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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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Background

High human epidermal growth factor receptor 3 (HER3) expression is associated with poor clinical outcomes across tumor types, including melanoma. An unmet need remains in patients (pts) with melanoma whose tumors progress on anti-programmed death (ligand) 1 (PD-[L]1) treatment (tx). HERTHENA-PanTumor01 (NCT06172478) is a global, multicohort, open-label, single-arm, phase 2 trial evaluating HER3-DXd, a first-in-class HER3-directed antibody-drug conjugate, in previously treated pts with advanced solid tumors. Here, we present a primary analysis of the melanoma cohort.

Methods

Pts with unresectable or metastatic melanoma (mucosal and uveal excluded) whose tumors progressed on ≥1 prior anti-PD-(L)1-based tx, and BRAF/MEK inhibitor tx if indicated, received HER3-DXd 5.6 mg/kg IV Q3W. Primary endpoint: confirmed objective response rate (cORR) by investigator (INV) per RECIST v1.1. Secondary endpoints: disease control rate (DCR), duration of response (DOR), PFS (all by INV), OS, and safety. Exploratory endpoint: efficacy by blinded independent central review (BICR).

Results

As of 23 Sep 2025, 42 pts with melanoma received HER3-DXd (median age, 61 y; female, 50%; White, 67%; BRAF mutations, 36%; acral, 17%; nonacral cutaneous, 83%; median prior txs, 2.5; M0 stage, 7%). Median follow-up was 11.7 mo. cORR by INV was 21% (9 PRs; 95% CI, 10%-37%) (Table). Of 10 second-line (2L) pts, 8 had BRAF wild-type tumors (data unavailable for 2 pts). For pts on 2L HER3-DXd (n=10), cORR was 20% (n=2/10); 3L+, 23% (7/30). Median PFS in all pts was 5.3 mo, median OS was 13.0 mo. Gastrointestinal and hematologic toxicities were the most common adverse events (AEs). Tx-related AEs (grade ≥3, 57%) led to dose reduction, delay, and death in 26%, 19%, and 0% of pts, respectively. No adjudicated tx-related interstitial lung disease cases were seen.

Conclusions

HER3-DXd demonstrated meaningful clinical activity in pts with advanced melanoma, supporting continued studies in this population. Table: 2073RO

|                              | By INV [95%<br>CI] <sup>a</sup> | By BICR [95% CI] <sup>a,<br/>b</sup> | mOS, mo          |               |                    |                     |                 |                   |                   |
|------------------------------|---------------------------------|--------------------------------------|------------------|---------------|--------------------|---------------------|-----------------|-------------------|-------------------|
|                              | cORR, n (%)                     | DCR, n (%)                           |                  | mDOR, mo      | mPFS, mo           | cORR, n (%)         | DCR, n (%)      | mDOR, mo          | mPFS, mo          |
| Overall<br>N=42 <sup>c</sup> | 9 (21) [10-37]                  | 32 (76) [61-88]                      | 8.0 [2.8-<br>NE] | 5.3 [3.0-6.9] | 9 (21) [10-<br>37] | 29 (69) [53-<br>82] | NR [2.8-<br>NE] | 5.5 [2.8-<br>8.3] | 13.0 [9.4-<br>NE] |

|          | By INV [95% CI] <sup>a</sup> | By BICR [95% CI] <sup>a, b</sup> | mOS, mo      |                |                 |                 |             |               |          |               |
|----------|------------------------------|----------------------------------|--------------|----------------|-----------------|-----------------|-------------|---------------|----------|---------------|
|          | cORR, n (%)                  | DCR, n (%)                       |              | mDOR, mo       | mPFS, mo        | cORR, n (%)     | DCR, n (%)  | mDOR, mo      | mPFS, mo |               |
| 2L n=10  | 2 (20) [2.5-56]              | 7 (70) [35-93]                   | NR [8.0-NE]  | 6.9 [1.4-10.7] | 2 (20) [2.5-56] | 6 (60) [26-88]  | NR [5.7-NE] | 5.5 [1.2-NE]  |          | NR [3.5-NE]   |
| 3L+ n=30 | 7 (23) [10-42]               | 24 (80) [61-92]                  | 4.2 [2.8-NE] | 4.4 [2.8-5.5]  | 7 (23) [10-42]  | 22 (73) [54-88] | NR [2.8-NE] | 5.5 [2.6-9.9] |          | 13.0 [7.7-NE] |

m, median; NE, not estimable; NR, not reached. <sup>a</sup> Per RECIST 1.1. <sup>b</sup> Exploratory endpoint. <sup>c</sup> 2 pts had only received prior (neo)adjuvant therapy.

### Clinical trial identification

NCT06172478.

### Editorial acknowledgement

Medical writing support was provided by Simon Foale, PhD (Nucleus Global, an Inizio company), and was funded by Daiichi Sankyo, Inc.

### Legal entity responsible for the study

Daiichi Sankyo, Inc.

### Funding

Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

### Disclosure

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Gambardella: Financial Interests, Personal, Advisory Board: Boehringer Ingelheim; Financial Interests, Institutional, Other, Research: Research Funding: Bayer, Boehringer Ingelheim, Roche; Financial Interests, Institutional, Other, Institutional: Institutional Funding: Genentech, Merck, Roche, Bayer, Lilly, Novartis, Takeda, AstraZeneca, BM. C. Gaudy-Marqueste: Financial Interests, Personal, Advisory Board: BMS, Pierre Fabre, MSD, Sun Pharma, Regeneron, Iovance; Financial Interests, Personal, Invited Speaker: BMS, Pierre Fabre, UCB; Financial Interests, Institutional, Local PI: BMS, MSD, Pfizer, Amgen, GSK, Roche, Novartis, Pierre Fabre, Replimune, Jansen, Kartos, IFX, Huyabio, Regeneron, IO Biotech, Philogen, Sotio, Kinnate, AstraZeneca, Day One biopharmaceuticals, Sairopa, Catalyst, Sanofi, Immunocore, Daiichi, Dragonfly, Erasca, Microbiotica; Other, Other, Travel expenses: BMS, Pierre Fabre, MSD, Janssen. J. 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