

A New Hope for Cisplatin-Ineligible Muscle-Invasive Bladder Cancer: Perioperative Enfortumab Vedotin Plus Pembrolizumab Shows Promise

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ABSTRACT

Background: Cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy is the established treatment pathway for eligible patients with muscle-invasive bladder cancer (MIBC). A substantial proportion of patients are cisplatin-ineligible or decline cisplatin, leaving surgery alone as a common but clinically inadequate approach.

Objective: This study presents an original secondary analysis of aggregate data. Published aggregate results were used to calculate absolute risk differences, relative risks, number needed to treat (NNT), number needed to harm (NNH), and a structured benefit-risk interpretation.

Methods: The intervention group received perioperative enfortumab vedotin plus pembrolizumab and radical cystectomy with pelvic lymph-node dissection; the control group underwent surgery alone. A total of 344 participants were randomized: 170 to enfortumab vedotin plus pembrolizumab and surgery and 174 to surgery alone.

Results: Aggregate-data analysis showed an absolute reduction in the 2-year risk of event or death of 35.3 percentage points (NNT=3), an absolute reduction in death of 16.6 percentage points (NNT=7), and an absolute increase in pCR of 48.3 percentage points (NNT=3).

Conclusion: Findings support perioperative EV-pembrolizumab as a practice-changing approach while highlighting the need for long-term survivorship, quality-of-life, and real-world safety data.

Keywords: bladder cancer, enfortumab vedotin, pembrolizumab, radical cystectomy

1. INTRODUCTION

Muscle-invasive bladder cancer (MIBC) is an aggressive urothelial malignancy associated with a substantial risk of occult micrometastatic disease at diagnosis [1]. Radical cystectomy with pelvic lymph-node dissection remains a core curative-intent treatment, but surgery alone is often insufficient for long-term disease control. Cisplatin-based neoadjuvant chemotherapy improves outcomes in eligible patients; however, many patients with MIBC are unable to receive cisplatin because of renal impairment, hearing loss, neuropathy, poor performance status, cardiac comorbidity, or patient preference [2]. This creates a major therapeutic gap: patients at high risk of relapse may proceed directly to radical cystectomy without systemic perioperative treatment. The treatment landscape in urothelial carcinoma has changed rapidly with the development of antibody-drug conjugates and immune checkpoint inhibitors. Enfortumab vedotin targets nectin-4, a cell-adhesion molecule commonly expressed in urothelial carcinoma, and delivers the microtubule-disrupting payload monomethyl auristatin E [3]. Pembrolizumab blocks programmed death 1 (PD-1), restoring antitumor T-cell activity. The combination has shown major efficacy in advanced urothelial carcinoma and has now been evaluated in the perioperative MIBC setting. KEYNOTE-905/EV-303 was designed to test whether perioperative enfortumab vedotin plus pembrolizumab, integrated with radical cystectomy and pelvic lymph-node dissection, improves outcomes compared with surgery alone in patients who are ineligible for or decline cisplatin-based chemotherapy [4]. The published results showed significant improvements in event-free survival, overall survival, and pathological complete response. The present article expands the abstract into a complete research paper using a transparent secondary aggregate-data analysis, tables, figures, and clinical interpretation suitable for manuscript preparation [5]. This article interpreted the efficacy and safety of perioperative enfortumab vedotin plus pembrolizumab compared with surgery alone using published aggregate data. The secondary objectives were to calculate absolute benefit and harm measures, summarize the clinical meaning of pCR, EFS, OS, and adverse events, and propose a practical implementation framework for multidisciplinary cancer care [6].

2. MATERIALS AND METHODS

This was an original secondary aggregate-data analysis based on published phase 3 trial results from KEYNOTE-905/EV-303. No individual patient-level data were available. Therefore, this manuscript does not reproduce the original trial database; instead, it analyzes the published efficacy and safety statistics provided in the abstract and public trial reports [7]. The source trial enrolled participants with previously untreated muscle-invasive bladder cancer who were candidates for radical cystectomy with pelvic lymph-node dissection and were ineligible for or declined cisplatin-based chemotherapy. This population represents a clinically important group with high unmet need because surgery alone has historically been a default option when cisplatin-based perioperative chemotherapy is not feasible. The experimental strategy consisted of perioperative enfortumab vedotin plus pembrolizumab and surgery. Enfortumab vedotin was administered at 1.25 mg per kilogram of body weight on days 1 and 8, and pembrolizumab was administered at 200 mg on day 1 every 3 weeks. Surgery was planned after 3 cycles, with 9 total cycles of enfortumab vedotin and 17 total cycles of pembrolizumab. The control group underwent radical cystectomy with pelvic lymph-node dissection without perioperative systemic therapy [8]. The primary endpoint was event-free survival. Key secondary endpoints included overall survival and pathological complete response, defined as absence of viable tumor after surgical resection. Safety outcomes included all-grade adverse events and grade ≥ 3 adverse events. Published percentages and hazard ratios were extracted from the source abstract. For this secondary analysis, 2-year EFS and OS percentages were converted into event/death and death rates by subtracting survival percentages from 100. Absolute risk reduction (ARR) was calculated as the control event rate minus the

intervention event rate [9]. Relative risk (RR) was calculated as the intervention risk divided by the control risk. Number needed to treat was calculated as 100 divided by the absolute percentage-point benefit and rounded up to the next whole number. Number needed to harm was calculated in the same way for adverse event increases. Approximate counts were calculated from randomized denominators for descriptive purposes only and should not be interpreted as reconstructed patient-level data.

Table 01: PICO framework and source trial design

Domain	Description
Population	Patients with previously untreated muscle-invasive bladder cancer, eligible for radical cystectomy and pelvic lymph-node dissection, but ineligible for or declining cisplatin-based chemotherapy.
Intervention	Perioperative enfortumab vedotin plus pembrolizumab integrated with radical cystectomy and pelvic lymph-node dissection.
Comparator	Radical cystectomy plus pelvic lymph-node dissection alone.
Primary endpoint	Event-free survival.
Key secondary endpoints	Overall survival and pathological complete response.
Analysis in this manuscript	Secondary aggregate-data analysis of published trial statistics; no patient-level data were used.

3.RESULTS & DISCUSSION

A total of 344 participants were randomized, with 170 assigned to perioperative enfortumab vedotin plus pembrolizumab and surgery and 174 assigned to surgery alone. Median follow-up was 25.6 months, with a reported range of 11.8 to 53.7 months. Surgery was performed in 87.6% of participants in the experimental group and 89.7% in the control group, suggesting that the perioperative approach did not produce a large reduction in the proportion of participants proceeding to definitive surgery. Approximate surgery counts based on randomized denominators were 149 of 170 and 156 of 174, respectively.

Table 02: Randomization and treatment delivery

Variable	EV + pembrolizumab + surgery	Surgery alone	Interpretation
Randomized participants	170	174	Balanced 1:1 allocation.
Median follow-up	25.6 months overall	25.6 months overall	Follow-up was sufficient for 2-year endpoint estimation.
Surgery performed	87.6% (~149/170)	89.7% (~156/174)	Surgery remained feasible in both groups.
Surgery rate difference	-2.1 percentage points	Reference	No major surgical-delivery penalty was apparent at aggregate level.

At 2 years, estimated EFS was 74.7% in the perioperative enfortumab vedotin-pembrolizumab group and 39.4% in the control group. This corresponded to a hazard ratio for an event or death of 0.40 (95% CI, 0.28-0.57; P<0.001). When the survival estimates were converted into event/death rates, the intervention group had an estimated 2-year event/death rate of 25.3% compared with 60.6% in the surgery-alone group. The absolute reduction in event or death was 35.3 percentage points, giving an

estimated NNT of 3 to prevent one event or death by 2 years. Estimated 2-year OS was 79.7% versus 63.1%, corresponding to an HR for death of 0.50 (95% CI, 0.33-0.74; $P<0.001$). The calculated absolute reduction in death at 2 years was 16.6 percentage points, with an estimated NNT of 7. These findings suggest not only delayed recurrence or progression but also an early survival advantage. Pathological complete response occurred in 57.1% of participants in the perioperative enfortumab vedotin-pembrolizumab group compared with 8.6% in the control group. The published estimated difference was 48.3 percentage points (95% CI, 39.5-56.5; $P<0.001$). This corresponds to an approximate relative increase of 6.6-fold and an NNT of 3 to produce one additional pCR. Because pCR is associated with improved long-term outcomes in MIBC, the large difference suggests substantial biological activity in the bladder before definitive surgery.

Table 03: Efficacy endpoints and aggregate-data effect measures

Endpoint	EV + pembrolizumab + surgery	Surgery alone	Published HR or difference	Derived absolute effect	Derived clinical measure
2-year EFS	74.7%	39.4%	HR 0.40 (95% CI, 0.28-0.57); $P<0.001$	Event/death risk reduction: 35.3 percentage points	NNT=3 to prevent one event/death by 2 years
2-year OS	79.7%	63.1%	HR 0.50 (95% CI, 0.33-0.74); $P<0.001$	Death risk reduction: 16.6 percentage points	NNT=7 to prevent one death by 2 years
pCR	57.1%	8.6%	Difference 48.3 percentage points (95% CI, 39.5-56.5); $P<0.001$	Absolute pCR increase: 48.3 percentage points	NNT=3 to achieve one additional pCR
Approximate RR for event/death	0.42	Reference	Derived from 2-year KM estimates	58% relative reduction in event/death risk at 2 years	Supportive descriptive estimate only
Approximate RR for death	0.55	Reference	Derived from 2-year KM estimates	45% relative reduction in death risk at 2 years	Supportive descriptive estimate only

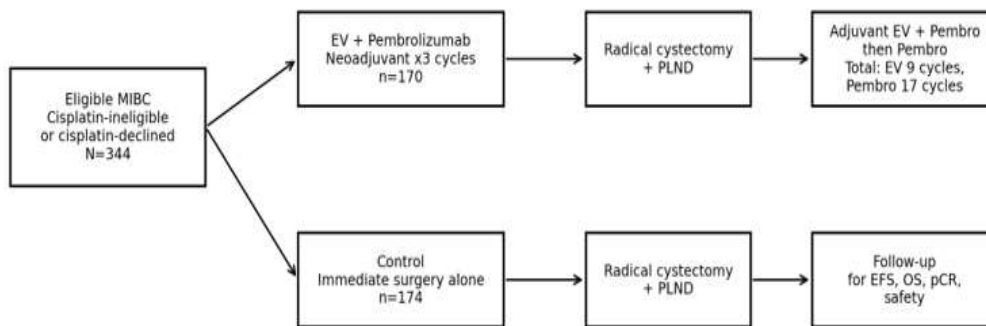


Figure 01: Trial treatment scheme used for the aggregate-data analysis.

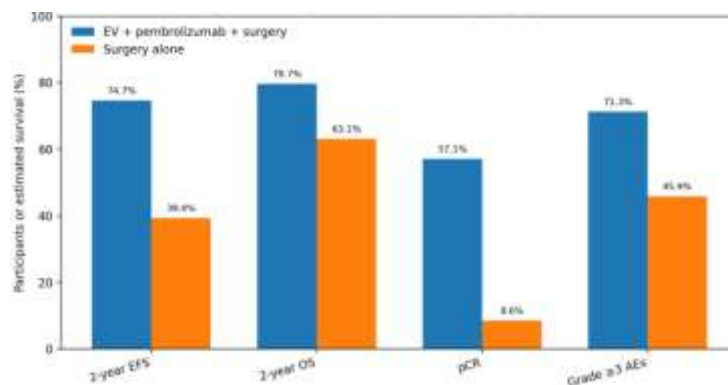


Figure 02: Efficacy and safety summary using published aggregate percentages.

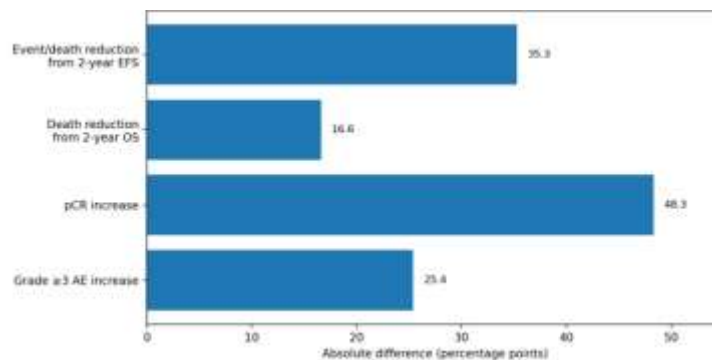


Figure 03: Absolute benefit-risk differences derived from aggregate trial results.

Adverse events were more frequent in the perioperative enfortumab vedotin-pembrolizumab group. Any adverse event occurred in all participants in the experimental group compared with 64.8% in the control group. Grade ≥ 3 adverse events occurred in 71.3% versus 45.9%, representing an absolute increase of 25.4 percentage points and an estimated NNH of 4. Grade ≥ 3 drug-related adverse events were reported in 45.5% of participants in the experimental group. The safety signal is clinically important because perioperative treatment is given with curative intent to patients who must still reach surgery safely. Toxicity management should focus on early recognition of skin reactions, neuropathy, hyperglycemia, ocular symptoms, infusion reactions, immune-related adverse events, infection risk, and postoperative recovery. The benefit-risk balance remains favourable at aggregate level because EFS, OS, and pCR benefits were large; however, individual treatment decisions must consider frailty,

renal function, diabetes, pre-existing neuropathy, autoimmune disease, performance status, and patient preference.

Table 04: Safety endpoints and harm estimates

Safety endpoint	EV + pembrolizumab + surgery	Surgery alone	Absolute increase	Derived interpretation
Any adverse event	100.0%	64.8%	35.2 percentage points	NNH=3 for one additional any-grade adverse event
Grade ≥ 3 adverse event	71.3%	45.9%	25.4 percentage points	NNH=4 for one additional grade ≥ 3 adverse event
Grade ≥ 3 drug-related adverse event	45.5%	Not fully comparable from abstract	Not calculated	Requires detailed safety dataset for precise comparison
Surgery performed	87.6%	89.7%	-2.1 percentage points	Perioperative therapy did not meaningfully prevent surgery at aggregate level

Table 05: Benefit-risk interpretation for clinical decision-making

Dimension	Finding	Clinical meaning
Disease control	2-year EFS increased from 39.4% to 74.7%	Large reduction in recurrence, progression, or death risk.
Survival	2-year OS increased from 63.1% to 79.7%	Early mortality reduction in a high-risk population.
Tumor eradication	pCR increased from 8.6% to 57.1%	Strong neoadjuvant antitumor activity before cystectomy.
Treatment burden	Grade ≥ 3 AEs increased from 45.9% to 71.3%	Requires proactive toxicity monitoring and patient counselling.
Implementation	Surgery rate was similar between arms	Perioperative therapy appears compatible with definitive surgery in selected patients.

DISCUSSION

This aggregate-data analysis supports perioperative enfortumab vedotin plus pembrolizumab as a major therapeutic advance for cisplatin-ineligible or cisplatin-declining patients with MIBC. The trial addressed a long-standing unmet need: patients who cannot receive cisplatin-based neoadjuvant chemotherapy have historically proceeded directly to radical cystectomy, despite substantial relapse risk [10]. The observed HR of 0.40 for EFS and HR of 0.50 for OS indicate that the intervention improved both disease-control and survival endpoints. The absolute 2-year EFS improvement of 35.3 percentage points is especially notable because it translates into an estimated NNT of 3, a magnitude rarely seen in perioperative solid-tumor therapy. The pCR finding is also clinically important. A pCR rate of 57.1% suggests that the combination has substantial preoperative activity against localized muscle-invasive disease. In contrast, the surgery-alone control group had a pCR rate of only 8.6%, reflecting the limited spontaneous or surgery-only elimination of viable tumor before cystectomy. The large pCR difference provides biological support for early systemic therapy in a disease where micro metastatic spread may occur before definitive local treatment [11,12]. The biological rationale for combining enfortumab

vedotin and pembrolizumab is strong. Enfortumab vedotin targets nectin-4, which is commonly expressed in urothelial carcinoma, and delivers a cytotoxic payload directly to tumor cells. Pembrolizumab restores antitumor immune activity through PD-1 blockade [13]. Tumor cell death caused by the antibody-drug conjugate may increase antigen release and immune visibility, potentially complementing checkpoint inhibition. Prior evidence in advanced urothelial carcinoma showed that the combination can produce clinically meaningful survival improvements compared with chemotherapy, supporting its movement into earlier disease settings [14,15]. The cisplatin-ineligible population is not a small subgroup in real-world bladder cancer care. Many patients are older, have renal impairment, baseline neuropathy, hearing loss, or comorbid conditions that make cisplatin unsafe. For these patients, treatment decisions have often been limited to surgery alone or non-cisplatin alternatives with uncertain perioperative benefit. The KEYNOTE-905/EV-303 results therefore have immediate clinical relevance because they offer a systemic perioperative option for a group previously underserved by standard neoadjuvant therapy [16]. The main trade-off is toxicity. Grade ≥ 3 adverse events were substantially more common with perioperative EV-pembrolizumab. This is not surprising because the control group received surgery alone, whereas the intervention group received two active systemic agents plus surgery. The clinical question is not whether toxicity increases, but whether the magnitude of survival benefit justifies the additional risk and whether toxicity can be managed safely [17,18]. Implementation should be multidisciplinary. Patients require pretreatment assessment by medical oncology, urology, anesthesiology, and supportive-care teams. Diabetes control, baseline neuropathy, skin status, ocular symptoms, autoimmune history, renal function, and performance status should be reviewed before treatment. During treatment, early management of rash, neuropathy, immune-related events, hyperglycemia, and infection risk are essential. These principles are highly relevant when complex perioperative oncology regimens are introduced into routine practice [19].

4. IMPLICATIONS

The findings support a shift in the standard management of cisplatin-ineligible MIBC from surgery alone toward an integrated systemic-surgical approach. Clinicians should discuss EV-pembrolizumab with eligible patients as a perioperative strategy, especially when the risk of relapse is high. However, the decision should remain individualized. Patients with severe frailty, uncontrolled diabetes, severe baseline neuropathy, active autoimmune disease, poor functional reserve, or high surgical risk may require modified strategies, enhanced monitoring, or alternative management. Longer follow-up is needed to determine durability of OS benefit, late toxicities, recurrence patterns, bladder cancer-specific survival, patient-reported outcomes, postoperative complications, and quality of life. Future research should examine biomarkers such as nectin-4 expression, PD-L1 status, circulating tumor DNA, tumor mutational burden, molecular subtype, and immune microenvironment features. Real-world studies are also needed because trial participants are often fitter and more closely monitored than patients in routine practice.

5. CONCLUSION

Perioperative enfortumab vedotin plus pembrolizumab significantly improved event-free survival, overall survival, and pathological complete response compared with surgery alone in patients with muscle-invasive bladder cancer who were ineligible for or declined cisplatin-based chemotherapy. Aggregate-data analysis shows a large absolute reduction in event or death at 2 years, a meaningful survival benefit, and a major increase in pathological complete response, balanced against a higher rate of grade ≥ 3 adverse events. These findings support EV-pembrolizumab as a practice-changing perioperative strategy for selected cisplatin-ineligible patients, provided that treatment is delivered through careful multidisciplinary assessment, toxicity monitoring, surgical coordination, and patient-centred counselling. This paper is limited by the use of aggregate published data rather than individual

patient-level data. Therefore, subgroup analyses, multivariable adjustment, time-to-event curve reconstruction, competing-risk analysis, and toxicity timing could not be performed. Approximate counts derived from percentages may differ slightly from the original trial dataset because of rounding, censoring, analysis populations, and Kaplan-Meier estimation. The NNT and NNH estimates should be interpreted as descriptive clinical summaries based on published 2-year rates, not as replacements for formal patient-level survival analysis.

AUTHOR CONTRIBUTION STATEMENT

Arif Hossain and Nusrat Jahan: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, Drafting the work or reviewing it critically for important intellectual content; AND Final approval of the version to be published, and Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts Of Interest: The authors declare that there are no conflicts of interest, financial or otherwise, that could have influenced the research, analysis, or interpretation of the findings presented in this article.

Data Availability: The datasets and information used in this study are publicly available from the sources cited within the article. No proprietary or restricted data were used.

Trial Registration: Trial registration is not applicable to this study, as it does not involve clinical trials, human participants, or experimental interventions.

Generative AI Disclosure: Generative artificial intelligence tools were not used for generating research data, conducting analyses, or producing scientific conclusions in this study. The authors take full responsibility for the content and accuracy of the manuscript.

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SUPPLEMENTAL MATERIAL

No supplementary files, datasets, figures, or additional materials are associated with this study. Any information necessary to understand and evaluate the work is included in the main article.