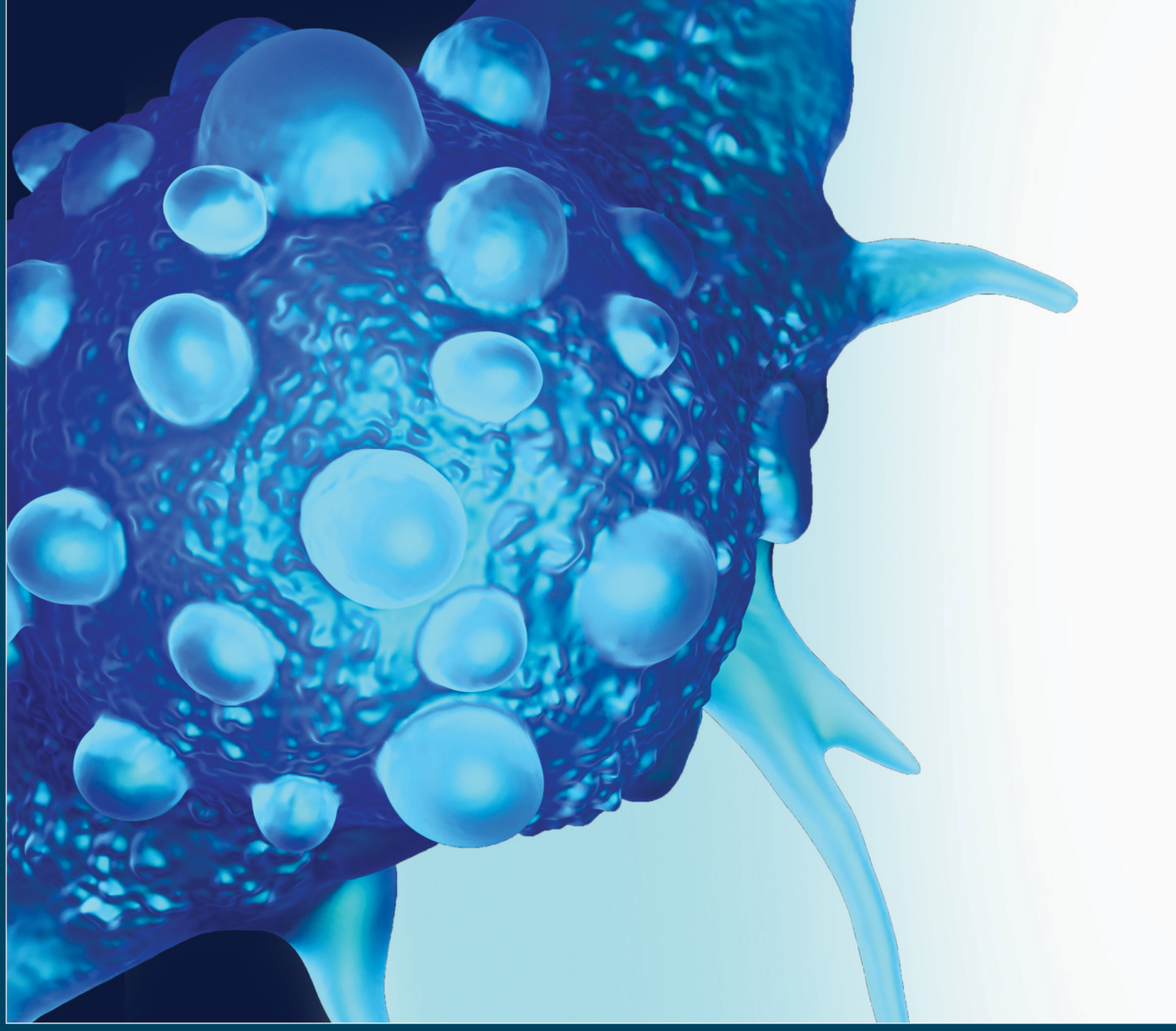

IMMUNOTHERAPY *of* BLADDER CANCER:

Integrating New Biomarkers and Treatment Guidelines into Clinical Practice

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 an educational grant from Bristol Myers Squibb.

Immunotherapy of Bladder Cancer: Integrating New Biomarkers and Treatment Guidelines into Clinical Practice

PROGRAM CHAIR
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SPEAKER FACULTY

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Assistant Professor of Medicine Director, Genitourinary Medical Oncology Program Laura and Isaac Perlmutter Cancer Center NYU Langone Health New York, NY	Staff, Hematology and Oncology Leader, Bladder Cancer Program Taussig Cancer Institute Cleveland Clinic Foundation Cleveland, OH	Associate Professor of Medicine The University of Chicago Medicine Chicago, IL

PROGRAM OVERVIEW
This activity will cover the treatment and management of patients with bladder cancer.

TARGET AUDIENCE
This activity is designed to meet the educational needs primarily of urologists and other clinicians involved in the treatment of patients with bladder cancer.

LEARNING OBJECTIVES
On completing the program, attendees should be able to:

- Critically evaluate the advantages and drawbacks of various CPGs for treating bladder cancer (BC), and apply the most useful and practical recommendations in clinical practice
- Understand the molecular pathways involved in the development and progression of MIBC and NMIBC, and adopt diagnostic, predictive, and prognostic biomarkers into clinical practice, as they are perfected and become widely available for clinical use
- Implement tactics for the successful management of irAEs experienced by BC patients treated with ICIs and other immunotherapies, allowing uninterrupted courses of treatment and minimizing diminishment of patients' QOL

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NURSING CREDIT INFORMATION

Purpose:

This program would be beneficial for nurses involved and/or interested in the therapeutic management of patients with bladder cancer.

CNE Credits: 1.0 ANCC Contact Hour

CNE Accreditation Statement:

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Faculty Member	Disclosure
Daniel P. Petrylak, MD	**Dr. Petrylak** reports that he serves as a consultant for Ada Cap (Advanced Accelerator Applications) Amgen, Astellas, AstraZeneca, Bayer, Bicycle Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis Oncology, Eli Lilly, Exelixis, Incyte, Janssen, Mirati, Monopteros, Pfizer, Pharmacyclics, Roche, Seattle Genetics, and Urogen. He has also received grant support from Ada Cap (Advanced Accelerator Applications), Agensys Inc, *Astellas, AstraZeneca, *Bayer, BioXcel Therapeutics, Bristol-Myers Squibb, Clovis Oncology, Eisai, *Eli Lilly,*Endocyte, Genentech, *Innocrin, MedImmune, Medivation, Merck, Mirati,*Novartis, Pfizer, *Progenics, Replimune, Roche, *Sanofi Aventis, and Seattle Genetics. Dr. Petrylak also had ownership interest/investment in Bellicum (sold 7/2020), Tyme (sold 10/2019).
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.
Shilpa Gupta, MD	**Dr. Gupta** reports that she is on the speakers bureau for Seattle Genetics and BMS. She also serves as a consultant for AstraZeneca, BMS and Merck.
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.

CME Content Review

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The reviewer of this activity has nothing to disclose.

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Provided by Med Learning Group

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Agenda

I. **Overview of Bladder Cancer**
   a. Epidemiology/prevalence/incidence
   b. Susceptible populations/risk factors
   c. Anatomy/histology
   d. Outcomes NMIBC/MIBC
   e. Current treatment options
      i. Trans urethral resection of bladder tumor (TURBT)
      ii. Cystectomy
      iii. Bacillus Calmette-Guerin (BCG)
      iv. Radiotherapy
      v. Immunotherapy
   f. Mechanism of immune checkpoint inhibitors
   g. Checkpoint inhibitors approved for bladder cancer

II. **Treatment Recommendations for Non-muscle Invasive Bladder Cancer**
   a. Guideline recommendations
   b. Clinical data supporting recommendations on immunotherapy
      i. BCG-unresponsive, high-risk NMIBC
      ii. Novel intravesical immunotherapies

III. **Treatment Recommendations Muscle Invasive Bladder Cancer**
   a. Guideline recommendations
      i. Nonmetastatic disease
      ii. Metastatic/advanced disease
   b. Clinical data supporting recommendations on immunotherapy
      i. First-line in cisplatin ineligible disease
      ii. Second-line therapy
      iii. Maintenance therapy
      iv. Adjuvant therapy

IV. **Advances in Urinary Biomarker Discovery**
   a. FDA-approved assays
   b. Commercially available but not FDA-approved
   c. Urinary biomarkers under investigation
   d. Emerging biomarkers

V. **Managing Immune Related Adverse Events in Bladder Cancer**
   a. Clinical spectrum of irAEs
   b. irAEs of PD-1/L-1 inhibitors
   c. Management of irAEs
      i. Grade 1/2
      ii. Grade 3

VI. **Conclusions**

VII. **Questions and Answers**

Immunotherapy of Bladder Cancer: Integrating New Biomarkers and Treatment Guidelines into Clinical Practice

PROGRAM CHAIR:

Daniel P. Petrylak, MD

Professor of Medicine (Medical Oncology) and of Urology

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1

Disclosures

- Please see Program Overview for specific speaker disclosure information
- During the course of this lecture, the presenter will discuss the use of medications for both FDA-approved and non-approved indications.

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3

Learning Objectives

- Critically evaluate the advantages and drawbacks of various clinical practice guidelines for treating bladder cancer, and apply the most useful and practical recommendations in clinical practice
- Explain the molecular pathways involved in the development and progression of muscle-invasive bladder cancer (MIBC) and non-muscle-invasive bladder cancer (NMIBC), and adopt diagnostic, predictive, and prognostic biomarkers into clinical practice, as they are perfected and become widely available for clinical use
- Implement tactics for the successful management of immune-related adverse events (irAEs) experience by bladder cancer patients treated with immune checkpoint inhibitors and other immunotherapies, allowing uninterrupted courses of treatment and minimizing diminishment of patients' quality of life

4

Overview of Bladder Cancer

5

Urothelial Bladder Cancer: Epidemiology

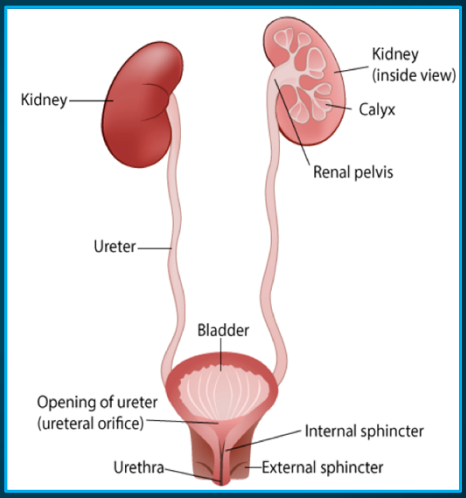
- United States will have an estimated 83,730 new cases and 17,200 deaths in 20211
- Average age at diagnosis is 73 years2
- 3:1 → male:female ratio
- Risk factors
  - Smoking is the strongest risk factor
  - Chemical industry (aromatic amines, aniline dyes)
- Panurothelial disease, ie, concern for synchronous or metachronous disease
  - Field cancerization vs monoclonality
- 75–80% superficial, 25% muscle invasive, and 5% metastatic

1. 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/). Accessed 2/23/2021.

6

Anatomy and Histology of Urothelial Carcinoma

Urothelial/Transitional cell) carcinoma (UC/TC)*	90%
Non-muscle invasive bladder cancer (NMIBC)	~70%
Muscle-invasive bladder cancer (MIBC)	30%
Squamous cell carcinoma	5%
Adenocarcinoma	0.5–2%
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.

ACS. Bladder cancer (www.cancer.org/cancer/bladder-cancer/). Accessed 2/23/2021. Kirkali Z, et al. Urology. 2005;66(6 Suppl 1):4. Burger M, et al. Eur Urol. 2013;63:234-241.

7

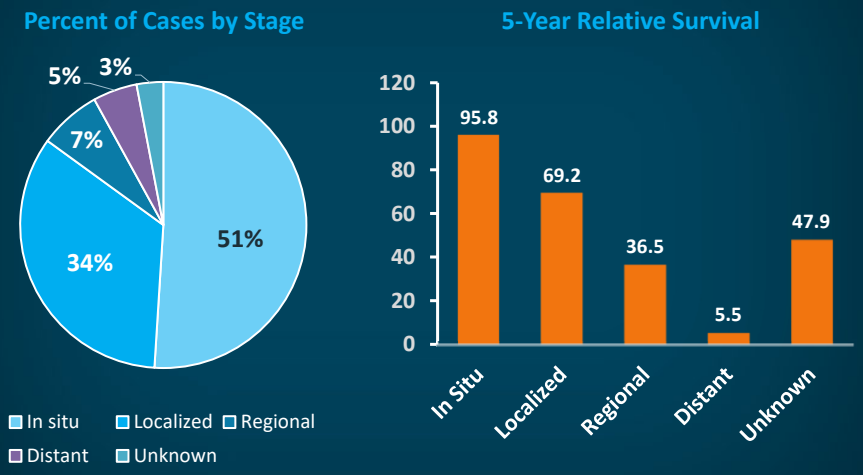
Anatomy and Histology of Urothelial Carcinoma

Classification	Tumor Stage	Depth of Invasion
Non-muscle-invasive bladder cancer	Ta	Noninvasive papillary carcinoma
	T1	Invades lamina propria
Muscle-invasive bladder cancer	T2	Invades muscularis propria
	T3	Invades perivesical tissue
	T4	Extravesical extension into adjacent organs

National Comprehensive Cancer Network (NCCN). Bladder cancer, version 6.2020 (www.nccn.org/professionals/physician_gls/pdf/bladder.pdf). Accessed 2/23/2021.

8

5-Year Relative Survival by Stage at Diagnosis



National Cancer Institute (NCI). Surveillance, Epidemiology, and End Results Program (https://seer.cancer.gov/statfacts/html/urinb.html). Accessed 3/1/2021.

9

Current Treatment Options for Bladder Cancer

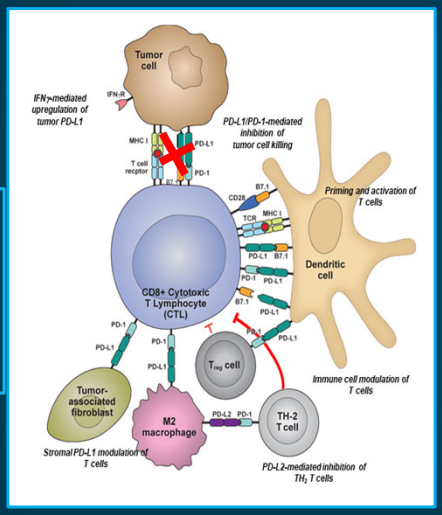
- Transurethral resection of the bladder (TURBT) for early-stage disease
- Intravesical immunotherapy/chemotherapy directly to bladder after surgery for NMIBC
- Bacillus Calmette-Guérin (BCG) therapy for high-risk disease after surgery
- Cystectomy ± neoadjuvant chemotherapy for muscle-invasive disease
- Chemoradiation therapy for muscle-invasive disease
- Systemic chemotherapy for metastatic disease
- Immunotherapy as initial treatment, maintenance, or salvage for metastatic disease
- Immunotherapy as salvage after progression on chemotherapy

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).

10

Mechanism of Immune Checkpoint Inhibitors

Key attributes of the immune system
- Specificity
- Memory
- Adaptive



- Cancer cells develop many mutations that can make them appear foreign to immune system
- T cells can recognize, attack, and kill these "foreign" cancer cells
- Cancer cells can evade immune attack by expressing PD-L1
- Adaptive tumor expression of PD-L1 turns the immune system OFF
- Clinically, we want to block PD-1 or PD-L1 to **reactivate** immune system
- PD-L1 plays an important role in dampening anti-tumor immune response

PD-1 = programmed (cell) death 1; PD-L1 = PD-1 ligand; IFN = interferon; CD = cluster of differentiation; MHC = major histocompatibility complex; TCR = T-cell receptor; Treg = regulatory T cell.

Herbst RS et al. *J Clin Oncol*. 2013;31(suppl 15): abstract 3000. Adapted from Chen DS, et al. *Clin Cancer Res*. 2012;18:6580-6587.

11

Checkpoint Inhibitors Approved for Bladder Cancer

Drug	Trial	ORR, % (95% CI)	Median PFS (95% CI)	Median OS (95% CI)	Indication*
Atezolizumab[1]	IMvigor210	23 (16–31)	2.7 mos (2.1–4.2)	15.9 mos (10.4–NE)	1st-line, cisplatin-ineligible, ± PD-1/PD-L1 status
Nivolumab[2]	CheckMate 275	**19.6 (15.0–24.9)**	2.0 mos (1.87–2.63)	**8.74 mos (6.05–NR)**	2nd-line, disease progression after platinum-based chemotherapy
Pembrolizumab[3]	KEYNOTE-045	**21.1 (16.4–26.5)**	2.1 mos (2.0–2.2)	**10.3 mos (8.0–11.8)**	First-line for cisplatin-ineligible, ± PD-1/PD-L1 status
Avelumab[4]	JAVELIN Bladder 100	9.7 (6.8–13.3)	**3.7 mos (3.5–5.5)**	**21.4 mos (18.9–26.1)**	Maintenance therapy for stable disease or progression after platinum-based chemotherapy
Durvalumab[5]	S				m-based chemotherapy

Indication withdrawn as of February 2021

ORR = overall/objective response rate; CI = confidence interval; PFS = progression-free survival; mo(s) = month(s); OS = overall survival; NR = not reached; NE = not estimable.

***Prescribing information (PI) for each agent. 1. Balar AV, et al. *Lancet*. 2017;389:67-76. 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. *J N Engl J Med*. 2020;383:1218-1230. 5. Powles T, et al. *JAMA Oncol*. 2017;3:e172411.**

12

Treatment Recommendations for Non-Muscle-Invasive Bladder Cancer

13

Standard of Care for NMIBC

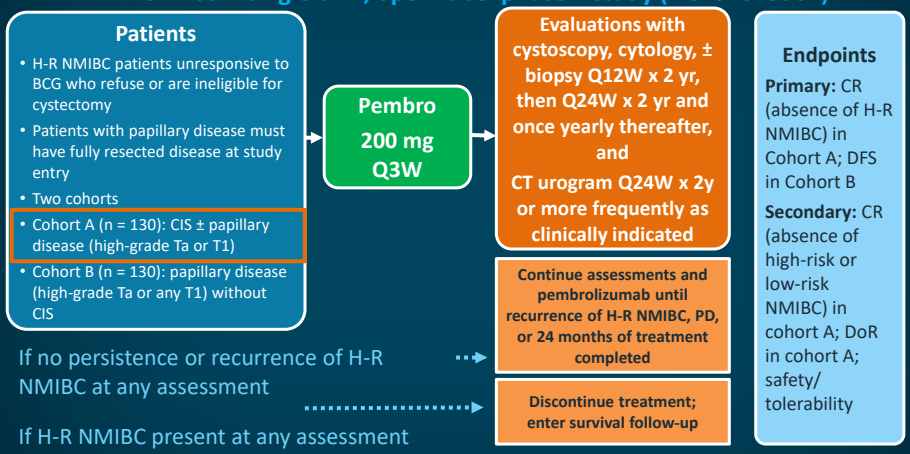
Disease	Recommendation
Low-risk[1]	TURBT + cytoscopic surveillance
High-grade, stage Ta[1] **or T1**[1,2]	Repeat resection because of risk of understaged or persistent disease
Intermediate-risk[1,2]	TURBT + intravesical therapy (chemotherapy or BCG)
High-risk[1–3]	• Intravesical therapy (chemotherapy or BCG) • **Pembrolizumab for BCG-unresponsive disease**

1. Chang SS, et al. *J Urol*. 2016;196:1021-1029. 2. Babjuk M, et al. *Eur Urol*. 2019;76:639-657. 3. Pembrolizumab (Keytruda) PI, 2020 (www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf). Accessed 2/23/2021.

14

Pembrolizumab for BCG-Unresponsive, High-Risk NMIBC

KEYNOTE-057: single-arm, open-label phase 2 study (NCT02625961)



H-R = high risk; CIS = carcinoma in situ; Q12W = every 12 weeks; yr = year(s); Q24W = every 24 weeks; CT = computed tomography; PD = progressive disease; CR = complete response; DFS = disease-free survival ; DoR = duration of response.

Balar AV, et al. *J Clin Oncol*. 2019;37(suppl 7): abstract 350. NCT02625961 (https://clinicaltrials.gov/ct2/show/NCT02625961?term=NCT02625961&draw=2&rank=1). Accessed 2/24/2021.

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Keynote-057: Baseline Characteristics

Characteristic	N = 102	Characteristic	N = 102
Age, median (range), years	73 (44–92)	Number of prior BCG instillations, median (range)	12.0 (6.0–45.0)
≥65, n (%)	72 (70.6)		
<65, n (%)	30 (29.4)		
Gender, n (%)	85 (83.3)	Tumor histology: urothelial (transitional cell) carcinoma	103 (100.0)
Male	17 (16.7)	Tumor pattern at study entry (pretreatment BC stage)	
Female		CIS with T1	12 (11.8)
		CIS (TIS) with high-grade Ta	25 (24.5)
		CIS (TIS) alone	65 (63.7)
Race, n (%)		PD-L1 status	
White	69 (67.6)	CPS ≥10	39 (38.2)
Asian	27 (26.5)	CPS <10	58 (56.9)
Missing	6 (5.9)	Not evaluable	5 (4.9)
ECOG PS, n (%)			
0 (normal activity)	75 (73.5)		
1 (symptomatic but ambulatory)	27 (26.5)		

ECOG = Eastern Cooperative Oncology Group; PS = performance status; BC = bladder cancer; Tis = cancer in situ (same as CIS); CPS = combined positive score

Combined FDA and Applicant ODAC Briefing Document. High-risk Non-muscle Invasive Bladder Cancer (https://www.fda.gov/media/133542/download). Accessed 3/1/2021.

16

Keynote-057: Over Two Years Follow-up

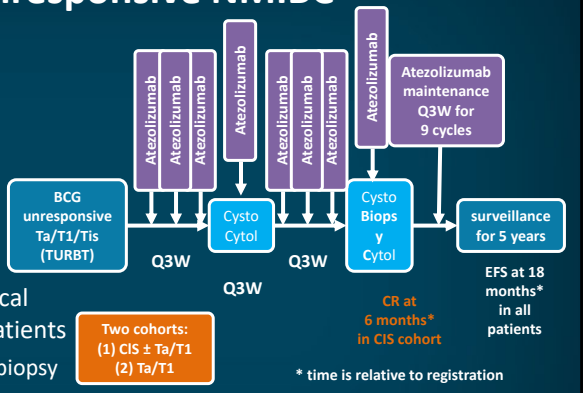
CRR at 3 months, N = 102[1]	**38.8%**	
Efficacy population, n = 96[2]		
CRR, n=39	40.6%	95% CI
Median duration of response	16.2 months	30.7-51.1
CRR > 12 months	18 (46.2%)	0 to >30.4
Median PFS and OS not reached	NA	months
PFS at 12 months	82.7%	
OS at 12 months	97.9%	

1. Balar AV, et al. *J Clin Oncol*. 2019;37(suppl 7):350. 2. Balar AV, et al. *J Clin Oncol*. 2020;38(suppl 15):5041.

17

SWOG S1605: Phase 2 Trial of Atezolizumab in BCG-Unresponsive NMIBC

- Single-arm phase 2
- BCG-unresponsive high-risk NMIBC:
  - CIS ± Ta/T1
  - Ta/T1
- 1-year atezolizumab
  - 1200 mg Q3W x 17 cycles
- Primary endpoint: pathological CR rate at 6 months in CIS patients
  - Determined by mandatory biopsy
  - Null hypothesis of 30% and alternative of 50% with 1-sided alpha = 0.05 and 96% power



SWOG = Southwest Oncology Group; Q3W = every 3 weeks; Cysto = cystoscopy; Cytol = cytology; EFS = event-free survival.

Black PC, et al. *J Clin Oncol*. 2020;38(suppl 15): abstract 5022. NCT02844816 (https://clinicaltrials.gov/ct2/show/NCT02844816?term=SWOG+S1605&draw=2&rank=1). Accessed 2/24/2021.

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SWOG S1605

- Trial launch in Feb 2017
- FDA-mandated futility analysis after 25 eligible CIS patients reached 6-month endpoint
- Needed 7 CR to continue trial, but observed only 5
- Early accrual closure: July 2019
- Total enrollment: 172 patients at 68 centers
- Total eligible: 128
  - 74 CIS (planned ≥70)
  - 54 Ta/T1 (planned 65)

Baseline Characteristics for Eligible/Evaluable Patients with CIS Component at Study Entry (n = 73)	
Sex, %: Male	85%
Age, median years	73.4
Race, %: White Other/unknown	95% 5%
Performance status, %: 0 1	77% 23%
Median number of prior BCG doses	12
Days since last dose BCG, median no. (range)	154 (5–346)
Histology: TIS only TIS/Ta TIS/T1 TIS/Ta/T1	 58% 19% 18% 5%

FDA = US Food and Drug Administration.

Black PC, et al. *J Clin Oncol*. 2020;38(suppl 15): abstract 5022.

19

S1605: Results for CIS Cohort

- Primary endpoint (mandatory biopsy)
  - CR in CIS patients at 6 months: 19/74 = **26%**; 95% CI, 16.5–37.6%
- Unplanned secondary endpoint
  - CR in CIS patients at 3 months: 30/74 = **41.1%**; 95% CI, 29.7–53.2%

Reasons Patients Went Off Protocol Treatment (subset of eligible/evaluable patients with CIS component at study entry) n = 74	
Completed therapy	6
Recurred	48
Patient refusal	5
Toxicity	6
Other (new brain tumor)	1
Currently under review	2

6 patients were still on protocol treatment as of 4/29/2020

Black PC, et al. *J Clin Oncol*. 2020;38(suppl 15): abstract 5022.

20

Novel Intravesical Immunotherapies for BCG-Unresponsive NMIBC

- Nadofaragene firadenovec[1,2]
  - Nonreplicating recombinant adenovirus carrying the IFNa2b gene
- Vicinium (VB4-845)[3]
  - Anti-EpCAM antibody fused with pseudomonas cytotoxin
- ALT-803[4]
  - IL-15 superagonist

IL = interleukin.

1. *URO Today,* 2020 (www.urotoday.com/conference-highlights/eau-2020/bladder-cancer/123164-eau-2020-results-from-the-phase-iii-study-of-nadofaregene-firadenovec-safety-and-efficacy-in-patients-with-high-grade-bcg-unresponsive-non-muscle-invasive-bladder-cancer.html). 2. Mayo Clinic, 2021 (www.mayoclinic.org/medical-professionals/urology/news/high-risk-nonmuscle-invasive-bladder-cancer/mac-20507327). 3. *URO Today,* 2020 (www.urotoday.com/conference-highlights/aua-2020/aua-2020-bladder-cancer/122653-aua-2020-phase-3-results-of-vicinium-in-bcg-unresponsive-non-muscle-invasive-bladder-cancer.html). 4. *Immuno-Oncology News*, 2019 (immuno-oncologynews.com/2019/12/09/fda-grants-breakthrough-therapy-status-n-803-combo-non-muscle-invasivebladder-cancer-nmibc/). URLs accessed 2/24/2021.

21

Treatment Recommendations for Muscle-Invasive Bladder Cancer

22

Nonmetastatic MIBC: Treatment Options

Treatment Options for Nonmetastatic MIBC	
Cisplatin eligible	• Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy • Trimodal therapy with maximal TURBT and concurrent chemoradiation
Cisplatin ineligible	Up-front radical cystectomy
Alternatives	Partial cystectomy or maximal TURBT in select patients

Chang SS, et al. *J Urol*. 2017;198:552-559.

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Metastatic/Advanced Disease: Treatment Options

Treatment Options for Metastatic/Advanced Bladder Cancer	
Cisplatin eligible	Combination cisplatin-based chemotherapy
Cisplatin ineligible	• Atezolizumab/pembrolizumab if tumor expresses PD-L1 OR not eligible for any platin-based therapy • Combination carboplatin-based chemotherapy if negative PD-L1 • Gemcitabine ± paclitaxel • Ifosfamide, doxorubicin, gemcitabine

NCCN. Bladder cancer, version 6.2020 (www.nccn.org/professionals/physician_gls/pdf/bladder.pdf). Accessed 2/23/2021.

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Metastatic/Advanced Disease

- Most patients will have disease progression within 9 months after first-line therapy[1–5]
- Median overall survival is 14–15 months with cisplatin-based regimens[1–3]
- Median overall survival is 9–13 months with carboplatin-based regimens[4,5]
- Pembrolizumab* and atezolizumab* are first-line options for PD-L1 + platinum-ineligible patients
- Pembrolizumab*, atezolizumab*, nivolumab*, and avelumab*† are approved for second-line therapy

*See individual PIs for indications; †Approved June 2020

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. Dogliotti L, et al. *Eur Urol.* 2007;52:134-141. 4. De Santis M, et al. *J Clin Oncol.* 2012;30:191-199. 5. Bukhari N, et al. *ScientificWorldJournal.* 2018;2018:5682078.

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Long-Term Outcomes in KEYNOTE-052 First-Line Pembrolizumab in Cisplatin-Ineligible Patients with Locally Advanced or mUC

Multicenter, single-arm, phase 2 trial

Inclusion criteria
- Histologically or cytologically confirmed locally advanced/unresectable or mUC
- Had not received prior systemic chemotherapy for advanced/ unresectable (inoperable) or mUC
- Cisplatin-ineligible

→ **Pembrolizumab 200 mg IV**
Q3W for up to 24 mos
N = 370

- Primary endpoint: ORR based on RECIST v1.1
- Secondary efficacy endpoints: DoR, PFS, OS, safety, and tolerability

mUC = metastatic urothelial cancer; IV = intravenous; RECIST = Response Evaluation Criteria in Solid Tumors.

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

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KEYNOTE-052 Primary Outcome Results

ORR in all patients and in Patients with CPS ≥10 or CPS <10

Response	All Patients (N = 370)		CPS ≥10 (n = 110)		CPS <10 (n = 251)	
	Response n (%)	95% CI	Response n (%)	95% CI	Response n (%)	95% CI
Objective response (ORR)	106 (28.6)	24.1–33.5	52 (47.3)	37.7–57.0	51 (20.3)	15.5–25.8
Complete response (CR)	33 (8.9)	6.2–12.3	22 (20.0)	13.0–28.7	10 (4.0)	1.9–7.2
Partial response (PR)	73 (19.7)	15.8–24.2	30 (27.3)	19.2–36.6	41 (16.3)	12.0–21.5
Stable disease (SD)	67 (18.1)	14.3–22.4	22 (20.0)	13.0–28.7	44 (17.5)	13.0–22.8
Progressive disease (PD)	157 (42.4)	37.3–47.6	30 (27.3)	19.2–36.6	123 (49.0)	42.7–55.4
No assessment	31 (8.4)	5.8–11.7	6 (5.5)	2.0–11.5	24 (9.6)	6.2–13.9
NE	9 (2.4)	1.1–4.6	0 (0)	0.0–3.3	9 (3.6)	1.7–6.7

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

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KEYNOTE-052 Pembrolizumab Secondary Endpoints: DoR, OS, PFS

Duration of response

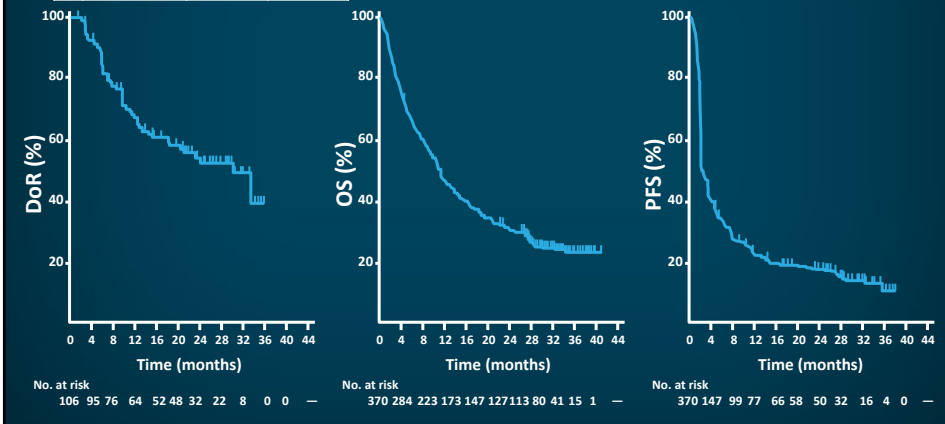
No.	Median DoR (mos) (95% CI)	Response ≥12 mos	Response ≥24 mos
106	30 (18.1–NR)	67.0%	52.0%

Overall survival

No.	Median OS (mos) (95% CI)	12-mo OS	24-mo OS
277	11.3 (9.7–13.1)	46.9 %	31.2%

Progression-free survival

No.	Median PFS (mos) (95% CI)	12-mo PFS	24-mo PFS
313	2.2 (2.1–3.4)	33.4%	22.0%



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

28

IMvigor210 Cohort 1: Accelerated FDA Approval for Patients Not Eligible for Cisplatin-containing Chemotherapy

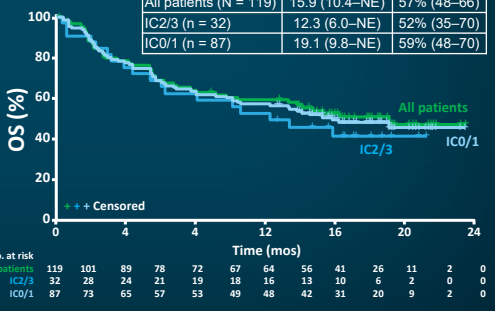
	IC2/3 (n = 32)	IC1/2/3 (n = 80)	All Patients (N = 119)	IC1 (n = 48)	IC0 (n = 39)
ORR (95% CI)	28% (14–47)	24% (15–35)	23% (16–31)	21% (10–35)	21% (9–36)
CR	13%	10%	9%	8%	8%
PR	16%	14%	14%	13%	13%

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
  - ECOG PS 2

Median DoR not reached
Median OS = 15.9 months

Overall survival	Median OS mos (95% CI)	12-mo OS, % (95% CI)
All patients (N = 119)	15.9 (10.4–NE)	57% (48–66)
IC2/3 (n = 32)	12.3 (6.0–NE)	52% (35–70)
IC0/1 (n = 87)	19.1 (9.8–NE)	59% (48–70)



No. at risk												
All patients	119	101	89	78	72	67	64	56	41	26	11	2	0
IC2/3	32	28	24	21	19	18	16	13	10	6	2	0	0
IC0/1	87	73	65	57	53	49	48	42	31	20	9	2	0

GFR = glomerular filtration rate; IC = tumor-infiltrating cell; chemo = chemotherapy.

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

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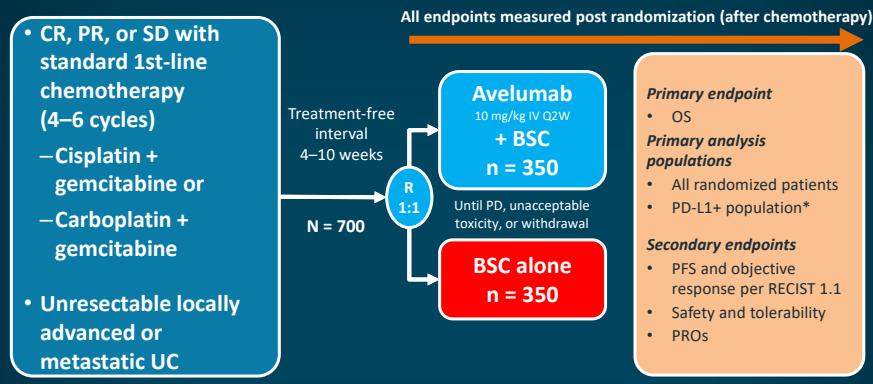
JAVELIN Bladder 100 Study Design (NCT02603432)



Stratification

- Best response to 1st-line chemo (CR or PR vs SD)
- Metastatic site (visceral vs non-visceral)

*PD-L1+ status using SP263 assay, defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if percentage of immune cells was >1% or ≤1%, respectively
BSC = best supportive care; PRO = patient-reported outcome; R = randomized; Q2W = every 2 weeks.

Powles T, et al. *N Engl J Med.* 2020;383:1218-1230. Powles T, et al. *J Clin Oncol.* 2020;38(suppl 18): abstract LBA1.

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JAVELIN Bladder 100: Select Baseline Characteristics

	Overall population (N = 700)		PD-L1+ population (n = 358)	
	Avelumab + BSC (n = 350)	BSC alone (n = 350)	Avelumab + BSC (n = 189)	BSC alone (n = 169)
Median age, years	68	69	70	70
Site of primary tumor, %				
Upper tract (renal pelvis, ureter)	30	23	23	21
Lower tract (bladder, urethra, prostate gland)	70	77	77	79
Site of baseline metastasis, %				
Visceral	55	55	47	47
Nonvisceral*	45	45	53	53
PD-L1 status, %†				
Positive	54	48	100	100
Negative	40	37	0	0
Unknown	6	14	0	0
1st-line chemotherapy regimen, %				
Gemcitabine + cisplatin	52	59	53	58
Gemcitabine + carboplatin	42	35	39	32
Gemcitabine + cisplatin/carboplatin‡	6	6	7	9
Not reported	0	1	0	1
Best response to 1st-line chemotherapy, %				
CR or PR	72	72	74	76
SD	28	28	27	24

*Nonvisceral includes patients with locally advanced disease or only nonvisceral disease, including bone metastasis; †PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively (SP263 assay); ‡Patients who switched platinum regimens while receiving 1st-line chemotherapy

Powles T, et al. *N Engl J Med.* 2020;383:1218-1230. Powles T, et al. *J Clin Oncol.* 2020;38(suppl 18): abstract LBA1.

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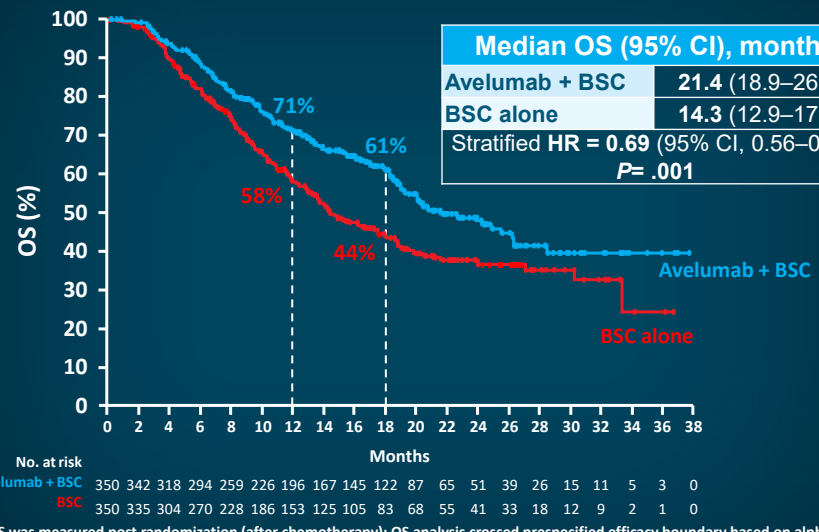
Avelumab Improves OS* in Overall Study Population



Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9–26.1)
BSC alone	**14.3** (12.9–17.9)
Stratified **HR = 0.69** (95% CI, 0.56–0.86)	
***P*= .001**	

No. at risk																			
Avelumab + BSC	350	342	318	294	259	226	196	167	145	122	87	65	51	39	26	15	11	5	3	0
BSC	350	335	304	270	228	186	153	125	105	83	68	55	41	33	18	12	9	2	1	0

*OS was measured post randomization (after chemotherapy); OS analysis crossed prespecified efficacy boundary based on alpha-spending function (*P* <.0053)

HR = hazard ratio.

Powles T, et al. *N Engl J Med.* 2020;383:1218-1230. Powles T, et al. *J Clin Oncol.* 2020;38(suppl 18): abstract LBA1.

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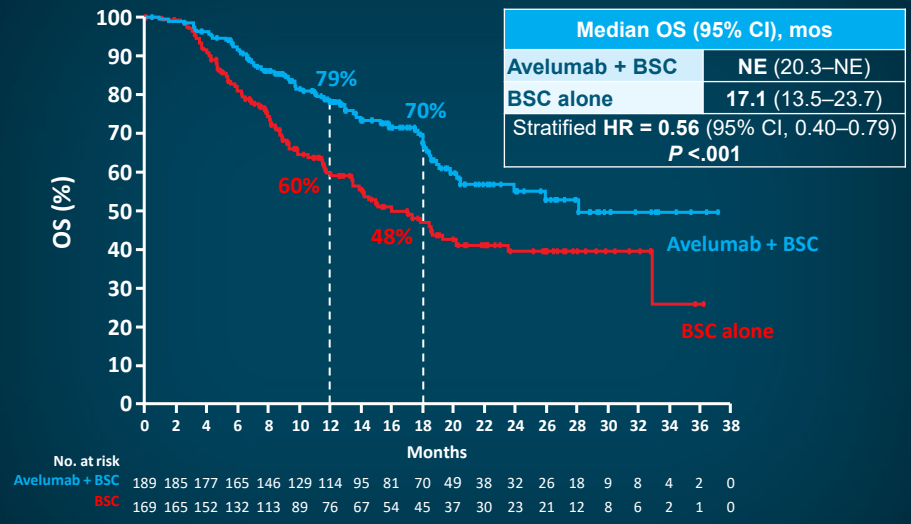
Avelumab Improves OS* in PD-L1+ Population



Median OS (95% CI), mos	
Avelumab + BSC	**NE** (20.3–NE)
BSC alone	**17.1** (13.5–23.7)
Stratified **HR = 0.56** (95% CI, 0.40–0.79) ***P* <.001**	

No. at risk																			
Avelumab + BSC	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
BSC	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

*OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* <.0014).

Powles T, et al. *N Engl J Med.* 2020;383:1218-1230. Powles T, et al. *J Clin Oncol.* 2020;38(suppl 18): abstract LBA1.

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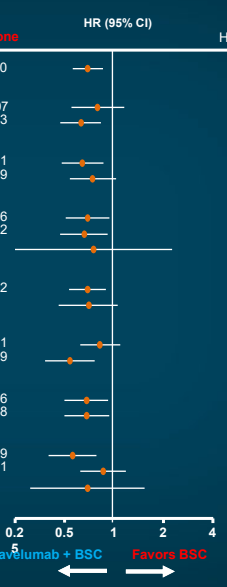
Subgroup Analysis of OS in the Overall Population

Subgroup		Events/patients, n: Avelumab + BSC	Events/patients, n: 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 chemotherapy regimen	Gemcitabine + cisplatin	71/183	98/206	**0.69** (0.51–0.94)
	Gemcitabine + carboplatin	68/147	73/122	**0.66** (0.47–0.91)
	Gemcitabine + cisplatin/carboplatin	6/20	7/20	**0.75** (0.25–2.25)
Best response to 1st-line chemotherapy	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	72/131	**0.86** (0.62–1.18)
	Unknown	8/22	25/50	**0.69** (0.31–1.53)



*Stratified; all other analyses are unstratified

Powles T, et al. *N Engl J Med.* 2020;383:1218-1230 supplement. Powles T, et al. *J Clin Oncol.* 2020;38(suppl 18): abstract LBA1.

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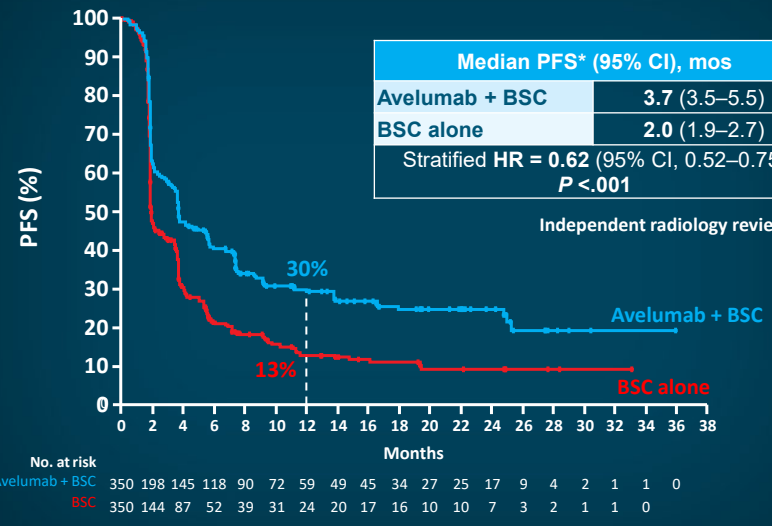
Avelumab Improves PFS in the Overall Population



Median PFS* (95% CI), mos	
Avelumab + BSC	**3.7** (3.5–5.5)
BSC alone	**2.0** (1.9–2.7)
Stratified **HR = 0.62** (95% CI, 0.52–0.75) ***P* <.001**	

Independent radiology review

*PFS was measured post randomization (from end of chemotherapy)

Powles T, et al. *N Engl J Med.* 2020;383:1218-1230. Powles T, et al. *J Clin Oncol.* 2020;38(suppl 18): abstract LBA1.

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Low Confirmed ORR with Maintenance Avelumab

Response to maintenance therapy post randomization—patients already had response or SD to chemotherapy

	Overall Population		PD-L1+ Population	
	Avelumab + BSC (n = 350)	BSC alone (n = 350)	Avelumab + BSC (n = 189)	BSC alone (n = 169)
ORR, % (95% CI)	**9.7** (6.8–13.3)	**1.4** (0.5–3.3)	**13.8** (9.2–19.5)	**1.2** (0.1–4.2)
Stratified odds ratio (95% CI)	7.46 (2.82–24.45)		12.70 (3.16–114.12)	
Best overall response, %				
Complete response	6.0	0.9	9.5	0.6
Partial response	3.7	0.6	4.2	0.6
Stable disease	12.6	13.1	10.1	13.6
Non-CR/non-PD	18.9	12.9	20.1	13.0
Progressive disease	37.1	48.3	31.2	48.5
Not evaluable	21.7	24.3	24.9	23.7
Disease control, %*	41.1	27.4	43.9	27.8

*Patients with a best overall response of CR, PR, SD, or non-CR/non-PD

Powles T, et al. *N Engl J Med.* 2020;383:1218-1230. Powles T, et al. *J Clin Oncol.* 2020;38(suppl 18): abstract LBA1.

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Javelin 100 Bladder: Subsequent Anticancer Therapy

About half of BSC patients received subsequent PD-L1 inhibitor
Results similar to historical data in US and elsewhere

	Overall population		Subgroup that discontinued study therapy due to PD	
	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	–	–

All percentages were calculated using the denominator of all patients in the treatment arm within each population; some patients received >1 category of subsequent therapy

Powles T, et al. *J Clin Oncol*. 2020;38(suppl 18): abstract LBA1.

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Avelumab as Maintenance Therapy: Metastatic Bladder Cancer Not Progressing With 4 to 6 Cycles of First-line Platinum-containing Chemotherapy

Improves median OS by more than 7 months

- All subgroups benefit
- Access to 2nd-line checkpoint therapy may have been limited in some countries, but 50% is similar to historical data
- PFS improvement is concordant

31 (9.0%) of avelumab-treated patients required corticosteroids for irAEs

HCRN pembrolizumab phase 2 maintenance trial showed PFS advantage but not OS

- Small sample size
- Crossover to pembrolizumab

Standard option for patients once approved

- Post-chemotherapy maintenance for responders or SD
- Pembrolizumab for patients with PD during front-line chemotherapy
- First-line IO may be appropriate in selected patients

irAE = immune-related adverse event; HCRN = Hoosier Cancer Research Network; IO = immuno-oncology.

Powles T, et al. *N Engl J Med*. 2020;383:1218-1230. Powles T, et al. *J Clin Oncol*. 2020;38(suppl 18): abstract LBA1. Galsky MD, et al. *J Clin Oncol*. 2020;38:1797-1806.

38

Adjuvant Immune Checkpoint Inhibitors for High-Risk Metastatic UC After Radical Surgery

- Adjuvant therapy after radical surgery for metastatic UC is not currently recommended for patients who received neoadjuvant therapy[1,2]
- No immune checkpoint inhibitor has shown efficacy as adjuvant therapy for metastatic UC at high risk of recurrence after surgery[3,4]

1. NCCN. Bladder cancer, version 6.2020 (www.nccn.org/professionals/physician_gls/pdf/bladder.pdf). Accessed 2/23/2021. 2. Witjes JA, et al. *Eur Urol*. 2017;71:462-475. 3. Kim HS, Seo HK. *Investig Clin Urol*. 2018;59:285-296. 4. Hussain MHA et al. *J Clin Oncol*. 2020;38(suppl 15):5000.

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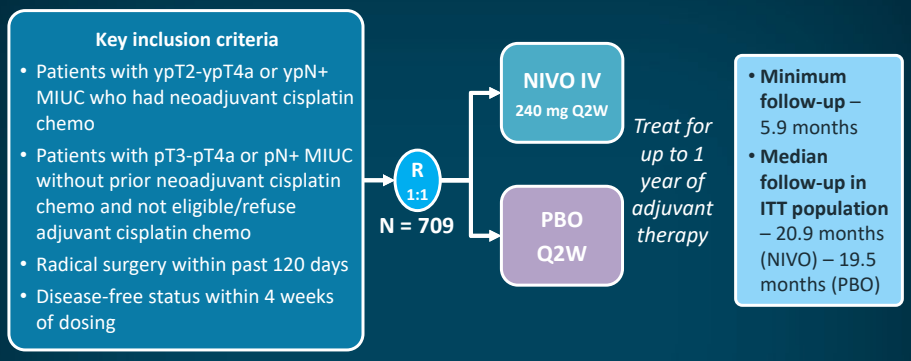
CheckMate 274: Nivolumab in the Adjuvant Setting



- **Stratification factors:** PD-L1 status (<1% vs ≥1%), prior neoadjuvant cisplatin-based chemotherapy, and nodal status
- **Primary endpoints:** DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥1%
- **Secondary endpoints:** NUTRFS, DSS, and OS
- Exploratory endpoints included: DMFS, safety, HRQoL

NIVO = nivolumab; PBO = placebo; DMFS = distant metastasis-free survival; DSS = disease-specific survival; HRQoL = health-related quality of life; IHC = immunohistochemistry; ITT = intent-to-treat; NUTRFS = non-urothelial tract recurrence-free survival.

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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CheckMate 274: Statistical Design

- Two primary objectives
  - To compare DFS for NIVO versus PBO in all randomized patients (ITT)
  - To compare DFS for NIVO versus PBO in all randomized patients with PD-L1 ≥1%
- Sample size calculation (~700 patients)

	ITT	PD-L1 ≥1%
Power considerations	~410 DFS events would provide ~87% power to detect an average HR of 0.72 with an overall type I error of 2.5% (2-sided)	~162 DFS events would provide ~80% power to detect an average HR of 0.61 with an overall type I error of 2.5% (2-sided)
Interim analysis	One interim analysis planned at ~85% of targeted DFS events	
Adjusted alpha level at interim analysis	0.01694 (based on 348 observed DFS events)	0.01131 (based on 137 observed DFS events)

- Key secondary objective
  - OS (secondary endpoint) to be tested using hierarchical procedure in each population, according to statistical analysis plan

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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CheckMate 274: Patient Disposition in All Treated Patients

	NIVO (n = 351)	PBO (n = 348)
Ongoing treatment, %	6.0	5.7
Completed treatment, %	40.7	37.9
Discontinued treatment, %	53.3	56.3
Reason for treatment discontinuation, %		
Disease recurrence	25.6	42.2
Study drug toxicity	14.0	2.3
Patient request	5.4	1.1
AE unrelated to study drug	4.6	4.3
Patient withdrew consent	1.4	2.0
Death	0	0.3
Other	2.3	4.0

AE = adverse event.

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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CheckMate 274: Select Baseline Demographic and Disease Characteristics in All Randomized Patients

		NIVO (n = 353)	PBO (n = 356)
Mean age (range), years		65.3 (30–92)	65.9 (42–88)
Male, %		75.1	77.2
Region, %	United States	13.9	14.9
	Europe	48.2	48.0
	Asia	22.7	20.8
	Rest of the world	15.3	16.3
ECOG PS, %	0	63.5	62.1
	1	34.6	35.1
	2	2.0	2.5
Tumor origin at initial diagnosis, %	Urinary bladder	79.0	78.9
	Upper tract disease	21.0	21.1
Minor histological variants present, %		41.1	39.6
PD-L1 ≥1% by IRVS, %		39.7	39.9
Prior neoadjuvant cisplatin, %		43.3	43.5
Pathologic T stage at resection, %	pT0-2	22.7	24.2
	pT3	58.4	57.3
	pT4a	16.1	17.4
	Other	2.5	0.8
Nodal status at resection, %	N+	47.3	47.2
	N0/x with <10 nodes removed	26.6	27.8
	N0 with ≥10 nodes removed	25.8	24.7

IVRS = interactive-voice response system.

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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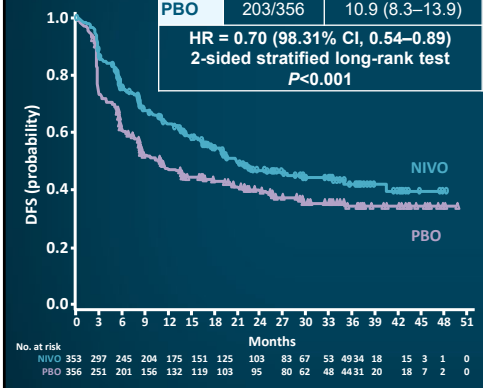
CheckMate 274: Disease-Free Survival

ITT

	Events/ patients	Median DFS, mos (95% CI)
NIVO	166/353	21.0 (17.1–33.4)
PBO	203/356	10.9 (8.3–13.9)

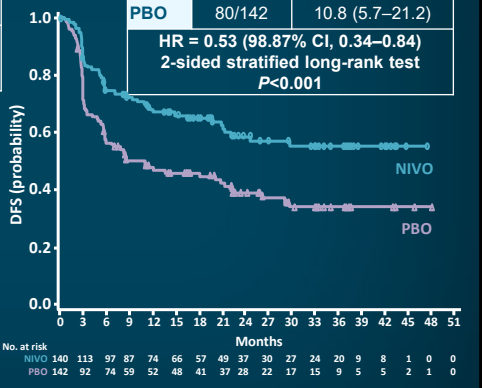
HR = 0.70 (98.31% CI, 0.54–0.89)
2-sided stratified long-rank test
P<0.001



PD-L1 ≥1%

	Events/ patients	Median DFS, mos (95% CI)
NIVO	52/140	NR (22.0–NE)
PBO	80/142	10.8 (5.7–21.2)

HR = 0.53 (98.87% CI, 0.34–0.84)
2-sided stratified long-rank test
P<0.001



Minimum follow-up = 5.9 months

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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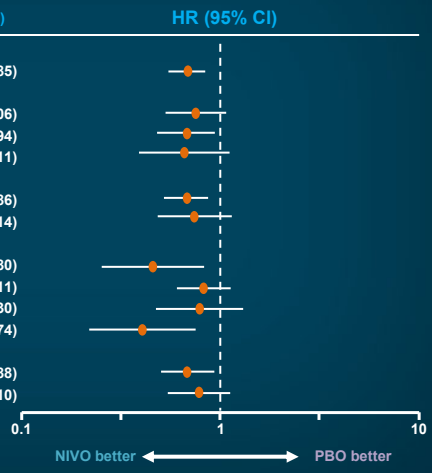
CheckMate 274: Disease-Free Survival in Select Subgroups—ITT Patients

Subgroup	Nivolumab Events/patients	Placebo Events/patients	HR (95% CI)
Overall	166/353	203/356	0.70 (0.57–0.85)
Age			
<65 years	71/155	69/136	0.76 (0.54–1.06)
≥65 and <75 years	63/131	100/164	0.68 (0.49–0.94)
≥75 years	32/67	34/56	0.67 (0.40–1.11)
Sex			
Male	122/265	155/275	0.68 (0.53–0.86)
Female	44/88	48/81	0.75 (0.49–1.14)
Region			
United States	25/49	36/53	0.45 (0.26–0.80)
Europe	85/170	96/171	0.83 (0.61–1.11)
Asia	35/80	34/74	0.78 (0.47–1.30)
Rest of world	21/54	37/58	0.41 (0.22–0.74)
Baseline ECOG PS			
0	101/224	125/221	0.67 (0.52–0.88)
1	64/122	71/125	0.78 (0.55–1.10)



Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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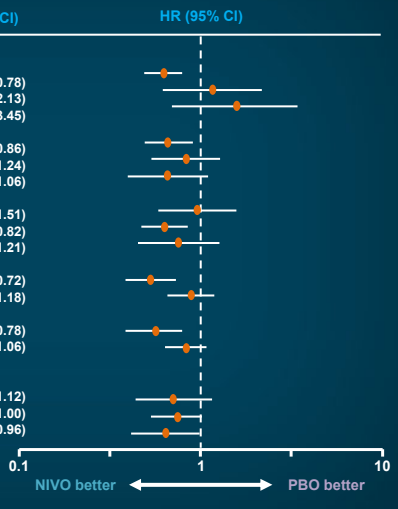
CheckMate 274: DFS in Select Subgroups—ITT Patients (continued)

Subgroup	Nivolumab Events/patients	Placebo Events/patients	HR (95% CI)
Initial tumor origin			
Urinary bladder	126/279	165/281	0.62 (0.49–0.78)
Renal pelvis	23/44	25/52	1.16 (0.63–2.13)
Ureter	17/30	13/23	1.55 (0.70–3.45)
Pathologic lymph node status			
N+	95/167	115/168	0.65 (0.49–0.86)
N0/x with <10 nodes removed	44/94	50/99	0.82 (0.54–1.24)
N0 with ≥10 nodes removed	27/91	37/88	0.64 (0.39–1.06)
Pathologic status			
pT0–2	36/80	40/86	0.93 (0.58–1.51)
pT3	94/206	119/204	0.62 (0.47–0.82)
pT4a	34/57	40/62	0.74 (0.45–1.21)
Prior neoadjuvant cisplatin			
Yes	69/153	99/155	0.53 (0.39–0.72)
No	97/200	104/201	0.89 (0.67–1.18)
Baseline PD-L1 expression			
≥1%	52/139	78/141	0.55 (0.39–0.78)
<1%	113/210	120/209	0.82 (0.63–1.06)
Time from IUC surgery to randomization, days			
30–60	43/79	39/70	0.70 (0.43–1.12)
60–90	76/165	93/177	0.73 (0.53–1.00)
90–120	45/103	62/95	0.64 (0.42–0.96)



IUC = indwelling urethral catheter.

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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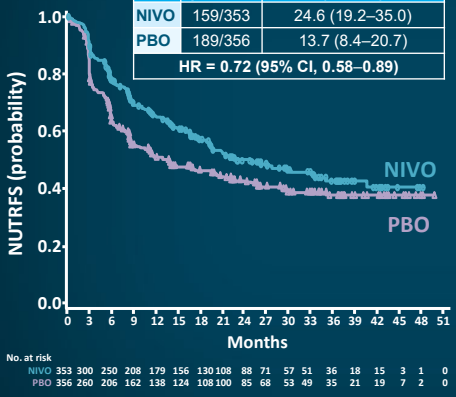
CheckMate 274: Non-Urothelial Tract Recurrence-Free Survival (NUTRFS)*

ITT

	Events/ patients	Median NUTRFS, mos (95% CI)
NIVO	159/353	24.6 (19.2–35.0)
PBO	189/356	13.7 (8.4–20.7)
HR = 0.72 (95% CI, 0.58–0.89)		

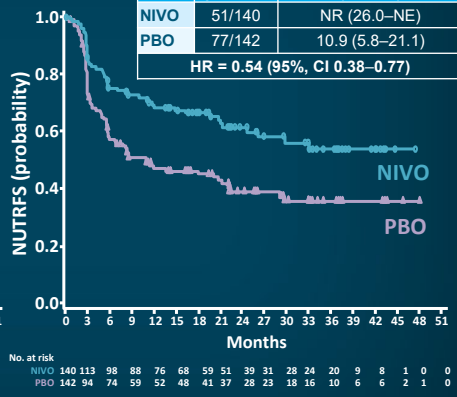


No. at risk

NIVO	353	300	250	208	179	156	130	108	88	71	57	51	36	18	15	3	1	0
PBO	356	260	206	162	138	124	108	100	85	68	53	49	35	21	19	7	2	0

PD-L1 ≥1%

	Events/ patients	Median NUTRFS, mos (95% CI)
NIVO	51/140	NR (26.0–NE)
PBO	77/142	10.9 (5.8–21.1)
HR = 0.54 (95%, CI 0.38–0.77)		



No. at risk

NIVO	140	113	98	88	76	68	59	51	39	31	28	24	20	9	8	1	0	0
PBO	142	94	74	59	52	48	41	37	28	23	18	16	10	6	6	2	1	0

Minimum follow-up = 5.9 months

*NUTRFS was defined as the time between date of randomization and date of first local non-urothelial tract or distant recurrence or death.

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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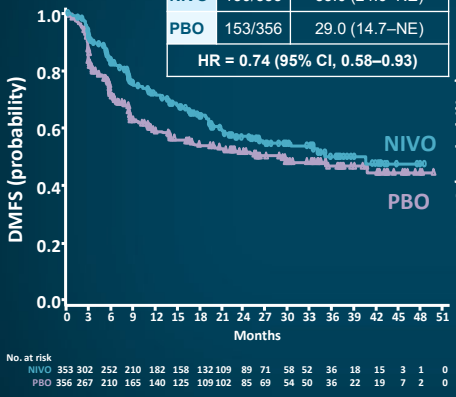
CheckMate 274: Distant Metastasis-Free Survival*

ITT

	Events/ patients	Median DMFS, mos (95% CI)
NIVO	130/353	35.0 (24.6–NE)
PBO	153/356	29.0 (14.7–NE)
HR = 0.74 (95% CI, 0.58–0.93)		

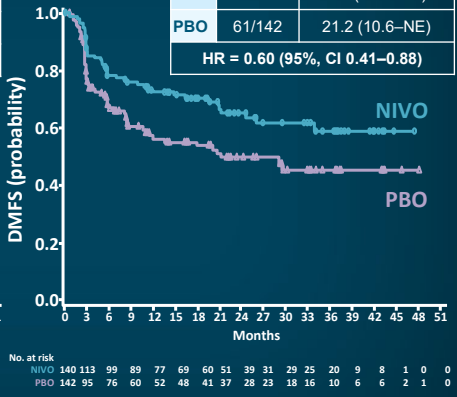


No. at risk

NIVO	353	302	252	210	182	158	132	109	89	71	58	52	36	18	15	3	1	0
PBO	356	267	210	165	140	125	109	102	85	69	54	50	36	22	19	7	2	0

PD-L1 ≥1%

	Events/ patients	Median DMFS, mos (95% CI)
NIVO	45/140	NR (33.9–NE)
PBO	61/142	21.2 (10.6–NE)
HR = 0.60 (95%, CI 0.41–0.88)		



No. at risk

NIVO	140	113	99	89	77	69	60	51	39	31	29	25	20	9	8	1	0	0
PBO	142	95	76	60	52	48	41	37	28	23	18	16	10	6	6	2	1	0

Minimum follow-up = 5.9 months

*DMFS was defined as the time between date of randomization and date of first distant recurrence (non-local) or date of death.

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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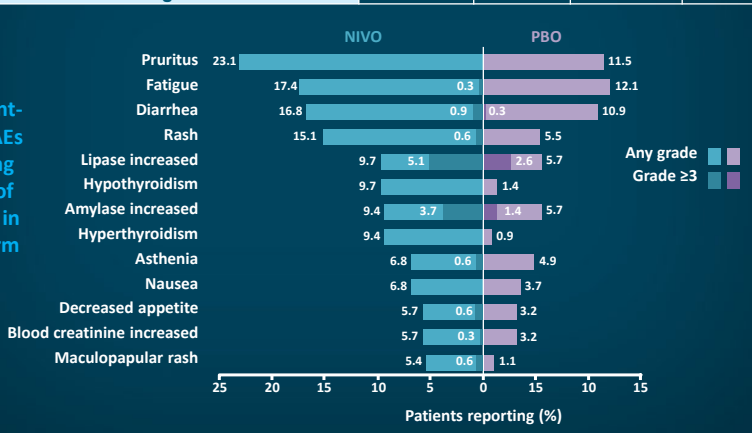
CheckMate 274: Safety Summary in All Treated Patients

	NIVO (n = 351)		PBO (n = 348)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any-cause AEs	98.9%	42.7%	95.4%	36.8%
Treatment-related AEs*	77.5%	17.9%	55.5%	7.2%
Treatment-related AEs leading to discontinuation	12.8%	7.1%	2.0%	1.4%

Treatment-related AEs occurring in ≥5% of patients in either arm



*2 treatment-related deaths due to pneumonitis in NIVO arm and none in PBO arm.

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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CheckMate 274: Treatment-Related Select AEs*

	NIVO (n = 351)		PBO (n = 348)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Skin	40.7	1.7	17.8	0
Endocrine	19.1	0.3	3.7	0
Gastrointestinal	18.5	1.7	11.2	0.9
Hepatic	8.3	1.7	4.9	0.3
Renal	7.1	1.1	3.4	0
Pulmonary	5.4	1.4†	1.4	0

- Most common grade ≥3 treatment-related select AEs were:
- Diarrhea (0.9%), colitis (0.9%), and pneumonitis (0.9%) in NIVO arm
- Colitis (0.6%), diarrhea (0.3%), GGT increase (0.3%), and hepatitis (0.3%) in PBO arm

Select AEs are those with potential inflammatory mechanism requiring more frequent monitoring and/or specific intervention such as immunosuppressants or endocrine replacement therapy; †1 patient with grade 4 treatment-related pneumonitis and 1 patient with grade 3 treatment-related immune-mediated pneumonitis had a fatal outcome.

GGT = gamma-glutamyltransferase.

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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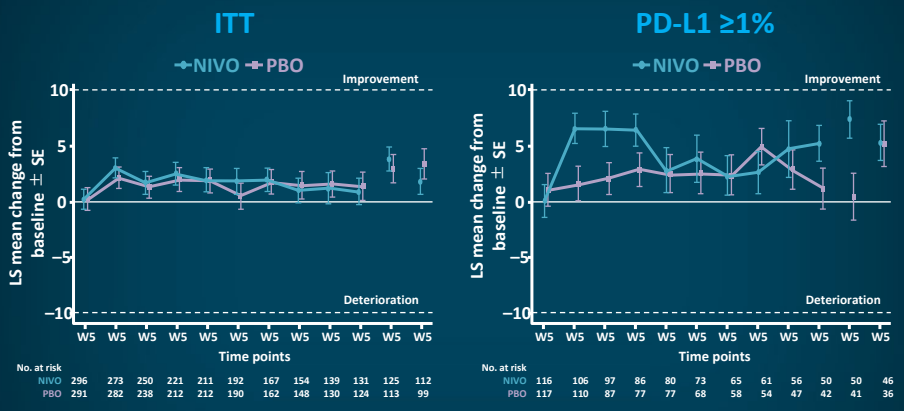
CheckMate 274: Health-Related Quality of Life

Change from Baseline in EORTC-QLQ-C30 Global Health Status Score



No deterioration in HRQoL with NIVO versus PBO was observed in either ITT or PD-L1 >1% populations

EORTC = European Organisation for Research and Treatment of Cancer; QLQ = quality-of-life questionnaire; LS = least square; SE = standard error; W = week.

Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391.

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Summary of Initial Results of CheckMate-274

- Nivolumab showed statistically significant and clinically meaningful improvement in disease-free survival after radical surgery versus placebo for both the ITT and PD-L1 ≥1% groups[1]
- Secondary endpoint (NUTRFS) and exploratory endpoint (DMFS) were also improved with nivolumab in both study populations[1]
- Adverse events were manageable and consistent with previous reports in other tumor types, including patients with metastatic UC[2–4]
- No deterioration in HRQoL was observed with nivolumab versus placebo[1]
- Nivolumab is the first systemic immunotherapy to show a statistically significant and clinical meaningful improvement as adjuvant therapy in this setting

1. Bajorin DF, et al. *J Clin Oncol.* 2021;39(suppl 6): abstract 391. 2. Sharma P et al. *Lancet Oncol*. 2016;17:1590-1598. 3. Sharma P et al. *Lancet Oncol*. 2017;18:312-322. 4. Motzer R et al. *N Engl J Med*. 2015;373:1803-1813.

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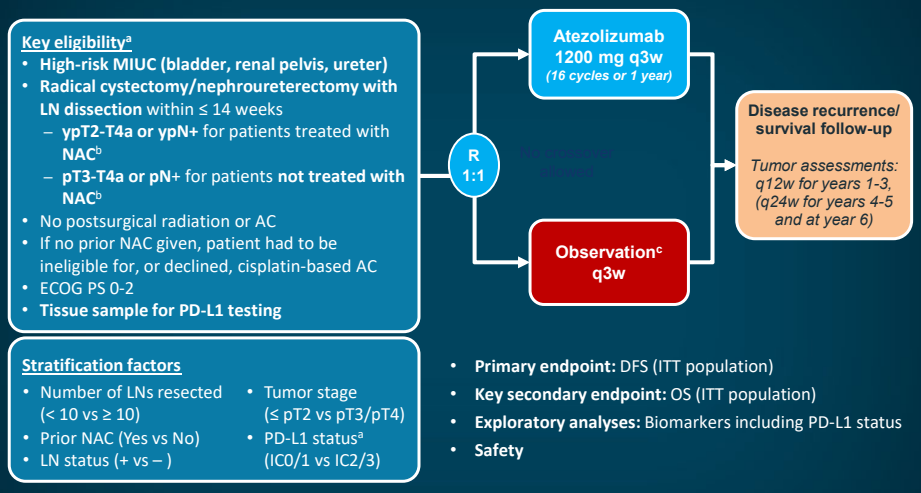
IMvigor010: Atezolizumab in the Adjuvant Setting



AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b] Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c] Alternating clinic visits and phone calls.

Hussain MHA, et al. *J Clin Oncol*. 2020;38(suppl 15):5000.

5 3

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IMvigor010: Baseline Characteristics

Characteristic	Atezolizumab (N = 406)	Observation (N = 403)
Median age, years (range)	67 (31-86)	66 (22-88)
Male, n (%)	**322 (79)**	**316 (78)**
ECOG PS, n (%) 0 1 2	 248 (61) 142 (35) 16 (4)	 259 (64) 130 (32) 14 (4)
Primary tumor site, n (%) **Bladder** Upper tract (ureter, renal pelvis)	 **377 (93)** 29 (7)	 **378 (94)** 25 (6)
Prior neoadjuvant chemotherapy, n (%)[a]	**196 (48)**	**189 (47)**
Pathologic tumor stage, n (%)[b] pT2N0 **pT3N0** **pT4N0**	 34 (8) **124 (31)** **32 (8)**	 39 (10) **119 (30)** **33 (8)**
≤pT2-4 and pN+, n (%)[a]	**212 (52)**	**208 (52)**
PD-L1 IHC status, n (%)[c] IC0 IC1 IC2 IC3	 57 (14) 152 (37) 147 (36) 50 (12)	 66 (16) 138 (34) 144 (36) 55 (14)

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Per interactive voice/web response system (IxRS). [b] Per electronic case report form (eCRF). [c] Archival and/or fresh pre-treatment FFPE tumor tissue from all patients (surgical resection or lymph node dissection) were prospectively tested for PD-L1 status per a central laboratory and used as a stratification factor; 119 patients were enrolled using IC2/3 selection, and 690 patients were enrolled under an "all-comer" protocol.

Hussain MHA, et al. *J Clin Oncol*. 2020;38(suppl 15):5000.

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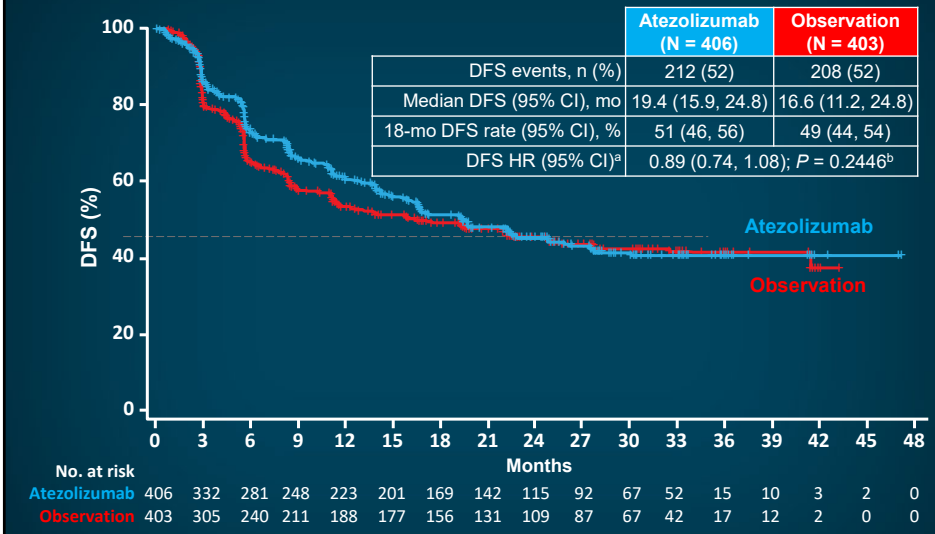
IMvigor010: DFS in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

No. at risk																	
Atezolizumab	406	332	281	248	223	201	169	142	115	92	67	52	15	10	3	2	0
Observation	403	305	240	211	188	177	156	131	109	87	67	42	17	12	2	0	0

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

Hussain MHA, et al. *J Clin Oncol*. 2020;38(suppl 15):5000.

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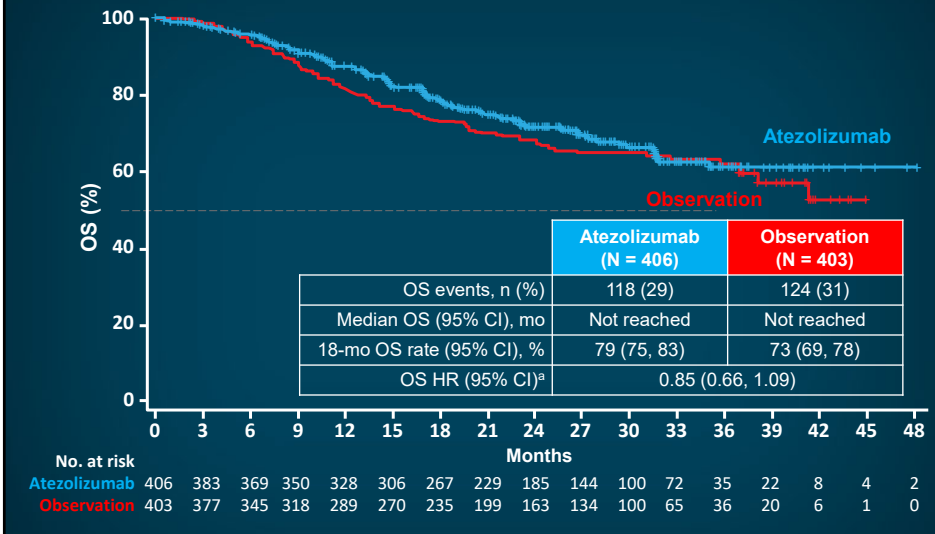
IMvigor010: Interim OS Analysis in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

No. at risk																	
Atezolizumab	406	383	369	350	328	306	267	229	185	144	100	72	35	22	8	4	2
Observation	403	377	345	318	289	270	235	199	163	134	100	65	36	20	6	1	0

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%).
[a] OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

Hussain MHA, et al. *J Clin Oncol*. 2020;38(suppl 15):5000.

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Advances in Urinary Biomarker Discovery

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Targeting Molecular Pathology of Bladder Cancer PD-L1 and Beyond

- In bladder cancer, PD-L1 staining appears to be associated with higher response rate and may be linked to overall survival;1 however, multiple assays exist and are under evaluation in bladder cancer
- Other biomarkers beyond PD-L1 are needed
  - Data in multiple cancer types suggest that mutation load is associated with treatment outcome with immune checkpoint blockade2,3
  - Gene expression subtypes may be predictive of ORR with immunotherapy4,5

1. Havez N, Petrylak DP. *Immunotherapy.* 2015;7:1-2. 2. Snyder A, et al. *N Engl J Med.* 2014;371:2189-2199. 3. Rizvi NA, et al. *Science.* 2015;348:124-128. 4. Rosenberg JE, et al. *J Clin Oncol.* 2016;34(suppl): abstract 104. 5. Choi W, et al. *Nat Rev Urol.* 2014;11:400-410.

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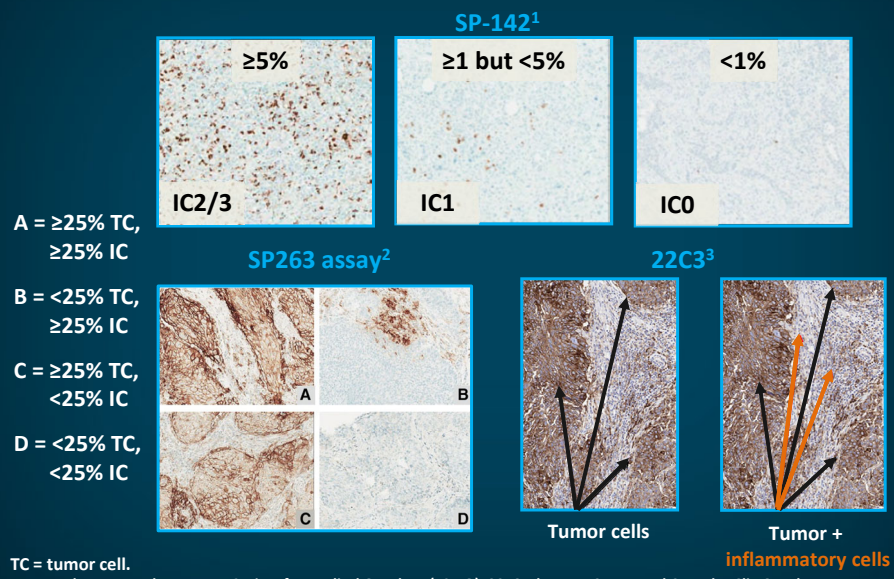
Examples of Different Staining Patterns and Antibodies



TC = tumor cell.

1. Rosenberg JE, et al. European Society for Medical Oncology (ESMO). 2016: abstract 2. Massard C, et al. *J Clin Oncol*. 2016;34:3119-2125. 3. Courtesy of Elizabeth Plimack, MD, MS.

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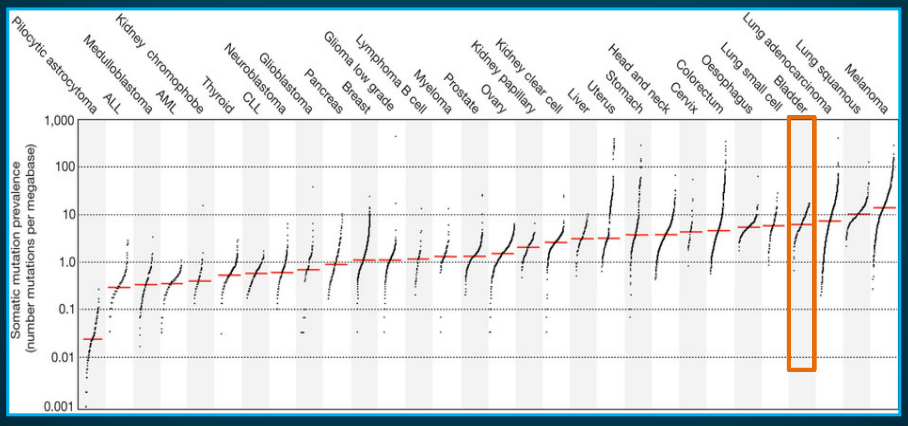
Other Biomarkers Beyond PD-L1 IHC Are Needed

- Bladder cancer has high mutation burden, second only to lung cancer and melanoma[1]

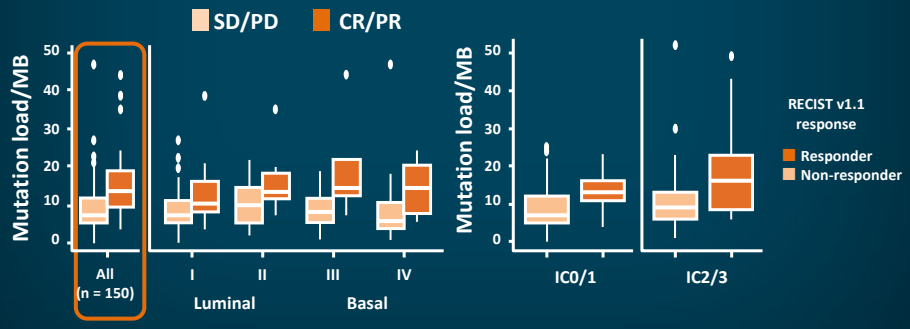


Alexandrov LB, et al. *Nature*. 2013;500:415-421.

60

Estimated Mutation Load Associated with Higher Objective Responses With Atezolizumab in Platinum-pre-Treated Patients

- Estimated using a targeted panel
- Focuses on non-hotspot alterations
- Extrapolates from 3% of genome covered in assay

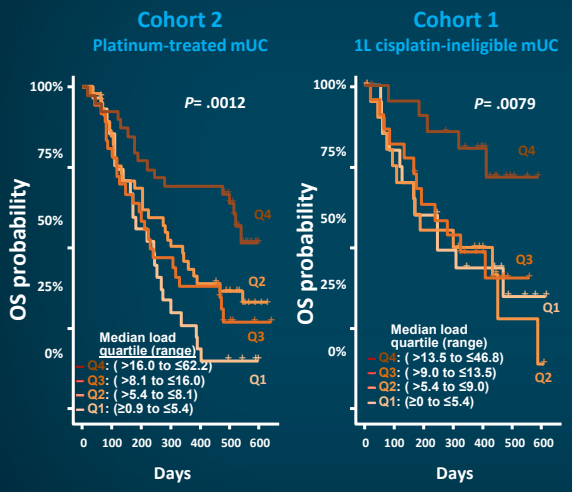


MB = megabase RECIST = Response Evaluation Criteria In Solid Tumors

Rosenberg JE, et al. *Lancet*. 2016;387:1909-1920.

61

Mutation Load Is Associated with OS in Patients Treated with Atezolizumab



- Mutation load associated with ORR
- Quartile-split mutation load was associated with OS in platinum-treated patients (cohort 2)
- Similar results were seen for 1L cisplatin-ineligible patients (cohort 1)
  - In both cohorts, patients with highest median mutation load (Q4) had significantly longer OS versus those in Q1–Q3a

1L = first-line.

Rosenberg JE, et al. *J Clin Oncol*. 2016;34(suppl): abstract 104. Rosenberg JE, et al. *Lancet*. 2016;387:1909-1920.

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TMB as Biomarker of Response to Nivolumab

Extended Follow-up From CheckMate 275

- Exploratory biomarker analyses of response to nivolumab in platinum-resistant metastatic and advanced bladder cancer
- Of 270 patient, 139 had tumors with measurable TMB
- Higher TMB (P <.05) was associated with:
  - Improved ORR, PFS, and OS
  - Combined with PD-L1, TMB better predicted ORR, PFS, and OS than PD-L1 alone
  - Higher mutational signature 2 score was associated with better OS but did not improve predictive value of TMB

TMB = tumor mutational burden.

Galsky MD, et al. *Clin Cancer Res*. 2020;26:5120-5128.

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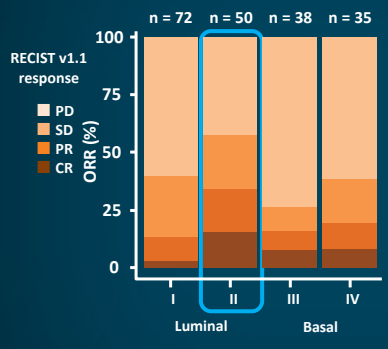
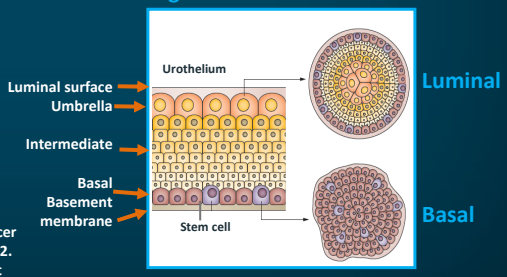
Expression Subtype Associated with ORR

Response distributions by TCGA subtype[1,2]



- Gene expression data used to classify IMvigor210 tumor samples recapitulated TCGA subtypes[3]
- Responses occurred in all subtypes, but ORR was significantly higher in luminal II versus other subtypes (*P*= .0072) [3]
- What might be drivers of this subtype-specific response?

Possible origins of basal and luminal MIBCs[4]



TCGA = The Cancer Genome Atlas.

1. Rosenberg JE, et al. *Lancet*. 2016;387:1909-1920. 2. Cancer Genome Atlas Research Network. *Nature*. 2014;507:315-322. 3. Rosenberg JE, et al. *J Clin Oncol*. 2016;34(suppl): abstract 104. 4. Choi W, et al. *Nat Rev Urol*. 2014;11:400-410.

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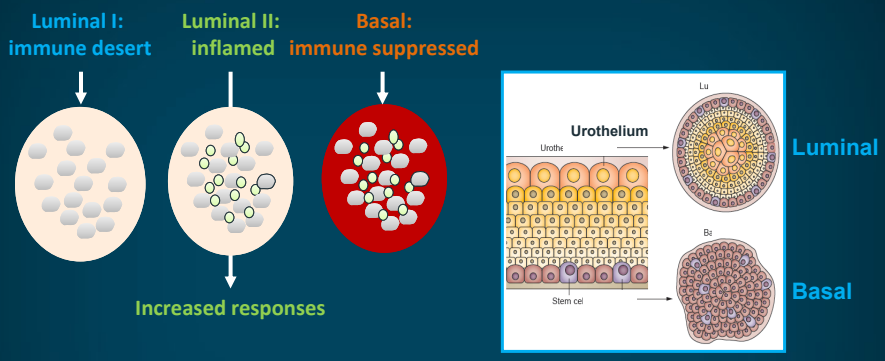
CD8+ T-effector (T_{eff}) Cells



- Luminal I tumors have low T_{eff} expression
- Luminal II tumors have high T_{eff} and low stromal gene expression
- Basal tumors have high T_{eff} and high stromal gene expression

Choi W, et al. *Nat Rev Urol*. 2014;11:400-410.

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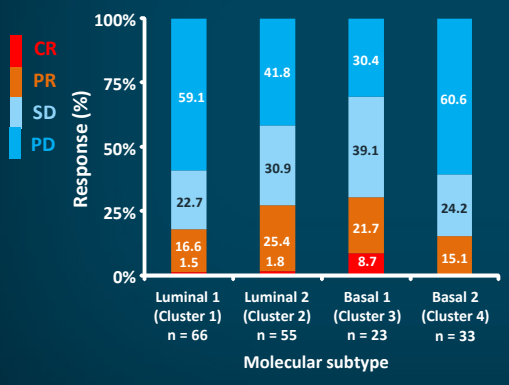
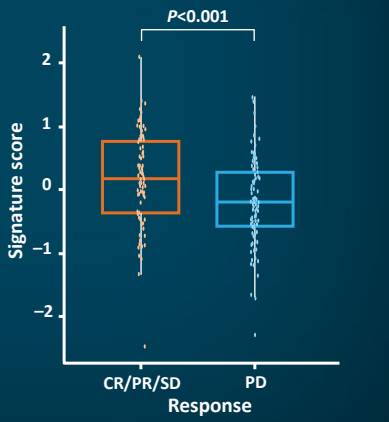
Association Between UC Molecular Subtype, 25-gene Interferon-γ Signature, and Response to Nivolumab

- Basal 1 and luminal 2 have higher response rates versus other 2 subtypes
- Interferon-γ genes are enriched in responders/SD versus those with PD (P <.01)



Basal 2 CR = 0%; luminal 1 CR = 1.5%; luminal 2 CR = 1.8%



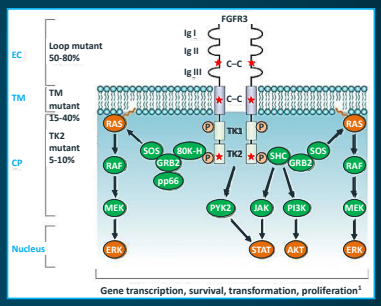
Signature score, 25-gene interferon-γ signature expression

Galsky MD, et al. *Ann Oncol*. 2016;27(6): abstract LBA31_PR.

66

FGFR3—Fibroblast Growth Factor Receptor

- Membrane-based TKR involved in cellular proliferation, differentiation, and steroid biosynthesis (figure)[1,2]
- FGFR mutations and overexpression have been implicated in bladder cancer[3]
- April 12, 2019—FDA granted accelerated approval to FGFR inhibitor erdafitinib for locally advanced/metastatic bladder cancer with a FGFR2 or FGFR3 alteration that has progressed during or after platinum chemo[4]
- FGFR inhibitors and anti-FGFR ADCs are in ongoing and upcoming trials in advanced UC[5]



TKR = tyrosine kinase receptor; ADC = antibody-drug conjugate; Ig = immunoglobulin; TK = tyrosine kinase; EC = extracellular; transmembrane domain; CP = cytoplasmic; RAS = MEK = mitogen activated protein kinase kinase; ERK = extracellular regulated kinase; SHC = SRC-homology-2-domain-containing; GRB2 = growth factor-receptor-bound protein 2; SOS = son of sevenless; STAT = signal transducer and activator of transcription; PYK2 = proline-rich tyrosine kinase 2; JAK = Janus kinase; RAF = proto-oncogene serine/threonine-protein kinase; RAS = gene initially isolated from genes in rat sarcoma.

1. Wu X-R. *Nat Rev Cancer*. 2005;5:713-725. 2. Ai X, et al. *Oncol Lett.* 2015;10(1):543-549. 3. Turo R, et al. *J Urol*. 2015;193:325-330. 4. FDA. Erdafitinib, 2019 (https://tinyurl.com/y2cnn9eu). Accessed 2/23/2021. 5. ClinicalTrials.gov.

67

Summary

- Checkpoint inhibition therapy demonstrates significant antitumor activity in advanced urothelial carcinoma
  - As initial therapy in cisplatin-ineligible patients
  - In patients with cisplatin-pretreated disease
- Trials are ongoing to explore immunotherapy-based combinations and the use of immunotherapy in earlier stages of disease
- A thorough understanding of the markers of resistance and response will help in designing future trials in earlier disease

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Managing Immune-Related Adverse Events in Bladder Cancer

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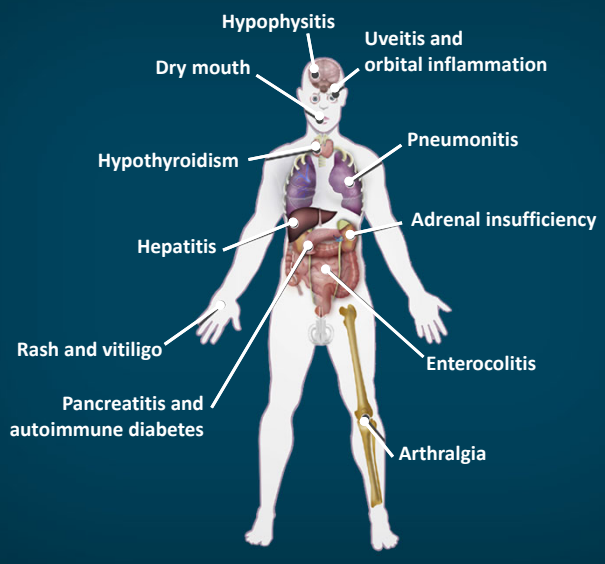
irAEs: Clinical Spectrum



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

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irAEs of PD-1/L-1 Inhibitors in Bladder Cancer

- Dermatologic toxicities are often first to appear
  - Rash (reticular, maculopapular, erythematous)
- Less common, but more serious
  - Eye: episcleritis, conjunctivitis, uveitis
  - Kidneys: nephritis, granulomatous lesions, thrombotic microangiopathy
- Grade 5 irAEs are rare

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.

71

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 wk	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 intensive care unit	Systemic steroids IV methylprednisolone 1–2 mg/kg/d and switch to oral prednisone for ≥3 d with taper over 4–6 wk	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; wk = week(s); d = day(s); IV = intravenous.

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.

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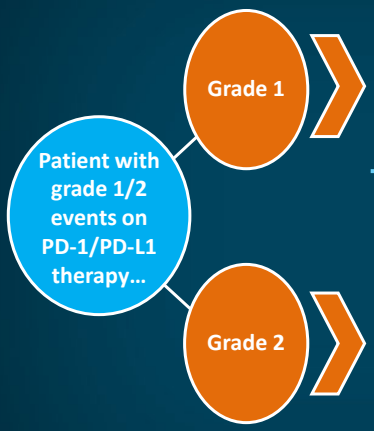
Managing Grade 1/2 irAEs



- 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. UpToDate, 2021 (www.uptodate.com/contents/toxicities-associated-with-checkpoint-inhibitor-immunotherapy). Accessed 2/27/2021. Brahmer J, et al. *J Clin Oncol*. 2018;36:1714-1768.

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Managing Grade 3 irAEs

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

- **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 were published in 2018.**

ASCO = American Society of Clinical Oncology.

Postow MA. *Am Soc Clin Oncol Educ Book*. 2015:76-83. Postow MA. UpToDate, 2021 (www.uptodate.com/contents/toxicities-associated-with-checkpoint-inhibitor-immunotherapy). Accessed 2/27/2021. Brahmer J, et al. *J Clin Oncol*. 2018;36:1714-1768. Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

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Case Studies

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Patient Case

A 78-year-old woman with MIBC presents with metastatic disease to the lung:

- PDL-1 stains positive with a CPS >10
- Creatinine clearance of 40 mL/min
- After 3 cycles of pembrolizumab, patient begins having 3 watery bowel movements per day

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Case Question

What is the next best step in this patient's management?

A. Hold pembrolizumab and treat symptoms with loperamide
B. Prednisone 40 mg PO QD
C. Prednisone 80 mg PO QD
D. Infliximab 5 mg/kg every 2 weeks

PO = by mouth; QD = each day.

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Case Question

Despite your efforts, she now has 4–6 watery bowel movements per day. What do you include for management of your patient's symptoms?

A. Loperamide/anti-colitis diet
B. Prednisone 40 mg PO QD
C. Prednisone 80 mg PO QD
D. Infliximab 5 mg/kg every 2 weeks

PO = by mouth; QD = each day.

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Management of Grade 1/2 Gastrointestinal irAEs

GI irAE Grade	Description	Management
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output over baseline	• Managed symptomatically – ADA colitis diet – Anti-motility agents (eg, loperamide) • Continue therapy
Grade 2	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output over baseline	• Initially managed symptomatically • If not improved: colonoscopy recommended • If colitis found, recommend initiate treatment with "moderate-dose corticosteroids" – Budesonide 9 mg daily – Prednisone ~40 mg daily

GI = gastrointestinal.

Villadolid J, Amin A. *Transl Lung Cancer Res*. 2015;4:560-575. Tarhini A. *Scientifica*. 2013;2013:857519.

79

Management of Grade 3/4 irAEs

GI irAE Grade	Description	Management
Grade 3	Increase of 7 or more stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; limited self-care activities of daily living	• Permanently discontinue therapy • Initiate treatment with high dose corticosteroids (1–2 mg/kg prednisone daily) • In refractory cases, infliximab 5 mg/kg every 2 weeks
Grade 4	Life-threatening consequences; urgent intervention indicated	

Villadolid J, Amin A. *Transl Lung Cancer Res*. 2015;4:560-575. Tarhini A. *Scientifica*. 2013;2013:857519.

80

Patient Case

A 52-year-old man presents with gross hematuria:

- TURBT demonstrates a poorly differentiated urothelial cancer with muscle invasion
- CT scan of the chest/abdomen/pelvis demonstrates no evidence of metastatic disease
- Patient receives 4 cycles of dose-dense MVAC
- He undergoes a radical cystectomy, which demonstrates a T3N1 urothelial cancer

MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin.

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Case Question

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

A. 2 more cycles of dose-dense MVAC

B. 4 cycles of gemcitabine/cisplatin

C. 1 year of atezolizumab

D. 1 year of nivolumab

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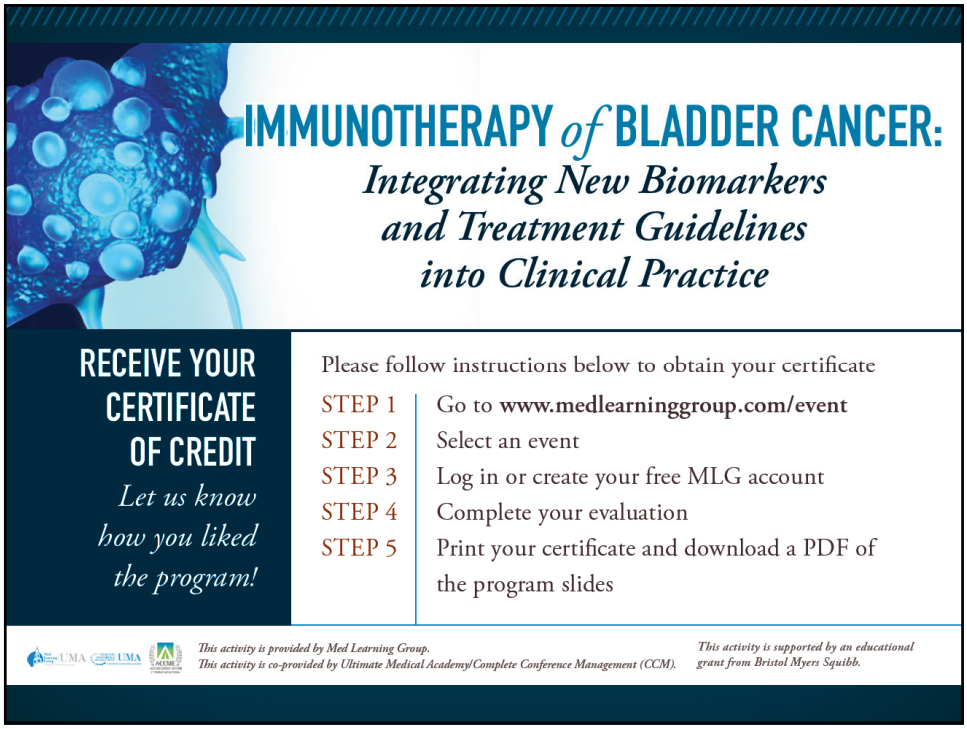
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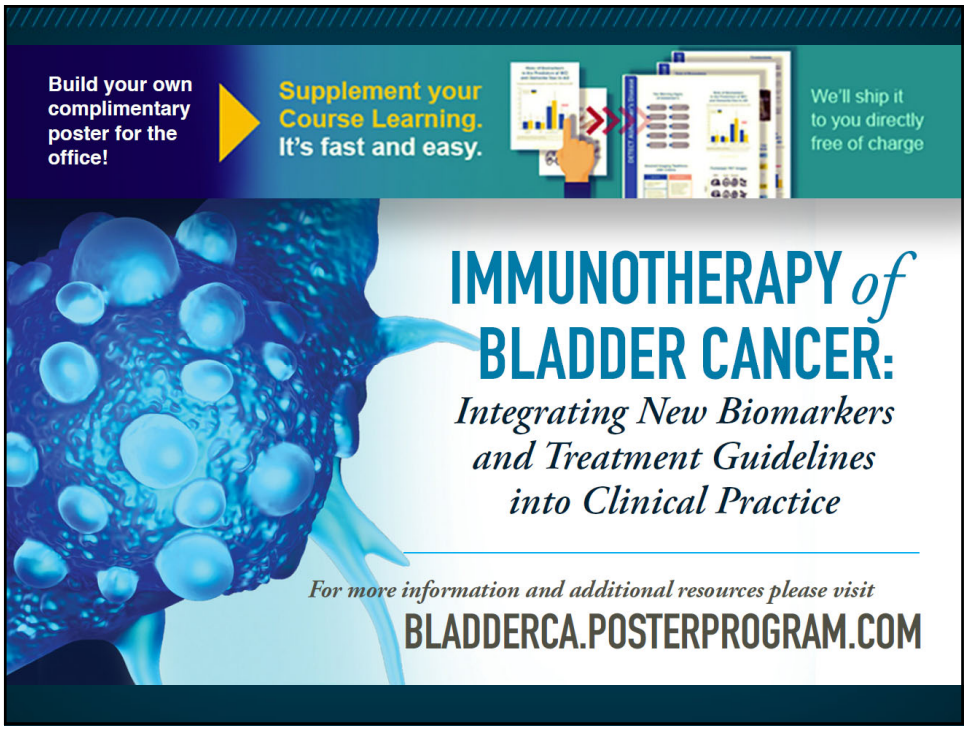
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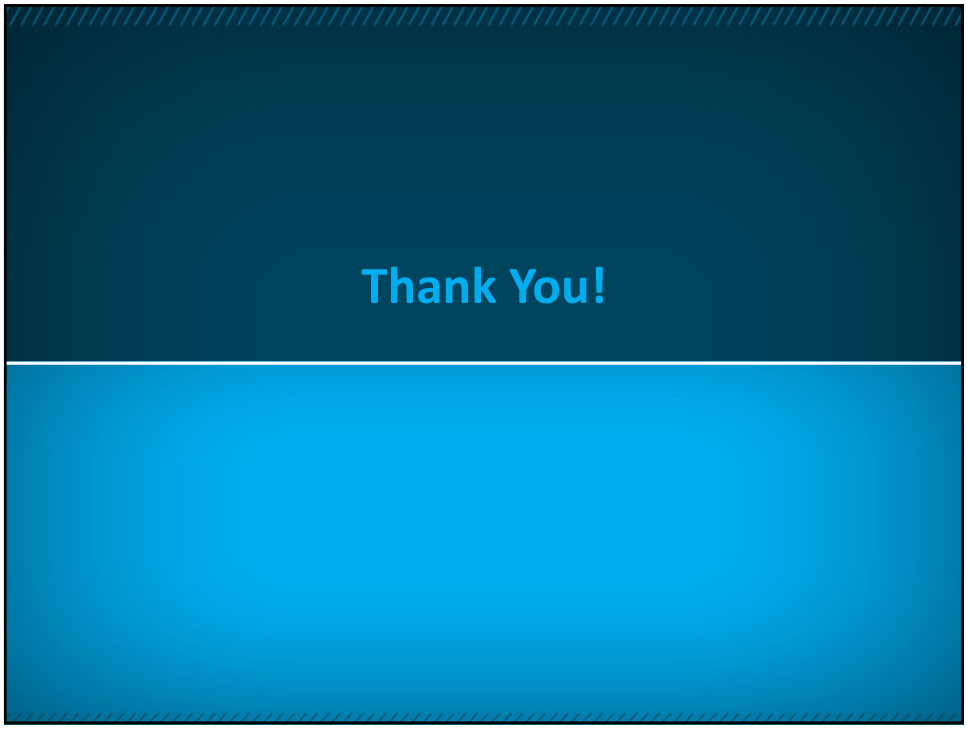

85

Overview of Bladder Cancer

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Treatment Recommendations for Non-muscle Invasive Bladder Cancer

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Treatment Recommendations for Muscle Invasive Bladder Cancer

Resource	Address
Bajorin DF, Witjes JA, Gschwend J, et al. First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab vs placebo in patients who underwent radical surgery for high-risk muscle-invasive urothelial carcinoma (MIUC). *J Clin Oncol.* 2021;39(suppl 6):391.	https://meetinglibrary.asco.org/record/195264/abstract
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Resource	Address
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Turo R, Harnden P, Thygesen H, et al. FGFR3 expression in primary invasive bladder cancers and matched lymph node metastases. *J Urol*. 2015;193:325-330.	https://pubmed.ncbi.nlm.nih.gov/24933362/
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Managing Immune Related Adverse Events in Bladder Cancer

Resource	Address
Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36:1714-1768.	https://pubmed.ncbi.nlm.nih.gov/29442540/
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