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Patritumab Deruxtecan (HER3-DXd) in Melanoma After Anti–PD-(L)1 Therapy: Primary Analysis From HERTHENA-PanTumor01

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Declaration of Interests

Dr Meredith McKean

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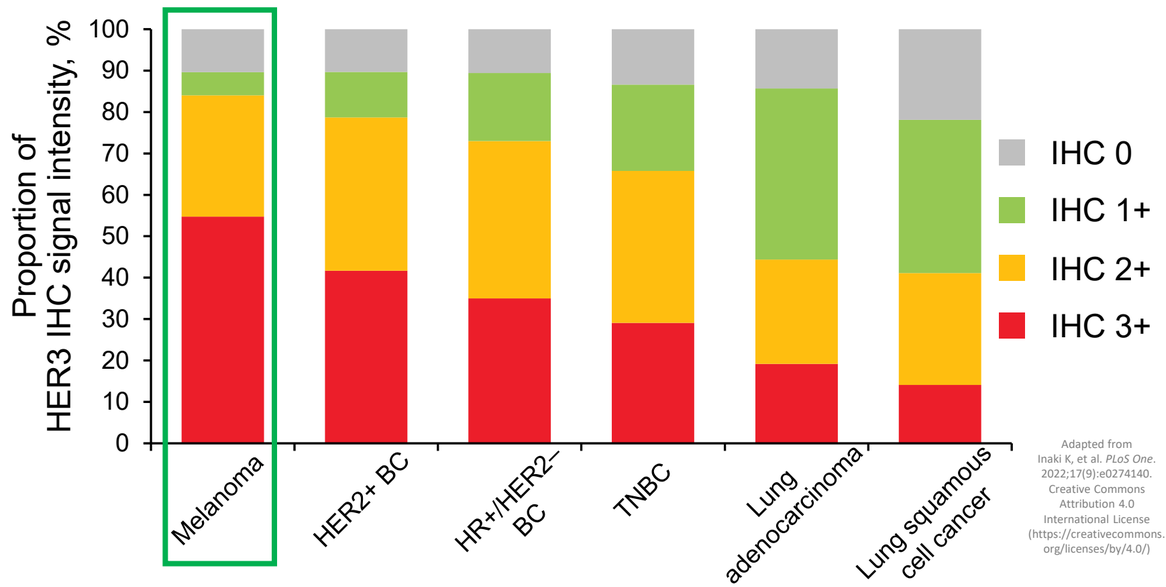
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Background

- Following progression on immunotherapy and/or BRAF inhibitor–based therapies, patients with melanoma have limited treatment options, with a median PFS of 2-4 mo[1-4]

- **HER3** is a member of the EGFR/ErbB family
  - High expression levels of HER3 are associated with poor clinical outcomes[5,6]
- HER3 is highly expressed in a number of solid tumor types, including melanoma[7]

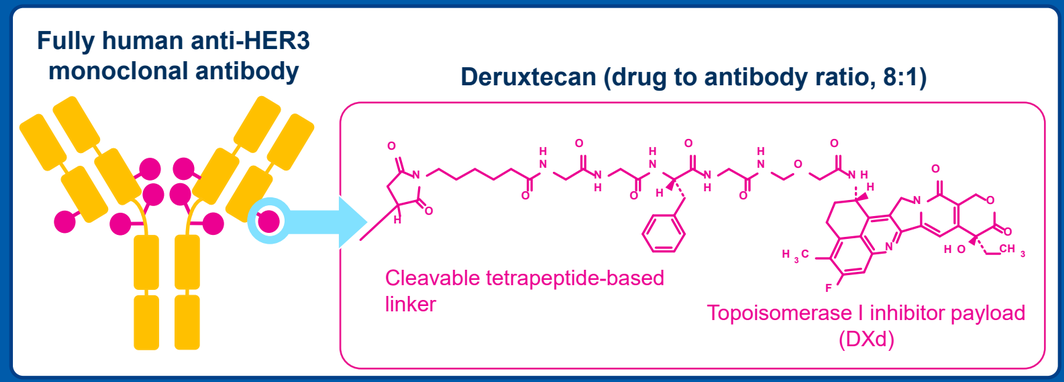
HER3 expression across selected cancer types



Adapted from Inaki K, et al. *PLoS One*. 2022;17(9):e0274140. Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

HER3-DXd

- A potential first-in-class HER3-directed antibody-drug conjugate:[8-10]
  - High potency topoisomerase I inhibitor payload with a short systemic half-life and bystander antitumor effect



- Antitumor activity along with a manageable safety profile has been demonstrated for HER3-DXd in various cancer types across a range of HER3 expression levels[11-13]

BC, breast cancer; EGFR, epidermal growth factor receptor; ErbB, erythroblastic leukemia viral oncogene B; HER, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; PFS, progression-free survival; TNBC, triple-negative breast cancer.

1. Vestergaard CD, et al. *Am J Clin Dermatol*. 2025;26(5):777-794. 2. Pires da Silva I, et al. *Lancet Oncol*. 2021;22(6):836-847. 3. Ascierto PA, et al. *J Clin Oncol*. 2023;41(15):2724-2735. 4. Chesney J, et al. *J Immunother Cancer*. 2022;10(12):e005755. 5. Scharpenseel H, et al. *Sci Rep*. 2019;9(1):7406. 6. Witton CJ, et al. *J Pathol*. 2003;200(3):290-297. 7. Inaki K, et al. *PLoS One*. 2022;17(9):e0274140. 8. Hashimoto Y, et al. *Clin Cancer Res*. 2019;25(23):7151-7161. 9. Koganemaru S, et al. *Mol Cancer Ther*. 2019;18(11):2043-2050. 10. Koyama K, et al. *PLoS One*. 2022;17(5):e0267027. 11. Yu HA, et al. *J Clin Oncol*. 2023;41(35):5363-5375. 12. Pistilli B, et al. *Nat Med*. 2025;31(10):3492-3503. 13. Krop IE, et al. *J Clin Oncol*. 2023;41(36):5550-5560.

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Study Design for Melanoma Cohort

- **HERTHENA-PanTumor01** (NCT06172478) is a global, multicohort, open-label, single-arm, phase 2 trial evaluating **HER3-DXd** in patients with previously treated advanced solid tumors
- Here, we present the primary analysis of HER3-DXd monotherapy for patients in the **melanoma cohort**

Key inclusion criteria

- Unresectable, locally advanced/metastatic cutaneous melanoma (including acral)
- Post progression on anti–PD-(L)1–based therapy[a]
- If *BRAF*m melanoma, progression on a BRAF/MEK inhibitor
- ECOG PS 0-1
- No current ILD or pneumonitis, or prior history of either that required corticosteroids
- Patients with brain metastases are allowed, provided that the brain metastases are clinically inactive or asymptomatic following treatment[b]

- Mandatory collection of archival or fresh biopsies
- No preselection based on HER3 expression

HER3-DXd
5.6 mg/kg IV Q3W
(N=42)

Endpoints

Primary:
- cORR per INV[c]

Select Secondary:
- Safety and tolerability
- CBR, DCR, DOR, and PFS per INV[c]
- OS

Select Exploratory:
- cORR per BICR[c]
- Intracranial cORR per BICR[d]

Treatment continues until disease progression, TEAE leading to study drug discontinuation, patient withdrawal, death, or pregnancy

Additional study cohorts include HNSCC, gastric (2L/3L+ gastric/GEJ adenocarcinoma and 2L gastric cancer), ovarian carcinoma, cervical cancer, endometrial cancer, bladder cancer, esophageal carcinoma, pancreatic carcinoma, prostate cancer, non-AGA NSCLC, and HR+/HER2- breast cancer.

Data cutoff: Sept 23, 2025

2L, second line; 3L, third line; AGA, actionable genomic alteration; BICR, blinded independent central review; c, confirmed; CBR, clinical benefit rate; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER, human epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; HR, hormone receptor; ILD, interstitial lung disease; INV, investigator; IV, intravenous; m, mutated; MEK, mitogen-activated protein kinase kinase; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death protein (ligand) 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event.
[a] Prior anti–PD-(L)1 therapy in the adjuvant setting was allowed if there was recurrence within 12 weeks of the last dose. [b] Patients with clinically inactive or treated brain metastases who were asymptomatic and did not require treatment with corticosteroids or anticonvulsants were eligible for inclusion in the study, provided that they had a stable neurologic status for ≥4 weeks prior to cycle 1 day 1. [c] By RECIST 1.1. [d] By CNS-RECIST.

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Baseline Characteristics and Patient Disposition

Demographics and characteristics	HER3-DXd 5.6 mg/kg N=42
Median age, years (range)	61 (37-84)
Sex, n (%)	
Male/female	21 (50)/21 (50)
Race, n (%)	
White	28 (67)
Asian	5 (12)
Black or African American	1 (2)
Other/unknown	8 (19)
ECOG PS at screening, n (%)	
0	17 (40)
1	25 (60)
Baseline LDH > ULN, n (%)	16 (38)
***BRAF* V600 mutation, n (%)**	15 (36)
Subtype, n (%)	
Acral	7 (17)
Nonacral cutaneous	35 (83)

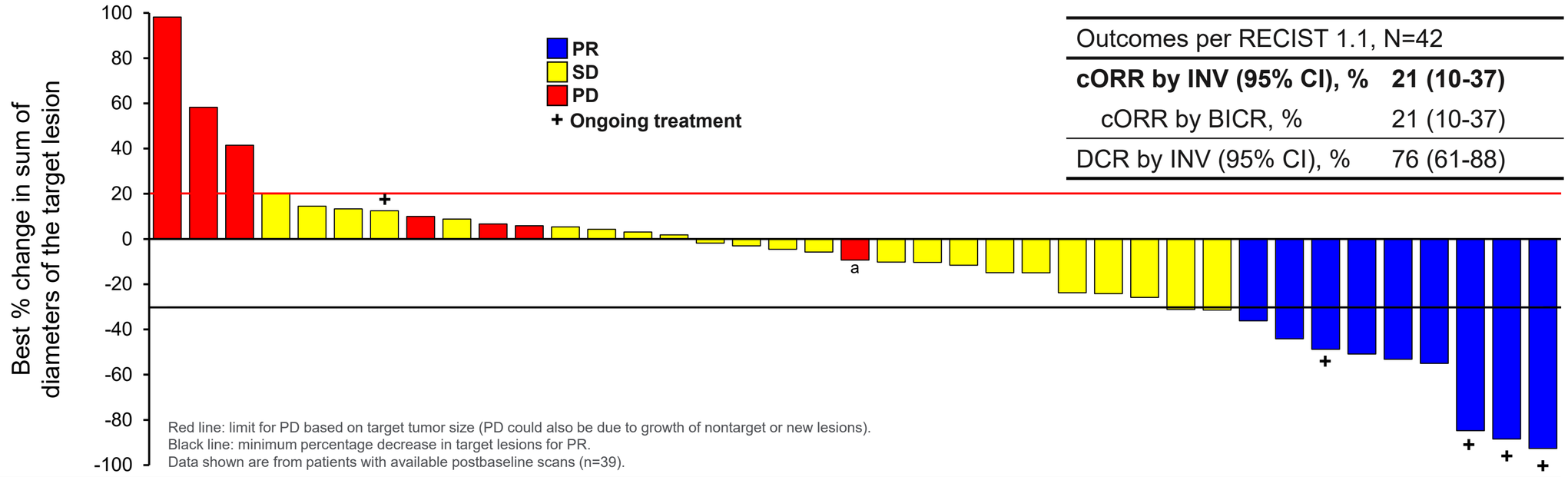
Demographics and characteristics	HER3-DXd 5.6 mg/kg N=42
Tumor stage, n (%)	
Stage III, unresectable (M0)	3 (7)[a]
Stage IV	39 (93)
M1a	5 (12)
M1b	8 (19)
M1c	8 (19)
M1d	2 (5)[b]
M1 unknown	16 (38)
No. of prior LOTs, median (range)	3.0 (1-11)
No. of prior LOTs for advanced disease, median (range)	2.5 (1-11)
1 Prior LOT	10 (24)
≥2 Prior LOTs	30 (71)
Prior anti–PD-1 therapies, n (%)	42 (100)[c]
Prior anti–PD-1 + anti–CTLA-4, n (%)	33 (79)[d]

Over a median study follow-up of 11.7 mo (range, 9.0-17.3 mo), 5 patients (12%) were ongoing in treatment; 37 (88%) had discontinued, most (29 patients [69%]) due to progressive disease

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LOT, line of therapy; PD-1, programmed cell death protein 1; ULN, upper limit of normal.
[a] For 1 patient, M staging was reported in the database as M0, while tumor stage at study entry was reported as stage IV; M0 disease (stage III) was subsequently confirmed by the study site. [b] An additional 3 patients with a history of brain metastases were reported; however, these brain metastases were resolved at study entry, so the tumor stage was not categorized as M1d. [c] A total of 3 patients received immunotherapy as an adjuvant therapy only. [d] One patient received anti–PD-1 and anti–CTLA-4 therapy sequentially rather than in combination.

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HER3-DXd Demonstrated Promising Antitumor Activity



Outcomes per RECIST 1.1, N=42	
cORR by INV (95% CI), %	**21 (10-37)**
cORR by BICR, %	21 (10-37)
DCR by INV (95% CI), %	76 (61-88)

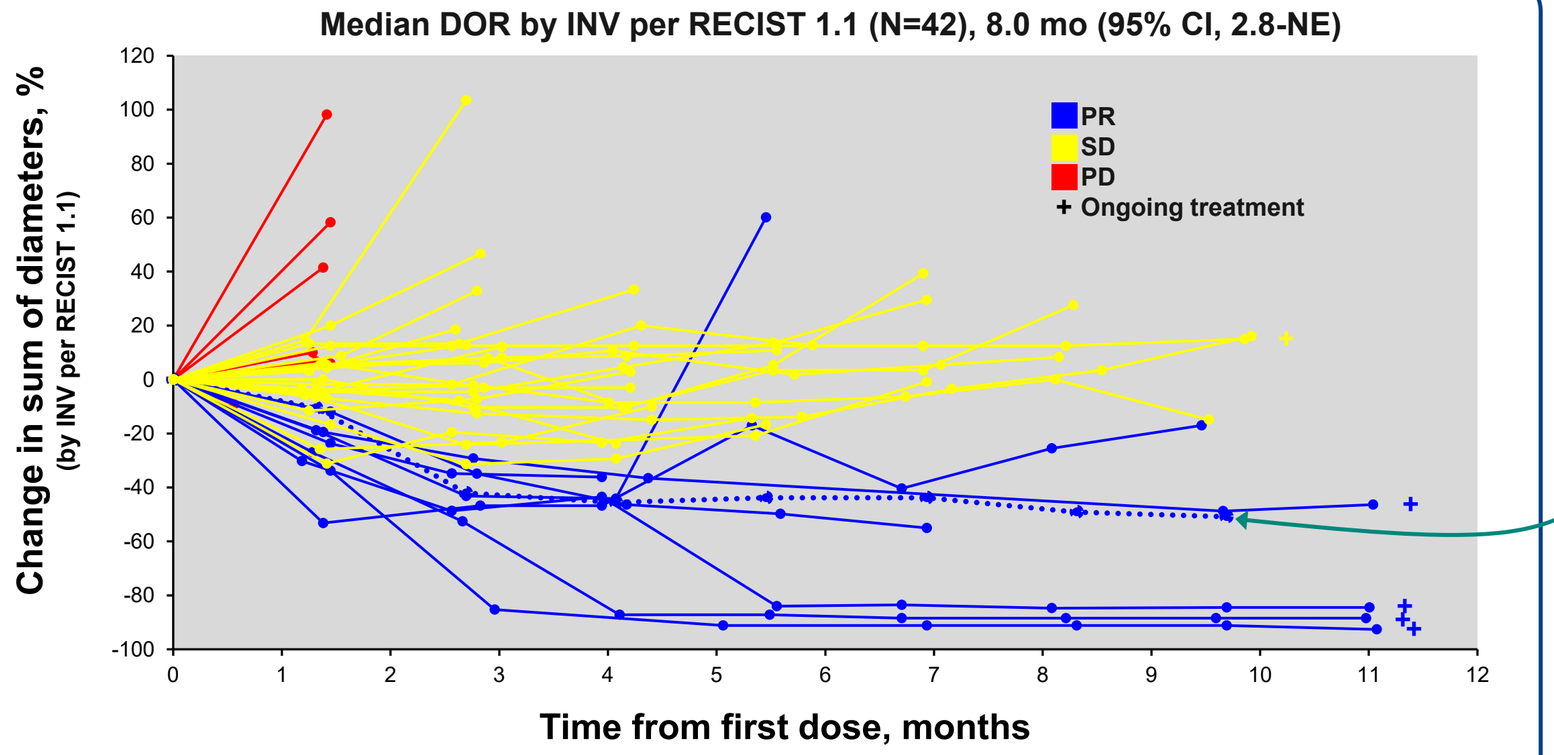
Three patients had no on-treatment assessments.

- **In this pretreated population, the overall cORR by INV assessment was 21%, with all responders achieving a PR**
- **Among the 6 patients with baseline CNS lesions by CNS BICR[g] per CNS-RECIST, the intracranial BORs were 3 cCRs, 1 cPR, and 2 PDs**

2L, second line; 3L, third line; BICR, blinded independent central review; BOR, best overall response; c, confirmed; CNS, central nervous system; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DCR, disease control rate; INV, investigator; m, mutated; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a] Although a reduction in the target lesion size was observed, non-target PD was reported. [b] All other cases were cutaneous. [c] All *BRAF*m tumors were V600 mutations per case report form. [d] All other cases were 3L+. [e] Patient only received prior adjuvant therapies, including pembrolizumab monotherapy, dabrafenib + trametinib, ipilimumab + pembrolizumab, and binimetinib + encorafenib (bridging therapy). [f] Patient received ipilimumab + nivolumab in the neoadjuvant setting. [g] The CNS analysis set (n=6) included patients with baseline target and non-target CNS lesions identified by CNS BICR, regardless of brain metastasis stage or history reported by the investigator/site. Neuroradiologists will assess at each timepoint for response in accordance with RECIST 1.1 criteria in a 2 reader with adjudication paradigm.

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HER3-DXd Demonstrated Durable Response and Disease Control



Data shown are from patients with available postbaseline scans (n=39).

Clinical benefit rate of 31% by INV
(BOR of PR or of SD lasting ≥6 months)



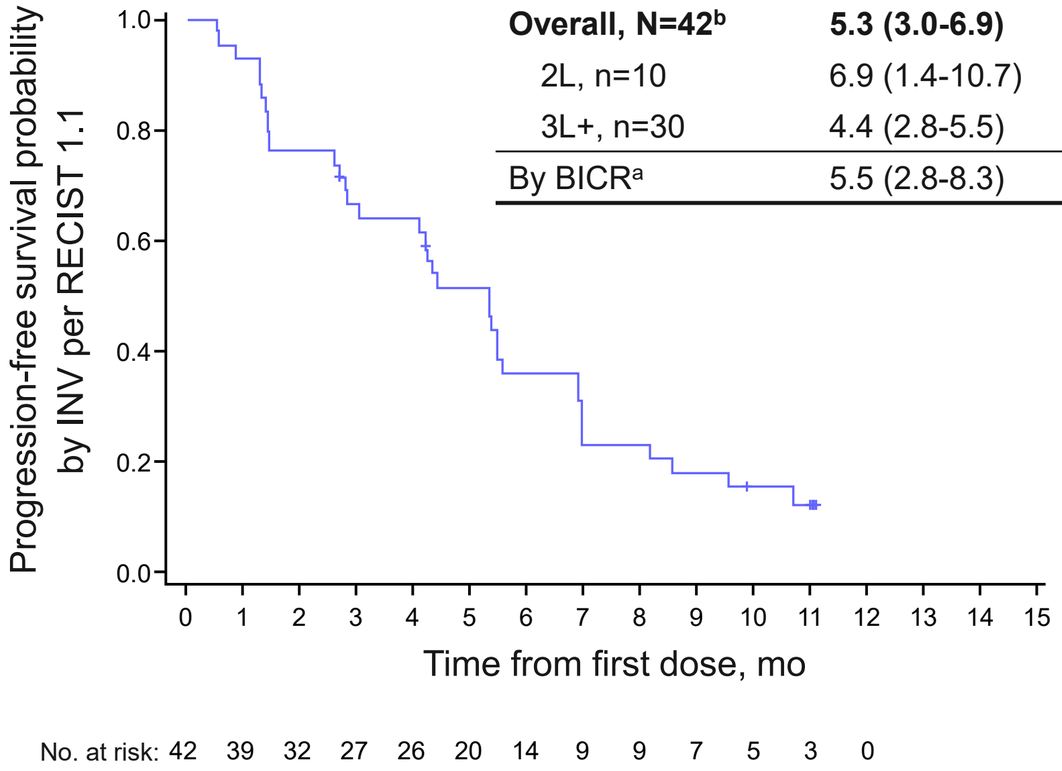
Data cutoff: Sept 23, 2025.
C, cycle; CBR, clinical benefit rate; BOR, best overall response; D, day; DOR, duration of response; INV, investigator; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; WF, White female; yo, year old.

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HER3-DXd Demonstrated Promising Survival Outcomes

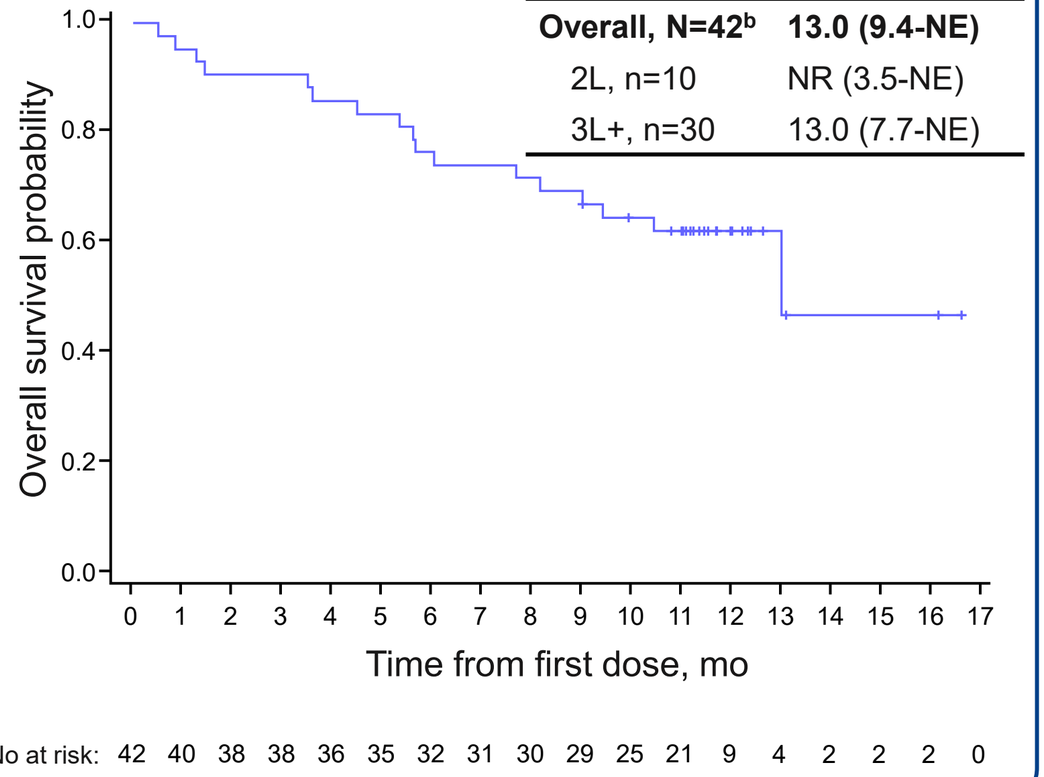
PFS

mPFS by INV (95% CI), mo[a]	
Overall, N=42[b]	**5.3 (3.0-6.9)**
2L, n=10	6.9 (1.4-10.7)
3L+, n=30	4.4 (2.8-5.5)
By BICR[a]	5.5 (2.8-8.3)



OS

mOS (95% CI), mo	
Overall, N=42[b]	**13.0 (9.4-NE)**
2L, n=10	NR (3.5-NE)
3L+, n=30	13.0 (7.7-NE)



Data cutoff: Sept 23, 2025.

2L, second line; 3L, third line; BICR, blinded independent central review; INV, investigator; mPFS, median progression-free survival; mOS, median overall survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

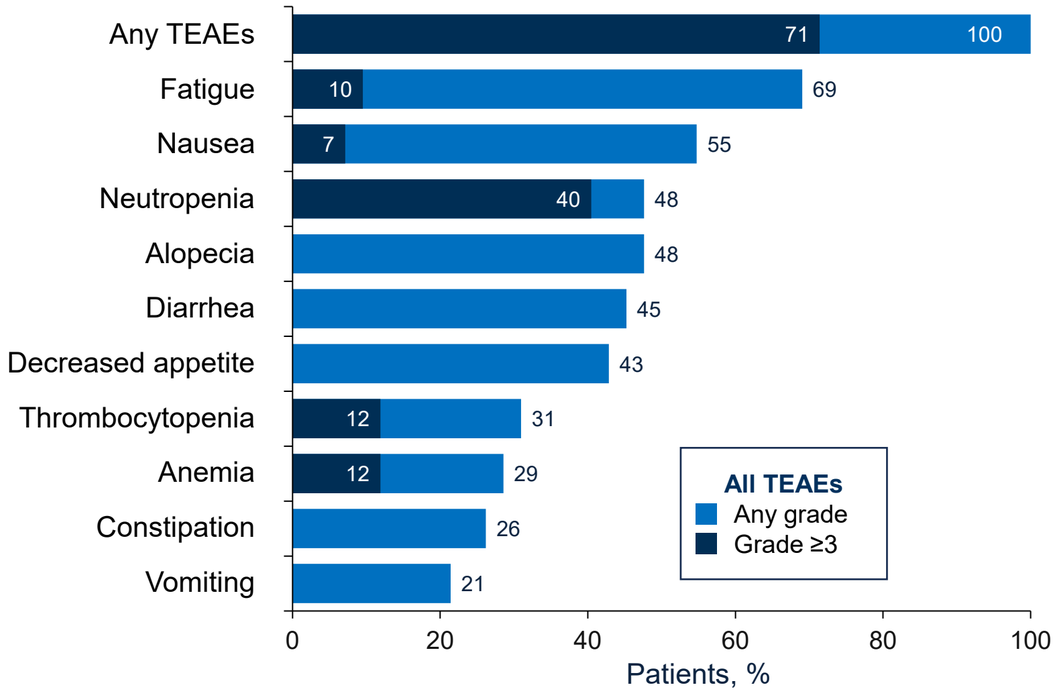
[a] Per RECIST 1.1. [b] Two patients only received prior (neo)adjuvant/bridging therapy.

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Manageable Safety, Consistent With Prior HER3-DXd Studies[1-4]

Category, n (%)	HER3-DXd 5.6 mg/kg N=42	
	TEAEs	TRAEs
All TEAEs	42 (100)	40 (95)
Grade ≥3	30 (71)	24 (57)
Grade 5	6 (14)	0
SAE	15 (36)	8 (19)
Associated with treatment discontinuation	1 (2.4)	0
Associated with dose delay	13 (31)	8 (19)
Associated with dose reduction	12 (29)	11 (26)
Potential ILD events	4 (10)	
Adjudicated as drug-related ILD	0	
Adjudicated as not drug-related ILD	1 (2)[a]	

Most frequent TEAEs[b]



- **ILD events were rare, with none adjudicated as study drug related**
- **Gastrointestinal and hematologic toxicities were the most common TEAEs**

Data cutoff: Sept 23, 2025.

CT, computed tomography; ILD, interstitial lung disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

[a] Adjudicated as grade 2 not drug-related ILD. 71-year-old male with melanoma. Radiation therapy was performed in Jul 2024. Event onset date was Dec 17, 2024. Patient had no symptoms but received steroid treatment. Bronchoalveolar lavage results showed low-inflammatory washing liquid. CT scan on Dec 17, 2024, showed consolidation and ground-glass opacities in left lower lobe, which was improved on Feb 4, 2025. Noted as radiation pneumonitis, grade 2 on Dec 17, 2024. [b] Any-grade TEAEs occurring in ≥20% of patients. Grouped preferred terms include fatigue (asthenia, fatigue, lethargy, malaise), neutropenia (neutropenia, neutrophil count decreased), thrombocytopenia (platelet count decreased, thrombocytopenia), and anemia (hematocrit decreased, hemoglobin decreased, red blood cell count decreased).

1. Yu HA, et al. *J Clin Oncol*. 2023;41(35):5363-5375. 2. Jänne PA, et al. *Cancer Discov*. 2022;12(1):74-89. 3. Pistilli B, et al. *Nat Med*. 2025;31(10):3492-3503. 4. Krop IE, et al. *J Clin Oncol*. 2023;41(36):5550-5560.

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Conclusions

- In patients with heavily pretreated advanced melanoma that progressed on prior anti–PD-1 therapies, HER3-DXd demonstrated promising antitumor activity
  - Confirmed ORR, 21% (95% CI, 10%-37%); DCR, 76% (95% CI, 61%-88%)
  - mDOR, 8.0 mo (95% CI, 2.8-NE)
  - Median PFS, 5.3 mo (95% CI, 3.0-6.9)
  - All but one of the responders received prior ipilimumab + nivolumab therapy, demonstrating that HER3-DXd may be of benefit in this population with limited treatment options after disease progression
- The safety profile of this outpatient therapy was manageable and consistent with previously reported data for lung and breast cancer
  - No cases of adjudicated HER3-DXd–related ILD were observed
- Data from this study support further evaluation of HER3-DXd in advanced melanoma that has progressed on prior immunotherapy

DCR, disease control rate; ILD, interstitial lung disease; mDOR, median duration of response; NE, not evaluable; ORR, objective response rate; PD-1, programmed cell death protein 1; PFS, progression-free survival.

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