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Learning Objectives

1. Appraise the expanding clinical trial evidentiary base across all stages of the bladder cancer disease continuum, including newly-approved indications, recently-reported data, and current consensus guideline recommendations for treatment of NMIBC, MIBC, and locally advanced/mUC.
2. Examine the evolving bladder cancer management calculus, with a focus on evidence-based treatment sequencing strategies and/or combinatorial regimens incorporating platinum chemotherapy, immune checkpoint inhibitors, targeted therapies, and antibody-drug conjugates.
3. Review practical patient counseling strategies related to the safety, efficacy, and therapeutic rationale of novel treatments in bladder cancer, with an emphasis on the provision of adaptive emotional support infrastructures.
4. Identify immune-mediated adverse events (imAEs) that may occur in patients with bladder cancer receiving immune checkpoint inhibitors, either as monotherapy or in combination, and implement adaptive imAE anticipation, recognition, and management strategies.

Overview

- Bladder cancer is the 6th most common cancer in the United States
- Median age of diagnosis is 73 years old
- Most common risk factors
  - Male sex
  - White race
  - **Smoking**
  - Personal or family history of bladder cancer
  - Prior pelvic radiation
  - Environmental/occupation exposures
  - Chronic infection or irritation of the urinary tract
  - Comorbidities including obesity and diabetes

Flaig T, et al. *J Natl Compr Canc Netw.* 2020.

Urothelial Carcinoma of the Bladder Disease Spectrum

- Non–muscle-invasive bladder cancer (NMIBC)
  - Bacillus Calmette-Guérin (BCG)-unresponsive disease
- Muscle-invasive bladder cancer (MIBC)
  - Neoadjuvant therapy
  - Adjuvant therapy
- Advanced bladder cancer (mUC)
  - First-line options
  - Second-line options and beyond

https://www.cancer.org/cancer/bladder-cancer/about/key-statistics.html.

Non–muscle-invasive Bladder Cancer

NMIBC

Non–muscle-invasive Bladder Cancer

- Exophytic tumors involving mucosa = Ta
- Extension to the lamina propria = T1
- Flat tumors = Tis
- ~75% of newly diagnosed patients with bladder cancer are NMIBC
- Bacillus Calmette-Guérin (BCG) recommended treatment for intermediate and high-risk disease
  - Pitfalls of treatment
    - BCG shortage
    - Side effects
    - Weekly treatments

Flaig T, et al. *J Natl Compr Canc Netw*. 2020.

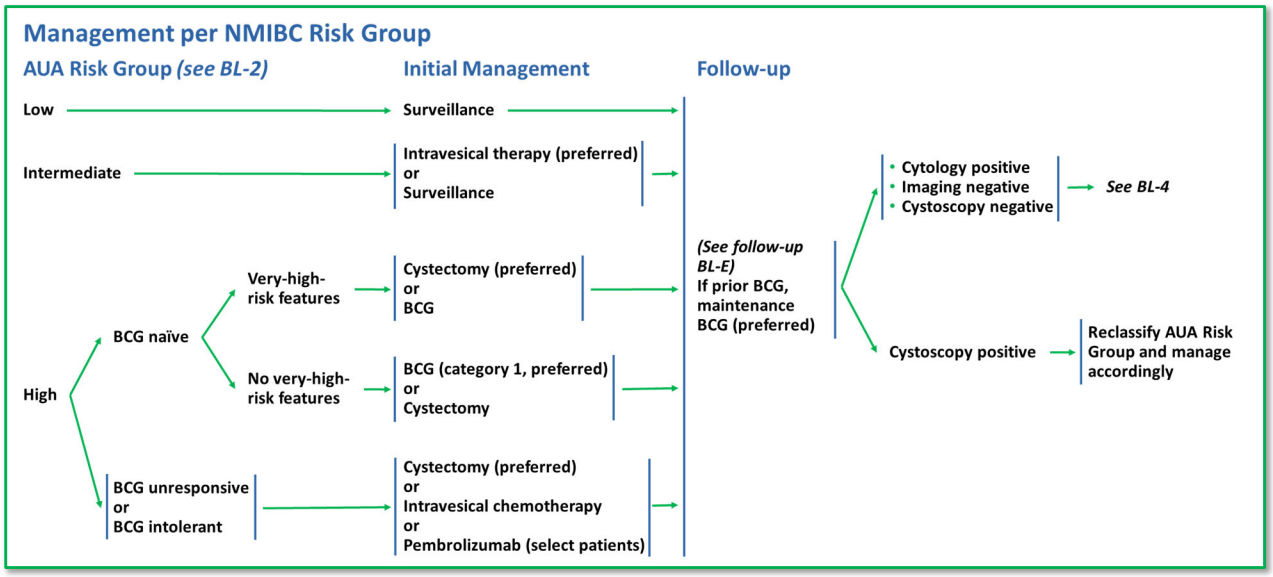
AUA Risk Stratification for Non–muscle-invasive Bladder Cancer

Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential	• Low-grade urothelial carcinoma • T1 or • >3 cm or • Multifocal or • Recurrence within 1 year	• High-grade urothelial carcinoma • CIS or • T1 or • >3 cm or • Multifocal
• Low-grade urothelial carcinoma • Ta and • ≤3 cm and • Solitary	• High-grade urothelial carcinoma • TA and • ≤3 cm and • Solitary	• Very high-risk features (any) • BCG unresponsive • Variant histologies • Lymphovascular invasion • Prostatic urethral invasion

*Within each of these risk strata, an individual patient may have more or less concerning features that can influence care.

NCCN Guidelines. Bladder Cancer. v2.2022; Chang SS, et al. *J Urol.* 2016.

Management per NMIBC Risk Group



NCCN Guidelines. Bladder Cancer. v2.2022.

NMIBC Guidelines 2022

European Association of Urology

Risk Group	
Low Risk	• A primary, single, Ta/T1 LG/G1 tumor <3 cm in diameter without CIS in a patient <70 years • A primary Ta LG/G1 tumor without CIS with at most ONE of the additional clinical risk factors (see above)
Intermediate Risk	Patients without CIS who are not included in either the low, high, or very-high-risk groups
High Risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very-high-risk group • All CIS patients, EXCEPT those included in the very-high-risk group Stage, grade with additional clinical risk factors • Ta LG/G2 or T1 G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1 G2 no CIS with at least 1 risk factor
Very High Risk	Stage, grade with additional clinical risk factors • Ta HG/G3 and CIS with all 3 risk factors • Ta G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

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• Eki$B;4
• Q ypxtpi$tetmpev}$xyq sw
• Xyq syv$meq ixiv$B7$gq

Babjuk M, et al. *Eur Urol*. 2022.

AUA 2020–2021—Guideline Update
Key Points

- In a patient fit for surgery with high-grade T1 disease after a single course of induction intravesical BCG, a clinician should offer radical cystectomy.
- In a patient with persistent or recurrent intermediate- or high-risk NMIBC within 12 months of completion of adequate BCG therapy (two induction courses or one induction course plus one maintenance cycle) who is unwilling or unfit for cystectomy, a clinician may recommend clinical trial enrollment or offer alternative intravesical therapy (e.g., valrubicin, gemcitabine, docetaxel, combination chemotherapy) when clinical trials are unavailable. A clinician may also offer systemic immunotherapy with pembrolizumab to a patient with CIS within 12 months of completion of adequate BCG therapy.

Chang SS, et al. *J Urol*. 2016, amended 2020.

Understanding Gaps in Practice in UC Management

Understanding gaps facilitates communication among care teams to optimize treatment selection and decision making.

- NMIBC
  - BCG shortage
- Advanced or mUC
  - Optimizing chemotherapy vs immunotherapy in the front-line setting
  - Selecting appropriate treatment options following progression on chemotherapy or immunotherapy
  - Cost of therapy
  - Role of PD-L1 expression testing
  - Access to ongoing clinical trials
- Next generation of therapies likely to be based on patient-specific targetable mutations or combination chemo-immunotherapy

Drug Approvals in Urothelial Cancer

FDA-approved Drugs for Bladder Cancer

Non–muscle-invasive bladder cancer

- Valrubicin 1998
- BCG 1998
- Pembrolizumab 2020

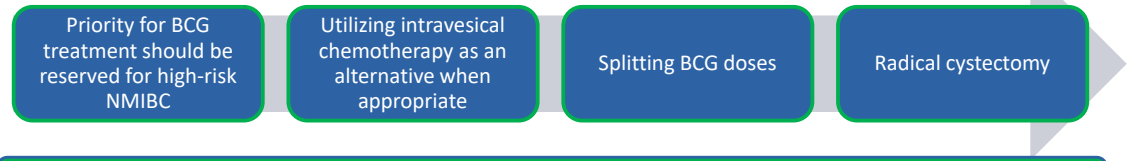
Advanced

- Cisplatin 1993
- Gemcitabine 2008 (European Medicine Agency harmonization)
- Vinflunine 2009 (European Medicine Agency)
- Atezolizumab 2016 (2020 switch maintenance)
- Nivolumab, durvalumab, pembrolizumab, avelumab 2017
- Erdafitinib 2019
- Enfortumab vedotin 2019
- Sacituzumab govitecan 2021

FDA Prescribing Information.

Mitigating BCG Shortages

National Comprehensive Cancer Network (NCCN), American Urological Association (AUA), American Association of Clinical Urologists (AACU), Bladder Cancer Advocacy Network (BCAN), Society of Urologic Oncology (SUO), the Large Urology Group Practice Association (LUGPA), and the Urology Care Foundation (UCF) **issued a notice outlining strategies to maximize care for patients with NMIBC.**



Prognostic Factors Multiple tumors, tumor ≥3 cm, >1 recurrence per year, recurrence within 1 year after transurethral resection	
0	Same as treatment for low-risk disease
1–2	• Single immediate postoperative instillation of intravesical chemotherapeutic drug • Induction + maintenance with either an intravesical chemotherapy or BCG (1 year)
≥3	Same as treatment for high-risk disease

NCCN Guideline. Bladder Cancer. v6.2020; Kamat A, et al. *Lancet.* 2016.

Impact of BCG Shortage
Increased Recurrence and Cystectomy Rates

Characteristics of Treatment and Disease Recurrence According to Group Study

	November 2011–September 2013 Control Group			October 2013–December 2016 Study Group (period of restricted supply)		
	Intermediate Risk (n=131; 68.6%)	High Risk (n=60; 31.4%)	Total (n=191; 100%)	Intermediate Risk (n=140; 63.3%)	High Risk (n=71; 33.6%)	Total (n=211; 100%)
Induction completed, n (%)	125 (95.4)	51 (85.0)	176 (92.1)		61 (85.9)	61 (28.9)
Consolidation completed, n (%)	112 (85.5)	50 (83.3)	162 (84.9)			
Maintenance ≥1 year, n (%)	101 (77.0)	46 (76.7)	147 (77.0)			
Mitomycin C, n (%)				135 (96.4)		
Interruption for grade III toxicity	22 (16.8)	9 (15)	31 (16.2)	2 (1.5)	8 (11.3)	10 (4.8)
Recurrence, n (%)	17 (12.9)	14 (23.3)	31 (16.2)	61 (43.6)	38 (53.5)	99 (46.9)
New course of BCG, n (%)	16 (12.2)	10 (16.6)	26 (13.6)	28 (20.0)	20 (28.1)	48 (22.7)
New course of mitomycin C, n (%)	2 (6.4)		2 (1.0)	21 (15)	7 (9.8)	28 (13.2)
Cystectomy, n (%)		3 (5.0)	3 (1.5)	4 (2.8)	11 (15.5)	15 (7.1)

Recurrence rates: 290% increase
Cystectomy rates: 473% increase

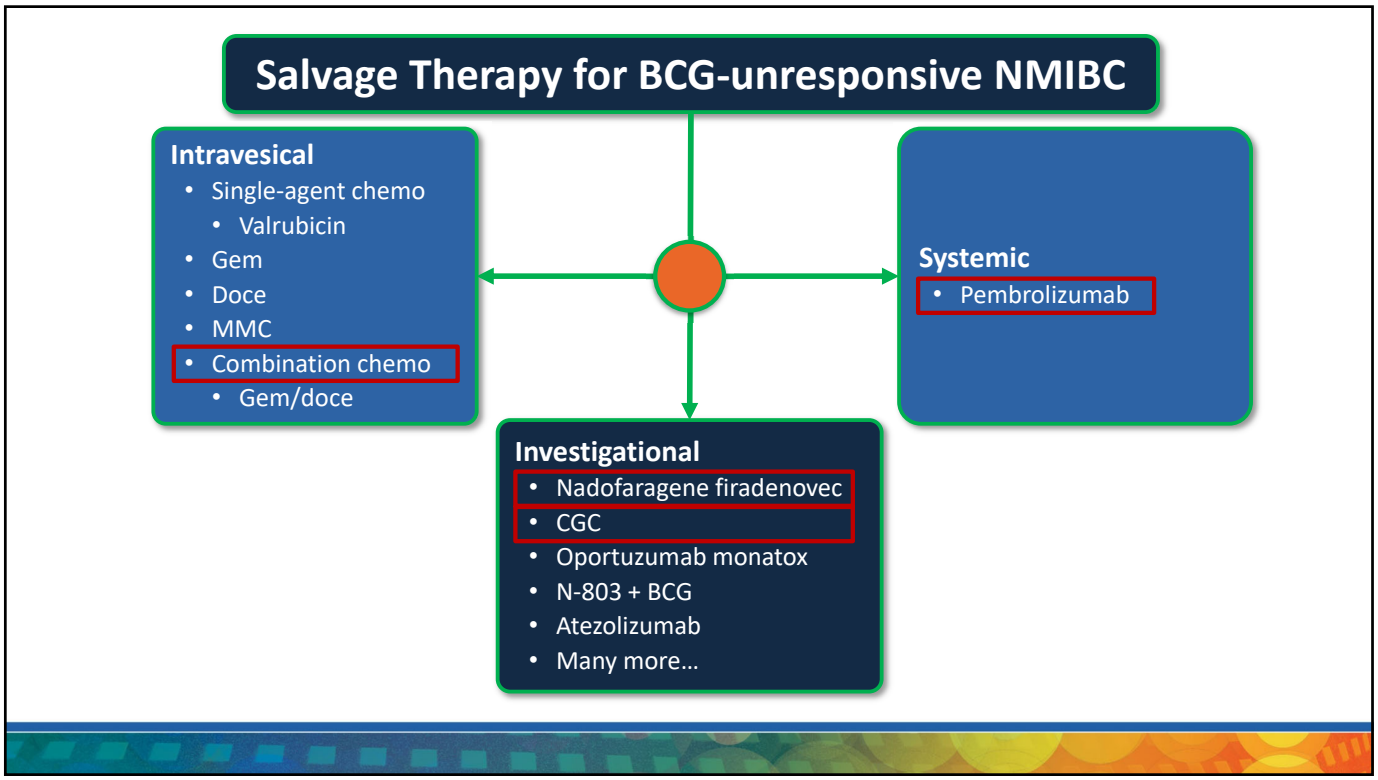
Ourfali S, et al. *Eur Urol Focus.* 2019.

Non–muscle-invasive Bladder Cancer
Options for BCG Unresponsive Disease

But what happens when BCG does not work?

BCG Unresponsive Disease

- Multiple options currently exist for BCG unresponsive disease
  - Intravesical options
  - Systemic therapy
  - Radical cystectomy
- Multiple clinical trials open
  - Intravesical options ± BCG
  - Systemic options ± BCG



Treatment Options for BCG Unresponsive NMIBC

	Options	Pro	Con
PRESENT	**Radical cystectomy with LND and diversion**	• Definitive • LUTS addressed	• Morbidity (competing risks, frailty for this patient)
PRESENT	**Intravesical chemotherapy**	• Avoid major surgery, doublet preferred (gem/docetaxel: 42% 2-year RFS)	• Already has severe LUTS (? tolerability) • Efficacy/durability
PRESENT	**Systemic therapy Pembrolizumab FDA approved 2020**	• Not intravesical therapy (i.e., minimize LUTS) • Avoid major surgery	• Efficacy/durability • Rare, but severe side effects • Cost
FUTURE	**Intravesical therapy** (e.g., nadofaragene, oportuzumab monatox-qqrs) ***Clinical trial**	• Avoid major surgery, early phase data good!	• Already has severe LUTS (? tolerability) • Efficacy/durability

* Clinical trials available at time of discussion

Slide courtesy of Sima Porten, MD.

Intravesical Nadofaragene Firadenovec Gene Therapy for BCG-unresponsive Non–muscle-invasive Bladder Cancer

A Single-arm, Open-label, Repeat-dose Clinical Trial

Vista Trial

Phase 3 Registration Study of Vicineum for BCG-unresponsive NMIBC

Duration of response: 52% of CIS patients who had a CR at 3 months remained disease free for a total of 12 months after starting treatment.

- 40% CR with CIS at 3 months
- Durability of response
  - 52% retain CR at 9 months
  - 39% retain CR at 15 months

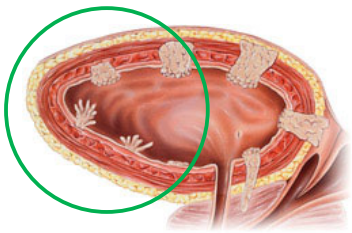
Dickstein RJ, et al. *J Urol*. 2018.

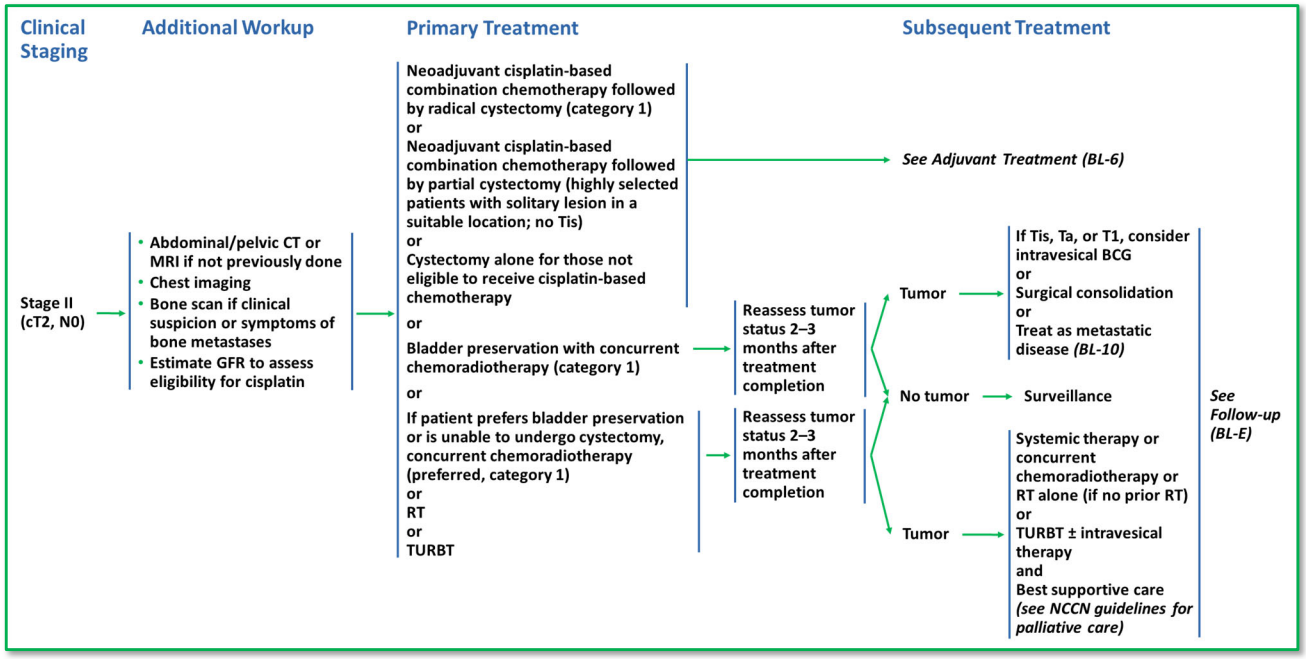
Muscle-invasive Bladder Cancer

(MIBC)

Muscle-invasive Bladder Cancer

- Invasion into the detrusor muscle layer = T2
- Extension into perivesical tissue = T3
- Invasion into the surrounding organs = T4
- Treatments
  - Radical cystectomy
  - Bladder sparing approach with trimodal therapy





NCCN Guidelines. Bladder Cancer. v2.2022.

Systemic Chemotherapy

	Median Survival	Response Rates	Deaths (Toxicity)	Neutropenic Sepsis*	Mucositis* (Grade 3/4)
Gemcitabine/ cisplatin	13.8 months	49.4%	1%	1%	1%
MVAC	14.8 months	45.7%	3%	12%	22%

- GC vs MVAC (category 1)
  - OS and TTP similar at 19 months and 5 years

	CR*	Overall Response	Median Survival	TTP	FN*
ddMVAC	21%	62%	15.5 months	11.1 months	10%
MVAC	9%	50%	14.1 months	9.6 months	26%

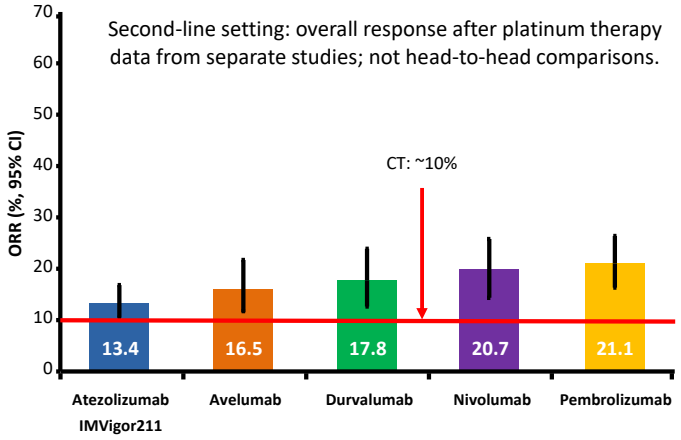
*p<0.05

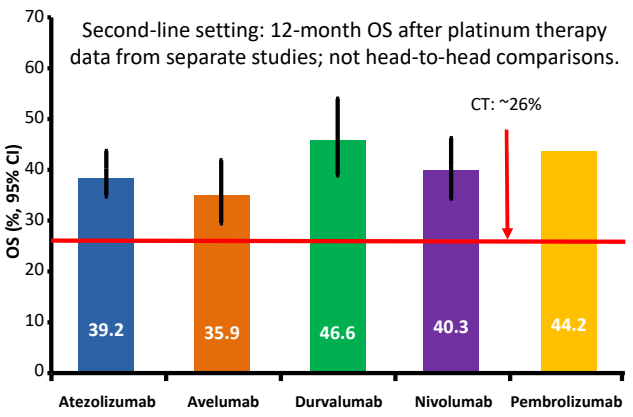
- ddMVAC vs MVAC (category 1)
  - 24.6% vs 13.2% alive at 7.3 years
  - Require growth factor support

FN, febrile neutropenia.

von der Maase, et al. *J Clin Oncol*. 2000; von der Maase, et al. *J Clin Oncol*. 2005; Sternberg, et al. *Eur J Cancer*. 2006; Sternberg, et al. *J Clin Oncol*. 2001; Hayes TG, et al. *Handbook of Prostate Cancer and Other Genitourinary Malignancies*. 2017.

Second-line Setting
Overall Response after Platinum Therapy





Powles T, et al. *Lancet*. 2018; Apolo AB, et al. 2019 ASCO GU Cancers Symposium. Abstract 425; Powles T, et al. *JAMA Oncol*. 2017; Siefker-Radtke AO, et al. 2019 ASCO Annual Meeting. Abstract 4524; Fradet Y, et al. *Ann Oncol*. 2019; O'Donnell P, et al. 2018 AACR Annual Meeting. Abstract CT031;

Does Neoadjuvant Checkpoint Inhibition Have a Role in Muscle-invasive Bladder Cancer?

	Pembrolizumab (n=80 UC)	Atezolizumab (n=95)
% patients cisplatin ineligible	0%	100%
% who also got neoadjuvant chemo	10%	0%
Duration of neoadjuvant therapy	3 cycles (9 weeks)	2 cycles (6 weeks)
Safe?	Yes	Yes
Pathologic complete response rate (pT0)	39%	31%

pT0 rates comparable to those seen with chemo

Gem Cis 15%–26%

ddMVAC 26%–43%

Despite multiple analyses, no predictive biomarker has emerged in this setting.

Necchi A, et al. *Eur Urol*. 2020; Powles T, et al. *Nat Med*. 2019.

Patients "Unfit" for Cisplatin-based Chemotherapy

- Represents 40%–60% of patients with advanced urothelial cancer
- Widely accepted definition includes
  - ECOG 2 or greater
  - Creatinine clearance ≤60 mL/min
  - Grade 2 or greater peripheral neuropathy/hearing loss
  - NYHA class III heart failure

Galsky MD, et al. *J Clin Oncol*. 2011.

Partial Listing *Current Clinical Trials Systemic Therapy + BCG*

- KEYNOTE-676
- ALBAN trial
- CREST trial
- CheckMate 9UT
- New agents and new delivery systems are being formulated and studied

Several Neoadjuvant Immunotherapy Trials Are Ongoing

Phase 3 Trial Primary endpoints	Population	Treatment Arms
NIAGARA[1] pCR, EFS	Resectable muscle-invasive transitional cell bladder cancer that will be surgically treated with radical cystectomy	Durvalumab + chemotherapy → adjuvant durvalumab vs chemotherapy
ENERGIZE[2] pCR, EFS	MIBC patients eligible for radical cystectomy	Nivolumab + chemotherapy or nivolumab/BMS-986205 + chemotherapy → immuno-oncology therapy after radical cystectomy vs chemotherapy
KEYNOTE-905[3] pCR, EFS	MIBC patients eligible for radical cystectomy; cisplatin-ineligible	Pembrolizumab → radical cystectomy + pelvic lymph node dissection → pembrolizumab
KEYNOTE-866[4] pCR, EFS	Cisplatin-eligible MIBC	Perioperative pembrolizumab + neoadjuvant chemotherapy vs perioperative placebo + neoadjuvant chemotherapy
Nivolumab/**NKTR-214**[5] pCR, EFS	MIBC; cisplatin-ineligible	Neoadjuvant and adjuvant nivolumab + NKTR-214 vs nivolumab alone vs SoC

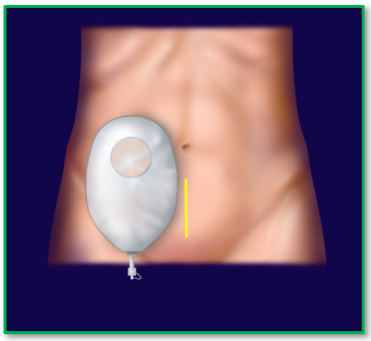
[1]ClinicalTrials.gov. Identifier: NCT03732677; [2]ClinicalTrials.gov. Identifier: NCT03661320; [3]ClinicalTrials.gov. Identifier: NCT03924895; [4]ClinicalTrials.gov. Identifier: NCT03924856; [5]ClinicalTrials.gov. Identifier: NCT04209114.

The Future of Neoadjuvant Therapy

- Neoadjuvant therapies continue to expand
- Improving outcomes will likely evolve to tailor treatments to avoid cystectomy
- Predictive biomarkers and identifying genetic characteristics of an individual's tumors will influence treatment choices and success

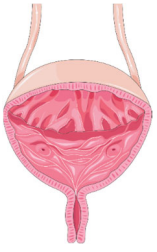
Will We Need to Perform Cystectomy after Successful Neoadjuvant Therapy?

Should We Consider Bladder Sparing Instead of…

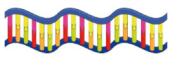


HCRN GU16-257

GC + Nivo with Selective Bladder Sparing



Gemcitabine + cisplatin + nivolumab × 4 cycles



DNA sequencing

Clinical Restaging
Cysto + biopsies
Urine cytology
MRI

Clinical CR → * → **No cystectomy** / **Cystectomy**

No Clinical CR → **Cystectomy**

Determine association between DDR panel and "benefit" in cCR patients

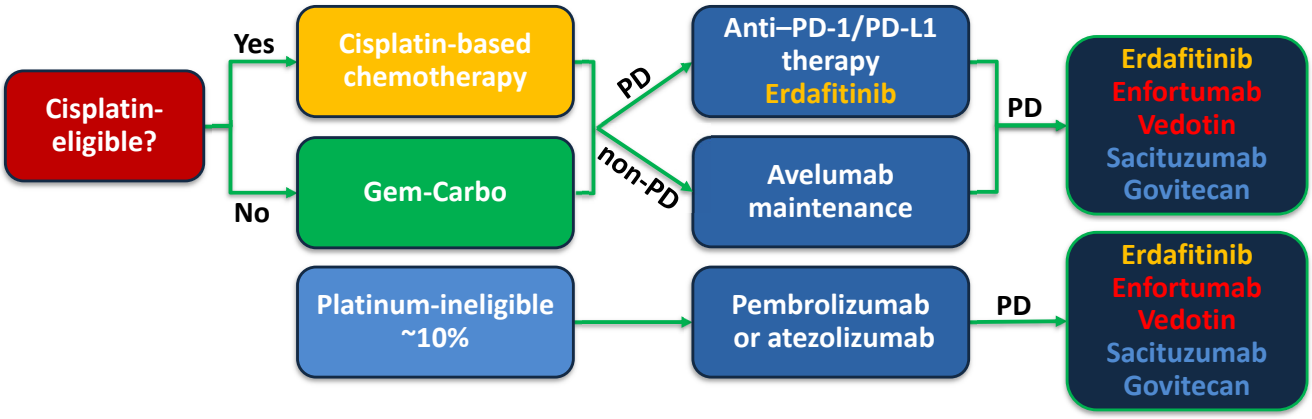
* Treatment based on patient choice

Slide courtesy of Principal Investigator Matt Galsky, MD.

What about Post Cystectomy?

Adjuvant Options Continue to Increase

Current Treatment Options for Advanced UC in 2022



Standard Therapy in Advanced Urothelial Cancer
The Current Paradigm

Setting		Regimen	Response Rate	Median Survival
First line	Cisplatin-eligible	ddMVAC Gem/Cis PGC	40%–50%	12–15 months
	Cisplatin-ineligible	Gem/Carbo	36%–56%	7–9 months
	Platinum-ineligible or PD-L1 positive	Atezolizumab Pembrolizumab	~24%	~15.9 months (atezolizumab)
Second line		Atezolizumab, nivolumab, durvalumab, avelumab, pembrolizumab	15%–19%	7.9–10.3 months
		Single-agent chemo	~10%	5–8 months
Second/third line		Erdafitinib	40%	13.8 months
Third line		Enfortumab vedotin	44%	Median DoR 7.6 months

Loehrer PJ Sr, et al. *J Clin Oncol*. 1992; von der Maase H, et al. *J Clin Oncol*. 2000; Bellmunt J, et al. *J Clin Oncol*. 2012; De Santis M, et al. *J Clin Oncol*. 2012; Linardou H, et al. *Urology*. 2004; Nogué-Aliguer M, et al. *Cancer*. 2003; Rosenberg JE, et al. *Lancet*. 2016; Loriot Y, et al. *N Engl J Med*. 2019; Rosenberg J, et al. *J Clin Oncol*. 2019.

Immune Checkpoint Inhibitors Currently FDA Approved for UC after Platinum-based Therapy

Agent	Target	Dosing Schedule	Post Platinum
Atezolizumab	PD-L1	840 mg Q2W 1,200 mg Q3W 1,680 mg Q4W	Accelerated
Nivolumab	PD-1	240 mg Q2W 480 mg Q4W	Accelerated
Durvalumab	PD-L1	10 mg/kg Q2W	Accelerated
Avelumab	PD-L1	800 mg Q2W	Accelerated
Pembrolizumab	PD-1	200 mg Q3W 400 mg Q6W	Level 1*

*Dosing regimen of 400 mg every 6 weeks is approved under accelerated approval.

Adapted from Ribas A. *N Engl J Med*. 2012.

Clinical Trial Update

- Select ICI Trials
  - IMvigor 210
  - CheckMate 275
  - Study 1108
  - JAVELIN, solid tumor
  - Keynote 045
  - Keynote 052
  - TROPHY-U-01, sacituzumab govitecan
  - PIVOT-02, bempegaldesleukin (NKTR-214)
  - IMvigor010, adjuvant atezolizumab vs observation
- New combinations are being evaluated to increase the efficacy of PD-1/PD-L1 inhibition
- Adjuvant therapy post cystectomy with atezolizumab does not improve PFS
- All patients should be check for FGFR3 expression
- Novel agents like infigratinib, sacituzumab govitecan, and bempegaldesleukin have promising activity in patients who have progressed on previous therapies

Novel Therapies

Antibody Conjugates	FGFR Inhibitors
Sacituzumab govitecan	Erdafitinib
Enfortumab vedotin	

Metastatic Bladder Cancer

(mBC)

Current Treatment Options for Metastatic Urothelial Cancer (mUC), June 2022

Therapy	First-line	Maintenance Non-PD	Post-platinum PD	Post-IO
Platinum (cisplatin or carboplatin)	Platinum-eligible			
Immunotherapy (IO)	Platinum-ineligible (pembrolizumab atezolizumab)	Avelumab	Pembrolizumab Nivolumab Avelumab	
Antibody-drug conjugates (ADCs)	? EV+ pembrolizumab (EV 103, 302)		Enfortumab vedotin (EV) Sacituzumab govitecan (SG)	
FGFR inhibitor			Erdafitinib	
Other targeted therapies (Her2, MET, VEGF, PARP, AR, etc.)	NEED INNOVATIVE TRIALS!			

Slide courtesy of Shilpa Gupta, MD.

Advanced Urothelial Cancer Therapeutics
Sequencing Questions

- "Relative" wealth of therapeutic options creates challenges
- NGS testing for urothelial cancer
- Timing of FGFR therapy in appropriate patients (i.e., prior/post IO Rx)
- Status of IO/chemo Rx combination therapies
- Is single-agent "salvage" chemotherapy now a thing of the past?

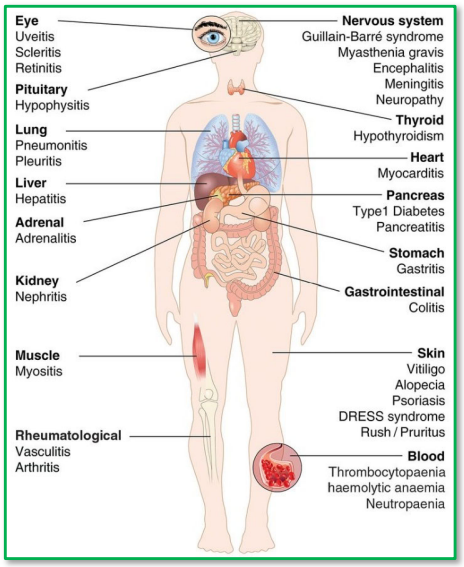
NGS=Next-Generation Solution For Genomic Profiling; FGFR=fibroblast growth factor receptors; IO=Immuno-oncology

Identification and Management of Immune-mediated Adverse Events

(imAEs)

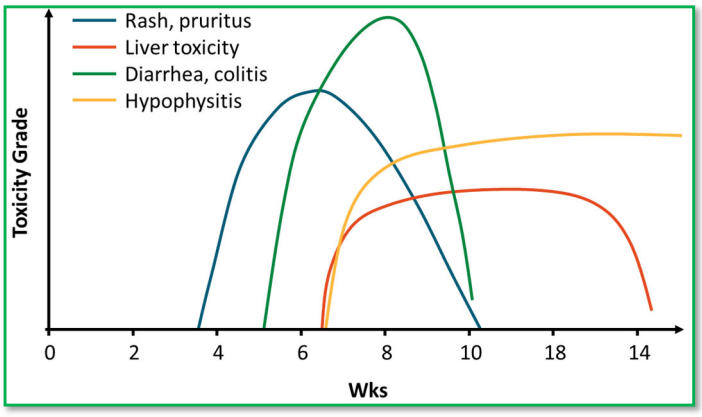
Immune-mediated Adverse Events *(imAEs)*

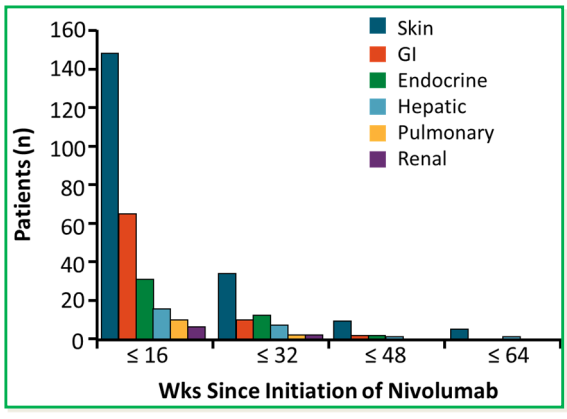
- ICIs introduce the potential for transformative, durable responses in multiple malignancies
- ICIs also introduce the potential for new toxicity
- imAEs
  - Activation of immune cells in non-tumor compartments
  - Can mimic autoimmune conditions



Varricchi G, et al. *ESMO Open*. 2017.

Onset of imAEs





Weber JS, et al. *J Clin Oncol*. 2017.

PD-1/PD-L1 Safety (Grade III–IV Toxicity)
Per UC Trials

Pembrolizumab	Atezolizumab	Nivolumab	Durvalumab	Avelumab
Fatigue (4%)	Urinary tract infection (9%)	Fatigue (1.9%)	Increased LFTs (2.6%)	Hyponatremia (16%)
Muscle spasms (2%)	Anemia (8%)	Diarrhea (1.9%)	Hypertension (1%)	Fatigue (7%)
Decreased appetite (1%)	Fatigue (6%)	Asthenia (1.5%)	Diarrhea (0.5%)	Anemia (6%)
Diarrhea (1%)	Dyspnea (4%)	Rash (1.1%)	Anemia (0.5%)	Hypertension (5%)

Balar A, et al. *Lancet Oncol.* 2017; Sharma P, et al. *Lancet Oncol*. 2017; Bellmunt J, et al. *N Engl J Med*. 2017; Apolo A, et al. ESMO 2017 Congress. Abstract 4042; Balar A, et al. 2016 ASCO Annual Meeting. Abstract LBA4500; Heery C, et al. *Lancet Oncol*. 2017; Powles T, et al. *JAMA Oncol*. 2017; Rosenberg J, et al. *Lancet*. 2016.

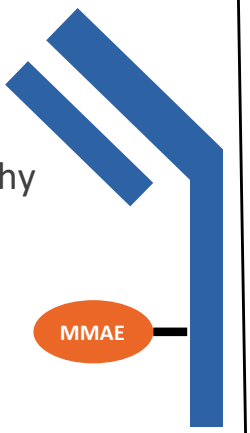
Novel Therapy
Erdafitinib Clinical Pearls

- Novel mechanism of action, first targeted therapy and orally available option in UC treatment
  - MOA: pan-FGFR inhibitor (FGFR 1–4)
  - **Approved** for FGFR 2–3 mutations or fusions
- 8 mg PO daily (with or without food) with dose increase to 9 mg daily if criteria are met
  - Day 14 to 21 phosphorus <5.5 mg/dL
  - No ocular disorders
  - No grade ≥2 AEs
- Increase occurred in **41% of patients**
- Restricted distribution (US Bioservices specialty pharmacy): tablets: 3 mg, 4 mg, 5 mg

Adverse Reaction (8 mg/day)	All Grade (%)	Grade 3–4 (%)
Any	100	67
Gastrointestinal disorders	92	24
Metabolism and nutrition disorders	90	16
General disorders and admin site conditions	69	13
Skin and subcutaneous disorders	75	16
Eye disorders	62	11
Nervous system disorders	57	5
Infections and infestations	56	20
Respiratory, thoracic, and mediastinal disorders	40	7
Renal and urinary tract disorders	38	10
Musculoskeletal and connective tissue disorders	31	0

FDA Prescribing Information.

Antibody-drug Conjugates in Advanced Urothelial Cancer



- Peripheral neuropathy
- Rash
- Hyperglycemia

Enfortumab vedotin

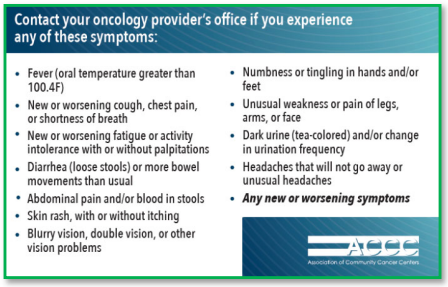
- Febrile neutropenia
- Diarrhea
- Nausea

Sacituzumab govitecan

O'Donnell PH, et al. *Ann Oncol*. 2020; Alva A, et al. *Ann Oncol*. 2020.

Key Questions to Ask Patients

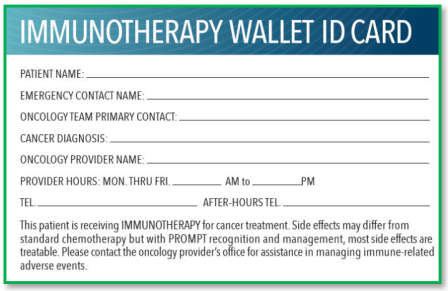
- Have you ever received an immune checkpoint inhibitor/immunotherapy?
  - imAEs can occur after discontinuation of ICIs
- Do you have an immunotherapy wallet card?
  - Wallet cards list the type of immunotherapy, key symptoms, and how to notify HCPs
- Do you have an autoimmune condition?
  - ICIs may exacerbate preexisting autoimmune conditions



Contact your oncology provider's office if you experience any of these symptoms:

- Fever (oral temperature greater than 100.4F)
- New or worsening cough, chest pain, or shortness of breath
- New or worsening fatigue or activity intolerance with or without palpitations
- Diarrhea (loose stools) or more bowel movements than usual
- Abdominal pain and/or blood in stools
- Skin rash, with or without itching
- Blurry vision, double vision, or other vision problems
- Numbness or tingling in hands and/or feet
- Unusual weakness or pain of legs, arms, or face
- Dark urine (tea-colored) and/or change in urination frequency
- Headaches that will not go away or unusual headaches
- ***Any new or worsening symptoms***

ACCC Association of Community Cancer Centers



IMMUNOTHERAPY WALLET ID CARD

PATIENT NAME: _____

EMERGENCY CONTACT NAME: _____

ONCOLOGY TEAM PRIMARY CONTACT: _____

CANCER DIAGNOSIS: _____

ONCOLOGY PROVIDER NAME: _____

PROVIDER HOURS: MON. THRU FRI. _____ AM to _____ PM

TEL. _____ AFTER-HOURS TEL. _____

This patient is receiving IMMUNOTHERAPY for cancer treatment. Side effects may differ from standard chemotherapy but with PROMPT recognition and management, most side effects are treatable. Please contact the oncology provider's office for assistance in managing immune-related adverse events.

Postow MA, et al. *N Engl J Med*. 2018; Brahmer JR. *J Clin Oncol*. 2018; Menzies AM, et al. *Ann Oncol*. 2017; Johnson DB, et al. *JAMA Oncol*. 2016.

PD-1/PD-L1 Education Principles

Prior to Start

- Document any underlying conditions
- History of autoimmune diseases
- Medication history
- Reproductive status
- Breastfeeding status
- Provide wallet card or other identification

Patient Instructions

- Notify HCPs of new signs and symptoms
- Fatigue, rash, cough, SOB, muscle pain, weight loss, etc.
- Symptoms should be monitored for 1 year after completion
- Medication changes and vaccines

Toxicity Management

- Review medications for DDIs
- Symptomatic management for mild to moderate irAEs
  - Supportive care
  - Hormone therapy
  - May delay until recovery
- Severe irAEs
  - Discontinue treatment
  - Steroids and other immunosuppressants
  - Hospitalization may be required

NCCN Guidelines. Management of Immunotherapy-related Toxicities. v1.2020.

Education Is KEY!

- Information about mechanism of action
- Understanding risks of imAEs
- How checkpoint inhibitors differ from chemotherapy and other oral cancer therapies
- Early recognition and treatment of imAEs
- How to recognize imAEs and know to monitor even when treatment has ended
- Importance of ongoing communication with oncology multidisciplinary care team
- Early identification of side effects is key
- Educate patients on possible, most common, and most severe imAEs
- Obtain a thorough baseline assessment of your patient prior to initiating treatment
- Perform a symptom check at each follow up to assess for differences from baseline
- Easy access to care and follow up

VanderWalde, et al. *ACCC.* 2018.

Generic Toxicity Management of imAEs

- Corticosteroids remain cornerstone of care for immune-mediated adverse events
  - Resolved most imAEs among UC trials
  - Mild skin reactions can be treated with topical steroids
  - Higher grade/persistent toxicity requires systemic steroids
  - Oral preferred; IV may be used when absorption compromised (i.e., colitis)
- Moderate cases (Grade II)
  - Hold drug, redose if toxicity improves, consider low-dose steroids (prednisone 0.5–1 mg/kg/day)
- Severe cases (Grade III/IV)
  - Start high-dose steroids (prednisone 1–2 mg/kg/day) with a slow taper (≥1 month)
  - Infliximab 5 mg/kg once every 2 weeks can be used
- Endocrine side effects
  - Hormonal replacement

CTCAE Grade	Corticosteroids	Other Adjunctive Therapies	Immunotherapy Action
1	Not required	Not required	Continue
2	Topical or systemic steroids	Not required	Hold temporarily
3	Systemic steroids	If no response to steroids after 3–5 days	Discontinue and may consider resuming therapy* based on risk/benefit
4	Systemic steroids	If no response to steroids after 3–5 days	Discontinue

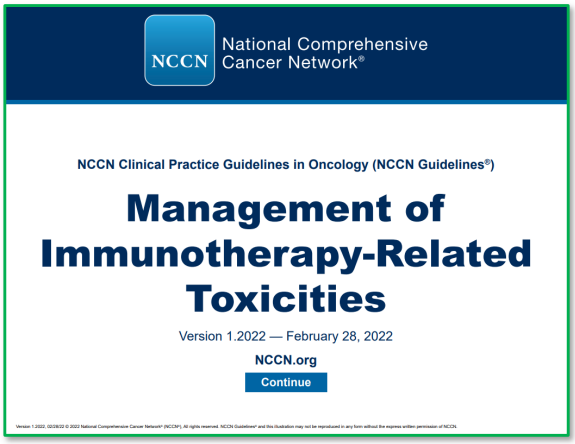
*Doses are either given in full or held in full; there are no dose reductions.

Petrylak DP. *Clin Genitourin Cancer*. 2017; Weber J, et al. *J Clin Oncol*. 2012; Brahmer JR, et al. *J Clin Oncol*. 2018.

Resources for Management of imAEs

Guidelines

NCCN Guidelines in Oncology for Management of Immunotherapy-related Toxicities


NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

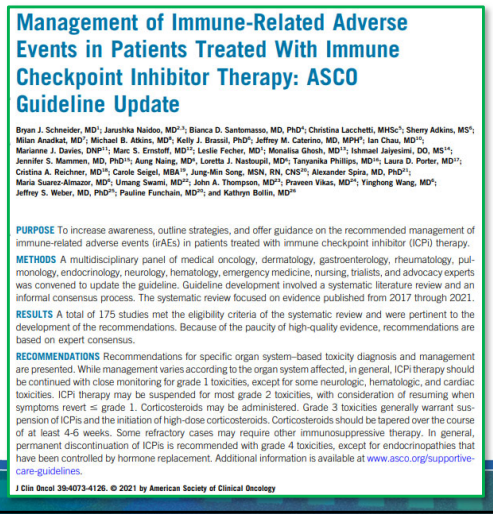
Management of Immunotherapy-Related Toxicities

Version 1.2022 — February 28, 2022

NCCN.org

Continue

ASCO Clinical Practice Guideline on Management of Immune-related Adverse Events


Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

Bryan J. Schneider, MD[1]; Jarushka Naidoo, MD[2,3]; Bianca D. Santomasso, MD, PhD[4]; Christina Lacchetti, MHSc[5]; Sherry Adkins, MS[5]; Milan Anadkat, MD[7]; Michael B. Atkins, MD[8]; Kelly J. Brassil, PhD[9]; Jeffrey M. Caterino, MD, MPH[9]; Ian Chau, MD[10]; Marianne J. Davies, DNP[11]; Marc S. Ernstoff, MD[12]; Leslie Fecher, MD[7]; Monalisa Ghosh, MD[13]; Ishmael Jaiyesimi, DO, MS[14]; Jennifer S. Mammen, MD, PhD[15]; Aung Naing, MD[6]; Loretta J. Nastoupil, MD[6]; Tanyanika Phillips, MD[16]; Laura D. Porter, MD[17]; Cristina A. Reichner, MD[18]; Carole Seigel, MBA[19]; Jung-Min Song, MSN, RN, CNS[20]; Alexander Spira, MD, PhD[21]; Maria Suarez-Almazor, MD[6]; Umang Swami, MD[22]; John A. Thompson, MD[23]; Praveen Vikas, MD[24]; Yinghong Wang, MD[6]; Jeffrey S. Weber, MD, PhD[25]; Pauline Funchain, MD[26]; and Kathryn Bollin, MD[26]

PURPOSE To increase awareness, outline strategies, and offer guidance on the recommended management of immune-related adverse events (irAEs) in patients treated with immune checkpoint inhibitor (ICPi) therapy.

METHODS A multidisciplinary panel of medical oncology, dermatology, gastroenterology, rheumatology, pulmonology, endocrinology, neurology, hematology, emergency medicine, nursing, trialists, and advocacy experts was convened to update the guideline. Guideline development involved a systematic literature review and an informal consensus process. The systematic review focused on evidence published from 2017 through 2021.

RESULTS A total of 175 studies met the eligibility criteria of the systematic review and were pertinent to the development of the recommendations. Because of the paucity of high-quality evidence, recommendations are based on expert consensus.

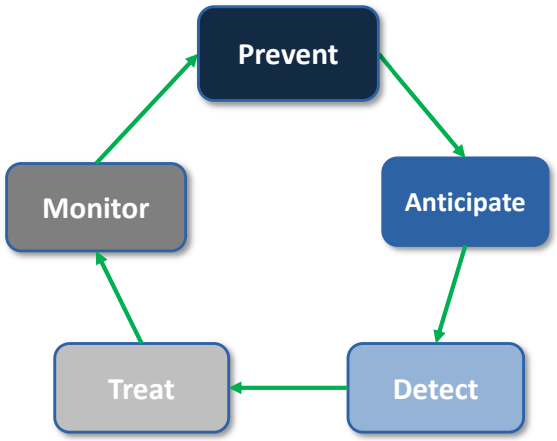
RECOMMENDATIONS Recommendations for specific organ system–based toxicity diagnosis and management are presented. While management varies according to the organ system affected, in general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, except for some neurologic, hematologic, and cardiac toxicities. ICPi therapy may be suspended for most grade 2 toxicities, with consideration of resuming when symptoms revert ≤ grade 1. Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of ICPis and the initiation of high-dose corticosteroids. Corticosteroids should be tapered over the course of at least 4-6 weeks. Some refractory cases may require other immunosuppressive therapy. In general, permanent discontinuation of ICPis is recommended with grade 4 toxicities, except for endocrinopathies that have been controlled by hormone replacement. Additional information is available at www.asco.org/supportive-care-guidelines.

J Clin Oncol 39:4073-4126. © 2021 by American Society of Clinical Oncology

Multidisciplinary Approach

Prevention/Preparing for Treatment

- Patient
  - Baseline assessment
  - Ongoing assessment
- Program/provider
  - Collaborative practice with specialists



Champiat S, et al. *Ann Oncol*. 2016.

Multidisciplinary Care *Redefined*

- Checkpoint blockade will likely be part of the treatment paradigm in NMIBC
- Ideal model will involve co-management
  - Expertise of both medical oncology and urologic oncology requisite for safe, effective care and optimal patient outcomes
    - Safety profiles of ICI differ widely from traditional platinum chemotherapy
    - Failure to promptly recognize and treat certain immune-related adverse events (irAEs) can be life-threatening

Liu YH, et al. *Biomed Pharmacother.* 2019.

Telephone Triage Guidelines

- Phone triage is critical as this is the first touch point with a patient and needs proper evaluation over the phone
- Early identification is critical to minimize severe AEs and keep patients on therapy
- AEs can happen even after treatment discontinuation
- Current triage practices may not consider immunotherapy-specific symptom evaluation
- CTCAE grading criteria is a great tool to educate nursing staff

Patient calls in reporting new diarrhea

Triage RN notified

RN triages the clinical concern

When did symptoms begin?
How many episodes per day?
Any sick contacts?
Any fevers/chills?
Are you able to eat/drink?

Additional IO-specific questions

What is your baseline?
Any associated abdominal pain/ cramping/nausea or vomiting?
Any blood or mucous in the stool?

- Documentation
  - Ideally create standardized documentation
- Determine need for clinic evaluation

Education for Providers

Relevant Providers

- Primary care providers
- Emergency department
- Hospitalists
- Urgent care
- Sub-specialists (IO champions)
- Advanced practice providers
- Pharmacists

Strategies/Tools for Education

- Outreach
- Tumor board
- Grand rounds
- CME access
- National meetings
- "IR-tox team"

IR-tox team, immune-related toxicity team.

Methods of Provider Education

- IR-tox team
- Immune tumor boards
- Immune-toxicity inpatient team
  - Consulted on patients with suspected or confirmed irAEs
  - Provide education to inpatient services

Patient Counseling Strategies

Practical Approaches to Educating Our Patients

Roles and Responsibilities

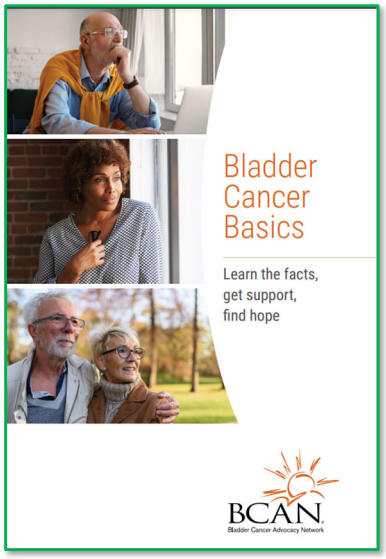
Physicians	Pharmacy, Mid-levels, Nursing	Patients

• Educate patients on available treatment options
• Ensure appropriate workup to optimize treatment selection
• Communicate with care teams the treatment plan to ensure timely initiation
• Implement treatment decisions, monitoring, and follow up
• Discuss clinical trial options with patients
	• P: Discuss and implement strategies to mitigate drug shortages
	• P: Serve as resource for education of staff and patients
	• P: Clinical monitoring and supportive care
	• M: Assist physicians in treatment decisions, monitoring, and follow up
	• N: Recognize symptoms and side effects
	• N: Medication administration and education
		• Inform care team of health history prior to treatment initiation
		• Ask questions on treatment options
		• Notify care team during treatment if
		  • Any symptoms or complications of chemotherapy or irAEs
		  • Fevers, chills, cough, illness
		• Carry wallet card
		• Enroll in clinical trials

Shared responsibilities: the needs of patients come first

Emotional Support Resources

- BCAN
  - Survivor 2 Survivor (S2S) program
- Survivorship clinics
- Resources for caregivers



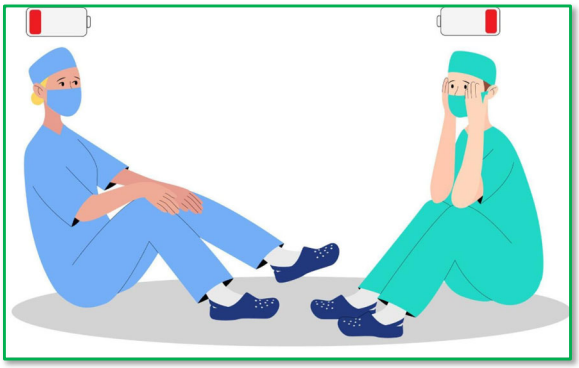
https://bcan.org

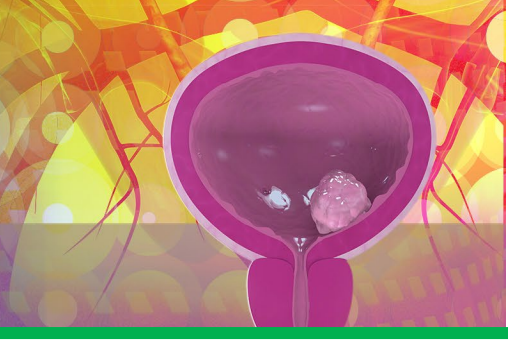
Nursing Resources

Remember, as new therapies emerge, it is a learning curve for ALL.

What can we do?

- Attend conferences
- Share patient experiences
- Connect with your peers





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