2025 ASCO ANNUAL MEETING

Patritumab deruxtecan (HER3-DXd) in active brain metastases from metastatic breast and non–small cell lung cancers, and leptomeningeal disease from advanced solid tumors: results from the TUXEDO-3 phase II trial

Preusser M*, Garde-Noguera J, Gion M, Ruíz-Borrego M, García-Mosquera JJ, Greil R, Valero M, Arumi M, Raimondi G, Campolier M, González-Alonso P, Guerrero-Martínez JA, Llombart-Cussac A, Oberndorfer F, Marhold M, Vaz-Batista M, Berghoff AS, Furtner J, Fuereder T, Bartsch R.

*Division of Oncology, Medical University of Vienna

Patritumab deruxtecan (HER3-DXd) may present a novel treatment option for patients with active brain metastases and leptomeningeal disease

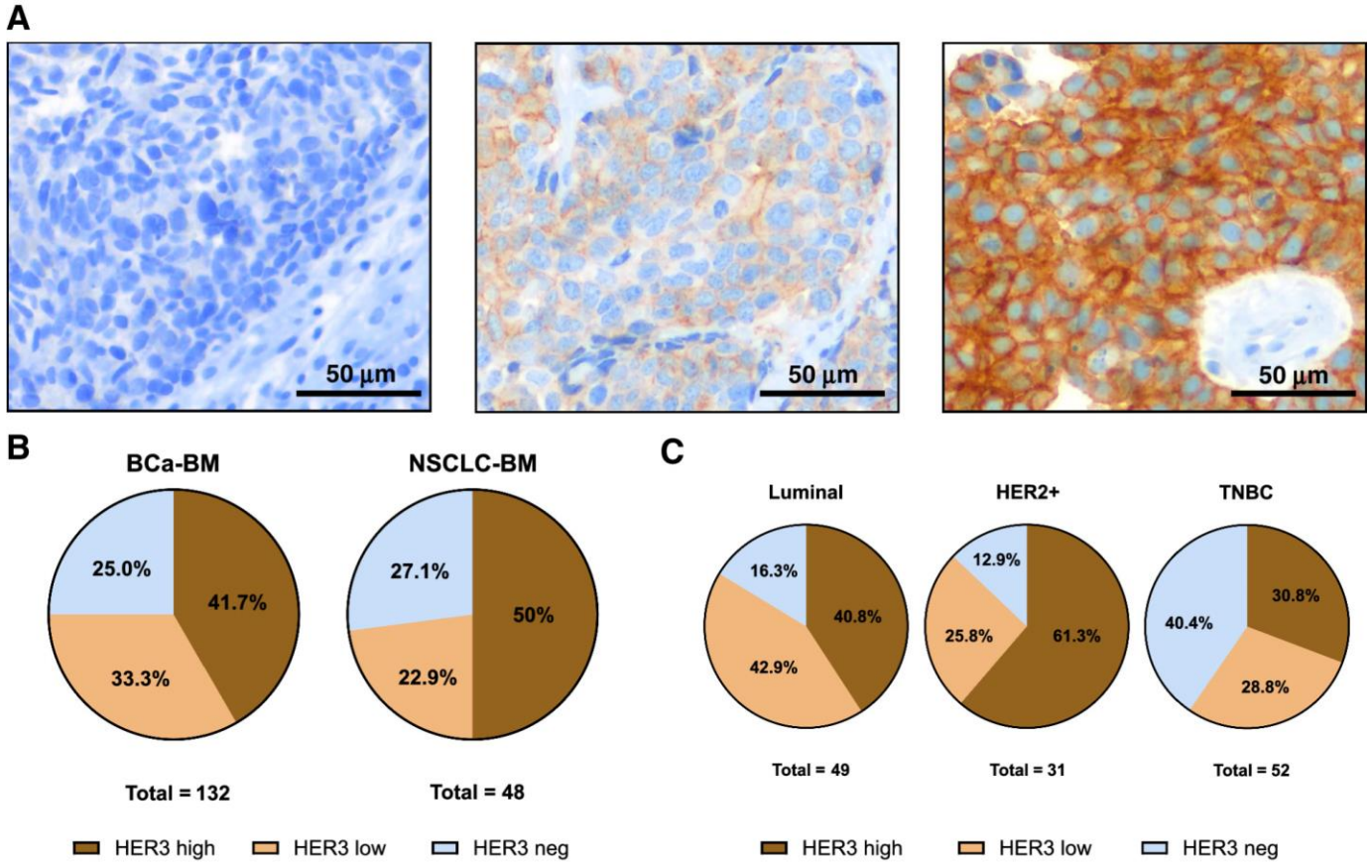
Background

- Brain metastases (BMs) and leptomeningeal disease (LMD) are common complications in breast and lung cancers[1,2]:
  - Poor prognosis;
  - High symptom burden;
  - Impaired quality of life.
- Novel therapies providing intra- and extracranial disease control needed.
- Antibody-drugs conjugates (ADCs) have shown CNS activity in BMs and LMD[3-6].
- HER3 is an emerging treatment target in oncology[7].

[1]Preusser M et al. *Curr Opin Neurol* (2012) | [2]Le Rhun E et al. *ESMO Open* (2019) | [3]Bartsch R et al. *Nat Med* (2022)
[4]Niikura N et al. *NPJ Breast Cancer* (2023) | [5]Harbeck N et al. *Nat Med* (2024) | [6]Vaz-Batista et al. *Med* (2025) | [7]Garret JT et al. *Nat Rev Clin Oncol* (2025)

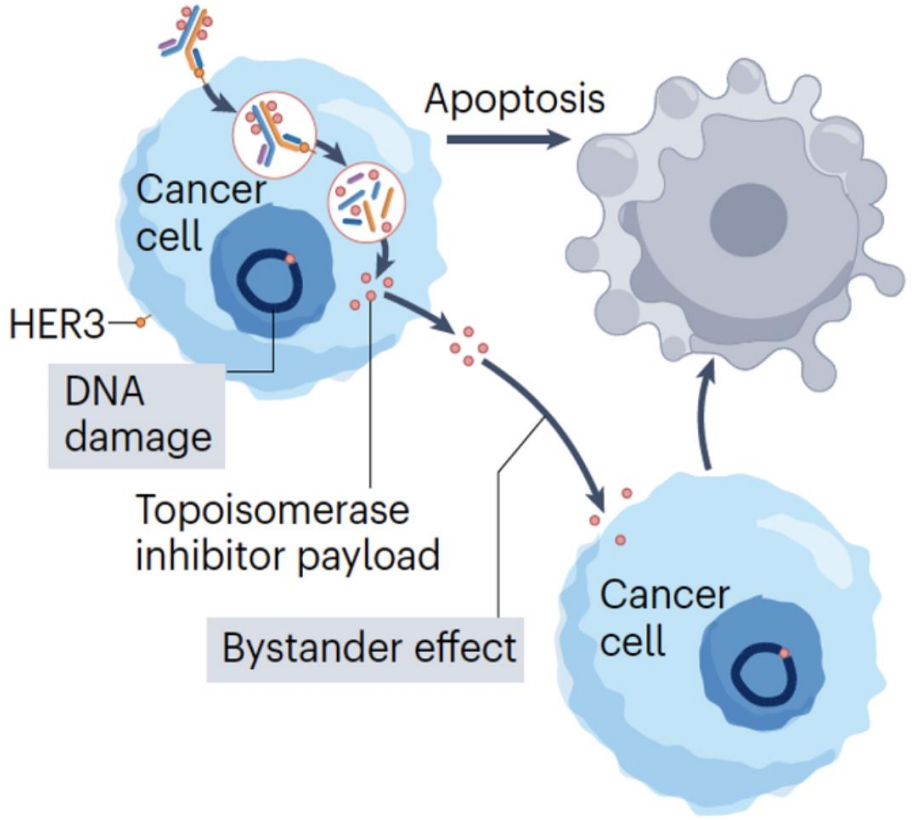
HER3 as ADC target

HER3 in BMs



Tomasich E et al. *Clin Cancer Res* (2023)

Patritumab deruxtecan (HER3-DXd)



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TUXEDO-3 Design

- Open-label, single-arm, three-cohort, non-comparative, phase 2 trial.

KEY INCLUSION CRITERIA

- Age ≥18 years
- Histologically documented:
  - Metastatic BC with active BMs (cohort 1).
  - Advanced NSCLC with active BMs (cohort 2).
  - Any advanced solid tumor with type I/II LMD* (cohort 3).
- ≥1 measurable (≥10 mm) brain lesion (cohorts 1 and 2).
- ≥1 line of systemic treatment in the advanced setting (cohort 1 and 2).
- KPS ≥ 70%, ECOG PS ≤ 2.
- LVEF ≥ 50%.

* Type I LMD: positive CSF cytology (confirmed LMD). Type II LMD: typical clinical and MRI findings (probable or possible LMD).

Cohort 1 (N=20)
Metastatic BC with active BMs

Cohort 2 (N=20)
Advanced NSCLC with active BMs

Cohort 3 (N=20)
Advanced solid tumors with LMD

Interim analysis:
Futility stop if 0/10 patients with intracranial ORR (cohorts 1 and 2) or alive after 3 months (cohort 3).

HER3-DXd

- 5.6 mg/kg intravenously.
- Every 21 days.
- Until progressive disease, discontinuation, or death.

PRIMARY ENDPOINTS

Cohorts 1 and 2
- **Intracranial ORR****.

Cohort 3
- **3-month OS rate.**

Primary endpoint met if:
- ≥ 15% patients with intracranial response (cohorts 1 and 2).
- ≥ 15% patients alive after 3 months (cohort 3).

SECONDARY ENDPOINTS

All cohorts
- **CBR, DCR, DoR, and TTR** for intracranial, extracranial and overall lesions**.
- **PFS.**
- **OS.**
- **Best percentage of change in tumor burden.**
- **Safety and tolerability** (CTCAE v.5.0).
- **QoL and neurocognitive function** (EORTC QLQ-c30, and BN20).
- **Neurologic function** (NANO scale).

Cohorts 1 and 2
- **Extracranial and bicompartmental ORR****.

Cohorts 3
- **Intracranial ORR****.

EXPLORATORY ENDPOINTS

All cohorts
- Association between HER3 expression with efficacy endpoints***.

** Intracranial assessments as per RANO-BM (Complete response: disappearance of all target and non-target lesions. Partial response: ≥30% decrease in the sum longest distance relative to baseline), Extracranial and bicompartmental assessments as per RECIST v.1.1.

*** HER3 expression was assessed in tissue simples for intracranial or extracranial lesions.

Statistical design

- Simon's two-stage design.

Cohort	Indication	Primary endpoint	Null hypothesis	Alternative hypothesis	Type I error	Power	N
1	BMs from mBC	Intracranial ORR*	<5%	≥25%	10%	88%	20
2	BMs from aNSCLC	Intracranial ORR*	<5%	≥25%	10%	88%	20
3	LMD from solid tumors	3-month OS rate	<5%	≥25%	10%	88%	20

* As per RANO-BM criteria

Patient characteristics (full analysis population)

	Cohort 1 (mBC with BMs) N=21 N (%)	Cohort 2 (aNSCLC with BMs) N=20 N (%)	Cohort 3 (LMD from solid tumors) N=20 N (%)
Age (years), median (range)	57.0 (35.0-75.0)	59.5 (37.0-72.0)	51.5 (40.0-66.0)
Gender			
Female	21 (100)	10 (50.0)	18 (90.0)
Male	0 (0)	10 (50.0)	2 (10.0)
ECOG PS			
0	13 (61.9)	5 (25.0)	6 (30.0)
1	7 (33.3)	13 (65.0)	9 (45.0)
2	1 (4.7)	2 (10.0)	5 (25.0)
Status of BMs or LMD*			
Newly diagnosed	6 (28.6)	7 (35.0)	20 (100)
Progressive after local therapy	15 (71.4)	13 (65.0)	0 (0)
Previous treatment lines in advanced disease, median (range)	4 (1-13)	1.5 (1-5)	2 (0-6)

* BMs in cohorts 1 and 2; LMD in cohort 3.

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Tumor (sub)types

	Cohort 1 (mBC with BMs) N=21 N (%)
Breast cancer phenotype	
HER2-positive	9 (42.9)
Luminal	5 (23.8)
Triple-negative	7 (33.3)

	Cohort 2 (aNSCLC with BMs) N=20 N (%)
Lung cancer phenotype	
Histological	
Non-squamous	17 (85.0)
Squamous	3 (15.0)
Molecular	
No activating driver mutations	15 (75.0)
Activating driver mutations	5 (25.0)
KRAS G12C	1 (5.0)
EGFR	4 (20.0)
Common	2 (10.0)
Uncommon	2 (10.0)

	Cohort 3 (LMD from solid tumors) N=20 N (%)
LMD type	
I	9 (45.0)
II	11 (55.0)
Primary tumor location	
Breast	12 (60.0)
Lung	6 (30.0)
Ovary	1 (5.0)
Melanoma	1 (5.0)
Breast cancer phenotype	
HER2-positive	1 (8.3)
Luminal	5 (41.7)
Triple-negative	6 (50.0)
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Histological	
Non-squamous	5 (83.3)
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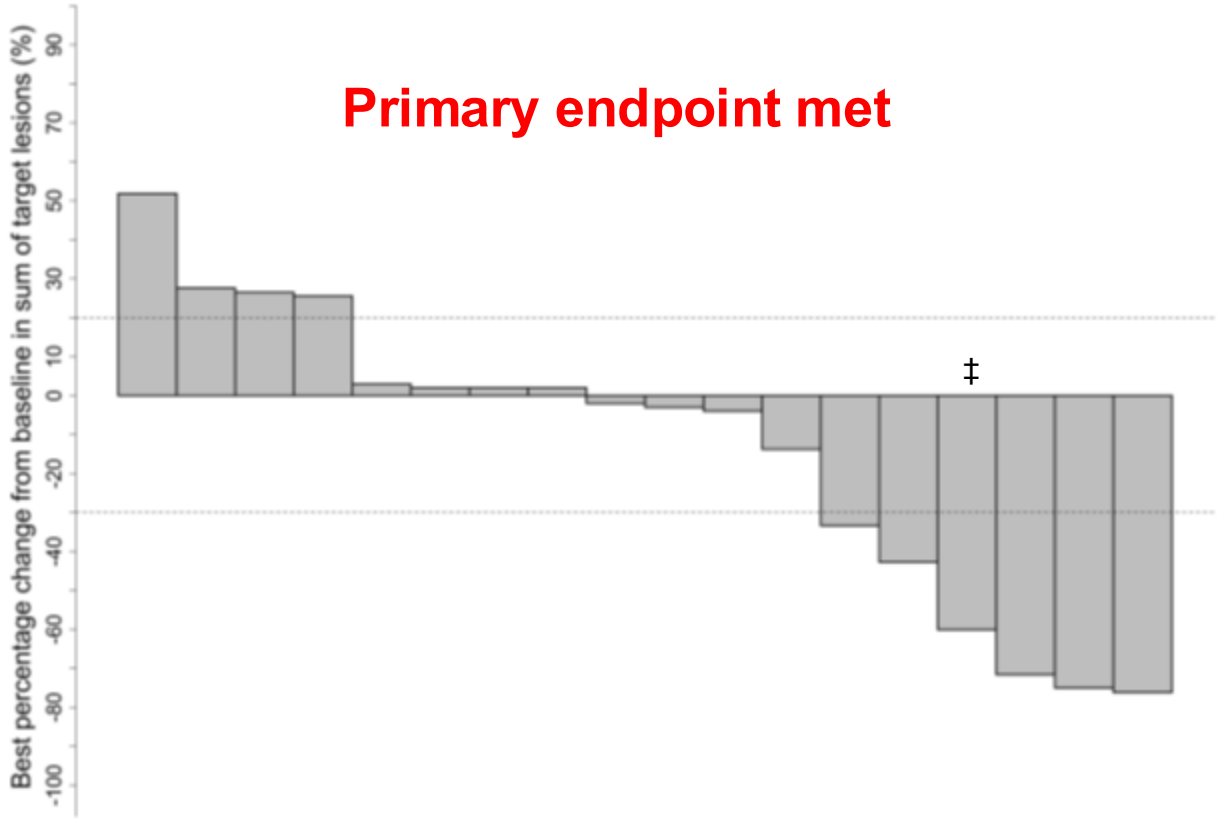
Primary endpoint: Cohort 1 (BC with BMs)

- Median follow-up: 4.9 (range: 1.4-14.5) months.
- 5/21 (23.8%) patients with intracranial response using RANO-BM.



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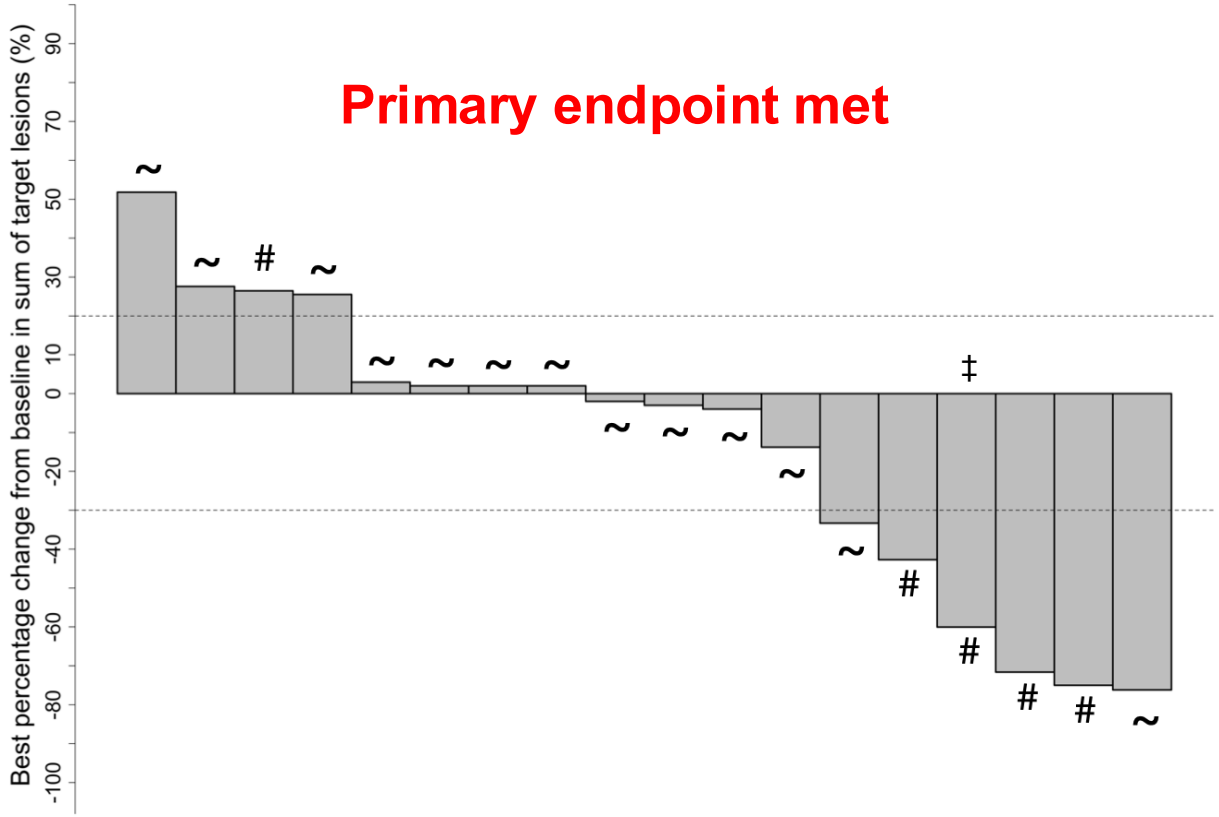

Status of brain metastases:

~ Newly diagnosed

\# Progressive after local therapy

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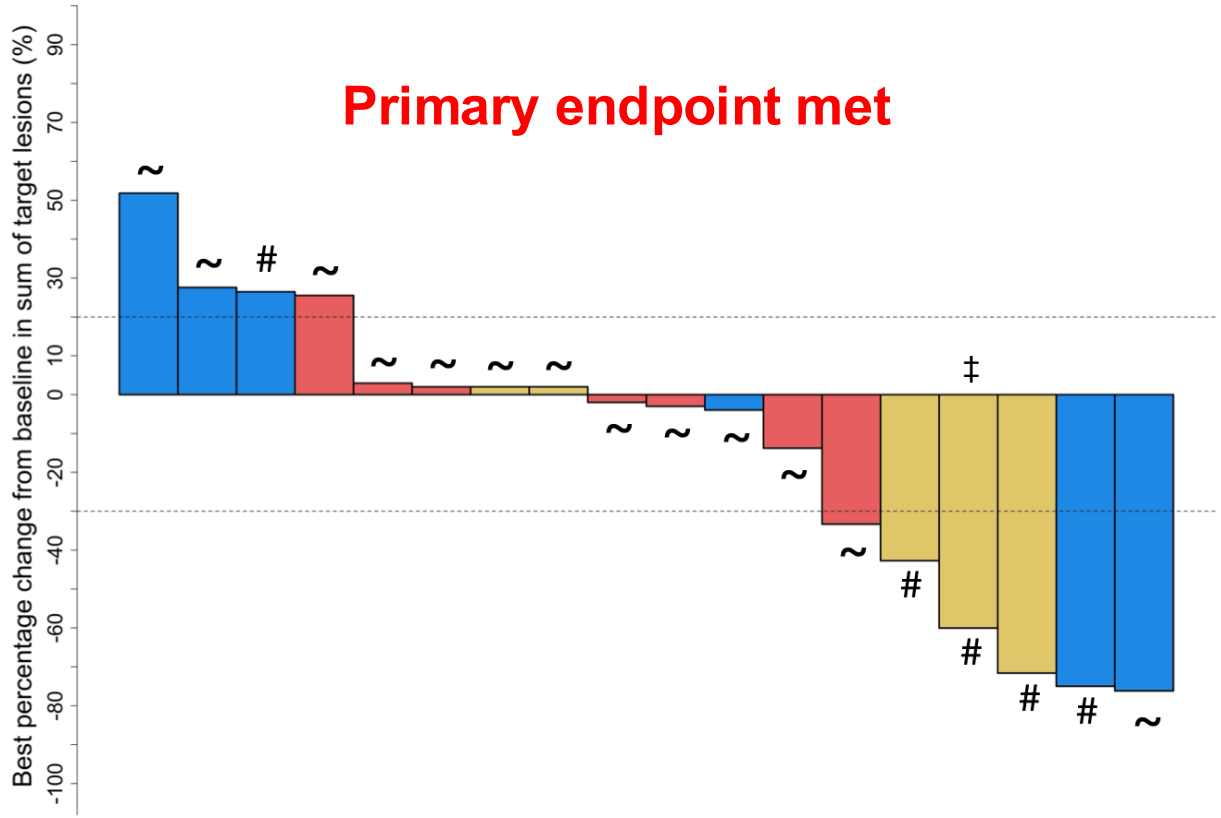

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Breast cancer subtype

HER2-positive

Luminal

Triple-negative

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PRESENTED BY: Matthias Preusser, MD

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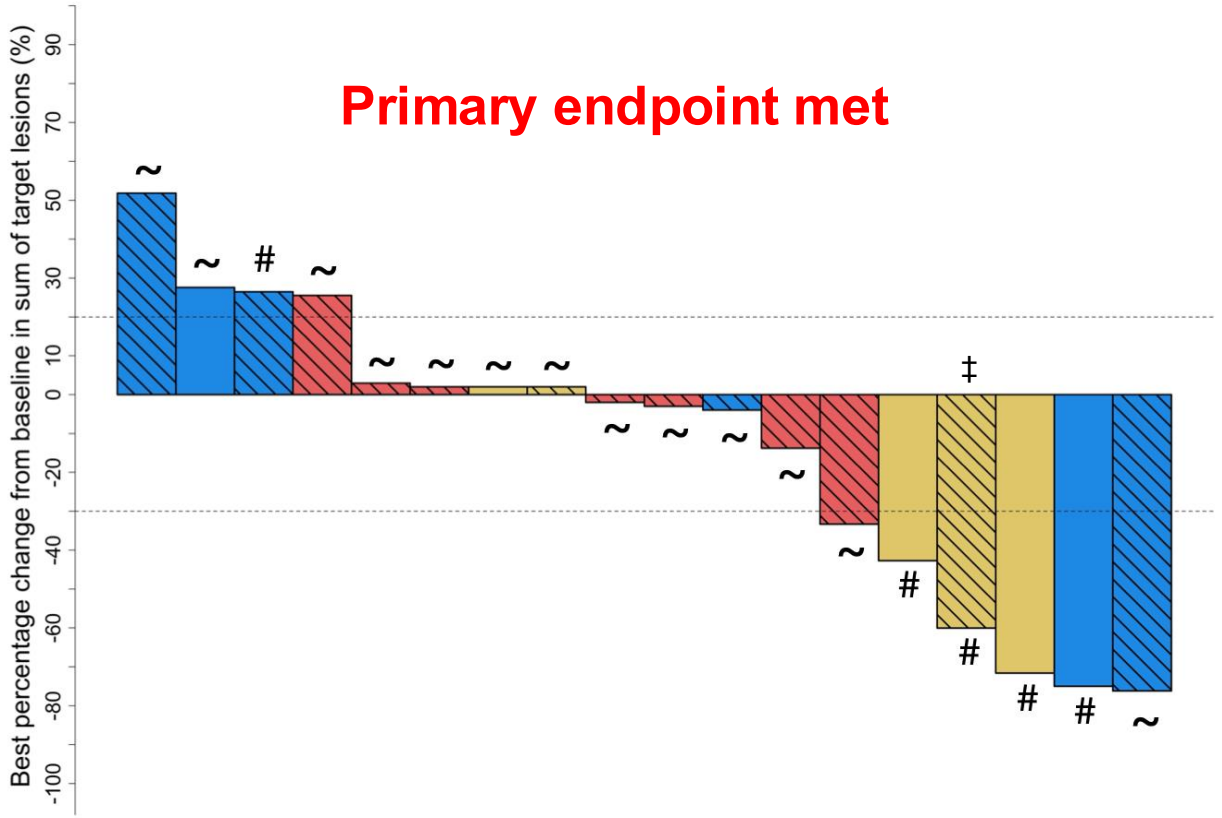

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HER2-positive

Luminal

Triple-negative

Previous ADCs*

Yes

No

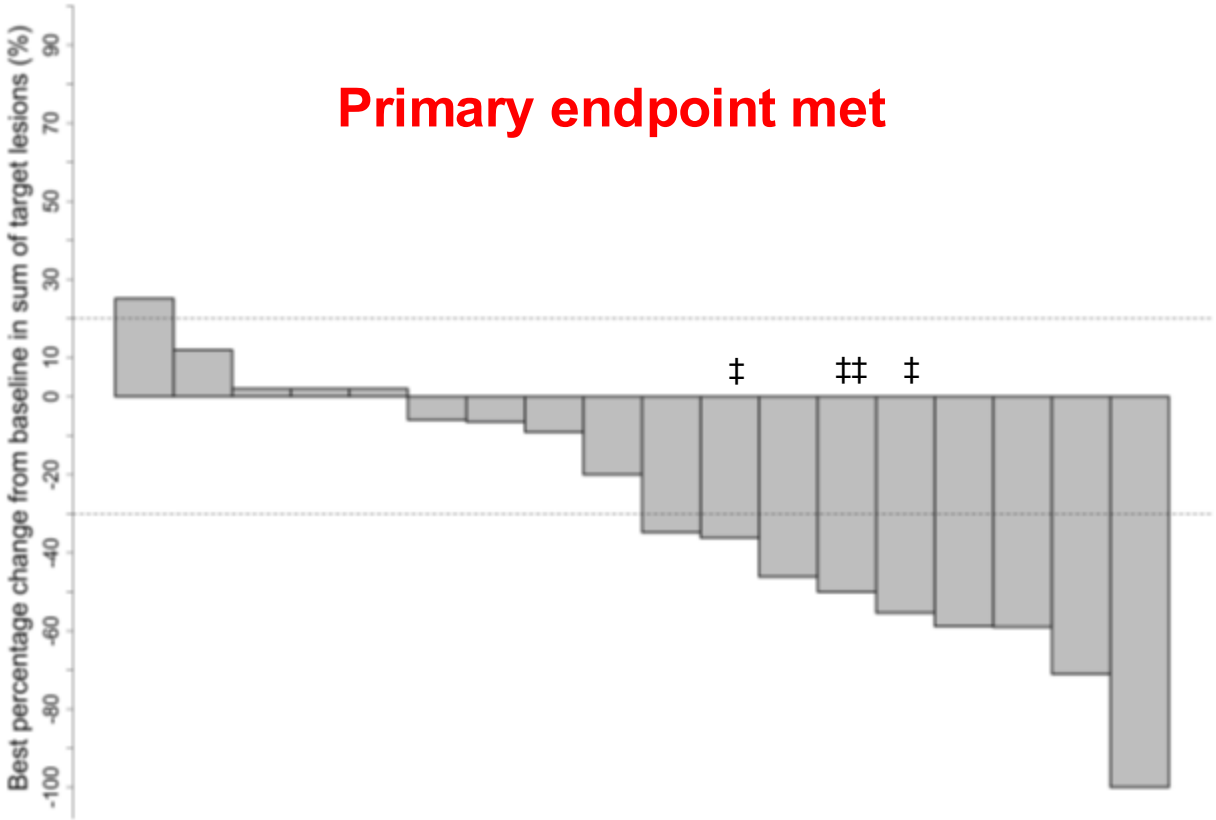
*All previous ADCs had a topoisomerase I inhibitor as payload.

‡Unconfirmed response.

PRESENTED BY: Matthias Preusser, MD

Primary endpoint: Cohort 2 (aNSCLC with BMs)

- Median follow-up: 5.3 (range: 0.2-13.1) months.
- 6/20 (30.0%) patients with intracranial response using RANO-BM.



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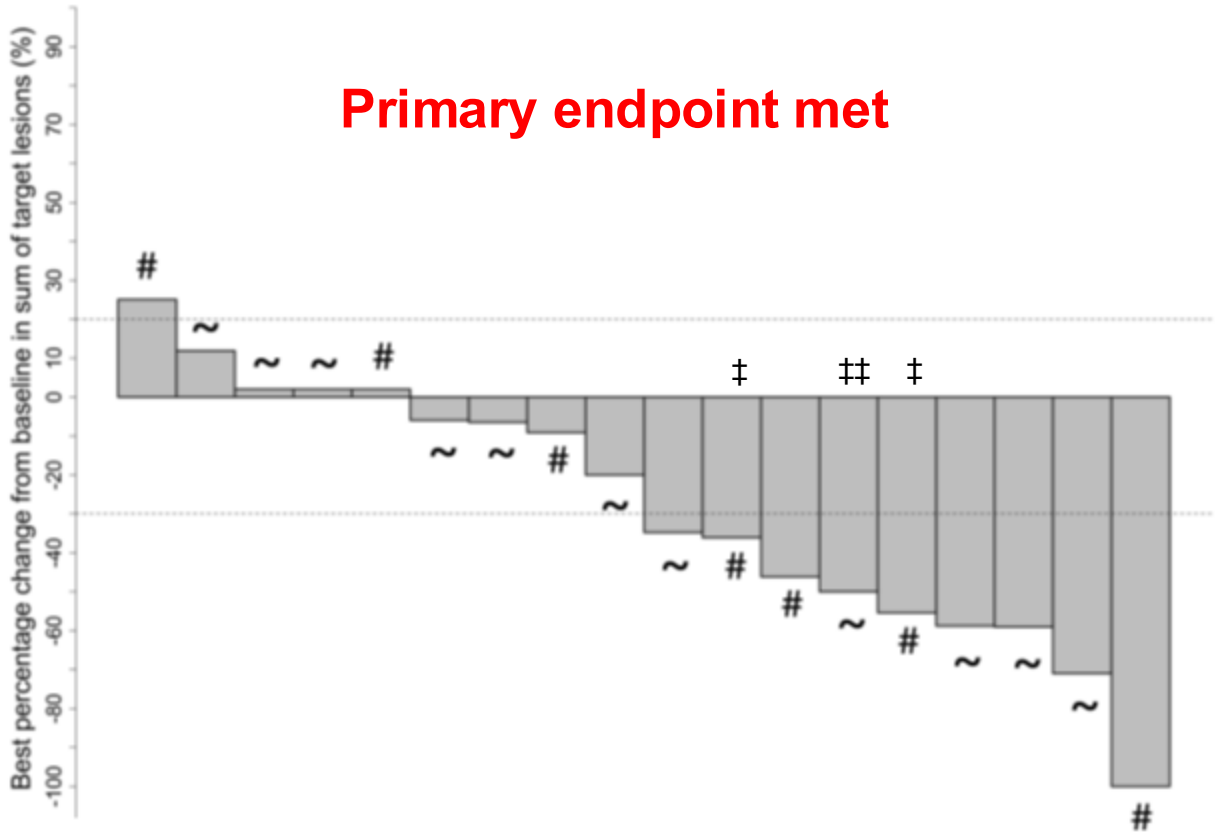

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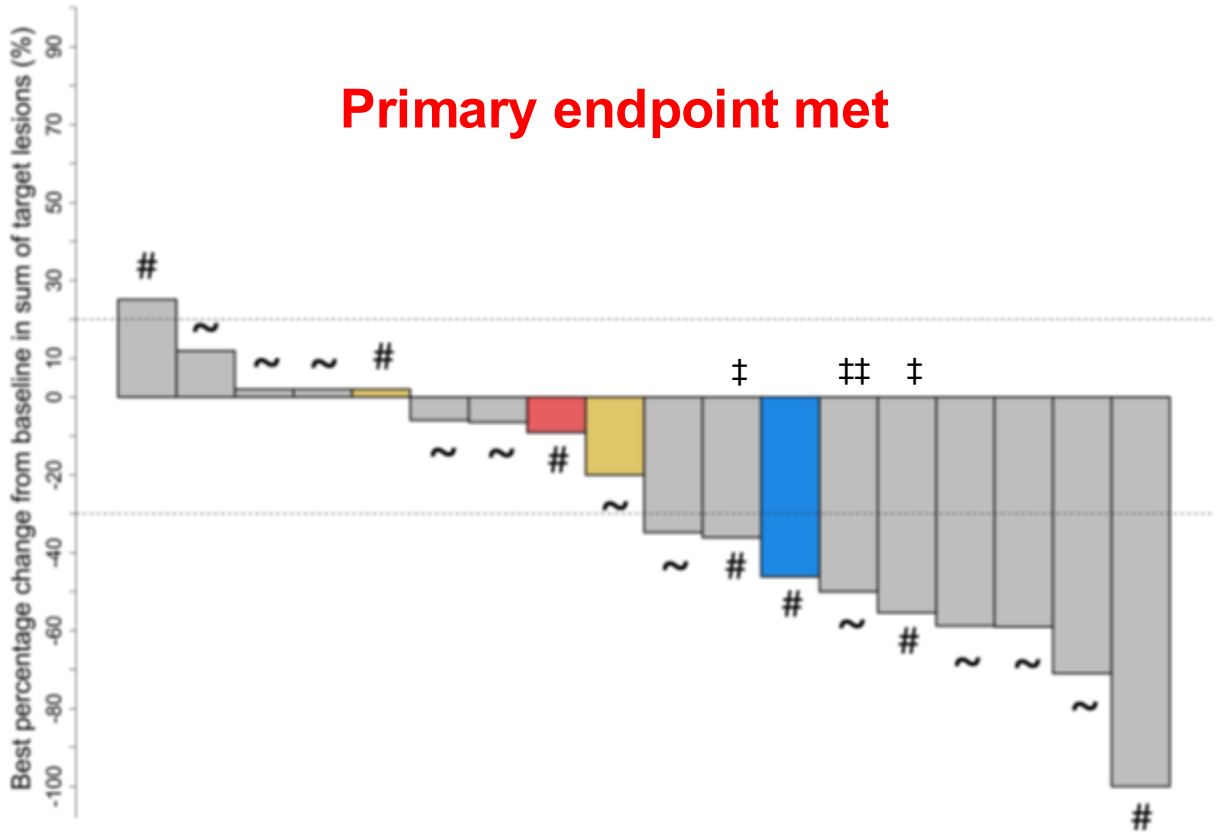

Status of brain metastases:

~ Newly diagnosed

\# Progressive after local therapy

Activating driver mutations

- Non-mutated
- *EGFR* (common)
- *EGFR* (uncommon)
- *KRAS G12C*

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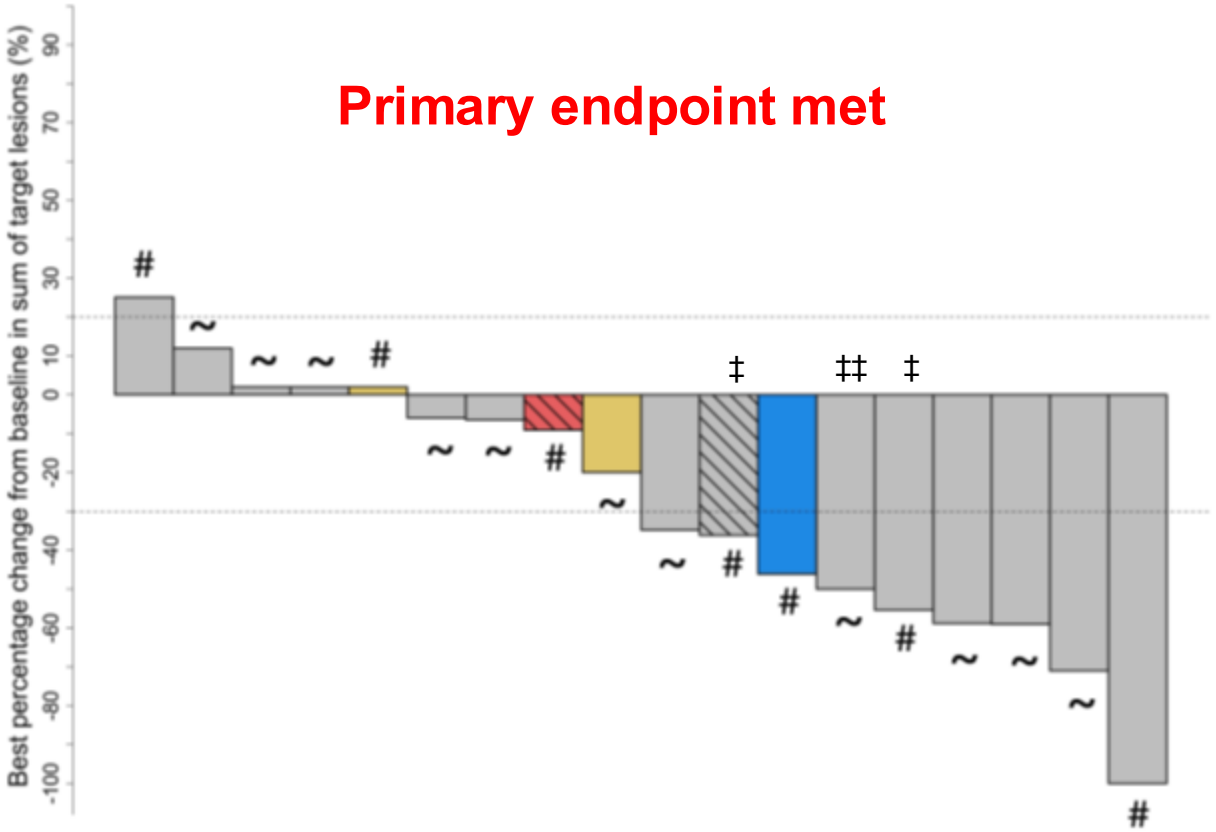

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Histologic type

- Squamous
- Non-squamous

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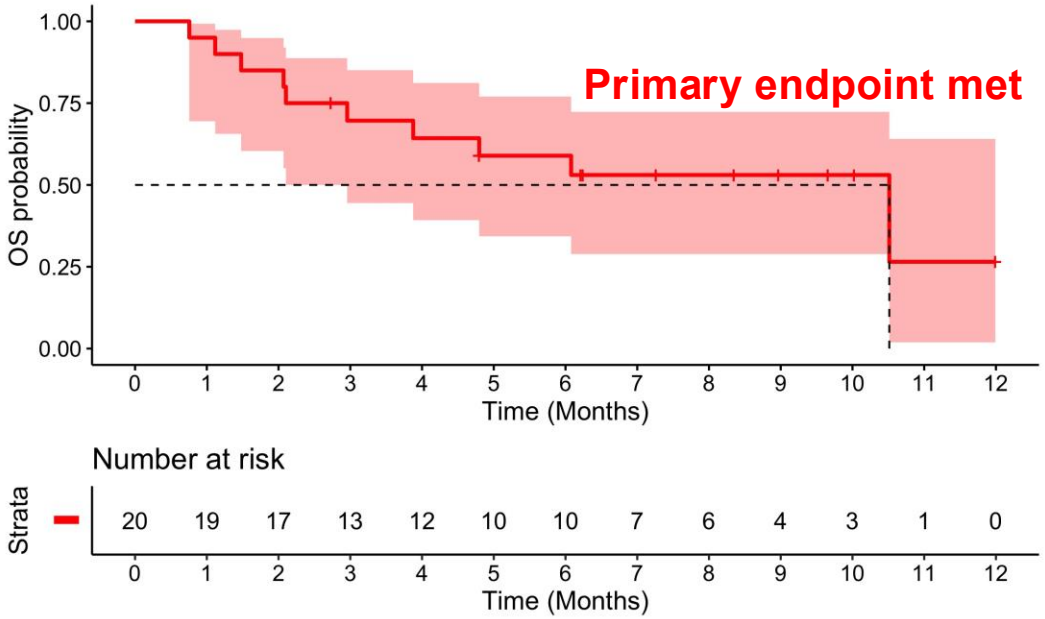
Primary endpoint: Cohort 3 (LMD from solid tumors)

- Median follow-up: 5.4 (range: 0.8-12.0) months.
- 13/20 (65%) patients alive after 3 months.



Events	3-month OS (95%CI), %	6-month OS (95%CI), %
10/20	69.6 (44.5-85.1)	58.9 (34.3-77.0)

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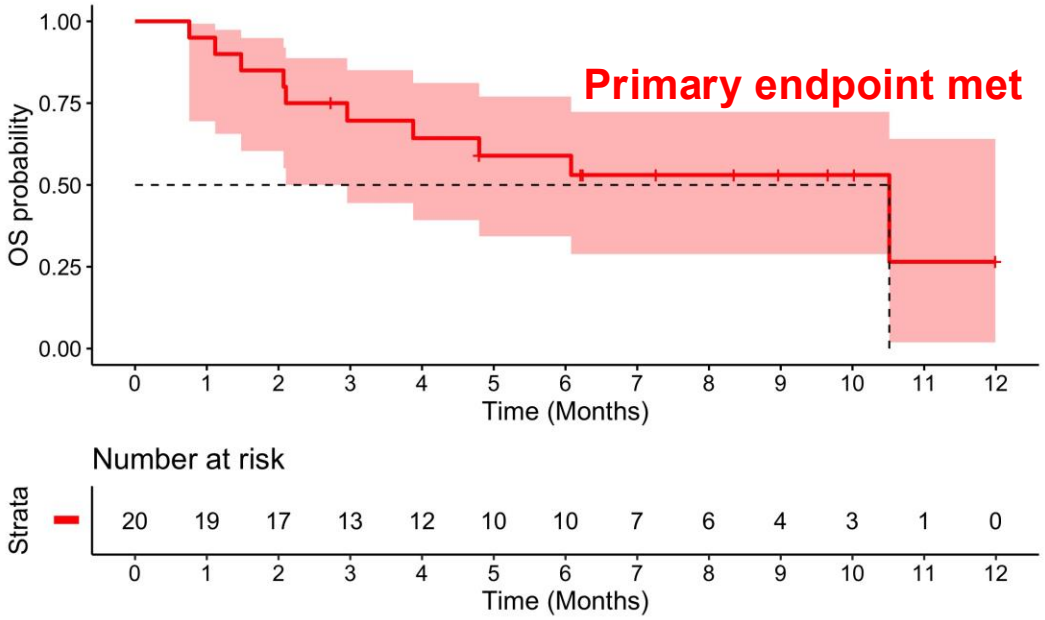

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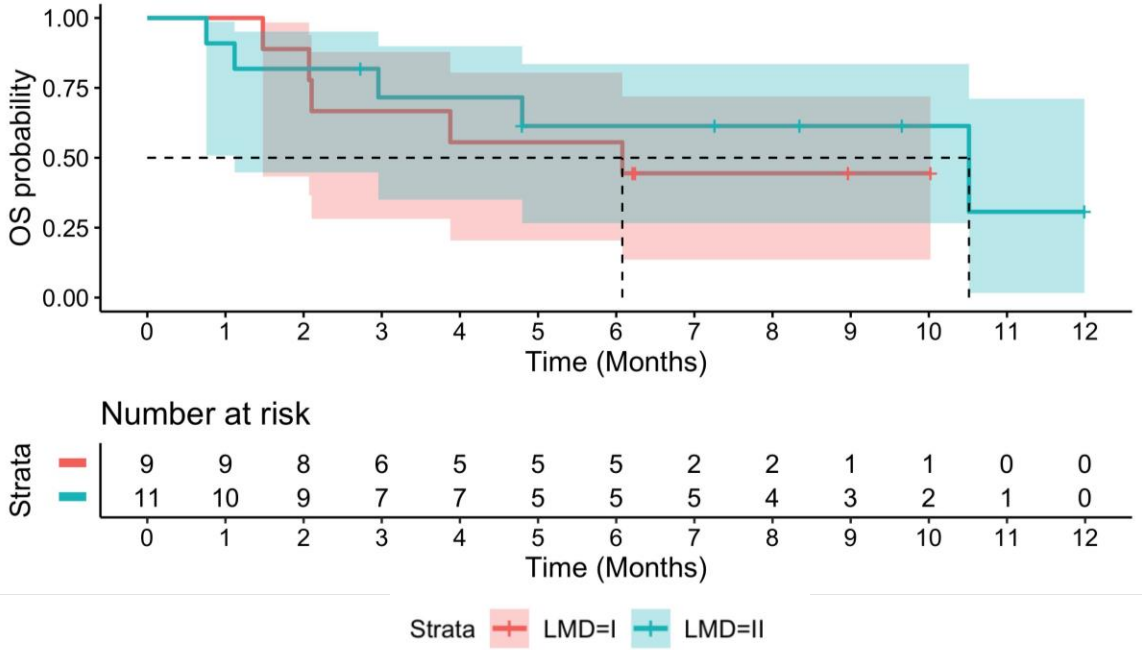
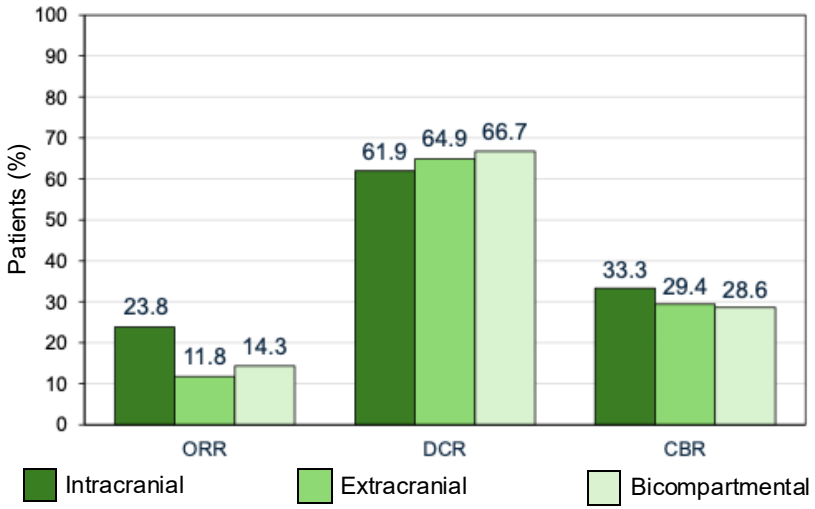


LMD type	Events	3-month OS (95%CI), %	6-month OS (95%CI), %
I	5/9	66.7 (28.2-87.8)	55.6 (20.4-80.5)
II	5/11	71.6 (35.0-89.9)	61.4 (26.6-83.5)

Secondary efficacy endpoints

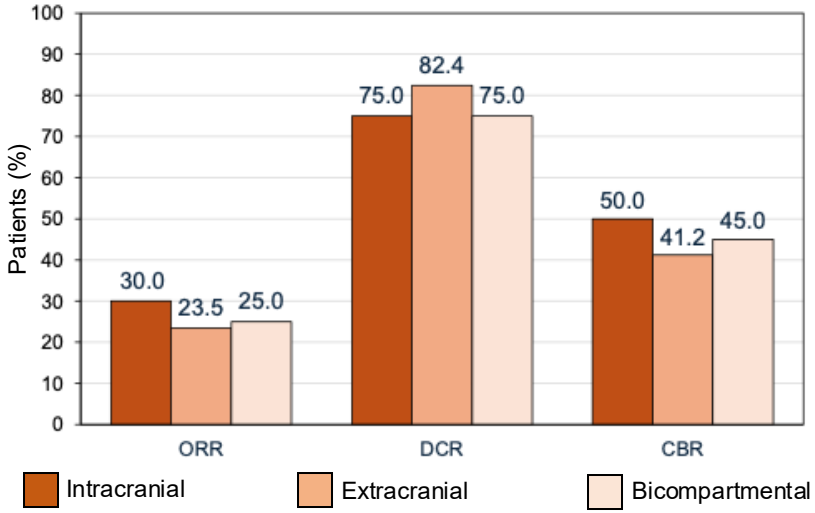
Cohort 1 (mBC with BMs)



Lesions	Events	mPFS (95%CI), months
Intracranial	14/21	4.0 (1.4-8.5)
Extracranial	9/21	4.7 (1.8-NR)
Bicompartmental	12/21	4.3 (1.6-8.5)

Events	mOS (95%CI), months
7/21	NR (5.9-NR)

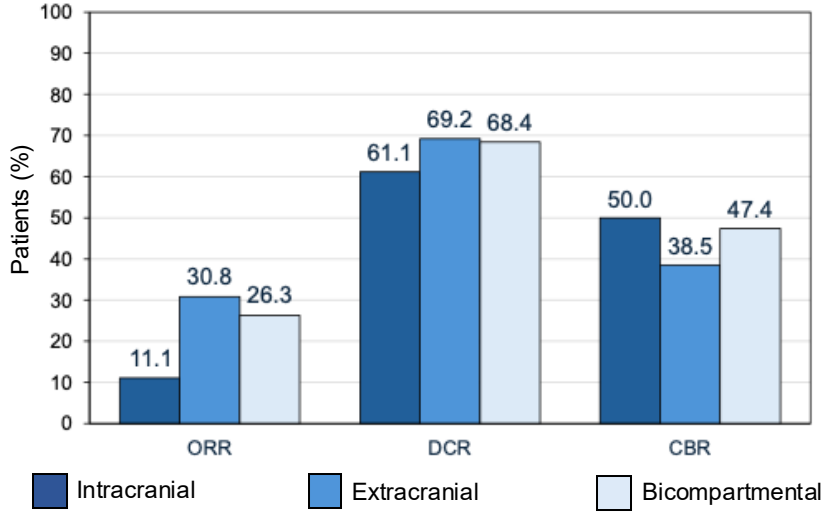
Cohort 2 (aNSCLC with BMs)



Lesions	Events	mPFS (95%CI), months
Intracranial	11/20	4.8 (2.1-NR)
Extracranial	11/20	8.1 (1.7-NR)
Bicompartmental	12/20	6.7 (2.2-9.6)

Events	mOS (95%CI), months
9/20	6.7 (4.1-NR)

Cohort 3 (LMD from solid tumors)

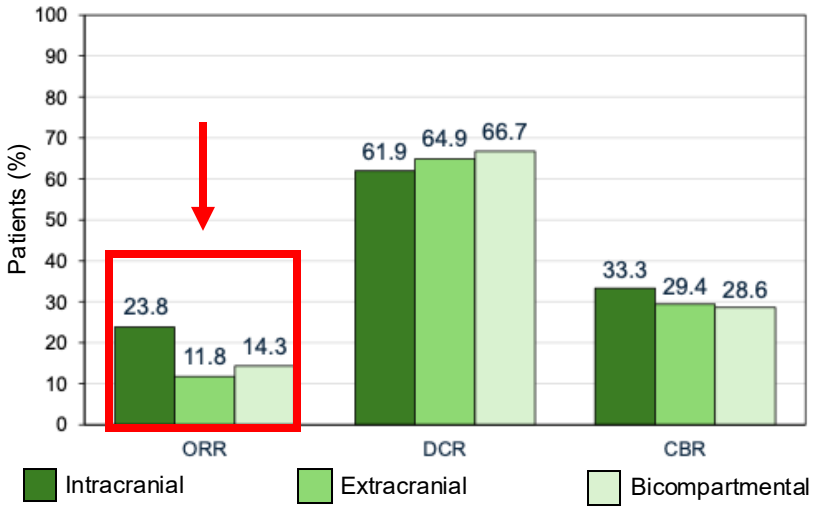


Lesions	Events	mPFS (95%CI), months
Intracranial	9/20	9.9 (1.6-NR)
Extracranial	10/20	6.8 (2.1-NR)
Bicompartmental	12/20	6.2 (3.0-NR)

Events	mOS (95%CI), months
10/20	10.5 (2.1-NR)

Secondary efficacy endpoints

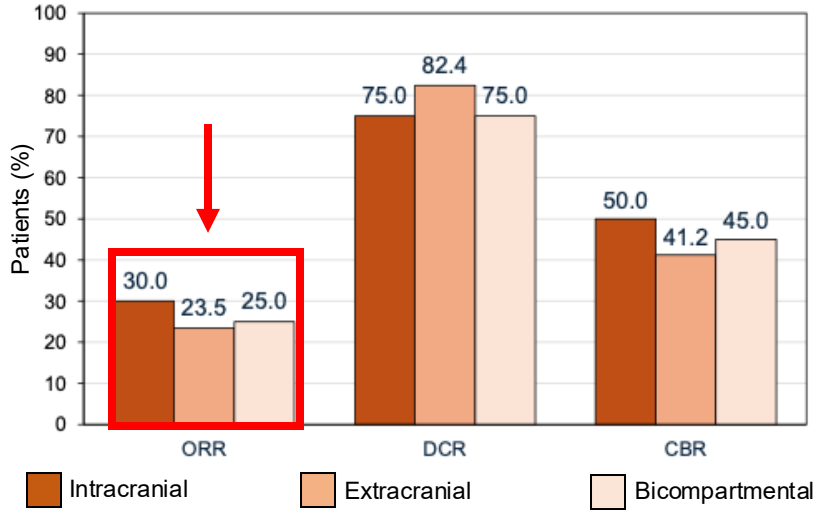
Cohort 1 (mBC with BMs)



Lesions	Events	mPFS (95%CI), months
Intracranial	14/21	4.0 (1.4-8.5)
Extracranial	9/21	4.7 (1.8-NR)
Bicompartmental	12/21	4.3 (1.6-8.5)

Events	mOS (95%CI), months
7/21	NR (5.9-NR)

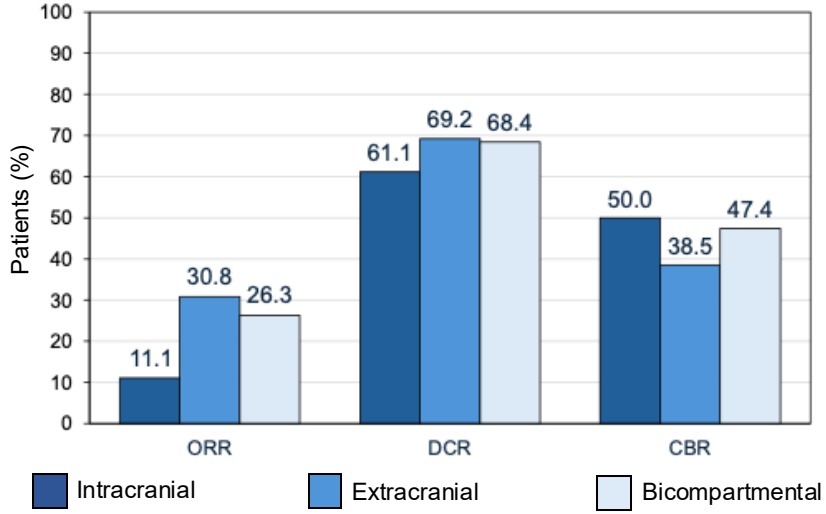
Cohort 2 (aNSCLC with BMs)



Lesions	Events	mPFS (95%CI), months
Intracranial	11/20	4.8 (2.1-NR)
Extracranial	11/20	8.1 (1.7-NR)
Bicompartmental	12/20	6.7 (2.2-9.6)

Events	mOS (95%CI), months
9/20	6.7 (4.1-NR)

Cohort 3 (LMD from solid tumors)

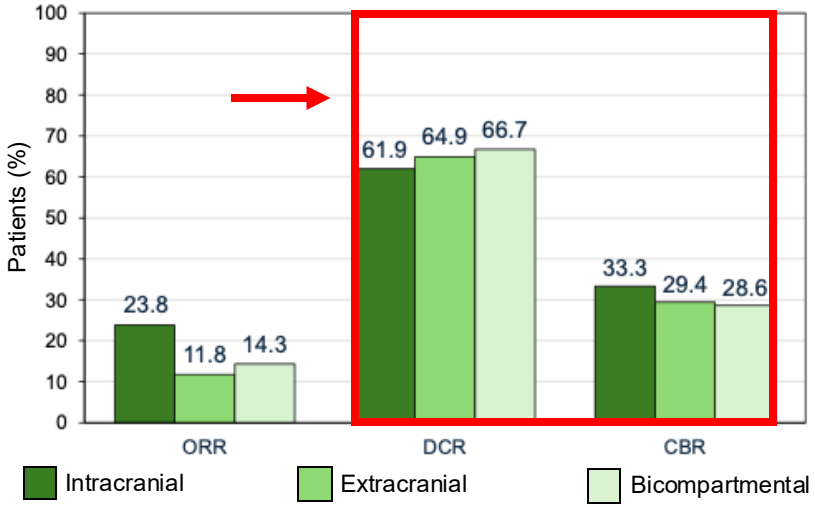


Lesions	Events	mPFS (95%CI), months
Intracranial	9/20	9.9 (1.6-NR)
Extracranial	10/20	6.8 (2.1-NR)
Bicompartmental	12/20	6.2 (3.0-NR)

Events	mOS (95%CI), months
10/20	10.5 (2.1-NR)

Secondary efficacy endpoints

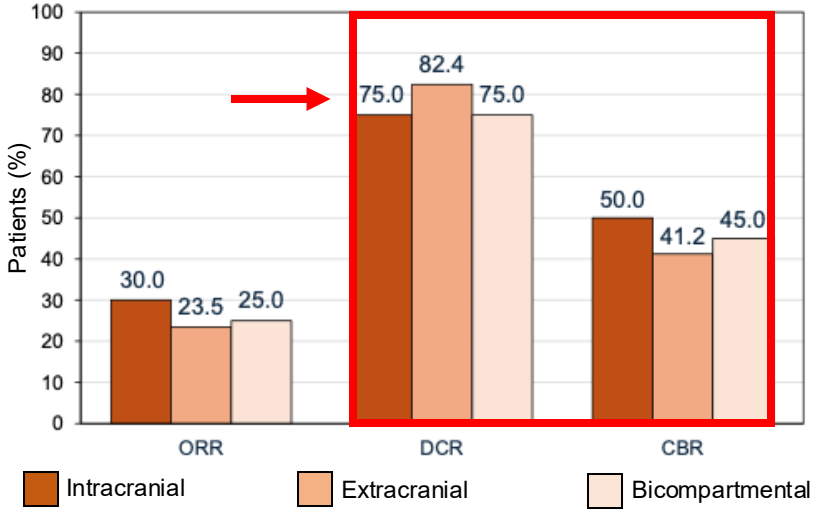
Cohort 1 (mBC with BMs)



Lesions	Events	mPFS (95%CI), months
Intracranial	14/21	4.0 (1.4-8.5)
Extracranial	9/21	4.7 (1.8-NR)
Bicompartmental	12/21	4.3 (1.6-8.5)

Events	mOS (95%CI), months
7/21	NR (5.9-NR)

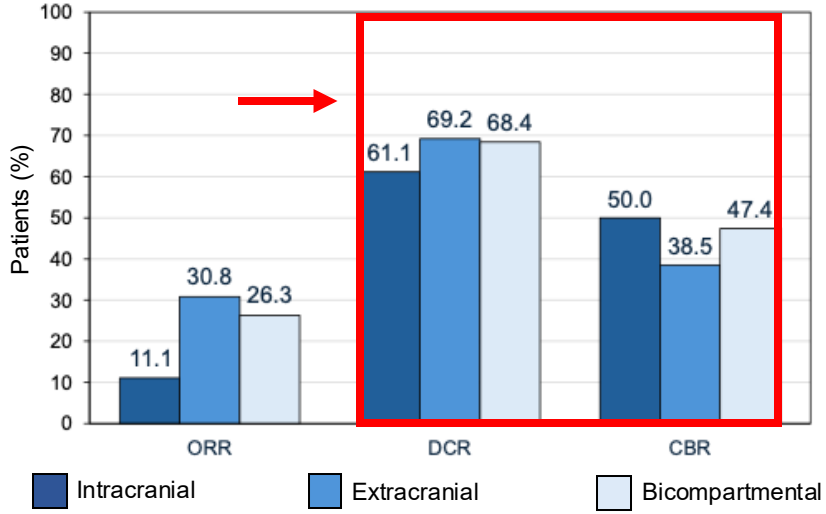
Cohort 2 (aNSCLC with BMs)



Lesions	Events	mPFS (95%CI), months
Intracranial	11/20	4.8 (2.1-NR)
Extracranial	11/20	8.1 (1.7-NR)
Bicompartmental	12/20	6.7 (2.2-9.6)

Events	mOS (95%CI), months
9/20	6.7 (4.1-NR)

Cohort 3 (LMD from solid tumors)



Lesions	Events	mPFS (95%CI), months
Intracranial	9/20	9.9 (1.6-NR)
Extracranial	10/20	6.8 (2.1-NR)
Bicompartmental	12/20	6.2 (3.0-NR)

Events	mOS (95%CI), months
10/20	10.5 (2.1-NR)

Safety

	Cohort 1 (mBC with BMs) N=21 N (%)	Cohort 2 (aNSCLC with BMs) N=20 N (%)	Cohort 3 (LMD from solid tumors) N=22 N (%)
Adverse Events (AEs)	18 (85.7)	18 (90.0)	21 (95.5)
Treatment-emergent AEs (TEAEs) HER3-DXd-related	18 (85.7) 17 (81.0)	18 (90.0) 16 (80.0)	21 (95.5) 18 (81.8)
Serious TEAEs HER3-DXd-related	6 (28.6) 1 (4.8)	10 (50.0) 4 (20.0)	11 (50.0) 4 (18.2)
Grade ≥3 TEAEs HER3-DXd-related	9 (42.9) 6 (28.6)	13 (65.0) 8 (40.0)	15 (68.2) 7 (31.8)
AEs of special interest HER3-DXd-related	1 (4.8) 0 (0)	1 (5.0) 1 (5.0)	1 (4.5) 1 (4.5)
Death due to TEAEs HER3-DXd-related	1 (4.8) 0 (0)	1 (5.0) 0 (0)	0 (0) 0 (0)
TEAEs leading to dose reduction	4 (19.0)	3 (15.0)	2 (9.1)
TEAEs leading to interruption	2 (9.5)	2 (10.0)	6 (27.3)
TEAEs leading to permanent discontinuation	1 (4.8)	1 (5.0)	1 (4.5)

Safety

	Cohort 1 (mBC with BMs) N=21 N (%)	Cohort 2 (aNSCLC with BMs) N=20 N (%)	Cohort 3 (LMD from solid tumors) N=22 N (%)
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Death due to TEAEs	1 (4.8)	1 (5.0)	0 (0)
HER3-DXd-related	0 (0)	0 (0)	0 (0)
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Safety

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Grade ≥3 TEAEs HER3-DXd-related	9 (42.9) 6 (28.6)	13 (65.0) 8 (40.0)	15 (68.2) 7 (31.8)
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Death due to TEAEs HER3-DXd-related	1 (4.8) 0 (0)	1 (5.0) 0 (0)	0 (0) 0 (0)
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Safety

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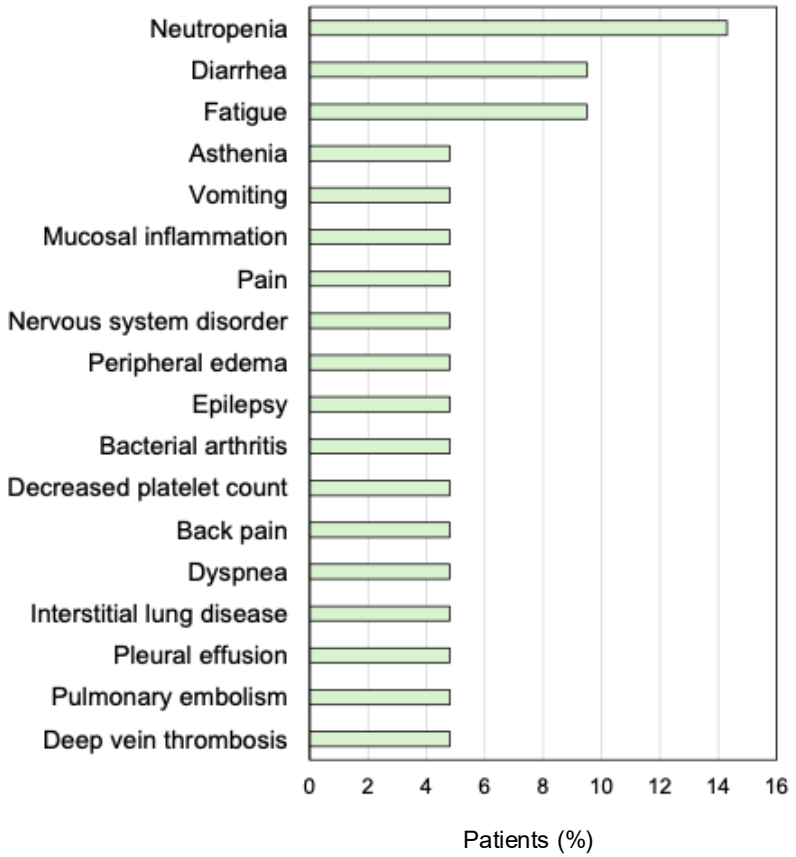
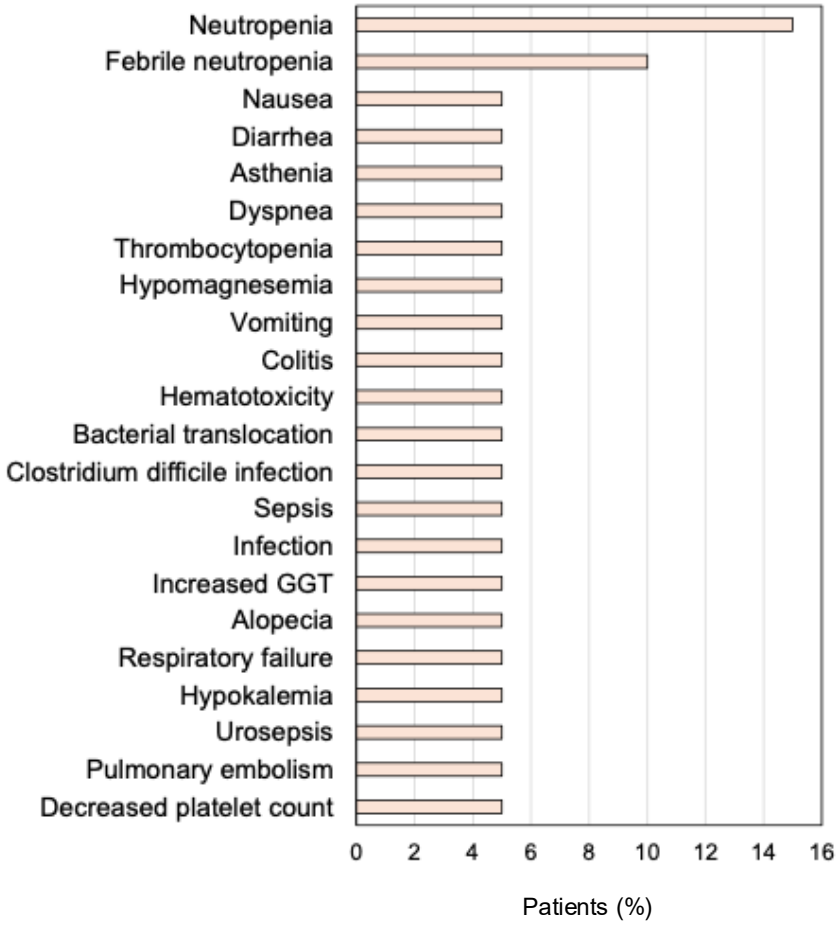
TEAEs leading to permanent discontinuation	1 (4.8)	1 (5.0)	1 (4.5)

Safety (Grade ≥3 TEAEs)

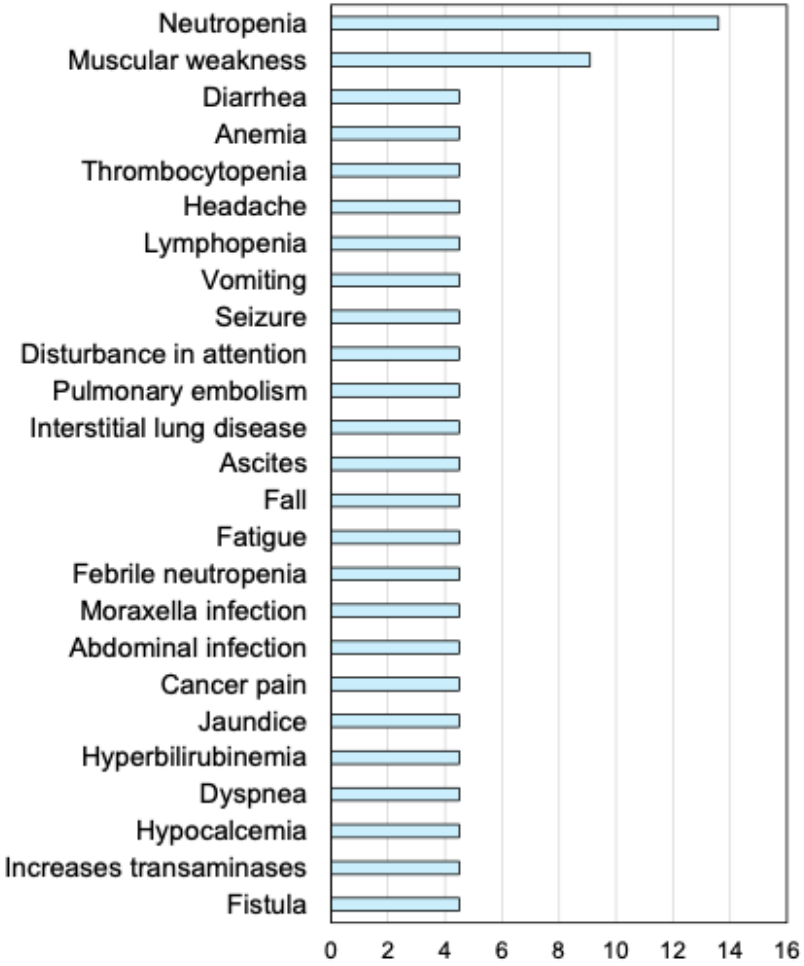
Cohort 1 (mBC with BMs)
N=21



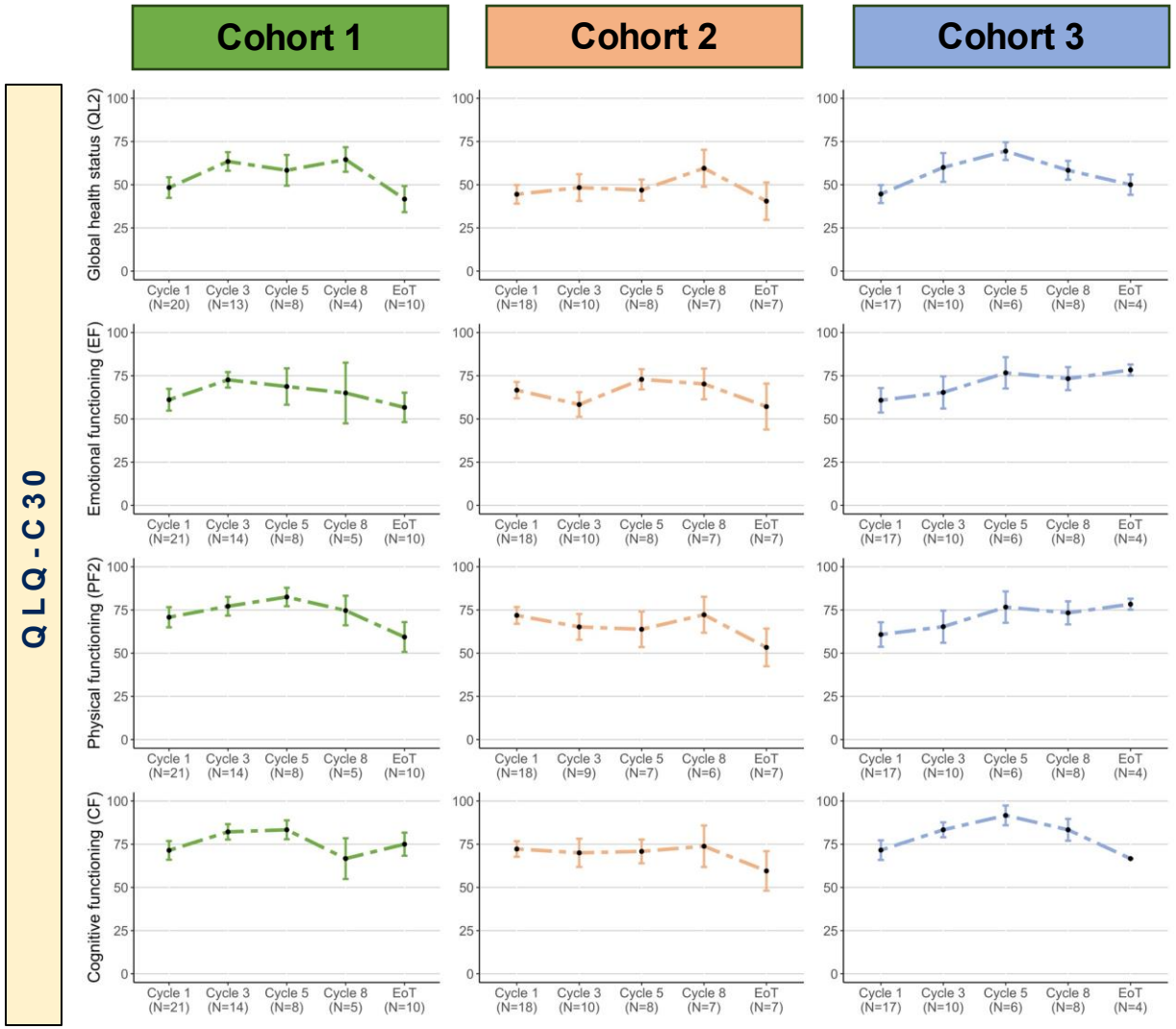
Cohort 2 (aNSCLC with BMs)
N=20

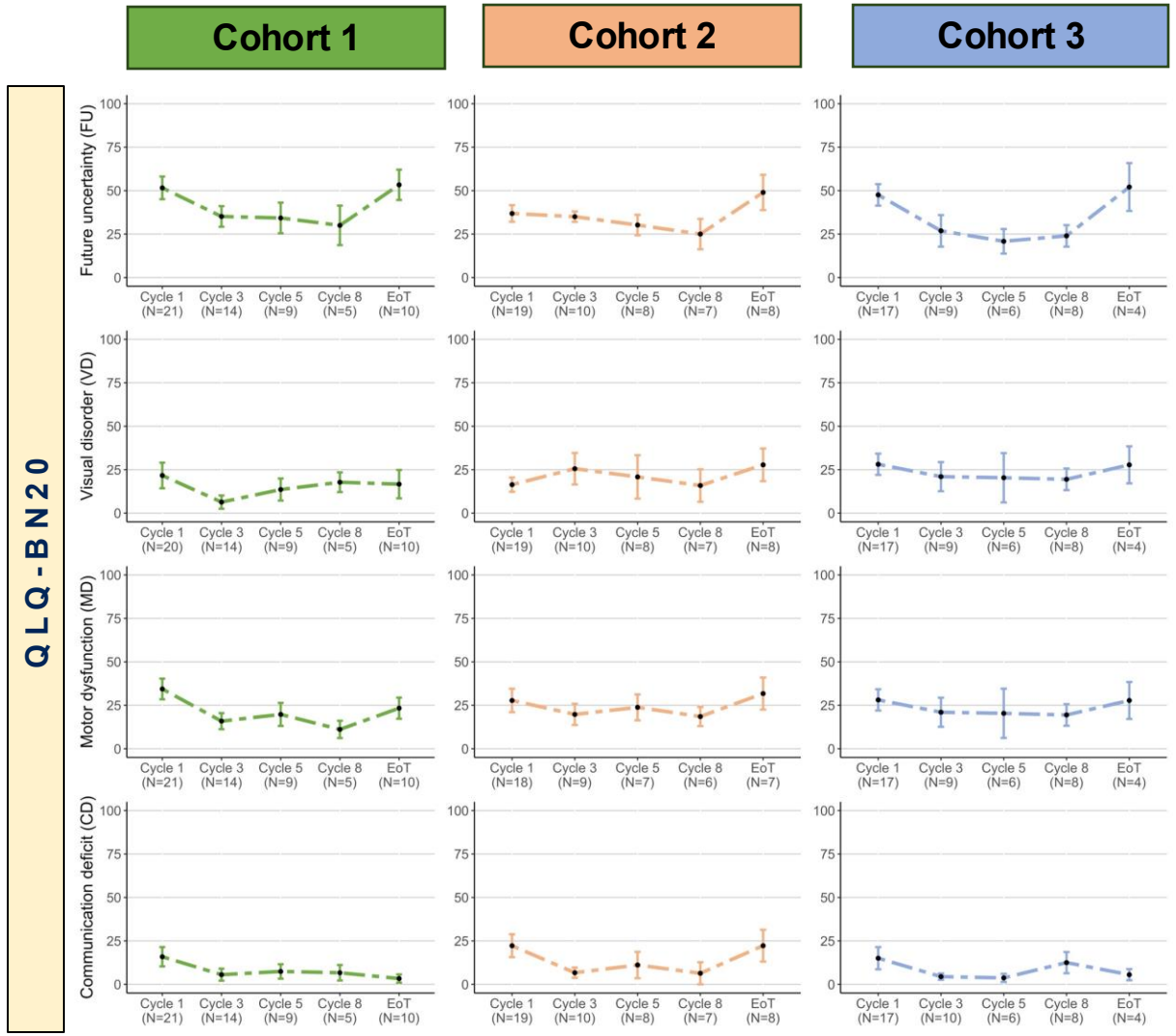


Cohort 3 (LMD from solid tumors)
N=22



Quality of life remained stable or improved





Conclusions

- HER3-DXd has CNS activity in patients with active BMs of breast and lung cancers, and LMD of solid cancers.
- Noteworthy observations:
  - HER3-DXd showed activity in BC after prior ADC and irrespective of the BC subtype.
  - HER3-DXd showed activity in NSCLC patients with *EGFR*-wild-type tumors.
- Neurological symptoms, QoL and neurocognitive function remained stable or improved during HER3-DXd treatment.
- No new safety signals were observed.

Acknowledgements

- Patients and their families.
- Trial teams of the participating sites in Austria and Spain.
- Trial sponsor: MedSIR.
- Trial funders: Daiichi-Sankyo, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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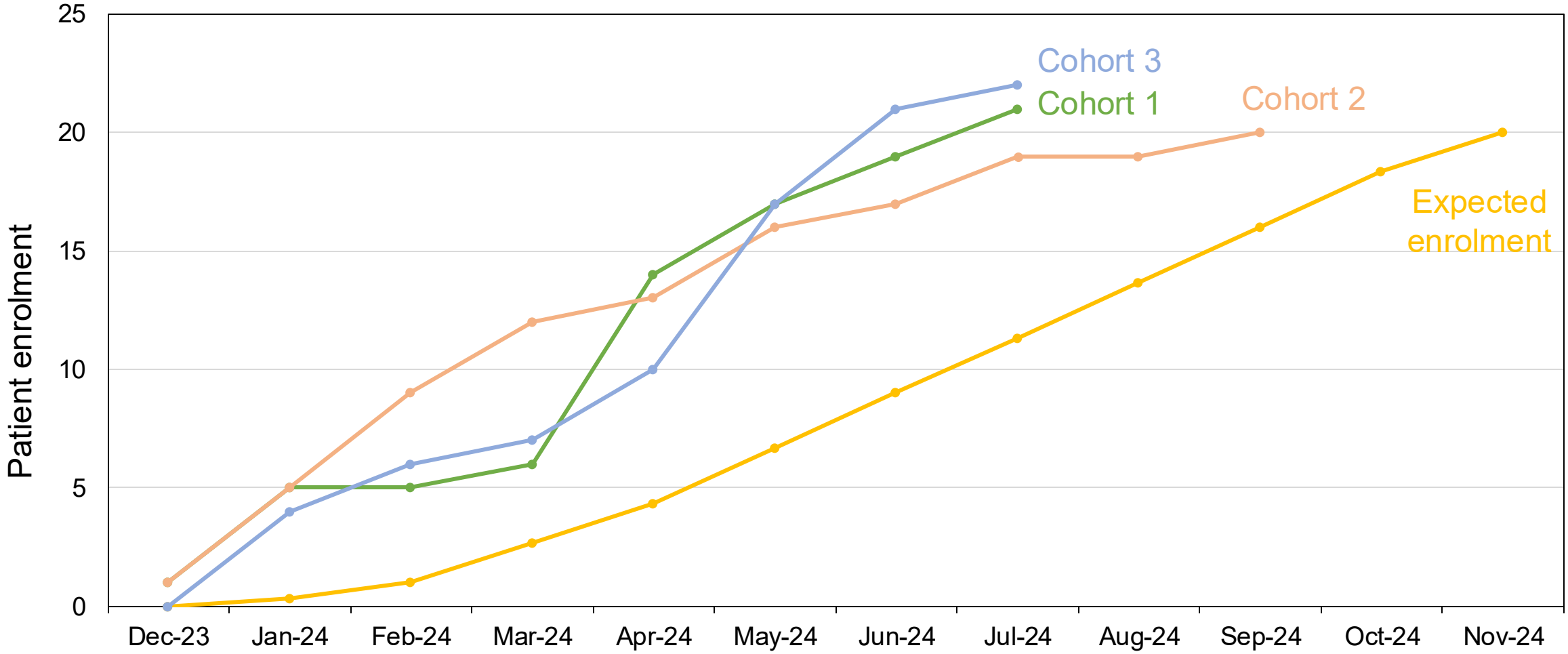
Patritumab deruxtecan in leptomeningeal metastatic disease of solid tumors: the phase 2 TUXEDO-3 trial

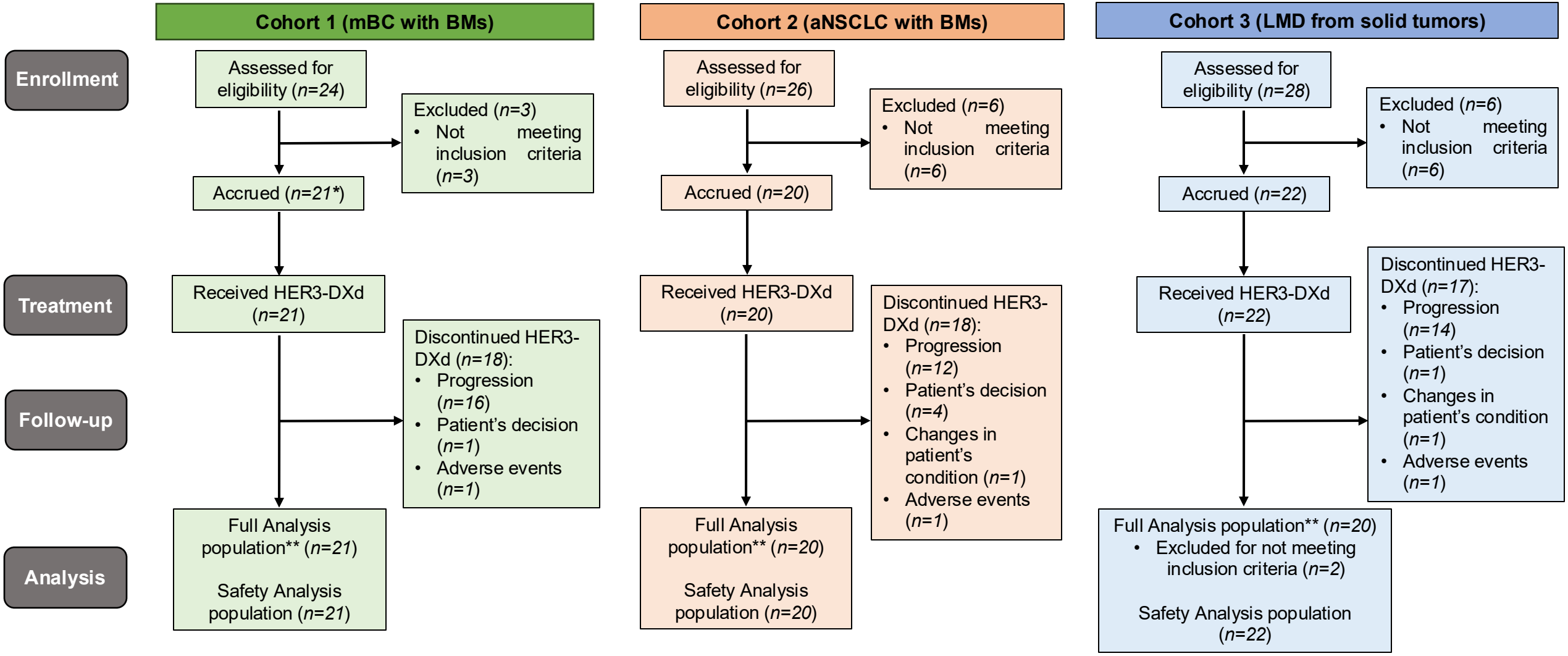
Matthias Preusser[1], Javier Garde-Noguera[2,3], Juan José García-Mosquera[4], María Gion[5,6], Richard Greil[7], Miriam Arumi[8], Manuel Ruiz-Borrego[9], Antonio Llombart-Cussac[2,3,10], María Valero[11], Javier Cortés[6,10,12,13,14], Marta Campolier[10], José Antonio Guerrero[10], Paula González-Alonso[10], Carlos Jiménez-Cortegana[10], Jose Rodriguez-Morató[10], Marta Vaz-Batista[10,15], Felicitas Oberndorfer[16], Maximilian Marhold[1], Anna Sophie Berghoff[1], Julia Furtner[17], Thorsten Fuereder[1] & Rupert Bartsch[1]

Extended data

Accrual



Consort diagrams



* The 2 last patients were enrolled in different sites simultaneously. Both were finally decided to be included in this trial.

** Full analysis population: Patients who meet selection criteria and receive at least one dose of study treatment.

Neurological symptoms

	Cohort 1 (mBC with BMs) N=21 N (%)	Cohort 2 (aNSCLC with BMs) N=20 N (%)	Cohort 3 (LMD from solid tumors) N=20 N (%)
Neurological symptoms at baseline			
No	13 (61.9)	12 (60.0)	8 (40.0)
Yes	8 (38.1)	8 (40.0)	12 (60.0)
Best neurological response*			
Neurological response	0 (0)	0 (0)	2 (10)
Neurological stability	17 (81.0)	12 (60.0)	11 (55.0)
Neurological progression	0 (0)	0 (0)	0 (0)
Not evaluated	4 (19.0)	8 (40.0)	7 (35.0)

* As per NANO scale.

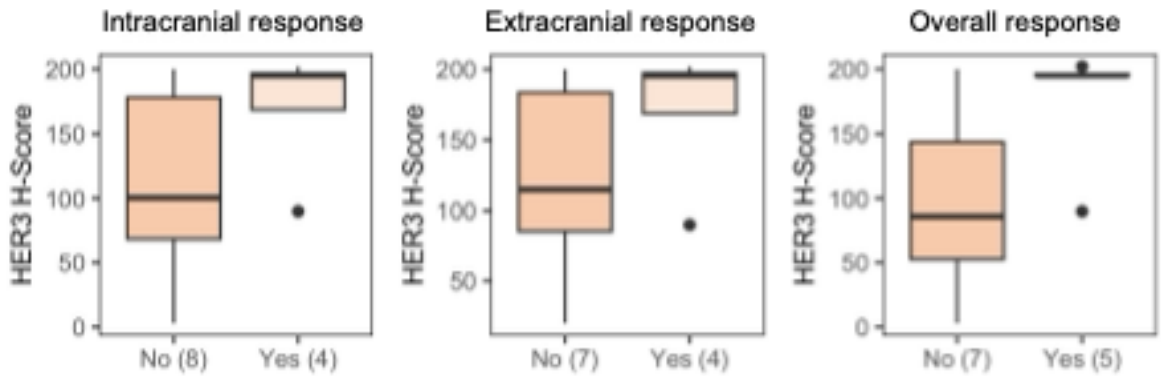
Neurological response: Improvement of ≥2 level in at least one domain, without worsening in others, from baseline or best function level, and not due to medication change or recovery from a comorbidity. Neurological stability: Neurologic function does not meet criteria for neurologic response, progression, non-evaluable, or not assessed. Neurological progression: Worsening of ≥2 level from baseline or best function in ≥1 domain, or worsening to the highest score in ≥1 domain, attributed to tumor progression (excluding medication changes or comorbidity).

HER3 expression

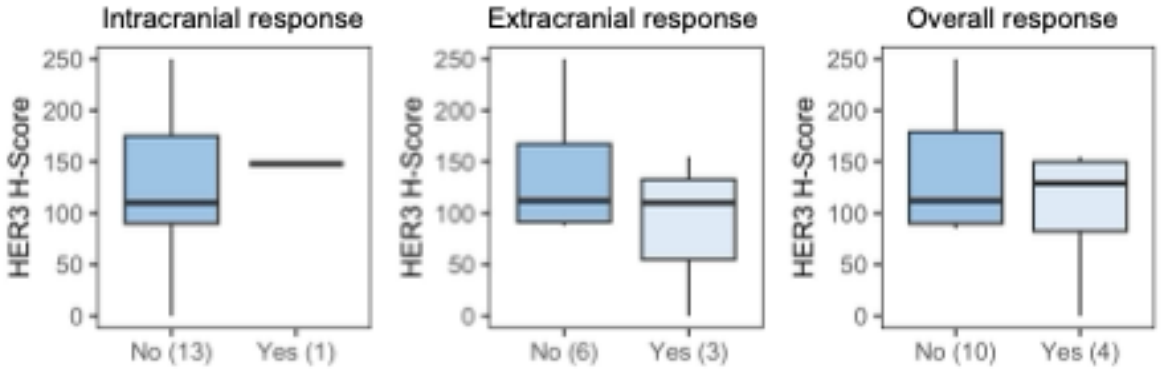
- There were no associations between HER3 expression and treatment response.

Cohort 1 (mBC with BMs)

Cohort 2 (aNSCLC with BMs)



Cohort 3 (LMD from solid tumors)



Cohort	Tumor tissue from CNS sites	Tumor tissue from non-CNS sites
1	3	14
2	1	11
3	2	13

The evaluation of HER3 expression by immunohistochemistry was performed using the anti-HER3 clone SP438 (Roche Diagnostics).