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Perioperative Enfortumab Vedotin Plus Pembrolizumab in Participants With Muscle-invasive Bladder Cancer Who Are Cisplatin-ineligible: Phase 3 KEYNOTE-905 Study

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Background

- Neoadjuvant cisplatin-based chemotherapy (with/without perioperative durvalumab, or adjuvant nivolumab for high-risk disease) and RC + PLND is standard of care for patients with MIBC[1,2]
- Nearly 50% of patients with MIBC are ineligible for cisplatin (per Galsky criteria)[3-6]
  - These patients have no neoadjuvant options and tend to be older, frailer, and have more comorbidities
- Limited literature in this cisplatin-ineligible population with MIBC suggests poor outcomes with RC + PLND alone, highlighting a significant unmet medical need[3-5]
  - No prior phase 3 trial has shown benefit from perioperative therapy in this population
- Enfortumab vedotin (EV) + pembrolizumab (pembro) has strong rationale for investigation in the perioperative setting in this population
- The randomized, open-label, phase 3 KEYNOTE-905 study compared perioperative EV + pembro with RC + PLND versus RC + PLND alone in participants with MIBC who are ineligible for or declined cisplatin-based chemotherapy

MIBC, muscle-invasive bladder cancer; RC + PLND, radical cystectomy with standard pelvic lymph node dissection.

1. Powles T, et al. *Ann Oncol* 2022; 2. NCCN Bladder cancer (v1.2025); 3. Fazili AN, et al. *J Urol* 2025; 4. Jiang DM, et al. *Nat Rev Urol* 2021; 5. Galsky MD, et al. *Lancet Oncol* 2011; 6. Dash A, et al. Cancer 2006.

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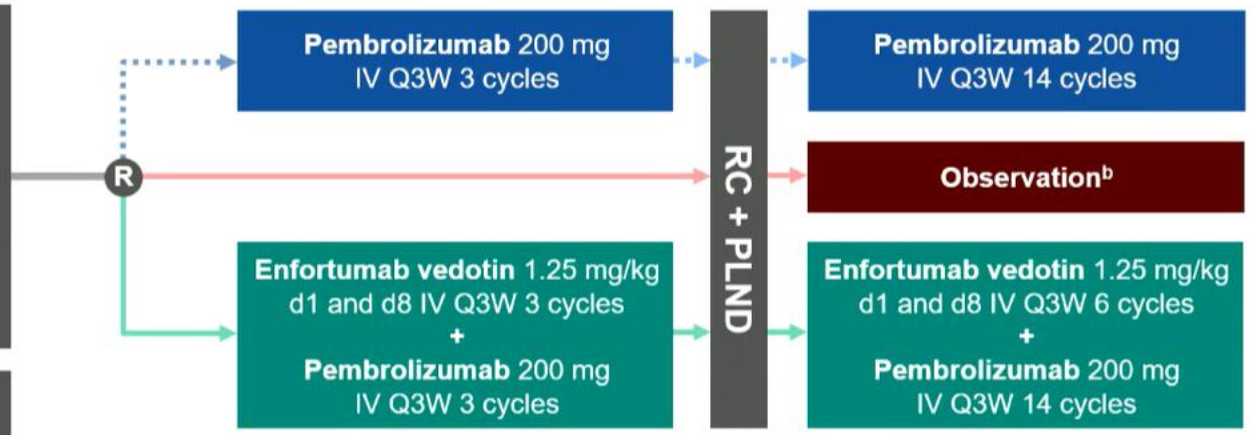
KEYNOTE-905/EV-303 Study (NCT03924895)

Key Eligibility Criteria

- Adults with MIBC
- Clinical stage T2-T4aN0M0 or T1-T4aN1M0 by central assessment
- ≥50% Urothelial histology
- Cisplatin-ineligible per Galsky criteria[a] or cisplatin-declining
- ECOG PS 0-2

Stratification Factors

- Cisplatin ineligibility (ineligible vs. eligible but declining)
- Clinical stage (T2N0 vs. T3/T4aN0 vs. T1-4aN1)
- Region (US vs. EU vs. Most of World)



Primary endpoint: Event-free survival (EFS) by BICR

Key secondary endpoints: OS and pathological complete response (pCR; pT0N0, i.e. absence of viable tumor in examined tissue from surgery) by central pathologist review

Other secondary endpoints include: Safety

Exploratory endpoints include: EFS by pCR status

BICR, blinded independent central review; IV, intravenous; Q3W, every 3 weeks. [a]Protocol-defined as having ≥1 of the following: impaired renal function (creatinine clearance 30–59 ml/min), ECOG PS 2, gr ≥2 audiometric hearing loss, or NYHA class III heart failure; [b]As of Nov 2022, adjuvant nivolumab was permitted when clinically indicated and regionally available.

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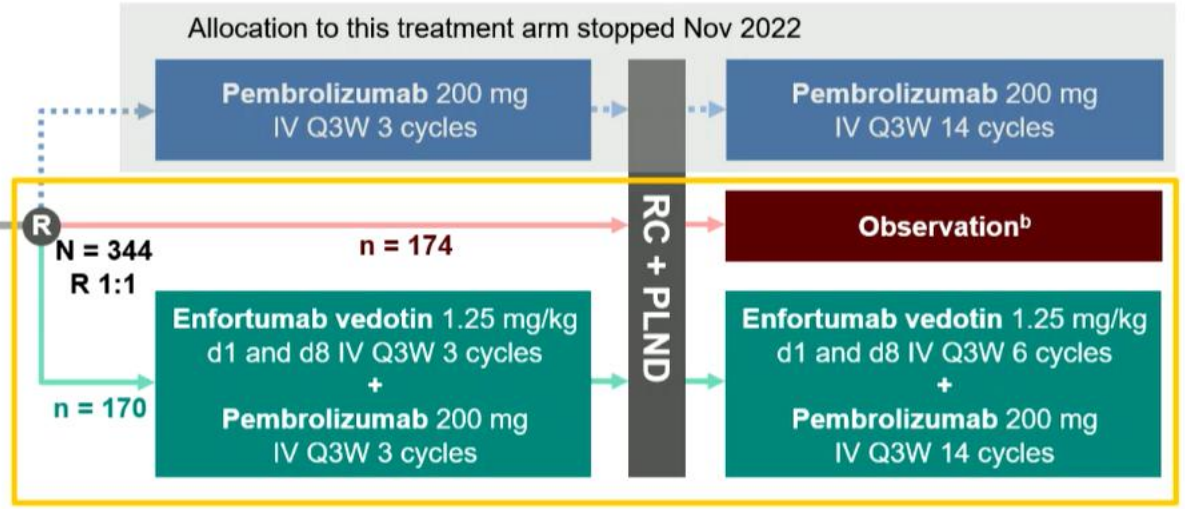

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Timeline of Study Design Development

2019
Study initiated with 2 arms:
- Perioperative **pembro with RC + PLND** vs. **RC + PLND**
- Randomized 1:1

2020
Third arm added:
- Perioperative **EV + pembro with RC + PLND**
- Randomization updated to 1:1:1

2022
Inclusion criteria expanded to include participants who are cisplatin-eligible but decline cisplatin-based chemotherapy

2022
- Randomization to **pembro with RC + PLND arm** stopped
- Randomization updated to 1:1 to perioperative **EV + pembro with RC + PLND (EV + pembro arm)** vs. **RC + PLND (control arm)**
- Adjuvant nivolumab permitted in the **control arm** when clinically indicated and regionally available

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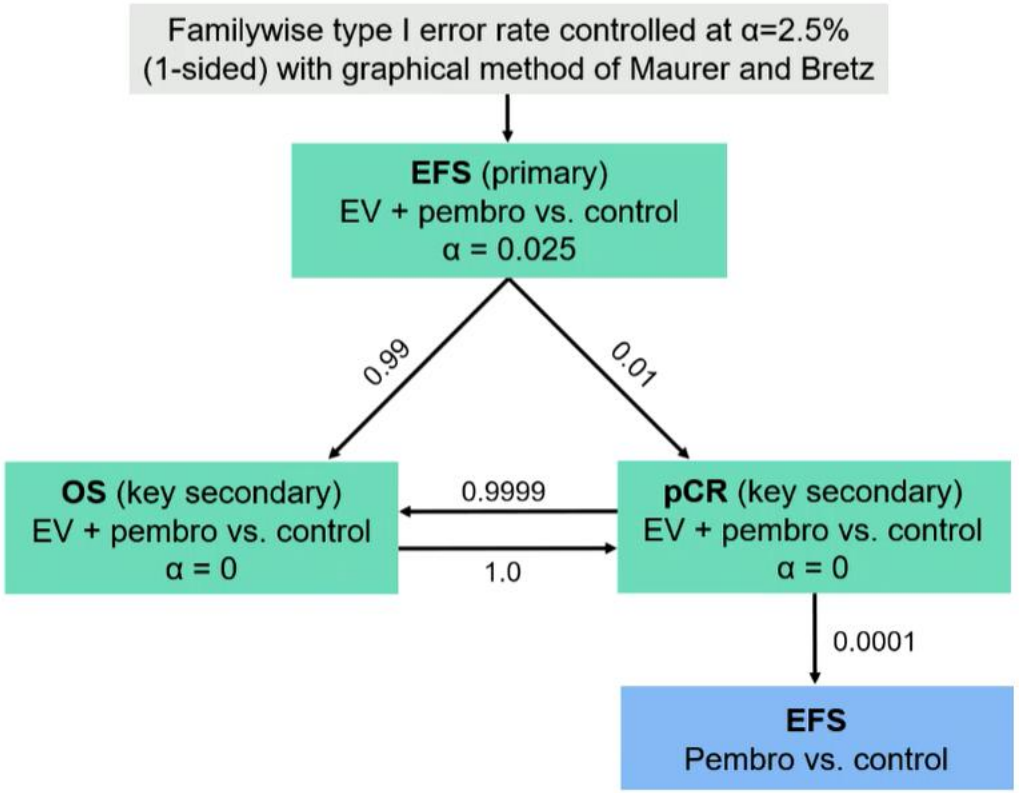
Statistical Considerations



- **Efficacy** for EV + pembro vs control was assessed in all concurrently randomized participants (ITT population) to the EV + pembro and control arms
- **TEAEs** were assessed in all participants with ≥1 dose of study treatment, including surgery
- Study continues to evaluate additional hypotheses for perioperative pembro arm

ITT, intention-to-treat; TEAE, treatment-emergent adverse event.

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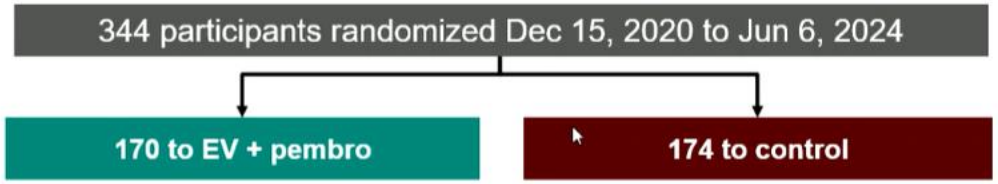
Participant Disposition



Time from randomization to data cutoff date (June 6, 2025):
median 25.6 months (range, 11.8–53.7)

[a]Included 3 pts who received surgery without on-study neoadjuvant therapy. [b]Incomplete resection included: unresectable tumor, newly discovered metastatic disease, or other.

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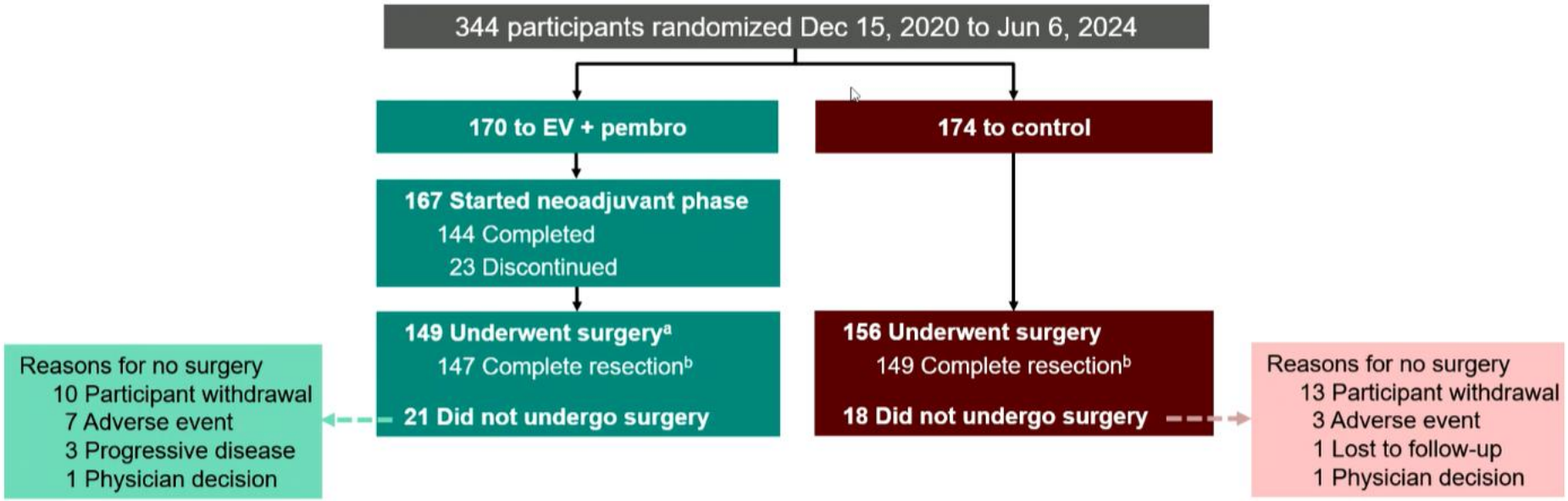

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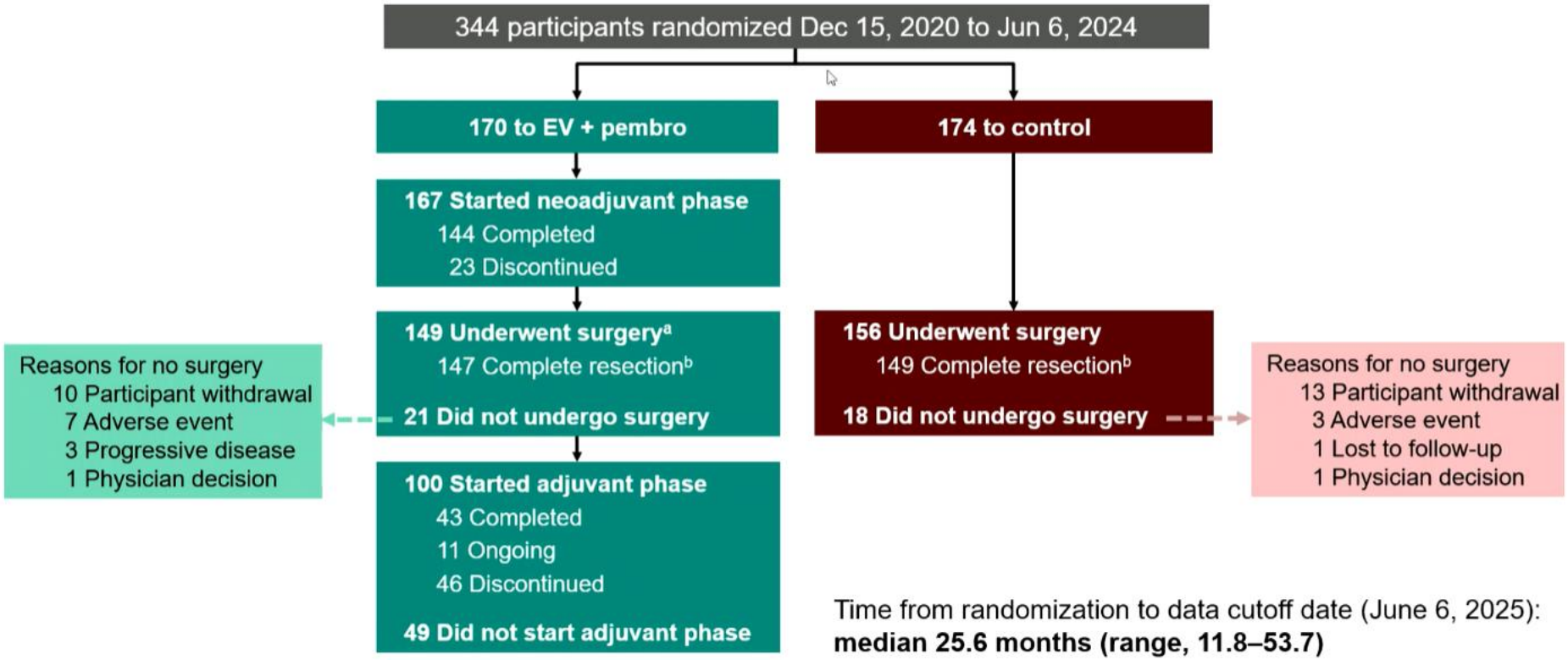

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Baseline Characteristics

Characteristic, n (%)	EV + pembro (N = 170)	Control (N = 174)
Median age (range), years	74.0 (47–87)	72.5 (46–87)
≥65 to <75 years	63 (37.1)	77 (44.3)
≥75 years	78 (45.9)	68 (39.1)
Male	137 (80.6)	131 (75.3)
ECOG PS		
0	102 (60.0)	95 (54.6)
1	47 (27.6)	53 (30.5)
2	21 (12.4)	26 (14.9)
Region		
United States	21 (12.4)	23 (13.2)
European Union	78 (45.9)	77 (44.3)
Most of World	71 (41.8)	74 (42.5)
Cisplatin eligibility status (per Galsky criteria)		
Ineligible	142 (83.5)	139 (79.9)
Eligible but declining	28 (16.5)	35 (20.1)
PD-L1 combined positive score (CPS) ≥10[a]	80 (47.1)	83 (47.7)
Tumor stage at baseline (*centrally assessed using both pathology of TURBT specimen and imaging*)[b]		
T2N0	30 (17.6)	32 (18.4)
T3/T4aN0	133 (78.2)	132 (75.9)
T1-4aN1	7 (4.1)	10 (5.7)
Creatinine clearance		
≥60 mL/min	68 (40.0)	72 (41.4)
≥30 and <60 mL/min	102 (60.0)	101 (58.0)
<30 mL/min	0	1 (0.6)
Pure urothelial carcinoma histology	152 (89.4)	161 (92.5)

TURBT, transurethral resection of bladder tumor. [a]By PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA); CPS = # PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) ÷ total # viable tumor cells × 100. [b]By investigator assessment, 124 pts (72.9%) in the EV + pembro arm and 119 pts (68.4%) in the control had T2N0 stage MIBC at baseline.

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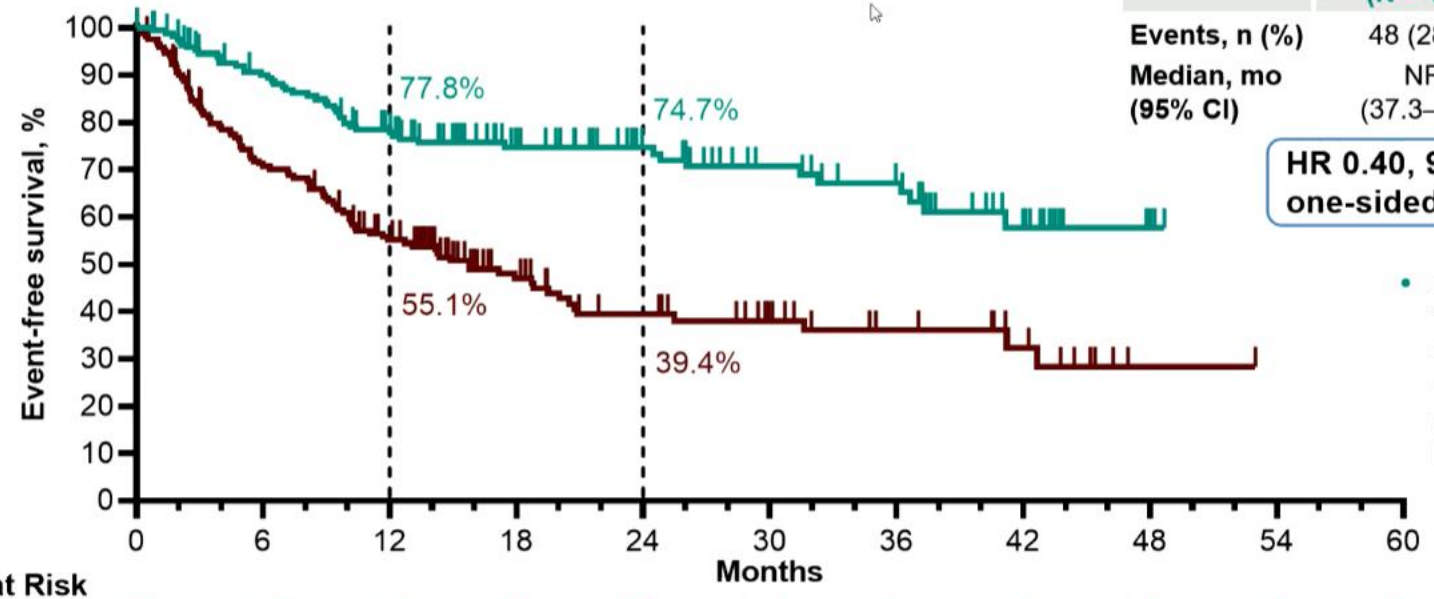
Primary Endpoint: EFS[a] by BICR

ITT Population



	EV + pembro (N = 170)	Control (N = 174)
Events, n (%)	48 (28.2)	95 (54.6)
Median, mo (95% CI)	NR (37.3–NR)	15.7 (10.3–20.5)

HR 0.40, 95% CI 0.28–0.57, one-sided *P* <.0001*

- 29/174 pts (16.7%) in the control arm received adjuvant nivolumab as of data cutoff per local guidelines/prescribing information

No. at Risk

EV + pembro	170	140	116	73	56	42	35	16	3	0	0
Control	174	116	84	48	33	22	14	9	1	0	0

NR, not reached. * denotes statistical significance (one-sided boundary 0.0097). [a]Time from randomization to first occurrence of: radiographic PD precluding surgery; biopsy-proven residual MIBC (pts who did not undergo surgery); gross residual disease post-surgery or newly detected metastatic disease at surgery; local/distant recurrence post-surgery (imaging or biopsy); or death (any cause). Any new high-risk NMIUC was also considered an event. Pts who did not undergo surgery were considered as having an EFS event if they met criteria for EFS events at any point in time or were censored within ≤16 wks from last dose of neoadjuvant therapy or surgery.

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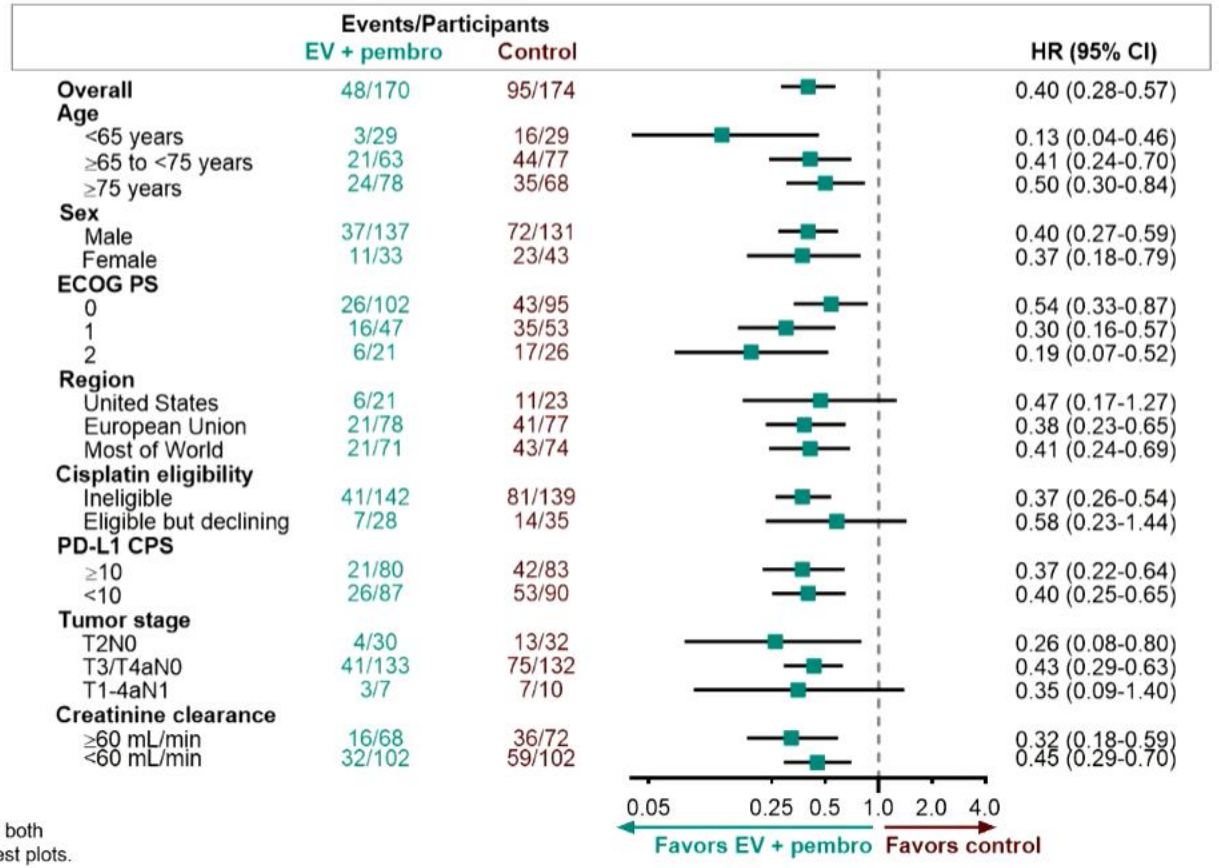
EFS by BICR in Key Subgroups

ITT Population



Subgroup levels with <10 events across both treatment arms were not included in forest plots.

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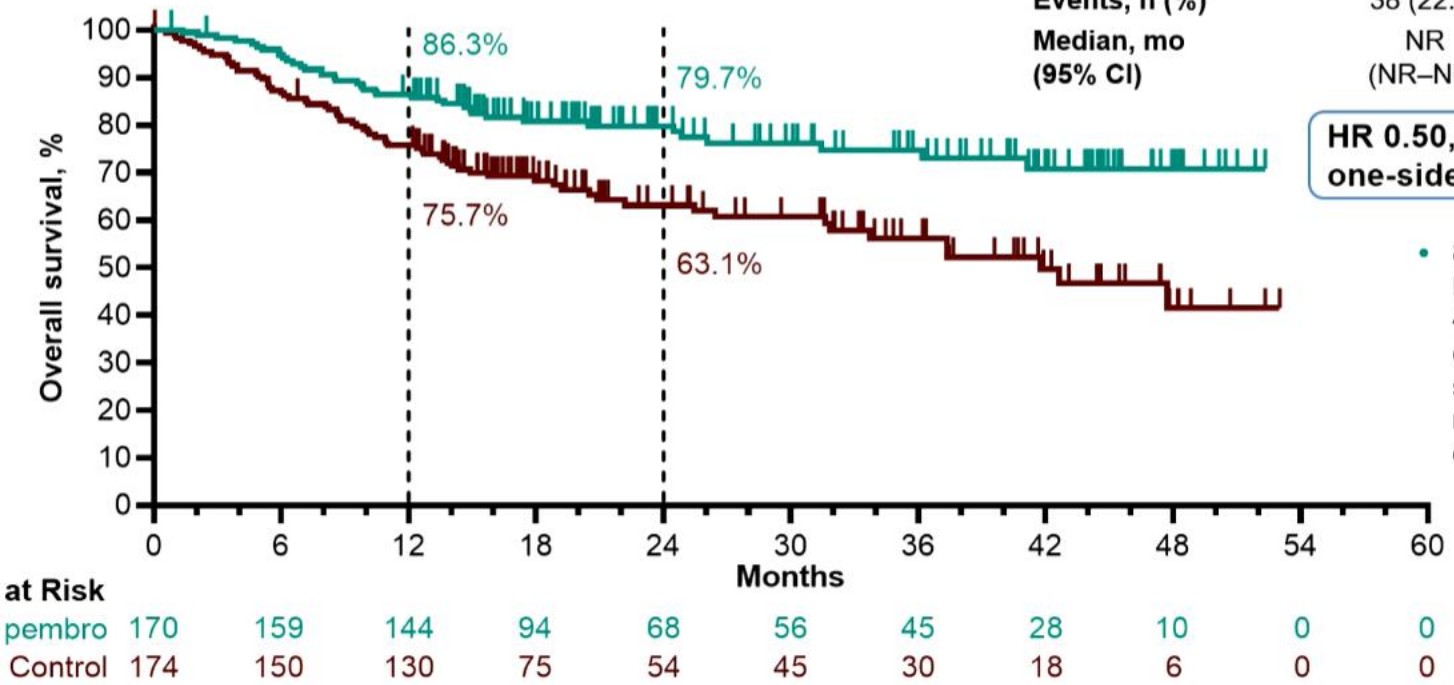
Key Secondary Endpoint: OS

ITT Population



	EV + pembro (N = 170)	Control (N = 174)
Events, n (%)	38 (22.4)	68 (39.1)
Median, mo (95% CI)	NR (NR–NR)	41.7 (31.8–NR)

HR 0.50, 95% CI 0.33–0.74, one-sided *P* =.0002*

- 8/170 pts (4.7%) in the EV + pembro arm and 46/174 (26.4%) in the control arm received subsequent therapy for recurrent/metastatic disease

No. at Risk

EV + pembro	170	159	144	94	68	56	45	28	10	0	0
Control	174	150	130	75	54	45	30	18	6	0	0

NR, not reached. * denotes statistical significance (one-sided boundary 0.00488).

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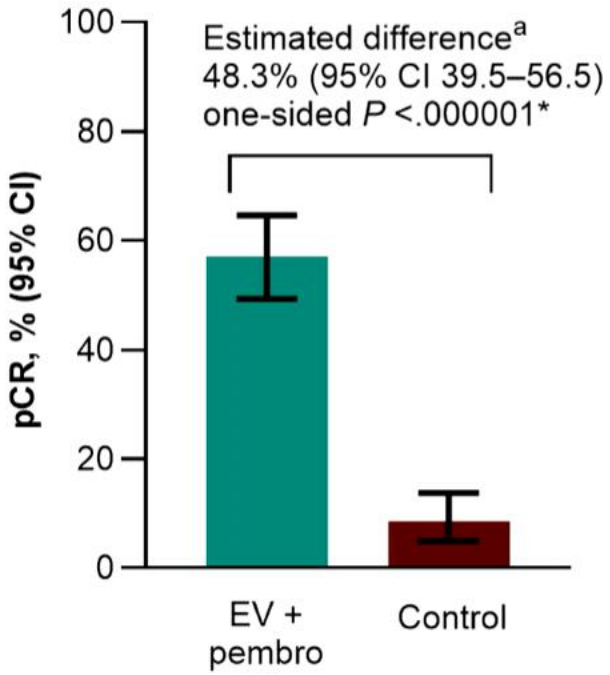
Key Secondary Endpoint: pCR by Central Pathology Review

ITT Population



	EV + pembro (N = 170)	Control (N = 174)
pCR, n	97	15
pCR rate, % (95% CI)	57.1 (49.3–64.6)	8.6 (4.9–13.8)

- **pCR:** absence of viable tumor (pT0N0) in examined tissue from RC + PLND
- Pts who did not undergo surgery, including those with clinical complete response after neoadjuvant therapy, were considered non-responders

* denotes statistical significance (one-sided boundary 0.00025).
[a]Based on stratified Miettinen and Nurminen method.

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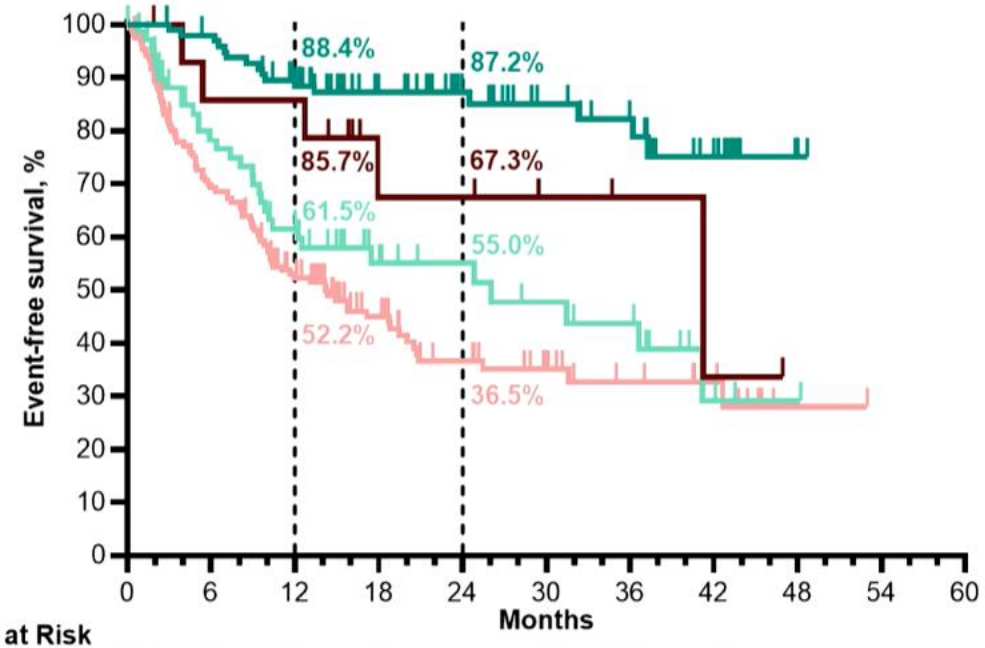
EFS by pCR Status

ITT Population



No. at Risk											
EV + pembro (pCR)	97	93	80	54	41	30	25	13	2	0	0
EV + pembro (no pCR)	73	47	36	19	15	12	10	3	1	0	0
Control (pCR)	15	12	12	6	6	3	2	1	0	0	0
Control (no pCR)	159	104	72	42	27	19	12	8	1	0	0

NR, not reached.

Status: pCR

	EV + pembro (n = 97)	Control (n = 15)
Events, n (%)	16 (16.5)	5 (33.3)
Median, mo (95% CI)	NR (NR–NR)	41.2 (12.7–NR)
HR (95% CI)	0.43 (0.16–1.16)	

Status: No pCR

	EV + pembro (n = 73)	Control (n = 159)
Events, n (%)	32 (43.8)	90 (56.6)
Median, mo (95% CI)	26.1 (10.1–41.2)	14.2 (10.1–19.5)
HR (95% CI)	0.76 (0.51–1.14)	

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Summary of AEs, All Phases of Treatment

Safety Analysis Population

- Median (range) duration of **neoadjuvant therapy** in the EV + pembro arm (N = 167): 1.6 months (0.03–2.8)
  - Median cycles of neoadjuvant EV + pembro: 3.0 (range, 1.0–3.0)
- Median (range) duration of **adjuvant therapy** in the EV + pembro arm (N = 100): 8.0 months (0.03–12.9)
  - Median (range) number adjuvant cycles of EV was 6.0 (1.0–6.0) and of pembro was 12.0 (1.0–14.0)

	EV + pembro (N = 167)	Control (N = 159)
Any grade TEAE[a]	167 (100)	103 (64.8)
Surgery phase only[b]	99/146 (67.8)	103 (64.8)
Grade ≥3 TEAE	119 (71.3)	73 (45.9)
Surgery phase only	52/146 (35.6)	73 (45.9)
Serious TEAE	97 (58.1)	65 (40.9)
Surgery phase only	42/146 (28.8)	65 (40.9)
AE leading to surgery delay[c]	6/149 (4.0)	1/156 (0.6)
TEAE leading to dose reduction of EV	28 (16.8)	NA
TEAE leading to discontinuation of EV	69 (41.3)	NA
TEAE leading to discontinuation of pembro	57 (34.1)	NA
TEAE leading to death	13 (7.8)*	9 (5.7)
Surgery phase only	4/146 (2.7)	9 (5.7)

TEAE, treatment-emergent adverse event. Data are n (%) when denominator matches header, and n/N (%) when denominator is different.
*Included 2 drug-related deaths (both during neoadjuvant phase: n = 1 myasthenia gravis and n = 1 toxic epidermal necrolysis).

[a]Collected up to 30 days after cessation of study treatment (serious AEs collected up to 90 days, or 30 days after if pt started a new anticancer therapy). [b]Defined as time from date of surgery to 30 days post-surgery for nonserious events (90 days for serious events) and prior to date of first postoperative study drug (if applicable). [c]Surgery delay defined as >8 weeks from last preoperative drug dose (or randomization if no preoperative drug received) to surgery for the EV + pembro arm (18/149 pts; 12.1%); and >8 weeks from randomization to surgery for the control arm (25/156 pts; 16.0%). Data cutoff date: 6 June 2025

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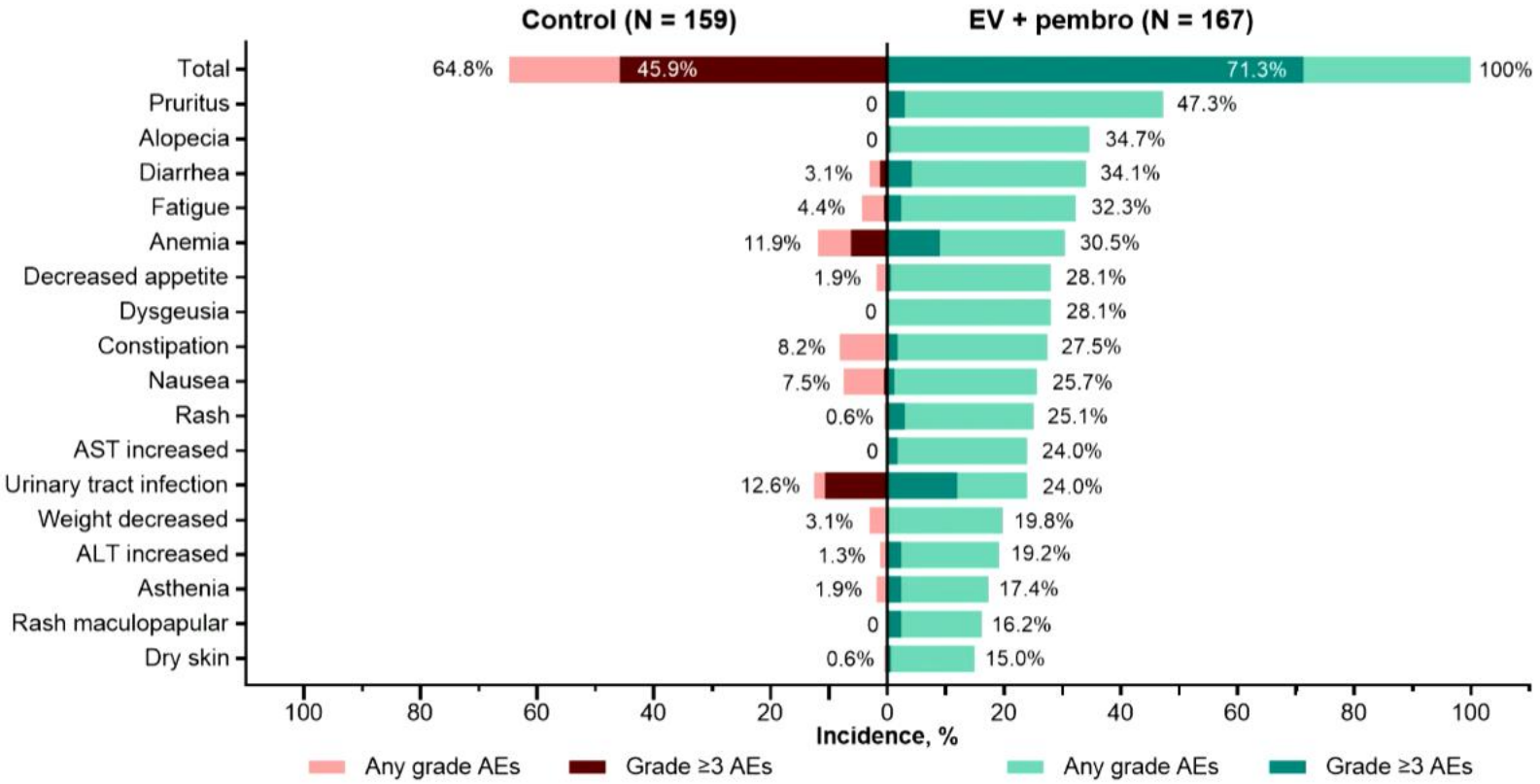
Common TEAEs[a] (Incidence ≥15%), All Phases of Treatment

Safety Analysis Population



[a]Collected up to 30 days after cessation of study treatment.

Data cutoff date: 6 June 2025

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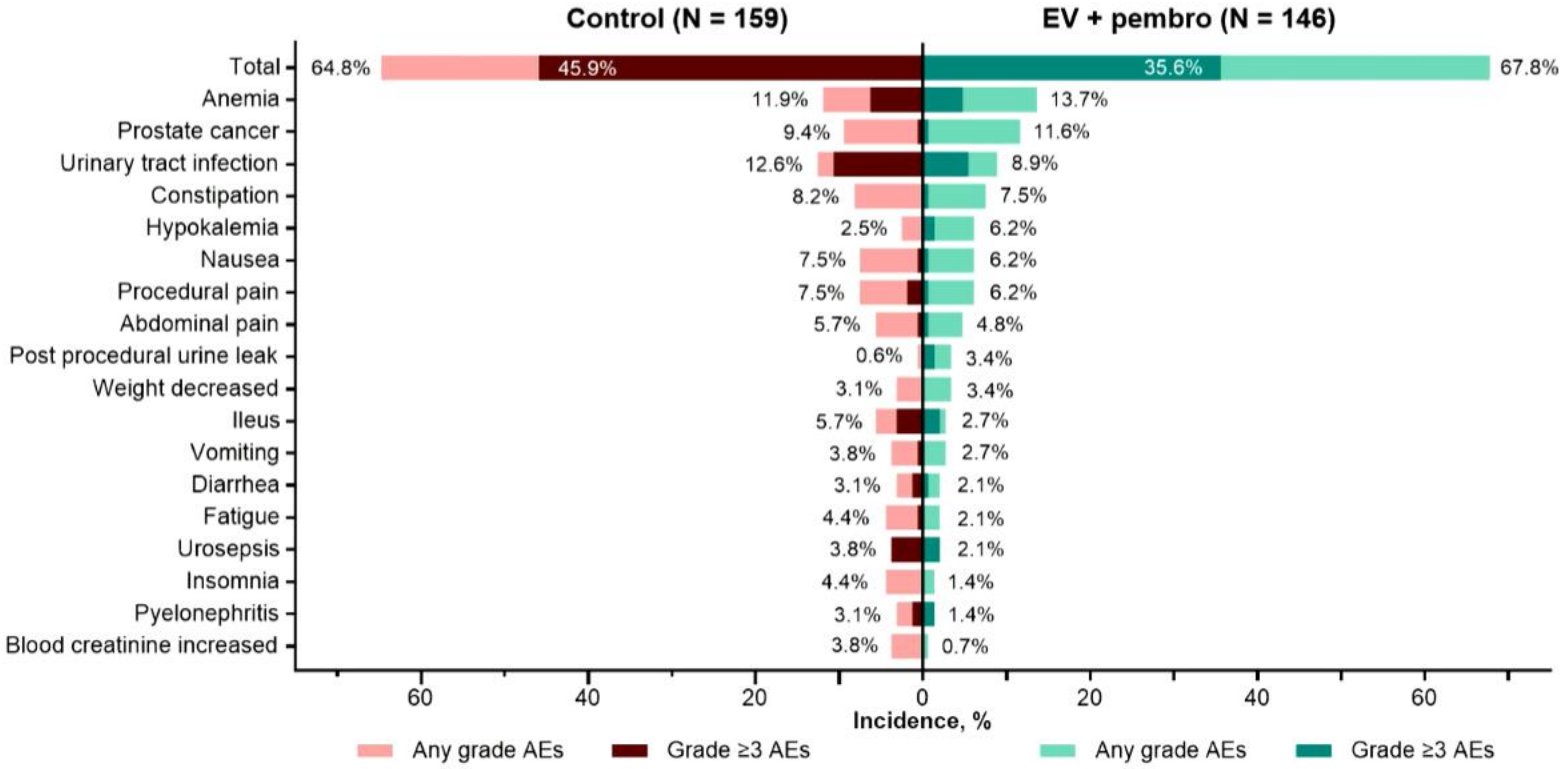
TEAEs During Surgery Phase

Safety Analysis Population; Incidence ≥3.0%



[a]Defined as time from date of surgery to 30 days post-surgery for nonserious events (90 days for serious events) and prior to date of first postoperative study drug (if applicable).

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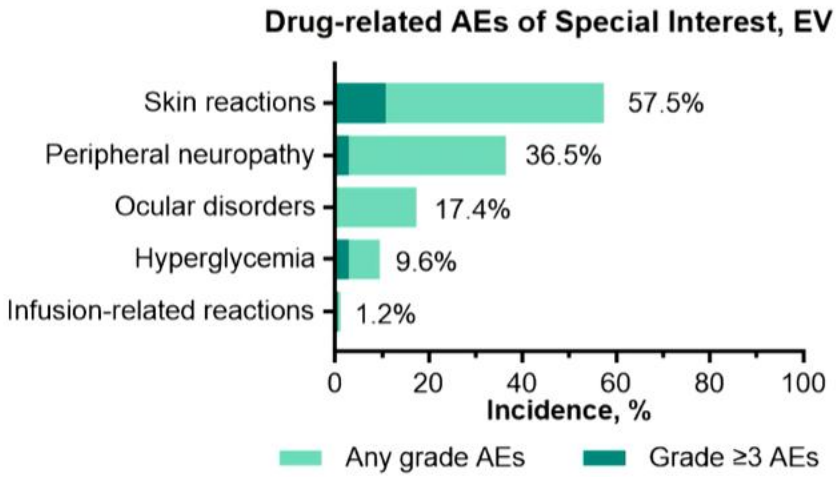
AEs of Special Interest[a]

Safety Analysis Population, EV + Pembro Arm



[a]Based on separate prespecified lists of preferred terms (grouped) of known risks associated with EV and pembro treatment. [b]Considered regardless of attribution to study treatment by the investigator. [c]Infusion reactions, reported separately, occurred in 1 pt (0.6%); no grade ≥3 infusion reactions occurred.

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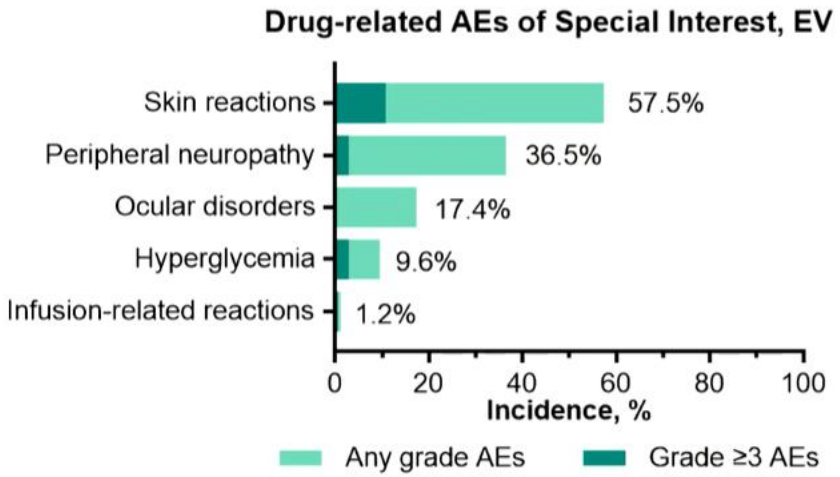
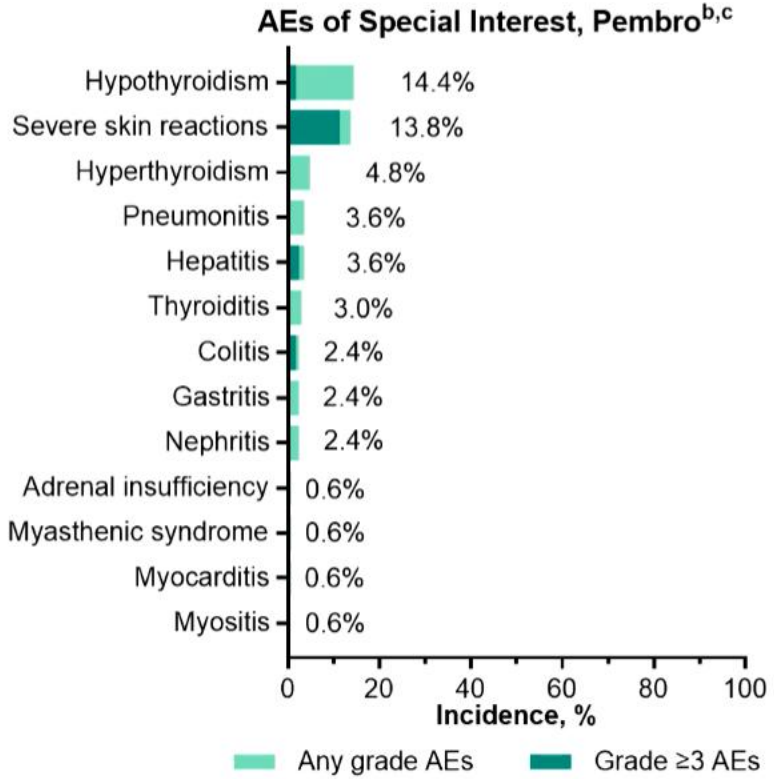
AEs of Special Interest[a]

Safety Analysis Population, EV + Pembro Arm





[a]Based on separate prespecified lists of preferred terms (grouped) of known risks associated with EV and pembro treatment. [b]Considered regardless of attribution to study treatment by the investigator. [c]Infusion reactions, reported separately, occurred in 1 pt (0.6%); no grade ≥3 infusion reactions occurred.

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Summary and Conclusions

- Neoadjuvant EV + pembro, RC + PLND, and adjuvant EV + pembro significantly and meaningfully improved EFS, OS, and pCR rate in participants with MIBC who are ineligible for or declined cisplatin-based chemotherapy
  - EFS and OS benefit was generally consistent across key subgroups
- Perioperative EV + pembro did not impact the ability of participants to undergo curative intent surgery
- The safety profile of perioperative EV + pembro was manageable and consistent with prior reports of this regimen in the locally advanced/metastatic urothelial carcinoma setting; no new safety signals were observed
- KEYNOTE-905 is the first phase 3 study to show improved efficacy outcomes with perioperative therapy relative to surgery for patients with MIBC who are ineligible for cisplatin-based chemotherapy
  - Perioperative EV + pembro added to RC + PLND may represent a new standard of care in this population with high unmet clinical need

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