

LBA2

Perioperative (periop) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants (pts) with muscle-invasive bladder cancer (MIBC) who are cisplatin-ineligible: The phase III KEYNOTE-905 study

C. Vulsteke¹, H. Kaimakliotis², P. Danhaivijitr³, M.Y. Sabadash⁴, A. Rodriguez-Vida⁵, Z. Zhang⁶, V. Atduev⁷, Y.E. Goger⁸, S. Rausch⁹, S.H. Kang¹⁰, Y. Loriot¹¹, J. Bedke¹², M.D. Galsky¹³, P.H. O'Donnell¹⁴, M. Mihm¹⁵, C. Meng¹⁶, D. Huang¹⁷, C. Ramamurthy¹⁸, B. Homet Moreno¹⁸, A. Ullén¹⁹

¹ Integrated Cancer Center Ghent, AZ Maria Middelaers AZMMSJ, Ghent, Belgium, ² School of Medicine, Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, United States of America, ³ Division of Medical Oncology, Mahidol University - Faculty of Medicine, Bangkok, Thailand, ⁴ Urology Department, Lviv State Regional Treatment and Diagnostics Oncology Center, Lviv, Ukraine, ⁵ Medical Oncology Department, Hospital del Mar - Parc de Salut Mar, Barcelona, Spain, ⁶ Oncology, Parkview Cancer Institute - Parkview Health, Fort Wayne, United States of America, ⁷ Medical Oncology, Privolzhsky District Medical Center - Clinical Hospital No.1 - FBUZ POMC FMBA of Russia, Nizhny Novgorod, Russian Federation, ⁸ Oncology, Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi Hastanesi, Konya, Türkiye, ⁹ Department of Urology, Eberhard Karls University, Tuebingen, Germany, ¹⁰ Department of Urology, Korea University Anam Hospital, Seoul, Republic of Korea, ¹¹ Cancer Medicine Department / DITEP, Institut Gustave Roussy, Villejuif, France, ¹² Urology Dept., Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart - Katharinenhospital, Stuttgart, Germany, ¹³ Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, United States of America, ¹⁴ Medicine Department, The University of Chicago, Chicago, United States of America, ¹⁵ Clinical, Astellas, Chicago, United States of America, ¹⁶ Pfizer Inc., Groton, United States of America, ¹⁷ Medical Oncology, Merck & Co., Inc., Rahway, United States of America, ¹⁸ Clinical, Merck & Co., Inc., Rahway, United States of America, ¹⁹ Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden

Background

Radical cystectomy + pelvic lymph node dissection (RC + PLND) is the standard treatment for pts with MIBC who are cisplatin-ineligible. Periop therapy may improve outcomes in these pts.

Methods

The phase 3 KEYNOTE-905/EV-303 study (NCT03924895) evaluated efficacy and safety of periop EV + pembro and RC + PLND vs RC + PLND in adult pts with MIBC (T2-T4aN0M0 or T1-T4aN1M0) who were cisplatin-ineligible or declined cisplatin. Pts were randomized 1:1 to EV + pembro (3 cycles EV 1.25 mg/kg on d1 and d8 + pembro 200 mg on d1 Q3W, followed by RC + PLND, then 6 cycles EV + 14 cycles pembro) vs control (RC + PLND only). Study therapy continued until progression, unacceptable adverse events (AEs), withdrawal of consent, or completion of planned treatment. The primary endpoint was event-free survival (EFS) by blinded independent central review. Secondary endpoints were overall survival (OS; key), pathological complete response (pCR) rate (key), and safety.

Results

170 pts were randomized to EV + pembro and 174 pts to control. >80% of pts were cisplatin-ineligible per Galsky criteria. As of Jun 6, 2025, median follow-up time was 25.6 mo (range, 11.8–53.7). 149 pts (87.6%) in the EV + pembro arm and 156 (89.7%) in the control underwent surgery. EV + pembro significantly improved EFS (median not reached [NR] vs 15.7 mo; HR 0.40; 95% CI 0.28–0.57; $P<.001$), OS (NR vs 41.7 mo; HR 0.50; 95% CI 0.33–0.74; $P<.001$), and pCR rate (57.1% vs 8.6%; estimated difference 48.3%; 95% CI 39.5–56.5; $P<.001$) vs control. Treatment-emergent AEs occurred in 100% (gr ≥ 3 , 71.3%) of pts in the EV + pembro arm and 64.8% (gr ≥ 3 , 45.9%) in the control. Most frequent gr ≥ 3 AE of special interest (based on distinct prespecified lists for each drug) was severe skin reactions (grouped term; 11.4%) for pembro, and skin reactions (grouped term; 10.8%) for EV.

Conclusions

Adding periop EV + pembro to surgery significantly and meaningfully improved EFS, OS, and pCR rate in pts with MIBC who were predominantly cisplatin-ineligible. The safety profile of EV + pembro was manageable and consistent with prior reports. This is the first periop regimen to improve outcomes vs RC + PLND in this setting and may be a new standard of care.

Clinical trial identification

NCT03924895.

Editorial acknowledgement

Editorial assistance was provided by Ina Bremer, PhD, an employee of 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 in collaboration with Astellas Pharma Inc., Northbrook, IL, USA and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in Dec. 2023.

Funding

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

Disclosure

C. Vulsteke: Financial Interests, Personal, Advisory Board: MSD, janssens-Cilag, GSK, Astellas Pharma, BMS, Leo Pharma, Bayer, AstraZeneca, Pfizer, Merck; Financial Interests, Institutional, Research Grant, Funding for research project on immune related toxicities: MSD. H. Kaimakliotis: Financial Interests, Institutional, Research Funding: MSD. P. Danchaivijitr: Financial Interests, Personal, Advisory Board: MSD, Astellas, AstraZeneca, Johnson and Johnson; Financial Interests, Personal, Invited Speaker: MSD, Astellas, Johnson and Johnson, AstraZeneca, Roche, Eisai, BMS; Financial Interests, Institutional, Local PI: MSD, AstraZeneca, Roche, Daiichi Sankyo, Taiho, Pfizer. M.Y. Sabadash: Financial Interests, Institutional, Research Funding: MSD. A. Rodriguez-Vida: Financial Interests, Personal, Invited Speaker: Roche, BMS, Johnson and Johnson, ASTRA ZENECA, Ipsen; Financial Interests, Personal, Advisory Board: MSD, Pfizer, ASTELLAS, BAYER, MERCK. Z. Zhang: Financial Interests, Personal, Speaker, Consultant, Advisor: Astellas, Pfizer, DAVA, Cornerstone, Curio Science, Gilead, Research to Practice, MJH Life Sciences, Aptitude Health, Research America, MDoutlook, Aveo Oncology, MiBA; Financial Interests, Institutional, Research Funding: Merck & Co. Inc., Rahway, NJ, USA. V. Atduev: Financial Interests, Institutional, Research Funding: MSD. Y.E. Goger: Financial Interests, Institutional, Research Funding: MSD. S. Rausch: Financial Interests, Personal, Advisory Board: Merck Serono, Bayer, Eisai, MSD; Financial Interests, Personal, Invited Speaker: Ipsen, Lilly, Janssen-Cilag, Pfizer, Amgen, AstraZeneca, Merck Serono, Bayer, Astellas; Financial Interests, Personal, Writing Engagement: BMS; Financial Interests, Institutional, Local PI: Merck, Pfizer, Merck Serono, Steba Biotech, Lilly, Roche, AstraZeneca, Aveo Pharmaceuticals, BMS, Eisai, Exelixis, Immunomedics, Bicycle Therapeutics, Ipsen, Janssen-Cilag, Seattle Genetics, Gilead; Financial Interests, Personal, Coordinating PI: TriNetX, LCC. S.H. Kang: Financial Interests, Institutional, Research Funding: MSD. Y. Lorient: Financial Interests, Personal, Advisory Board: Merck Kga, Pfizer, Gilead, Seattle Genetics, Tahio; Financial Interests, Personal, Other, lectures, advisory boards: MSD, AstraZeneca, Astellas, Janssen; Financial Interests, Personal, Other, lectures, advisory boards: roche, BMS; Financial Interests, Institutional, Research Grant: janssen, sanofi, MSD, roche, celsius; Financial Interests, Institutional, Steering Committee Member: janssen; Financial Interests, Steering Committee Member: msd, Astellas, Gilead/immunomedics, tahio; Financial Interests, Personal, Steering Committee Member: basilea; Financial Interests, Institutional, Local PI: Pfizer, MSD, Janssen, exelixis, astra zeneca, Pfizer, Merck Kga, BMS, Astellas, Gilead, Incyte, Orion, TYRA, Lilly; Financial Interests, Institutional, Coordinating PI: janssen; Non-Financial Interests, Member: ESMO, ASCO, AACR; Non-Financial Interests, Other, scientific committee: ARC. J. Bedke: Financial Interests, Personal, Advisory Board: Astellas, AstraZeneca, Bristol Myers Squibb, Eisai, Ipsen, Janssen, Merck Sorono, MSD, Roche; Financial Interests, Personal and Institutional, Advisory Board: Pfizer; Financial Interests, Institutional, Coordinating PI: Astellas, BMS, Ipsen, MSD, Pfizer, Roche, Seagen; Financial Interests, Institutional, Local PI: AstraZeneca, Eisai, Nektar, Novartis; Financial Interests, Institutional, Steering Committee Member: BMS, MSD, Pfizer, Seagen; Financial Interests, Personal, Other, Member of the Renal Cell Carcinoma Guidelines Panel: European Association of Urology. M.D. Galsky: Financial Interests, Personal, Advisory Board: Janssen, Merck, Pfizer, EMD Serono, AstraZeneca, SeaGen, AbbVie, Gilead; Financial Interests, Institutional, Steering Committee Member: Merck, Bristol Myers-Squibb, Seagen; Financial Interests, Institutional, Coordinating PI: AstraZeneca. P.H. O'Donnell: Financial Interests, Personal, Other, honoraria: Adept Field Solutions, Advarra, Merck, Astellas, AbbVie, Pfizer, Custom Learning Designs, Axiom Healthcare Strategies, EMD Serono, IntrinsiQ, ISMIE, ImmunityBio, NAMCP, Seagen, Curio Science, FirstWord, Gilead, MedIQ, MedLearning Group, Medscape, Research to Practice, Great Debates and Updates, Loxo/Lilly, MJH Life Sciences, Peerview, Vaniam Group, Institute for Enquiring Minds, Pharmavision UK, PRIME Education LLC, Amerisource Bergen, Health Advances, Parexel Intl Corp, Vida Ventures LLC; Financial Interests, Institutional, Research Funding: Boehringer Ingelheim, Merck & Co., Inc., Rahway, NJ, USA, Genentech/Roche, AstraZeneca/MedImmune, Acerta Pharma, Janssen, Seagen, Bristol Myers Squibb, Astellas Pharma, Pfizer, Loxo/Lilly; Financial Interests, Personal, Expert Testimony: Hart Wagner LLP, O'Brien and Ryan LLP; Financial Interests, Personal, Other, travel: Curio Science, Astellas, SeaGen, Merck; Financial Interests, Personal, Advisory Board, Data Safety Monitoring Board: NIH (via Duke U), Janssen, Nektar, Dragonfly Therapeutics, G1 Therapeutics. M. Mihm: Financial Interests, Personal, Full or part-time Employment, I am a full time employee of Astellas Pharma.: Astellas. C. Meng: Financial Interests, Personal, Full or part-time Employment: Pfizer, Bothell, WA, USA; Financial Interests, Personal, Stocks/Shares: Pfizer, Bothell, WA, USA. D. Huang: Financial Interests, Personal, Full or part-time Employment: Merck & Co., Inc.; Financial Interests, Personal, Stocks/Shares: Merck & Co., Inc. C. Ramamurthy: Financial Interests, Personal, Full or part-time Employment: Merck & Co., Inc.; Financial Interests, Personal, Stocks/Shares: Merck & Co., Inc. B. Homet Moreno: Financial Interests, Personal, Full or part-time Employment: Merck & Co., Inc.; Financial Interests, Personal, Stocks/Shares: Merck & Co., Inc. A. Ullén: Financial Interests, Personal, Invited Speaker, Advisory Board: Astellas Pharma, Merck KGaA, Janssen-Cilag, BMS; Financial Interests, Institutional, Invited Speaker, Advisory Board: AstraZeneca; Financial Interests, Institutional, Research Grant, Research funding for RWD study on Avelumab. PI

for project.: Merck; Financial Interests, Institutional, Coordinating PI, TROPICS-04 _coordinating PI in Sweden: Gilead; Financial Interests, Institutional, Coordinating PI, KN-905 _coordinating PI in Sweden: MSD; Financial Interests, Institutional, Coordinating PI, Javelin Bladder100 _coordinating PI in Sweden: Merck KGaA; Financial Interests, Institutional, Coordinating PI, C5731001/SGNDV-001/KN-D74 _coordinating PI in Sweden: Seagen; Financial Interests, Institutional, Coordinating PI, INTerpath-005 _coordinating PI in Sweden: MSD; Non-Financial Interests, Leadership Role, Steering committee member and chair for advanced bladder cancer section: Swedish Society for Urological Oncology; Non-Financial Interests, Member: Swedish Society for Oncology; Non-Financial Interests, Leadership Role, Co-chair advanced bladder cancer: Nordic Urothelial Cancer Oncology Group; Non-Financial Interests, Leadership Role, Scientific secretary: Radiumhemmet Reserach Funds.

© *European Society for Medical Oncology*