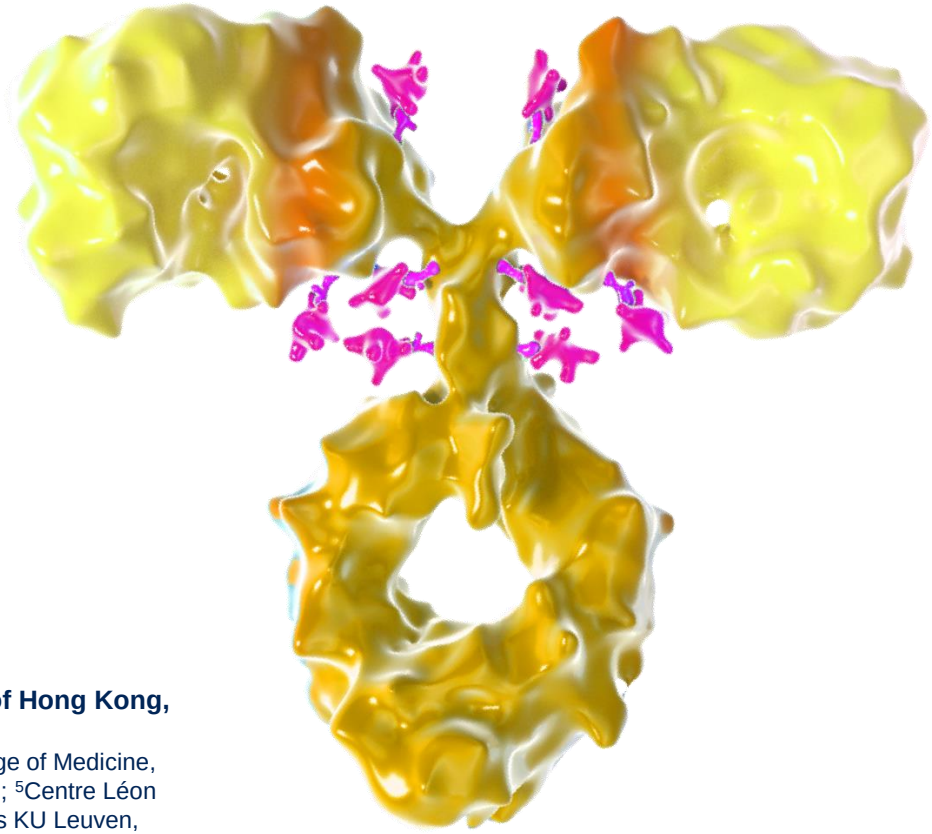
Patritumab Deruxtecan (HER3-DXd) in Resistant *EGFR*-Mutated Advanced NSCLC After a Third-Generation EGFR TKI: The Phase 3 HERTHENA-Lung02 Study



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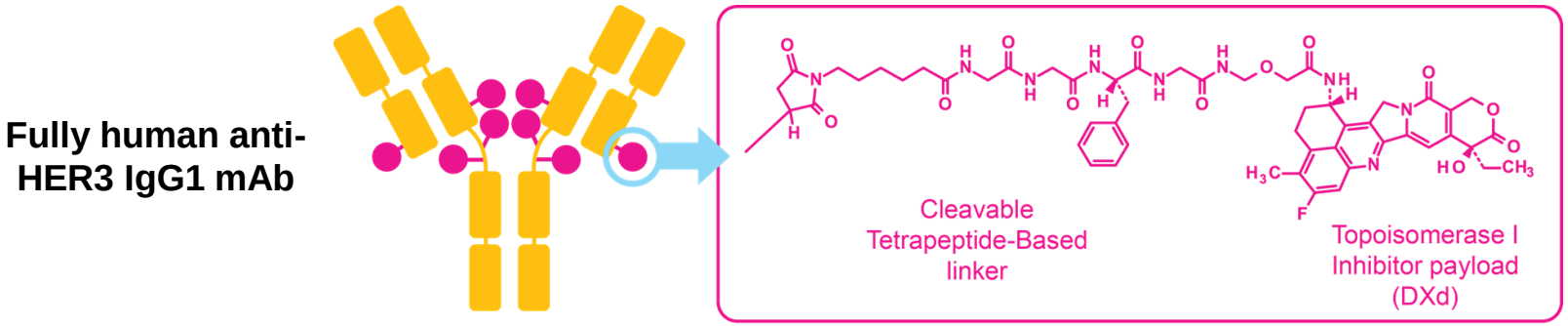
Despite recent advances, an unmet need still exists in advanced *EGFR*-mutated NSCLC

- *EGFR*-sensitizing mutations are found in **32% of patients** with NSCLC globally[1]
- First-line treatment containing a third-generation EGFR TKI, such as osimertinib, is standard therapy for advanced *EGFR*-mutated NSCLC; however, **most patients develop resistance** to these treatments[2,3] and the mechanisms of resistance are diverse[4]
- **Following progression on a third-generation EGFR TKI**, subsequent treatment options include platinum-based chemotherapy and amivantamab plus chemotherapy;[a] however, an **unmet need remains for options with greater efficacy and safety**
- **HER3-DXd** is an investigational **HER3-directed ADC** (DAR=8) that has shown promising antitumor activity (ORR, 30%) in patients previously treated with an EGFR TKI and chemotherapy in the **Phase 2, HERTHENA-Lung01 study[5]**



ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; EGFR, epidermal growth factor receptor; HER3. Human epidermal growth factor receptor 3; IgG1, immunoglobulin G1; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

[a] Subsequent therapies are usually platinum-based chemotherapy, sometimes in combination with immunotherapy, antiangiogenic therapy, or further EGFR TKI therapy

1. Zhang Y-L, et al. *Oncotarget.* 2016;7(48):78985-78993. 2. Schoenfeld AJ, Yu HA. *J Thorac Oncol*. 2020;15(1):18-21. 3. Passaro A, et al. *Nat Cancer* 2021;2(4):377-391. 4. Choudhury NJ, et al. *J Thorac Oncol.* 2023;18(4):463-475.
5. Yu HA, et al. *J Clin Oncol* 2023;41(35):5363-5375

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.

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ClinicalTrials.gov Identifier: NCT05338970
EudraCT Identifier: 2021-005879-40
Japan Registry of Clinical Trials: jRCT2021220002

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**)

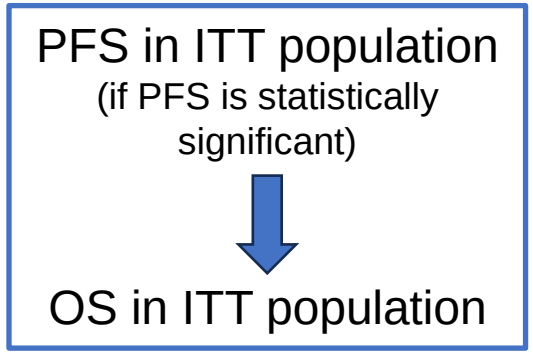
Primary endpoint (PFS by BICR)

- **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



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.

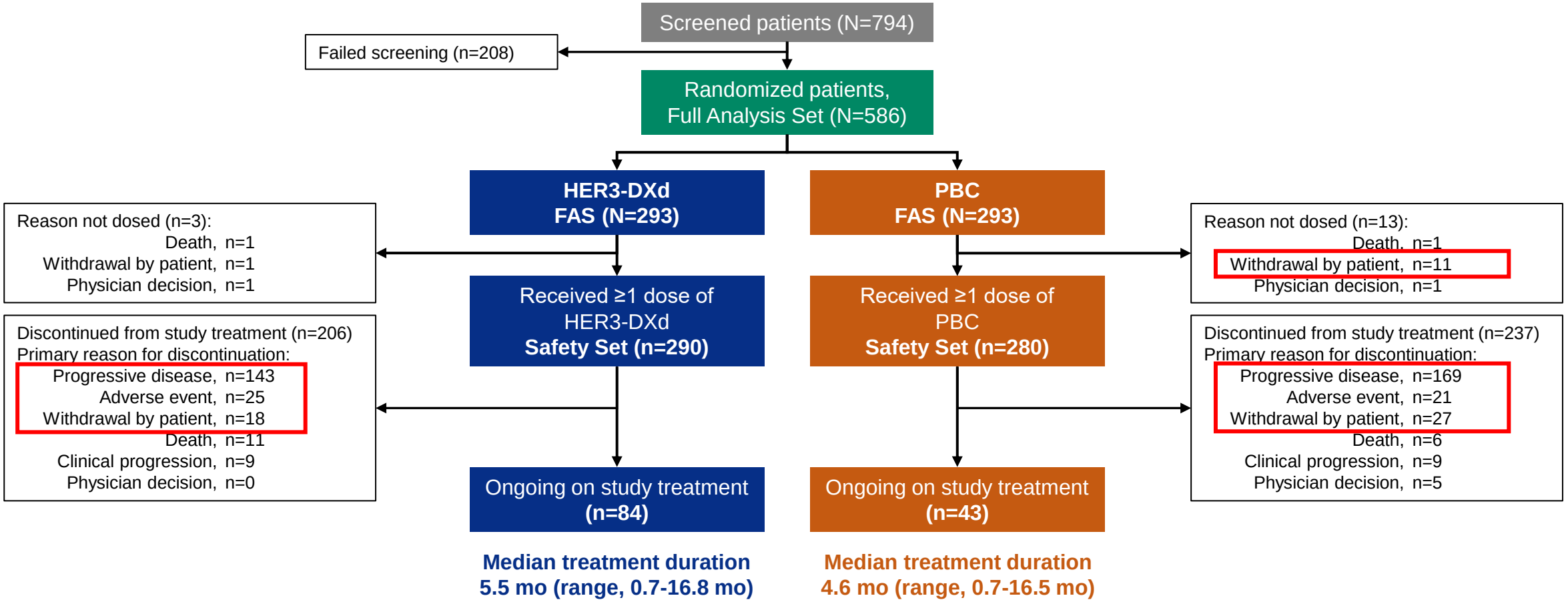
Baseline population characteristics were balanced across treatment arms and were typical of patients with *EGFR*-mutated NSCLC in this treatment line

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.

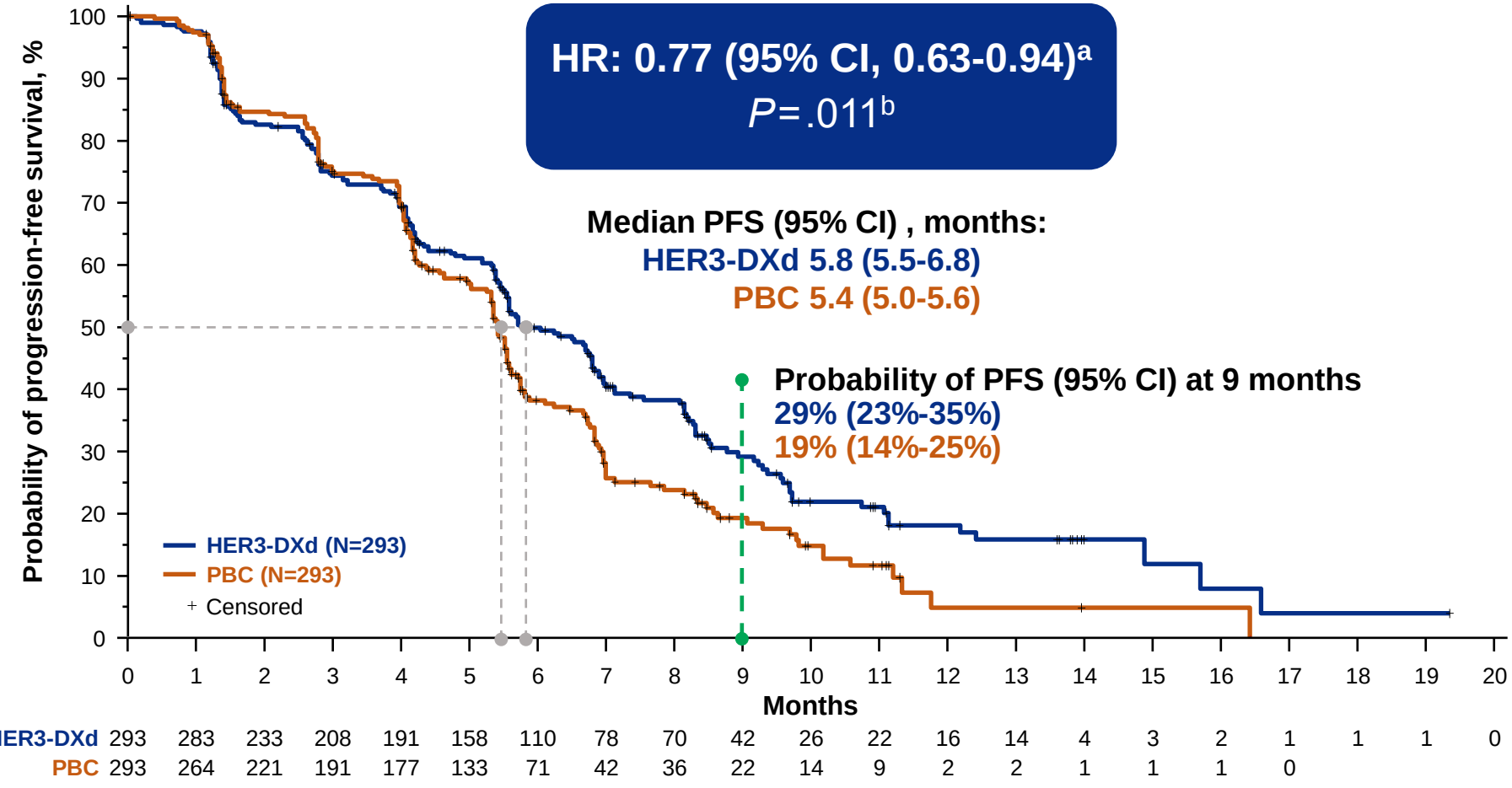
Patient disposition at the primary analysis of PFS

Primary analysis for PFS, 2nd interim analysis for OS (data cutoff: May 31, 2024)



FAS, full analysis set; PBC, platinum-based chemotherapy; PFS, progression-free survival.

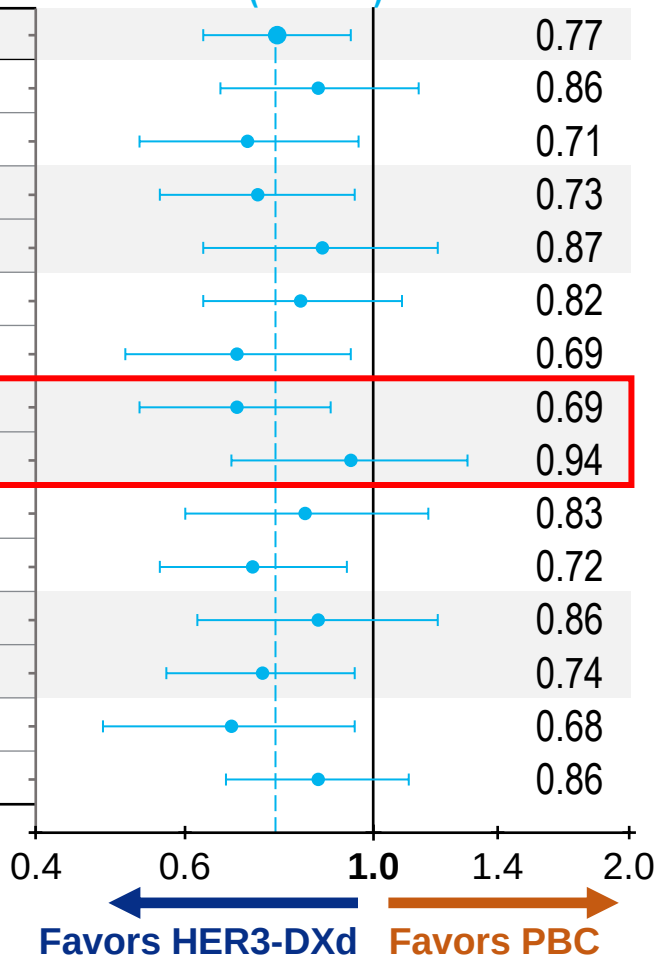
HER3-DXd significantly reduced the risk of disease progression (by BICR per RECIST 1.1) or death vs PBC



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

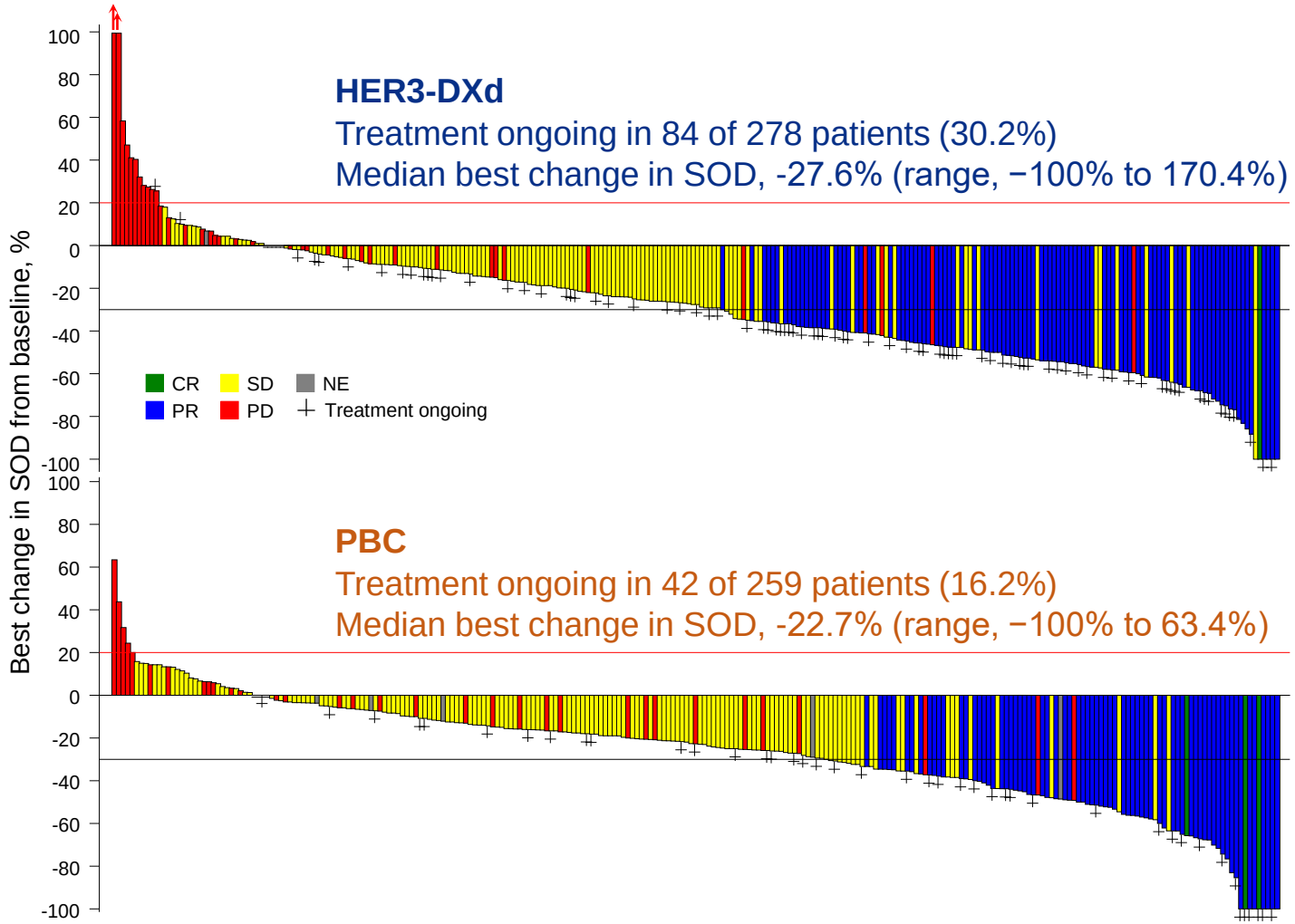
Subgroup		No. of events/n HER3-DXd	PBC	HR
Overall		194/293	195/293	0.77
Age	<65 y	105/153	108/149	0.86
	≥65 y	89/140	87/144	0.71
Sex	Female	117/184	116/175	0.73
	Male	77/109	79/118	0.87
Region	Asia	105/160	107/160	0.82
	Non-Asia	89/133	88/133	0.69
EGFR activating mutation	Ex19del	113/177	124/178	0.69
	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.

HER3-DXd demonstrated intracranial activity

Evaluation in patients with brain metastases at baseline according to CNS BICR

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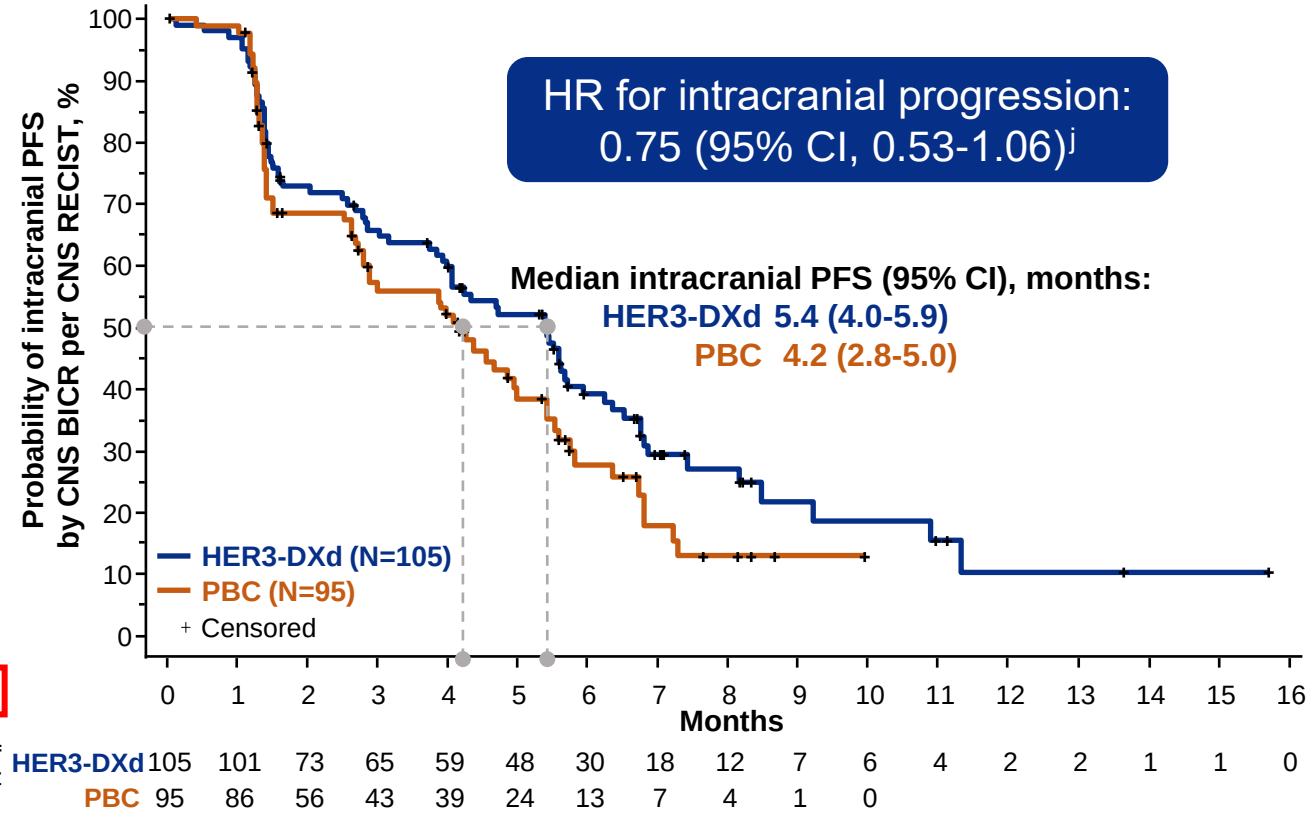
Intracranial response by CNS BICR per CNS RECIST[a]		Patients with ≥1 CNS lesion (target or non-target) at baseline (CNS BICR) HER3-DXd (N=105)[b]	PBC (N=95)[c]
Confirmed intracranial ORR (95% CI), %		**19.0 (12.0-27.9)**	**11.6 (5.9-19.8)**
Best overall intracranial response, n (%)	CR	13 (12.4)[d]	4 (4.2)[e]
	PR	7 (6.7)	7 (7.4)
	SD[f]	52 (49.5)	47 (49.5)
	PD	27 (25.7)	26 (27.4)
	NE	6 (5.7)[g]	11 (11.6)[h]
BOR to be confirmed, n (%)		2 (1.9)[i]	0
Intracranial DCR (95% CI), %		68.6 (58.8-77.3)	61.1 (50.5-70.9)
Median intracranial TTR (range), mo		2.1 (1.2-6.9)	2.6 (1.2-4.7)
Median intracranial DOR (95% CI), mo		4.5 (4.1-NE)	4.2 (2.4-NE)
Prior radiation to the brain, n (%)		39 (37.1)	36 (37.9)



Data cutoff May 31, 2024.
BICR, blinded independent central review; BOR, best overall response; CNS, central nervous system; CR, complete response; DCR, disease control rate (CR+PR+SD); DOR, duration of response; HR, hazard ratio; NE, not evaluable; ORR, objective response rate; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTR, time to response.
[a] Brain imaging was centrally assessed by a separate, blinded group of neuro-oncologists (CNS BICR) according to the CNS RECIST criteria. [b] 24 patients had measurable target lesions; 81 had only nontarget lesions. [c] 28 patients had measurable target lesions; 67 had only nontarget lesions. [d] All 13 patients had only nontarget lesions. [e] All 4 patients had only nontarget lesions. [f] Includes non-CR/non-PD. [g] No adequate postbaseline tumor assessment (n=6). [h] No adequate postbaseline tumor assessment (n=9); SD too Early (SD <5 weeks after randomization [n=1]); PD too late (PD >12 weeks after randomization [n=1]). [i] Unconfirmed CR (n=1) and unconfirmed PR (n=1) in patients who were ongoing without disease progression. [j] Among patients with ≥1 CNS lesion (target and/or non-target) at baseline by CNS BICR per CNS RECIST.

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

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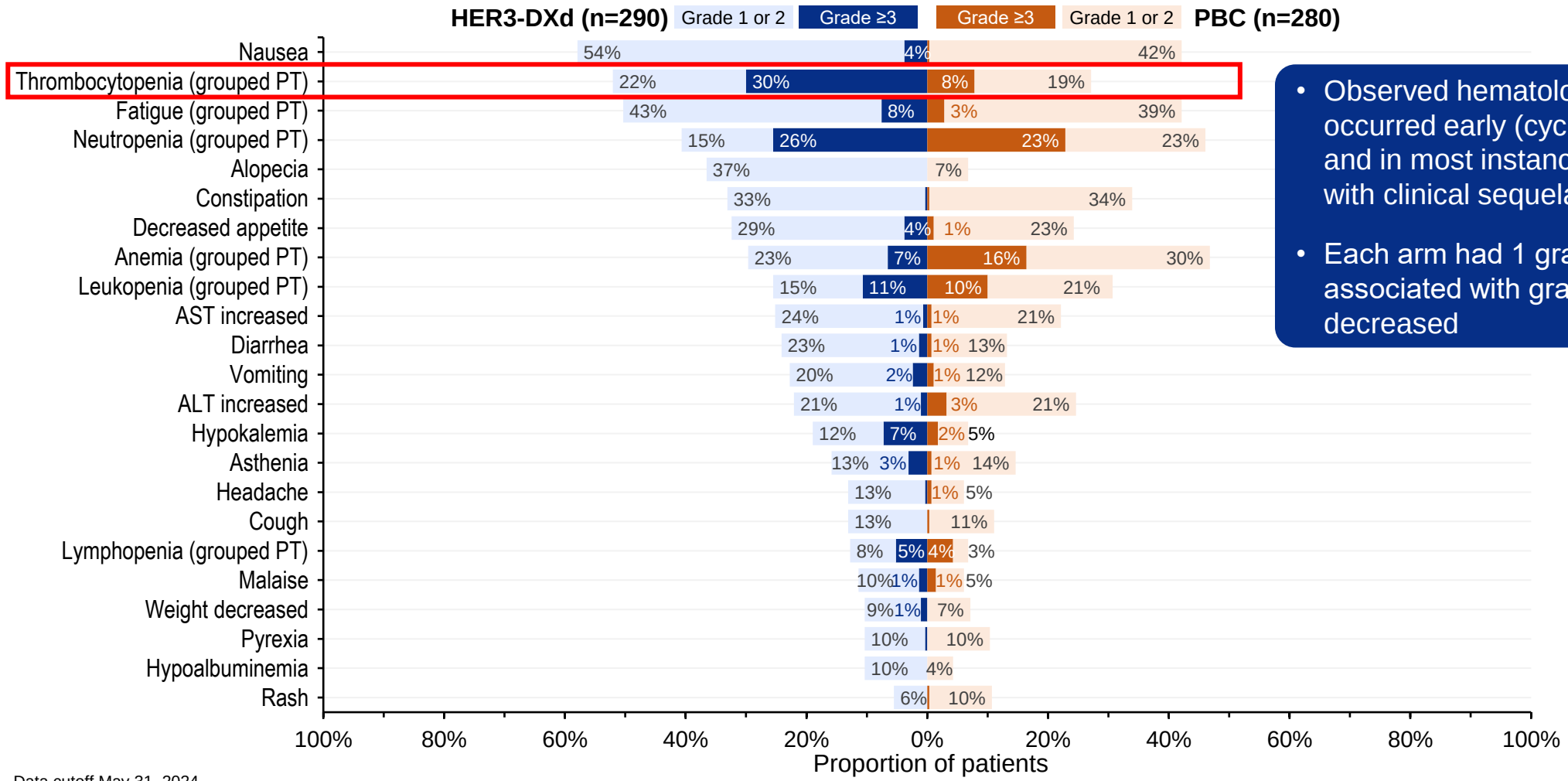
TEAEs Occurring in ≥10% of Patients



- 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.

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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%)

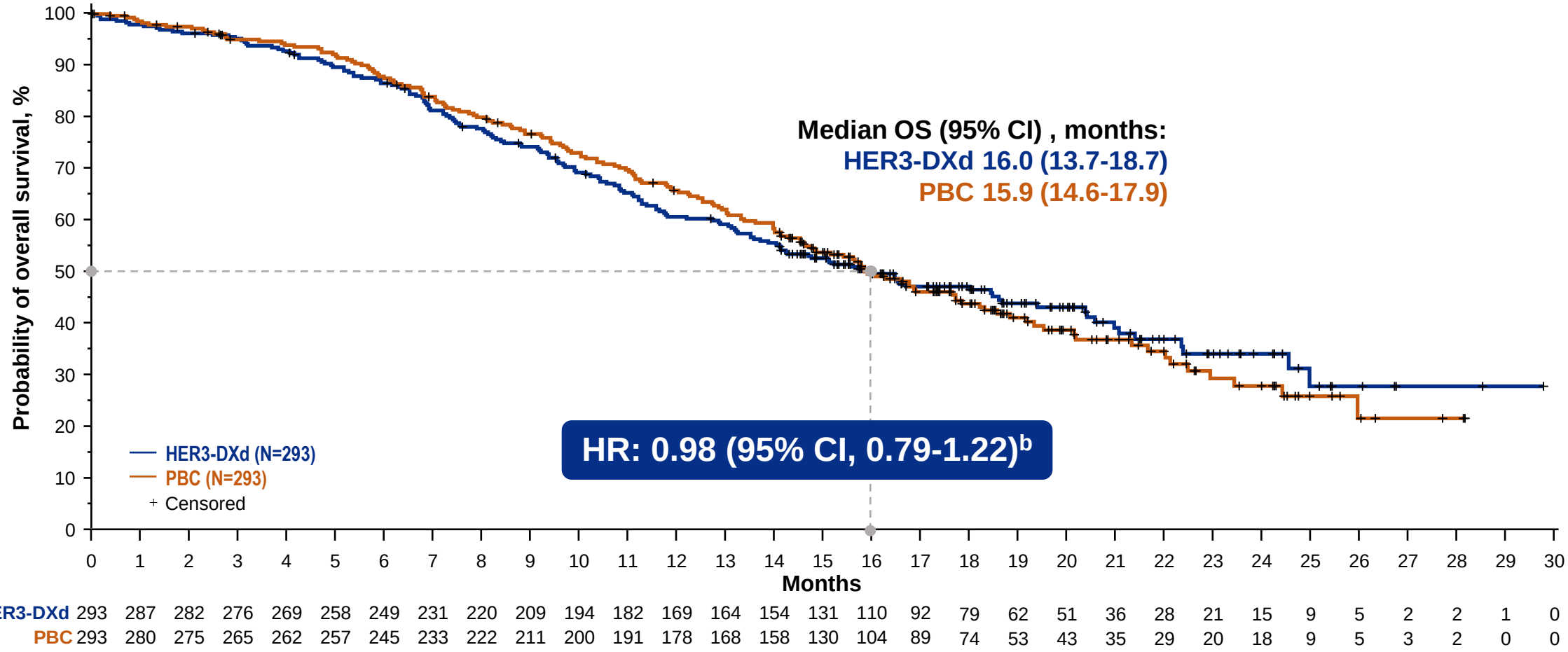
ILD Adjudication, n (%)	Grade by *investigator* or **adjudication committee**					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total ILD
HER3-DXd (n=290)						
Patients with Potential ILD Events (per investigator)	*8 (2.8)*	*13 (4.5)*	*3 (1.0)*	*0*	*4 (1.4)*	*28 (9.7)*
Adjudicated as ILD	**2 (0.7)**	**10 (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



No. of patients at risk:																														
HER3-DXd	293	287	282	276	269	258	249	231	220	209	194	182	169	164	154	131	110	92	79	62	51	36	28	21	15	9	5	2	2	1	0
PBC	293	280	275	265	262	257	245	233	222	211	200	191	178	168	158	130	104	89	74	53	43	35	29	20	18	9	5	3	2	0	0

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.

Acknowledgments

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