MADRID 2026 ESMO congress

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ctDNA analysis of the phase 3 KEYNOTE-B15 trial: Neoadjuvant and adjuvant (neoadj-adj) enfortumab vedotin (EV) + pembrolizumab (pembro) for participants (pts) with muscle-invasive bladder cancer (MIBC) who are eligible for cisplatin

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Background

In KEYNOTE-B15/EV-304 (NCT04700124), neoadj-adj EV + pembro and radical cystectomy plus pelvic lymph node dissection (RC + PLND) had significantly improved EFS, OS, and pCR rate vs neoadj chemotherapy (chemo; cisplatin + gemcitabine) and RC + PLND in pts with T2-T4aN0M0 or T1-T4aN1M0 MIBC. We report exploratory analyses of ctDNA using the Natera Signatera™ assay.

Methods

ctDNA was assessed at 2 timepoints during neoadj treatment (pre-neoadj [pre-neo; W1D1], pre-surgery after neoadj [pre-surg; W13 ± 7D]) and 2 timepoints after surgery (post-surgery before adj [post-surg; W6 ± 14D after surgery] and during adj phase [W30-34]). Outcomes (EFS; pCR rate) by ctDNA status were evaluated at pre-neo and post-surg and by ctDNA status change from pre-neo to pre-surg (clearance).

Results

808 pts were randomized to EV + pembro (n = 405) or chemo (n = 403). EV + pembro had greater reduction of ctDNA+ at the pre- and post-surg timepoints (Table). ctDNA- status pre-neo or post-surg showed improved outcomes (EFS and pCR) compared with ctDNA+ in both arms. EV + pembro showed EFS benefit vs chemo regardless of ctDNA status pre-neo (ctDNA+ HR 0.54 [95% CI 0.37-0.80]; ctDNA- HR 0.68 [0.37-1.26]) or post-surg (ctDNA+ HR 0.63 [0.30-1.35]; ctDNA- HR 0.48 [0.29-0.81]). ctDNA clearance had improved EFS and pCR compared with lack of ctDNA clearance for both arms. The percentage of ctDNA clearance was higher in the EV + pembro arm (82.1%) vs the chemo arm (66.7%). Pts in the EV + pembro arm with ctDNA clearance had improved EFS and pCR vs pts in the chemo arm with ctDNA clearance.Table: 47340

ctDNA positivity rates

Timepoint (samples analyzed)	EV + pembro ctDNA+, n (%)	Cisplatin + gemcitabine ctDNA+, n (%)
Pre-neo (n = 490)	133 (52.4)	134 (56.8)
Pre-surg (n = 436)	27 (13.0)	45 (19.7)
Post-surg (n = 432)	10 (4.8)	30 (13.5)

Conclusions

In this study, ctDNA+ status was associated with poor prognosis. EV + pembro showed improved EFS outcomes vs chemo regardless of ctDNA status pre-neo or post-surg. Pts with ctDNA clearance had more favorable outcomes compared with those without; ctDNA clearance was higher with EV + pembro.

Clinical trial identification

NCT04700124.

Editorial acknowledgement

Medical writing and/or editorial assistance was provided by Obinna T. Ezeokoli, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Legal entity responsible for the study

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), Astellas Pharma Inc., Northbrook, IL, USA, and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

Funding

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), Astellas Pharma Inc., Northbrook, IL, USA, and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

Disclosure

J.A. Chatzkel: Financial Interests, Institutional, Other, Site Principal Investigator: Allogene Therapeutics, Eisai, Exelixis, Merck; Financial Interests, Institutional, Officer, Site Principal Investigator: Arsenal Bio; Financial Interests, Institutional, Principal Investigator: AVEO Pharmaceuticals, Clinigen Inc, Genentech, Merck; Financial Interests, Personal, Other, Invited trip to provide two scientific talks; was not able to attend: Dava Oncology; Financial Interests, Personal, Other, Educational item (per open payments; detail not specified): Janssen Biotech; Financial Interests, Personal, Other, Informational dinner: Natera. A. 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Gilead; Financial Interests, Personal, Stocks/Shares: CellCarta; Financial Interests, Institutional, Research Grant: AstraZeneca, Roche, Bristol-Myers Squibb, Exelixis, Ipsen, Merck, MSD, Seattle Genetics, Novartis, Pfizer, Merck Serono, Astellas, Johnson & Johnson, Eisai; Financial Interests, Institutional, Other, Honoraria: Gilead. All other authors have declared no conflicts of interest.

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