizumab ± Pt-CT in a/mNSCLC without actionable genomic alterations[a]

Key eligibility criteria

- a/mNSCLC
- Dose escalation[b]: ≤2 lines of prior therapy[c]
- Dose expansion
  - ≤1 line of Pt-CT (cohorts 1 and 2)[c]
  - Treatment-naive (cohort 2)[c,d]
  - Treatment-naive (cohorts 3–6)[c]



Objectives

Primary: Safety and tolerability

Secondary: Efficacy

Data cutoff: April 29, 2024. Median study duration was 18.7 months (range, 11–33.8) for doublet and 24.6 months (range, 15.4–32.4) for triplet combinations.

[a]Patients with known actionable genomic alterations in *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *RET*, or *MET*, or with alterations in other actionable oncogenic driver kinases were not eligible for this study. [b]The first 3 to 6 patients in each cohort were enrolled to confirm acceptable safety/DLT rate; the remaining patients are considered part of dose expansion. [c]Prior therapy requirements are for treatment in the a/m setting. [d]Enrollment after June 30, 2022.

1L, first line; a/m, advanced or metastatic; CT, chemotherapy; DLT, dose-limiting toxicity; IV, intravenous; NSCLC, non-small cell lung cancer; Pt-CT, platinum-based chemotherapy; Q3W, every 3 weeks.

Demographics and Baseline Characteristics, 1L Patients

	All 1L (N=96)	
	Doublet (n=42)	**Triplet (n=54)**
Age, median (range), years	65 (48–83)	64 (33–78)
Male, n (%)	32 (76.2)	34 (63.0)
Asian race, n (%)	31 (73.8)	23 (42.6)
Histology, n (%)		
Nonsquamous	32 (76.2)	40 (74.1)
Squamous	10 (23.8)	14 (25.9)
History of brain metastases, n (%)	4 (9.5)	10 (18.5)
ECOG PS 1, n (%)	24 (57.1)	33 (61.1)
Dato-DXd dosing, n (%)		
4 mg/kg	2 (4.8)	22 (40.7)
6 mg/kg	40 (95.2)	32 (59.3)
PD-L1 expression[a], n (%)		
<50%	30 (71.4)	40 (74.1)
≥50%	5 (11.9)	10 (18.5)
NE	7 (16.7)	4 (7.4)

Data cutoff: April 29, 2024.

[a]Evaluated using immunohistochemistry (22C3 assay). 1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not evaluable; PD-L1, programmed death ligand 1.

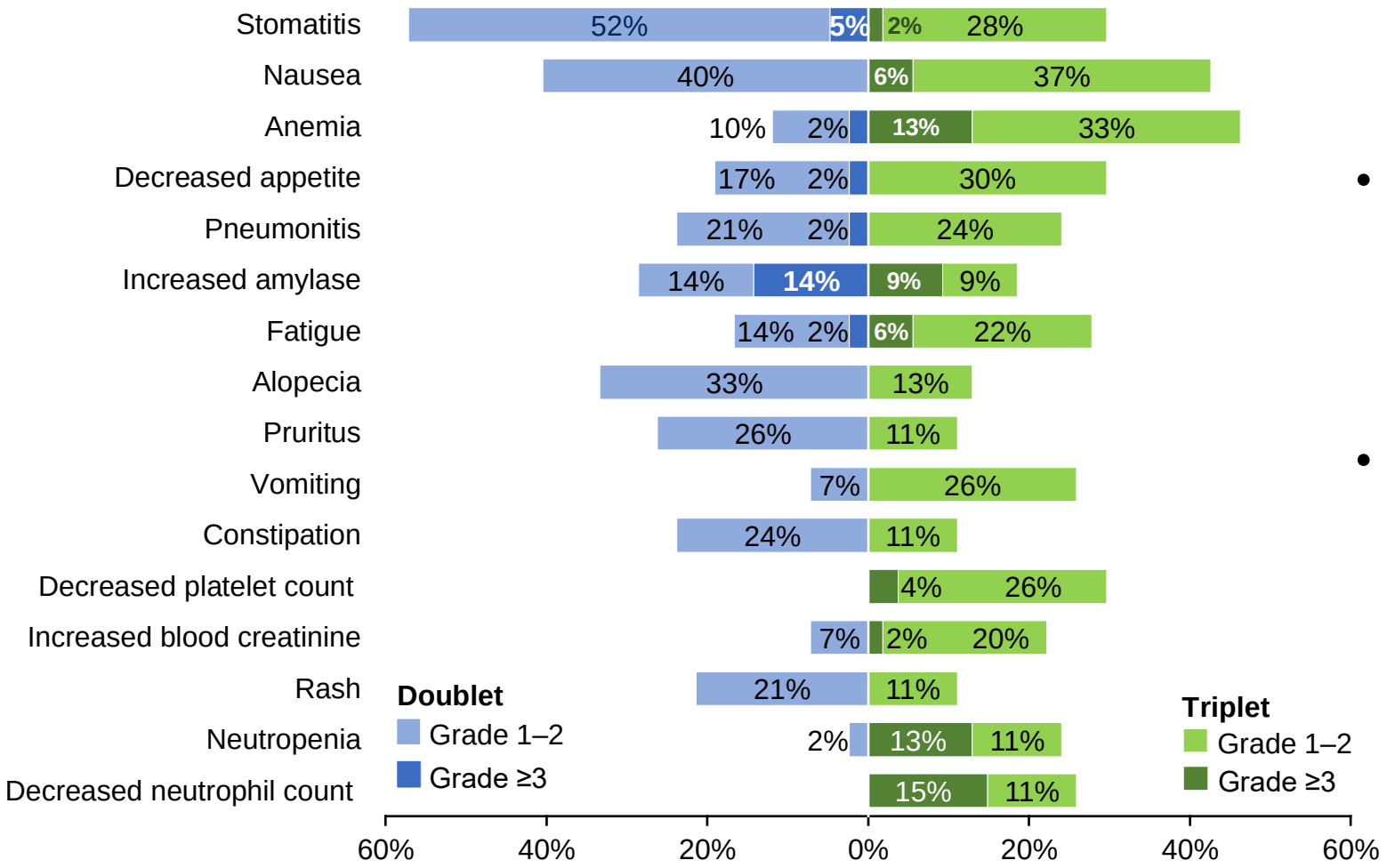
Safety Summary, 1L Patients

	All 1L (N=96)	
Event, n (%)	**Doublet (n=42)**	**Triplet (n=54)**
TRAEs	39 (92.9)	54 (100)
Grade ≥3	17 (40.5)	30 (55.6)
Associated with death	0	0
TRAEs associated with dose modifications		
Dose reduction of any drug	8 (19.0)	14 (25.9)
Dose reduction of Dato-DXd	8 (19.0)	7 (13.0)
Discontinuation of any drug	14 (33.3)	20 (37.0)
Discontinuation of Dato-DXd	13 (31.0)	16 (29.6)
Serious TRAEs	5 (11.9)	12 (22.2)
Grade ≥3	4 (9.5)	9 (16.7)
AESIs		
Oral mucositis/stomatitis	26 (61.9)	22 (40.7)
Grade 3	2 (4.8)	1 (1.9)
Adjudicated drug-related ILD/pneumonitis	11 (26.2)	14 (25.9)
Grade 3	2 (4.8)	1 (1.9)
Ocular surface events	9 (21.4)	18 (33.3)
Grade 3	1 (2.4)	2 (3.7)

- Median treatment durations for the doublet and triplet combinations were 6.9 and 5.7 months, respectively
- No grade 4 or 5 AESI events were observed

Data cutoff: April 29, 2024. 1L, first line; AESI, adverse event of special interest; ILD, interstitial lung disease; TRAE, treatment-related adverse event.

TRAEs Occurring in ≥20% of 1L Patients

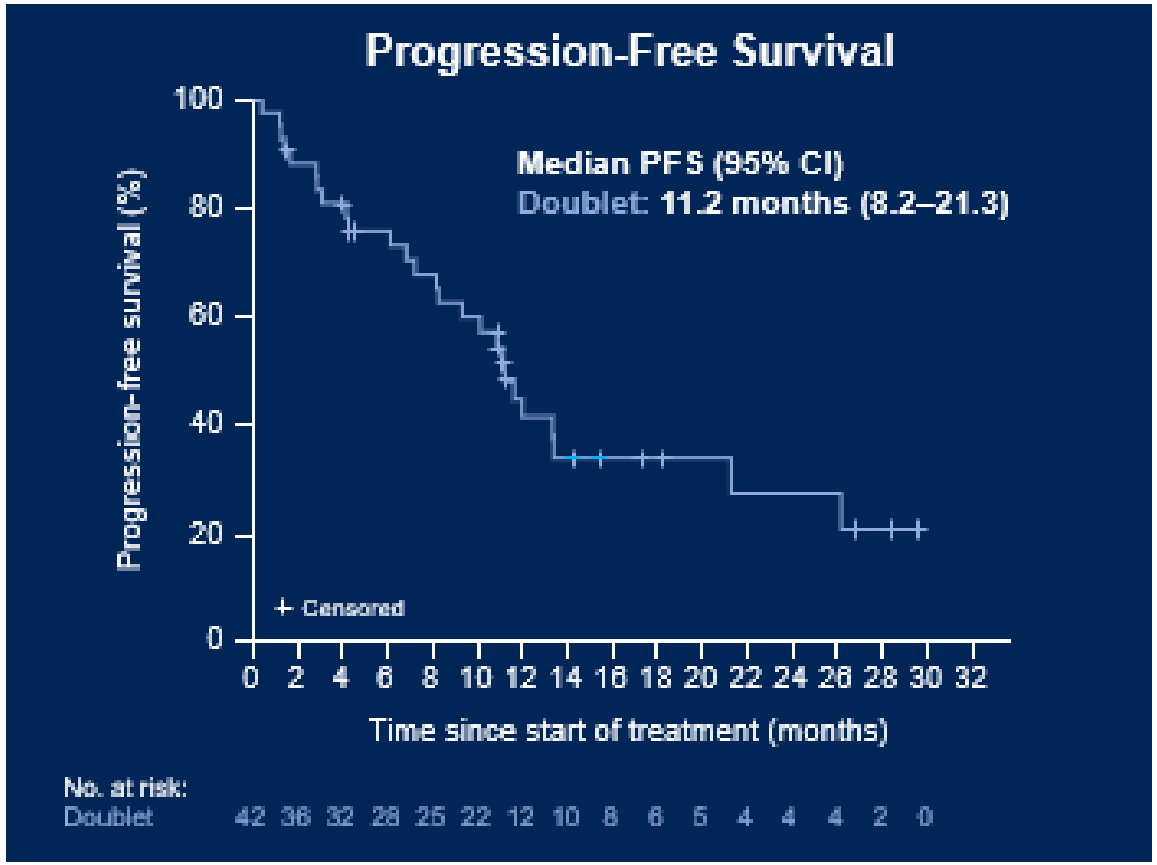


- The most frequent TRAEs of any grade across regimens were nausea, stomatitis, anemia, decreased appetite, and pneumonitis
- Hematologic toxicities occurred more frequently in the triplet cohorts

Data cutoff: April 29, 2024.
1L, first-line; TRAE, treatment-related adverse event.

Efficacy, 1L Doublet

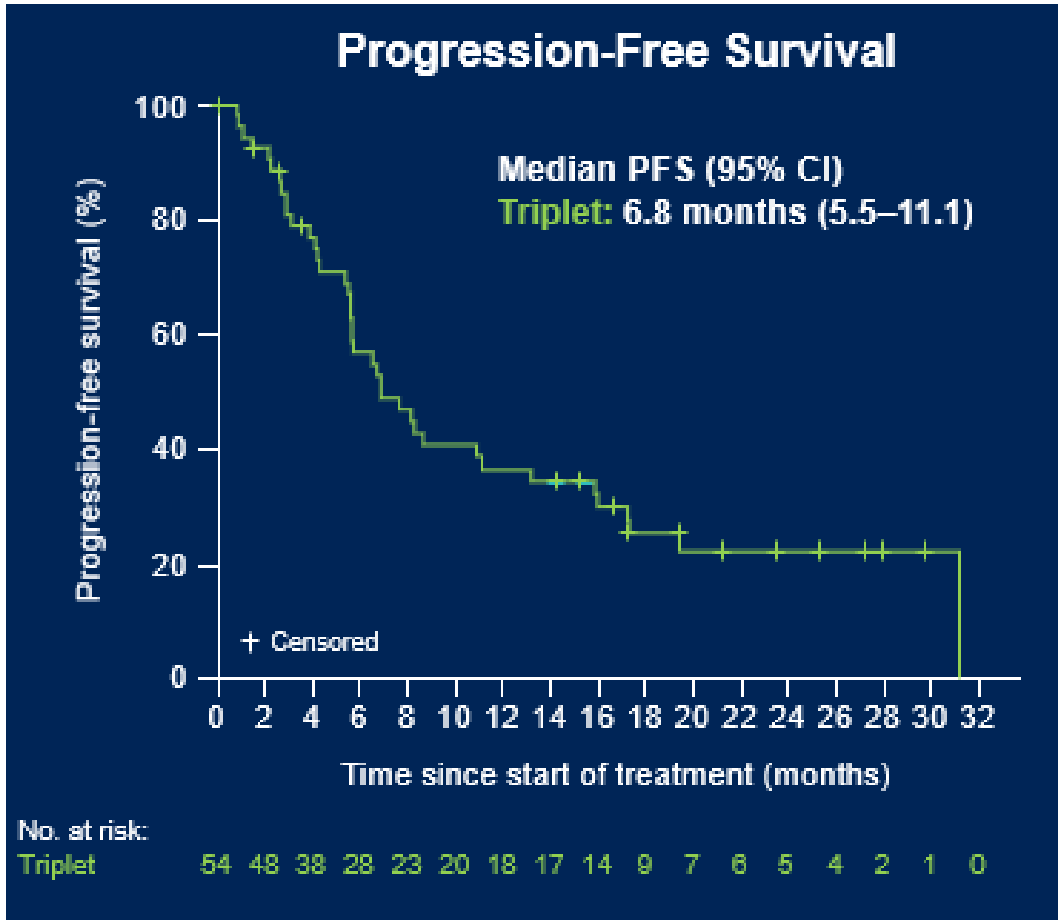
	Doublet (n=42)
Confirmed ORR, n (%)	**23 (54.8)**
95% CI	**38.7–70.2**
BOR, n (%)	
CR	**1 (2.4)**
PR	**22 (52.4)**
Median DOR, months	**20.1**
95% CI	**9.7–NE**
DCR, n (%)	**37 (88.1)**
95% CI	**74.4–96.0**
Median TTR, months	**1.4**
Range	**1.2–7.0**



Data cutoff: April 29, 2024.
1L, first line; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PR, partial response; TTR, time to response.

Efficacy, 1L Triplet

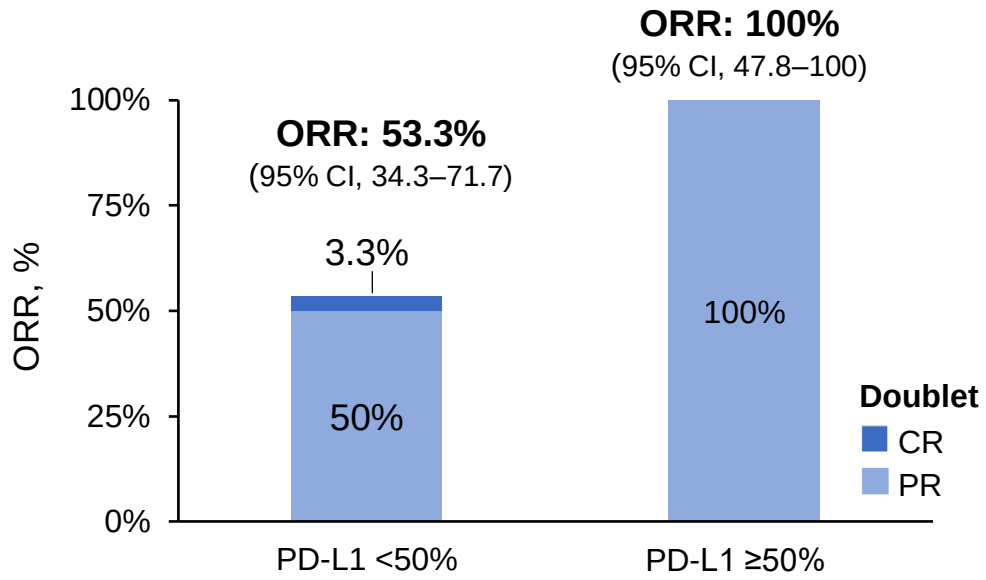
	Triplet (n=54)
Confirmed ORR, n (%)	**30 (55.6)**
95% CI	**41.4–69.1**
BOR, n (%)	
CR	**2 (3.7)**
PR	**28 (51.9)**
Median DOR, months	**13.7**
95% CI	**5.7–NE**
DCR, n (%)	**48 (88.9)**
95% CI	**77.4–95.8**
Median TTR, months	**1.4**
Range	**1.2–9.6**



Data cutoff: April 29, 2024.
1L, first line; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PR, partial response; TTR, time to response.

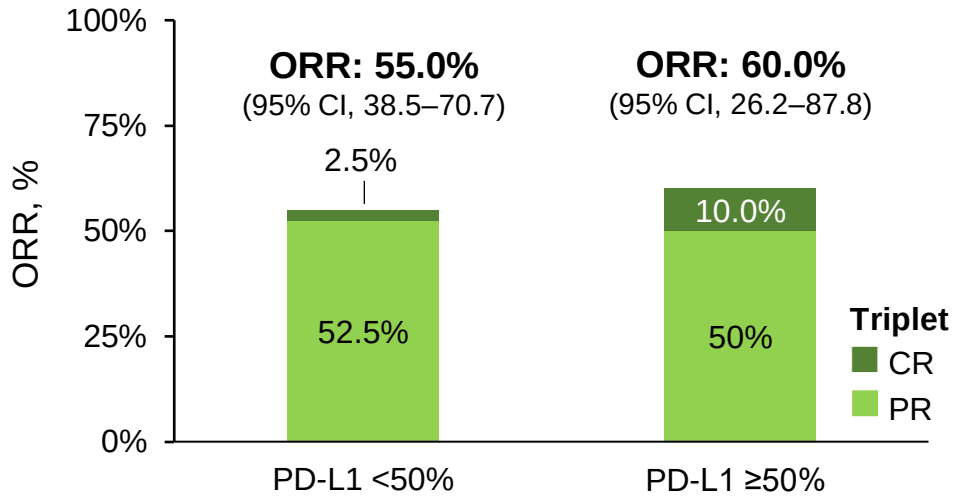
Response by PD-L1 Status[a], 1L Patients

Doublet (n=35)



	PD-L1 <50% (n=30)	PD-L1 ≥50% (n=5)
Median DOR, months	**12.0**	**NE**
95% CI	8.0–NE	5.5–NE
DCR, n (%)	**29 (96.7)**	**5 (100)**
95% CI	82.8–99.9	47.8–100

Triplet (n=50)



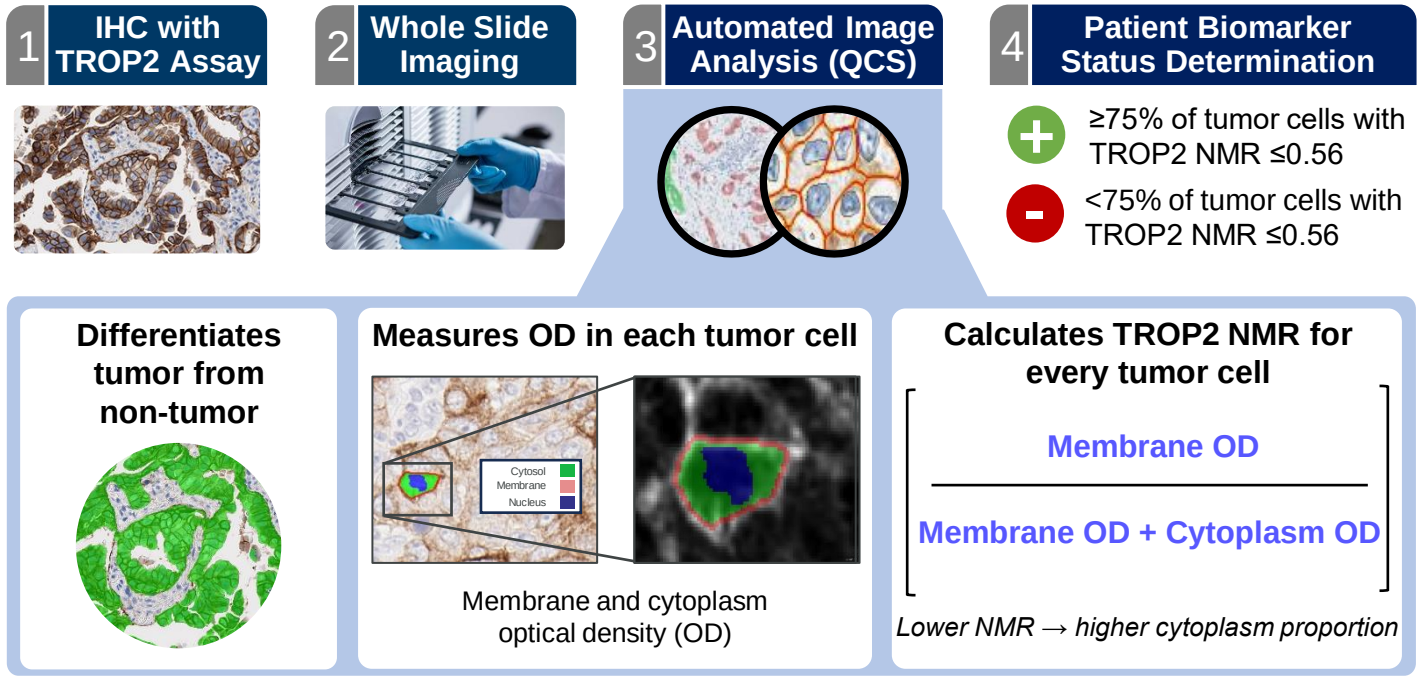
	PD-L1 <50% (n=40)	PD-L1 ≥50% (n=10)
Median DOR, months	**14.6**	**NE**
95% CI	5.3–NE	4.1–NE
DCR, n (%)	**35 (87.5)**	**9 (90.0)**
95% CI	73.2–95.8	55.5–99.7

Data cutoff: April 29, 2024.
[a]Evaluated using immunohistochemistry (22C3 assay).
1L, first line; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD-L1, programmed death receptor-ligand 1.

TROP2 Normalized Membrane Ratio (NMR) Measured by Quantitative Continuous Scoring (QCS)

QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

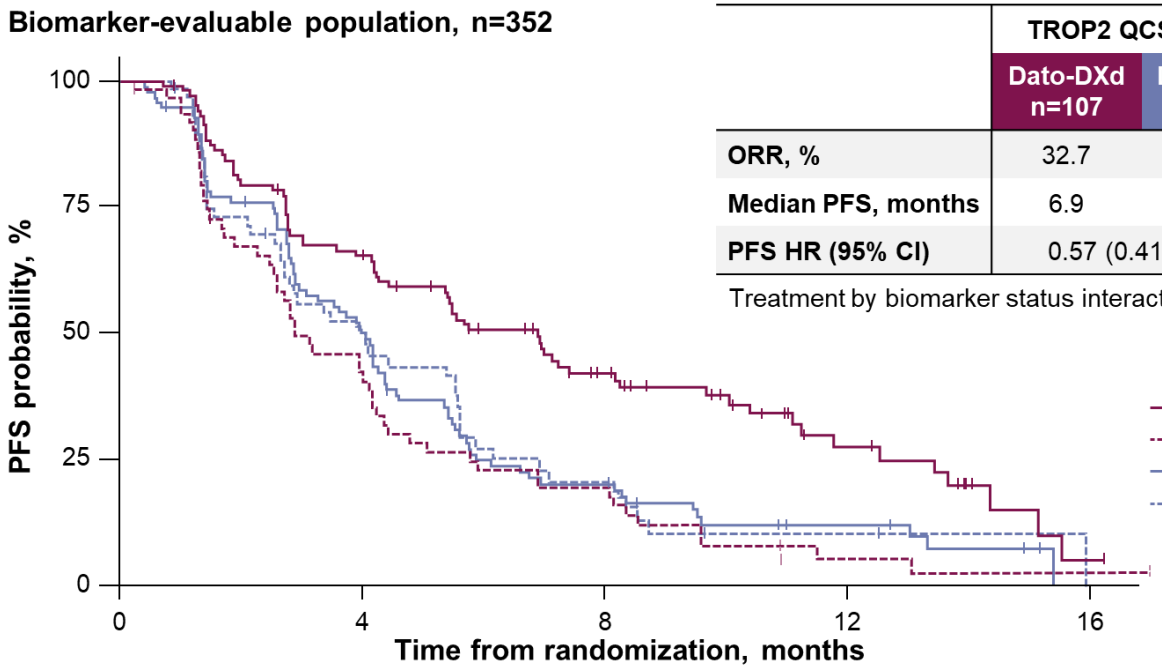
- TROP2 Tumor membrane expression using conventional IHC and pathology visual scoring does not enrich for response
- TROP2 NMR as measured by QCS reflects the expression of TROP2 in the membrane relative to total TROP2 (membrane and cytoplasm)



1L, first line; 2L+, second line and beyond; IHC, immunohistochemistry; NMR, normalized membrane ratio; OD, optical density; QCS, quantitative continuous scoring; TROP2, trophoblast cell-surface antigen 2.

TROP2 QCS-NMR positivity was predictive for longer PFS with Dato-DXd in TROPION-Lung01[1]

TROP2 QCS-NMR predicted outcomes in an exploratory analysis in the TROPION-Lung01 trial evaluating Dato-DXd as monotherapy in the 2L+ setting[1]



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Treatment by biomarker status interaction: p=0.0063

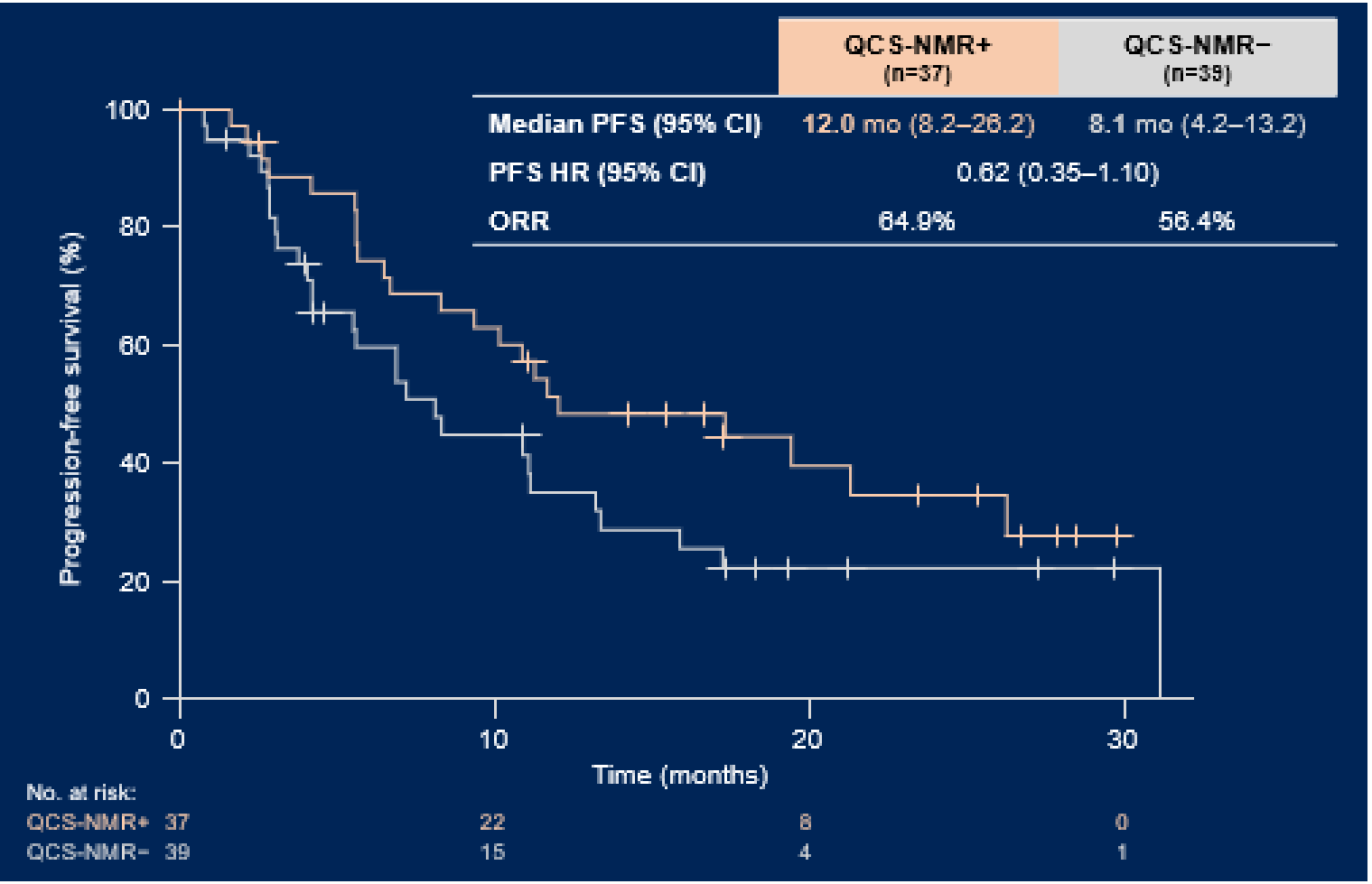
We applied the same cut-off identified for Dato-DXd as 2L+ monotherapy to evaluate enrichment for patient response in the 1L combination setting.

1L, first line; 2L+, second line and beyond; HR, hazard ratio; NMR, normalized membrane ratio; ORR, objective response rate; PFS, progression-free survival; QCS, quantitative continuous scoring; TROP2, trophoblast cell-surface antigen 2.

1. Garassino MC et al. *J Thorac Oncol*. 2024;19:S2–S3.

PFS by TROP2 QCS-NMR, 1L Biomarker Evaluable Population

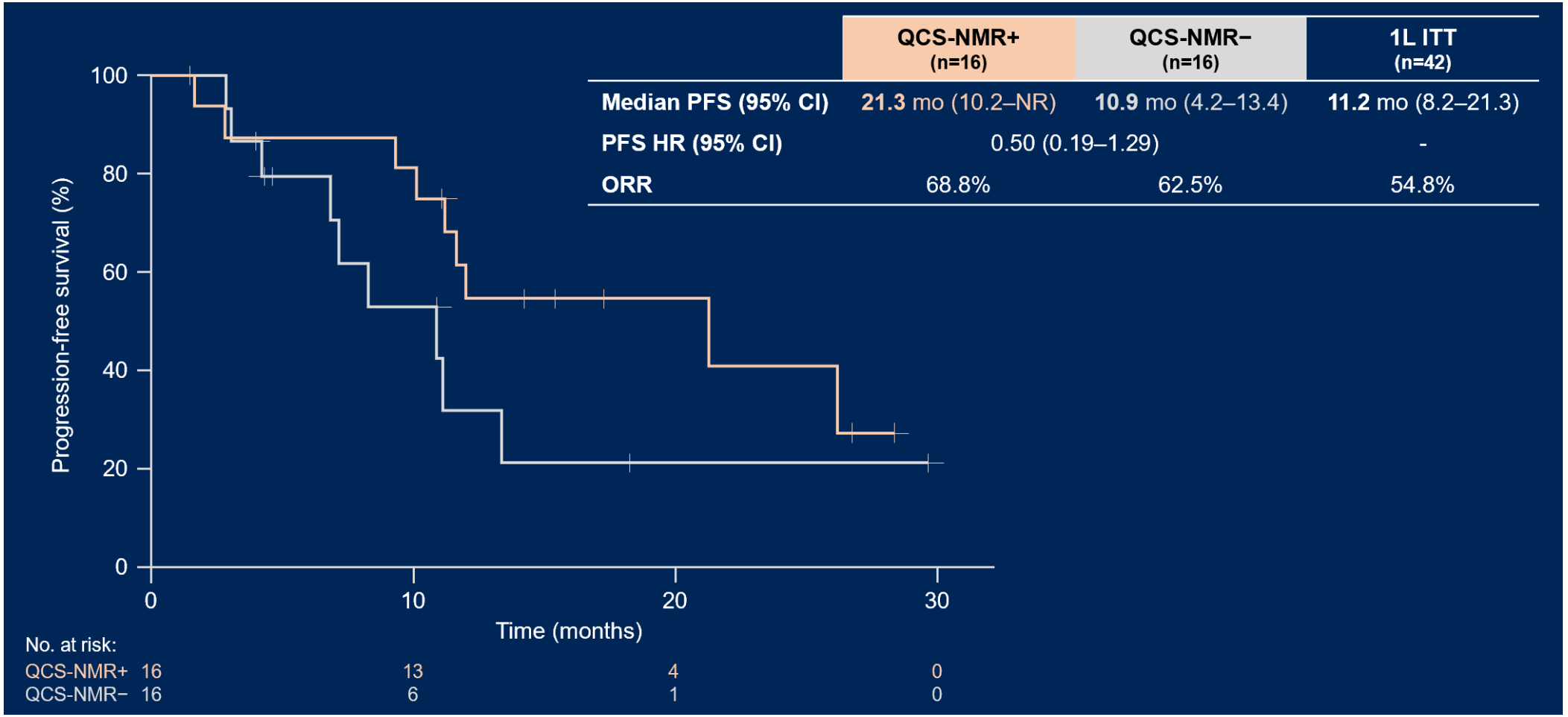
Prevalence, n (%)	
All biomarker evaluable	
QCS-NMR+	37 (48.7)
QCS-NMR−	39 (51.3)
Doublet	
QCS-NMR+	16 (50.0)
QCS-NMR−	16 (50.0)
Triplet	
QCS-NMR+	21 (47.7)
QCS-NMR−	23 (52.3)



Data cutoff: April 29, 2024.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NMR, normalized membrane ratio; ORR, objective response rate PFS, progression-free survival; QCS, quantitative continuous scoring; TROP2, trophoblast cell surface antigen 2.

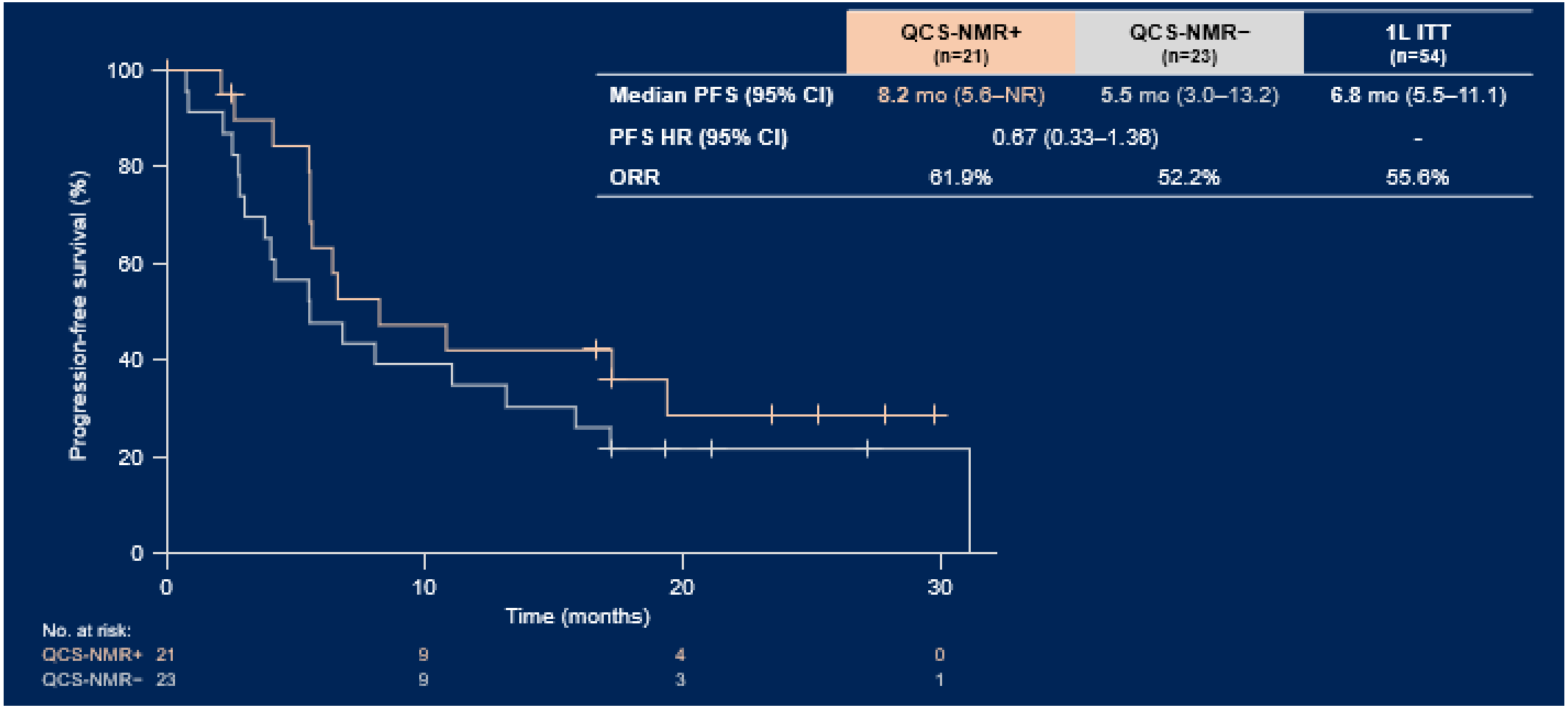
PFS by TROP2 QCS-NMR, 1L Biomarker Evaluable - Doublet



Data cutoff: April 29, 2024.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; NMR, normalized membrane ratio; PFS, progression-free survival; QCS, quantitative continuous scoring; TROP2, trophoblast cell surface antigen 2.

PFS by TROP2 QCS-NMR, 1L Biomarker Evaluable - Triplet



Data cutoff: April 29, 2024.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; NMR, normalized membrane ratio; PFS, progression-free survival; QCS, quantitative continuous scoring; TROP2, trophoblast cell surface antigen 2.

Conclusions

- At TROPION-Lung02 final analysis, the combination of Dato-DXd + pembrolizumab ± Pt-CT continued to elicit durable antitumor activity in patients with a/mNSCLC, with efficacy observed in both high and low PD-L1 expression subgroups
- Tolerability of the combinations was as expected based on known profiles of the individual agents
- In this nonrandomized study, exploratory retrospective TROP2 QCS-NMR testing showed a trend towards prolonged PFS in biomarker positive patients for both the doublet and triplet cohorts
- These data support the evaluation of Dato-DXd + pembrolizumab ± Pt-CT vs standard-of-care therapies in the 1L setting in the ongoing pivotal phase 3 TROPION-Lung07 and TROPION-Lung08 studies

1L, first line; a/mNSCLC, advanced or metastatic non-small cell lung cancer; Dato-DXd, datopotamab deruxtecan; Pt-CT, platinum-based chemotherapy.

Limitations

- TROPION-Lung02 was a non-randomized study and comparisons cannot be made between the doublet and triplet cohorts
- Limited sample sizes to clearly interpret the various subgroups of the study (including by PD-L1 status)
- Patients who received different doses of Dato-DXd (4–6 mg/kg) and different chemotherapy drugs (carboplatin/cisplatin) were grouped together to evaluate safety and efficacy
- TROP2 biomarker analyses were conducted retrospectively with the evolving development of QCS as a novel computational approach to assess TROP2 expression patterns in NSCLC

Neoadjuvant durvalumab + chemotherapy + novel anticancer agents and adjuvant durvalumab ± novel agents in resectable NSCLC: Updated outcomes from NeoCOAST-2

Tina Cascone,[1] Laura Bonanno,[2,3] Florian Guisier,[4] Amelia Insa,[5] Moishe Liberman,[6,7] Olivier Bylicki,[8,9] Lorenzo Livi,[10] Thomas Egenod,[11] Romain Corre,[12] Agata A Bielska,[13] Alula R Yohannes,[14] Yun He,[13] Adam Dowson,[15] Lara McGrath,[13] Gozde Kar,[15] Rakesh Kumar,[14] Italia Grenga,[13] Jonathan Spicer,[16] Patrick M Forde[17]

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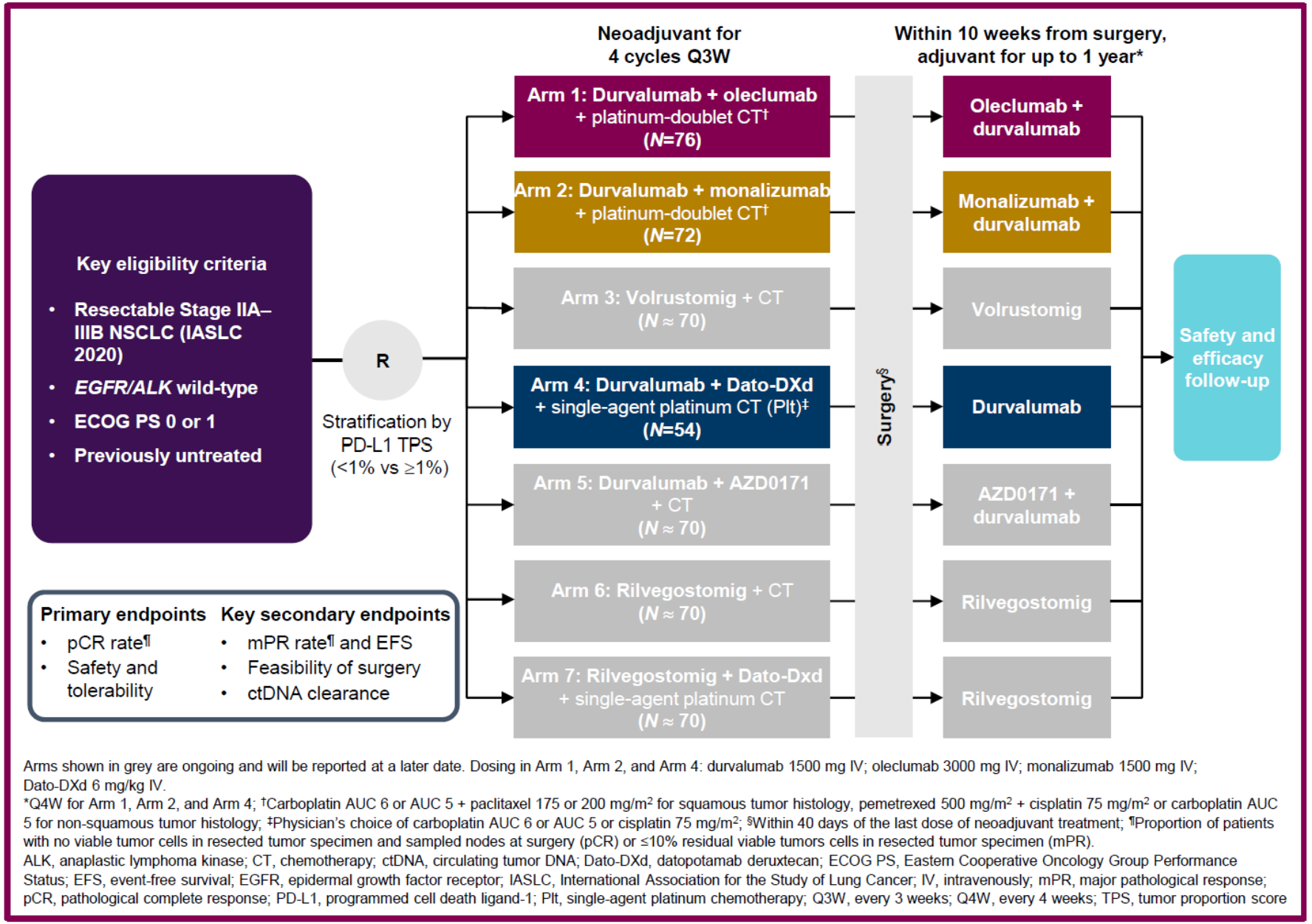
Methods

Figure 1. NeoCOAST-2 study design



Arms shown in grey are ongoing and will be reported at a later date. Dosing in Arm 1, Arm 2, and Arm 4: durvalumab 1500 mg IV; oleclumab 3000 mg IV; monalizumab 1500 mg IV; Dato-DXd 6 mg/kg IV.

*Q4W for Arm 1, Arm 2, and Arm 4; †Carboplatin AUC 6 or AUC 5 + paclitaxel 175 or 200 mg/m^2 for squamous tumor histology, pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC 5 for non-squamous tumor histology; ‡Physician's choice of carboplatin AUC 6 or AUC 5 or cisplatin 75 mg/m^2; §Within 40 days of the last dose of neoadjuvant treatment; ¶Proportion of patients with no viable tumor cells in resected tumor specimen and sampled nodes at surgery (pCR) or ≤10% residual viable tumors cells in resected tumor specimen (mPR).

ALK, anaplastic lymphoma kinase; CT, chemotherapy; ctDNA, circulating tumor DNA; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; EGFR, epidermal growth factor receptor; IASLC, International Association for the Study of Lung Cancer; IV, intravenously; mPR, major pathological response; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Plt, single-agent platinum chemotherapy; Q3W, every 3 weeks; Q4W, every 4 weeks; TPS, tumor proportion score

Results

Table 1. Baseline demographic and disease characteristics (mITT population)

Parameter	Arm 1 Durvalumab + oleclumab + CT (N=74)	Arm 2 Durvalumab + monalizumab + CT (N=70)	Arm 4 Durvalumab + Dato-DXd + Plt (N=54)
Median age (range), years	66.5 (30–79)	66.0 (48–83)	65.0 (38–81)
Male / Female, n (%)	46 (62.2) / 28 (37.8)	42 (60.0) / 28 (40.0)	32 (59.3) / 22 (40.7)
Smoking status, n (%)			
Current / former / never	15 (20.3) / 55 (74.3) / 4 (5.4)	22 (31.4) / 46 (65.7) / 2 (2.9)	15 (27.8) / 36 (66.7) / 3 (5.6)
Race, n (%)			
White	46 (62.2)	42 (60.0)	37 (68.5)
Asian	7 (9.5)	5 (7.1)	5 (9.3)
Black or African American	1 (1.4)	0	0
Not reported	20 (27.0)	23 (32.9)	12 (22.2)
ECOG PS 0 / 1, n (%)*	45 (61.6) / 28 (38.4)	48 (68.6) / 22 (31.4)	35 (64.8) / 19 (35.2)
PD-L1 TPS <1% / ≥1%, n (%)†	25 (33.8) / 49 (66.2)	28 (40.0) / 42 (60.0)	16 (29.6) / 38 (70.4)
Planned platinum agent, n (%)			
Carboplatin / cisplatin	53 (71.6) / 21 (28.4)	55 (78.6) / 15 (21.4)	47 (87.0) / 7 (13.0)
Stage, n (%)			
IIA / IIB	7 (9.5) / 15 (20.3)	8 (11.4) / 17 (24.3)	2 (3.7) / 13 (24.1)
IIIA / IIIB	38 (51.4) / 14 (18.9)	32 (45.7) / 13 (18.6)	28 (51.9) / 11 (20.4)
Histology, n (%)			
Adenocarcinoma	49 (66.2)	46 (65.7)	33 (61.1)
Squamous cell carcinoma	23 (31.1)	19 (27.1)	17 (31.5)
Other‡	2 (2.7)	5 (7.1)	4 (7.4)

*Percentages calculated with the number of patients with reported performance status as denominator; †Based on central results for 70.3%, 75.7%, and 63.0% of patients and local results for 29.7%, 24.3%, and 37.0% of patients in Arms 1, 2, and 4, respectively; ‡Arm 1: carcinoma, type not determined (n=2); Arm 2: carcinoma, type not determined (n=1), other (n=4); Arm 4: large cell carcinoma (n=2), carcinoma, type not determined (n=1), other (n=1).
CT, platinum-doublet chemotherapy; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mITT, modified intention-to-treat; PD-L1, programmed cell death ligand-1; Plt, single-agent platinum chemotherapy; TPS, tumor proportion score

Patient disposition and characteristics

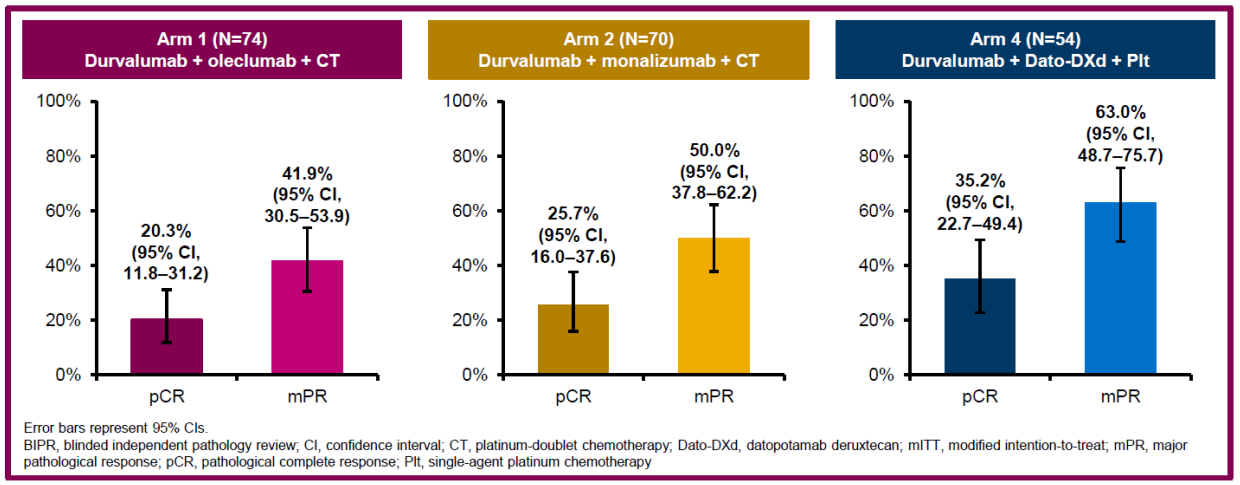
- At DCO (19 December, 2024), all patients in Arms 1, 2, and 4 had the opportunity to complete neoadjuvant therapy and receive surgery.
- 202 patients were randomized (ITT population), of whom 199 were in the safety population and 198 were in the mITT population.
  - -**Table 1** shows baseline demographics and disease characteristics in the mITT population and **Figure 2** shows patient disposition in the ITT population.
- Approximately half of patients had Stage IIIA NSCLC and two-thirds had a programmed cell death ligand-1 (PD-L1) tumor proportion score (TPS) ≥1%.

Results

Efficacy

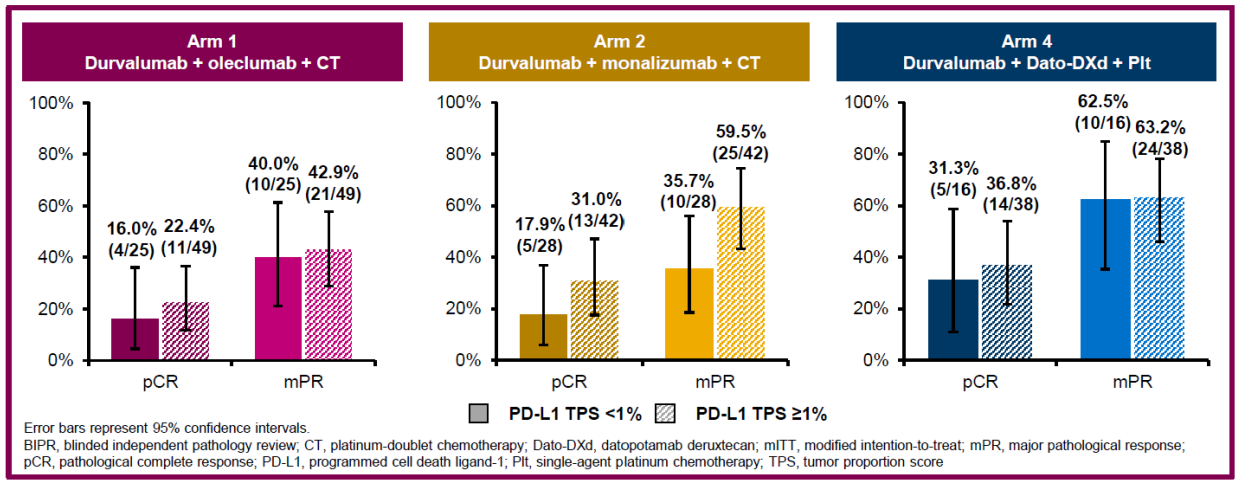
- pCR and mPR rates at final analysis are shown in **Figure 3**.
- In Arms 1 and 2, pCR and mPR rates were numerically higher in patients with PD-L1 TPS ≥1% vs <1%; in Arm 4, pCR and mPR rates were similar in patients with PD-L1 TPS ≥1% or <1% (**Figure 4**).
- Higher pCR and mPR rates were seen in patients with squamous cell carcinoma vs adenocarcinoma in all arms (**Figure 5**).

Figure 3. pCR and mPR rates across arms (mITT population, per central BIPR)



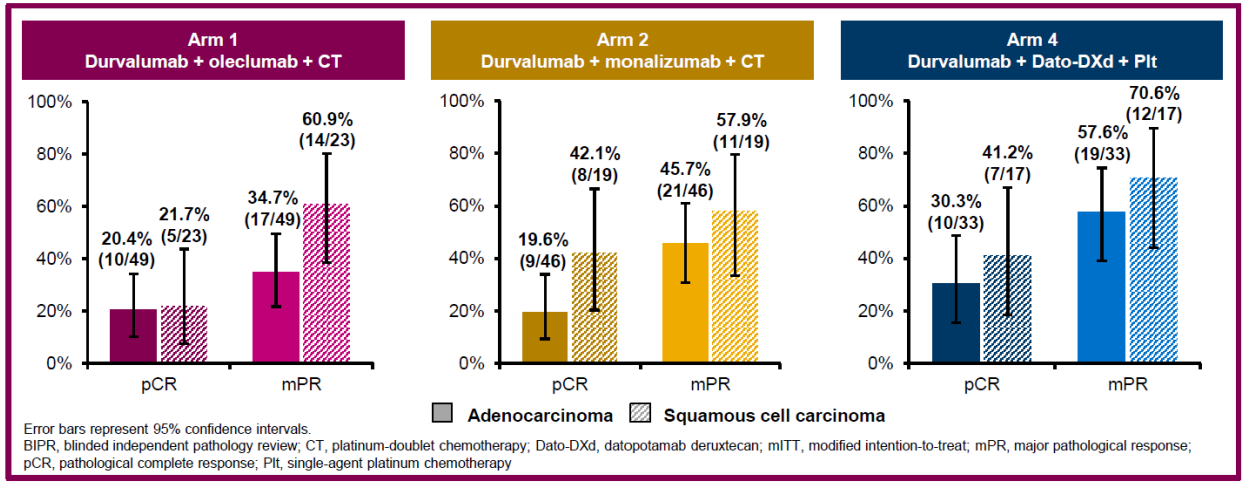
Error bars represent 95% CIs.
BIPR, blinded independent pathology review; CI, confidence interval; CT, platinum-doublet chemotherapy; Dato-DXd, datopotamab deruxtecan; mITT, modified intention-to-treat; mPR, major pathological response; pCR, pathological complete response; Plt, single-agent platinum chemotherapy

Figure 4. pCR and mPR rates by tumoral PD-L1 expression across arms (mITT population, per central BIPR)



Error bars represent 95% confidence intervals.
BIPR, blinded independent pathology review; CT, platinum-doublet chemotherapy; Dato-DXd, datopotamab deruxtecan; mITT, modified intention-to-treat; mPR, major pathological response; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Plt, single-agent platinum chemotherapy; TPS, tumor proportion score

Figure 5. pCR and mPR rates by tumor histology across arms (mITT population, per central BIPR)



Error bars represent 95% confidence intervals.
BIPR, blinded independent pathology review; CT, platinum-doublet chemotherapy; Dato-DXd, datopotamab deruxtecan; mITT, modified intention-to-treat; mPR, major pathological response; pCR, pathological complete response; Plt, single-agent platinum chemotherapy

Results

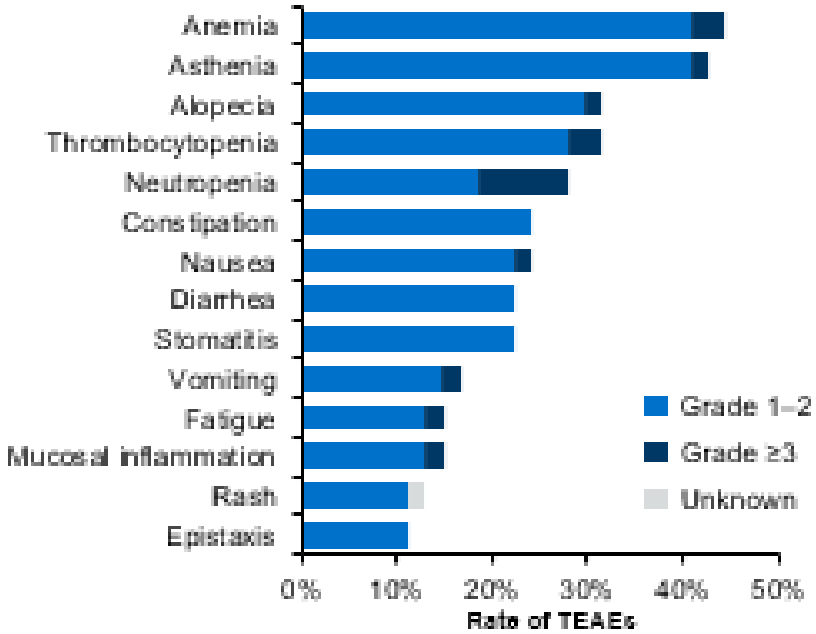
Table 4. Safety summary in Arm 4 (durvalumab + Dato-DXd + Plt)

n (%)	Neoadjuvant (N=54)	Post-surgery (N=51)	Adjuvant (N=47)
Any TEAE	53 (98.1)	32 (62.7)	40 (85.1)
Any TRAE	52 (96.3)	8 (15.7)	26 (55.3)
Grade ≥3 TEAE	13 (24.1)	7 (13.7)	8 (17.0)
Grade ≥3 TRAE	10 (18.5)	1 (2.0)	3 (6.4)
TEAE leading to discontinuation of any study treatment	6 (11.1)	1 (2.0)	0
SAE	10 (18.5)	7 (13.7)	5 (10.6)
SAE with outcome of death	0	1 (2.0)*	1 (2.1)†

*Due to idiopathic pulmonary fibrosis unrelated to treatment as per the principal investigator and related to study treatment per independent adjudication; †Infectious endocarditis, not related to any drugs or surgery.

Dato-DXd, datopotamab deruxtecan; Plt, single-agent platinum chemotherapy; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

Figure 8. TEAEs occurring in ≥10% of patients in Arm 4 in the neoadjuvant period*



*Post-surgery period: dyspnea, 11.8%. Adjuvant period: 74.5% of patients ongoing at data cutoff.

TEAE, treatment-emergent adverse event

Safety

- At DCO (19 Dec 2024), the median (range) duration of safety follow-up was 11.2 (3.5–15.7) months in Arm 4.
- Safety data are summarized in Table 4 (Arm 4).
- The most common TEAEs are summarized in Figure 8 (Arm 4).

Conclusions

- Results showed a numerically higher pCR rate in Arm 4 compared to current standard-of-care options and promising mPR rates.
- Data from Arm 4 showed manageable safety and maintained feasibility of surgery of novel perioperative combinations.
- Encouraging pathological response rates were observed in both PD-L1 subgroups in Arm 4.
- The pCR and mPR rates in Arm 4 are the first reported for an antibody-drug conjugate in the neoadjuvant setting and confirm the encouraging efficacy and manageable safety profile of neoadjuvant durvalumab + Dato-DXd + Plt in this context.
- Presurgical ctDNA clearance was associated with pathological responses in all arms, with the numerically highest rate of ctDNA clearance observed in Arm 4.
- NeoCOAST-2 is ongoing, including newly added arms assessing (1) neoadjuvant rilvegostomig + CT and adjuvant rilvegostomig, and (2) neoadjuvant Dato-DXd + rilvegostomig + Plt and adjuvant rilvegostomig.
- A manuscript containing the full efficacy and safety data for the arms described in this poster has been published simultaneously in Nature Medicine: https://doi.org/10.1038/s41591-025-03746-z

HER3-DXd

Patritumab Deruxtecan (HER3-DXd) in Resistant *EGFR*-Mutated Advanced NSCLC After a Third-Generation EGFR TKI: The Phase 3 HERTHENA-Lung02 Study

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Study Design

HERTHENA-Lung02: A phase 3, global, multi-center, randomized, open-label study[1]

586 patients; study start date, 08 July 2022

Select Eligibility Criteria

- **Advanced nonsquamous NSCLC with an *EGFR*-activating mutation (exon 19 deletion or L858R)**
- **1 or 2 prior line(s) of an approved EGFR TKI (must include a third-generation EGFR TKI)**
  - Non-osimertinib third-generation TKIs ≤20% in each arm
- **Disease progression while or after receiving a third-generation EGFR TKI**
- **Stable brain metastases (asymptomatic and not requiring corticosteroids or anticonvulsants) were permitted**

Randomized 1:1

HER3-DXd (N=293)
Patritumab deruxtecan
5.6 mg/kg IV Q3W

No crossover

PBC (N=293)
Cisplatin 75 mg/m^2
or carboplatin AUC5
Q3W (× 4 cycles)
+ Pemetrexed 500 mg/m^2 Q3W[a]

Primary analysis of PFS (primary endpoint)

2nd interim analysis for OS

3rd interim analysis for OS

End of study

Primary Endpoint

- PFS (by BICR per RECIST version 1.1)

Secondary Endpoints

- Key secondary: OS
- Other Secondary:
  - Safety
  - Intracranial PFS in patients with baseline brain metastases (by CNS BICR per CNS RECIST)[b]
  - HER3 protein expression and its relationship with efficacy
    - Analysis of the potential role of HER3 expression by IHC as a predictive biomarker of response to HER3-DXd in HERTHENA-Lung02 is ongoing

Stratification

- Third generation EGFR TKI (osimertinib, other)
- Line of third generation EGFR TKI (first, second)
- Region (Asia, Non-Asia)
- Presence of stable brain metastases (yes, no)

AUC5, area under the curve of 5 mg/mL•min; BICR, blinded independent central review; CNS, central nervous system; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.
[a] No limit to the number of cycles of pemetrexed, as it is given as maintenance as per labeling. [b] Brain imaging was centrally assessed by a separate, blinded group of neuro-oncologists (CNS BICR) according to the CNS RECIST criteria.[2]

1. Mok TSK, et al. *Future Oncol.* 2024;20(15):969-980. 2. Yu HA, et al. *J Clin Oncol.* 2023;41(35):5363-5375.

Statistical analyses

Sample size

- The planned enrollment of 560 patients was chosen to provide:
  ≈99% power to detect an HR of 0.64 in **PFS** at the **final analysis** (at **≈363 events**)
  - And subsequently (assuming a statistically significant difference in PFS), ≈80% power to detect an HR of 0.75 in **OS** at the **final analysis** (at **≈393 events**)

Primary endpoint (PFS by BICR)

- **At the PFS primary analysis** (DCO May 31, 2024), **389 PFS events** had occurred
  - 127 patients remained on treatment (84 on HER3-DXd and 43 on PBC)
  - Median follow-up was 8.5 months in the HER3-DXd arm and 8.3 months in the PBC arm
- Stopping boundary:
  - Efficacy boundary for superiority: *P*<0.04998

Key secondary endpoint (OS)

- At the 3rd interim OS analysis (DCO Feb 28, 2025) data were mature, with 327 events
  - OS information fraction, 83% (327 of 393 events)
  - Median follow-up was 18.7 months in the HER3-DXd arm and 18.6 months in the PBC arm

Hierarchical testing

PFS in ITT population
(if PFS is statistically significant)
↓
OS in ITT population

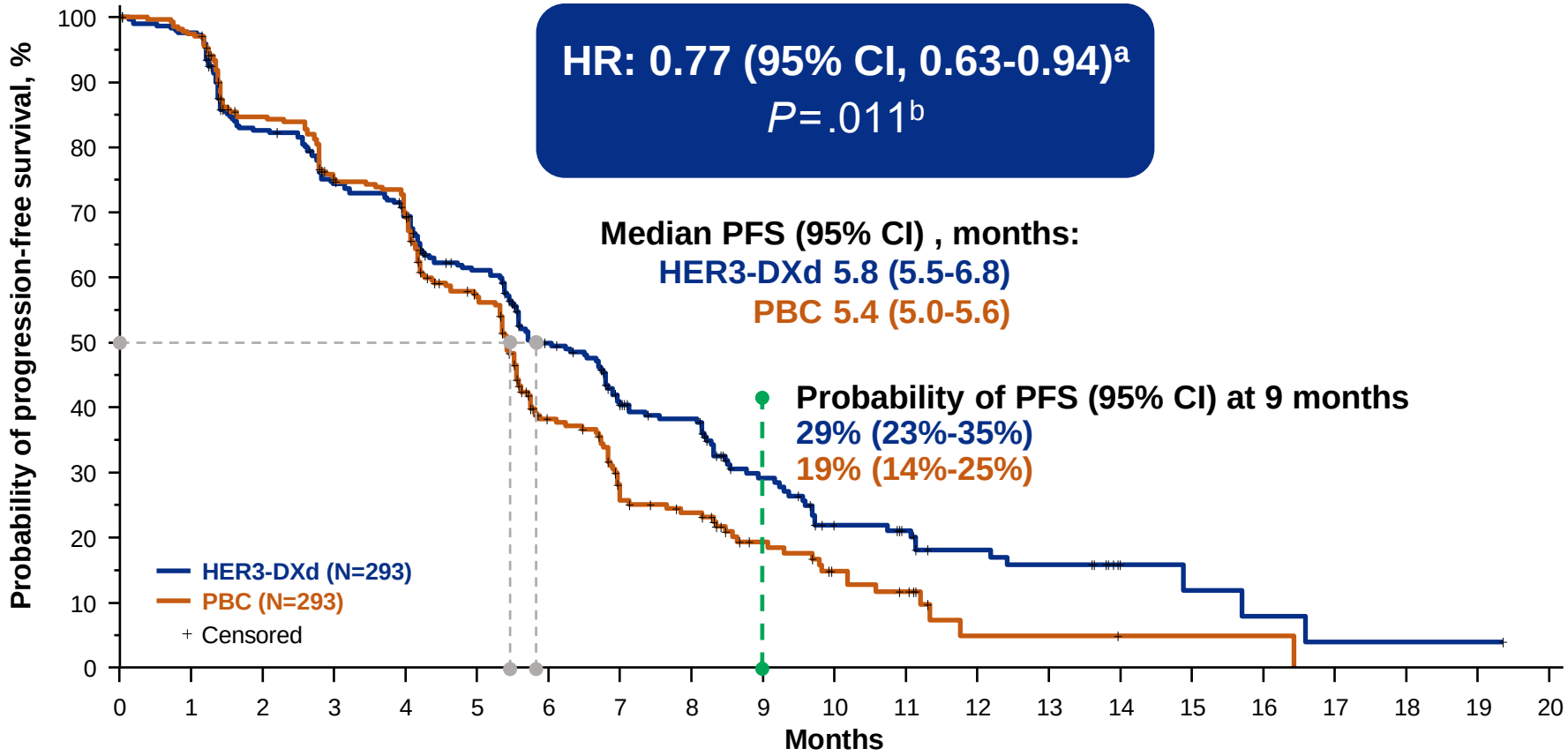
BICR, blinded independent central review; DCO, data cutoff; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival.

Baseline population characteristics were balanced across treatment arms and were typical of patients with *EGFR*-mutated NSCLC in this treatment line

Baseline characteristics		HER3-DXd (N=293)	PBC (N=293)
Age, median (range), years		64 (35-82)	64 (34-86)
Female, n (%)		184 (62.8)	175 (59.7)
Asian, n (%)		176 (60.1)	178 (60.8)
Smoking history, n (%)	Never	187 (63.8)	185 (63.1)
	Ever	106 (36.2)	108 (36.9)
Time since initial NSCLC diagnosis, median (range), months		24.2 (2.5-121.1)	24.1 (3.2-146.1)
ECOG PS at baseline, n (%)	0	110 (37.5)	102 (34.8)
	1	183 (62.5)	190 (64.8)
	2[a]	0	1 (0.3)
History of brain metastasis, n (%)[b]		127 (43.3)	132 (45.1)
Brain metastasis at baseline (by CNS BICR per CNS RECIST), n (%)[c]		105 (35.8)	95 (32.4)
EGFR activating mutations, n (%)	Ex19del	177 (60.4)	178 (60.8)
	L858R	113 (38.6)	112 (38.2)
	Dual Ex19del and L858R	3 (1.0)	3 (1.0)
Prior EGFR TKI, n (%)	Only 3rd-generation	225 (76.8)	223 (76.1)
	3rd- and 1st/2nd-generation	68 (23.2)	70 (23.9)
Line of treatment for prior 3rd-generation EGFR TKI, n (%)	First line	226 (77.1)	227 (77.5)
	Second line	67 (22.9)	66 (22.5)
Type of prior 3rd-generation EGFR TKI, n (%)	Osimertinib	266 (90.8)	263 (89.8)
	Other 3rd-generation[d]	27 (9.2)	30 (10.2)

BICR, blinded independent central review; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PBC, platinum-based chemotherapy; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.
[a] All patients had an ECOG PS of 0 or 1 at screening. [b] Including brain metastases that were previously treated. [c] Brain imaging was centrally assessed by a separate, blinded group of neuro-oncologists (CNS BICR) according to the CNS RECIST criteria.
[d] Aumolertinib, befotertinib, furmonertinib, and lazertinib.

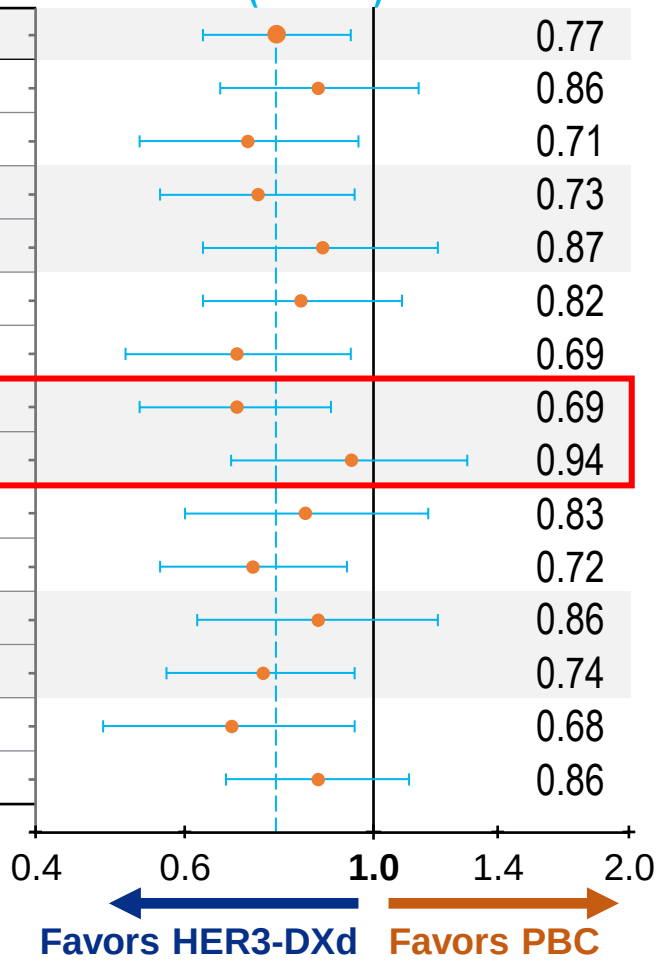
HER3-DXd significantly reduced the risk of disease progression (by BICR per RECIST 1.1) or death vs PBC



Data cutoff May 31, 2024. Median follow-up: HER3-DXd, 8.5 months (95% CI, 8.2-10.9 months); PBC, 8.3 months (95% CI, 6.9-8.8 months).
BICR, blinded independent central review; HR, hazard ratio; ITT, intention to treat; PBC, platinum-based chemotherapy; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] For disease progression or death. Cox proportional hazards model stratified by randomization stratification factors. [b] Stratified log-rank test, ITT population; efficacy boundary for superiority, $P<0.04998$.

The PFS benefit observed was generally consistent across subgroups

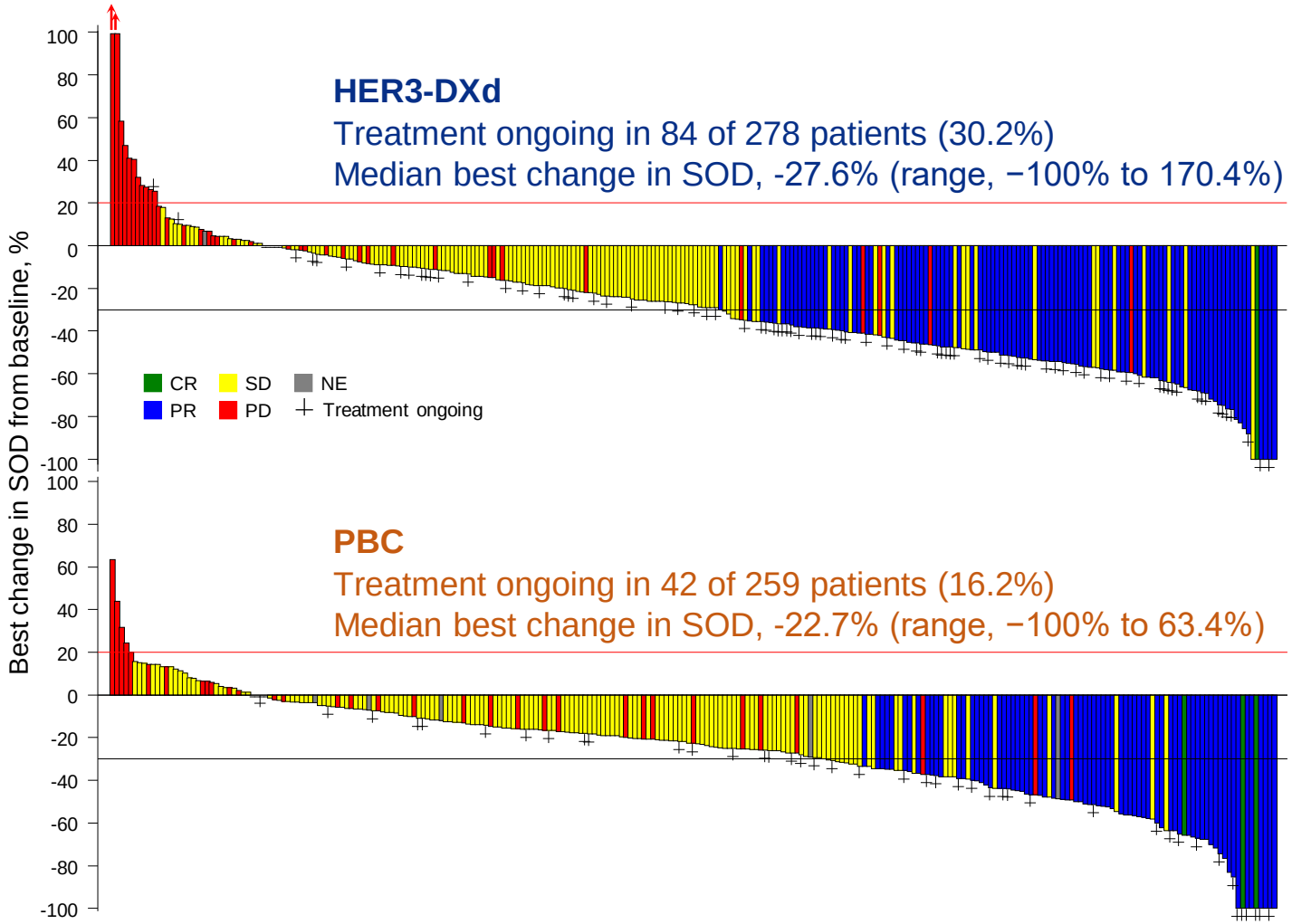
Subgroup		No. of events/n HER3-DXd	PBC	HR
Overall		194/293	195/293	0.77
Age	<65 y	105/153	108/149	0.86
	≥65 y	89/140	87/144	0.71
Sex	Female	117/184	116/175	0.73
	Male	77/109	79/118	0.87
Region	Asia	105/160	107/160	0.82
	Non-Asia	89/133	88/133	0.69
EGFR activating mutation	Ex19del	113/177	124/178	0.69
	L858R	79/113	69/112	0.94
Brain metastasis at baseline (by BICR per RECIST)	Yes	78/98	69/91	0.83
	No	116/195	126/202	0.72
Smoking status	Ever	76/106	73/108	0.86
	Never	118/187	122/185	0.74
ECOG PS at screening	0	69/111	65/103	0.68
	1	125/182	130/190	0.86



Data cutoff May 31, 2024.
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; PBC, platinum-based chemotherapy; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Observed efficacy by ORR confirmed previous observations in later treatment lines

Responses by BICR per RECIST		HER3-DXd (N=293)	PBC (N=293)
Confirmed ORR (95% CI), %		**35.2 (29.7-40.9)**	**25.3 (20.4-30.6)**
Best overall response, n (%)	CR	1 (0.3)	3 (1.0)
	PR	102 (34.8)	71 (24.2)
	SD[a]	133 (45.4)	148 (50.5)
	PD	40 (13.7)	35 (11.9)
	NE	17 (5.8)[b]	36 (12.3)[c]
BOR to be confirmed, n (%)		2 (0.7)[d]	2 (0.7)[d]
DCR (95% CI), %		80.5 (75.5-84.9)	75.8 (70.4-80.6)
Median TTR (range), mo		1.5 (0.3-8.1)	1.5 (1.2-6.9)
Median DOR (95% CI), mo		5.7 (5.1-7.3)	5.4 (4.1-5.6)



Data cutoff May 31, 2024.

BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate (CR or PR confirmed ≥4 weeks after initial response [per RECIST 1.1]); PBC, platinum-based chemotherapy; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOD, sum of diameters; TTR, time to response. [a] Includes non-CR/non-PD. [b] No adequate postbaseline tumor assessment (n=15); SD too early (SD <5 weeks after randomization; n=2). [c] No adequate postbaseline tumor assessment (n=30); SD too early (SD <5 weeks after randomization; n=5); PD too late (PD >12 weeks after randomization; n=1). [d] All were unconfirmed PR in patients who were ongoing without disease progression.

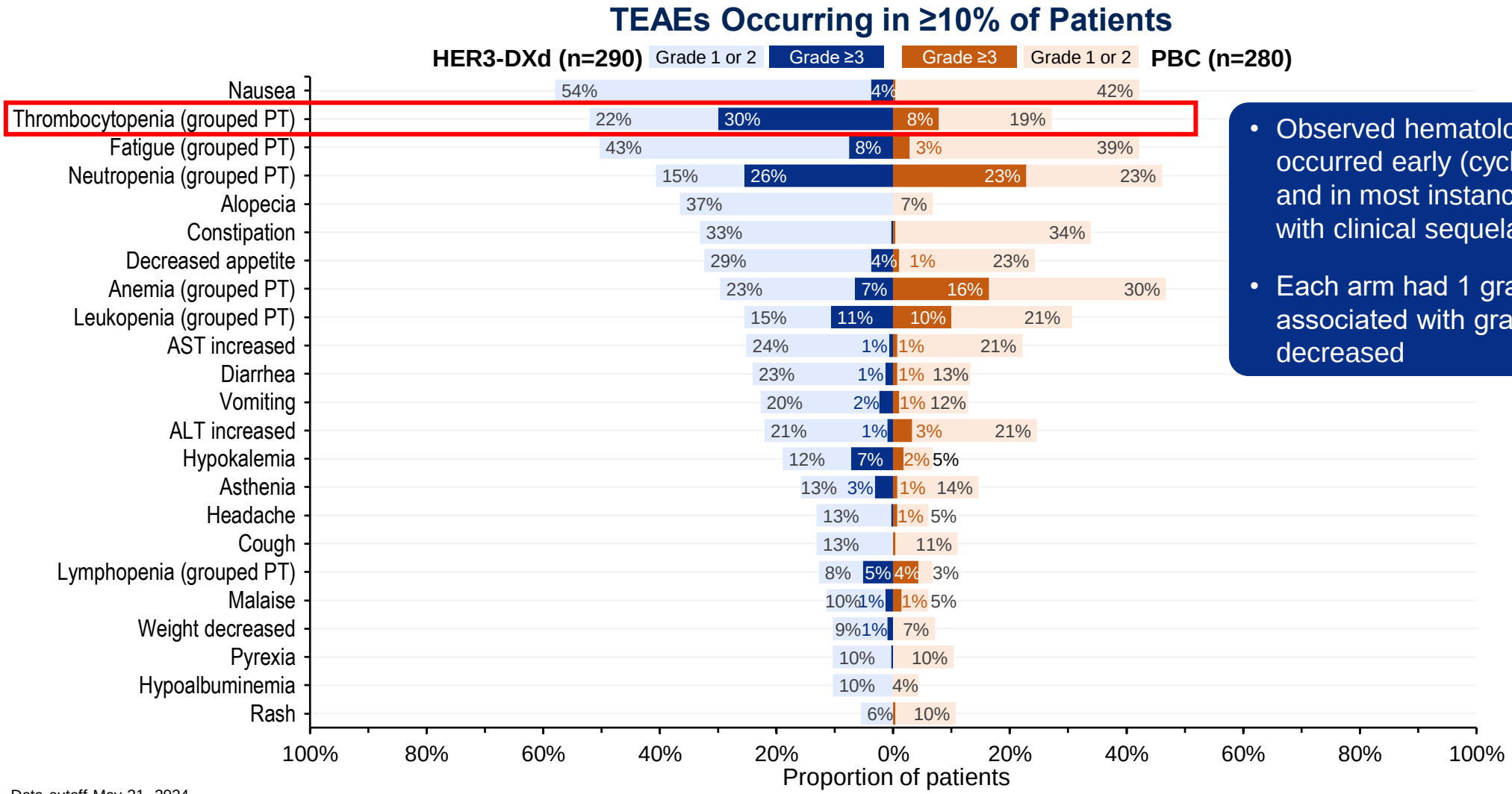
The safety profile of HER3-DXd was generally manageable and was consistent with previously reported trials

Safety Summary

All cause TEAEs	HER3-DXd (n=290)	PBC (n=280)
Any, n (%)	290 (100)	277 (98.9)
Grade ≥3	211 (72.8)	160 (57.1)
Treatment related	168 (57.9)	129 (46.1)
Serious	124 (42.8)	80 (28.6)
Treatment related	65 (22.4)	35 (12.5)
Associated with treatment discontinuation	33 (11.4)	27 (9.6)
Associated with dose reduction	94 (32.4)	59 (21.1)
Associated with dose interruption	131 (45.2)	105 (37.5)
Associated with death	22 (7.6)	14 (5.0)
Treatment related	4 (1.4)[a]	1 (0.4)[b]
Median treatment duration (range), months	5.5 (0.7-16.8)	4.6 (0.7-16.5)

Data cutoff May 31, 2024.
PBC, platinum-based chemotherapy; TEAE, treatment emergent adverse event.
[a] Interstitial lung disease/pneumonitis (n=2), pneumonia (n=1), and septic shock (n=1), per investigator assessment.
[b] Cerebral hemorrhage (n=1), per investigator assessment.

The safety profile of HER3-DXd was generally manageable and was consistent with previously reported trials



- Observed hematologic toxicities generally occurred early (cycle 1 or 2), were transient, and in most instances were not associated with clinical sequelae
- Each arm had 1 grade ≥3 bleeding event associated with grade ≥3 platelet count decreased

Data cutoff May 31, 2024.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBC, platinum-based chemotherapy; PT, preferred term; TEAE, treatment emergent adverse event.

The incidence of adjudicated ILD was consistent with previous studies, with most events being grade 1 or 2

- ILD, adjudicated by an independent committee,[a] occurred in 5.2% of patients treated with HER3-DXd
  - Median time to first onset was 126 days (range 29-304 days)
  - ILD was associated with dose interruption in 4 patients (1.4%), treatment discontinuation in 12 (4.1%), and death in 2 (0.7%)

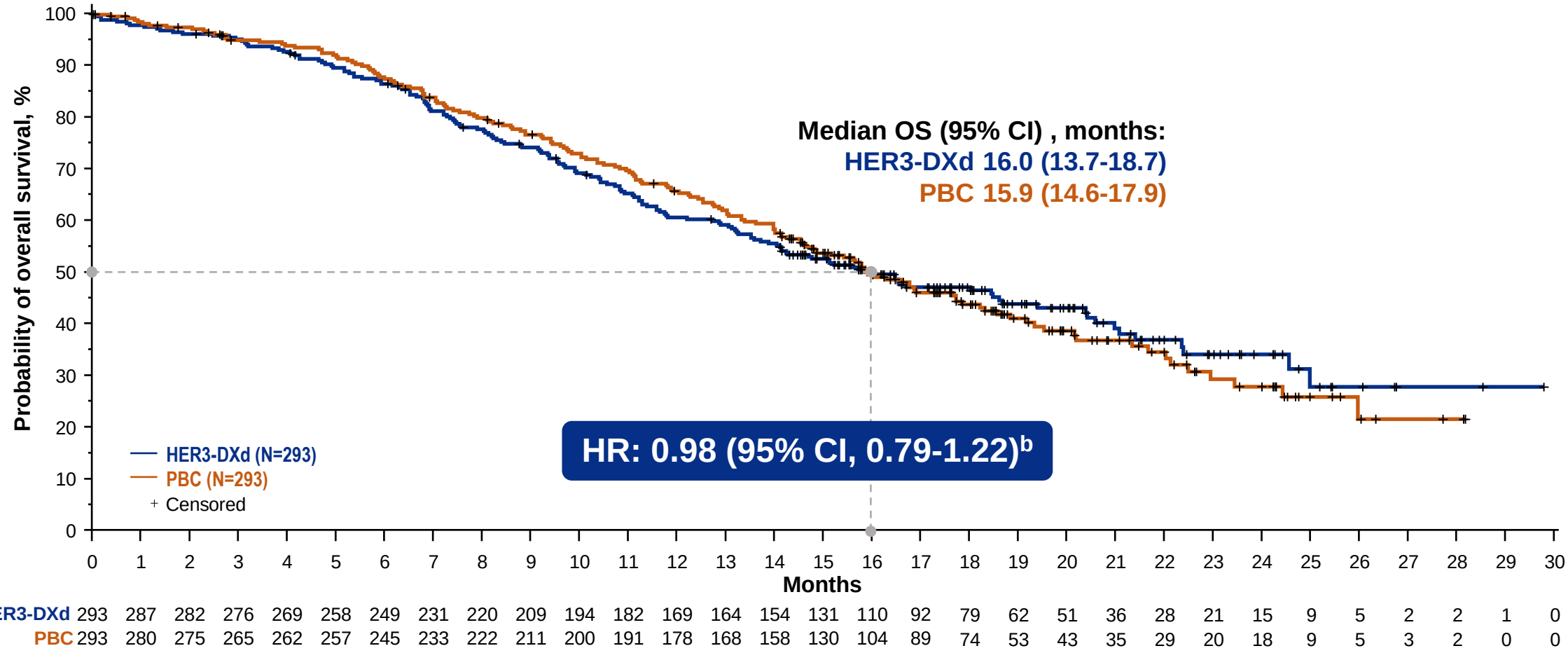
ILD Adjudication, n (%)	Grade by *investigator* or **adjudication committee**					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total ILD
HER3-DXd (n=290)						
Patients with Potential ILD Events (per investigator)	*8 (2.8)*	*13 (4.5)*	*3 (1.0)*	*0*	*4 (1.4)*	*28 (9.7)*
Adjudicated as ILD	**2 (0.7)**	**10 (3.4)**	**1 (0.3)**	**0**	**2 (0.7)**	**15 (5.2)**
Adjudicated as treatment-related ILD	**2 (0.7)**	**9 (3.1)**	**1 (0.3)**	**0**	**2 (0.7)[b]**	**14 (4.8)**
PBC (n=280)						
Patients with Potential ILD Events (per investigator)	*1 (0.4)*	*0*	*0*	*1 (0.4)*	*0*	*2 (0.7)*
Adjudicated as ILD	**0**	**0**	**0**	**0**	**0**	**0**
Adjudicated as treatment-related ILD	**0**	**0**	**0**	**0**	**0**	**0**

- ILD is acknowledged as an AE of Special Interest and well-established treatment management guidelines are in place

Data cutoff May 31, 2024.
AE, adverse event; ILD, interstitial lung disease; PBC, platinum-based chemotherapy.
[a] The ILD adjudication committee consists of 15 physicians, including radiologists, pulmonologists, and oncologists. A panel with a representative from each specialty reviews all clinical and radiographic data to make an independent assessment of each case.
[b] Patient 1: 75-year-old woman, pneumonia. Course was consistent with disease progression with superimposed drug toxicity. Patient 2: 71-year-old man, ILD. Treated with steroid and antibiotic therapies.

Newly available mature data from extended follow-up (data cutoff: Feb 28, 2025)[a]

OS for patients treated with HER3-DXd compared to PBC



Median follow-up: HER3-DXd, 18.7 months (95% CI, 17.9-19.9 months); PBC, 18.6 months (95% CI, 17.9-19.6 months).

HR, hazard ratio; OS, overall survival; PBC, platinum-based chemotherapy.

[a] 327 of 393 events had occurred; information fraction, 83%. [b] For death from any cause. Cox proportional hazards model stratified by randomization stratification factors.

Conclusions

- Primary analysis of the HERTHENA-Lung02 study demonstrated a statistically significant improvement in PFS for HER3-DXd vs PBC in patients with *EGFR*-mutated NSCLC that progressed on third-generation TKI therapy (HR 0.77, p=0.011)
- Newly available 3rd interim analysis demonstrated that OS for patients treated with HER3-DXd did not show an improvement compared to those receiving PBC[a]
- HER3-DXd monotherapy demonstrated intracranial antitumor activity
  - Intracranial ORR (95% CI) and median intracranial PFS (95% CI) were 19.0% (12.0%-27.9%) and 5.4 months (4.0-5.9 months) with HER3-DXd vs 11.6% (5.9%-19.8%) and 4.2 months (2.8-5.0 months) with PBC
- The safety profile of HER3-DXd was generally manageable, consistent with previous reports
  - Most common TEAEs were hematologic and gastrointestinal
  - The incidence of adjudicated ILD was 5.2%
- Evaluation of the association of biomarkers, including HER3 IHC, with efficacy parameters in HERTHENA-Lung02 and their suitability as a predictive biomarker is ongoing

EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; HR, hazard ratio; IHC, immunohistochemistry; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival, TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

[a] HERTHENA-Lung02 is an ongoing trial, and further results regarding key secondary data will be presented at a future congress.

HER3-DXd : Clinical Studies

Ph2 (Ph1/2)

Ph1

NSCLC	EGFRm	1L/2L, osimertinib combo	
	Non-AGA	KEYMAKER-U01 substudy 01A 1L, pembrolizumab combo	KEYMAKER-U01 substudy 01G 1L, pembrolizumab combo
BC	HER2+	HERTHENA-Breast01 2L+	
	TNBC	HERTHENA-Breast03* high-risk early stage, neoadjuvant pembrolizumab combo	
Other tumors		HERTHENA-PanTumor01	HERTHENA-PanTumor02

*HERTHENA-Breast03 includes high-risk early stage HR low and HER2 negative breast cancer

BC: breast cancer, EGFRm: EGFR mutated, HR: hormone receptor, NSQ: non-squamous , NSCLC: non-small cell lung cancer, TNBC: triple negative breast cancer

Next Wave

A Phase 1, first-in-human study of DS-2243, an HLA-A*02/NY-ESO–directed bispecific T-cell engager, in patients with advanced solid tumors

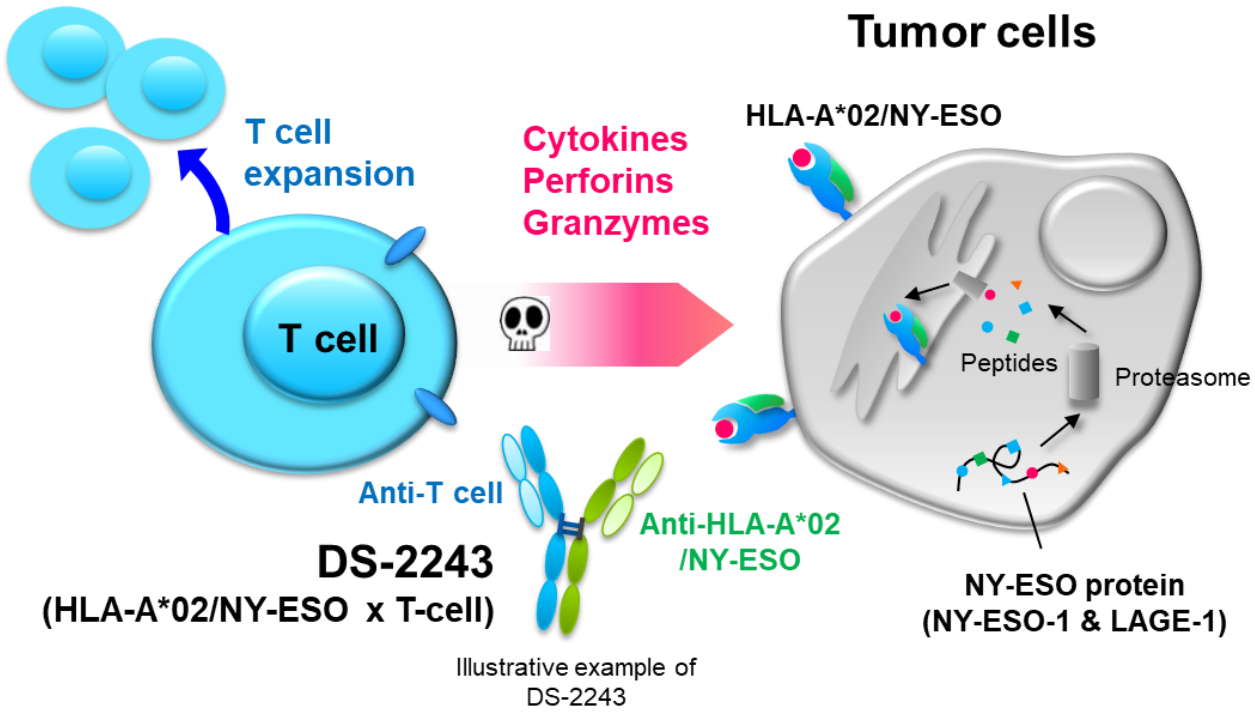
Sandra P. D'Angelo,[1] Vivek Subbiah,[2] Jean-Yves Blay,[3] Michael J. Wagner,[4] Neeltje Steeghs,[5] Jeonghwan Youk,[6] Hideki Mizusako,[7] Yoshihiro Ohue,[8] Jin Jin,[8] Abdul Waheed Rajper,[8] Nicole Tesar,[8] Patrick Schöffski[9]

1 Memorial Sloan Kettering Cancer Center, New York, NY, USA; 2 Sarah Cannon Research Institute, Nashville, TN, USA; 3 Centre Léon Bérard, Lyon, France; 4Dana-Farber Cancer Institute, Boston, MA, USA; 5 Netherlands Cancer Institute, Amsterdam,The Netherlands; 6 Seoul National University Hospital, Seoul, South Korea; 7 Daiichi Sankyo Co., Ltd., Tokyo, Japan; 8 Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; 9 Universitaire Ziekenhuizen Leuven, Leuven, Belgium.

DS-2243, a New T-cell Engager

A Potential First-in-Class Bispecific T-cell Engager (Bi-TCE) Targeting HLA-A*02/NY-ESO Tumors

Mode of Action



Illustrative example of DS-2243

- **Cutting-Edge Bi-TCE:** Engineered to selectively engage both tumor antigens and T-cells, driving a targeted and potent immune response.
- **Tumor-Specific Targeting**: Precise targeting through the HLA-A*02/NY-ESO complex mediated by NY-ESO, a highly tumor-specific antigen. NY-ESO is only expressed in the testis in normal tissue, where it is present without HLA-A molecules.
- **Broad Applicability**: High/moderate frequency of NY-ESO expression observed in Synovial Sarcoma, Myxoid/Round Cell Liposarcoma, NSCLC, UC etc.
- **Promising Efficacy**: Exhibits robust anti-tumor activity and significant combination therapy potential in preclinical studies.

NSCLC: non-small cell lung cancer, UC: urothelial cancer

Agenda

1. Welcome message
2. R&D overview
3. Highlights from ASCO 2025
4. **Q&A**

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