ORIGINAL ARTICLE

Perioperative Enfortumab Vedotin and Pembrolizumab in Bladder Cancer

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ABSTRACT

BACKGROUND

Patients with muscle-invasive bladder cancer who are ineligible for cisplatin-based chemotherapy proceed directly to radical cystectomy with pelvic lymph-node dissection. Perioperative therapy may improve outcomes in this population.

METHODS

In this phase 3, open-label trial, participants with muscle-invasive bladder cancer who were ineligible for or declined cisplatin-based chemotherapy were randomly assigned to perioperative (neoadjuvant and adjuvant) enfortumab vedotin, an antibody–drug conjugate directed at nectin-4, plus pembrolizumab and surgery (9 total cycles of enfortumab vedotin [1.25 mg per kilogram of body weight on days 1 and 8] plus 17 total cycles of pembrolizumab [200 mg on day 1 every 3 weeks], with surgery after 3 cycles) or surgery alone (control). The primary end point was event-free survival. Key secondary end points were overall survival and pathological complete response (absence of viable tumor after surgical resection). Other secondary end points included safety.

RESULTS

A total of 344 participants underwent randomization (170 in the enfortumab vedotin–pembrolizumab group and 174 in the control group). At data cutoff, median follow-up was 25.6 months (range, 11.8 to 53.7). Surgery was performed in 87.6% of participants in the enfortumab vedotin–pembrolizumab group and in 89.7% in the control group. At 2 years, estimated event-free survival was 74.7% in the enfortumab vedotin–pembrolizumab group and 39.4% in the control group (hazard ratio for an event or death, 0.40; 95% confidence interval [CI], 0.28 to 0.57; two-sided P<0.001); estimated overall survival was 79.7% and 63.1% (hazard ratio for death, 0.50; 95% CI, 0.33 to 0.74; two-sided P<0.001). A pathological complete response had occurred in 57.1% and 8.6% of the participants (estimated difference, 48.3 percentage points; 95% CI, 39.5 to 56.5; two-sided P<0.001). Adverse events occurred in all participants in the enfortumab vedotin–pembrolizumab group (grade ≥3, 71.3%; grade ≥3 drug-related, 45.5%) and in 64.8% in the control group (grade ≥3, 45.9%).

CONCLUSIONS

Perioperative enfortumab vedotin plus pembrolizumab and surgery led to significantly better event-free and overall survival outcomes and a greater percentage of participants with pathological complete response than surgery alone in a predominantly cisplatin-ineligible population with muscle-invasive bladder cancer. Safety was also assessed. (Funded by Merck Sharp and Dohme, a subsidiary of Merck [Rahway, NJ]; KEYNOTE-905 ClinicalTrials.gov number, NCT03924895.)

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*The complete list of principal investigators who participated in the KEYNOTE-905 trial is provided in the Supplementary Appendix, available at NEJM.org.

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