Perioperative pembrolizumab therapy in muscle-invasive bladder cancer: Phase III KEYNOTE-866 and KEYNOTE-905/EV-303

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Trial registration numbers: NCT3924856 and NCT03924895

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Objectives

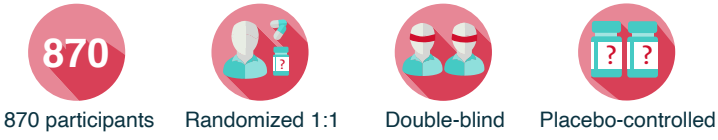
KEYNOTE-866
To evaluate the efficacy and safety of perioperative pembrolizumab or placebo plus neoadjuvant chemotherapy in cisplatin-eligible patients with MIBC undergoing RC+PLND

KEYNOTE-905/EV-303
To evaluate the efficacy and safety of perioperative pembrolizumab monotherapy versus pembrolizumab plus enfortumab vedotin versus RC+PLND alone in cisplatin-ineligible patients with MIBC undergoing RC+PLND

Key eligibility criteria

- Eligible for treatment with cisplatin (KEYNOTE-866)
- Ineligible for treatment with cisplatin (KEYNOTE-905/EV-303)
- Histologically confirmed diagnosis of MIBC with predominant urothelial histology
- Clinically nonmetastatic bladder cancer (N ≤ 1M0)
- Eligible for and agree to undergo curative-intent standard RC+PLND per AUA/ASTRO/ASCO/SUO guidelines
- No prior systemic antineoplastic treatment for MIBC
- Underwent TURBT ≤74 days before enrollment that is adequate for evaluation of histology and PD-L1 expression
- ECOG PS score 0 or 1 (KEYNOTE-866)
- ECOG PS score 0, 1, or 2 (KEYNOTE-905/EV-303)

KEYNOTE-866: Study design and treatment



Stratification

R 1:1

Neoadjuvant phase

Placebo + Gemcitabine 1000 mg/m² and Cisplatin 70 mg/m² Q3W ×4 cycles

Pembrolizumab 200 mg Q3W IV + Gemcitabine 1000 mg/m² and Cisplatin 70 mg/m² Q3W ×4 cycles

RC+PLND

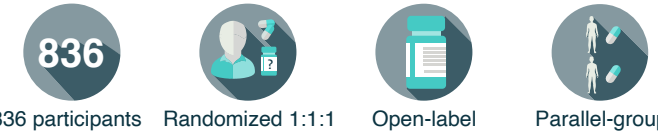
Adjuvant phase

Placebo ×13 cycles

Pembrolizumab 200 mg Q3W IV ×13 cycles

Post-treatment follow-up will assess:
• EFS • OS • Safety • PROs

KEYNOTE-905/EV-303: Study design and treatment



Stratification

R 1:1:1

Observation

Pembrolizumab 200 mg Q3W IV ×3 cycles + Enfortumab vedotin 1.25 mg/kg Q3W IV ×3 cycles

Neoadjuvant phase

Pembrolizumab 200 mg Q3W IV ×3 cycles

Time from randomization to RC+PLND ≤12 weeks for pembrolizumab ± enfortumab vedotin arms, ≤8 weeks for observation arm

RC+PLND

Adjuvant phase

Observation

Pembrolizumab 200 mg Q3W IV ×14 cycles + Enfortumab vedotin 1.25 mg/kg Q3W IV ×6 cycles

Pembrolizumab 200 mg Q3W IV ×14 cycles

Post-treatment follow-up will assess:
• Survival • Pathologic downstaging • Safety • PROs

Outcome measures/end points

Primary end points (both studies)

- pCR (absence of viable tumor [T0N0] in examined tissue from RC+PLND per central pathologic review)
- EFS, defined as the time from randomization to first occurrence of radiographic progressive disease per RECIST v1.1

Key secondary end points (both studies)

- OS (time from randomization to death from any cause)
- DFS (time from postsurgery baseline imaging until the first occurrence of local or distant recurrence or death from any cause)
- Proportion of patients with pathologic downstaging (<pT2 and N0 in examined tissue from RC+PLND)
- Safety and tolerability

Patient-reported outcomes were a secondary end point for KEYNOTE-866 and an exploratory end point for KEYNOTE-905/EV-303

Glossary

ASCO: American Society of Clinical Oncology; ASTRO: American Society for Radiation Oncology; AUA: American Urological Association; DFS: Disease-free survival; ECOG PS: Eastern Cooperative Oncology Group performance status; EFS: Event-free survival; IV: Intravenously; MIBC: Muscle-invasive bladder cancer; NMIBC: Non–muscle-invasive bladder cancer; OS: Overall survival; pCR: Pathologic complete response; PD-L1: Programmed death ligand 1; Q3W: Every 3 weeks; RC+PLND: Radical cystectomy + pelvic lymph node dissection; RECIST: Response Evaluation Criteria in Solid Tumors; SUO: Society of Urologic Oncology; TURBT: Transurethral resection of bladder tumor.