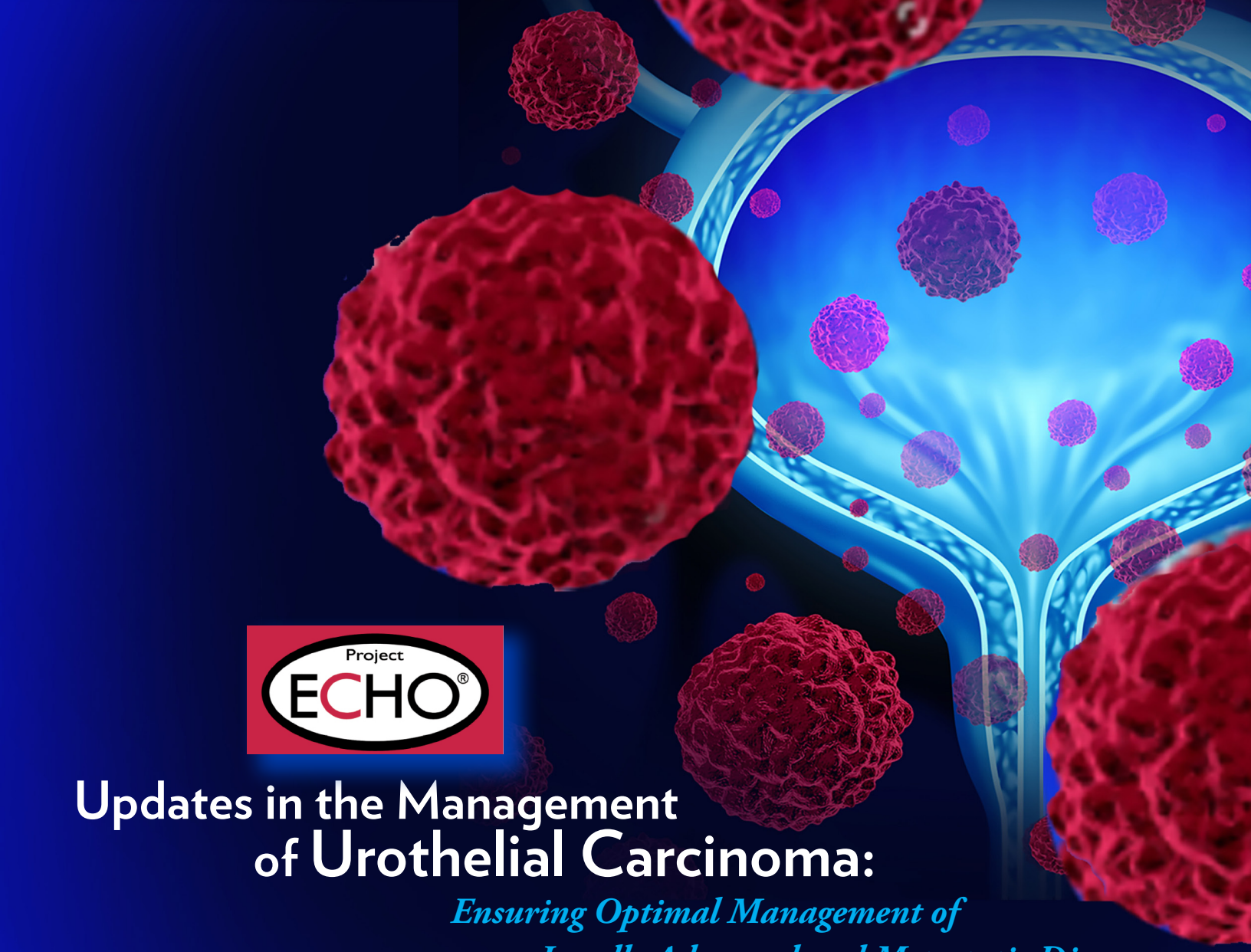

Project ECHO®

Updates in the Management of Urothelial Carcinoma:

Ensuring Optimal Management of Locally Advanced and Metastatic Disease

MED LEARNING GROUP

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This activity is supported by an educational grant from Seagen Inc.

Updates in the Management of Urothelial Carcinoma: Ensuring Optimal Management of Locally Advanced and Metastatic Disease

PROGRAM CHAIR
Matthew D. Galsky, MD, FASCO
Professor of Medicine
Icahn School of Medicine at Mount Sinai
Director, Genitourinary Medical Oncology
Associate Director, Translational Research
Tisch Cancer Institute
New York, NY

PROGRAM OVERVIEW

This virtually live activity focuses on improving care for patients with urothelial carcinoma with regard to effective risk assessment, individualized treatment selection, and adverse event management. This interactive program integrates didactic presentation with robust case-based discussions between you, your colleagues, and the expert faculty moderator to explore new treatment paradigms and clinical challenges in the treatment of bladder cancer.

TARGET AUDIENCE

This activity is intended for urologists, urologic oncologists, and multidisciplinary healthcare providers involved in the care of patients with bladder cancer.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Explain the latest therapeutic developments in the management of locally advanced and metastatic urothelial carcinoma in consideration of patient-specific factors
- Assess current clinical efficacy and safety data concerning the use of treatments in the management of urothelial carcinoma, both in frontline and later-line settings
- Relate current best practices in potential adverse event monitoring and management strategies in urothelial carcinoma

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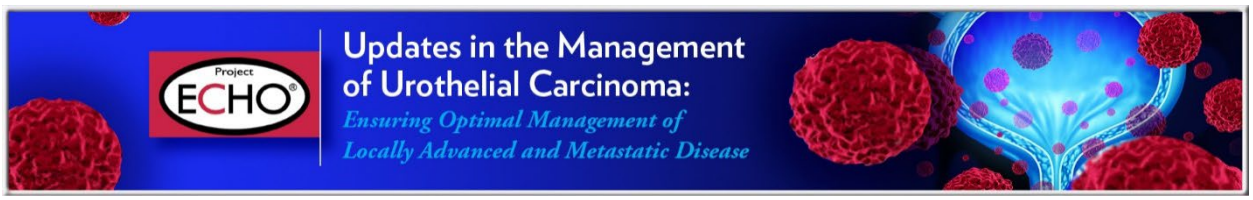

Agenda:

Topic	Contents
Introductions **5 min**	Welcome and introductory remarks • What have we learned from recent phase 3 clinical trial data?
Therapies in the Development in Bladder Cancer **5 min**	Current clinical data and developments in bladder cancer • Key clinical studies evaluating immune checkpoint inhibition and antibody-drug conjugates in bladder cancer
Therapeutic Sequencing for Bladder Cancer **5 min**	Evaluating current sequencing options • Considerations for first-line treatment of metastatic urothelial carcinoma • Proposed treatment algorithm for advanced/metastatic urothelial carcinoma
Case-Based Discussions **30 min**	Adjuvant therapy for muscle invasive bladder cancer • Risk assessment • Use of immune checkpoint inhibition in the adjuvant setting • Role of circulating tumor DNA testing in treatment planning

	Metastatic urothelial carcinoma
	• Adverse event management for patients receiving:
	  ○ First-line enfortumab vedotin plus pembrolizumab
	  ○ Avelumab switch maintenance therapy after platinum-based chemotherapy

Question & Answer **10 min**	Interactive question-and-answer/discussion session
Conclusion **5 min**	Closing remarks and key takeaways

Updates in the Management of Urothelial Carcinoma: Ensuring Optimal Management of Locally Advanced and Metastatic Disease

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Director, Genitourinary Medical Oncology
Associate Director, Translational Research
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New York, New York

1

Disclosures

- **Dr. Galsky** discloses receiving consulting fees from Bristol Myers Squibb, Merck, Genentech, AstraZeneca, Pfizer, EMD Serono, Seagen Inc., Janssen, Numab Therapeutics, Dragonfly Therapeutics, GlaxoSmithKline, Basilea Pharmaceutica, UroGen Pharma, and Rappta Therapeutics
- During the course of this lecture, the presenter may discuss the use of medications for both FDA-approved and non-approved indications
- All relevant financial relationships have been mitigated

This activity is supported by an educational grant from *Seagen Inc.*

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Learning Objectives

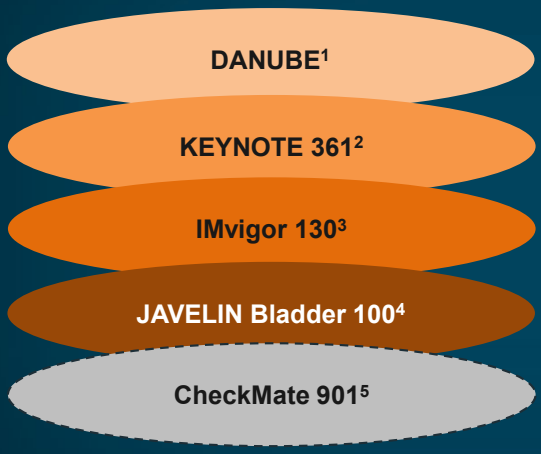
- Explain the latest therapeutic developments in the management of locally advanced and metastatic urothelial carcinoma in consideration of patient specific factors
- Assess current clinical efficacy and safety data concerning the use of treatments in the management of urothelial carcinoma, both in frontline and later-line settings
- Relate current best practices in potential adverse event monitoring and management strategies in urothelial carcinoma

3

Therapeutic Developments in Locally Advanced/Metastatic Urothelial Carcinoma

4

Pre-ESMO 2023, What Had We Learned From This Series of Contemporary Phase 3 Trials in mUC?



- Single-agent PD-(L)1 blockade not ideal strategy and hard to define population for whom sufficient[2]
- Early second-line (ie, switch maintenance) PD-(L)1 is a good strategy[4,6,7]
- Combination CTLA-4 + PD-(L)1 blockade not an ideal strategy (?)[1,8]
- Concurrent combination platinum-based chemotherapy + PD-(L)1 blockade not an ideal strategy[6]

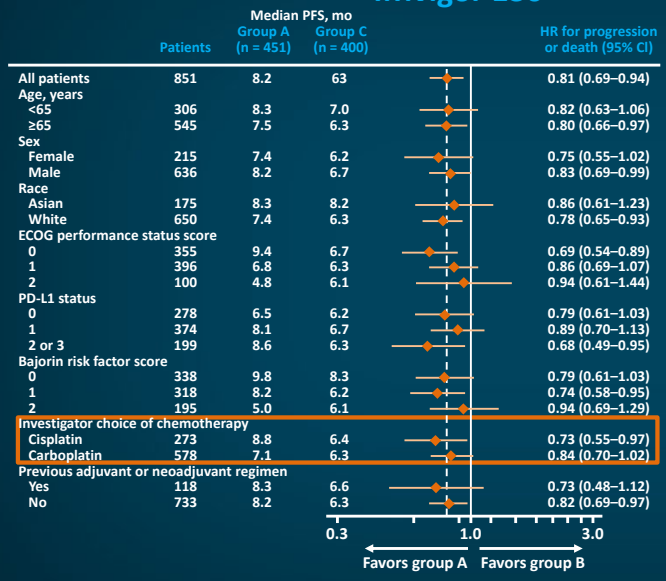
CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; mUC = metastatic urothelial carcinoma; PD-(L)1 = programmed (cell) death 1 (PD-1) or PD-L1.

1. Powles T, et al. *Lancet Oncol*, 2020;21(12):1574-1588. 2. Powles et al, *Lancet Oncol.* 2021;22(7):931-945. 3. Galsky MD, et al. *Lancet*. 2020;395(10236):1547-1557. 4. Powles T, et al. *N Engl J Med.* 2020;381:1218-1230. 5. van der Heijden MS, et al. *N Engl J Med*. 2023;389(19):1778-1789. 6. Galsky MD, et al. J Clin Oncol. 2020;38(16):1797-1806. 7. Galsky MD, Grande E, et al. *Lancet* 2021;396:1977-1978. 7. de Velasco G, et al. *J Clin Oncol*. 41(16_suppl):TPS4606. 8. Galsky MD, et al. J Clin Oncol. 2020;38(16):1797-1806;.

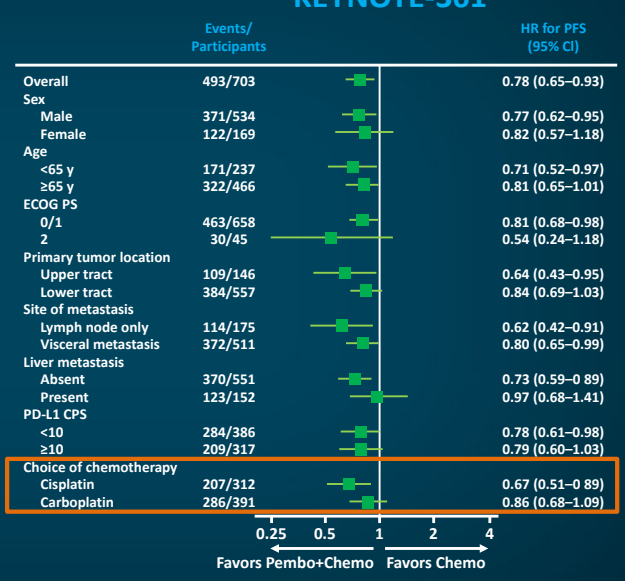
5

Is There Relevant Biology Hidden in These Results?

IMvigor 130[1]



KEYNOTE-361[2]



1. Galsky MD, et al. *Lancet*. 2020;395:1547-1557.
2. Alva A, et al. *Ann Oncol*. 2020;31(suppl 4): abstract LBA23.

Chemo = chemotherapy; CI = confidence interval; CPS = combined positive score; HR = hazard ratio; Pembro = pembrolizumab; PFS = progression-free survival.

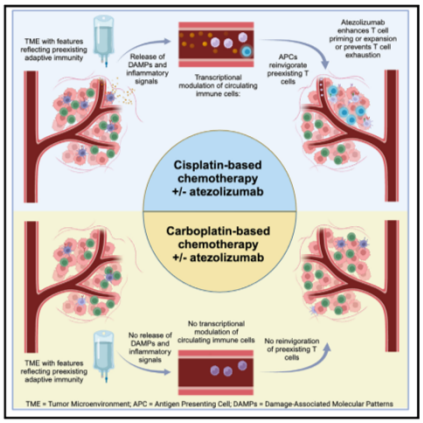
6

Cell Reports Medicine

Article

Immunomodulatory effects and improved outcomes with cisplatin- versus carboplatin-based chemotherapy plus atezolizumab in urothelial cancer

Graphical abstract



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Correspondence

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In brief

Galsky et al. demonstrate that durable cancer control with cisplatin versus carboplatin is most prominent in patients with pretreatment tumors demonstrating features of restrained adaptive immunity. *In vitro*, they demonstrate that cisplatin versus carboplatin exerts direct immunomodulatory effects on cancer cells, promoting dendritic cell activation and antigen-specific T cell killing.

- Patients with tumors showing preexisting adaptive immunity benefit more from cisplatin
- Cisplatin versus carboplatin modulates immune-related transcriptional programs
- Tumor cells primed by cisplatin versus carboplatin are sensitive to T cell killing

Galsky MD, et al. *Cell Rep Med*. 2024;5(2):101393.

7

CheckMate 901: Phase 3 Trial of Nivolumab in Combination

N = 1307
- Previously untreated unresectable or metastatic UC (1L)
- Cisplatin eligible or ineligible
- ECOG PS 0-1

Stratification Factors
- PD-L1 expression <1%
- Cisplatin eligibility
- Presence of liver metastases

n = 707

Cisplatin-ineligible patients → R 1:1
- A: **Nivo** 1 mg/kg + **Ipi** 3 mg/kg Q3W up to 4 doses → 6 weeks → **Nivo** 480 mg Q4W until disease progression, unacceptable toxicity, withdrawal, or 24 months
- B: **Gem + Cis or Gem + Carbo** Q3W up to 6 cycles

Cisplatin-eligible patients → R 1:1
- C: **Nivo** 360 mg + **Gem + Cis** Q3W up to 6 cycles → 3 weeks → **Nivo** 480 mg Q4W until disease progression, unacceptable toxicity, withdrawal, or 24 months
- D: **Gem + Cis** Q3W up to 6 cycles

Primary endpoints

- OS in patients with PD-L1 ≥1% (A vs B)
- OS in cisplatin-ineligible patients (A vs B)
- OS and PFS in cisplatin-eligible patients (C vs D)

Carbo = carboplatin; Cis = cisplatin; Gem = gemcitabine; Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival; Q3W = every 3 weeks; Q4W = every 4 weeks.

Galsky MD, et al. *J Clin Oncol.* 2018;36(15_suppl):TPS4588. 2. NCT03036098 (https://clinicaltrials.gov/ct2/show/NCT03036098). Accessed 4/5/23.

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CheckMate 901: Baseline Characteristics

	Nivo + Gem-Cis (n = 304)	Gem-Cis (n = 304)
Median age, y (range)	65 (32–86)	65 (35–85)
Male sex, n (%)	236 (77.6)	234 (77.0)
Race		
White	211 (69.4)	225 (74.0)
Asian	75 (24.7)	63 (20.7)
Geographic region, n (%)		
United States	19 (6.2)	21 (6.9)
Europe	134 (44.1)	142 (46.7)
Asia	72 (23.7)	61 (20.1)
Other	79 (26.0)	80 (26.3)
ECOG PS, n (%)		
0	162 (53.3)	162 (53.3)
1	140 (46.1)	142 (46.7)
>1	2 (0.7)	0

	Nivo + Gem-Cis (n = 304)	Gem-Cis (n = 304)
Tumor type at initial diagnosis, n (%)		
Urinary bladder	235 (77.3)	219 (72.0)
Renal pelvis	33 (10.9)	44 (14.5)
Other	36 (11.8)	41 (13.5)
Tumor PD-L1 expression, n (%)		
≥1%	111 (36.5)	110 (36.2)
<1%	193 (63.5)	194 (63.8)
Liver metastasis, n (%)		
Yes	64 (21.1)	64 (21.1)
No	240 (78.9)	240 (78.9)

van der Heijden MS, et al. *N Engl J Med*. 2023;389:1778-1789.

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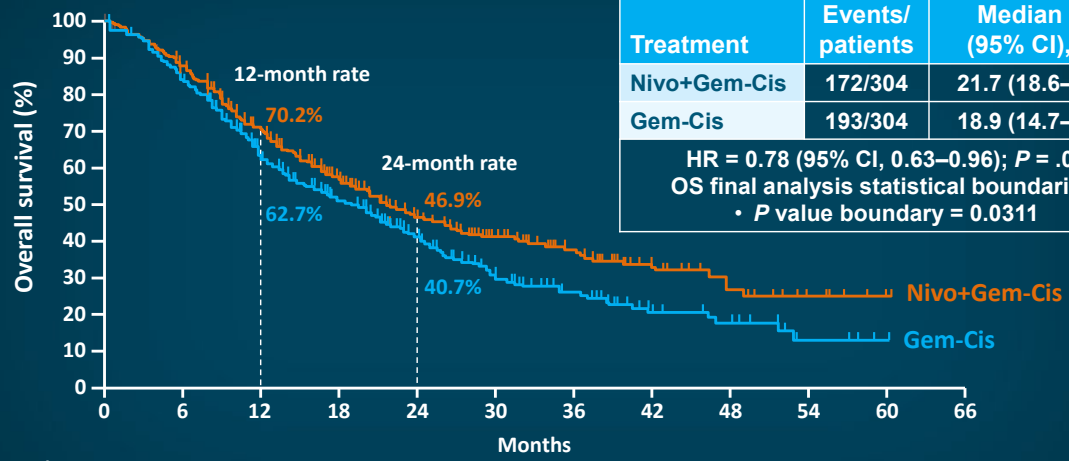
CheckMate 901: Overall Survival in Cisplatin-Eligible Patients



Treatment	Events/ patients	Median OS (95% CI), mo
Nivo+Gem-Cis	172/304	21.7 (18.6–26.4)
Gem-Cis	193/304	18.9 (14.7–22.4)

HR = 0.78 (95% CI, 0.63–0.96); *P* = .02
OS final analysis statistical boundaries:
• *P* value boundary = 0.0311

No. at risk												
Nivo+Gem-Cis	304	264	196	142	97	69	48	25	15	7	2	0
Gem-Cis	304	242	166	122	82	49	33	17	13	4	1	0

van der Heijden MS, et al. *N Engl J Med*. 2023;389:1778-1789.

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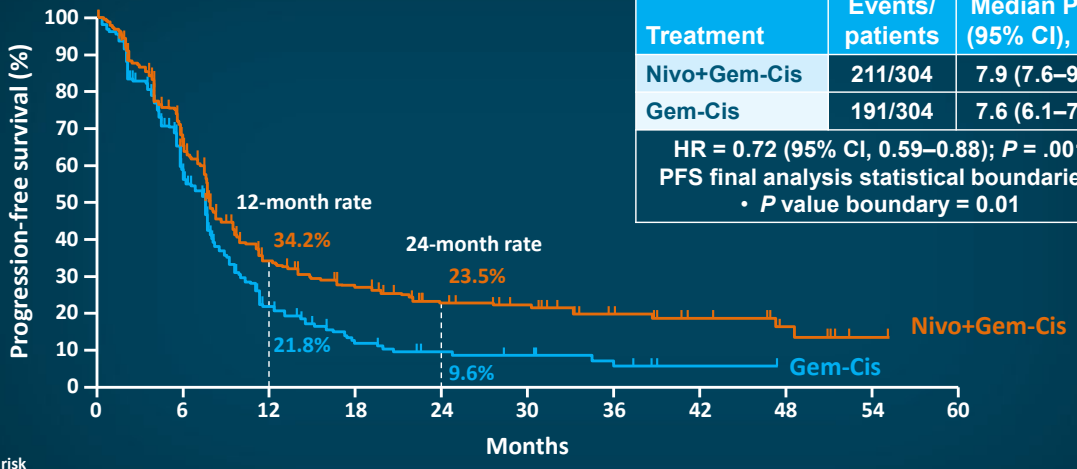
CheckMate 901: Progression-Free Survival in Cisplatin-Eligible Patients



Treatment	Events/ patients	Median PFS (95% CI), mo
Nivo+Gem-Cis	211/304	7.9 (7.6–9.5)
Gem-Cis	191/304	7.6 (6.1–7.8)

HR = 0.72 (95% CI, 0.59–0.88); *P* = .001
PFS final analysis statistical boundaries:
- *P* value boundary = 0.01

No. at risk

Nivo+Gem-Cis	304	179	82	57	41	31	19	11	6	1	0
Gem-Cis	304	119	35	17	10	8	5	1	0	0	0

van der Heijden MS, et al. *N Engl J Med*. 2023;389:1778-1789.

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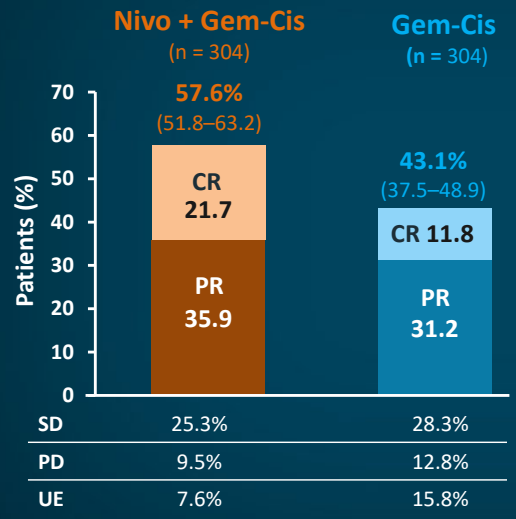
CheckMate 901: Quantity and Quality of Complete Responses Are Different When Nivolumab Is Added to Gemcitabine + Cisplatin



SD	25.3%	28.3%
PD	9.5%	12.8%
UE	7.6%	15.8%

Time to and duration of responses		
	Nivo+Gem-Cis	Gem-Cis
Any objective response, no.	175	131
Median TTR (Q1–Q3), mo	2.1 (2.0–2.3)	2.1 (2.0–2.2)
Median DoR (95% CI), mo	9.5 (7.6–15.1)	7.3 (5.7–8.9)
Complete response, no.	66	36
Median TTCR (Q1–Q3), mo	2.1 (1.9–2.2)	2.1 (1.9–2.2)
Median DoCR (95% CI), mo	37.1 (18.1–NE)	13.2 (7.3–18.4)

CR = complete response; DoCR = duration of CR; DoR = duration of response; NE = not evaluable/estimable; PR = partial response; Q = quartile; SD = stable disease; TTCR = time to CR; TTR = time to response; UE = unevaluable.

van der Heijden MS, et al. *N Engl J Med*. 2023;389:1778-1789.

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CheckMate 901: Treatment-Related AEs in Cisplatin-Eligible Patients

TRAEs occurring in ≥20% of any grade or ≥5% of grade ≥3				
Treatment-related adverse events	Nivo + Gem-Cis (n = 304)		Gem-Cis (n = 288)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	**296 (97.4)**	**188 (61.8)**	**267 (92.7)**	**149 (51.7)**
Anemia	174 (57.2)	67 (22.0)	137 (47.6)	51 (17.7)
Nausea	142 (46.7)	1 (0.3)	138 (47.9)	3 (1.0)
Neutropenia	93 (30.6)	57 (18.8)	86 (29.9)	44 (15.3)
Decreased neutrophil count	75 (24.7)	44 (14.5)	60 (20.8)	32 (11.1)
Fatigue	74 (24.3)	6 (2.0)	69 (24.0)	4 (1.4)
Decreased appetite	68 (22.4)	4 (1.3)	45 (15.6)	1 (0.3)
Decreased platelet count	66 (21.7)	23 (7.6)	43 (14.9)	14 (4.9)
Decreased white-cell count	64 (21.1)	30 (9.9)	40 (13.9)	11 (3.8)
Thrombocytopenia	45 (14.8)	20 (6.6)	35 (12.2)	13 (4.5)

AE = adverse event; TRAE = treatment-related AE.

van der Heijden MS, et al. *N Engl J Med*. 2023;389:1778-1789.

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EV-302: Phase 3 Trial of Enfortumab Vedotin (EV) + Pembrolizumab

- Previously untreated la/mUC
- Eligible for platinum, EV, and pembrolizumab
- PD-(L)1 inhibitor naive
- ECOG PS 0-2*

N = 886

R 1:1

n = 442

EV + Pembro
EV 1.25 mg/kg on Days 1 and 8
Pembrolizumab 200 mg on Day 1
21-day cycle
No maximum treatment cycles for EV; maximum 35 cycles for Pembro

n = 444

Chemotherapy†
Cisplatin or carboplatin + gemcitabine
Maximum 6 cycles
Cisplatin eligibility and assignment/dosing were protocol-defined

- **Dual primary endpoints:** PFS per BICR, OS
- **Select secondary endpoints:** ORR per RECIST v1.1 by BICR and investigator assessment, DoR, time to pain progression, safety
- **Stratified by** cisplatin eligibility, PD-L1 expression, and liver metastases

*Patients with ECOG PS of 2 were required to also meet additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure; †maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy.

BICR = blinded independent central review; la = locally advanced; RECIST = response evaluation criteria in solid tumors.

Powles TB, et al. *Ann Oncol.* 2023;34(suppl 2): abstract LBA6. Powles T, et al. *N Engl J Med*. 2024;390:875-888 and supplement.

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EV-302: Baseline Characteristics

	EV+Pembro (n = 442)	Chemo (n = 444)
Male sex, n (%)	344 (77.8)	336 (75.7)
Median age, y (range)	69 (37–87)	69 (22–91)
Race, n (%)		
White	308 (69.7)	290 (65.3)
Asian	99 (22.4)	92 (20.7)
Geographic location, n (%)		
North America	103 (23.3)	85 (19.1)
Europe	172 (38.9)	197 (44.4)
Rest of world	167 (37.8)	162 (36.5)
ECOG PS, n (%)		
0	223 (50.5)	215 (48.4)
1	204 (46.2)	216 (48.6)
2	15 (3.4)	11 (2.5)

	EV+Pembro (n = 442)	Chemo (n = 444)
Primary tumor location, n (%)		
Upper tract	135 (30.5)	104 (23.4)
Lower tract	305 (69.0)	339 (76.4)
Cisplatin eligible, n (%)	240 (54.3)	242 (54.5)
Metastatic category, n (%)		
Visceral metastases	318 (71.9)	318 (71.6)
Bone	81 (18.3)	102 (23.0)
Liver	100 (22.6)	99 (22.3)
Lung	170 (38.5)	157 (35.4)
Lymph node only	103 (23.3)	104 (23.4)
PD-L1 expression, n/N (%)		
High (CPS* ≥10)	254/438 (58.0)	254/439 (57.9)
Low (CPS* <10)	184/438 (42.0)	185/439 (42.1)

*CPS is defined as total number of PD-L1-staining cells (tumor and immune cells, lymphocytes, macrophages) divided by total number of viable tumor cells, multiplied by 100.

Powles TB, et al. *N Engl J Med*. 2024;390:875-888.

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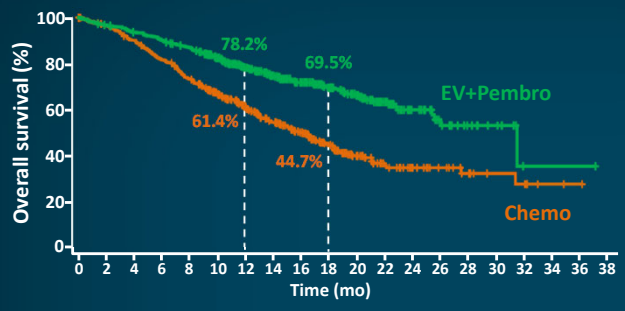
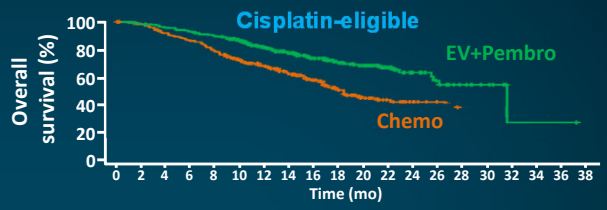
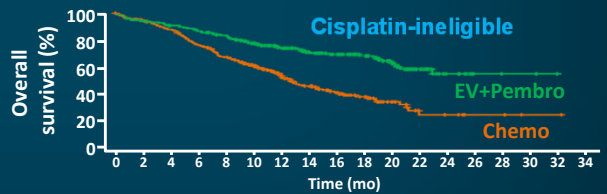
EV-302: Overall Survival



	N	Events (%)	mOS (95% CI), mo
EV+Pembro	442	133 (30.1)	**31.5 (25.4–NE)**
Chemo	444	226 (50.9)	**16.1 (13.9–18.3)**
HR = 0.47 (95% CI, 0.38–0.58); 2-sided *P* < .001 Median survival follow-up = 17.2 mo			



	Events, n/N	mOS (95% CI), mo
EV+Pembro	69/244	**31.5 (25.4–NE)**
Chemo	106/234	**18.4 (16.4–27.5)**
HR = 0.53 (95% CI, 0.39–0.72)		



	Events, n/N	mOS (95% CI), mo
EV+Pembro	64/198	**NE (20.7–NE)**
Chemo	120/210	**12.7 (11.4–15.5)**
HR = 0.43 (95% CI, 0.31–0.59)		

Powles TB, et al. *N Engl J Med*. 2024;390:875-888.

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EV-302: ORR, PFS, and Subsequent Therapy

Response rates	EV+Pembro (n = 437)	Chemo (n = 441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7)** (63.1–72.1)	**196 (44.4)** (39.7–49.2)
2-sided *P* value	< .001	
Best overall response, n (%)		
CR	127 (29.1)	55 (12.5)
PR	169 (38.7)	141 (32.0)
SD	82 (18.8)	149 (33.8)
PD	38 (8.7)	60 (13.6)
Not evaluated	21 (4.8)	36 (8.2)

Subsequent systemic therapy	EV+Pembro (n = 442) n (%)	Chemo (n = 444) n (%)
First subsequent systemic therapy	128 (29.0)	294 (66.2)
Platinum-based	**110 (24.9)**	**17 (3.8)**
PD-(L)1 inhibitor-containing	**7 (1.6)**	**260 (58.6)**
Maintenance therapy	0	143 (32.2)
Following progression	7 (1.6)	117 (26.4)
Other	**11 (2.5)**	**17 (3.8)**

Progression-free survival per BICR	N	Events (%)	mPFS (95% CI), mo
EV+Pembro	442	223 (50.5)	**12.5 (10.4–16.6)**
Chemo	444	307 (69.1)	**6.3 (6.2–6.5)**
HR = 0.45 (95% CI, 0.38–0.54); 2-sided *P* < .001			

mPFS = median PFS; ORR = overall/objective response rate.

Powles TB, et al. *Ann Oncol.* 2023;34(suppl 2): abstract LBA6. Powles T, et al. *N Engl J Med.* 2024;390:875-888.

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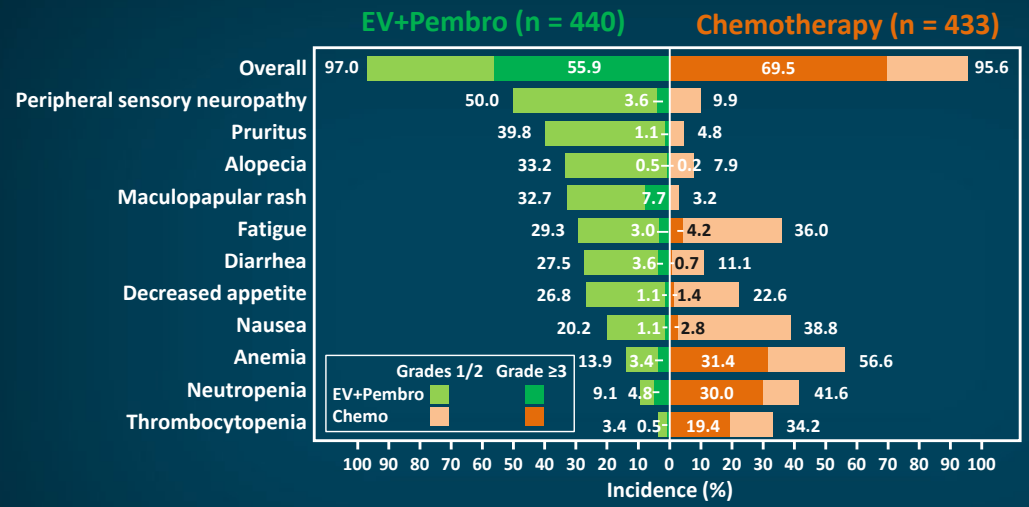
EV-302: Treatment-Related Adverse Events



Median number of cycles (range)

- EV+Pembro = 12.0 (1–46)
- Chemo = 6.0 (1–6)

TRAEs leading to death per investigator

- EV+Pembro: 4 (0.9%)—asthenia, diarrhea, immune-mediated lung disease, multiorgan dysfunction syndrome
- Chemo: 4 (0.9%)—febrile neutropenia, myocardial infarction, neutropenic sepsis, sepsis

Powles TB, et al. *Ann Oncol.* 2023;34(suppl 2): abstract LBA6. Powles T, et al. *N Engl J Med.* 2024;390:875-888.

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Considerations for First-line Treatment of Metastatic UC

Acknowledging the limitations of cross-trial comparisons, the effect size on OS for EV + Pembro versus Chemo is larger than that observed with gemcitabine + Nivo versus Chemo, **but…**

1. **Are both regimens potentially curative for a small subset?**
2. **How do the potential toxicities of both regimens compare?**
3. **How do the durations of treatment compare?**
4. **How to we contextualize 2nd-line treatment options?**

Slide courtesy of M Galsky.

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TROPiCS-04 Study Design

Eligibility criteria
- Locally advanced unresectable or mUC
- Upper/lower tract tumors
- Mixed histologic types are allowed if urothelial is predominant
- Progression after platinum-based **and** ICPi therapy

OR
- Cisplatin in neoadjuvant/adjuvant setting if progression within 12 mo and subsequent ICPi

N = 600

R 1:1

SG arm
Sacituzumab govitecan
10 mg/kg
D1 and D8 of 21-day cycle

TPC arm
- Docetaxel, 75 mg/m^2 OR
- Paclitaxel, 175 mg/m^2 or
- Vinflunine, 320 mg/m^2 on D1 of 21-day cycle

Continue treatment until loss of clinical benefit or toxicity

- **Primary endpoint:** OS
- **Secondary endpoints:** PFS by PI assessment and BICR using RECIST 1.1; ORR, DoR, and CBR by PI assessment and BICR using RECIST 1.1; EORTC QLQ-C30 score and EuroQOL EQ-5D-5L QOL score; safety and tolerability

CBR = clinical benefit rate; ICPi = immune checkpoint inhibitor; EORTC = European Organization for the Research and Treatment of Cancer; EuroQOL EQ-5D-5L QOL = European Quality of Life 5-Dimensions 5 Levels Instrument; PI = principal investigator; QLQ-C30 = Quality of Life Questionnaire Core 30; TPC = treatment of physician's choice.

Vulsteke C, et al. *J Clin Oncol.* 2022;40(6 suppl): abstract TPS582. NCT04527991 (https://classic.clinicaltrials.gov/ct2/show/NCT04527991). Accessed 3/22/24.

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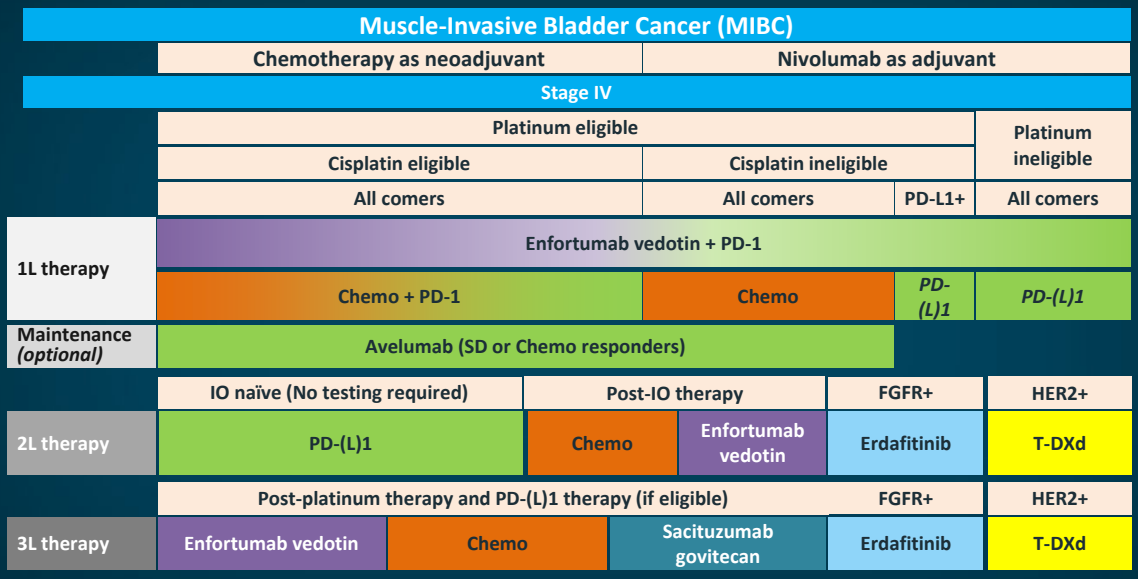
Treatment of Urothelial Cancer 2024



2L = second line; 3L = third line; FGFR = fibroblast growth factor receptor; IO = immunotherapy; T-DXd = trastuzumab deruxtecan.

Slide courtesy of M Galsky. Modified from NCCN Guidelines.

Chemotherapy | PD-(L)1 inhibitor | Nectin-4 ADC
FGFR inhibitor | HER2 ADC | Trop-2 ADC

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Thank you!

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Updates in the Management of Urothelial Carcinoma: Ensuring Optimal Management of Locally Advanced and Metastatic Disease

Antibody-Drug Conjugates for Urothelial Carcinoma: Background

Resource	Address
Abd El-Salam M, Smith CEP, Pan CX. Insights on recent innovations in bladder cancer immunotherapy. *Cancer Cytopathol*. 2022;130:667-683.	https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncy.22603
American Cancer Society (ACS). Cancer Facts & Figures 2024.	https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2024/2024-cancer-facts-and-figures-acs.pdf
Fu Z, Li S, Han S, Shi C, Zhang Y. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Signal Transduct Target Ther*. Mar 22 2022;7(1):93.	https://www.nature.com/articles/s41392-022-00947-7
Goldenberg DM, Cardillo TM, Govindan SV, Rossi EA, Sharkey RM. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). *Oncotarget*. 2015;6:22496-22512.	https://www.oncotarget.com/article/4318/text/
International Agency for Research on Cancer. Bladder Cancer.	https://www.iarc.who.int/cancer-type/bladder-cancer
Liu AB, Snead K, Gosink J, et al. Enfortumab vedotin, an anti-Nectin-4 ADC demonstrates bystander cell killing and immunogenic cell death anti-tumor activity mechanisms of action in urothelial cancers. *Cancer Res*. 2020;80(16_suppl):5581.	https://aacrjournals.org/cancerres/article/80/16_Supplement/5581/644117/Abstract-5581-Enfortumab-vedotin-an-anti-Nectin-4
National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer. Version 2.2024.	www.nccn.org/professionals/physician_gls/pdf/bladder.pdf
Wong JL, Rosenberg JE. Targeting nectin-4 by antibody-drug conjugates for the treatment of urothelial carcinoma. *Expert Opin Biol Ther.* 2021;21:863-873.	https://www.tandfonline.com/doi/full/10.1080/14712598.2021.1929168

Therapeutic Developments in Locally Advanced/Metastatic Urothelial Carcinoma

Resource	Address
Galsky MD, Arranz Arija JA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): A multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2020;395:1547-1557.	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30230-0/abstract
Galsky MD, Guan X, Rishipathak, et al. Immunomodulatory effects and improved outcomes with cisplatin- versus carboplatin-based chemotherapy plus atezolizumab in urothelial cancer. *Cell Rep Med*. 2024;5:101393.	https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(24)00002-8

Galsky MD, Mortazavi A, Milowsky MI, et al. Randomized double-blind phase ii study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer. *J Clin Oncol*. 2020;38:1797-1806.	https://ascopubs.org/doi/10.1200/JCO.19.03091
Powles T, Csőszi T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): A randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22:931-945.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00152-2/abstract
Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med.* 2020;381:1218-1230.	https://www.nejm.org/doi/10.1056/NEJMoa2002788
Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med.* 2024;390:875-888.	https://www.nejm.org/doi/10.1056/NEJMoa2312117
Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): A randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2020;21:1574-1588.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30541-6/abstract
van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. *N Engl J Med*. 2023;389:1778-1789.	https://www.nejm.org/doi/10.1056/NEJMoa2309863

Therapeutic Developments in Adjuvant Immunotherapy for Urothelial Carcinoma

Resource	Address
Bellmunt J, Hussain M, Gschwend J, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22:525-537.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00004-8/abstract
Bajorin DF, Witjes JA, Gschwend J, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med.* 2021;384:2102-2114.	https://www.nejm.org/doi/10.1056/NEJMoa2034442
Powles T, Assaf ZJ, Davarpanah N, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. *Nature.* 2021;595:432-437.	https://www.nature.com/articles/s41586-021-03642-9
Powles T, Assaf ZJ, Degaonkar V, et al. Updated overall survival by circulating tumor dna status from the phase 3 imvigor010 trial: Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma. *Eur Urol*. 2024;85:114-122.	https://www.sciencedirect.com/science/article/pii/S0302283823029020

Management of Immune-Related Adverse Events

Resource	Address
Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: Epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019;16:563-580.	https://www.nature.com/articles/s41571-019-0218-0
National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. Version 1.2024.	https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol*. 2021;39:4073-4126.	https://ascopubs.org/doi/10.1200/JCO.21.01440

All URLs accessed April 18, 2024