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Final results of the TUXEDO-3 phase II trial of patritumab deruxtecan (HER3-DXd) in active brain metastases and leptomeningeal disease

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Disclosures

- **Honoraria:** Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group, CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, AstraZeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, MSD, Tocagen, Adastra, Gan & Leen Pharmaceuticals, Janssen, Servier, Miltenyi, Böhringer-Ingelheim, Telix, Medscape, OncLive, Medac, MEDSIR, Nerviano Medical Sciences, ITM Oncologics GmbH, AdAcAp, Crinetics.

- **Consulting or advisory role:** Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group, CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, AstraZeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, MSD, Tocagen, Adastra, Gan & Leen Pharmaceuticals, Janssen, Servier, Miltenyi, Böhringer-Ingelheim, Telix, Medscape, OncLive, Medac, MEDSIR, Nerviano Medical Sciences, ITM Oncologics GmbH, AdAcAp, Crinetics.

- **Travel, accomodation, and expenses:** Bristol-Myers Squibb, Novartis, Mundipharma, Servier, Miltenyi, Roche, Daiichi Sankyo, MEDSIR, Böhringer-Ingelheim, Telix, Medscape.

Background

- Brain metastases (BMs) and leptomeningeal disease (LMD) are frequent in breast and lung cancers and they are linked to poor outcomes, with LMD associated with particularly short survival, highlighting the need for novel therapies[1,2].
- HER3 is overexpressed in CNS metastases from breast and lung cancers, representing a promising therapeutic target[3,4].
- Antibody-drug conjugates (ADCs) have demonstrated CNS activity in BMs and LMD[5-8], providing the rationale for evaluating patritumab deruxtecan (HER3-DXd).
- TUXEDO-3 (NCT05865990) evaluated the activity and safety of HER3-DXd in:
  - Newly diagnosed BMs or BMs progressing after local therapy (active BMs) from metastatic breast cancer (mBC; cohort 1).
  - Active BMs from advanced non-small cell lung cancer (aNSCLC; cohort 2).
  - LMD arising from any solid tumor malignancy (cohort 3).

ADCs, antibody-drug conjugates; aNSCLC, advanced non-small cell lung cancer; BMs, brain metastases; CNS, central nervous system; HER3, human epidermal growth factor receptor 3; HER3-DXd, patritumab deruxtecan; LMD, leptomeningeal disease; mBC, metastatic breast cancer.

1. Preusser M et al. *Curr Opin Neurol* (2012); 2. Le Rhun E et al. *ESMO Open* (2019); 3. Garret JT et al. *Nat Rev Clin Oncol* (2025); 4. Tomasich E et al. *Clin Cancer Res* (2025); 5. Bartsch R et al. *Nat Med* (2022); 6. Niikura N et al. *NPJ Breast Cancer* (2023); 7. Harbeck N et al. *Nat Med* (2024); 8. Vaz Batista et al. *Med* (2025).

Study design

- Open label, single-arm, three-cohort, non-comparative, Simon's two-stage design, phase II trial.

Key inclusion criteria

- Age ≥18 years
- Histologically documented mBC (cohort 1), aNSCLC (cohort 2), or advanced solid tumors with LMD (cohort 3).
- KPS ≥70%.
- ECOG PS ≤2.
- LVEF ≥50 %.
- Newly diagnosed BMs or BMs progressing after local therapy (cohorts 1 and 2).
- ≥1 measurable brain lesions (≥10 mm; cohorts 1 and 2).
- ≥1 line of systemic treatment in the advanced setting (cohorts 1 and 2).

COHORT 1
mBC with active BMs

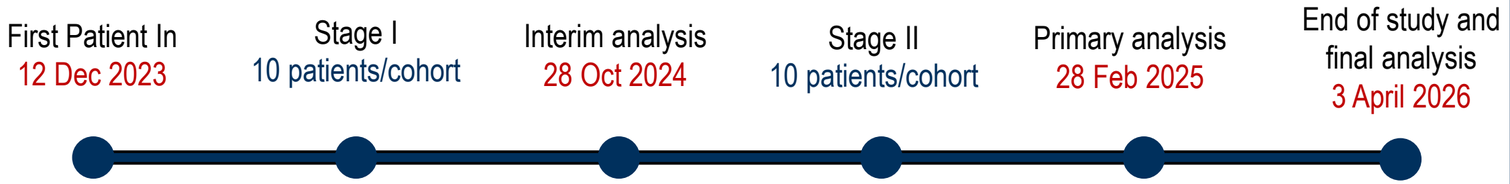
n = 21*

COHORT 2
aNSCLC with active BMs

n = 20

COHORT 3
LMD from solid tumors

n = 22**



HER3-DXd 5.6 mg/kg IV Q3W

Until disease progression, unacceptable toxicity, or withdrawal for any reason

* The last two patients from cohort 1 were enrolled simultaneously at different sites and both were finally included in the study.

** 20 patients were initially treated with HER3-DXd; however, 2 were subsequently determined not to meet the inclusion criteria. They were excluded from the full analysis set but included in the safety analysis set. 2 additional patients were enrolled.

Primary endpoints

- Intracranial ORR (cohorts 1 and 2).
- 3-month OS rate (cohort 3).

Key secondary endpoints

- ORR, CBR, DCR, PFS, DoR, TTR for intracranial, extracranial, and bicompartmental lesions as per central review.
- OS.
- Safety and tolerability (CTCAE v.5.0).
- Quality of life and neurocognitive function (EORTC QLQ-C30, and BN20).
- Neurologic function (NANO scale).

Key exploratory endpoints

- Association between HER3 expression with efficacy endpoints.

aNSCLC, advanced non-small cell lung cancer; BMs, brain metastases; CBR, clinical benefit rate; CTCAE v.5.0, Common Terminology Criteria for Adverse Events version 5.0; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HER3, human epidermal growth factor receptor 3; HER3-DXd: patritumab deruxtecan; IV, intravenously; KPS, Karnofsky Performance Status; LMD, leptomeningeal disease; LVEF, left ventricular ejection fraction; mBC, metastatic breast cancer; NANO, Neurologic Assessment in Neuro-Oncology; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QW3, once every 3 weeks; TTR, time to response.

Baseline characteristics

	Cohort 1 (mBC with active BMs) N=21 N (%)	Cohort 2 (aNSCLC with active 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)
Sex			
Female	21 (100.0)	10 (50.0)	18 (90.0)
Male	0 (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 *			
Progressing after local therapy	15 (71.4)	13 (65.0)	0 (0.0)
Untreated	6 (28.6)	7 (35.0)	20 (100.0)
Neurologic symptoms at baseline			
No	13 (61.9)	12 (60.0)	8 (40.0)
Yes	8 (38.1)	8 (40.0)	12 (60.0)
Previous treatment lines in advanced disease, median (range)	4 (1 - 13)	1.5 (1 - 5)	2 (0 - 6)

* BMs for cohorts 1 and 2. and LMD for cohort 3.

aNSCLC, advanced non-small cell lung cancer; BMs, brain metastases; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LMD, leptomeningeal disease; mBC, metastatic breast cancer.

Baseline characteristics

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

	Cohort 2 (aNSCLC with active BMs) N=20 N (%)
Lung cancer phenotype	
Histological	
Non-squamous	17 (85.0)
Squamous	3 (15.0)
Activating genomic alteration	
Negative	15 (75.0)
Positive	5 (25.0)
KRAS G12C	1 (5.0)
EGFR	4 (20.0)

	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	1 (8.3)
Luminal	5 (41.7)
Triple-negative	6 (50.0)
Lung cancer phenotype	
Histological	
Non-squamous	5 (83.3)
Squamous	1 (16.7)
Activating genomic alteration	
Negative	16 (80.0)
Positive	4 (20.0)
KRAS G12C	1 (5.0)
EGFR	3 (15.0)

aNSCLC, advanced non-small cell lung cancer; BMs, brain metastases; HER2, human epidermal growth factor receptor 2; LMD, leptomeningeal disease; mBC, metastatic breast cancer.

Primary endpoint outcomes

Cohort 1 (mBC with active BMs)

23.8% intracranial ORR as per RANO-BM criteria

Bartsch R et al. *Lancet Oncol,* 2025

Cohort 2 (aNSCLC with active BMs)

30.0% intracranial ORR as per RANO-BM criteria

Fuereder T et al. *Lancet Oncol,* 2025

Cohort 3 (LMD from solid tumors)

65.0% 3-month OS rate

Preusser M et al. *Nat Med,* 2025

	Intracranial, % (n=21)	Extracranial, % (n=19*)	Bicompartmental, % (n=21)
ORR	19.0	10.5	14.3
DCR	61.9	57.9	66.7

	Intracranial, % (n=18*)	Extracranial, % (n=18*)	Bicompartmental, % (n=19*)
ORR	27.8	27.8	26.3
DCR	77.8	77.8	73.7

	Intracranial, % (n=17*)	Extracranial, % (n=15*)	Bicompartmental, % (n=19*)
ORR	23.5	26.7	31.6
DCR	58.8	60.0	57.9

- We now report mature survival data together with final efficacy, safety, quality of life, and neurological outcomes.

* Patients without a valid baseline assessment or without baseline lesions in the corresponding compartment were excluded.

ADCs, antibody-drug conjugates; aNSCLC, advanced non-small cell lung cancer; BMs, brain metastases; DCR, disease control rate; LMD, leptomeningeal disease; mBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; RANO-BM: Response Assessment in Neuro-Oncology Brain Metastases..

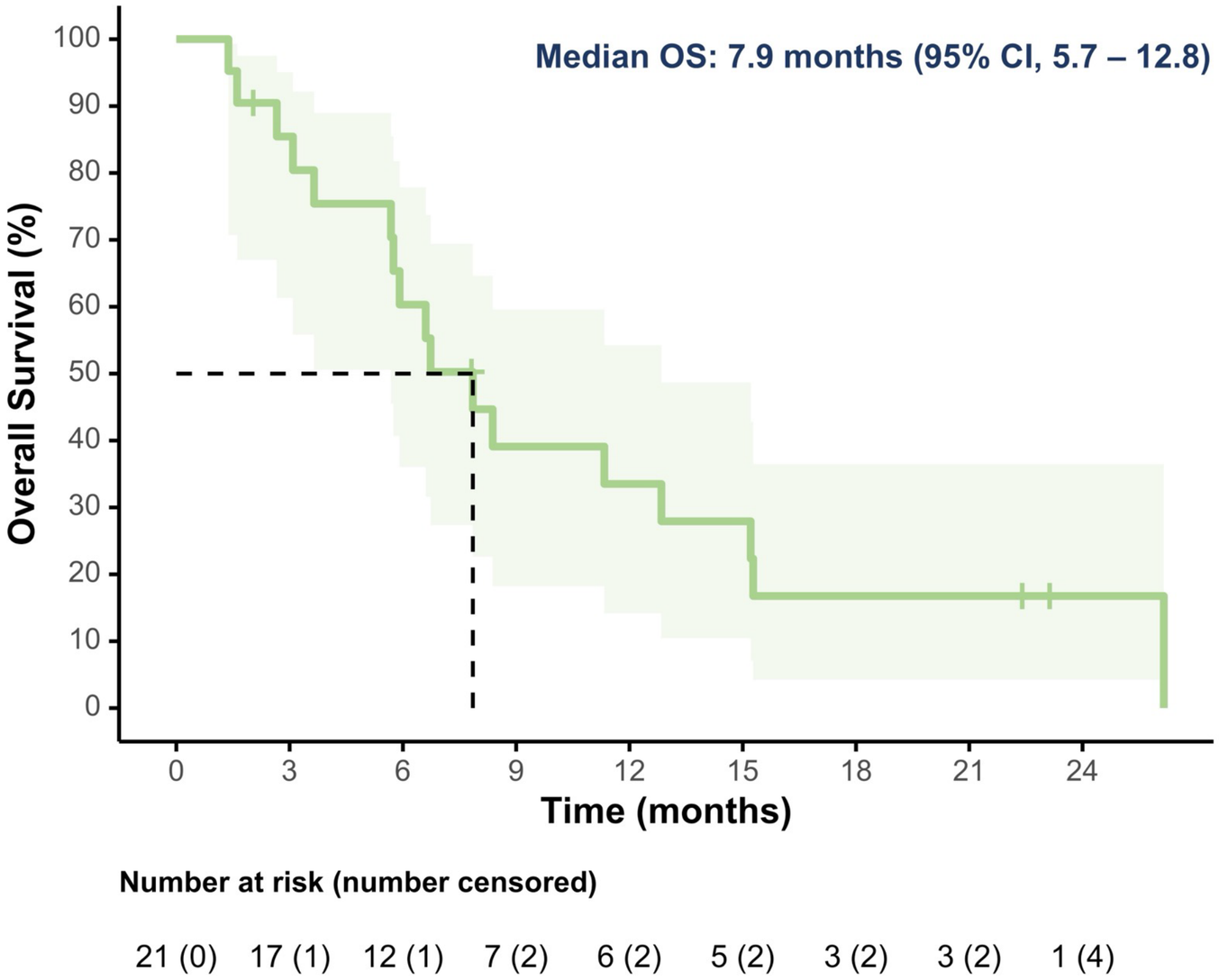
Overall survival

Cohort 1: mBC with active BMs

- Median follow-up:

  6.7 months (range, 1.4-26.2).

- Events: 81.0% (17/21).



BMs, brain metastases; CI, confidence interval; mBC, metastatic breast cancer; OS, overall survival.

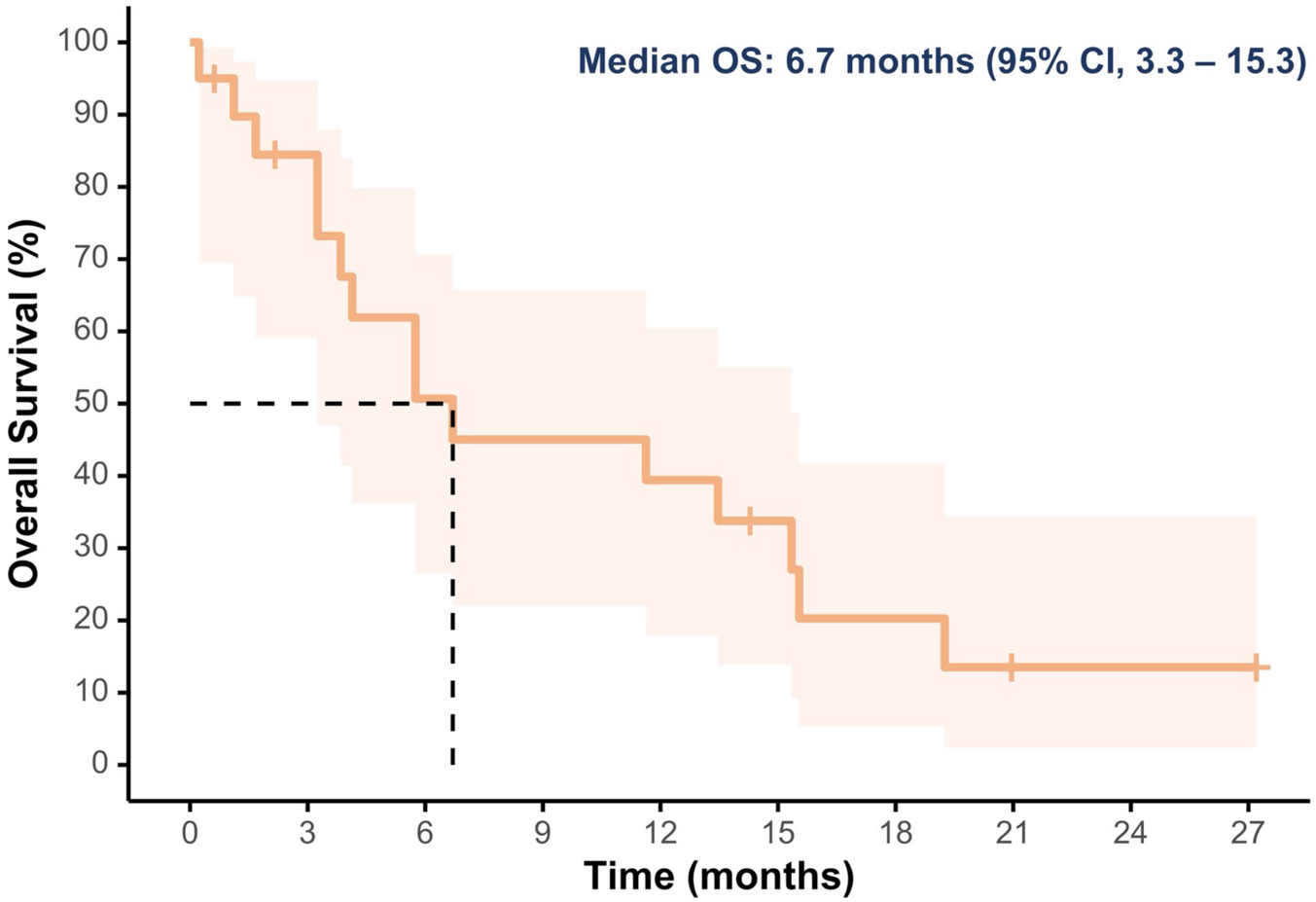
Overall survival

Cohort 2: aNSCLC with active BMs

- Median follow-up:

  5.7 months (range, 0.2-27.2).

- Events: 75.0% (15/20).



Number at risk (number censored)

20 (0)	15 (2)	9 (2)	8 (2)	7 (2)	5 (3)	3 (3)	1 (4)	1 (4)	1 (4)

CI, confidence interval; OS, overall survival.

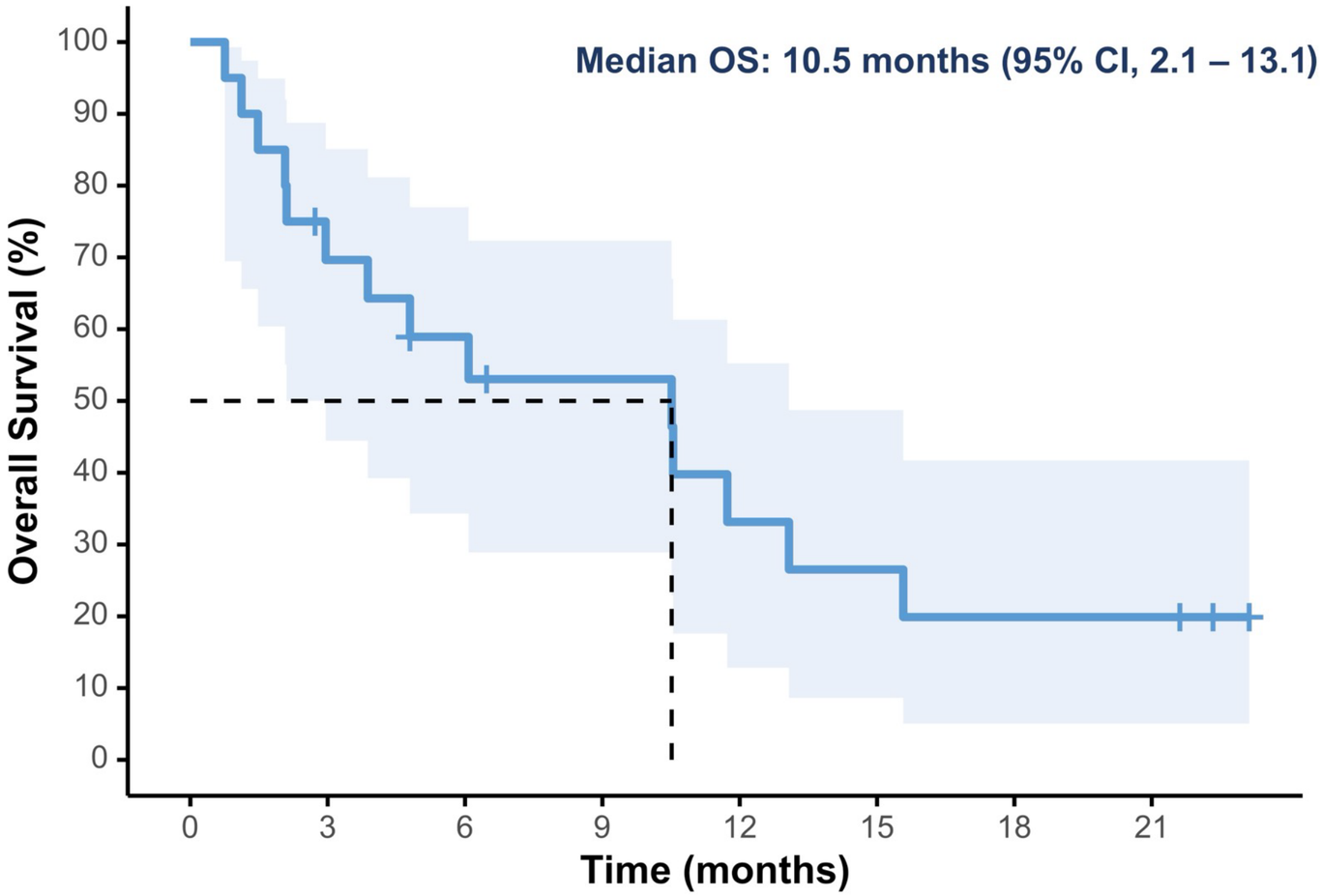
Overall survival

Cohort 3: LMD from solid tumors

- Median follow-up:

  5.4 months (range, 0.8-23.1).

- Events: 70.0% (14/20).



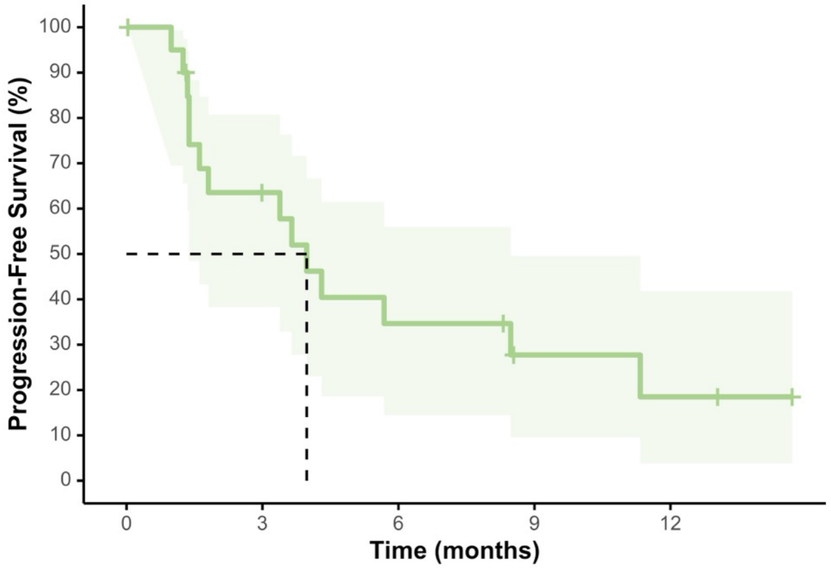
Number at risk (number censored)

20 (0)	13 (1)	10 (2)	8 (3)	5 (3)	4 (3)	3 (3)	3 (3)

CI, confidence interval; OS, overall survival.

Intracranial progression-free survival

Cohort 1 mBC with active BMs

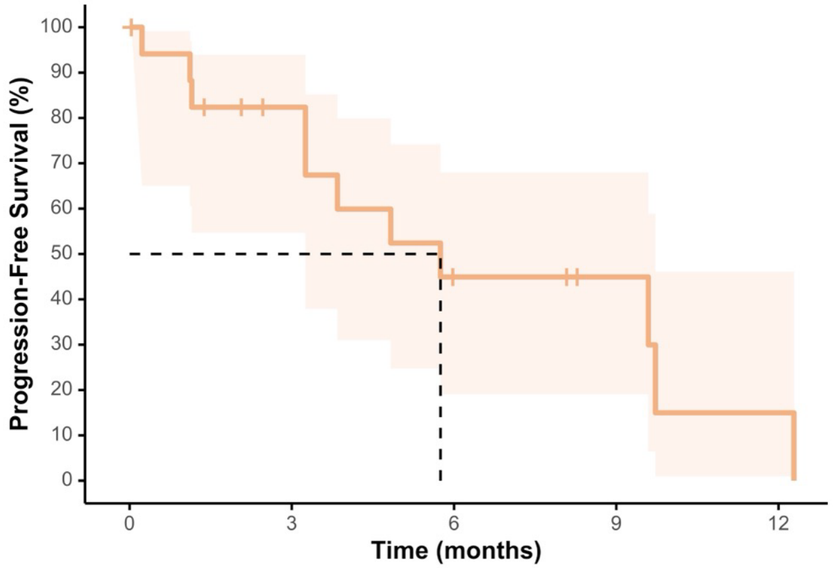


Number at risk (number censored)

21 (0)	11 (3)	6 (3)	3 (5)	2 (5)

Events/Total, %	14/21, 66.7
Median (95% CI), months	**4.0 (1.4 – 8.5)**

Cohort 2 aNSCLC with active BMs

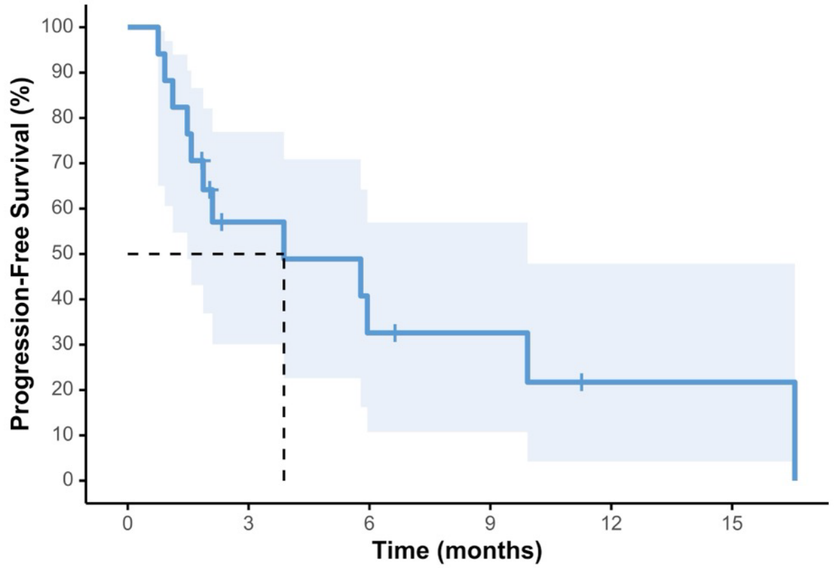


Number at risk (number censored)

18 (0)	11 (4)	5 (5)	3 (7)	1 (7)

Events/Total, %	11/18*, 61.1
Median (95% CI), months	**5.7 (3.3 – 9.7)**

Cohort 3 LMD from solid tumors



Number at risk (number censored)

17 (0)	7 (3)	4 (3)	3 (4)	1 (5)	1 (5)

Events/Total, %	12/17*, 70.6
Median (95% CI), months	**3.9 (1.5 – 9.9)**

Intracranial PFS was assessed by central review according to RANO-BM criteria. All patients with a valid baseline central assessment were included.

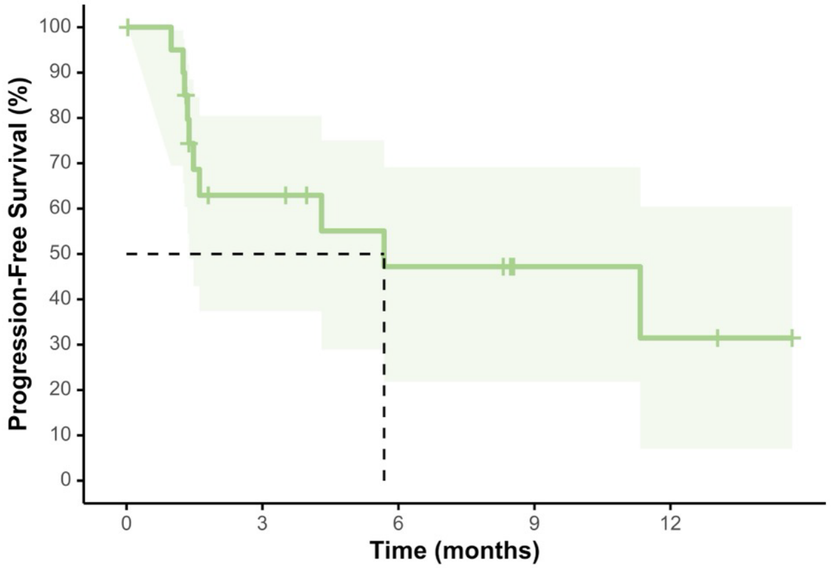
* 2 patients in cohort 2 and 3 patients in cohort 3 were excluded due to the absence of a valid baseline central assessment.

aNSCLC, advanced non-small cell lung cancer; BMs, brain metastases; CI, confidence interval; LMD, leptomeningeal disease; mBC, metastatic breast cancer; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases.

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Extracranial progression-free survival

Cohort 1 mBC with active BMs

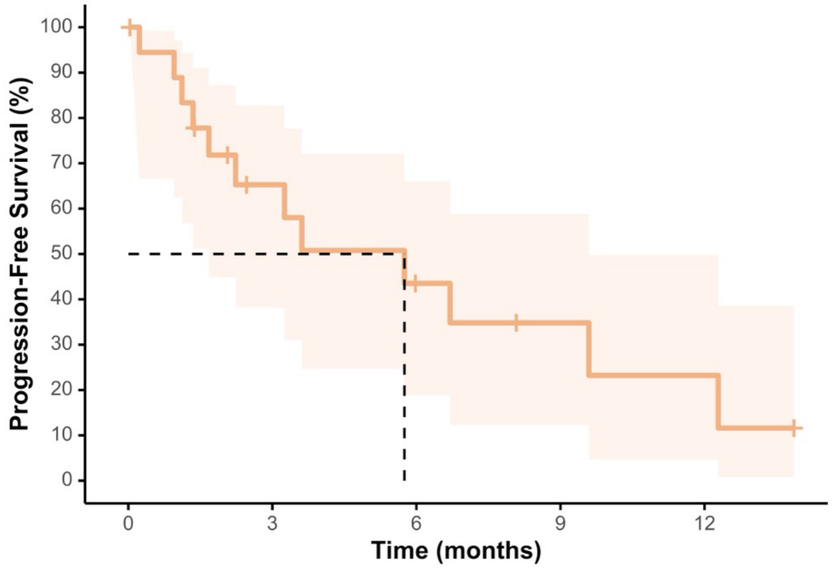


Number at risk (number censored)

21 (0)	10 (4)	6 (6)	3 (9)	2 (9)

Events/Total, %	10/21, 47.6
Median (95% CI), months	**5.7 (1.4 – NA)**

Cohort 2 aNSCLC with active BMs

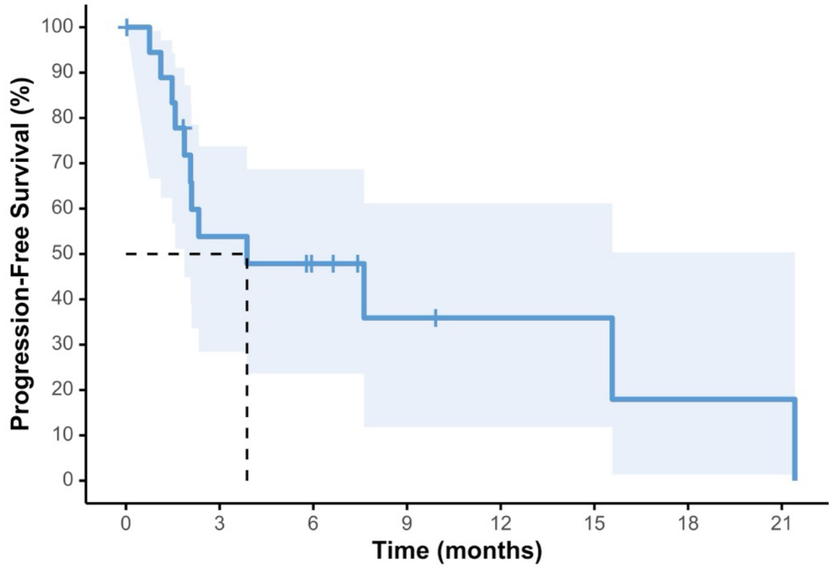


Number at risk (number censored)

20 (0)	9 (5)	5 (6)	3 (7)	2 (7)

Events/Total, %	12/20, 60.0
Median (95% CI), months	**5.7 (1.7 – 9.6)**

Cohort 3 LMD from solid tumors



Number at risk (number censored)

19 (0)	9 (2)	6 (4)	3 (6)	2 (7)	2 (7)	1 (7)	1 (7)

Events/Total, %	12/19*, 63.2
Median (95% CI), months	**3.9 (1.9 – NA)**

Extracranial PFS was assessed by central review according to RECIST v1.1. All patients with a valid baseline central assessment were included.

* 1 patient in cohort 3 was excluded due to the absence of a valid baseline central assessment.

aNSCLC, advanced non-small cell lung cancer; BMs, brain metastases; CI, confidence interval; LMD, leptomeningeal disease; mBC, metastatic breast cancer; NA, not achieved; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Survival in other LMD cohorts

Study	Year	Sample size	Treatment	Cohort	Median iPFS (months)	Median OS (months)
TUXEDO-3	2026	20	Patritumab deruxtecan	LMD from any solid tumor	3.9	10.5
Real-world	2026	30 (8 with LMD)	Sacituzumab govitecan	LMD from any mBC subtype	4.5 (LMD and/or BMs)	11.7 (all patients)
Real-world	2026	54 (4 with LMD)	Sacituzumab govitecan	LMD from TNBC	4.1	9.5 (all patients)
Real-world	2025	7	Sacituzumab govitecan	LMD from HER2-negative mBC	2.1	3.8
BLOSSOM	2024	73	Osimertinib	LMD from *EGFR*-mut NSCLC	12.5	15.6
NCT04343573	2022	42	Proton craniospinal irradiation	LMD from NSCLC and breast cancer	5.8	6.6
NCT03091478	2021	13	Pembrolizumab	LMD from solid tumors	2.9	4.9
NCT02939300	2021	18	Ipilimumab + nivolumab	LMD from solid tumors	1.9	2.9
NCT02886585	2020	20	Pembrolizumab	LMD from solid tumors	2.6	3.6
NCT02048059	2020	28	ANG1005	LMD from any mBC subtype	2.8	8.0
Metanalysis	2020	39	Intrathecal trastuzumab	LMD from HER2-positive mBC	5.2	13.2

BMs, brain metastases; HER2, human epidermal growth factor receptor 2; iPFS, intracraial progression-free survival; LMD, leptomeningeal disease; mBC, metastatic breast cancer; NSCLC, advanced non-small cell lung cancer; OS, overall survival; TNBC, triple-negative breast cancer.

Safety

Median treatment duration, months (range):

- Cohort 1: 3.0 (0.0-14.0)
- Cohort 2: 2.0 (0.0-13.6)
- Cohort 3: 3.4 (0.0-21.4)

	Cohort 1 (mBC with active BMs) N=21 N (%)	Cohort 2 (aNSCLC with active BMs) N=20 N (%)	Cohort 3 (LMD from solid tumors) N=22 N (%)
TEAEs	**18 (85.7)**	**18 (90.0)**	**22 (100.0)**
HER3-DXd-related	17 (81.0)	16 (80.0)	19 (86.4)
Serious TEAEs	**7 (33.3)**	**10 (50.0)**	**13 (59.1)**
HER3-DXd-related	2 (9.5)	4 (20.5)	4 (18.2)
Grade ≥3 TEAEs	**12 (57.2)**	**14 (70.0)**	**16 (72.7)**
HER3-DXd-related	6 (28.6)	8 (40.0)	7 (31.8)
AEs of special interest*	**2 (9.5)**	**1 (5.0)**	**1 (4.5)**
HER3-DXd-related	1 (4.8)	1 (5.0)	1 (4.5)
Deaths due to TEAEs	**2 (9.5)**	**1 (5.0)**	**1 (4.5)**
HER3-DXd-related	1 (4.8)**	0 (0.0)	0 (0.0)
TEAEs leading to dose reduction	**4 (19.0)**	**5 (25.0)**	**3 (13.6)**
TEAEs leading to dose interruption	**2 (9.5)**	**2 (10.0)**	**6 (27.3)**
TEAEs leading to permanent discontinuation	**2 (9.5)**	**1 (5.0)**	**1 (4.5)**

*AEs of special interest were grade 3 chest pain and treatment-related grade 5 intertitial lung disease in cohort 1, treatment-related grade 4 febrile neutropenia in cohort 2, and treatment-related grade 1 pneumonitis in cohort 3.
**Interstitial lung disease

AEs, adverse events; aNSCLC, advanced non-small cell lung cancer; BMs, brain metastases; HER3-DXd, patritumab deruxtecan; LMD, leptomeningeal disease; mBC, metastatic breast cancer; TEAEs, teatment-emergent adverse events.

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Safety (≥15% patients in any grade)

Cohort 1

Cohort 2

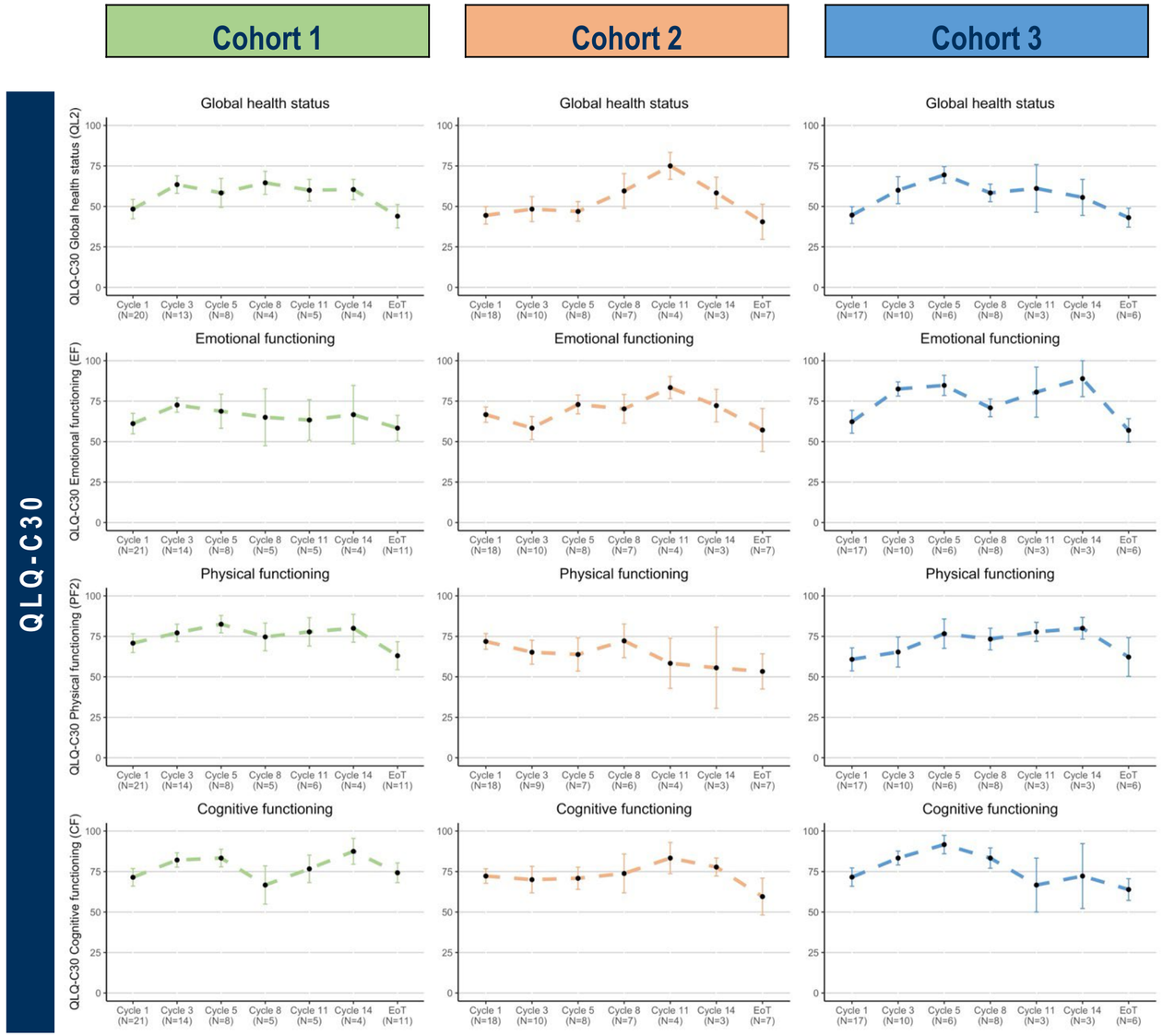
Cohort 3

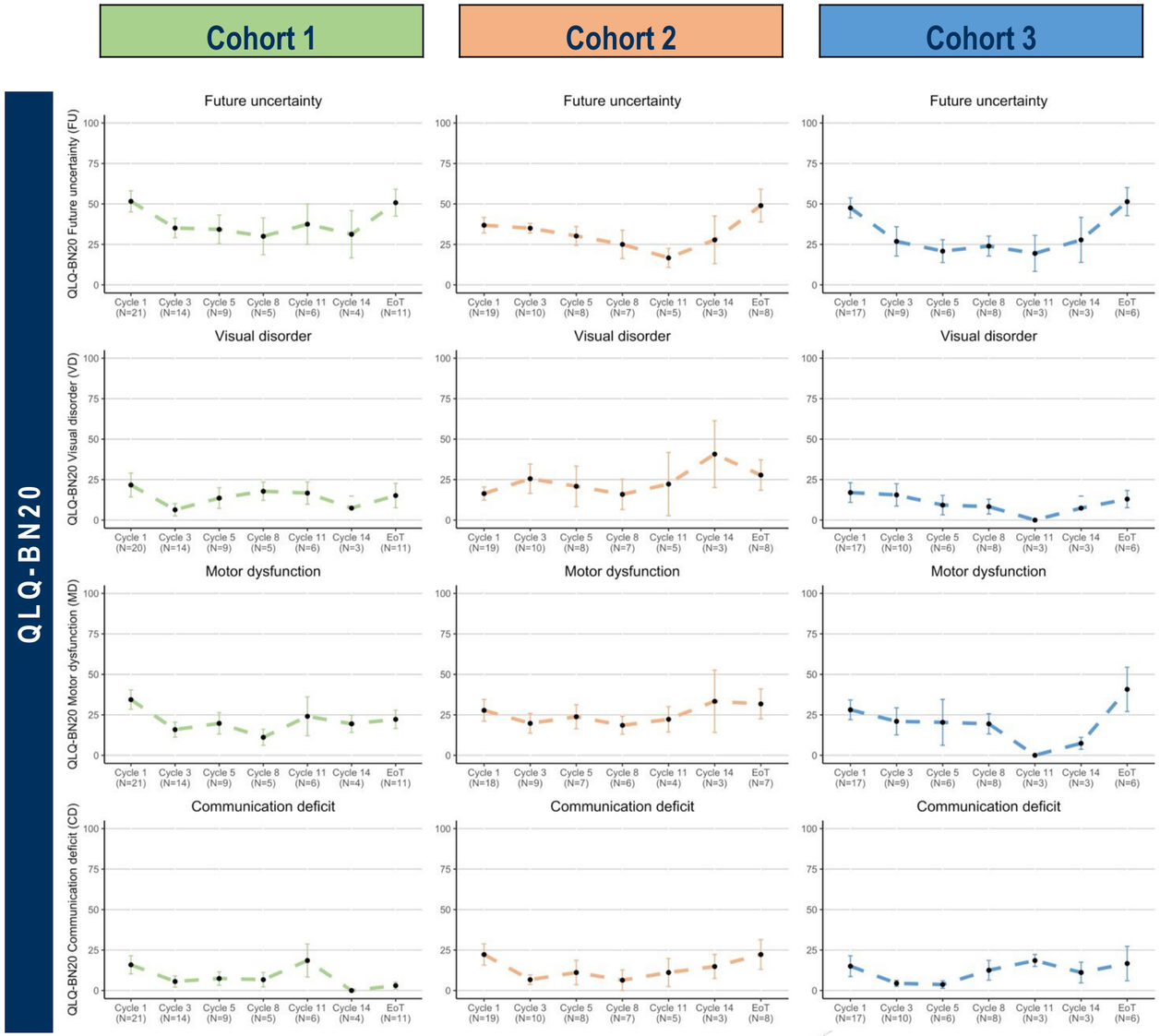
Any grade

Grade ≥3

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Quality of life remained stable or improved





QLQ, quality of life questionnaire.

Conclusions

- HER3-DXd demonstrated clinically meaningful intracranial activity in patients with active BMs of breast and lung cancers, and LMD of solid tumors.
- With extended follow-up, median overall survival reached 7.9 months in cohort 1, 6.7 months in cohort 2, and 10.5 months in cohort 3, suggesting clinical benefit across all cohorts.
- Neurological symptoms, quality of life, and neurocognitive function remained stable or improved during HER3-DXd treatment.
- No new safety signals with HER3-DXd were observed.

TUXEDO-3 supports the therapeutic value of HER3-DXd and reinforces the role of antibody-drug conjugates as a promising treatment approach in secondary CNS disease.

BMs, brain metastases; CNS, central nervous system; HER3-DXd, patritumab deruxtecan; LMD, leptomeningeal disease.

Acknowledgements

Patients and families

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Participating sites

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