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Perioperative pembrolizumab (pembro) or placebo (pbo) + neoadjuvant cisplatin (cis) and gemcitabine (gem) in participants (pts) with muscle-invasive bladder cancer (MIBC): The double-blind, phase 3 KEYNOTE-866 study

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Background

Perioperative PD-(L)1 inhibitors (either added to cis-based chemotherapy [chemo] or enfortumab vedotin) have improved outcomes in pts with MIBC who are cis-eligible. KEYNOTE-866 (NCT03924856) evaluated perioperative (neoadjuvant and adjuvant) pembro vs pbo added to neoadjuvant gem + cis and radical cystectomy with pelvic lymph node dissection (RC + PLND) in pts with MIBC.

Methods

Pts were adults with centrally assessed clinical stage T2-T4aN0M0 or T1-T4aN1M0 MIBC with ≥50% urothelial histology, had ECOG PS 0 or 1, no prior systemic therapy, and were eligible for cis-based chemo and RC + PLND. Pts were randomized 1:1 to neoadjuvant pembro 200 mg or pbo on d1 + chemo (gem 1000 mg/m² on d1 and d8 + cis 70 mg/m² on d1) Q3W for 4 cycles, followed by RC + PLND, and adjuvant pembro or pbo Q3W for 13 cycles. The primary end point was EFS by investigator assessment. Pathological complete response (pCR) rate by blinded independent central pathological review and OS were key secondary end points. Safety was a secondary end point. Results are reported for the second interim analysis.

Results

907 pts were randomized (pembro n = 453; pbo n = 454). As of January 26, 2026, median follow-up was 60.9 mo (range 40.7-78.7). 91.6% of pts in the pembro arm and 87.9% in the pbo arm underwent surgery. Median EFS was 74.1 mo with pembro vs not reached (NR) with pbo (HR 0.88 [95% CI 0.71-1.10]; *P* = .1366). pCR rate was 44.4% vs 35.8% (estimated difference 8.9%; 95% CI 2.5-15.1), and median OS was NR in both arms (HR 1.00; 95% CI 0.79-1.27). Treatment-emergent AEs occurred in 99.8% of pts with pembro (grade 3-5, 80.2%; grade 5, 3.8%) and 98.7% with pbo (grade 3-5, 75.1%; grade 5, 4.5%). In the pembro arm, the most frequent immune-mediated AE (per a prespecified list) was hypothyroidism (10.4%; grade 3-5, 0%).

Conclusions

The addition of perioperative pembro to neoadjuvant chemo and RC + PLND did not confer a statistically significant benefit in EFS in pts with MIBC who were eligible for cis-based chemo. Due to the statistical design, pCR and OS were not formally tested. The safety profile of pembro was manageable and consistent with prior reports.

Clinical trial identification

NCT03924856.

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.

Funding

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Disclosure

J. Bedke: Financial Interests, Personal, Invited Speaker: AstraZeneca, Astellas, Apogepha; Financial Interests, Personal, Advisory Board, Advisory Board and Speaker’s Bureau: BMS, Ipsen, MSD, Pfizer, Roche, Janssen; Financial Interests, Personal, Advisory Board: Eisai, Daiichi Sankyo, Novartis; Financial Interests, Institutional, Advisory Board: Pfizer, MSD; Financial Interests, Institutional, Coordinating PI: BMS, MSD, Pfizer, Roche, Seagen; Financial Interests, Personal and Institutional, Steering Committee Member: BMS; Financial Interests, Institutional, Steering Committee Member: MSD, Seagen, Daiichi Sankyo; Financial Interests, Personal, Steering Committee Member: Pfizer; Financial Interests, Institutional, Local PI: Janssen; Other, Other, Vice-Chairman of the Renal Cell Carcinoma Guidelines Panel: European Association of Urology. H. Nishiyama: Financial Interests, Personal, Advisory Board: AstraZeneca, Chugai Pharma, Ferring, Janssen, MSD; Financial Interests, Personal, Speaker’s Bureau: Astellas Pharma, Chugai Pharma, MSD; Financial Interests, Institutional, Research Funding: Astellas Pharma, Chugai Pharma, Ono Pharmaceutical, Pfizer; Financial Interests, Personal, Research Funding: Bristol-Myers Squibb Japan, Merck, Nippon Kayaku. C. Vulsteke: Financial Interests, Personal, Advisory Board: MSD, Janssens-Cilag, GSK, Astellas Pharma, BMS, Bayer, AstraZeneca, Pfizer, Merck, atheneum partners, Daiichi Sankyo; Financial Interests, Personal, Invited Speaker: MSD, Astellas, Ipsen; Financial Interests, Institutional, Research Grant, Funding for research project on immune related toxicities: MSD. M.J. Juan Fita: Financial Interests, Personal, Advisory Board: Johnson & Johnson, Pierre Fabre; Financial Interests, Personal, Invited Speaker: AstraZeneca, Astellas, Bristol-Myers Squibb International, MSD, Merck. E. Verzoni: Financial Interests, Personal, Advisory Board: MSD, Janssen, AstraZeneca, Eisai; Financial Interests, Personal, Invited Speaker: BMS, Astellas, Ipsen, Pfizer, Novartis; Non-Financial Interests, Principal Investigator: MSD, Ipsen, Astellas, Janssen, Lilly, Pfizer. A. Rodriguez-Vida: Financial Interests, Personal, Invited Speaker: Roche, BMS, Johnson & Johnson, AstraZeneca, Ipsen, Novartis; Financial Interests, Personal, Advisory Board: MSD, Pfizer, Astellas, Bayer, Merck. A. Peer: Financial Interests, Personal, Invited Speaker: Roche, Exelixis; Financial Interests, Personal, Advisory Board, And invited speaker travel grant: BMS; Financial Interests, Personal, Advisory Board, and Invited speaker travel grant: MSD; Financial Interests, Personal, Advisory Board, and invited speaker travel grant: Astellas; Financial Interests, Personal, Advisory Board, and invited speaker: Janssen, Bayer, Medison pharma, Novartis; Financial Interests, Personal, Advisory Board, Invited speaker Physician e- learning tools: Eisai. X. Fang: Financial Interests, Personal, Other, Employee: Merck & Co.; Financial Interests, Personal, Stocks/Shares: Merck & Co.; Financial Interests, Personal, Other, Travel/Accommodations/Expenses: Merck & Co.. S. Franco: Financial Interests, Personal, Other, Employee: Merck & Co.; Financial Interests, Personal, Stocks/Shares: Merck & Co.,. B. Homet Moreno: Financial Interests, Personal, Other, Employee: Merck & Co.; Financial Interests, Personal, Stocks/Shares: Merck & Co.. C.J. Hoimes: Financial Interests, Personal, Advisory Board: Astellas, BMS, Foundation Medicine, Merck &Co, Seagen, Tempus, Adaptimmune, Pfizer; Financial Interests, Personal, Invited Speaker: BMS, Eisai; Financial Interests, Institutional, Advisory Board: Dynavax; Financial Interests, Institutional, Local PI: AbbVie, Alkermes, Astellas, BMS, Bayer, Bellicum, BioNTech, Dynavax, Genentech, Janssen, Mirati, NeoImmune Tech, Pfizer, Promontory, Tyra, Xencor, CRISPR, Arsenal Biosciences, Clasp Therapeutics, Synthekine, Janux, Evolveimmune; Financial Interests, Personal and Institutional, Steering Committee Member: Merck &Co, Seagen; Financial Interests, Institutional, Funding: Xencor. A.O. Siefker-Radtke: Financial Interests, Personal, Advisory Board: Janssen, Merck, NCCN, Bristol-Myers Squibb, Seattle Genetics, Taiho Pharmaceutical, Gilead Sciences, AstraZeneca, Bavarian Nordic, Basilea Pharmaceutical, Genentech, G1 Therapeutic, Ideeya Biosciences, Immunomedics, Mirati Therapeutics, Nektar; Financial Interests, Institutional, Research Funding: NIH, Janssen, Bristol-Myers Squibb, Nektar, Merck, Basilea. All other authors have declared no conflicts of interest.