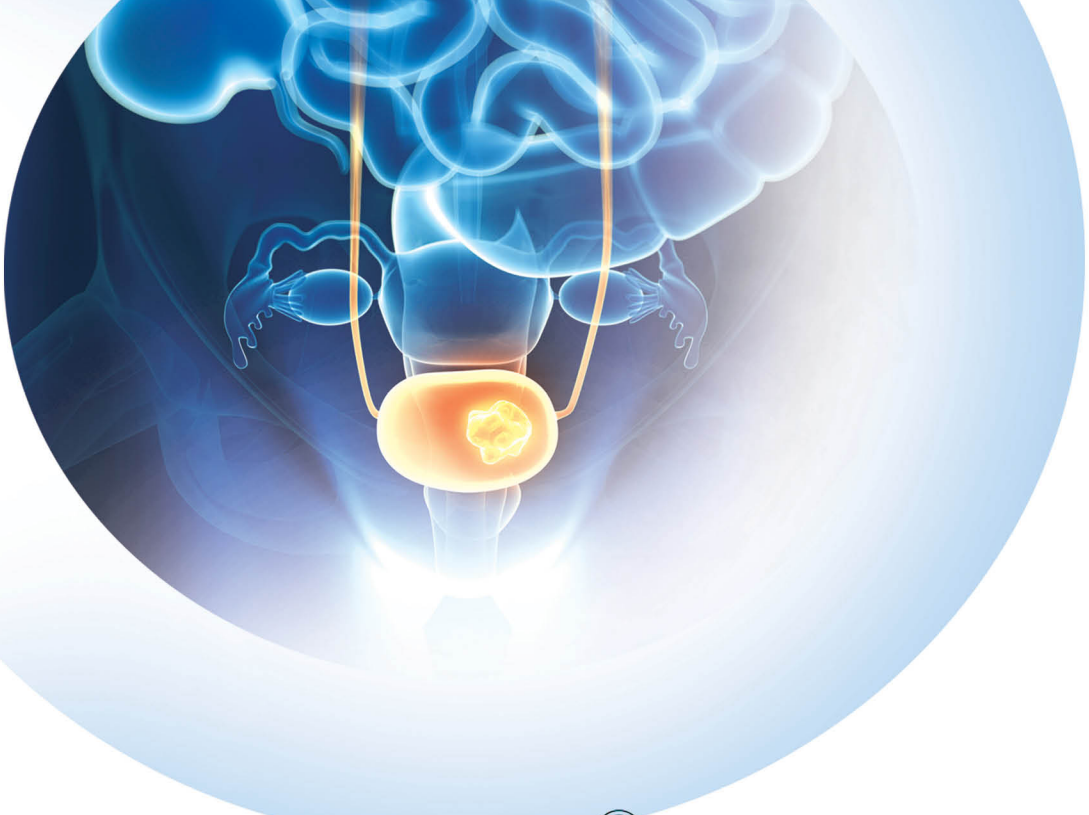

IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

Immunotherapy Collaborative of Oncology Networked Communities (IC-ONC)-

Optimizing the Sequencing of Immune Checkpoint Inhibitors in Locally Advanced or Metastatic Urothelial Carcinoma

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM) .
This activity is supported by educational grants from Pfizer and EMD Serono.

Immunotherapy Collaborative of Oncology Networked Communities (IC-ONC) - Optimizing the Sequencing of Immune Checkpoint Inhibitors in Locally Advanced or Metastatic Urothelial Carcinoma

PROGRAM CHAIR
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Associate Professor of Medicine
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SPEAKER FACULTY

Robert Dreicer, MD	**Alicia K. Morgans, MD, MPH**	**Peter H. O'Donnell, MD**
Deputy Director, University of Virginia Emily Couric Clinical Cancer Center Professor of Medicine and Urology, University of Virginia School of Medicine Charlottesville, VA	Associate Professor of Medicine Northwestern University Feinberg School of Medicine Chicago, IL	Associate Professor of Medicine The University of Chicago Medicine Chicago, IL

PROGRAM OVERVIEW

This activity will cover the treatment and management of patients locally-advanced or metastatic urothelial carcinoma.

TARGET AUDIENCE

This activity is designed to meet the educational needs of urologists, medical/genitourinary oncologists, surgeons, and other health care professionals (primary care physicians, physicians-in-training, urology nurses, oncology nurses, nurse practitioners, pharmacists, physician assistants, etc.) involved and/or interested in the therapeutic management of patients with locally-advanced or metastatic urothelial cancer.

LEARNING OBJECTIVES

On completing the program, attendees should be able to:

- Develop treatment plans that appropriately sequence chemotherapy and immunotherapy in patients with locally-advanced or metastatic urothelial carcinoma (UC)
- Evaluate evidence for the use of maintenance immunotherapy as first-line therapy for metastatic UC
- Identify patients with locally advanced or metastatic UC who are candidates for second-line treatment
- Apply current recommendations and emerging evidence regarding the use of immunotherapies for the management of locally-advanced UC during the COVID-19 pandemic, including the management of immune-related adverse events

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Purpose:

This program would be beneficial for nurses involved and/or interested in the therapeutic management of patients with locally advanced or metastatic urothelial carcinoma.

CNE Credits: 1.0 ANCC Contact Hour

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DISCLOSURE OF CONFLICTS OF INTEREST –

Faculty Member	Disclosure
Arjun Balar, MD	**Dr. Balar** reports that he serves as a consultant/advisor for Genentech, Incyte, Janssen, Merck, Pfizer, AstraZeneca/Medimmune, Nektar, Seattle Genetics, and Immunomedics. He has also done contracted research for Genentech, Nektar, Merck, AstraZeneca/MedImmune, Seattle Genetics, and Immunomedics. Dr. Balar has done speaking engagements for Genentech, Merck, and AstraZeneca/Medimmune. He has served on Steering Committees/Scientific Advisory Committees for Merck and Nektar. He receives equity and serves as a Scientific Advisory Board Member for EpiVax Oncology.
Robert Dreicer, MD	**Dr. Dreicer** reports that he serves as a consultant for Eisai, Infinity, Myovant, Bayer, EMD Serono, Pfizer, and Veru.
Alicia K. Morgans, MD, MPH	**Dr. Morgans** has disclosed that she serves as a consultant for Astellas, AstraZeneca, Bayer, Clovis, Myovant, Janssen, Sanofi, Pfizer, AAA, Dendreon, and Seattle Genetics.
Peter H. O'Donnell, MD	**Dr. O'Donnell** reports that he serves as a consultant/advisor for Merck and has done contracted research on behalf of his institution for Boehringer Ingelheim, Merck, Genentech/Roche, AstraZeneca/MedImmune, Acerta Pharma, Janssen, Seattle Genetics, Bristol-Myers Squibb, and Astellas Pharma. He has stock and other ownership interests with Allergan and receives honoraria from Genentech/Roche, Merck, Astellas Pharma, Seattle Genetics, Atheneum, Health Advances, Janssen, Dedham Group, Schlesinger Associates, FirstWord, Pfizer, and CLD. Dr. O'Donnell also has other relationships with Janssen, Nektar, NIH, and Dragonfly Therapeutics.

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The reviewer of this activity has nothing to disclose.

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Agenda

I. Locally Advanced or Metastatic Urothelial Carcinoma: An Overview

a. Epidemiology
b. Histology
c. Evolution of treatment strategies

II. Sequencing Strategies for Locally Advanced or Metastatic UC

a. Clinical trial data on the use of immune checkpoint inhibitors in the second-line setting
b. FDA-approved immune checkpoint inhibitors in the second-line setting
c. Cisplatin-ineligible MIBC and metastatic UC
d. Immunotherapy in the first-line setting
e. Assays for PD-L1 expression in UC
f. Maintenance therapy for UC
    i. Resistance to chemotherapy and the rationale for the use of maintenance therapy
    ii. Clinical trial data on the use of maintenance therapy in the first-line setting
g. Chemotherapy vs immunotherapy in the first-line
h. Review of differences between upfront treatment and sequencing strategies for the management of patients with locally advanced or metastatic UC

III. Immune-Related Adverse Events Secondary to ICI Therapy

a. Types of irAEs associated with immunotherapies for the treatment of advanced HCC
b. Pathophysiologic basis for irAEs
c. Surveillance and management of most common irAEs

IV. COVID-19 and Cancer

a. Malignancy as a risk factor for infection
b. Studies of clinical impacts of COVID-19 on patients with cancer
c. Effect of infection-risk on immunotherapy selection/initiation/continuation
d. Symptoms consistent with irAEs and COVID-19
e. Managing bladder cancer in the era of COVID-19

VI. Case study

VII. Conclusions

IC–ONC: Optimizing the Sequencing of Immune Checkpoint Inhibitors in Locally Advanced or Metastatic Urothelial Carcinoma

PROGRAM CHAIR:
Arjun Balar, MD
Associate Professor of Medicine
Director – Genitourinary Medical Oncology Program
Medical Director – Clinical Trials Office
Laura and Isaac Perlmutter Cancer Center
New York, NY

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Disclosures

- Please see Program Overview for specific speaker disclosure information
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3

Learning Objectives

- Develop treatment plans that appropriately sequence chemotherapy and immunotherapy in patients with locally-advanced or metastatic urothelial carcinoma (UC)
- Evaluate evidence for the use of maintenance immunotherapy as first-line therapy for metastatic UC
- Identify patients with locally advanced or metastatic UC who are candidates for second-line treatment
- Apply current recommendations and emerging evidence regarding the use of immunotherapies for the management of locally-advanced UC during the COVID-19 pandemic, including the management of immune-related adverse events

4

Locally Advanced or Metastatic Urothelial Carcinoma

An Overview

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Urothelial Bladder Cancer: Epidemiology

- In US, an estimated 83,730 new cases and 17,200 deaths in 2021
- Median age at diagnosis is 73 years
- Male:female ratio of 4:1 in new cases
- Smoking is the strongest risk factor
  - Chemical industry (aromatic amines, aniline dyes)
  - <5% are hereditary
- Panurothelial disease, ie, concern for synchronous or metachronous disease
  - Field cancerization vs monoclonality
- 75–80% superficial, 25% muscle invasive, and 5% metastatic

American Cancer Society (ACS). *Cancer Facts & Figures 2021* (www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf). ACS. Bladder cancer (www.cancer.org/cancer/bladder-cancer/). National Institutes of Health (NIH) bladder cancer (https://seer.cancer.gov/statfacts/html/urinb.html). All URLs accessed 1/27/2021.

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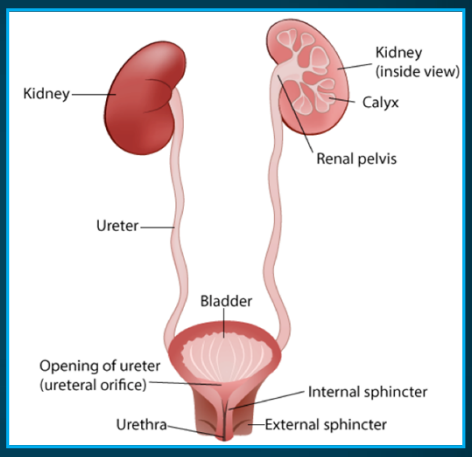
Anatomy and Histology of Bladder Cancer

Bladder Cancer	
Types	**Incidence**
Urothelial/ transitional-cell carcinoma (UC/TC)*	~90%
Squamous cell carcinoma	~5%
Adenocarcinoma	~1%
Small-cell carcinoma	~1%



*UC/TC of the bladder, ureter, and renal pelvis (5–10% of all renal tumors) have a similar natural history, and similar management principles may be applied to each type.

Memorial Sloan Kettering Cancer Center (MSKCC). Types of bladder cancer. (www.mskcc.org/cancer-care/types/bladder/types). Accessed 2/3/2021.

7

Metastatic Urothelial Cancer
Historical Perspective

- Urothelial cancer (UC) is a chemotherapy-sensitive disease
  - Cisplatin, carboplatin, methotrexate, doxorubicin, vinblastine, ifosfamide*, gemcitabine, paclitaxel, and docetaxel
- Cisplatin and methotrexate have highest response rates as single agents[1]
  - Basis for combination regimens (eg, MVAC, CISCA, etc)
- A small proportion of patients can be cured with cisplatin-based chemotherapy
- Cisplatin-based therapy is associated with significant toxicity

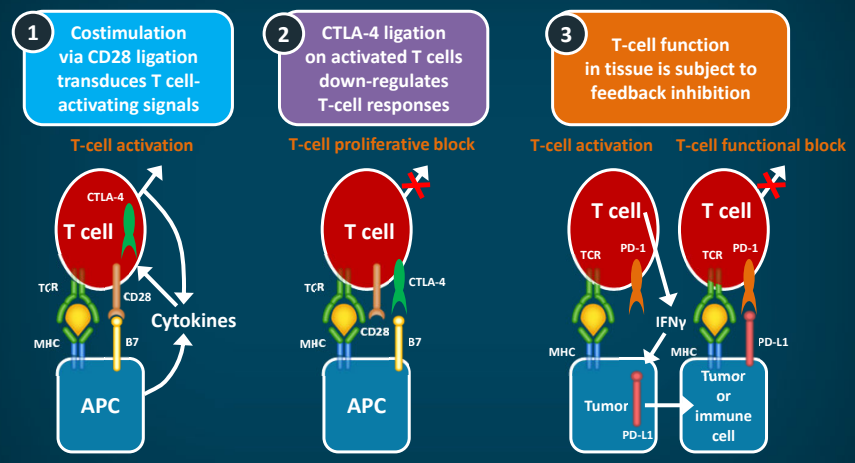
*Ifosfamide and cyclophosphamide are off-label use for bladder cancer.

MVAC = methotrexate, vinblastine, adriamycin, cisplatin; CISCA = cisplatin, cyclophosphamide*, doxorubicin.

Yagoda A. *Cancer.* 1987;60:574-585.

8

T-Cell Activation, Proliferation, and Function Controlled by Multiple Agonists and Antagonist Signals

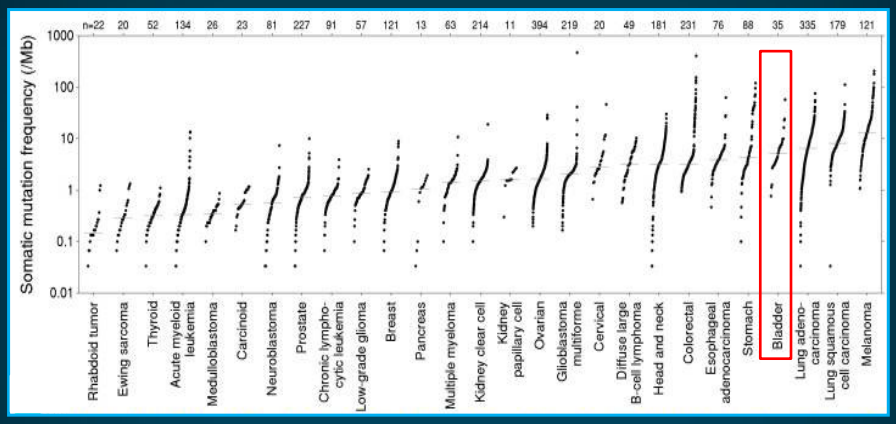


CD = cluster of differentiation; TCR = T-cell receptor; CTLA = cytotoxic T-lymphocyte antigen; PD-1 = programmed (cell) death 1; PD-L1 = PD-1 ligand; MHC = major histocompatibility complex; APC = antigen-presenting cell; IFN = interferon.

Melero I, et al. *Nat Rev Cancer.* 2007;7:95-106. Krummel MF, Allison JP. *J Exp Med.* 1995;182:459-465. Krummel MF, et al. *Int Immunol.* 1996;8:519-523.

9

Somatic Mutational Burden Is High in UBC



- High mutational complexity rates linked to tobacco/environmental carcinogen exposure[1]
- Potential for many neoantigens to be seen as foreign by host immune system[2]

UBC = urothelial bladder cancer.

1. Adapted from Lawrence MS, et al. *Nature.* 2013;499:214-218. 2. Bellmunt J, et al. *Cancer Treat Rev.* 2017;54:58-67.

10

Sequencing Strategies for Locally Advanced or Metastatic UC

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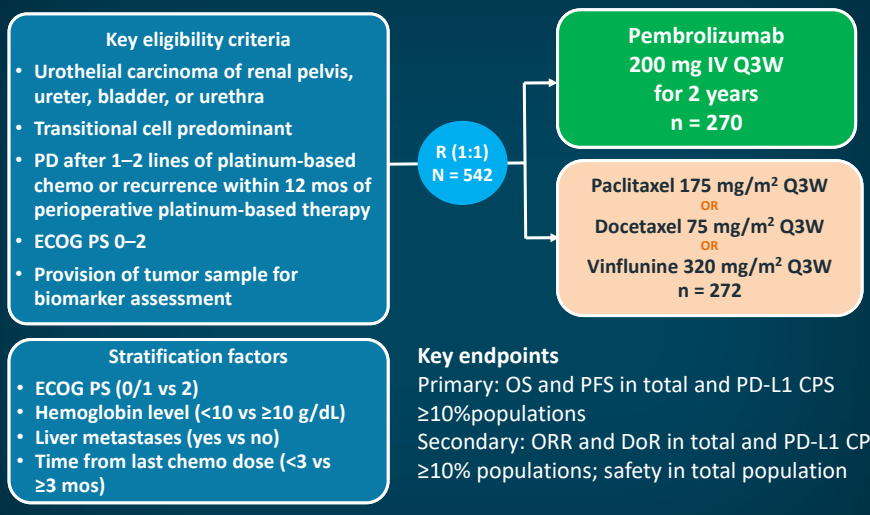
KEYNOTE-045 Study Design (NCT02256436)



Key endpoints

Primary: OS and PFS in total and PD-L1 CPS ≥10%populations

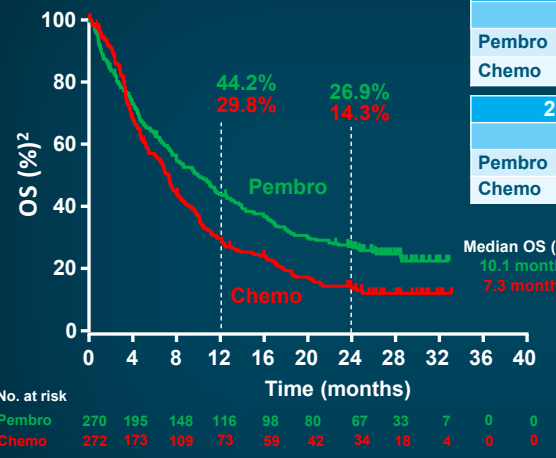
Secondary: ORR and DoR in total and PD-L1 CPS ≥10% populations; safety in total population

chemo = chemotherapy; PD = progressive disease; ECOG = Eastern Cooperative Oncology Group; PS = performance status; mo(s) = month(s); IV = intravenous; Q3W = every 3 weeks; OS = overall survival; PFS = progression-free survival; CPS = combined positive score; ORR = overall/objective response rate; DoR = duration of response.

Bellmunt J, et al. *N Engl J Med*. 2017;376:1015-1026.

12

KEYNOTE-045: OS in Total Population



14.1 months of follow-up[1]			
	Events, n	HR (95% CI)*	*P*-value
Pembro	155	0.73 (0.59-0.91)	.002
Chemo	179		

27.7 months of follow-up[2]			
	Events, n	HR (95% CI)*	*P*-value
Pembro	199	0.70 (0.57–0.85)	.00015
Chemo	218		

Median OS (95% CI):
10.1 months (8.0–12.3)
7.3 months (6.1–8.1)

60.6% in chemo arm at 24 mos received immunotherapeutic agent, including those receiving pembrolizumab as part of crossover[2]

Data cutoff date: October 26, 2017.

Pembro = pembrolizumab; HR = hazard ratio; CI = confidence interval.

1. Bellmunt J, et al. *N Engl J Med*. 2017;376:1015-1026. 2. Fradet Y, et al. *Ann Oncol*. 2019;30:970-976.

13

FDA-Approved Checkpoint Inhibitors for UC

Setting	Antibody (Study)	N	ORR	Median OS
Platinum-pretreated (second-line)	Atezolizumab[1] (Imvigor210, cohort 2)	310	15%	7.9 months
	Nivolumab[2] (CheckMate 275)	265	20%	8.74 months
	**Durvalumab[3] (Study 1108)	201	17.4%	10.5 months
	Avelumab[4] (JAVELIN Solid Tumor)	249	17%	6.5 months
	Pembrolizumab[5] (KEYNOTE-045 [Ph 3])	270*	21%	10.3 months

*Pembrolizumab arm.

**Bladder cancer indication withdrawn for durvalumab as of February 22, 2021.

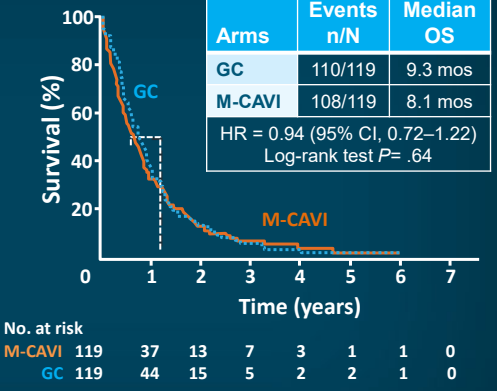
Note: Data presented were generated from trials with different study designs, methodologies, and patient groups and are not intended to be head-to-head comparisons; refer to individual studies for further information.

1. Rosenberg JE, et al. *Lancet*. 2016;387:1909-1920. 2. Sharma P, et al. *Lancet Oncol*. 2017;18:312-322. 3. O'Donnell PH, et al. *Cancer Res*. 2018;78(13): abstract CT031. 4. Patel MR, et al. *Lancet Oncol*. 2018;19:51-64. 5. Bajorin DF, et al. *J Clin Oncol*. 2017;35(15 suppl): abstract 4501.

14

Cisplatin in Muscle-Invasive and mUC

- Cisplatin improves survival (including some cures); however, >50% of patients ineligible due to comorbidities
  - PS and renal dysfunction
  - Neuropathy/hearing loss
  - Heart failure
- Cisplatin-ineligible
  - Outcomes very poor
  - 20–40% or more never treated[1]



Arms	Events n/N	Median OS
GC	110/119	9.3 mos
M-CAVI	108/119	8.1 mos

HR = 0.94 (95% CI, 0.72–1.22)
Log-rank test *P*= .64

No. at risk

M-CAVI	119	37	13	7	3	1	1	0
GC	119	44	15	5	2	2	1	0

mUC = metastatic urothelial carcinoma; GC = gemcitabine, carboplatin; M-CAVI = methotrexate, carboplatin, vinblastine; n/N = observed number of deaths/total number of patients.

1. Sonpavde G, et al. *Clin Genitourin Cancer*. 2014;12:71-73. 2. De Santis M, et al. *J Clin Oncol*. 2012;30:191-199.

15

IMvigor210 Cohort 1 Study Design:
Basis for Accelerated Approval of Atezolizumab

- Inoperable locally advanced or metastatic UC
- Predominantly UC histology
- Tumor tissue evaluable for PD-L1 testing

Cohort 1 (n = 119)
First-line
Cisplatin-ineligible

→ **Atezolizumab** 1200 mg IV Q3W until RECIST 1.1 progression

Cohort 2 (n = 310)
Platinum-treated mUC

→ **Atezolizumab** 1200 mg IV Q3W until loss of clinical benefit

Cohort 1: specific inclusion criteria
- No prior treatment for mUC (>12 mos since perioperative chemo)
- ECOG PS 0–2
- Cisplatin ineligibility based on ≥1 of the following
  - Renal impairment: GFR <60 and >30 mL/min
  - Grade ≥2 hearing loss or peripheral neuropathy

- Primary endpoint confirmed ORR by RECIST 1.1 by central IRF
- Key secondary endpoints: DoR, PFS, OS, and safety

mUC = metastatic UC; GFR = glomerular filtration rate; RECIST = Response Evaluation Criteria in Solid Tumors.

Balar AV, et al. *J Clin Oncol.* 2016;34(suppl): abstract LBA4500.

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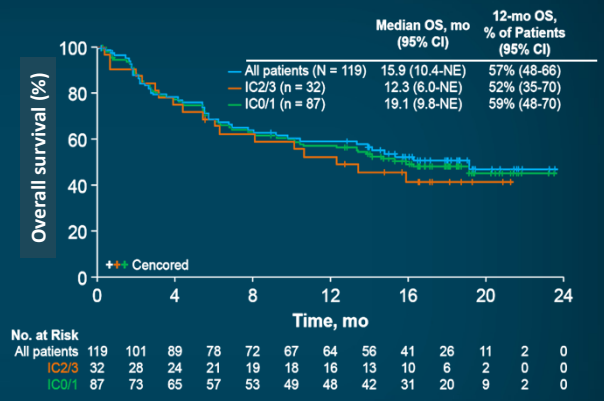
IMvigor210: Atezolizumab in Cisplatin-Ineligible Patients—Antitumor Activity

- 21% aged ≥80 years
- 70% of patients had renal impairment
- 20% were ECOG PS 2
- 2/3 had visceral metastases



	All Patients (N = 119)	IC2/3 (n = 32)	IC1/2/3 (n = 80)	IC1 (n = 48)	IC0 (n = 39)
ORR (95% CI)	23% (16–31)	28% (14–47)	24% (15–35)	21% (10–35)	21% (9–36)
CR	9%	13%	10%	8%	8%
PR	14%	16%	14%	13%	13%

CR = complete response; PR = partial response; IC = tumor-infiltrating immune cells; NE = not estimable.

Balar AV, et al. *Lancet*. 2017;389:67-76.

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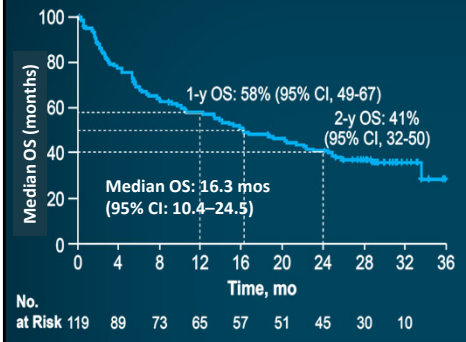
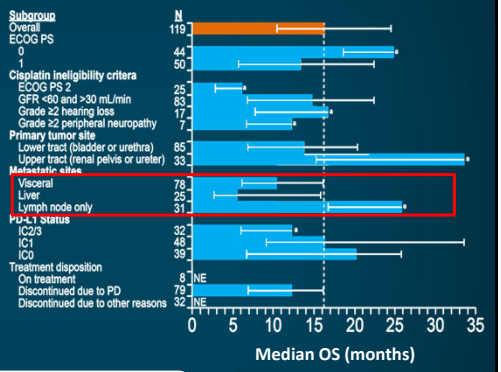
First-Line Atezolizumab: IMVigor210 Cohort 1

Long-Term Follow-Up*





- Well-tolerated regimen
- Any grade 3/4 AE = 19%

*Upper 95% CI is NE.

AE = adverse event.

Balar AV, et al. *Lancet*. 2017;389:67-76. Balar AV, et al. J Clin Oncol. 2018;36(15 suppl): abstract 4523.

18

KEYNOTE-052: Pembrolizumab as First-Line Therapy for Cisplatin-Ineligible Advanced UC

- Advanced urothelial cancer
- No prior chemo for metastatic disease
- ECOG PS 0–2
- Cisplatin-ineligible based on ≥1 of:
  - CrCl <60 mL/min
  - ECOG PS 2
  - Grade ≥2 neuropathy or hearing loss
  - NYHA class III CHF
- N = 370

→ **Pembrolizumab** 200 mg IV Q3W

Demographics
- 32% were ECOG PS 2
- 49% were aged ≥75 years
- 85% had visceral metastases
- 49% had renal impairment

- **Primary endpoints:** ORR in all patients and in patients with PD-L1–positive tumors
- **Secondary endpoints:** DoR, PFS, OS, and ORR in all patients, PD-L1–positive, and PD-L1–high expressing patients; safety and tolerability; establishing an assay cutpoint for high PD-L1 expression in first 100 patients, with validation in second 250 patients

CrCl = creatinine clearance; NYHA = New York Heart Association; CHF = congestive heart failure.

Balar AV, et al. *Lancet Oncol*. 2017;18:1483-1492.

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KEYNOTE-052—Confirmed ORR With Pembrolizumab

Responses in Total Population* (N = 370)

Response	n	%	95% CI
ORR	106	29	24–34
CR	33	9	6–12
PR	73	20	16–24
SD	67	18	14–22
PD	157	42	37–48

With longer follow-up:†
- 5% increase in ORR
- 16 additional CRs
- 1 additional PR

*As of data cutoff: September 26, 2018. Assessed per RECIST v1.1 by independent radiology review. Additional 31 patients had no postbaseline tumor assessment because of no available postbaseline imaging data.
†Compared with September 1, 2016 data cutoff.

SD = stable disease.

Vuky J, et al. *J Clin Oncol.* 2020;38:2658-2666. Balar AV, et al. *Lancet Oncol.* 2017;18:1483-1492. O'Donnell PH, et al. *J Clin Oncol*. 2017;35(suppl): abstract 4502.

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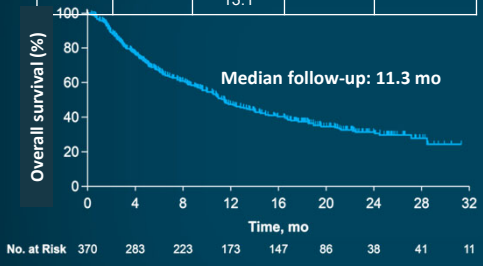
KEYNOTE-052 Long-Term Follow-Up:
First-Line Pembrolizumab

Events n	Median mos	95% CI	12-mo OS %	24-mo OS %
277	11.3	9.7 to 13.1	46.9	31.2



	N	Events, n (%)	Median OS, mo (95% CI)
PD-L1 subgroup			
PD-L1 CPS <10	251	206 (82)	9.7 (7.6–11.5)
PD-L1 CPS ≥10	110	66 (60)	18.5 (12.2–28.5)
Age, y			
<65	68	41 (60)	15.7 (6.9–NR)
≥65	302	206 (68)	11.9 (9.7–12.8)
ECOG PS			
0/1	214	152 (71)	13.0 (11.0–16.5)
2	156	125 (80)	9.6 (5.7–11.5)
Location of metastases			
Lymph node only	51	28 (55)	27.0 (12.4–NR)
Visceral disease	315	247 (78)	10.6 (8.7–11.7)

- Overall well tolerated
- Grade 3/4 AEs were 16%
- One death reported as treatment related (myositis)

NR = not reached.

Vuky J, et al. *J Clin Oncol*. 2020;38:2658-2666 plus supplement.

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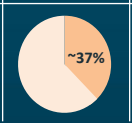
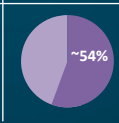
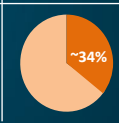
Assays for PD-L1 Expression in UC
Infinite Number of Possibilities

Immunotherapy (IO)	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Durvalumab[4]	Avelumab[5]
Detection antibody	SP142	28-8	22C3	SP263	73-10
IHC platform	Ventana	Dako	Dako	Ventana	Dako
Cell types scored for UC	IC	TC	TC + IC	IC + TC	IC + TC
Cut-off definitions for UC	PD-L1+ (IC2/3) as ≥5% of ICs PD-L1+	PD-L1+ ≥1% TC expression	PD-L1+ ≥10% TC and IC staining	PD-L1+ as ≥25% of ICs and TCs with membrane PD-L1 staining	PD-L1+ as ≥5% TC staining or ≥10% IC staining
Estimated PD-L1 prevalence in UC trials					

TC = tumor cell.

1. Rosenberg JE, et al. *Lancet*. 2016;387:1909-1920. 2. Sharma P, et al. *Lancet Oncol*. 2017;18:312-322. 3. Bellmunt J, et al. *N Engl J Med*. 2017;376:1015-1026. 4. Powles T, et al. *JAMA Oncol*. 2017;3:e172411. 5. Apolo AB, et al. *J Clin Oncol*. 2016;34(suppl): abstract 4514.

22

Regulatory Updates for PD-1/PD-L1 Therapy in Advanced Cisplatin-Ineligible UC

Requires the use of an FDA-approved companion diagnostic test to determine PD-L1 levels in tumor tissue

- Pembrolizumab is indicated for treating patients with locally advanced or metastatic UC not eligible for cisplatin-containing chemotherapy and *whose tumors express PD-L1 (CPS ≥10)* as determined by an FDA-approved test, or in patients not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status.
- Atezolizumab is indicated for treating patients with locally advanced or metastatic UC not eligible for cisplatin-containing chemotherapy and *whose tumors express PD-L1 (PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area),* as determined by an FDA-approved test, or in patients not eligible for any platinum-containing therapy, regardless of PD-L1 status

Pembrolizumab (Keytruda®) prescribing information (PI) 2020 (www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf). Atezolizumab (Tecentriq®) PI 2020(www.gene.com/download/pdf/tecentriq_prescribing.pdf) . 2.US Food and Drug Administration (FDA) (www.fda.gov/drugs/resources-information-approved-drugs/fda-limits-use-tecentriq-and-keytruda-some-urothelial-cancer-patients). URLs accessed 2/4/2021.

23

IMvigor130: Atezolizumab ± Platinum-Based Chemotherapy In Previously Untreated mUC

- Locally advanced or mUC
- No prior systemic therapy in metastatic setting
- ECOG PS ≤2
- First-line platinum eligible
- Randomized 1:1:1
- **N = 1213**

→ **Arm A** Atezolizumab + Plat/Gem

→ **Arm B** Atezolizumab monotherapy

→ **Arm C** PBO + Plat/Gem

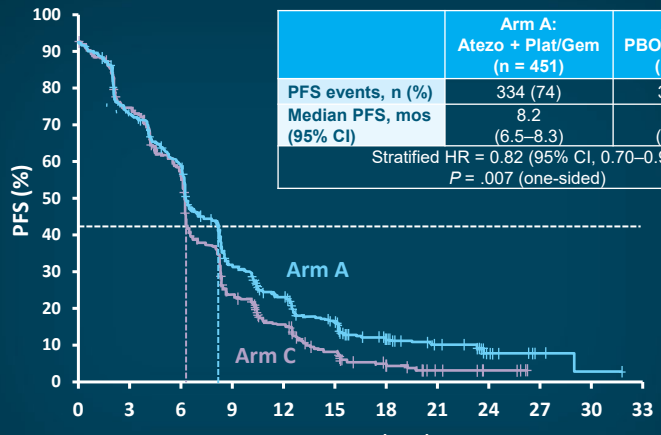
- **Stratification factors**
  - PD-L1 status (IC0 vs IC1 vs IC2/3)
  - Bajorin risk factor score, including KPS <80% vs ≥80% and presence of visceral metastases
  - Investigator choice of platinum/gemcitabine (cisplatin + gemcitabine or carboplatin + gemcitabine)
- **Coprimary endpoints:** INV-assessed PFS and OS (arm A vs C), OS (arm B vs C, hierarchical approach)
- **Key secondary endpoints:** INV-ORR and DoR, PFS and OS (arm B vs C; PD-L1 IC2/3 subgroup), and safety

PBO = placebo; Plat = platinum; Gem = gemcitabine; KPS = Karnofsky performance status; INV = investigator.

Galsky MD, et al. *Lancet.* 2020;395:1547-1557. NCT02807636 (https://clinicaltrials.gov/ct2/show/NCT02807636?term= NCT02807636&rank=1). *URO Today* (www.urotoday.com/conference-highlights/esmo-2019/esmo-2019-bladder-cancer/115398-esmo-2019-imvigor130-efficacy-and-safety-from-a-phase-3-study-of-atezolizumab-as-monotherapy-or-combined-with-platinum-based-chemotherapy-pbc-vs-placebo-pbc-in-previously-untreated-locally-advanced-or-metastatic-urothelial-carcinoma-muc.html). URLs accessed 1/27/2021

24

IMvigor130: PFS (Coprimary Endpoint)



	Arm A: Atezo + Plat/Gem (n = 451)	Arm C: PBO + Plat/Gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Median PFS, mos (95% CI)	8.2 (6.5–8.3)	6.3 (6.2–7.0)
Stratified HR = 0.82 (95% CI, 0.70–0.96) *P* = .007 (one-sided)		

No. at risk

Atezo + Plat/Gem	451	345	282	160	111	74	42	22	10	4	2	NE
PBO + Plat/Gem	400	317	246	116	73	40	18	11	4	NE	NE	NE

Data cutoff: May 31, 2019; median survival follow-up = 11.8 mos (all patients).

Galsky MD, et al. *Lancet.* 2020;395:1547-1557.

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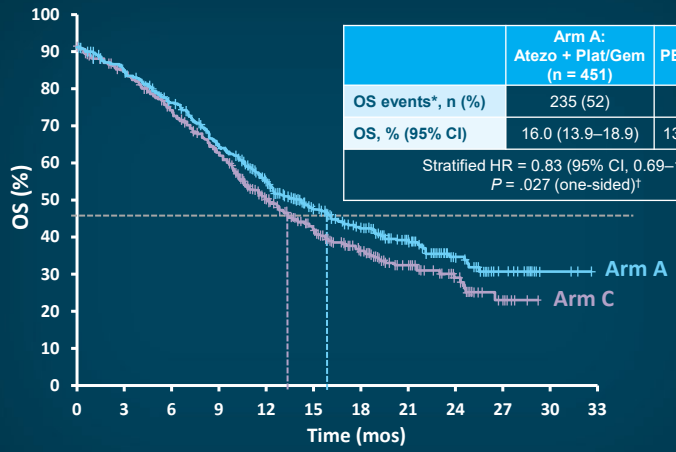
IMvigor130: OS (Coprimary Endpoint)
Arm A vs Arm C



	Arm A: Atezo + Plat/Gem (n = 451)	Arm C: PBO + Plat/Gem (n = 400)
OS events*, n (%)	235 (52)	228 (57)
OS, % (95% CI)	16.0 (13.9–18.9)	13.4 (12.0–15.2)
Stratified HR = 0.83 (95% CI, 0.69–1.00) *P* = .027 (one-sided)†		

No. at risk

Atezo + Plat/Gem	451	408	360	301	229	163	117	72	36	16	3	NE
PBO + Plat/Gem	400	359	308	255	182	123	79	49	25	8	NE	NE

*5% of patients from arm A and 20% of patients from arm C received nonprotocol immunotherapy; †Did not cross interim efficacy boundary of 0.007 for statistical significance.

Galsky MD, et al. *Lancet.* 2020;395:1547-1557.

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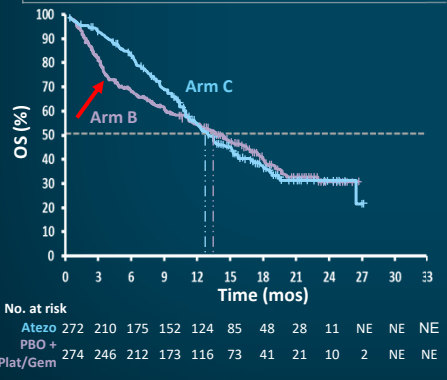
IMvigor130: OS According to PD-L1 Expression

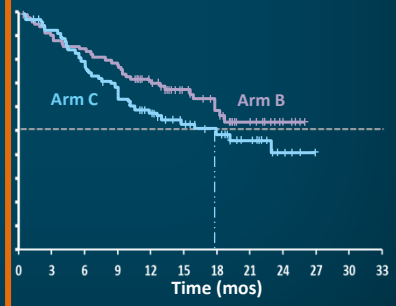
PD-L1 IC0/1	Arm B: Atezo (n = 272)	Arm C: PBO + Plat/Gem (n = 274)
OS events, n (%)	158 (58)	156 (57)
median OS, mos (95% CI)	13.5 (11.1–16.4)	12.9 (11.3–15.0)
Unstratified HR = 1.07 (95% CI, 0.86–1.33)		



No. at risk

Atezo	272	210	175	152	124	85	48	28	11	NE	NE	NE
PBO + Plat/Gem	274	246	212	173	116	73	41	21	10	2	NE	NE

PD-L1 IC2/3	Arm B: Atezo (n = 88)	Arm C: PBO + Plat/Gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Median OS, mos (95% CI)	NE (17.7–NE)	17.8 (10.0–NE)
Stratified HR = 0.68 (95% CI, 0.43–1.08)		



	0	3	6	9	12	15	18	21	24	27	30	33
Arm B	88	75	70	64	49	35	24	14	5	NE	NE	NE
Arm C	85	76	62	51	42	30	21	14	5	1	NE	NE

Galsky MD, et al. *Lancet.* 2020;395:1547-1557.

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Ongoing Phase 3 Trials

IMvigor130 (NCT02807636)[1]; N = 1213
- First-line cisplatin-eligible, locally advanced/metastatic UC
- ECOG PS ≤2
- Coprimary endpoints: PFS, OS, and safety

R → Atezolizumab; Platinum-based chemo + atezolizumab; PBO + Cisplatin + Gem or PBO + carboplatin + Gem

DANUBE (NCT02516241)[2]; N = 1005
- First-line unresectable/stage IV UC
- Eligible/ineligible for cisplatin-based chemo
- Coprimary endpoints: OS between groups

R → Durvalumab; Durvalumab + tremelimumab; Cisplatin + Gem or carboplatin + Gem

KEYN
- Firs
- EC
- Co

…em or …-Gem; Cisplatin-Gem or carboplatin-Gem

Phase III KEYNOTE-361 Trial Fails to Meet Primary End Points

1. Galsky MD, et al. *Lancet.* 2020;395:1547-1557. 2. Powles T, et al. *Lancet Oncol.* 2020;21:1574-1588. 3. Powles T, et al. *J Clin Oncol.* 2017;35(15 suppl): abstract TPS4590. Headline from CancerNetwork (www.cancernetwork.com/view/phase-iii-keynote-361-trial-fails-to-meet-primary-end-points. Accessed 2/4/2021.

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KEYNOTE-361 Study Design (NCT02853305)

Key eligibility criteria

- UC of renal pelvis, ureter, bladder or urethra
- Locally advanced unresectable or metastatic disease
- No prior systemic therapy for advanced disease
- ECOG PS 0, 1 or 2
- Tissue sample for PD-L1 assessment

Stratification factors

- PD-L1 expression (CPS ≥10 vs <10)
- Choice of platinum

R (1:1:1)

- Pembrolizumab 200 mg Q3W + Gemcitabine 1000 mg/m² + Cisplatin 70 mg/m² *OR* Carboplatin AUC 5 for ≤6 cycles → Pembrolizumab 200 mg Q3W for ≤29 cycles
- Pembrolizumab 200 mg Q3W for ≤35 cycles
- Gemcitabine 1000 mg/m² on days 1 and 8 Q3W + Cisplatin 70 mg/m² *OR* Carboplatin AUC 5 on day 1 Q3W for ≤6 cycles

- Dual primary endpoints: PFS per RECIST v1.1 by BICR and OS
- Secondary endpoints: ORR, DCR, and DoR by BICR per RECIST v1.1, safety

BICR = blinded independent central review.

Powles T, et al. *J Clin Oncol*. 2017;35(15 suppl): abstract TPS4590. NCT02853305 (https://clinicaltrials.gov/ct2/show/NCT02853305). Accessed 2/4/2021.

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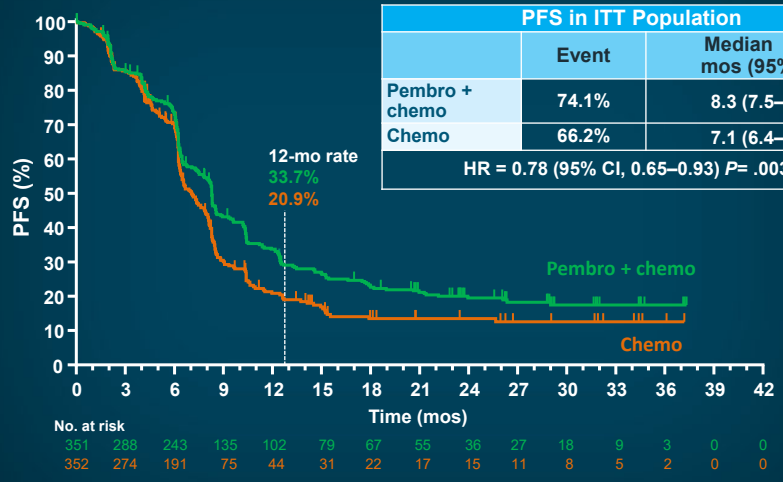
Pembro + Chemo vs Chemo: PFS by BICR
ITT Population (Primary Endpoint)



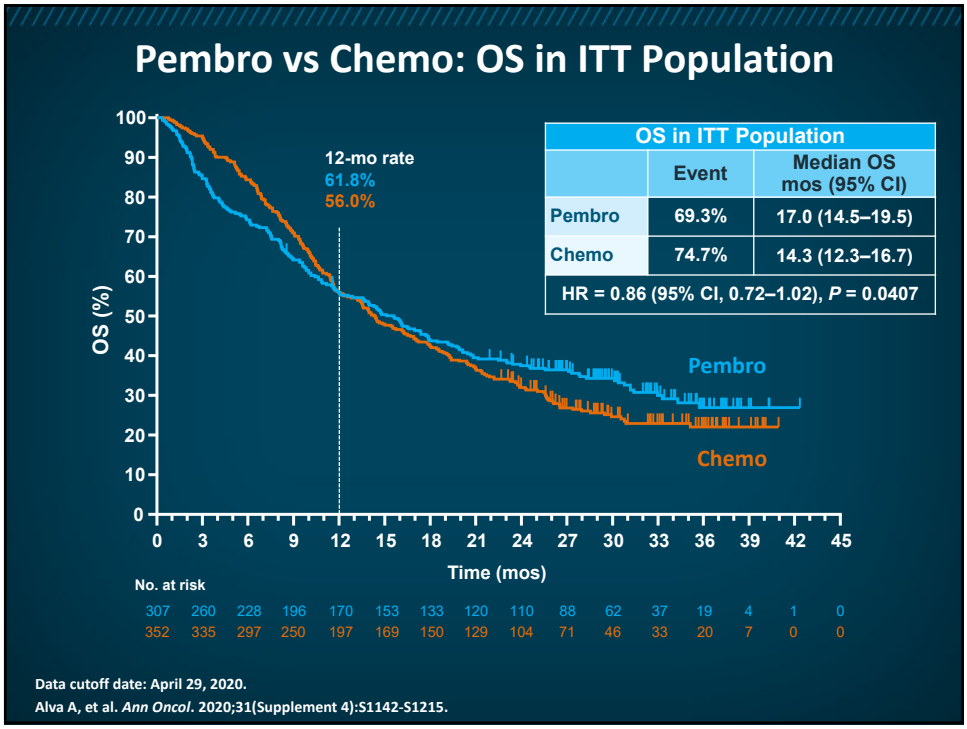
PFS in ITT Population		
	Event	Median PFS mos (95% CI)
Pembro + chemo	74.1%	8.3 (7.5–8.5)
Chemo	66.2%	7.1 (6.4–7.9)
HR = 0.78 (95% CI, 0.65–0.93) *P*= .0033		

PFS assessed per RECIST v1.1. Data cutoff date: April 29, 2020.

BICR = blinded independent central review; ITT = intention to treat.

Alva A, et al. *Ann Oncol*. 2020;31(Supplement 4):S1142-S1215.

30


Pembro vs Chemo: OS in ITT Population
OS (%)
100
90
80
70
60
50
40
30
20
10
0
12-mo rate
61.8%
56.0%
OS in ITT Population
Event
Median OS mos (95% CI)
Pembro
69.3%
17.0 (14.5–19.5)
Chemo
74.7%
14.3 (12.3–16.7)
HR = 0.86 (95% CI, 0.72–1.02), P = 0.0407
Pembro
Chemo
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45
Time (mos)
No. at risk
307 260 228 196 170 153 133 120 110 88 62 37 19 4 1 0
352 335 297 250 197 169 150 129 104 71 46 33 20 7 0 0
Data cutoff date: April 29, 2020.
Alva A, et al. Ann Oncol. 2020;31(Supplement 4):S1142-S1215.

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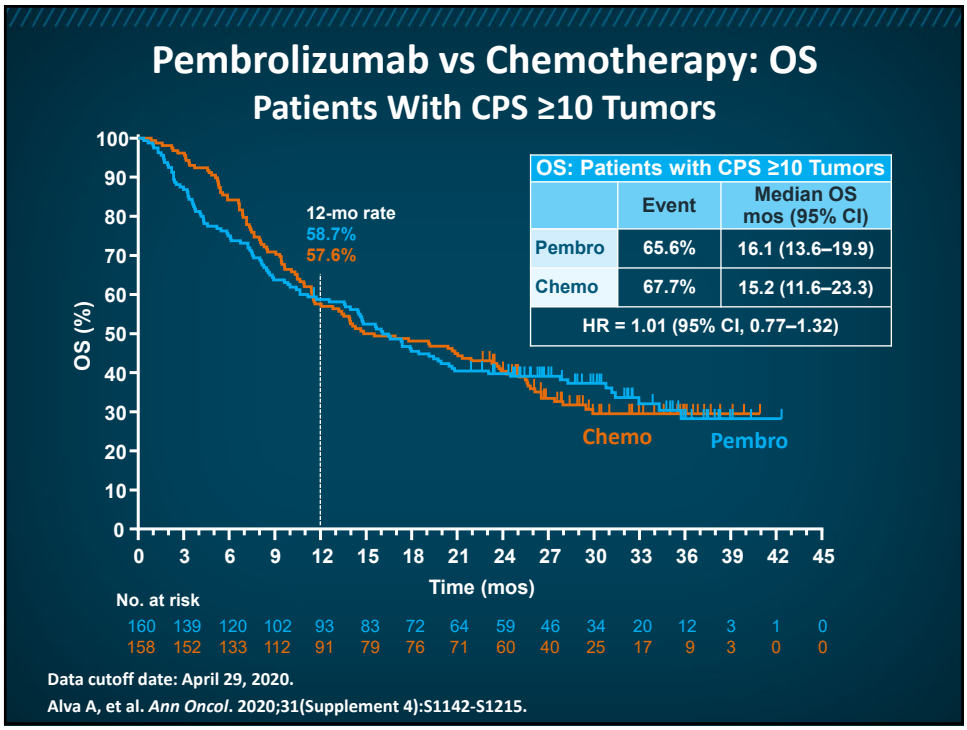
Pembrolizumab vs Chemotherapy: OS
Patients With CPS ≥10 Tumors
OS (%)
100
90
80
70
60
50
40
30
20
10
0
12-mo rate
58.7%
57.6%
OS: Patients with CPS ≥10 Tumors
Event
Median OS mos (95% CI)
Pembro
65.6%
16.1 (13.6–19.9)
Chemo
67.7%
15.2 (11.6–23.3)
HR = 1.01 (95% CI, 0.77–1.32)
Chemo
Pembro
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45
Time (mos)
No. at risk
160 139 120 102 93 83 72 64 59 46 34 20 12 3 1 0
158 152 133 112 91 79 76 71 60 40 25 17 9 3 0 0
Data cutoff date: April 29, 2020.
Alva A, et al. Ann Oncol. 2020;31(Supplement 4):S1142-S1215.

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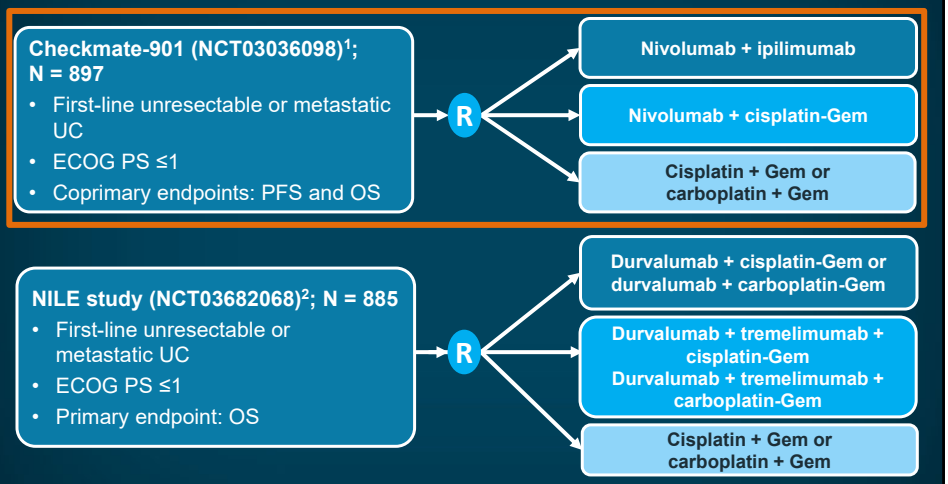
Ongoing Phase 3 Trials (continued)



NOTE: ipilimumab and tremelimumab are off-label use for bladder cancer.

1. NCT03036098 (https://clinicaltrials.gov/ct2/show/NCT03036098?term=NCT03036098&draw=2&rank=1). 2. NCT03682068 (https://clinicaltrials.gov/ct2/show/NCT03682068?term=NCT03682068&draw=2&rank=1). URLs accessed 2/5/2021.

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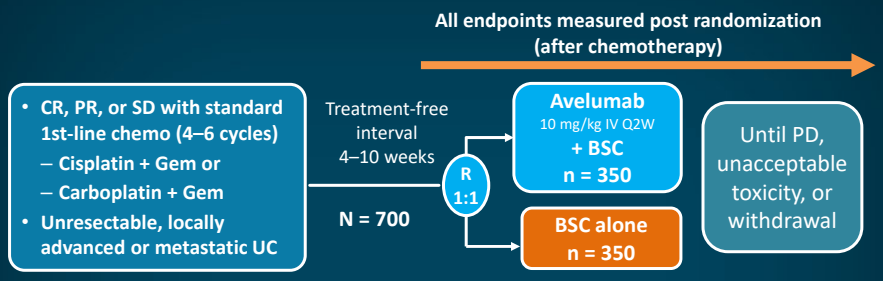
JAVELIN Bladder 100: "Switch" Maintenance



- **Stratification**
  - Best response to 1st-line chemo (CR or PR vs SD)
  - Metastatic site (visceral vs non-visceral)
- **Primary endpoint** = OS
- **Primary analysis populations:** all randomized patients and PD-L1+ population
- **Secondary endpoints** = PFS and objective response per RECIST 1.1; safety and tolerability; PROs

BSC = best supportive care; PRO = patient reported outcome; Q2W, every 2 weeks; R, randomization.

NCT02603432. Powles T, et al. *J Clin Oncol*. 2020;38(suppl): abstract LBA1.

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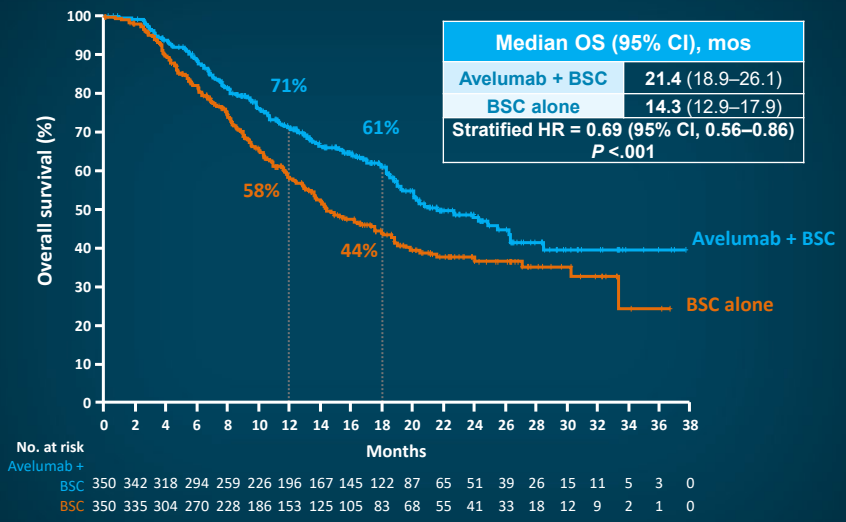
JAVELIN Bladder 100: OS in Overall Population



Powles T, et al. *J Clin Oncol.* 2020;38(suppl): abstract LBA1. *URO Today* (www.urotoday.com/conference-highlights/ asco-2020/asco-2020-bladder-cancer/121923-asco-2020-javelin-bladder-100-phase-iii-results-maintenance-avelumab-best-supportive-case-vs-bsc-alone-after-platinum-based-first-line-chemotherapy-in-advanced-urothelial-carcinoma.html). Accessed 1/27/2021.

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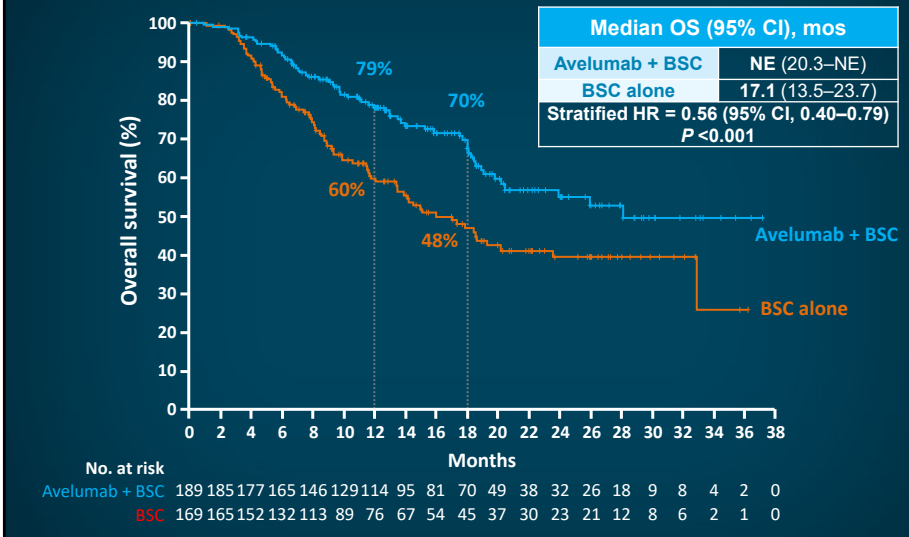
JAVELIN Bladder 100: OS in PD-L1+ Population



Powles T, et al. *J Clin Oncol.* 2020;38(suppl): abstract LBA1. *URO Today* (www.urotoday.com/conference-highlights/ asco-2020/asco-2020-bladder-cancer/121923-asco-2020-javelin-bladder-100-phase-iii-results-maintenance-avelumab-best-supportive-case-vs-bsc-alone-after-platinum-based-first-line-chemotherapy-in-advanced-urothelial-carcinoma.html). Accessed 1/27/2021.

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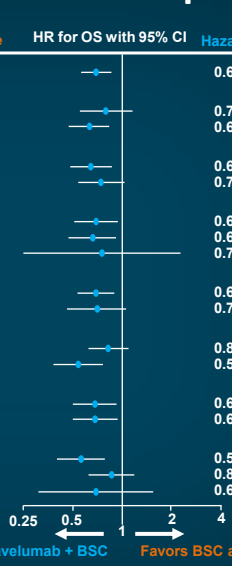
Subgroup Analysis of OS in Overall Population

Subgroup		Events/patients, n: Avelumab + BSC	BSC alone	Hazard ratio (95% CI)
All patients		145/350	179/350	**0.69** (0.56–0.86)*
Age	<65 years	61/129	53/107	**0.79** (0.55–1.15)
	≥65 years	84/221	126/243	**0.63** (0.47–0.83)
ECOG PS score	0	77/213	101/211	**0.64** (0.48–0.86)
	≥1	68/137	78/139	**0.74** (0.54–1.03)
1st-line chemo regimen	Gem + cisplatin	71/183	98/206	**0.69** (0.51–0.94)
	Gem + carboplatin	68/147	73/122	**0.66** (0.47–0.91)
	Gem + cisplatin/carboplatin	6/20	7/20	**0.75** (0.25–2.25)
Best response to 1st-line chemo	CR or PR	104/253	127/252	**0.69** (0.53–0.89)
	SD	41/97	52/98	**0.70** (0.46–1.05)
Site of baseline metastasis	Visceral	93/191	101/191	**0.82** (0.62–1.09)
	Nonvisceral	52/159	78/159	**0.54** (0.38–0.76)
Creatinine clearance	≥60 mL/min	74/181	97/196	**0.68** (0.50–0.92)
	<60 mL/min	71/168	81/148	**0.68** (0.50–0.94)
PD-L1 status	Positive	61/189	82/169	**0.56** (0.40–0.78)
	Negative	76/139	72/132	**0.86** (0.62–1.18)
	Unknown	8/22	25/49	**0.69** (0.31–1.53)



*Stratified (all other analyses are unstratified)

Powles T, et al. *J Clin Oncol.* 2020;38(suppl): abstract LBA1. *URO Today* (www.urotoday.com/conference-highlights/ asco-2020/asco-2020-bladder-cancer/121923-asco-2020-javelin-bladder-100-phase-iii-results-maintenance-avelumab-best-supportive-case-vs-bsc-alone-after-platinum-based-first-line-chemotherapy-in-advanced-urothelial-carcinoma.html). Accessed 1/27/2021.

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JAVELIN Bladder 100
Subsequent Anticancer Therapy

Subsequent Anticancer Therapy or Lack of Treatment	Overall population		Subgroup Discontinuing study therapy due to PD	
Subsequent therapy or lack of treatment	Avelumab + BSC (n = 350)	BSC alone (n = 350)	Avelumab + BSC (n = 189)	BSC alone (n = 263)
Discontinued and received subsequent drug therapy	**42.3%**	**61.7%**	**70.4%**	**75.3%**
PD-L1/PD-1 inhibitor	**6.3%**	**43.7%**	**9.0%**	**52.9%**
Fibroblast growth factor-receptor inhibitor	2.6%	2.3%	4.8%	3.0%
Any other drug	40.0%	34.0%	67.2%	41.8%
Discontinued with no subsequent drug therapy	33.4%	30.9%	29.6%	24.7%
Study treatment ongoing	24.3%	7.4%	—	—

Note: some patients received >1 category of subsequent therapy.

Powles T, et al. *J Clin Oncol.* 2020;38(suppl): abstract LBA1. *URO Today* (www.urotoday.com/conference-highlights/ asco-2020/asco-2020-bladder-cancer/121923-asco-2020-javelin-bladder-100-phase-iii-results-maintenance-avelumab-best-supportive-case-vs-bsc-alone-after-platinum-based-first-line-chemotherapy-in-advanced-urothelial-carcinoma.html). Accessed 1/27/2021.

38

Avelumab Receives FDA Approval for UC Maintenance

FDA approves avelumab for urothelial carcinoma maintenance treatment

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On June 30, 2020, the Food and Drug Administration approved avelumab (BAVENCIO, for maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

FDA (www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-avelumab-urothelial-carcinoma-maintenance-treatment). Accessed 1/27/2021.

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Immunotherapy vs Platinum
Platinum-Based Chemotherapy in the First-Line

- Pros
  - High probability of achieving disease control (41% to 49%)[1–4]
  - Allows rapid transition to maintenance immunotherapy after 4–6 cycles, which could improve access compared with waiting until progression.[5–10]
  - Ideal for symptomatic or rapidly progressive disease or high disease burden
- Cons
  - Short duration of response[2,3]
  - Chemotherapy-related toxicity and not all patients eligible[6]

1. von der Maase H, et al. *J Clin Oncol.* 2000;18:3068-3077. 2. von der Maase H, et al. *J Clin Oncol.* 2005;23:4602-4608. 3. De Santis M, et al. *J Clin Oncol.* 2012;30:191-199. 4. Dogliotti L, et al. *Eur Urol.* 2007;52:134-141. 5. Cheeseman S, et al. *Front Oncol.* 2020;10:167. 6. Aly A, et al. *J Med Econ.* 2019;22:662-670. 7. Galsky MD, et al. *Bladder Cancer.* 2018;4:227-238. 8. Fisher MD, et al. *Clin Genitourin Cancer.* 2018;16:e1171-e1179. 9. Niegisch G, et al. *J Cancer.* 2018;9:1337-1348. 10. Flannery K, et al. *Future Oncol.* 2019;15:1323-1334.

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Immunotherapy vs Platinum – Immunotherapy in the First-Line

- Pros
  - Responses higher in the first-line (as compared with second-line)
  - Responses very durable (sometimes years)
  - Improved QoL over chemotherapy (second-line)
  - Biomarker helps treatment decision making
- Cons
  - Lower-likelihood of response (compared with platinum-based chemotherapy)
  - Risk of disease progression and early death in randomized studies (compared with platinum-based chemotherapy)

QoL = quality of life.

O'Donnell PH, et al. *J Clin Oncol.* 2019;37(suppl 15): abstract 4546. Fradet Y, et al. *Ann Oncol.* 2019;30:970-976. Galsky MD, et al. *Lancet.* 2020;395:1547-1557. Hoffman-Censits JH, et al. *J Clin Oncol.* 2016;34(Suppl 2):355. Powles T, et al. *Lancet.* 2018;391:748-757. CancerNetwork (www.cancernetwork.com/view/phase-iii-keynote-361-trial-fails-to-meet-primary-end-points. Accessed 2/4/2021.

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Current Status of Novel Therapeutics in mUC (July 2020)

Newly diagnosed (cisplatin-eligible)	Newly diagnosed (cisplatin-ineligible, PD-L1+ *OR* any platinum-ineligible)	Prior platinum chemo or relapse within 1 year of perioperative/adjuvant cisplatin
Phase 3 evidence and clinical trials	**FDA Approvals**	
Regimens still under investigation	***Immunotherapy (CPIs)***	***Immunotherapy (CPIs)***
• Dual checkpoint blockade – CheckMate 901	• Atezolizumab • Pembrolizumab	• Pembrolizumab (category 1)* • Atezolizumab • Avelumab • Durvalumab • Nivolumab
	Phase 1b data but NOT approved	***FGFR inhibitor***
	Immunotherapy + ADC combinations	• Erdafitinib (*FGFR2/3* alterations)
	• Enfortumab vedotin + pembrolizumab	***ADC***
		• Enfortumab vedotin (after prior tx with a PD-1/PD-L1 inhibitor and platinum-based chemo)
		Switch maintenance
		• Chemotherapy → checkpoint blockade as switch maintenance

ADC = antibody-drug conjugate; CPI = immune checkpoint inhibitor; tx = treatment.

*NCCN. *Bladder Cancer*. V5.2020 (www.nccn.org/professionals/physician_gls/PDF/bladder.pdf). Accessed 1/27/2021.

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Managing irAEs in Bladder Cancer

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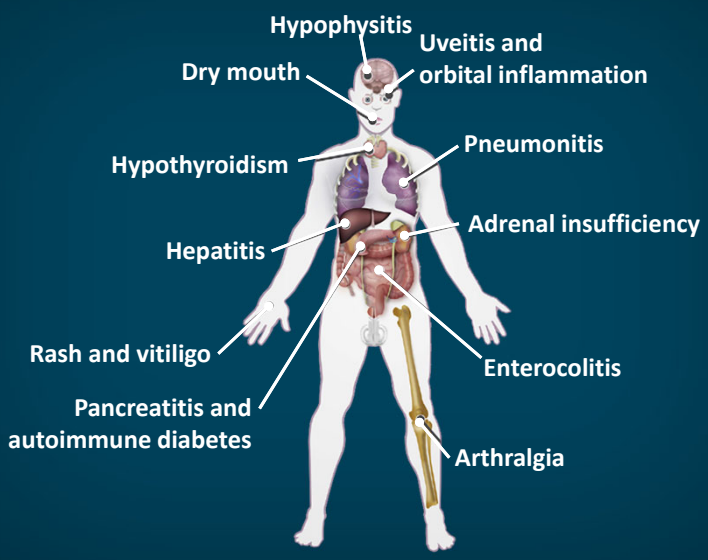
irAEs: Clinical Spectrum



irAE = immune-related adverse event.

Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

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Management of irAEs
Based on CTCAE Severity Grade

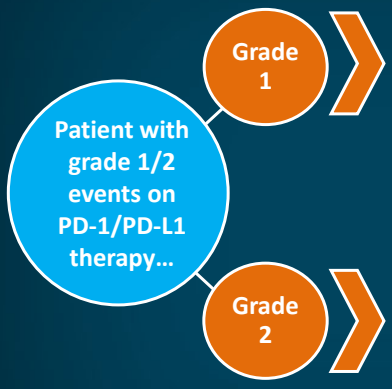
Severity CTCAE Grade	Patient Care Setting	Steroids	Other Immunosuppressive Drugs	Immunotherapy and Subsequent Approach
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Not recommended up front Topical steroids or systemic steroids oral 0.5–1 mg/kg/d for persistent grade 2	Not recommended	Suspend* temporarily
3	Hospitalization	Systemic steroids oral or IV 1–2 mg/kg/d for ≥3 d then taper over 4–6 weeks	Consider for patients with lack of improvement after 2–3 d of steroid course Organ specialist advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization; consider ICU	Systemic steroids IV methylprednisolone 1–2 mg/kg/d and switch to oral prednisone for ≥3 d with taper over 4–6 weeks	Consider for patients with lack of improvement after 2–3 d of steroid course Organ specialist advised	Discontinue permanently

***Outside of skin or endocrine disorders, where immunotherapy can be maintained.**
CTCAE = Common Terminology Criteria for Adverse Events; ICU = intensive care unit.

Michot JM, et al. *Eur J Cancer*. 2016;54:139-148. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768.

45

Managing Grade 1/2 irAEs



- Continue immunotherapy (or consider temporary delay)
- Symptomatic therapy

- Withhold immunotherapy
- Corticosteroids if symptoms do not resolve in 1 wk (prednisone 0.5 to 1 mg/kg/d or equivalent)
- Taper corticosteroids over ≥1 mo to reduce recurrence
- Redose if toxicity resolves to grade ≤1

Postow MA. *Am Soc Clin Oncol Educ Book*. 2015:76-83. Postow MA, et al (www.uptodate.com/contents/toxicities-associated-with-checkpoint-inhibitor-immunotherapy. Weber JS, et al. *J Clin Oncol*. 2015;33:2092-2099. Brahmer J, et al. *J Clin Oncol*. 2018;36:1714-1768.

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Managing Grade 3 irAEs

Patient with grade 3/4 events on PD-1/PD-L1 therapy…

- Discontinue immunotherapy; hospitalization, multidisciplinary evaluation indicated
- High-dose corticosteroids (prednisone 1 to 2 mg/kg/d or equivalent)
- Taper high-dose corticosteroids over ≥1 mo until toxicity resolves to grade ≤1 (prednisone 1 to 2 mg/kg/d or equivalent)

- **If no improvement or progression, consider additional immunosuppressant treatment, eg, anti-TNF therapy, infliximab, vedolizumab, or mycophenolate**
- **If >4 wk of corticosteroids or other immunosuppressants needed, administer antimicrobial/antifungal prophylaxis to prevent opportunistic infections**
- **ASCO recommendations on managing irAEs published (February 2018)**

Postow MA. *Am Soc Clin Oncol Educ Book*. 2015:76-83. Postow MA, et al (www.uptodate.com/contents/toxicities-associated-with-checkpoint-inhibitor-immunotherapy. Brahmer J, et al. *J Clin Oncol*. 2018;36:1714-1768.

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COVID-19 and Cancer

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Managing Bladder Cancer in Era of COVID-19

Patients with bladder cancer often have other medical comorbidities that may increase risk of serious symptoms of COVID-19

- Lung disease: COPD, emphysema
- CKD
- Cardiovascular disease
- Weakened immune system from cancer treatments
- Active malignancy
- Immune checkpoint inhibitor therapy

COVID-19 = coronavirus disease 2019; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease.

CDC. Certain medical conditions and risk for severe COVID-19 (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/ people-with-medical-conditions.html). Accessed 1/27/2021. Liang W, et al. *Lancet Oncol*. 2020;21:335-337. Dai M, et al. *Cancer Discov.* 2020;10:783-791. Miyashita H, et al. *Ann Oncol*. 2020;31:1088-1089. Sullivan RJ, et al. *J Immunother Cancer*. 2020;8:e000933.

49

Clinical Impacts of COVID-19 on Cancer Patients

Patients with active or previous malignancy + COVID-19

- Analyzed EMRs of patients with cancer and COVID-19 in the Mount Sinai Health System in New York City between March 1, 2020 and April 6, 2020
- 334 patients with COVID-19 and cancer (57 breast, 56 prostate, 23 lung, 18 urothelial, 16 colon cancer)

Results

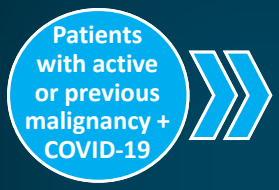
- **Patients with cancer were intubated more frequently (RR = 1.89, 95% CI, 1.37–2.61), particularly those aged 66–80 years (RR = 1.76, 95% CI, 1.15–2.70)**
- **Patients <50 years with cancer had significantly higher mortality rate (RR = 5.01, 95% CI, 1.55–16.2)**
- **Mortality rates of COVID-19 in patients with cancer were lower than in noncancer patients in age groups older than 50 years; difference was not statistically significant**

EMR = electronic medical record; RR = relative risk.

Miyashita H, et al. *Ann Oncol*. 2020;31:1088-1089.

50

Clinical Impacts of COVID-19 on Cancer Patients (continued 1)



- Analyzed EMRs of patients with cancer and COVID-19 in Montefiore Health System in New York City from March 18, 2020 to April 8, 2020
- 218 patients with COVID-19 and cancer (164 solid tumors, 54 hematologic malignancies)

Results

- **Sixty-one (28%) patients died from COVID-19 at the time of analysis**
- **Mortality was 37% among patients with hematologic malignancies**
- **Mortality was 25% among patients with solid tumors**
  - **67% pancreatic, 55% lung, 38% colorectal, 38% upper GI, 38% gynecologic malignancies, 15% genitourinary, 14% breast**

GI = gastrointestinal.

Mehta V, et al. *Cancer Discov*. 2020;10:935-941.

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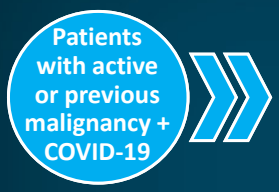
Clinical Impacts of COVID-19 on Cancer Patients (continued 2)



- Data collected between March 17 and April 16, 2020 from 928 patients from COVID-19 and Cancer Consortium (CCC19) database of patients in USA, Canada, and Spain
- Composite endpoint was combination of death, severe illness requiring admission to hospital, admission to ICU, or mechanical ventilation

Cases meeting composite endpoint

- **23% solid tumors; 35% hematological malignancies; 31% multiple cancers**
- **23% remission or no evidence of disease; 27% present, stable, or responding to treatment; 35% present, progressive disease**
- **ECOG performance status: 22% of 0 or 1; 43% of 2; 48% of 3 or 4**

Kuderer NM, et al. *Lancet*. 2020;395:1907-1918.

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Takeaway Points From Studies of Cancer and COVID-19

Increased risk of worse outcomes from COVID-19 may associated with:

- ECOG performance status of 2 or higher
- Active cancer, especially those with progressive disease
- Certain solid tumors (eg, pancreatic, lung)
- Hematologic malignancies

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COVID-19 and Immune CPIs (ICIs)

- ICIs could theoretically either mitigate or exacerbate COVID-19 severity[1]
- Augmented immune response to infection secondary to ICIs[1]
- ICIs, particularly PD-1/PD-L1 inhibitors, cause irAEs that can affect any organ, including life-threatening or fatal complications (ie, myocarditis or pneumonitis)[1–3]
- ICIs could impact the course of COVID-19[1]
  - Common pathological features included unrestrained immune and cytokine activation
- Data on effects of PD-1/PD-L1 inhibition on other viruses have been mixed[1,4–10]

Sullivan RJ, et al. *J Immunother Cancer*. 2020;8:e000933.

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Should Patients Initiate ICIs During This High-Risk Period?

- Given the lack of adverse data, ICIs should not be withheld in patients with metastatic disease without COVID-19
- Discretion may be used in other cases
  - Weigh advantages of relapse-free survival benefit against novel disadvantages
    - Risk of COVID-19 transmission between patient and infusion staff
    - Increasing use of healthcare resources

Sullivan RJ, et al. *J Immunother Cancer*. 2020;8:e000933.

55

Should ICI be Discontinued Early in Some Patients?

- Consider on a case-by-case basis, incorporating cancer-related risks and complications from COVID-19[1]
- May be strongly considered in patients with (near) complete responses[1–3]

1. Sullivan RJ, et al. *J Immunother Cancer*. 2020;8:e000933. 2. Robert C, et al. *J Clin Oncol*. 2018;36:1668-1674. 3. Ornstein MC, et al. *J Immunother Cancer*. 2019;7:127.

56

Symptoms Consistent With Either irAEs or COVID-19

COVID-19 can mimic commonly seen clinical presentations for patients with cancer

- Shortness of breath and cough (pneumonitis)
  - Radiographical appearance may be similar and include ground-glass opacities
- Elevated troponin or heart failure (myocarditis)
- Elevated liver function tests (hepatitis)
- Isolated fever
- Dry cough

Sullivan RJ, et al. *J Immunother Cancer*. 2020;8:e000933.

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Resuming ICI in Patients Recovering From COVID-19

- Hold treatment in those who are being tested for infection
- Wait 2 weeks following resolution of symptoms to (re)start treatment
- When feasible, 2 consecutive negative PCR tests before restarting therapy could also be considered in order to:
  - Avoid treating infected patients
  - Limit exposure to healthcare workers and other patients

PCR = polymerase chain reaction.

Sullivan RJ, et al. *J Immunother Cancer*. 2020;8:e000933.

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Managing Bladder Cancer in COVID-19 Era

- Factors to consider
  - Screen asymptomatic individuals before cancer treatments
  - Increase surveillance and testing for COVID-19
  - Evaluate schedule and frequency of infusion visits (ie, nivolumab Q4W vs pembrolizumab Q6W)
  - Minimize "points of contact" with healthcare system
  - Monitor and address toxicity/side effects closely (ie, avoid unnecessary ED visits)
- COVID-19 vaccination
  - Patients with cancer were excluded from trials
  - Consensus in medical community is that benefits of vaccination outweigh risks

Q4W = every 4 weeks; Q6W = every 6 weeks; ED = emergency department.

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Case Study

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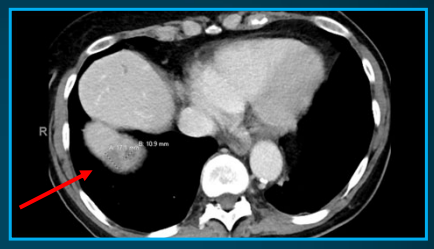
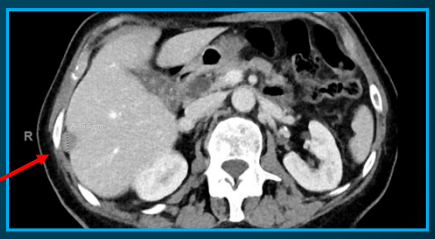
76-Year-Old Female…

- Past medical history of hypertension and PAD
- 8/2020: MRV pelvis
  - Incidental 1.3 cm right bladder wall mass, lost to follow-up
- 12/2020: hematuria
- 12/18/2020: CTAP
  - 2.2 cm right bladder mass and new liver metastases
- TURBT: High-grade MIBC
- IR biopsy liver:
  - Poorly differentiated carcinoma c/w urothelial origin





PAD = peripheral artery disease; MRV = magnetic resonance venography; CTAP = computed tomographic arterial portography; TURBT = transurethral resection of bladder tumor; MIBC = muscle-invasive bladder cancer; IR = interventional radiology; c/w = consistent with.

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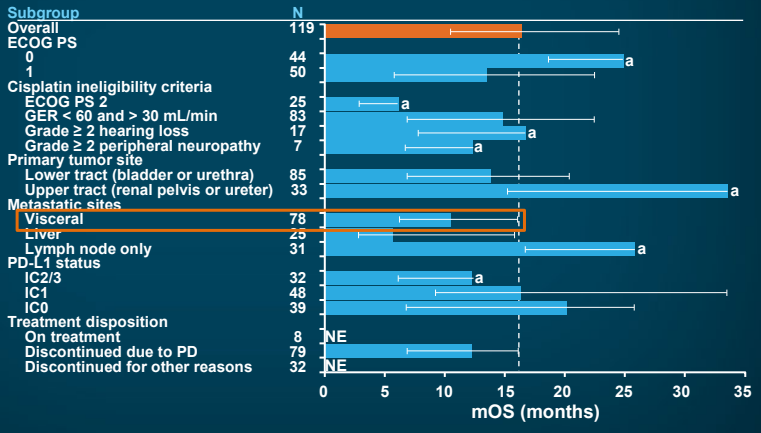
KEYNOTE-052: Long-Term Follow-Up for First-line Pembrolizumab:

Metastases	n/N	ORR	95% CI
Lymph node only	25/51	49.0	(34.8–63.4)
Visceral disease	79/315	25.1	(20.4–30.2)

IMvigor210: Subgroup Analysis for First-line Atezolizumab

1L cisplatin-ineligible patients with previously untreated mUC: cohort 1



Vuky J, et al. *J Clin Oncol*. 2020;38:2658-2666. O'Donnell PH, et al. *J Clin Oncol*. 2019;37(suppl 15): abstract 4546. Balar AV, et al. *Lancet*. 2017;389(10064):67-76.

62

76-Year-Old Female… (continued)

- ECOG PS = grade 1
- eGFR = 56 mL/min
- Tumor PD-L1 score
  - CPS 11
- Treatment options
  - Gemcitabine/carboplatin
  - Pembrolizumab or atezolizumab

eGFR = estimated GFR.

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Factors to Consider in First-Line Treatment in mUC

- Patient performance status, comorbidities
  - Tolerance of platinum-based chemotherapy
- Patient preference
  - Toxicity concerns, perceptions about chemotherapy
- PD-L1 status
- Other clinical biomarkers
  - Visceral metastatic disease
  - Patients with liver metastases do poorly with single-agent immunotherapy
- Platinum-based chemotherapy as first-line
  - Maintenance immunotherapy if stable disease or better

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Conclusions

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Summary of Available Data in Bladder Cancer

- Platinum-based chemotherapy and anti-PD1/L1 checkpoint blockade are firmly established as standards of care in advanced bladder cancer
- Completed and ongoing trials are refining role for anti-PD-1 vs platinum-based chemotherapy in first-line setting
  - Combination with platinum-based chemotherapy improves PFS but not yet OS in IMVigor130; KEYNOTE-361 was negative, but data are not yet presented
  - Monotherapy in PD-L1+ or platinum-ineligible (carboplatin or cisplatin) patients
  - Maintenance therapy with anti-PD1/L1 ICIs following disease control with platinum-based chemotherapy improves survival (Javelin 100)

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Key Take-Aways

- Immunotherapies can produce durable responses in patients with bladder cancer
- Antitumor immune responses can be unconventional and may be delayed
- Adverse events are often highly manageable, especially if reported and addressed at their onset
- Grading symptoms → guided management

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IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

Immunotherapy Collaborative of Oncology Networked Communities (IC-ONC)-
Optimizing the Sequencing of Immune Checkpoint Inhibitors in Locally Advanced or Metastatic Urothelial Carcinoma

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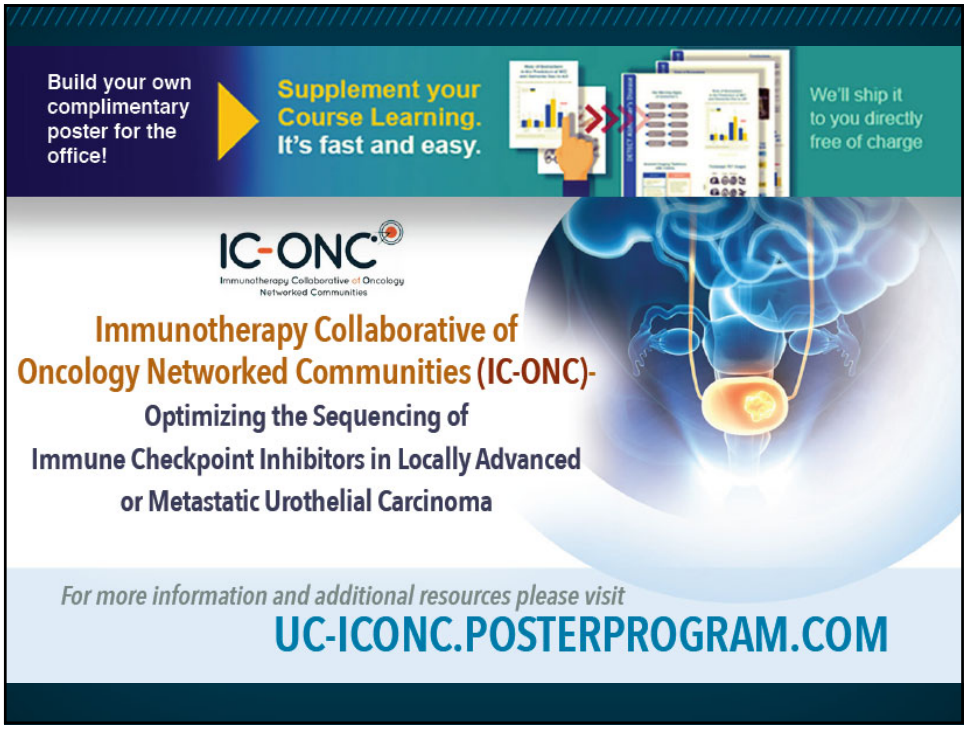

69

Thank You!

70

Locally Advanced or Metastatic Urothelial Carcinoma: An Overview

Resource	Address
American Cancer Society (ACS). Key Statistics for Bladder Cancer. Last reviewed January 12, 2021. Accessed January 27, 2021.	Key Statistics for Bladder Cancer
American Cancer Society (ACS). Cancer Facts & Figures 2021. Accessed January 27, 2021.	https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf
Bellmut J, Powles T, Vogelzang NJ. A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: The future is now. *Cancer Treat Rev*. 2017;54:58-67.	https://pubmed.ncbi.nlm.nih.gov/28214651/
Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. *J Exp Med*. 1995;182:459-465.	https://pubmed.ncbi.nlm.nih.gov/7543139/
Krummel MF, Sullivan TJ, Allison JP. Superantigen responses and co-stimulation: CD28 and CTLA-4 have opposing effects on T cell expansion in vitro and in vivo. *Int Immunol*. 1996;8:519-523.	https://pubmed.ncbi.nlm.nih.gov/8671638
Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature*. 2013;499:214-218.	https://pubmed.ncbi.nlm.nih.gov/23770567/
Melero I, Hervas-Stubbs S, Glennie M, Pardoll DM, Chen L. Immunostimulatory monoclonal antibodies for cancer therapy. *Nat Rev Cancer*. 2007;7:95-106.	https://pubmed.ncbi.nlm.nih.gov/17251916/
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Yagoda A. Chemotherapy of urothelial tract tumors. *Cancer*. 1987;60(3 suppl):574-585.	https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.1002/1097-0142%2819870801%2960%3A3%2B%3C574%3A%3AAID-CNCR2820601524%3E3.0.CO%3B2-C

Sequencing Strategies for Locally Advanced and Metastatic UC

Resource	Address
Alva A, Csőszi T, Ozguroglu M, et al. LBA23 - Pembrolizumab (P) combined with chemotherapy (C) vs C alone as first-line therapy for advanced urothelial carcinoma: KEYNOTE-361. *Ann Oncol*. 2020;31(suppl 4):S1142-S1215.	https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/pembrolizumab-p-combined-with-chemotherapy-c-vs-c-alone-as-first-line-1l-therapy-for-advanced-urothelial-carcinoma-uc-keynote-361
Aly A, Johnson C, Yang S, et al. Overall survival, costs, and healthcare resource use by line of therapy in Medicare patients with newly diagnosed metastatic urothelial carcinoma. *J Med Econ*. 2019;22(7):662-670.	https://pubmed.ncbi.nlm.nih.gov/30836812/
Apolo A, Infante JR, Hamid O, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with metastatic urothelial carcinoma from the JAVELIN solid tumor phase 1b trial: Analysis of safety, clinical activity, and PD-L1 expression. *J Clin Oncol*. 2016;34(15 suppl):4514.	https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.4514
Bajorin DF, de Wit R, Vaughn DJ, et al. Planned survival analysis from KEYNOTE-045: Phase 3, open-label study of pembrolizumab (pembro) versus paclitaxel, docetaxel, or vinflunine in recurrent, advanced urothelial cancer (UC). *J Clin Oncol*. 2017;35(15 suppl):4501.	https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.4501
Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2017;18:1483-1492.	https://pubmed.ncbi.nlm.nih.gov/28967485/
Balar AV, Dreicer R, Loriot Y, et al. Atezolizumab (atezo) in first-line cisplatin-ineligible or platinum-treated locally advanced or metastatic urothelial cancer (mUC): Long-term efficacy from phase 2 study IMvigor210. *J Clin Oncol*. 2018;36(15 suppl):4523.	https://ascopubs.org/doi/10.1200/JCO.2018.36.15_suppl.4523

Balar AV, Galsky MD, Loriot Y, et al. Atezolizumab (atezo) as first-line (1L) therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (mUC): Primary analysis of IMvigor210 cohort 1. *J Clin Oncol*. 2016;34:(18 suppl):LBA4500.	https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.18_suppl.LBA4500
Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. 2017;389:67-76.	https://pubmed.ncbi.nlm.nih.gov/27939400/
Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376:1015-1026.	https://pubmed.ncbi.nlm.nih.gov/28212060/
Cheeseman S, Thompson M, Sopwith W, et al. Current treatment and outcomes benchmark for locally advanced or metastatic urothelial cancer from a large UK-based single centre. *Front Oncol*. 2020;10:167.	https://pubmed.ncbi.nlm.nih.gov/32154169/
CheckMate901. Study of Nivolumab in Combination With Ipilimumab or Standard of Care Chemotherapy Compared to the Standard of Care Chemotherapy Alone in Treatment of Participants With Untreated Inoperable or Metastatic Urothelial Cancer. NCT03036098. Updated January 20, 2021. Accessed February 9, 2021.	https://clinicaltrials.gov/ct2/show/NCT03036098
De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol*. 2012;30:191-199.	https://pubmed.ncbi.nlm.nih.gov/22162575/
Dogliotti L, Cartenì G, Siena S, et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the	https://pubmed.ncbi.nlm.nih.gov/17207911/

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Fisher MD, Shenolikar R, Miller PJ, Fenton M, Walker MS. Treatment patterns and outcomes in stage IV bladder cancer in a community oncology setting: 2008-2015. *Clin Genitourin Cancer*. 2018;16:e1171-e1179.	https://pubmed.ncbi.nlm.nih.gov/30206026/
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Galsky MD, Arija JAA, 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://pubmed.ncbi.nlm.nih.gov/32416780/
Galsky MD, Pal SK, Lin SW, et al. Real-world effectiveness of chemotherapy in elderly patients with metastatic bladder cancer in the United States. *Bladder Cancer*. 2018;4:227-238.	https://pubmed.ncbi.nlm.nih.gov/29732393/
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