Evolving Treatment Paradigms in Bladder Cancer Across the Care Continuum

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DISCLOSURES

The following relevant financial relationships from the past 24 months have been identified and disclosed for the following planners of this CE activity:

- **Timothy Schieber, PharmD, MBA**
  - Pfizer, Bristol Myers Squibb
- **Andrew Ruplin, PharmD**
  - MJH Life Sciences, Dedham Group

There are no relevant conflicts of interest to disclose for this presentation for the following planners of this CE activity:

- **Tahsin Imam, PharmD**
- **Madelyn Floysand, PharmD**

Data supporting off-label indications or testing will be discussed along with expert opinion in select subject matters.

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OBJECTIVES

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1. Summarize recently approved and emerging bladder-sparing therapies for BCG-unresponsive non–muscle invasive bladder cancer (NMIBC), including systemic and intravesical treatment options.
2. Explore emerging data supporting the use of enfortumab vedotin plus pembrolizumab in muscle-invasive bladder cancer (MIBC), including perioperative strategies and implications for cisplatin-eligible and cisplatin-ineligible patients.
3. Review current treatment strategies and sequencing considerations in locally advanced and metastatic urothelial carcinoma, including integration of antibody–drug conjugates, targeted therapy, and immunotherapy combinations based on clinical trial data.
4. Discuss evolving administration strategies for immune checkpoint inhibitors, including intravenous and subcutaneous formulations of pembrolizumab and nivolumab, and their potential impact on patient care and clinic workflow.
5. Recognize key adverse effects and mitigation strategies associated with immune checkpoint inhibitors and antibody-drug conjugates used in bladder cancer treatment.

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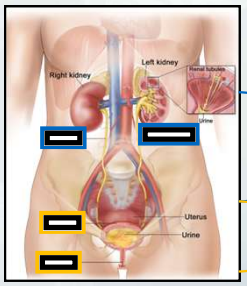
Bladder Cancer Overview



- 6th most common cancer in US
  - 4th most common in men
  - 12th most common in women
- Transitional cell urothelium line the urinary tract
  - Urothelial carcinoma can develop anywhere in urinary tract

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National Cancer Institute. https://www.cancer.gov/types/bladder/hp/bladder-treatment-pdq#_19.toc. Accessed March 9, 2026.

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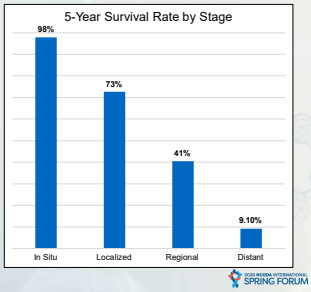
Epidemiology of Bladder Cancer in the US

Estimated New Cases in 2025	84,870
Percent of All New Cancer Cases	4.2%
Estimated Deaths in 2025	17,420
Percent of All Cancer Deaths	2.8%
5-Year Relative Survival (2015-2021)	79.0%



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National Cancer Institute. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed March 9, 2026.

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Histologic Subtypes

- **Urothelial carcinoma**
  - Begins in urothelial cells which line the urethra, bladder, ureters, renal pelvis, and other organs
- **Squamous cell carcinoma**
  - Begins in urothelium arising from squamous cells due to chronic inflammation or irritation (thin, flat cells lining the inside of the bladder)
- **Glandular neoplasms (adenocarcinoma and villous adenoma)**
  - Begins in glandular cells found in lining of the bladder, which make mucus and other substances
- **Small cell carcinoma**
  - Begins in multipotential stem cells withing the urothelium that differentiate into neuroendocrine cells

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Categories of Bladder Cancer

1. Non-Muscle Invasive Bladder Cancer (NMIBC)
2. Muscle Invasive Bladder Cancer (MIBC)
3. Locally Advanced/Metastatic Urothelial Carcinoma (la/mUC)

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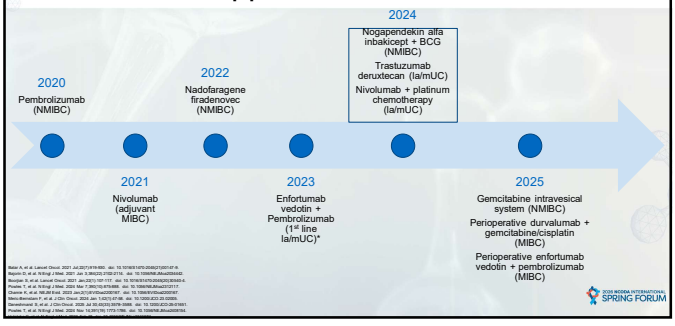
Recent FDA Approvals



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Non-Muscle Invasive Bladder Cancer

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Non-Muscle Invasive Bladder Cancer

- NMIBC management is risk adapted, with Bacillus Calmette–Guérin (BCG) serving as the cornerstone for high-risk disease and an important often preferred option for intermediate risk
- Outcomes diverge sharply once tumors become BCG unresponsive, highlighting a major **need for effective bladder sparing therapies**

Bladder-sparing options for BCG-unresponsive high-risk NMIBC		
Approval Year	Agent	Mechanism
2020	Pembrolizumab	Immune checkpoint inhibitor
2022	Nadofaragene firadenovec	Gene therapy
2024	Nogapendekin alfa inbakicept + BCG	IL-15 agonist
2025	Gemcitabine intravesical system	Antimetabolite

Bakr A, et al. Lancet Oncol. 2021 Jul;22(7):919-930. doi: 10.1016/S1470-2045(21)00147-9.
Boorjian S, et al. Lancet Oncol. 2021 Jan;22(1):107-117. doi: 10.1016/S1470-2045(20)30540-4.
Dhanani K, et al. NEJM Evid. 2023 Jan;2(1):EVIDoa2200167. doi: 10.1056/EVIDoa2200167.
Rosenblatt S, et al. J Clin Oncol. 2025 Jul 20;43(33):3578-3588. doi: 10.1200/JCO.25.01051.

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Gene Therapy

- Therapy that targets the underlying genetics of cancer or other disease state
- Several mechanisms of gene therapy can be used

Strategy	Mechanism	Example
Gene addition	Adds a working gene	**Nadofaragene firadenovec,** Voretigene Neparvovec
Gene editing	Fixes a mutation	Exagamglogene Autotemcel
Gene silencing	Turns off a harmful gene	Inclisiran

- **Nadofaragene firadenovec**: Non-replicating recombinant adenovirus vector that delivers a copy of the human interferon alpha-2b gene into urothelial and tumor cells
  - Alpha-2b induces expression of pleotropic cytokine which has a potent antitumor effect

Steinmetz A, et al. Bladder Cancer. 2024 Jun 18;10(2):105–112. doi: 10.3233/BLC-230083.
Boorjian S, et al. Lancet Oncol. 2021 Jan;22(1):107-117. doi: 10.1016/S1470-2045(20)30540-4.

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Nadofaragene firadenovec

- Nadofaragene firadenovec compared to historic standards
  - Single arm, multicenter, open-label trial

BCG-unresponsive non-muscle-invasive bladder cancer → Nadofaragene firadenovec intravesical 75 mL (3×10^{11} viral particles)*

*Repeat dosing at months 3, 6, and 9 was done in the absence of high-grade recurrence.

Endpoint	Result
Complete Response	53.4%
Maintained response at 12 months	45.5%
Grade 1-2 AE	66%
Grade 3 AE	4%
Grade 4-5 AE	0%

Boorjian S, et al. Lancet Oncol. 2021 Jan;22(1):107-117. doi: 10.1016/S1470-2045(20)30540-4.

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Nogapendekin alfa inbakicept-pmln + BCG

- Nogapendekin alfa inbakicept-pmln (NAI) +/- BCG compared to historic standards
  - Three arm, multicenter, open-label trial

BCG-unresponsive non-muscle-invasive bladder cancer →
- *NAI plus BCG (cohort A; n=82)
- **NAI plus BCG (cohort B; n=72)
- *NAI alone (cohort C; n=10) ✖

*CIS (+/- papillary disease)
**High grade papillary disease

Primary Endpoint	Cohort A	Cohort B
CR	71%	
DFS at 12 mo		55.4%

Treatment emergent adverse effect	Incidence (n=161)
Grade 1-2	86%
Grade 3	20%
Grade 4	2%
Grade 5	1%

Pharma A, et al. NEJM Evid. 2023 Jan;2(1):EVIDoa2200187. doi: 10.1056/EVIDoa2200187.

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Gemcitabine intravesical system

- Multiple agents including gemcitabine intravesical system (TAR-200) and combinations compared to historic standards
  - Four arm, multicenter, open-label trial

BCG-unresponsive non-muscle-invasive bladder cancer →
- *Cohort 1 (C1): ✖ etrelimab + TAR-200
- *Cohort 2 (C2): TAR-200
- *Cohort 3 (C3): ✖ etrelimab
- **Cohort 4 (C4): TAR-200

*CIS with or without papillary disease (high-grade Ta, any T1)
**Papillary disease-only (high-grade Ta, any T1 and absence of CIS)

Primary Endpoint	C2 (n=85)	C4 (n=52)
CR	82.4%	
DFS		NR
DFS at 12 months		70.2%

AE	C1	C2	C3	C4
Grade ≥3 treatment-related AE	37.7%	12.9%	7.1%	13.5%
Serious treatment-related AE	15.1%	5.9%	3.6%	5.8%

Grossman S, et al. J Clin Oncol. 2025 Jul 20:43(20):2529-2538. doi: 10.1200/JCO.25.01451.

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Pembrolizumab

- Pembrolizumab compared to historic standards
  - Single arm, multicenter trial

BCG-unresponsive non-muscle-invasive bladder cancer → carcinoma in situ with or without papillary tumors who were ineligible or declined radical cystectomy

Pembrolizumab 200 mg IV every 3 weeks for up to 2 years (n=101)

Endpoint	Pembrolizumab
CR	41%
Grade 3-4 TRAE	13%
Serious TRAE	8%

Bellmunt J, et al. Lancet Oncol. 2021 Jul;22(7):919-930. doi: 10.1016/S1470-2045(21)00147-9.

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Non-Muscle Invasive Bladder Cancer

Agent	Indication	Dosing Administration	Clinical Pearls
Gemcitabine Intravesical Device	**BCG-Unresponsive** NMIBC (CIS, with or without papillary tumors)	Induction: 225mg inserted **intravesical** once every 3 weeks for up to 8 doses Maintenance: 225mg inserted once every 12 weeks up to 6 doses	Other gemcitabine products are **NOT** interchangeable
Nogapendekin Alfa Inbakicept	**BCG-Unresponsive** NMIBC (CIS, with or without papillary tumors)	Induction: 400mcg **intravesical** once weekly for 6 weeks	Irritable bladder symptoms may occur during instillation, red-tinged urine may occur for first 24 hours following administration
Nadofaragene Firadenovec	**BCG-Unresponsive** NMIBC, High Risk (CIS, with or without papillary tumors)	75mL ($3x10^{11}$ viral particles) instilled **intravesical** once every 3 months for up to 12 months for 4 doses	Risk of hypersensitivity to polysorbate 80 and use caution in immunocompromised patients
Pembrolizumab	**BCG-Unresponsive** NMIBC, High Risk (CIS, with or without papillary tumors)	200mg IV every 3 weeks OR 400mg IV every 6 weeks **(systemic administration)**	Immune-mediated adverse reactions including severe and fatal IRAE's may occur

Bellmunt J, et al. Lancet Oncol. 2021 Jul;22(7):919-930. doi: 10.1016/S1470-2045(21)00147-9.
Rosiello G, et al. Lancet Oncol. 2021 Jan;22(1):107-117. doi: 10.1016/S1470-2045(20)30543-4.
Dinney R, et al. NEJM Evid. 2023 Jan;2(1):EVIDoa2200287. doi: 10.1056/EVIDoa2200287.
Balasubramanian R, et al. J Clin Oncol. 2025 Jul 20:JCO2501879. doi: 10.1200/JCO.25.01879.

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Unanswered Questions

- Patient selection for cystectomy versus bladder preserving therapy in BCG unresponsive disease
- Optimal bladder preserving therapy
- Overall survival outcomes

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Q1

Which of the following options for BCG unresponsive NMIBC is a gene therapy?

a. Gemcitabine Intravesical Device
b. Nogapendekin Alfa Inbakicept
c. Nadofaragene Firadenovec
d. Pembrolizumab

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Muscle Invasive Bladder Cancer

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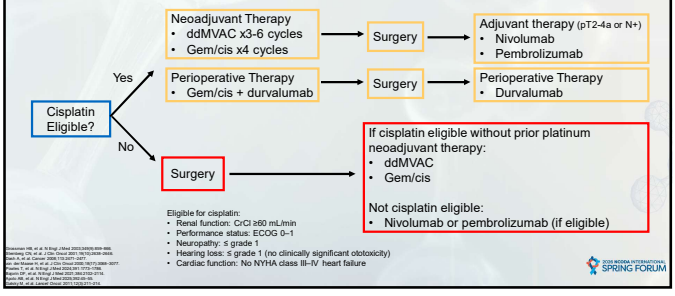
Foundation of MIBC Management



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KEYNOTE-905 / EV-303

- Perioperative pembrolizumab plus enfortumab vedotin (EV) versus surgery alone in cisplatin ineligible patients
  - Multicenter, randomized, open-label, phase III trial

February 2019
Trial was initiated to assess perioperative pembrolizumab versus surgery

June 2020
Trial was amended to add a third arm evaluating perioperative pembrolizumab plus EV

November 2022
Trial was amended to stop the pembrolizumab arm and prioritize the pembrolizumab plus EV arm with the control arm

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KEYNOTE-905 / EV-303

Randomized based on stage, region, and cisplatin eligibility

Muscle-invasive bladder cancer who were ineligible for or declined cisplatin-based chemotherapy

- *Pembrolizumab plus EV (n=170)
- Surgery alone (n=174)

*Enfortumab vedotin plus pembrolizumab (3 cycles of neoadjuvant intravenous enfortumab vedotin at a dose of 1.25 mg/kg on days 1 and 8 plus pembrolizumab at a dose of 200 mg on day 1 of every 3-week cycle, followed by surgery, and then 6 cycles of adjuvant enfortumab vedotin plus 14 cycles of adjuvant pembrolizumab).

Statistical analysis:
- Event-free survival tested at one-sided α = 0.025
  - 173 events → ~93% power to detect hazard ratio of 0.59
- After rejecting null hypothesis:
  - α = 0.02475 reassigned to overall survival
  - α = 0.00025 reassigned to pathological complete response

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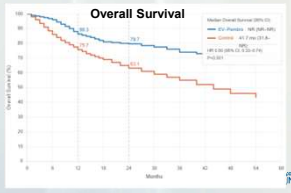
KEYNOTE-905 / EV-303

Characteristic	Pembro + EV (n=170)	Surgery alone (174)
Median Age	74.0	72.5
ECOG PS of 2, no. (%)	21 (12.4)	26 (14.9)
Cisplatin eligible, no. (%)	28 (16.5)	35 (20.1)
CrCl < 60 mL/min, no. (%)	102 (60)	102 (58.6)



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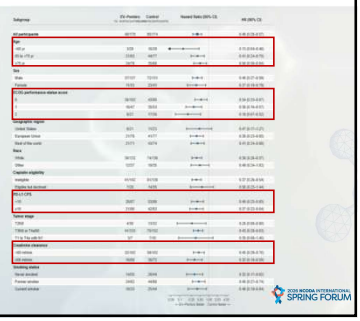
KEYNOTE-905 / EV-303

Adverse Event	Pembro + EV (n=167)	Surgery (n=159)
Grade 3+ AE	71.3%	64.8%
AE led to death • Neoadjuvant • Surgery phase • Adjuvant	7.8% • 1.2% • 2.4% • 4.2%	5.7% • 0% • 5.7% • 0%
Completed Surgery	87.6%	89.7%
Drug related AE	Skin reaction 58% Neuropathy 37%	



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Preliminary KEYNOTE-B15 / EV-304 Data

- Perioperative pembrolizumab plus EV versus cisplatin plus gemcitabine

Muscle-invasive bladder cancer who were eligible for cisplatin-based chemotherapy

- *Pembrolizumab plus EV (n=405)
- Gemcitabine plus cisplatin (n=403)

*Enfortumab vedotin plus pembrolizumab (4 cycles of neoadjuvant intravenous enfortumab vedotin at a dose of 1.25 mg/kg on days 1 and 8 plus pembrolizumab at a dose of 200 mg on day 1 of every 3-week cycle, followed by surgery, and then 5 cycles of adjuvant enfortumab vedotin plus 13 cycles of adjuvant pembrolizumab).

Results:

- **Pembrolizumab + EV significantly improved EFS** (median NR vs 48.5 mo; HR 0.53, 95% CI 0.41–0.70; P<.0001)
- **Pembrolizumab + EV significantly improved OS** (median NR vs NR; HR 0.65, 95% CI 0.48–0.89; P=.0029)
- **Pembrolizumab + EV significantly improved pCR rate** (55.8% vs 32.5%; P<.0001)

Perioperative pembrolizumab plus EV may likely become the new standard of care for the management of MIBC regardless of cisplatin eligibility

Gakiy MD, et al. J Clin Oncol. 2026;44(suppl):LBA630.

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Q2

Patient AM is a 75-year-old male with MIBC. He has an ECOG PS of 0, baseline Hgb of 11.5 g/dL, and CrCl of 29 mL/min. He has already been declared eligible for cystectomy.

Which of the following is the best option for the treatment of his MIBC?

a. Surgery followed by surveillance
b. Surgery followed by adjuvant carboplatin and gemcitabine
c. Perioperative pembrolizumab and enfortumab vedotin with surgery
d. Pembrolizumab and enfortumab vedotin until progression or unacceptable toxicity

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Locally Advanced/Metastatic Urothelial Carcinoma

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First Line Treatment for la/mUC

Trial	JAVELIN Bladder 100	EV-302	CheckMate 901
Population	**Maintenance Avelumab** vs SC without POD on platinum-based chemotherapy	**EV + P** vs platinum-based chemotherapy	**Nivo + platinum-based chemo** vs platinum-based chemo
ORR, %	**9.7** vs 1.4	**67.7** vs 44.4	**57.6** vs 43.1
CR, %	**6.0** vs 0.9	**29.1** vs 12.5	**21.7** vs 11.8
mPFS, mo HR (95% CI); p value	**3.7 (3.5 - 5.5)** vs 2.0 (1.9 - 2.7)	**12.5 (10.4 - 16.6)** vs 6.3 (6.2 - 6.5); p<0.001	**7.9 (7.6 - 9.5)** vs 7.6 (6.1 - 7.8); p=0.001
mOS, mo HR (95% CI); p value	**21.4 (18.9 - 26.1)** vs 14.3 (12.9 - 17.9); p=0.001	**31.5 (25.4 - NE)** vs 16.1 (13.9 - 18.3); p<0.001	**21.7 (18.6 - 26.4)** vs 18.9 (14.7 - 22.4); p=0.02
ICI maintenance prior to POD in SOC arm	N/A	30.4%	14.5%

SC= supportive care, POD= progression of disease, EV= enfortumab vedotin, P= pembrolizumab, chemo= chemotherapy, ORR= objective response rate, CR= complete response, mPFS= median progression free survival, mOS= median overall survival, ICI= immune checkpoint inhibitor, SOC= standard of care, N/A= not applicable, NE= not evaluable

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EV-302

EV + pembrolizumab	
Any Grade Side Effects	
Anemia	13.9%
Nausea	20.2%
Neutropenia	9.1%
Neuropathy	50%
Pruritus	39.8%
Maculopapular Rash	32.7%

Cisplatin Eligibility: NOT REQUIRED

CheckMate 901

Cisplatin/Gemcitabine + Nivolumab	
Any Grade Side Effects	
Anemia	57.2%
Nausea	46.7%
Neutropenia	30.6%
Neuropathy	< 12.5%
Pruritus	14.5%
Rash	13.5%

Cisplatin Eligibility: REQUIRED

EV + P should be considered the preferred first-line therapy option for la/mUC in most patients.

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Unanswered Questions in la/mUC

- When should cisplatin-based chemotherapy plus immunotherapy be used?
- How should prior immunotherapy in MIBC or NMIBC affect first-line la/mUC treatment?
- What resistance mechanisms lead to progression on pembrolizumab plus enfortumab vedotin?

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Subsequent Line Treatment for la/mUC

- Limited data post-progression on pembrolizumab plus enfortumab vedotin
- Targeted therapy options are an integral part of subsequent line therapy

Immunohistochemistry

- Detects protein expression in tumor cells using antibody staining
  - HER2 staining based on American Society of Clinical Oncology/College of American Pathologists guidelines for scoring HER2 for gastric cancer

Next Generation Sequencing

- Detects many types of genetic alterations driving the cancer
  - Mutations
  - Insertions/deletions
  - Copy number changes
  - Gene fusions

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DESTINY-PanTumor02

Patients
(N=267)

Locally advanced or metastatic cancer: breast, gastric, biliary tract, **bladder**, pancreatic, and gynecological tumors

≥1 prior systemic treatment

HER2 expression by IHC of **3+ or 2+**

ECOG 0-1

Intervention

Trastuzumab deruxtecan-nxki
5.4 mg/kg Q3W

Endpoints

Primary endpoint:
ORR

Key secondary endpoints:
DCR, DOR, PFS, OS, safety

HER2, Human Epidermal Growth Factor Receptor 2; IHC, immunohistochemistry; ORR, objective response rate; DCR, disease control rate; DOR, duration of response; PFS, progression free survival; OS, overall survival

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DESTINY-PanTumor02

Results (N=267)	
ORR	37.1%
DOR	11.3 months
Median PFS	6.9 months
Median OS	13.4 months

- Additional data from DESTINY-Lung01 and DESTINY-CRC02 supported the solid tumor data

Trastuzumab deruxtecan-nxki received FDA approval for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment.

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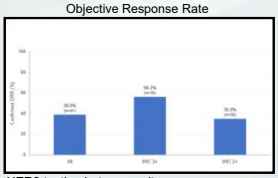
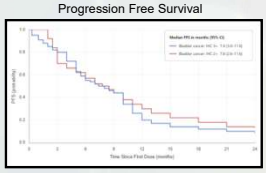
DESTINY-PanTumor02: Bladder Cancer

Objective Response Rate



Progression Free Survival



HER2 testing heterogeneity:

- Up to 45.7% of tumors show heterogenous IHC staining predominantly in HER2 2+ and 3+ scores
- Only 4.7% of cases achieved 100% agreement among 16 pathologists
- 21.4% of HER2 positive tumors turned negative after neoadjuvant breast cancer treatment

Expert Opinion: Trastuzumab deruxtecan-nxki is a reasonable off-label option in pre-treated patients with unresectable or metastatic bladder cancer with **HER2 2+ staining**.

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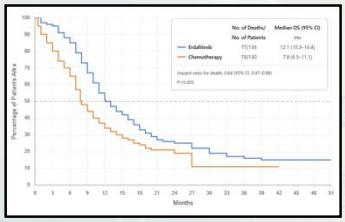
THOR Trial

- Erdafitinib versus chemotherapy
  - Phase III randomized controlled trial
  - Required at least one of the specified FGFR alterations*
  - Prior anti–PD-1 or anti–PD-L1
  - Progression on 1-2 prior lines of therapy for la/mUC
- Primary Endpoint: OS

Erdafitinib

Investigator's choice of docetaxel or vinflunine**



*Tumors were required to have one *or* more of certain *FGFR3* mutations (R248C, S249C, G370C, or Y373C) or one or more of the following fusions (translocations): *FGFR2–BICC1*, *FGFR2–CASP7*, *FGFR3–TACC3_V1*, *FGFR3–TACC3_V3*, or *FGFR3–BAIAP2L1*.
**Vinflunine is not approved in the not FDA-approved in the United States

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THOR Trial

Any Grade Side Effects		
Effect	Erdafitinib	Chemotherapy
Hyperphosphatemia	80%	0%
Diarrhea	62.2%	17.0%
Dry mouth	39.3%	3.6%
Palmar-plantar erythrodysesthesia	30.4%	0.9%
Alopecia	25.2%	24.1%
Neutropenia	0%	19.6%

Erdafitinib prolonged OS in comparison to investigator choice chemotherapy in patients with specified FGFR alterations

Loriot Y, et al. N Engl J Med. 2023 Nov 23;389(21):1961-1971. doi: 10.1056/NEJMoa2308849.

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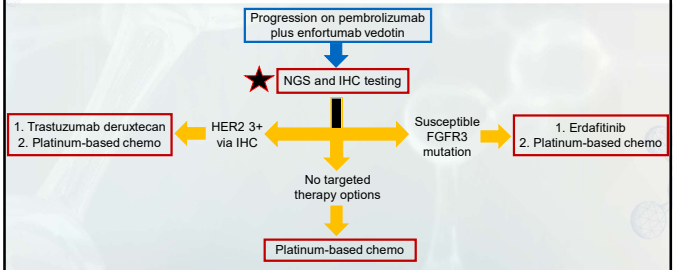
Treatment Algorithm for Subsequent Line la/mUC



Loriot Y, et al. N Engl J Med. 2023 Nov 23;389(21):1961-1971. doi: 10.1056/NEJMoa2308849.
Meic-Bernstein F, et al. J Clin Oncol. 2023 Oct 23;42(1):47-58. doi: 10.1200/JCO.23.02005.

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Q3

Which of the following should be completed before or after progression on pembrolizumab plus enfortumab vedotin to aid in treatment selection in the subsequent line setting?

a. Next generation sequencing
b. Immunohistochemistry
c. Both
d. Neither

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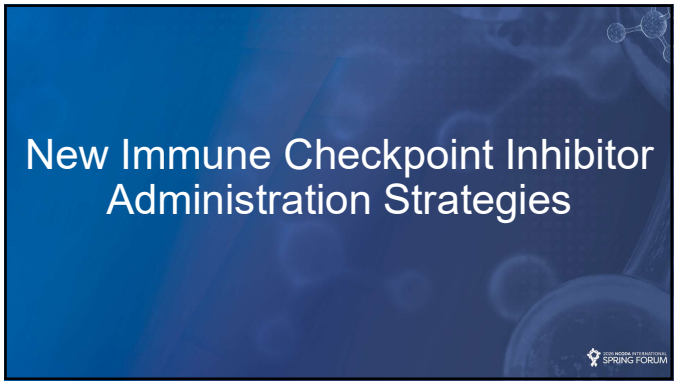
New Immune Checkpoint Inhibitor Administration Strategies

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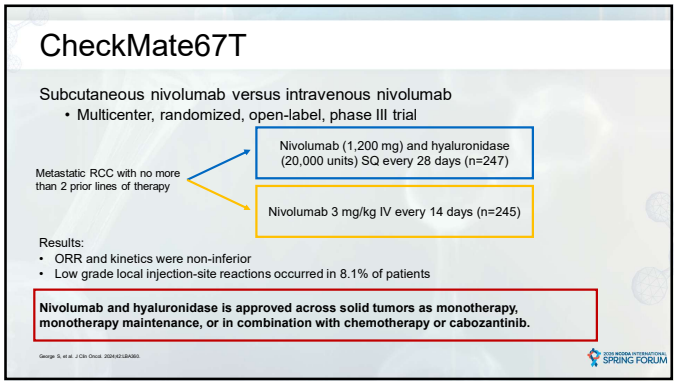
CheckMate67T
Subcutaneous nivolumab versus intravenous nivolumab
• Multicenter, randomized, open-label, phase III trial
Metastatic RCC with no more than 2 prior lines of therapy
Nivolumab (1,200 mg) and hyaluronidase (20,000 units) SQ every 28 days (n=247)
Nivolumab 3 mg/kg IV every 14 days (n=245)
Results:
• ORR and kinetics were non-inferior
• Low grade local injection-site reactions occurred in 8.1% of patients
Nivolumab and hyaluronidase is approved across solid tumors as monotherapy, monotherapy maintenance, or in combination with chemotherapy or cabozantinib.

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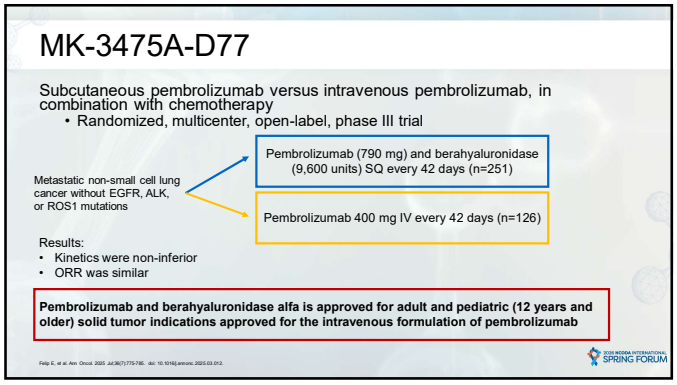
MK-3475A-D77
Subcutaneous pembrolizumab versus intravenous pembrolizumab, in combination with chemotherapy
• Randomized, multicenter, open-label, phase III trial
Metastatic non-small cell lung cancer without EGFR, ALK, or ROS1 mutations
Pembrolizumab (790 mg) and berahyaluronidase (9,600 units) SQ every 42 days (n=251)
Pembrolizumab 400 mg IV every 42 days (n=126)
Results:
• Kinetics were non-inferior
• ORR was similar
Pembrolizumab and berahyaluronidase alfa is approved for adult and pediatric (12 years and older) solid tumor indications approved for the intravenous formulation of pembrolizumab

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Subcutaneous versus Intravenous

Generic	Pembrolizumab IV	Pembrolizumab SQ	Nivolumab IV	Nivolumab SQ
Administration	30 minutes	2-5 minutes	30 minutes	3-5 minutes
Efficacy	Established	Comparable	Established	Comparable
Safety	Established	Comparable	Established	Comparable

George S, et al. J Clin Oncol. 2024;42:LBA380.
Fallo E, et al. Ann Oncol. 2025 Jul;36(7):775-785. doi: 10.1016/j.annonc.2025.03.012.

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Q4

Which of the following is a potential advantage of subcutaneous formulations of immune checkpoint inhibitors such as pembrolizumab or nivolumab compared with traditional intravenous administration?

a. Decreased risk of immune-related adverse events
b. Improved overall survival compared with IV formulations
c. Shorter administration time to reduce chair time
d. Requirement for more frequent dosing visits

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Toxicity Management

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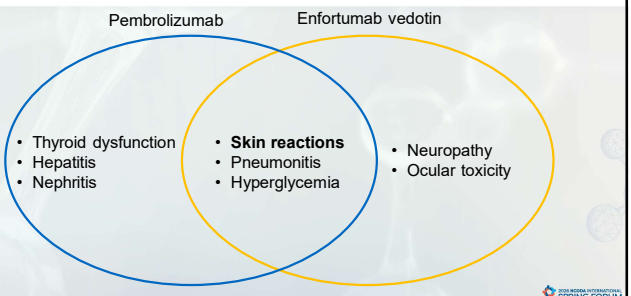
Overlapping Toxicity



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Clinical Pearls for Toxicity Management

Enfortumab vedotin

- PFS and OS improvements observed across all exposure quartiles in monotherapy trials, including with dose modifications
- Lower exposure is associated with reduced risk of key adverse events (rash, peripheral neuropathy, hyperglycemia)
- Higher exposure in cycles 1 & 2 leads to higher ORR

Pembrolizumab

- Dose reductions or modifications are not recommended

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Skin Reactions with Combination Therapy

- 70% of patients will have a skin reaction
- Roughly 17% of patients have grade 3+ skin reactions
- Median onset for grade 3 or 4 skin reactions was 1.7 months (range, 0.1-17.2 months)

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Skin Reaction Management Recommendations

Risk Factors	Prevention
• Dermatologic conditions, dry skin, high sun exposure, allergies, rash, or pruritus	• Emollients, sunscreen, proper hydration, avoid hot showers, and avoid skin irritants

Grade of Skin Reaction	Management
Grade 1	• Monitor and continue therapy with supportive care* as clinically indicated
Grade 2	• Monitor and continue therapy with supportive care* as clinically indicated • For worsening rash, concurrent fever, or persistent reaction hold therapy until ≤ grade 1 then resume EV at the same dose level or reduce by one dose level • Consider specialist referral
Grade 3	• HOLD THERAPY and start systemic corticosteroids • Specialist referral and consider skin biopsy • After improvement to ≤ grade 1 consider resuming EV at the same or reduced by one level and consider resuming pembrolizumab at the same dose
Grade 4	• Discontinue both agents and consider inpatient specialist consult with a biopsy

*Supportive care can include but not limited to emollient creams, topical steroids, topical antihistamines, oral antihistamines, anti-infectives, and other non-pharmacological interventions.

Peiyuk DF, et al. J Clin Oncol. 2004;22:4003.
Hussain B, et al. Oncologist. 2026 Nov 10;30(10):oyaf320. doi: 10.1093/oncolo/oyaf320.
Brower B, et al. Front Oncol. 2024 Apr 22;14:1329715. doi: 10.3389/fonc.2024.1329715.

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Lessons Learned from Ipilimumab and Nivolumab

Comparison of skin toxicity before and after the implementation of a prophylactic/early intervention strategy

- Single-center, retrospective, observational study (n=154)

Treatment naïve NSCLC patients who received a nivolumab + ipilimumab based regimen

- **No** prophylaxis/early intervention group (n=42)
- Prophylactic/early intervention group (n=112)

Intervention: Physician-prescribed medications, pharmacist-led patient education, and nurse-guided skincare.
- Prophylactic moisturizer with additional supportive care education
- Early intervention corticosteroid cream and antihistamine cream/tablet at onset of symptoms

Results (before and after intervention):
- Grade 3 skin toxicity: 21% to 8% (P = .045)
- Systemic corticosteroid use: 36% to 10% (P = .0004)
- Discontinuation due to skin toxicity 21% to 4% (P = .0012)

Grade 3 skin toxicities, systemic corticosteroid use, and treatment discontinuation rates due to skin toxicity significantly reduced in the prophylactic/early intervention group.

Soni T, et al. JCO Oncol Pract. 2025 Jun 30:OP2500103. doi: 10.1200/OP-25-00103.

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Expert Opinion: Skin Reaction Management

Skin Reaction	Management
Initiation of Therapy	• Consider **prophylactic moisturizing cream** and **supportive care education**
Grade 1	• Continue therapy with **early intervention of high potency topical steroids** and **early intervention antihistamines** at the onset of symptoms
Grade 2	• Continue therapy with **early intervention of high potency topical steroids** and **early intervention antihistamines** at the onset of symptoms • For worsening rash, concurrent fever, or persistent reaction hold therapy until ≤ grade 1 then consider resuming EV at the **same dose level (≤ cycle 2)** OR **reduce by one dose level (≥ cycle 3)** • Consider specialist referral with **biopsy as indicated**
Grade 3	• HOLD THERAPY and start systemic corticosteroids • Specialist referral and **get a skin biopsy** • After improvement to ≤ grade 1 **consider resuming EV at a reduced dose level** and consider resuming pembrolizumab
Grade 4	• Discontinue both agents and consider inpatient specialist consult with a biopsy

Soni T, et al. JCO Oncol Pract. 2025 Jun 30:OP2500103. doi: 10.1200/OP-25-00103.
Peiyuk DF, et al. J Clin Oncol. 2004;22:4003.
Hussain B, et al. Oncologist. 2026 Nov 10;30(10):oyaf320. doi: 10.1093/oncolo/oyaf320.
Brower B, et al. Front Oncol. 2024 Apr 22;14:1329715. doi: 10.3389/fonc.2024.1329715.

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Additional Toxicity Management

Peripheral Neuropathy

- More commonly associated with enfortumab vedotin
- Median onset: 5 months (cumulative effect)
- Managed predominantly with dose reductions
- Consider additional agents as indicated

Pneumonitis

- Occurs with both agents though higher rates with combination regimens
- Median onset: 4 months (range, 0.3-26 months)
- Consider referral to pulmonology with corticosteroids based on grade

Ocular Toxicity

- More commonly associated with enfortumab vedotin
- Dry eyes (24-40%)
- Artificial tears
- Ophthalmic topical steroids may be considered

Hyperglycemia

- More commonly associated with enfortumab vedotin
- Risk factors: baseline diabetes with higher HbA1C and higher BMI
- May require insulin

Pembrolizumab: Follow national guidelines on the management of immune checkpoint inhibitor related toxicity

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Q5

Which of the following supportive care interventions is the best option for the management of a new grade 2 skin rash on cycle 3 of pembrolizumab plus enfortumab vedotin?

a. Clobetasol propionate 0.05% cream topically
b. Diphenhydramine HCl 2% cream topically
c. Cetirizine 10 mg by mouth daily
d. Prednisone 5 mg/kg by mouth daily

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SUMMARY

- In BCG-unresponsive NMIBC, multiple bladder-sparing options are now available including nogapendekin alfa inbakicept + BCG, gemcitabine intravesical system, pembrolizumab, and nadofaragene firadenovec, but the optimal strategy remains uncertain
- In MIBC, enfortumab vedotin + pembrolizumab is likely to become the standard of care regardless of cisplatin eligibility, pending final publications and regulatory approvals
- In locally advanced and metastatic urothelial carcinoma, enfortumab vedotin + pembrolizumab should be considered a preferred first-line option for most patients with biomarker directed therapy guiding subsequent line treatment.
- Subcutaneous formulations of pembrolizumab and nivolumab reduce chair time and may improve clinic workflow while maintaining clinical efficacy
- Skin toxicity is one of the most common adverse effects with enfortumab vedotin + pembrolizumab and should be recognized early and managed aggressively with supportive care

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Q1

Which of the following options for BCG unresponsive NMIBC is given systemically?

a. Gemcitabine Intravesical Device
b. Nogapendekin Alfa Inbakicept
c. Nadofaragene Firadenovec
d. Pembrolizumab

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Q2

Patient AM is a 75-year-old male with MIBC. He has an ECOG PS of 2 and CrCl of 37 mL/min. He has already been declared eligible for cystectomy. Which of the following is the best option for the treatment of his MIBC?

a. Surgery followed by surveillance
b. Surgery followed by adjuvant carboplatin and gemcitabine
c. Perioperative pembrolizumab and enfortumab vedotin with surgery
d. Perioperative split-dose cisplatin + gemcitabine + durvalumab with surgery

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Q3

Patient AB is a 67-year-old male with metastatic bladder cancer. Key baseline characteristics include CrCl of 39 mL/min, ECOG PS of 0, and mild hearing loss. Which of the following is the best option for first line systemic therapy for metastatic bladder cancer for this patient?

a. Cisplatin + gemcitabine + nivolumab
b. Cisplatin + gemcitabine followed by avelumab maintenance
c. Pembrolizumab + enfortumab vedotin
d. Erdafitinib

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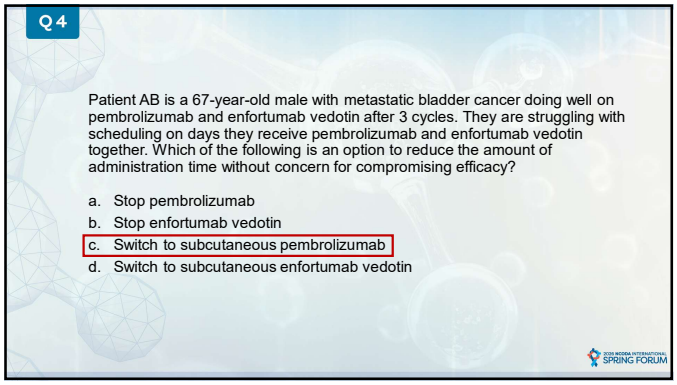
Q4
Patient AB is a 67-year-old male with metastatic bladder cancer doing well on pembrolizumab and enfortumab vedotin after 3 cycles. They are struggling with scheduling on days they receive pembrolizumab and enfortumab vedotin together. Which of the following is an option to reduce the amount of administration time without concern for compromising efficacy?
a. Stop pembrolizumab
b. Stop enfortumab vedotin
c. Switch to subcutaneous pembrolizumab
d. Switch to subcutaneous enfortumab vedotin

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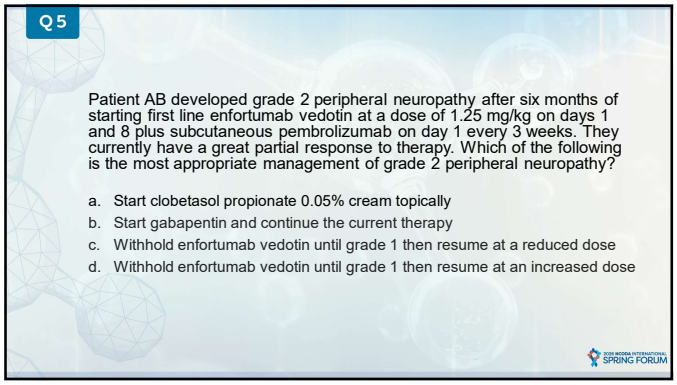
Q5
Patient AB developed grade 2 peripheral neuropathy after six months of starting first line enfortumab vedotin at a dose of 1.25 mg/kg on days 1 and 8 plus subcutaneous pembrolizumab on day 1 every 3 weeks. They currently have a great partial response to therapy. Which of the following is the most appropriate management of grade 2 peripheral neuropathy?
a. Start clobetasol propionate 0.05% cream topically
b. Start gabapentin and continue the current therapy
c. Withhold enfortumab vedotin until grade 1 then resume at a reduced dose
d. Withhold enfortumab vedotin until grade 1 then resume at an increased dose

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CE CODE
Evolving Treatment Paradigms in Bladder Cancer Across the Care Continuum

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