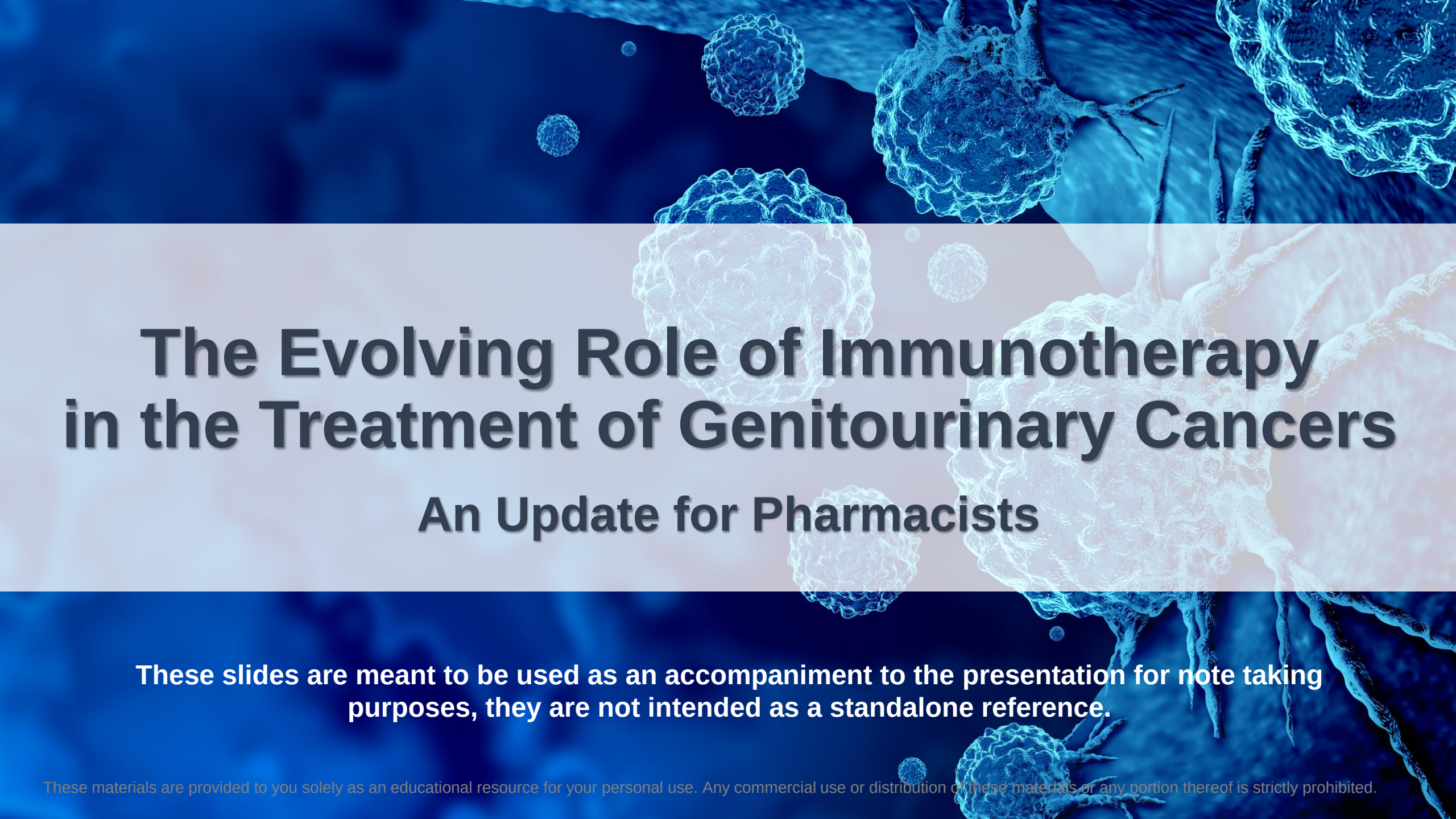
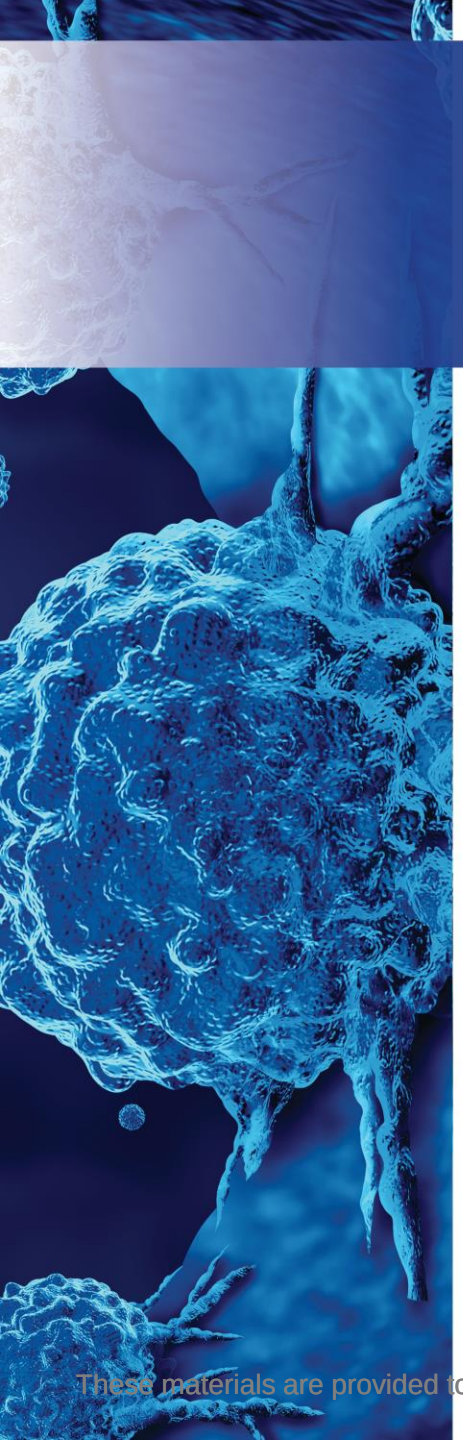


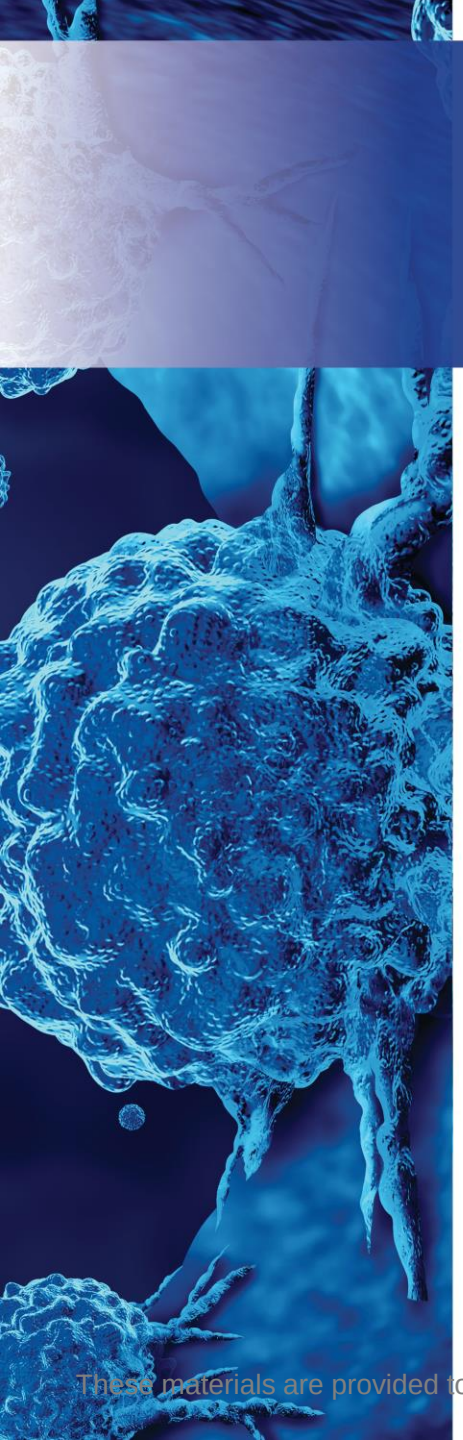
The Evolving Role of Immunotherapy in the Treatment of Genitourinary Cancers

An Update for Pharmacists

These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.



This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from Merck & Company, Inc.



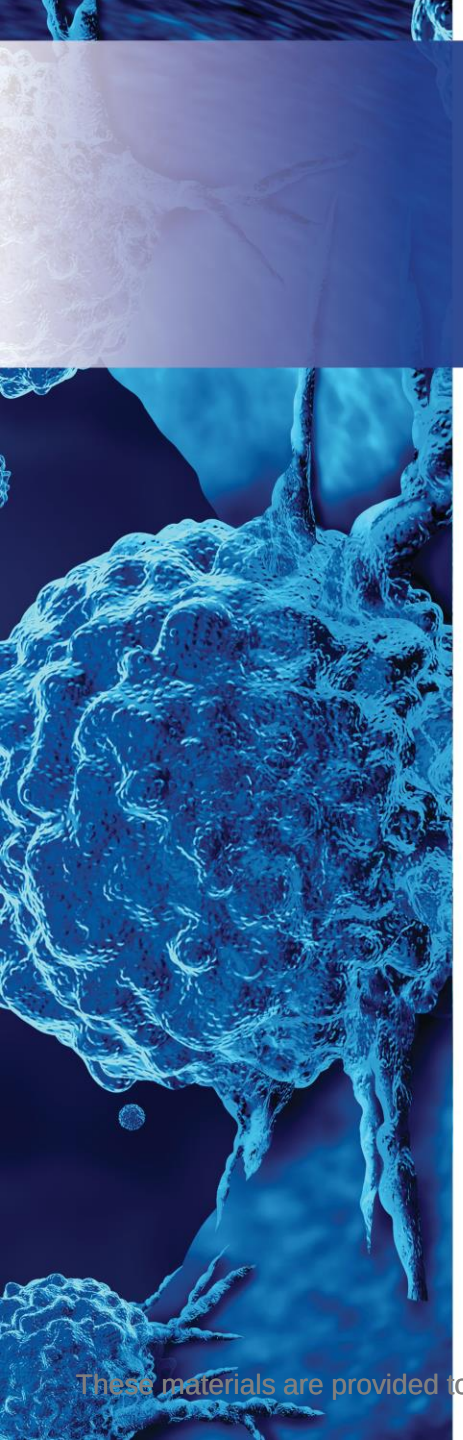
Faculty

Kirollos S. Hanna, PharmD, BCPS, BCOP

Oncology Pharmacy Manager
M Health Fairview, Maple Grove

Assistant Professor of Pharmacy
Mayo Clinic College of Medicine
Rochester, Minnesota

Dr. Hanna currently serves as an Assistant Professor of Pharmacy at the Mayo Clinic College of Medicine in Rochester, MN, and as the Oncology Pharmacy Manager at M Health Fairview, Maple Grove. He also serves as an Associate Editor for the *Journal of the Advanced Practitioner in Oncology*. Dr. Hanna received his PharmD from Florida A&M University, completed his general residency at St. Thomas Hospital in Nashville, TN, and his oncology residency at St. Luke's Mountain States Tumor Institute in Boise, ID. He is board certified in Oncology Pharmacy and Pharmacotherapy. Dr. Hanna's research interests are focused on B-cell malignancies and genitourinary cancers.



Disclosures

Dr. Hanna has disclosed that he has served as a paid consultant for AbbVie, Astellas, AstraZeneca, BeiGene, Bristol Myers Squibb, Rigel, and Seagen; and has received fees for other non-CE services from Astellas, BeiGene, Bristol Myers Squibb, and Seagen.

The clinical reviewer, **Lisa Holle, PharmD, BCOP, FHOPA**, has disclosed that she has served as a consultant for McGraw Hill Education and Postgraduate Healthcare Education, LLC (PHE); conducted research for the International Society of Oncology Pharmacy Practitioners; and has received honoraria for continuing education (CE) programs from AXIS Medical Education, Hematology/Oncology Pharmacy Association, HMP CME, Pharmacy Times Continuing Education, and PHE.

Susanne Batesko, RN, BSN, **Robin Soboti, RPh**, and **Susan R. Grady, MSN, RN**, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of PHE CE activities, hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.

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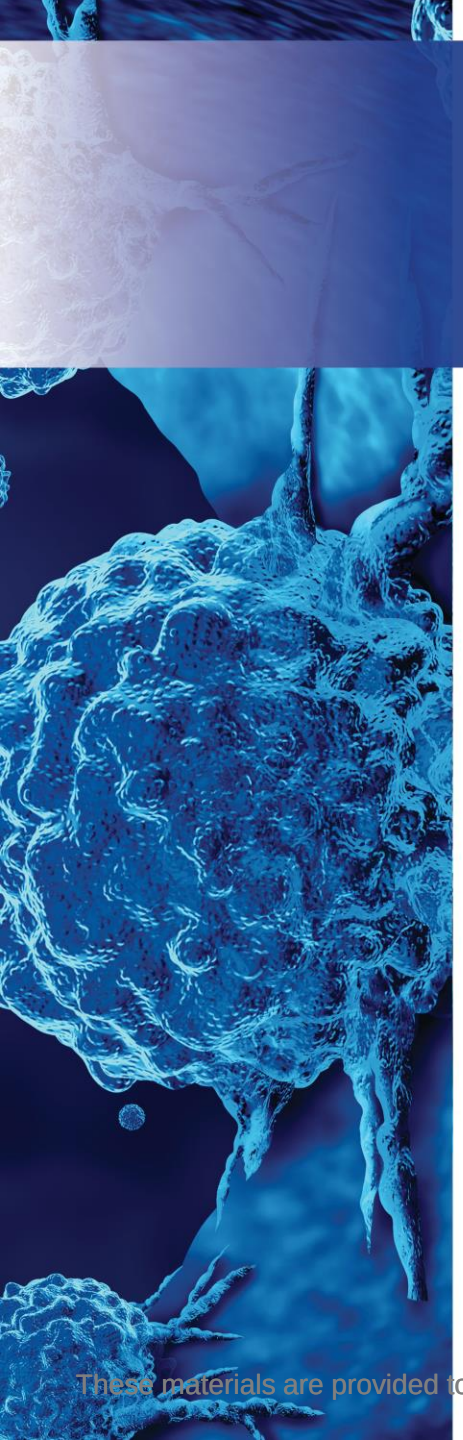

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UAN: 0430-0000-21-059-H01-P
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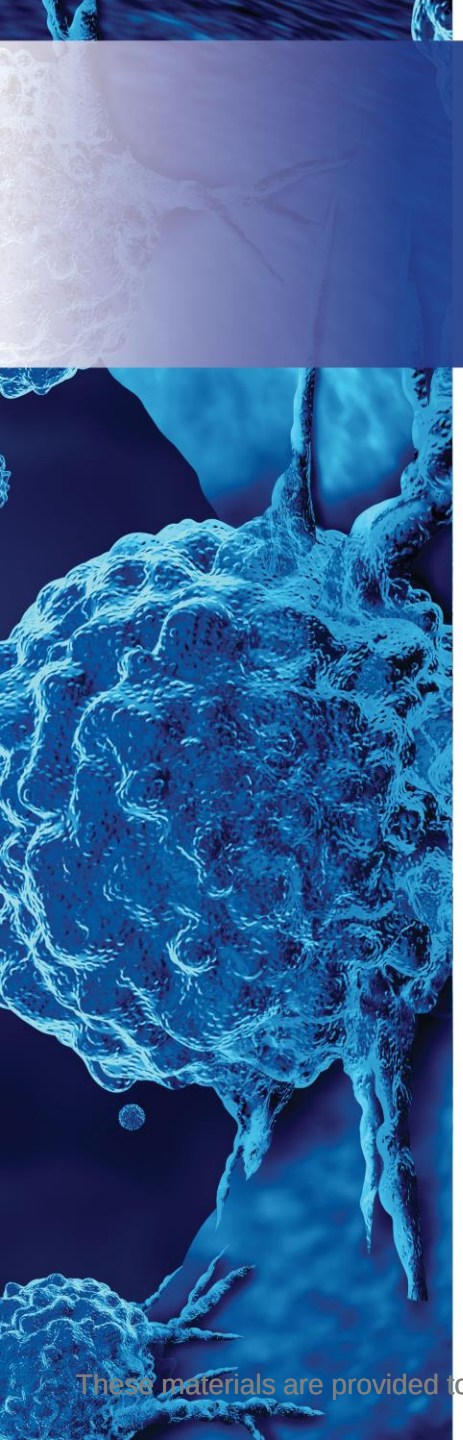
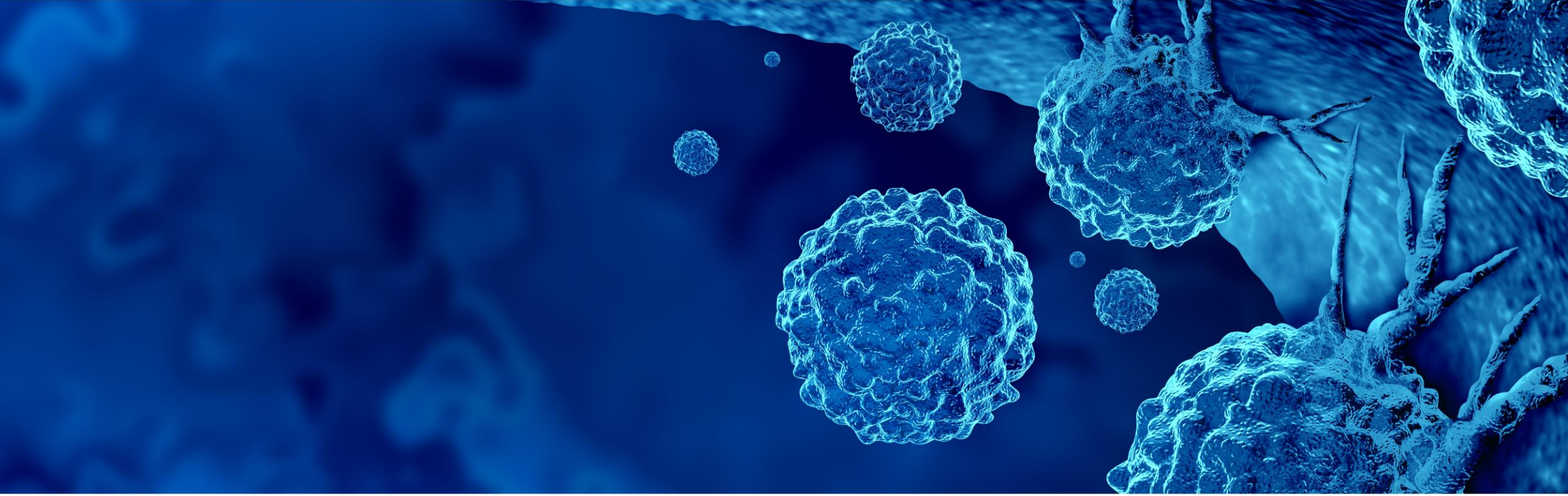
Type of Activity: Application



Learning Objectives

- **Discuss** current and emerging immune checkpoint inhibitor (ICI) use in genitourinary cancer treatment alone and in combination regimens
- **Identify** challenges to and best practices for ICI use in genitourinary cancer treatment
- **Demonstrate** approaches to effectively recognize and manage immune-related adverse events of immunotherapies alone and in combination regimens for genitourinary cancer treatment



Urothelial Carcinoma (UC)

The Evolving Role of Immunotherapy
in the Treatment of Genitourinary Cancers

Bladder Cancer: Background and Risk Factors

- 2021 statistics
  - ≈84,000 new cases
  - ≈17,200 deaths
- 6th most common cancer in the United States
  - 4th leading cancer diagnosis in men
  - 8th leading cause of cancer-related deaths in men
- Median age at diagnosis: 73 years
  - 90% are >55 years

- Risk factors
  - Smoking
  - Personal/family history of bladder cancer
  - Pelvic radiation
  - Chronic infection/irritation of urinary tract
  - Obesity
  - Diabetes
  - Sex/race (male/Caucasian)
- No screening recommendations

Siegel RL, et al. *Ca Cancer J Clin.* 2021;71(1):7-33; National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Bladder cancer, v3.2021.

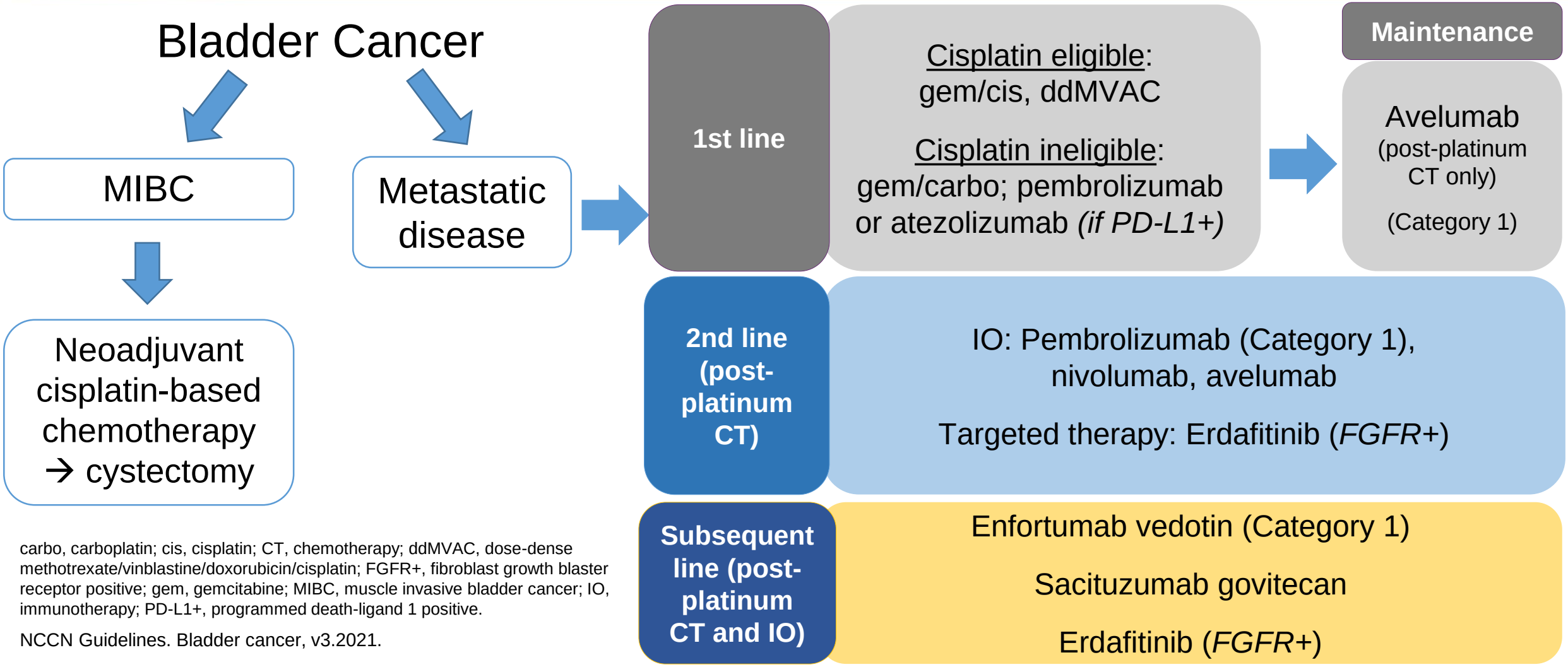
Bladder Cancer: Stages of Disease

- Prognosis, management, and therapeutic goals vary by stage of disease
- 5-year overall survival (OS): 77%

Stage of Bladder Cancer	% at Diagnosis	5-year Survival
Non-muscle invasive (NMIBC)	50%-75%	96% Note: 31%-78% will experience recurrence/ new occurrence within 5 years
Muscle-invasive (MIBC) - Local invasion only - Lymph node involvement	25%-30%	 69% 37%
Metastatic disease (MBC)	<5%	6%

American Cancer Society. *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. Accessed March 31, 2021.

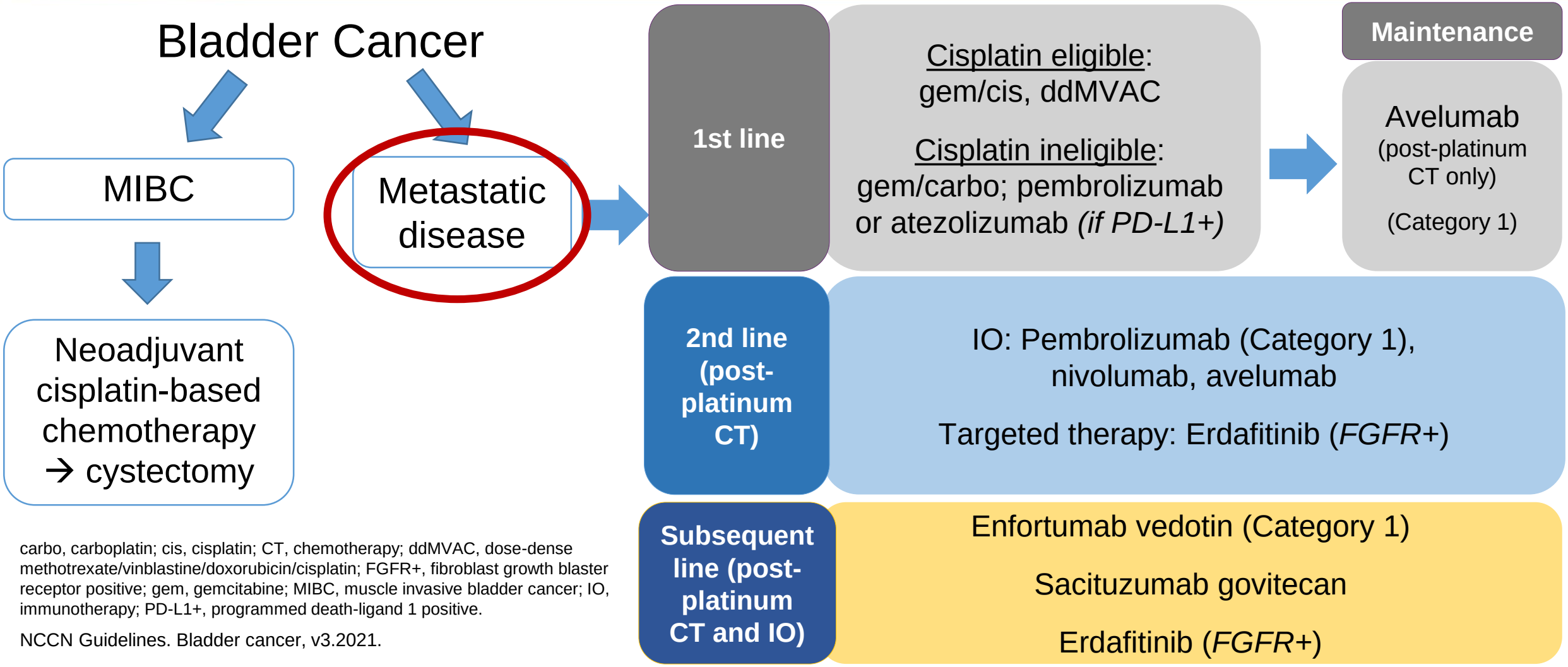
Bladder Cancer: Current Systemic Treatment Options



carbo, carboplatin; cis, cisplatin; CT, chemotherapy; ddMVAC, dose-dense methotrexate/vinblastine/doxorubicin/cisplatin; FGFR+, fibroblast growth blaster receptor positive; gem, gemcitabine; MIBC, muscle invasive bladder cancer; IO, immunotherapy; PD-L1+, programmed death-ligand 1 positive.

NCCN Guidelines. Bladder cancer, v3.2021.

Bladder Cancer: Current Systemic Treatment Options



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NCCN Guidelines. Bladder cancer, v3.2021.

Metastatic Bladder Cancer (MBC): First-line (1L) Platinum Chemotherapy

- **<u>Cisplatin/platinum chemotherapy eligibility</u>**
  - Renal function, performance status, ejection fraction, hearing loss, peripheral neuropathy
- Goals of therapy: prolonging life, maintaining/improving quality of life
- Platinum-based combination chemotherapy x 4-6 cycles
  - Median OS: 9-15 months
  - 5-year OS rate: 15%
  - Overall response rate (ORR): 40%-50%
- Choice of platinum: carboplatin vs cisplatin

Grossman HB, et al. *N Engl J Med*. 2003;349(9):859-866; Choueiri TK, et al. *J Clin Oncol*. 2014;32(18):1889-1894; Plimack ER, et al. *J Clin Oncol*. 2014;32(18):1895-1901; Von der Maase H, et al. *J Clin Oncol*. 2000;18(17):3068-3077; NCCN Guidelines. Bladder cancer, v3.2021.

MBC: 1L Maintenance Immunotherapy

- JAVELIN Bladder 100: phase 3, open-label trial
- N = 700
- Maintenance avelumab/BSC vs BSC
  - CR/PR/SD to platinum/gemcitabine x 4-6 cycles
- Avelumab 10 mg/kg IV D1 and D15 q28d until progression/unacceptable toxicity
  - Premeds for cycles 1-4: antihistamine + acetaminophen

Results	Avelumab vs BSC
Median OS (months) **Overall** **PD-L1+**	**21.4 vs 14.3** **NR vs 17.1**
1-year OS rate (%) Overall PD-L1+	 71.3 vs 58.4 79.1 vs 60.4
PFS (months) Overall PD-L1+	 3.7 vs 2.0 5.7 vs 2.1

Bold, statistically significant; BSC, best supportive care; CR, complete response; IV, intravenous; NR, not reached; OS, overall survival; PD-L1+, programmed death-ligand 1 positive; PFS, progression-free survival; PR, partial response; SD, stable disease.

Powles T, et al. *N Engl J Med*. 2020;383(13):1218-1230.

MBC: 1L Immunotherapy

- Patient eligibility
  - Non-cisplatin chemotherapy candidate **and** PD-L1+
  - Non-platinum chemotherapy candidate
- PD-L1+
  - Pembrolizumab: CPS ≥10
  - Atezolizumab: IC2/3

Results	Pembrolizumab (phase 2; n = 370)	Atezolizumab (phase 2; n = 119)
ORR (%)		
Overall	28.6	24
PD-L1+	47.3	28
CR (%)		
Overall	8.9	8
PD-L1+	20.0	12.5
Median OS (months)		
Overall	11.3	16.3
PD-L1+	18.5	12.3
Median DoR (months)		
Overall	30.1	NR
PD-L1+	NR	NR

CPS, combined positive score; CR, complete response; DoR, duration of response; IC, tumor-infiltrating immune cell; NR, not reached; ORR, overall response rate; OS, overall survival.

Balar AV, et al. *Lancet Oncol*. 2017;18(11):1483-1492; Vuky J, et al. *J Clin Oncol*. 2020;38(23):2658-2666; Balar AV, et al. *Lancet*. 2017;389(10064):67-76; ASCO 2018. www.urotoday.com/conference-highlights/asco-2018/asco-2018-bladder-cancer/104854-asco-2018-atezolizumab-in-first-line-cisplatin-ineligible-or-platinum-treated-locally-advanced-or-metastatic-urothelial-cancer-long-term-efficacy-from-phase-2-study-imvigor210.html. Accessed March 31, 2021.

Recent FDA News (Withdrawals)

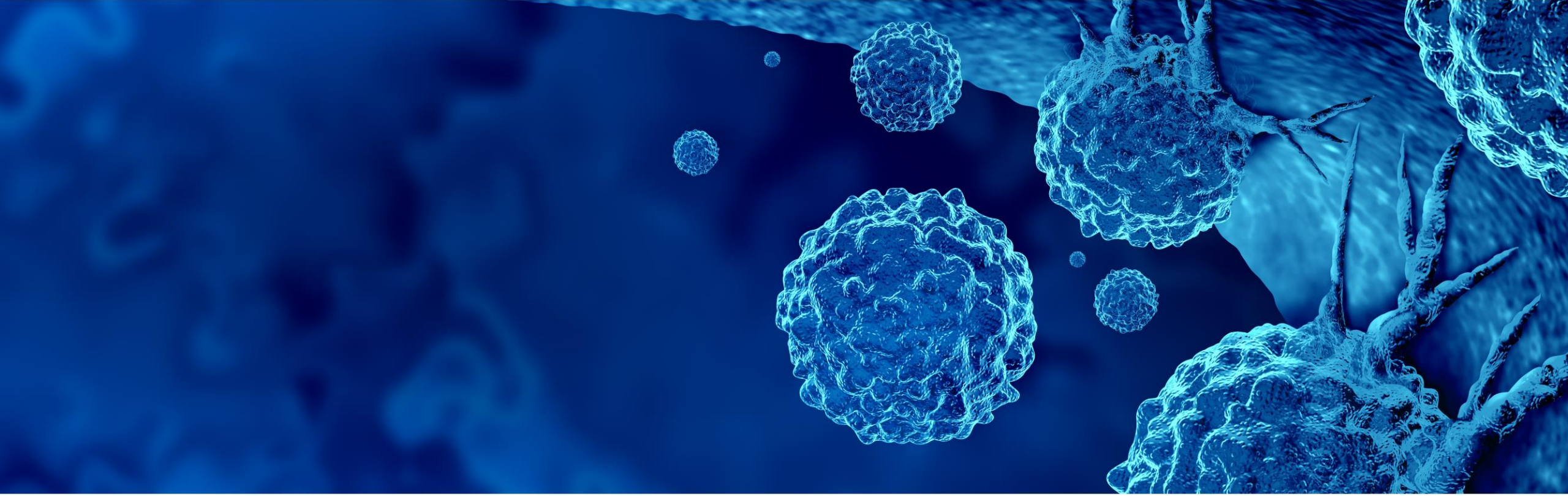
Agent	Indication
Atezolizumab Durvalumab	Locally advanced or metastatic urothelial carcinoma (UC) with disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy

FDA in Brief. March 11, 2021. www.fda.gov/news-events/fda-brief/fda-brief-fda-oncologic-drugs-advisory-committee-review-status-six-indications-granted-accelerated. Accessed March 29, 2021.

MBC: ≥2L Immunotherapy

Results	Pembrolizumab vs Chemo (phase 3; n = 270 vs 272)	Nivolumab (phase 2; n = 265)	Avelumab (phase 1; n = 161)
OS (months) - Overall - PD-L1+	 **10.1 (vs 7.3)** **8.0 (vs 4.0)**	 8.74 11.30	 6.5 8.2
PFS (months) - Overall - PD-L1+	 2.1 (vs 3.3) No difference	 2.00	 1.5 2.9
ORR (%) - Overall - PD-L1+	 21.1 (vs 11.4) 20.3 (vs 6.7)	 19.6 23.8	 17 24
CR rate (%) - Overall - PD-L1+	 9.3 (vs 2.9)	 2	 6 10

Bellmut J, et al. *N Engl J Med*. 2017;376(11):1015-1026; Fradet Y, et al. *Ann Oncol*. 2019;30(6):970-976; Sharma P, et al. *Lancet Oncol.* 2017;18(3):312-322; Patel MR, et al. *Lancet Oncol*. 2018;19(1):51-64.



Select Ongoing Trials in UC

The Evolving Role of Immunotherapy
in the Treatment of Genitourinary Cancers

Advanced Disease Treatment Algorithm

Metastatic Disease State	Setting	Preferred Option	Standard Options
No prior chemotherapy	Cisplatin eligible	Cisplatin/gemcitabine followed by avelumab maintenance	Cisplatin-based combination chemotherapy followed by avelumab maintenance
No prior chemotherapy	Cisplatin ineligible	▪ Gemcitabine/carboplatin ▪ PD-L1–low tumors in fit patients: Gemcitabine/carboplatin followed by avelumab maintenance	Gemcitabine/carboplatin followed by avelumab maintenance ▪ Pembrolizumab ▪ Atezolizumab ▪ Single-agent chemotherapy
Prior platinum chemotherapy or relapse within 1 year of perioperative cisplatin-based therapy		▪ Pembrolizumab OR ▪ If *FGFR2/3* alterations present: Erdafitinib	▪ Atezolizumab ▪ Avelumab ▪ Nivolumab
Prior chemotherapy and immunotherapy		▪ Enfortumab vedotin OR ▪ If *FGFR2/3* alterations present: Erdafitinib	▪ Taxane (US) ▪ Vinflunine (EU)

NCCN Guidelines. Bladder cancer, v3.2021.

Advanced Disease Treatment Algorithm

Metastatic Disease State	Setting	Preferred Option	Standard Options
No prior chemotherapy	Cisplatin eligible	Cisplatin/gemcitabine followed by avelumab maintenance	Cisplatin-based combination chemotherapy followed by avelumab maintenance
No prior chemotherapy	Cisplatin	▪ Gemcitabine/carboplatin OR ▪ If *FGFR2/3* alterations present: Erdafitinib	Gemcitabine/carboplatin followed
or relapse within 1 year of perioperative cisplatin-based therapy			▪ Avelumab ▪ Nivolumab
Prior chemotherapy and immunotherapy		▪ Enfortumab vedotin OR ▪ If *FGFR2/3* alterations present: Erdafitinib	▪ Taxane (US) ▪ Vinflunine (EU)

Clinical trials are critical throughout disease spectrum and treatment settings!

NCCN Guidelines. Bladder cancer, v3.2021.

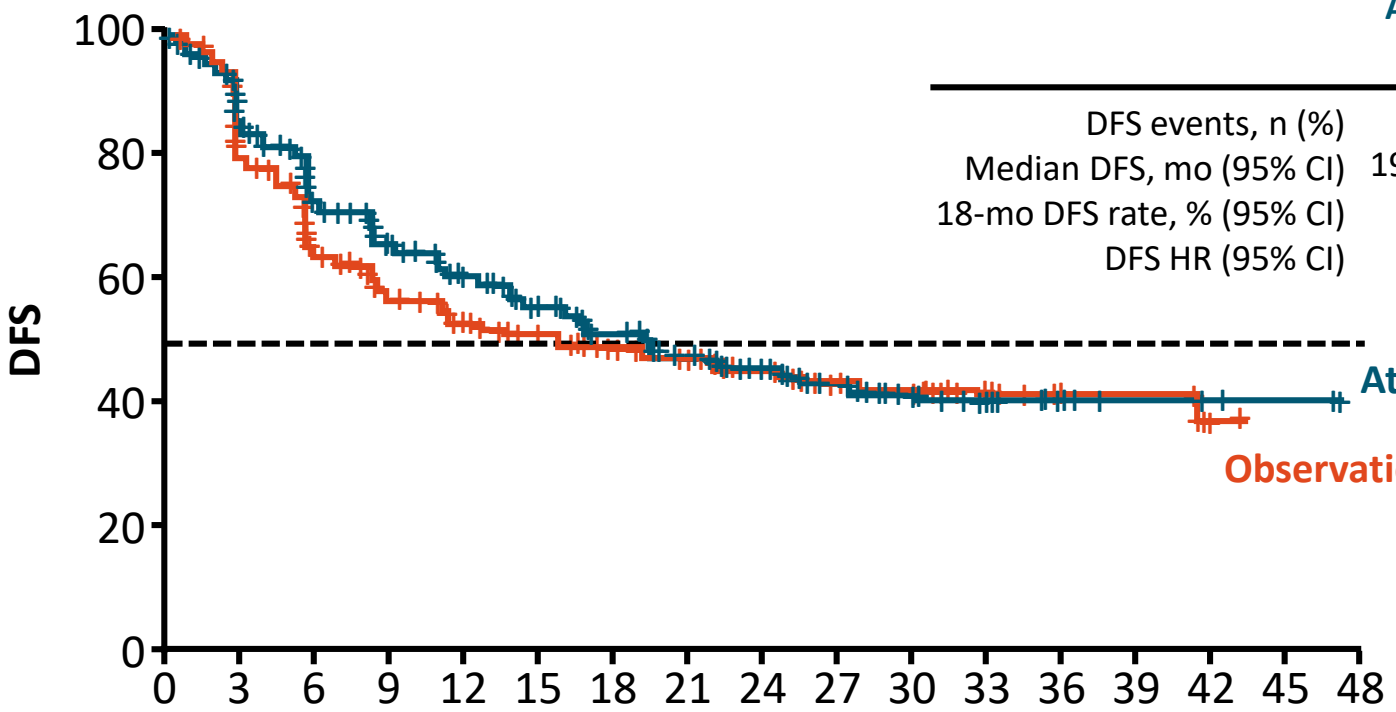
Adjuvant PD-1/PD-L1 Inhibitor Phase 3 Trials in UC

Trial	Population	Control Arm	Experimental Arm	Primary Endpoint
IMvigor010	All-comers MIBC Prior NAC: ≥ pT2 No AC: ≥ pT3	No therapy	Atezolizumab	DFS
CheckMate 274	All-comers MIBC Prior NAC: ≥ pT2 No AC: ≥ pT3	Placebo	Nivolumab	DFS
AMBASSADOR	All-comers MIBC Prior NAC: ≥ pT2 No AC: ≥ pT3	No therapy	Pembrolizumab	DFS/OS

AC, adjuvant chemotherapy; DFS, disease-free survival; MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; pT, primary tumor; OS, overall survival.

ClinicalTrials.gov Identifier: NCT02450331. Updated January 11, 2021. Accessed March 31, 2021.
ClinicalTrials.gov Identifier: NCT02632409. Updated September 10, 2020. Accessed March 31, 2021.
ClinicalTrials.gov Identifier: NCT03244384. Updated March 26, 2021. Accessed March 31, 2021.

IMvigor010: Atezolizumab vs Observation Adjuvant Therapy



	Atezolizumab (n = 406)	Observation (n = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS, mo (95% CI)	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)	0.89 (0.74-1.08; *P* = .2446)	

Patients at Risk, n																
Atezolizumab	406	332	281	248	223	201	169	142	115	92	67	52	15	10	3	2
Observation	403	305	240	211	188	177	156	131	109	87	67	42	17	12	2	

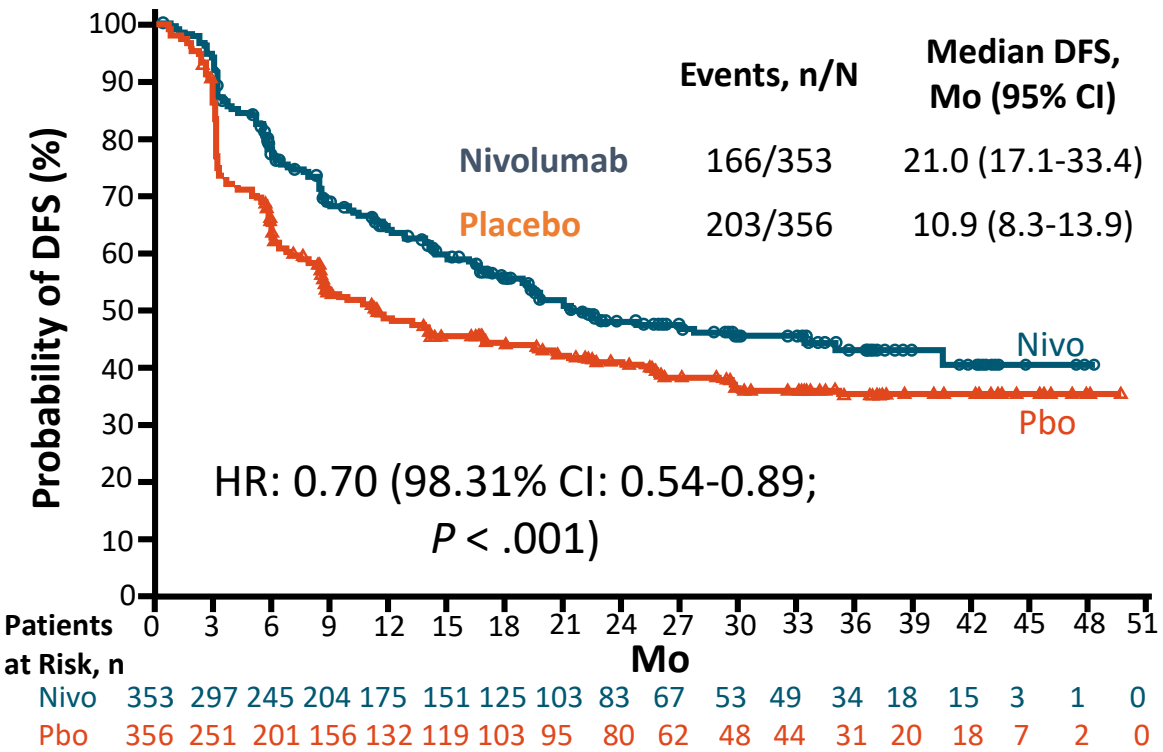
The trial did not meet its primary endpoint of improved disease-free survival (DFS) in the atezolizumab group over observation.

CI, confidence interval; HR, hazard ratio.

Bellmunt J, et al. *Lancet Oncol*. 2021;22(4):525-537.

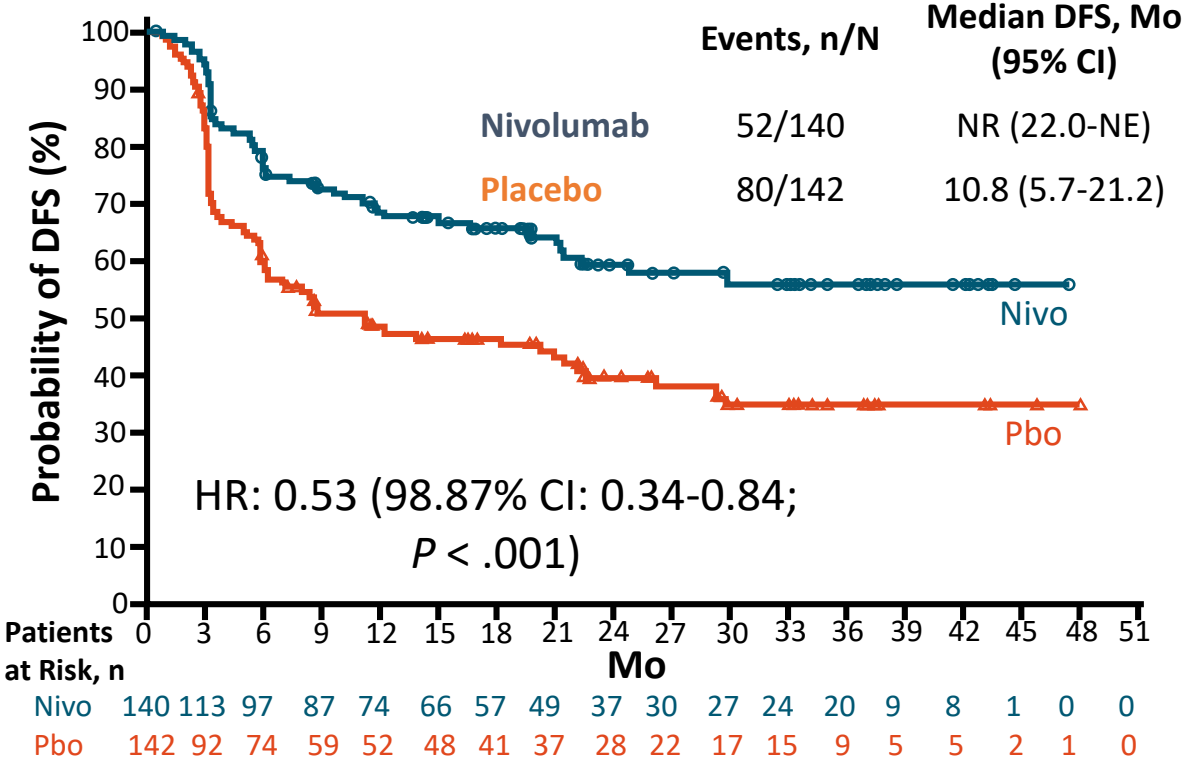
CheckMate 274: DFS With Adjuvant Nivolumab vs Placebo for High-Risk MIBC

Intention-to-Treat (ITT)



Patients at Risk, n																		
Nivo	353	297	245	204	175	151	125	103	83	67	53	49	34	18	15	3	1	0
Pbo	356	251	201	156	132	119	103	95	80	62	48	44	31	20	18	7	2	0

PD-L1 ≥1%



Patients at Risk, n																		
Nivo	140	113	97	87	74	66	57	49	37	30	27	24	20	9	8	1	0	0
Pbo	142	92	74	59	52	48	41	37	28	22	17	15	9	5	5	2	1	0

Bajorin DF, et al. ASCO Genitourinary (GU) Cancers Symposium 2021. Abstract 391.

Phase 1b/2 EV-103 Trial: First-Line Pembrolizumab/Enfortumab Vedotin

Best Overall Response	All Patients (N = 45)
Confirmed ORR, n (%) (95% CI)	33 (73.3) (58.1-85.4)
▪ CR, n (%)	7 (15.6)
▪ PR, n (%)	26 (57.8)
Stable disease (SD), n (%)	9 (20.0)
Progressive disease (PD), n (%)	1 (2.2)
ORR in patients with liver metastasis, n/N (%)	8/15 (53.3)
ORR by PD-L1 status, n/N (%) ▪ High expression ▪ Low expression	 11/14 (78.6) 12/19 (63.2)

- Treatment-naïve patients with locally advanced/ metastatic UC, not eligible for cisplatin-based therapy, regardless of PD-L1 expression levels
  - High RR regardless of PD-L1 expression (ORR, 73.3%)
  - Median PFS: 12.3 months (95% CI, 7.98-NR)
  - 12-month OS rate: 81.6%
- Safety profile for combination therapy as expected with no new safety signal

Breakthrough Therapy Designation granted

- **Future (phase 3 EV-302):** Enfortumab vedotin + pembrolizumab ± platinum-based chemotherapy vs platinum-based chemotherapy
  - Trial is currently recruiting

Rosenberg JE, et al. *J Clin Oncol*. 2020;38(suppl 6):Abstract 441; ClinicalTrials.gov Identifier: NCT04223856. Updated March 26, 2021. Accessed June 15, 2021.

CheckMate 032: Nivolumab vs Nivolumab/Ipilimumab

- Multicenter, international, open-label, randomized phase 1/2 trial
- Locally advanced or metastatic UC; PD within 1 year of ≥1 platinum agent or not chemotherapy candidate
- ECOG PS 0/1; brain metastases and autoimmune disease not allowed

	ORR Nivo 3 mg/kg	ORR Nivo 1 mg/kg + Ipi 3 mg/kg
Overall	20.5% (12.2-31.2)	37% (27.1-47.7)
PD-L1 <1%	20.9% (10-36)	21.4% (10.3-36.8)
PD-L1 ≥1%	19.2% (6.6-39.4)	54.8% (36-72.7)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Sharma P, et al. *J Clin Oncol*. 2019;37(19):1608-1616.

COSMIC-021: Nivolumab and Cabozantinib

- Ongoing, multicenter, single-arm phase 1b study
- Locally advanced or metastatic UC with transitional cell histology, radiographic evidence of progression on/after platinum-containing chemotherapy
- ECOG PS 0/1, and no prior immune checkpoint inhibitors or cabozantinib
- Cabozantinib 40 mg PO once daily PO + atezolizumab 1200 mg IV q3w
- Median PFS: 5.4 months (95% CI, 1.5-7.6)
- Reduction in target lesion size observed in 16 patients (53%)
- No association between PD-L1 expression and tumor response based on preliminary data

Investigator-Assessed Tumor Response (RECIST v1.1 Criteria)	UC Cohort 2 (N = 30)
ORR, % (80% CI)	27 (16-40)
Best overall response, n (%) ▪ CR ▪ PR ▪ SD ▪ PD ▪ Missing	 2 (6.7) 6 (20) 11 (37) 7 (23) 4 (13)
DCR (CR + PR + SD), n (%)	19 (63)
Median DoR, months (range)	NR (1.4+ to 15.6+)
Median time to objective response, months (range)	3 (1-6)

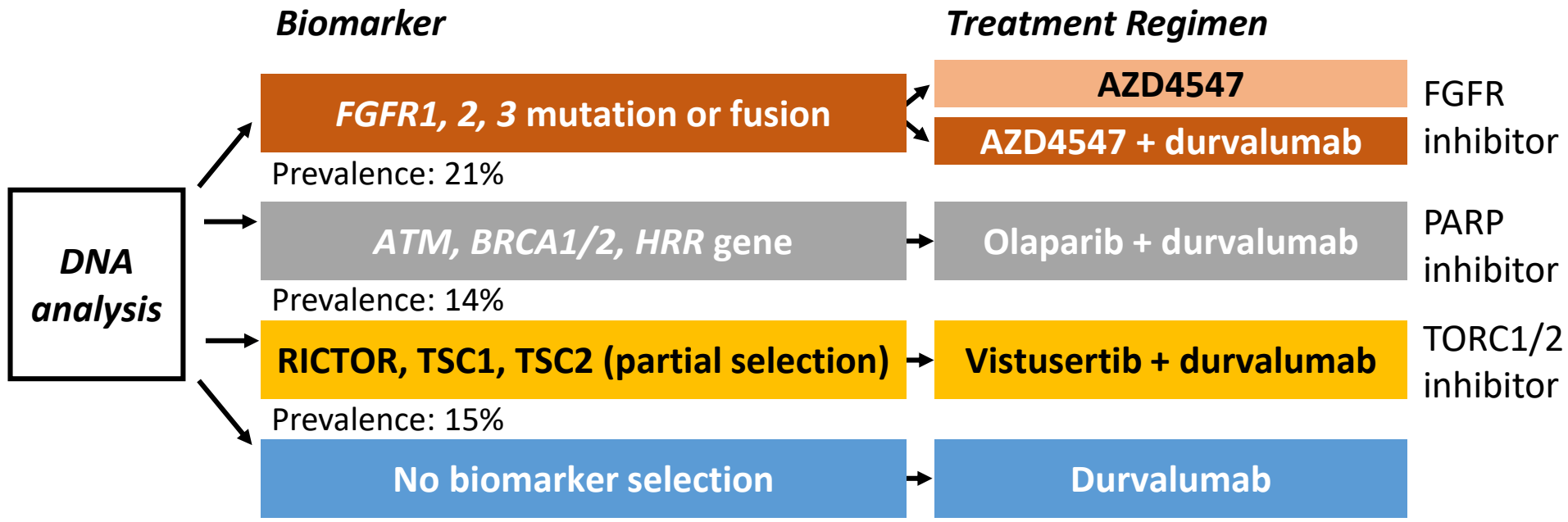
DCR, disease control rate.

Pal SK, et al. *J Clin Oncol*. 2020;38(suppl 15):Abstract 5013.

BISCAY: Biomarker-Directed, Randomized Trial

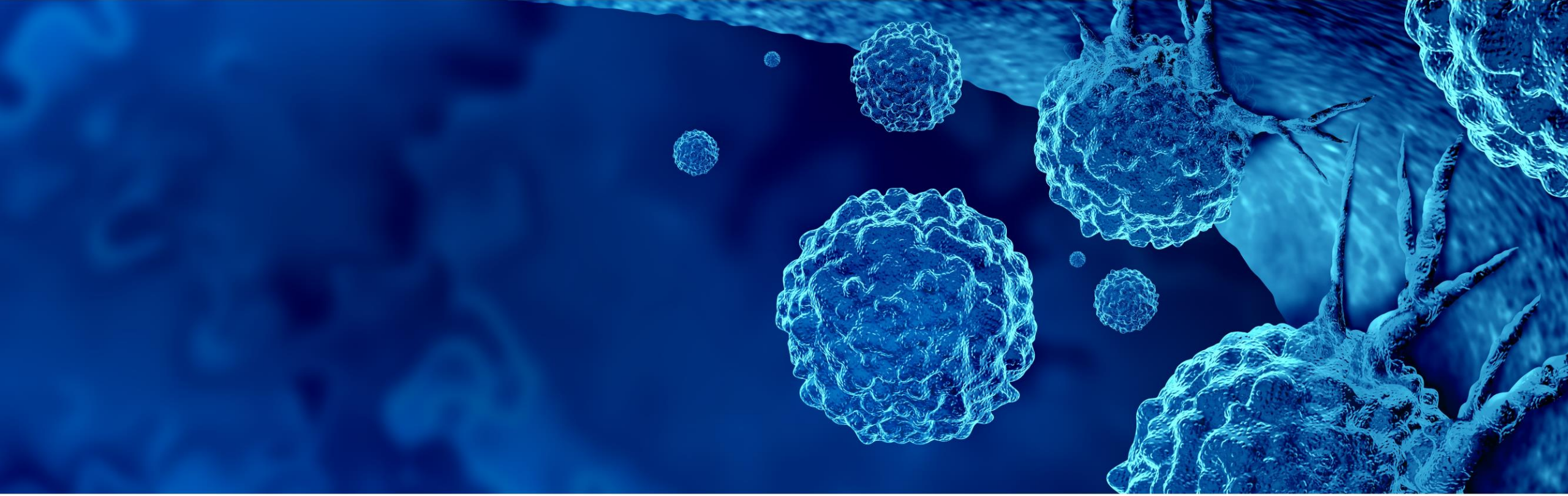
- Open-label, randomized, biomarker-directed, multi-arm, phase 1b trial

Patients with mUC and ≥1 previous line of platinum-based CT for mUC or PD <1 year of perioperative platinum-based CT; WHO PS 0/1; archived tissue for biomarker assessment (N = 108)



- Primary endpoint: safety and tolerability
- Secondary endpoints: efficacy (ORR, DCR, PFS, DoR, OS) of durvalumab alone or in combination; immunogenicity of durvalumab; pharmacokinetics

Powles TB, et al. *Ann Oncol.* 2019;30(suppl 5):Abstract 902O.

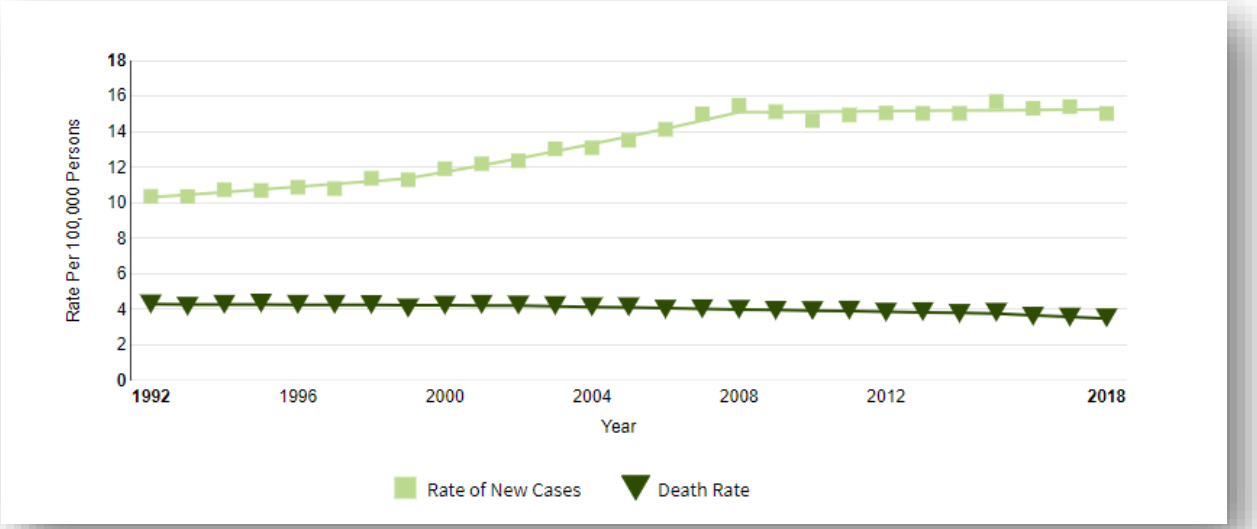


Renal Cell Carcinoma (RCC)

The Evolving Role of Immunotherapy
in the Treatment of Genitourinary Cancers

Kidney Cancer Overview

- **Incidence**: 76,080 new cases and 13,780 deaths in 2021
  - Eighth most common: 4% of new cases and 2.3% of deaths
  - Diagnosis median age: 64 years
  - Death median age: 71 years
  - Males > females (~2:1)
- **Types**: 85% renal cell carcinoma (RCC) and 70% clear cell histology
  - Other types: papillary, chromophobe, translocation, Bellini (collecting) duct tumors, medullary renal carcinoma
- **Risk Factors**: Smoking, obesity, hypertension, hereditary factors (von Hippel-Lindau disease)



Incidence rates rising but death rates falling on average 0.9% each year over 2011-2017

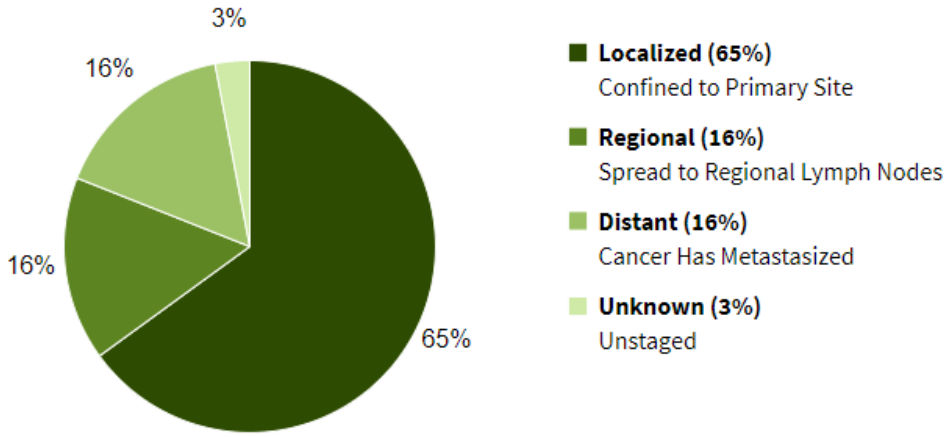
5-year OS = 75.6%

SEER Cancer Stat Facts. Kidney and renal pelvis cancer. https://seer.cancer.gov/statfacts/html/kidrp.html. Accessed June 15, 2021; NCCN Guidelines. Kidney cancer, v4.2021.

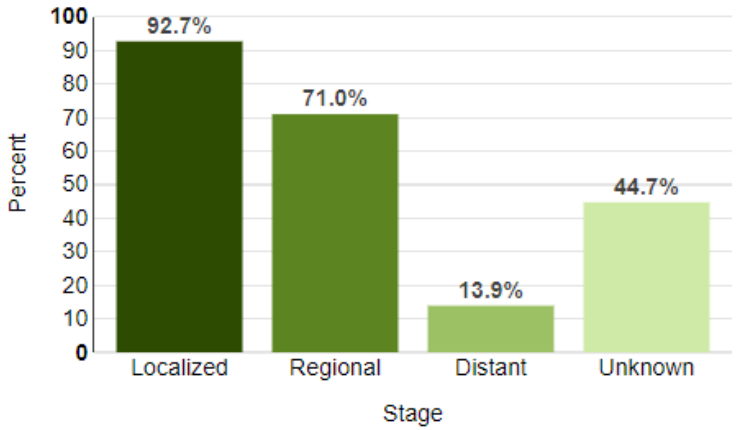
Survival by Stage of Disease

- **Prognostic determinants of 5-year survival:** tumor stage, grade, local extent of the tumor, presence of regional nodal metastases, and metastases at presentation
  - Primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain

Percent of Cases by Stage



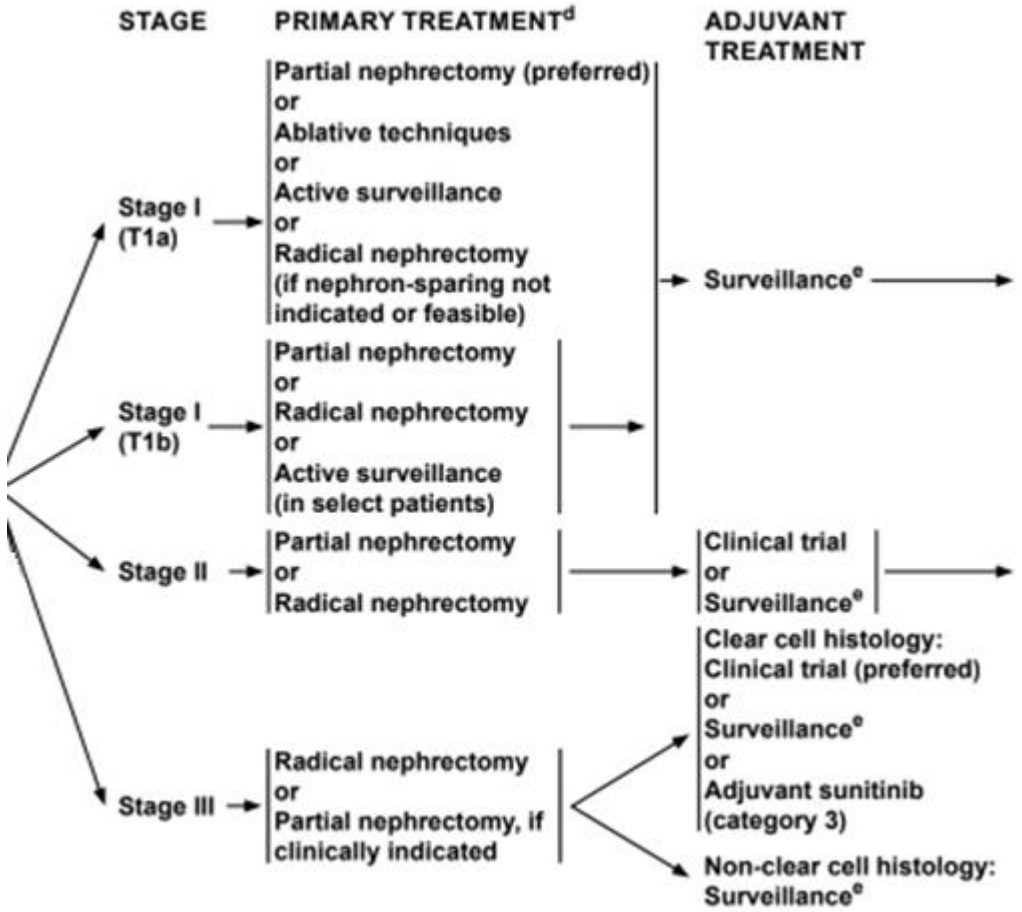
5-Year Relative Survival



SEER Cancer Stat Facts. Kidney and renal pelvis cancer. https://seer.cancer.gov/statfacts/html/kidrp.html. Accessed June 15, 2021; NCCN Guidelines. Kidney cancer, v4.2021.

Treatment of Stages I-III Disease

- **Partial nephrectomy** most appropriate in small unilateral tumors or to preserve renal function
  - Similar outcomes in T1a and T1b tumors
  - Generally, not suitable for locally advanced disease
- **Radical nephrectomy** is curative for stages II and III
  - Sunitinib as adjuvant treatment for *clear cell*, high-risk localized RCC (3)
    - ASSURE: no DFS or OS benefit
    - S-TRAC: longer median DFS vs placebo (6.8 years vs 5.6 years; *P* = .03)



NCCN Guidelines. Kidney cancer, v4.2021; Simmons MN, et al. *Urology*. 2009;73(5):1077-1082; Peycelon M, et al. *J Urol*. 2009;181(1):35-41; Haas NB, et al. *Lancet*. 2016;387(10032):2008-2016; Ravaud A, et al. *N Engl J Med*. 2016;375(23):2246-2254.

Overview of Stage IV Disease

- No single follow-up plan is appropriate for everyone (2B)
- Follow-up for first 5 years; additional at discretion of MD
- Dictated by treatment modality: surveillance vs ablation vs nephrectomy

- 20% to 30% of patients with localized tumors experience relapse
- Lung metastasis is the most common site of distant recurrence, occurring in 50% to 60% of patients
- The median time to relapse after surgery is 1 to 2 years, with most relapses occurring within 3 years

SEER Cancer Stat Facts. Kidney and renal pelvis cancer. https://seer.cancer.gov/statfacts/html/kidrp.html. Accessed June 15, 2021; NCCN Guidelines. Kidney cancer, v4.2021.

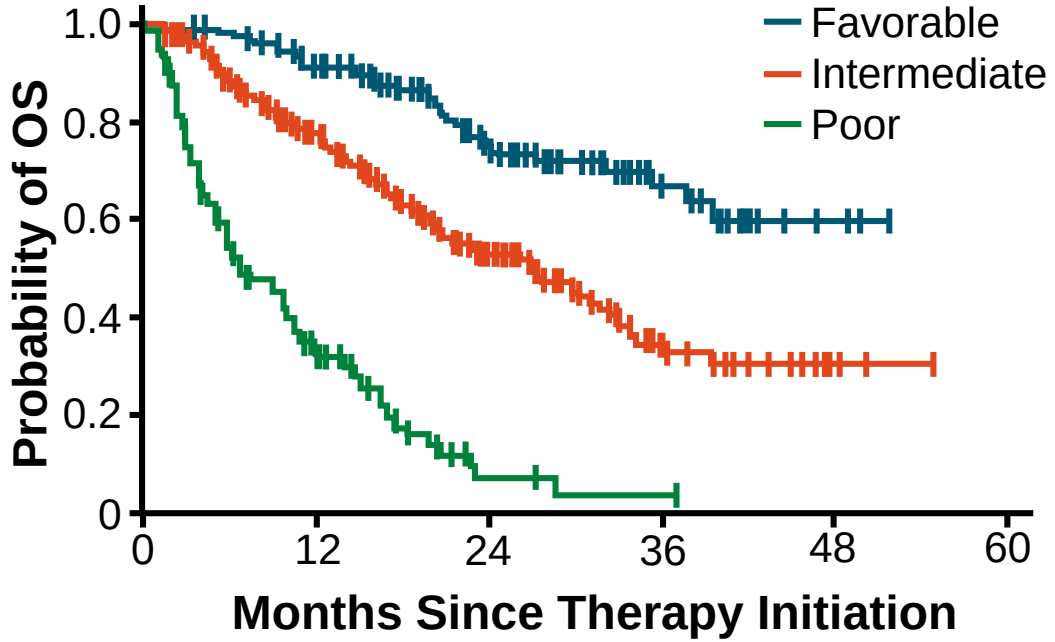
Prognostic Criteria

Prognostic Factor Model (MSKCC)
KPS <80%
LDH > 1.5 x ULN
Corrected calcium > ULN
Hemoglobin < LLN

No factors:
low risk, good prognosis

1 to 2 factors:
intermediate risk

≥3 factors:
poor risk



No. of Events/No. at Risk

Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

- **The MSKCC criteria have been additionally validated by an independent group at the Cleveland Clinic**
- **IMDC (Heng) Prognostic Criteria incorporates neutrophil and platelet count > ULN**

IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; LDH, lactase dehydrogenase; LLN, lower limit of normal; MSKCC, Memorial Sloan Kettering Cancer Center; ULN, upper limit of normal.

Heng DYC, et al. *J Clin Oncol*. 2009;27(34):5794-5799;
Mekhail TM, et al. *J Clin Oncol*. 2005;23(4):832-841.

Treatment of Stage IV Disease

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY*			
Risk	**Preferred**	**Other Recommended**	**Useful Under Certain Circumstances**
Favorable	• Axitinib + pembrolizumab • Cabozantinib + nivolumab (1) • Lenvatinib + pembrolizumab (1) • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (2B) • Axitinib + avelumab	• Active surveillance • Axitinib (2B) • High-dose IL-2
Poor/ Intermediate	• Ipilimumab + nivolumab (1) • Axitinib + pembrolizumab (1) • Cabozantinib + nivolumab (1) • Lenvatinib + pembrolizumab (1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (2B) • High-dose IL-2 • Temsirolimus
SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY*			
	• Cabozantinib (1) • Nivolumab (1) • Ipilimumab + nivolumab	• Axitinib (1) • Lenvatinib + everolimus (1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Tivozanib • Axitinib + avelumab (3)	• Bevacizumab or biosimilar (2B) • Sorafenib (2B) • High-dose IL-2 for selected patients (2B) • Temsirolimus (2B)

**All recommendations are category 2A unless indicated.*

NCCN Guidelines. Kidney cancer, v4.2021.

Treatment of Stage IV Disease

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY*

Risk	Preferred	Other Recommended	Useful Under Certain Circumstances
Favorable	• Axitinib + pembrolizumab • Cabozantinib + nivolumab (1) • Lenvatinib + pembrolizumab (1) • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (2B) • Axitinib + avelumab	• Active surveillance • Axitinib (2B) • High-dose IL-2
Poor/ Intermediate	• Ipilimumab + nivolumab (1) • Axitinib + pembrolizumab (1) • Cabozantinib + nivolumab (1) • Lenvatinib + pembrolizumab (1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (2B) • High-dose IL-2 • Temsirolimus

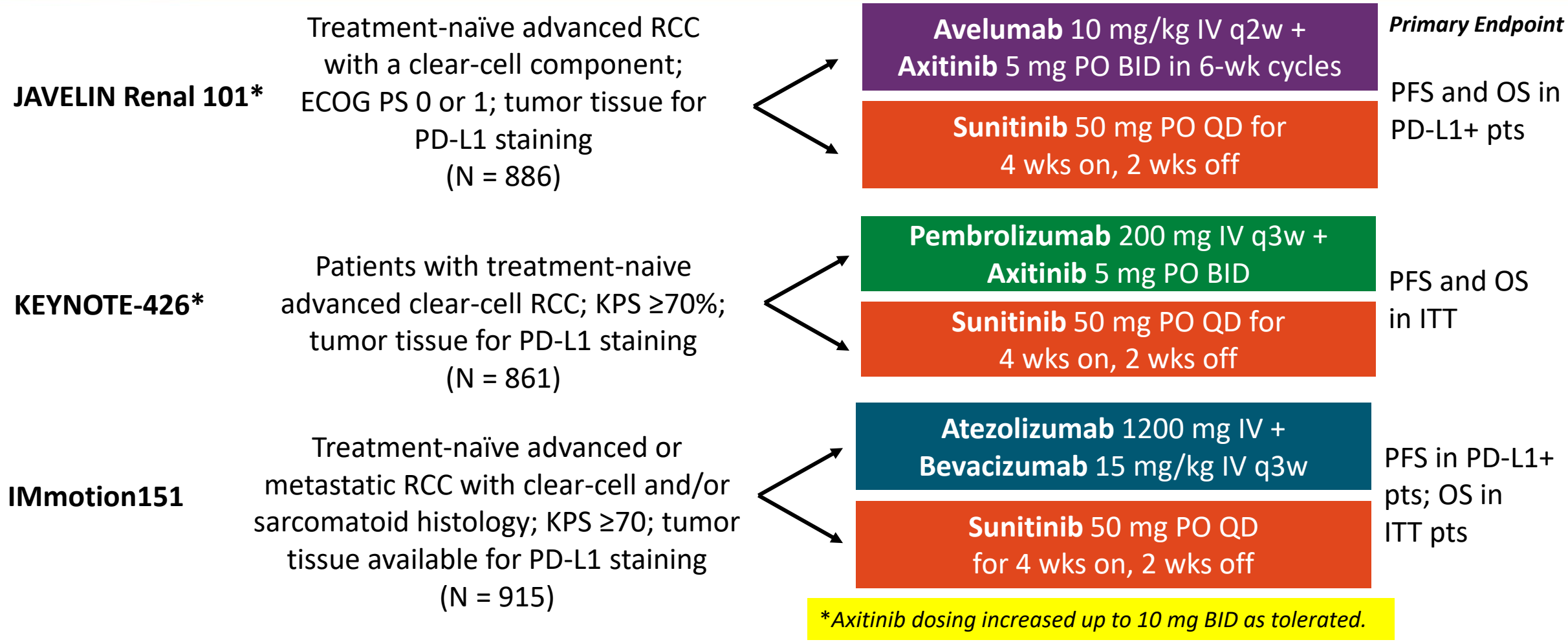
SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY*

	• Cabozantinib (1) • Nivolumab (1) • Ipilimumab + nivolumab	• Axitinib (1) • Lenvatinib + everolimus (1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Tivozanib • Axitinib + avelumab (3)	• Bevacizumab or biosimilar (2B) • Sorafenib (2B) • High-dose IL-2 for selected patients (2B) • Temsirolimus (2B)

**All recommendations are category 2A unless indicated.*

NCCN Guidelines. Kidney cancer, v4.2021.

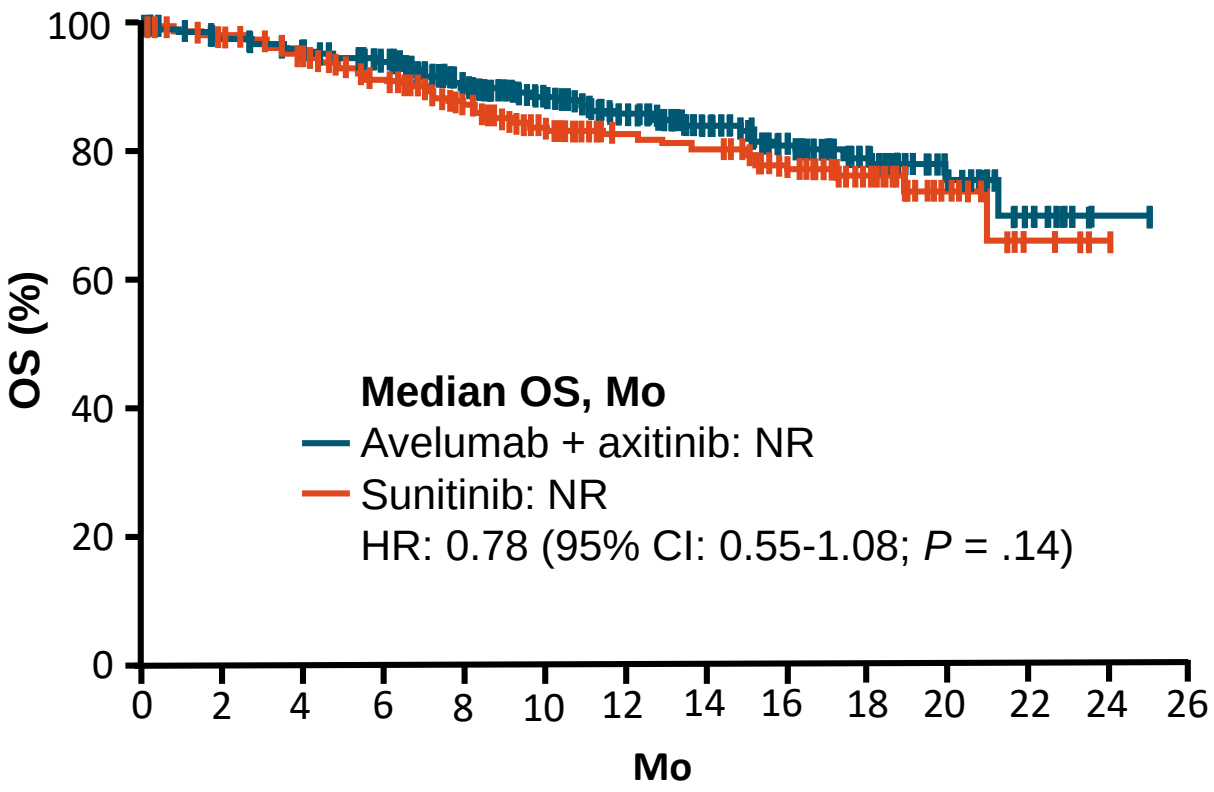
Notable Immune Checkpoint Inhibitor (ICI) Combination Trials



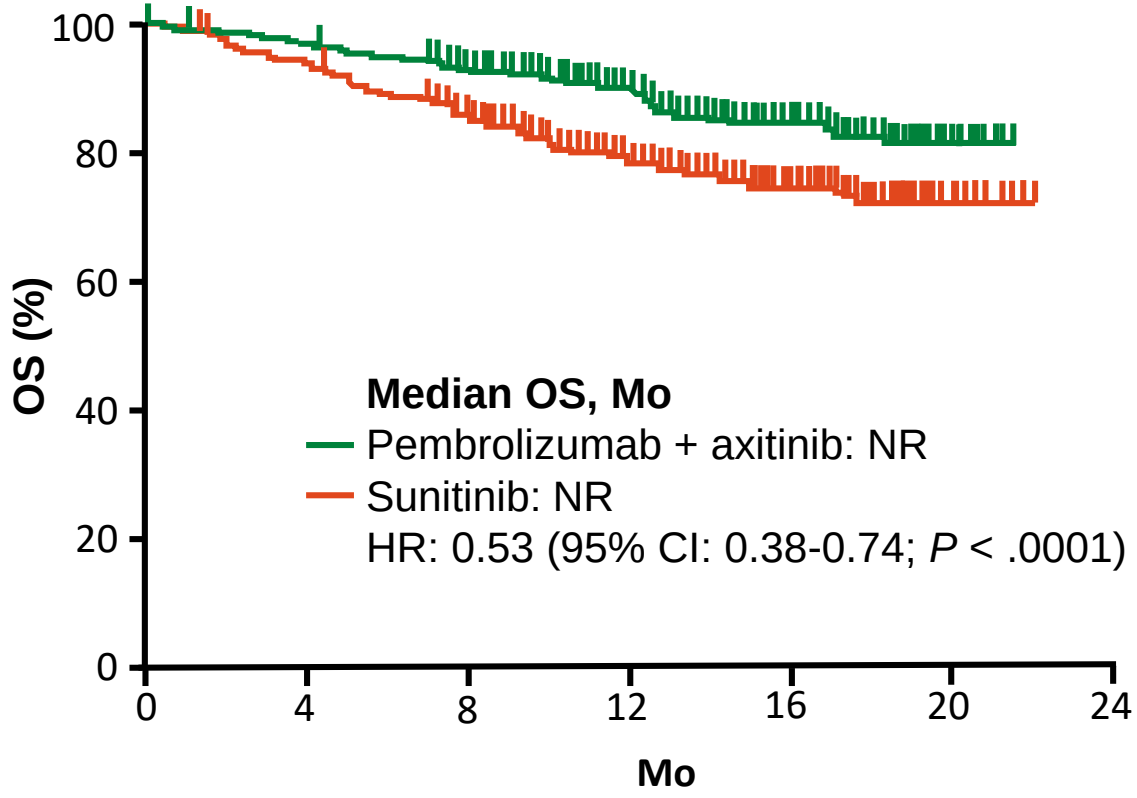
Motzer RJ, et al. ASCO GU 2018. Abstract 578; Motzer RJ, et al. ESMO 2018. Abstract LBA6; Powles T. ASCO GU 2019. Abstract 543.

Key Takeaway: AvelAxi vs PemAxi

JAVELIN Renal 101: OS in Overall Population



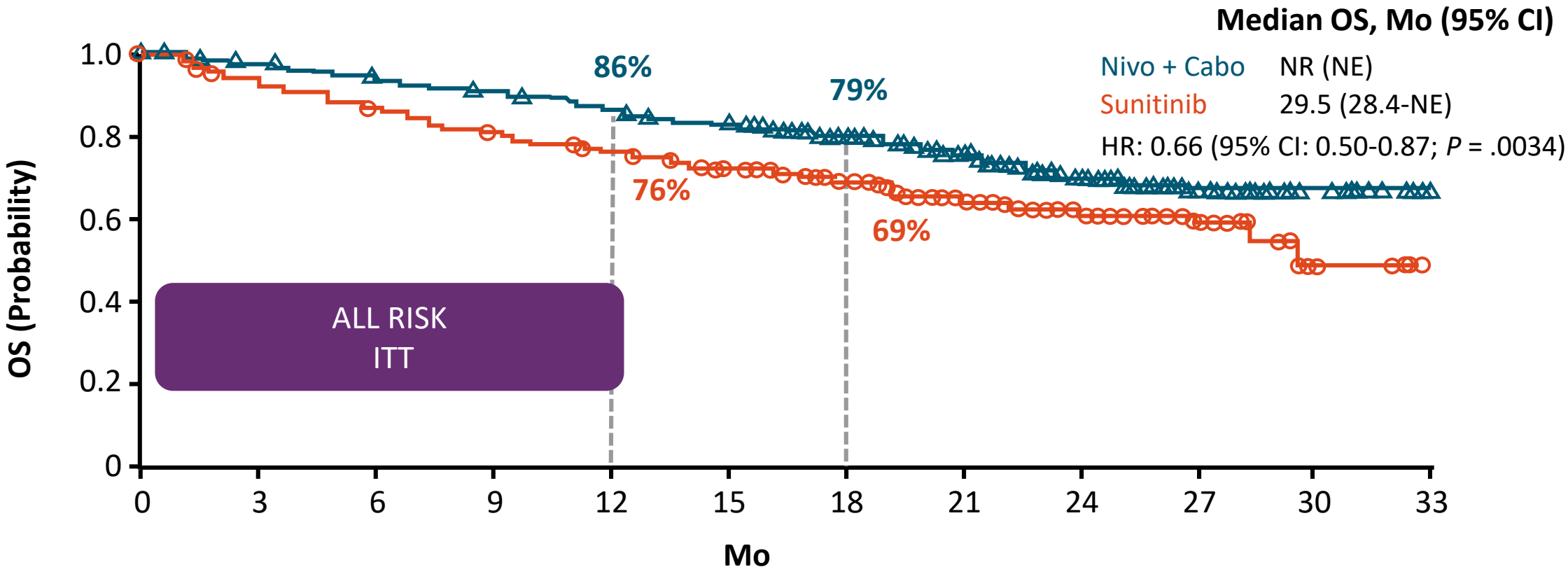
KEYNOTE-426: OS in Overall Population



NR, not reached.

Motzer RJ, et al. *N Engl J Med*. 2019;380(12):1103-1115; Rini BI, et al. *N Engl J Med*. 2019;380(12):1116-1127.

1L Nivolumab + Cabozantinib vs Sunitinib in Advanced or Metastatic RCC



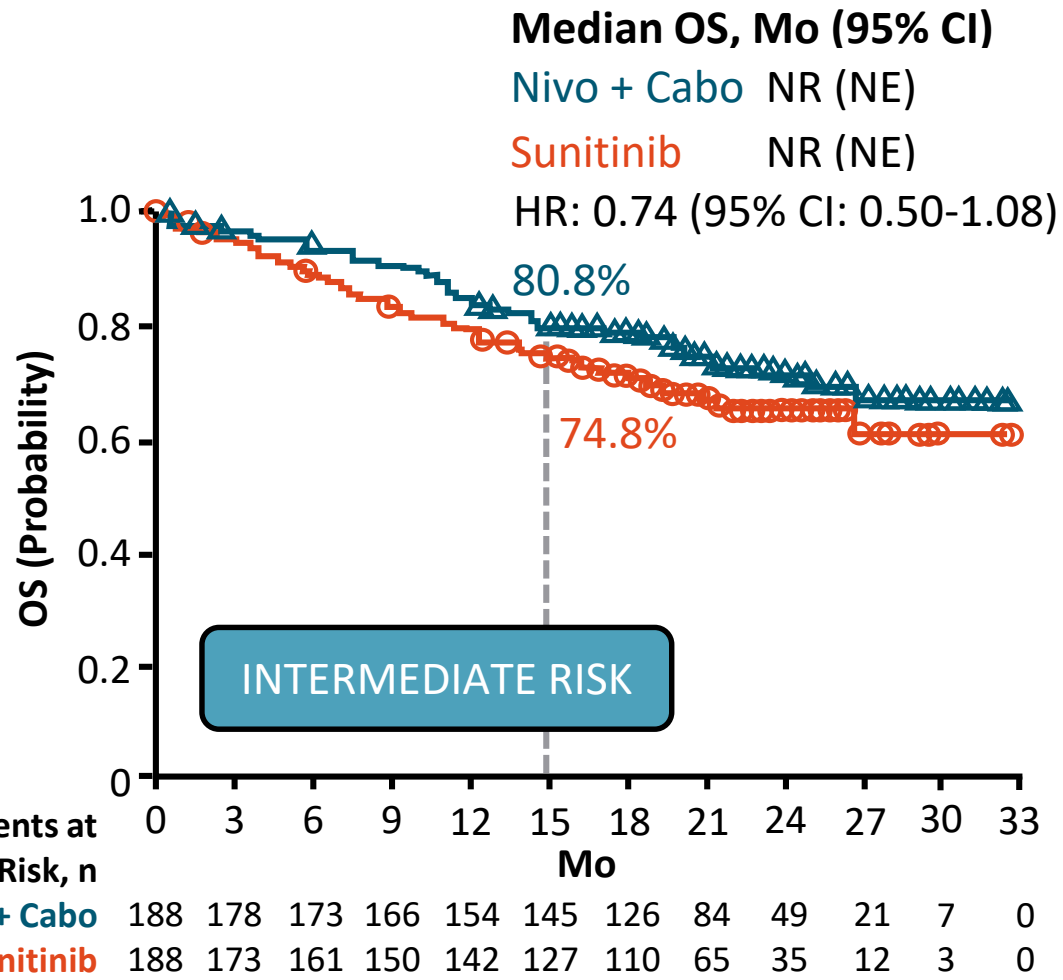
Patients at Risk, n

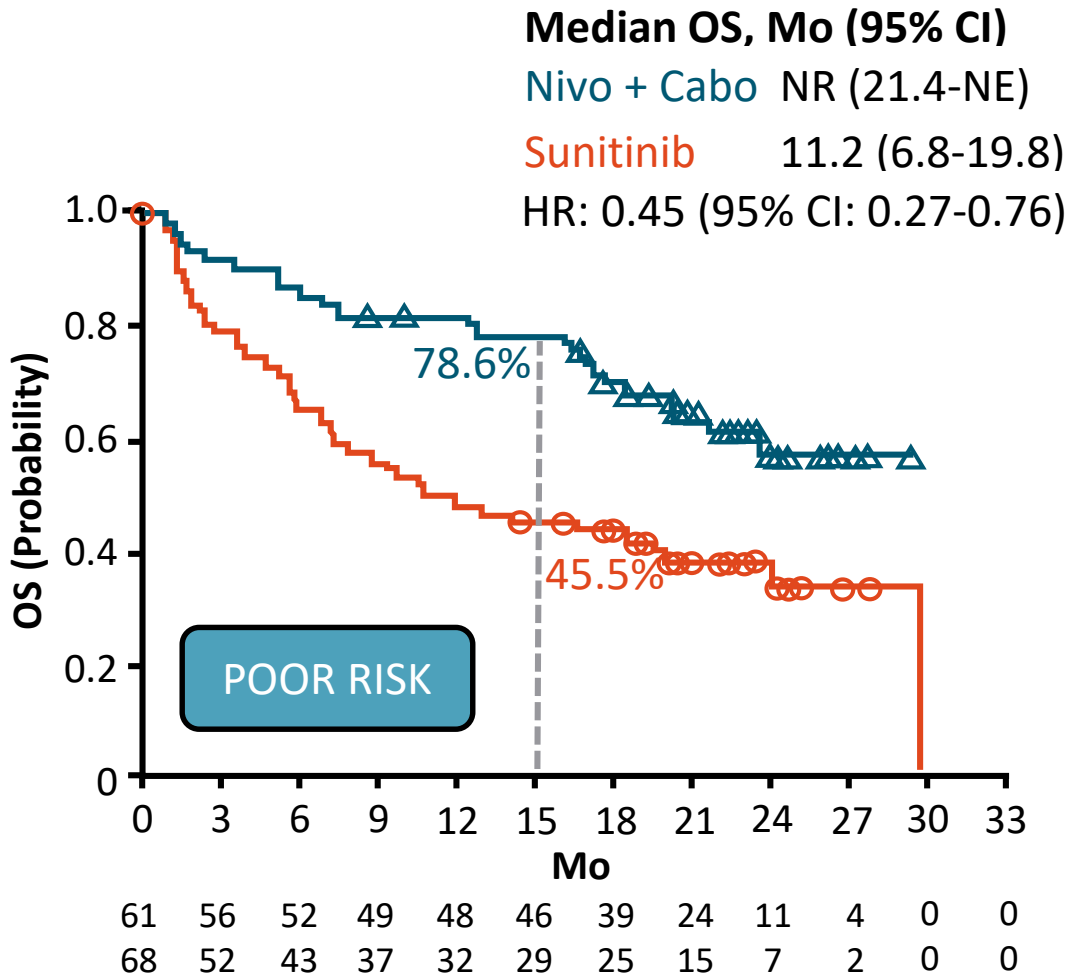
Nivo + Cabo	323	308	295	283	269	255	220	147	84	40	10	0
Sunitinib	328	295	272	254	236	217	189	118	62	22	4	0

NE, not estimable.

Motzer RJ. ASCO GU 2021. Abstract 308.

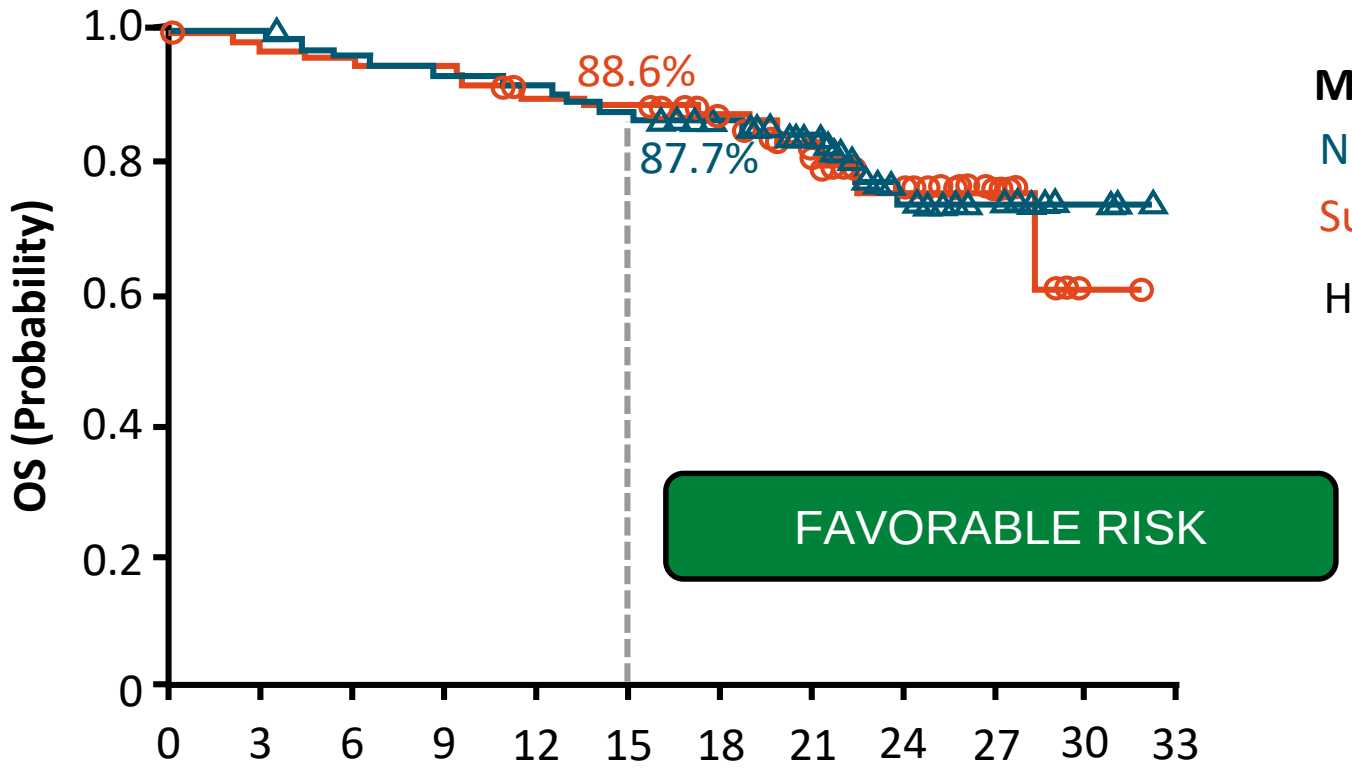
1L Nivolumab + Cabozantinib vs Sunitinib in Advanced or Metastatic RCC





Apolo AB, et al. ASCO GU 2021. Abstract 4553.

1L Nivolumab + Cabozantinib vs Sunitinib in Advanced or Metastatic RCC



Median OS, Mo (95% CI)

Nivo + Cabo NR (NE)

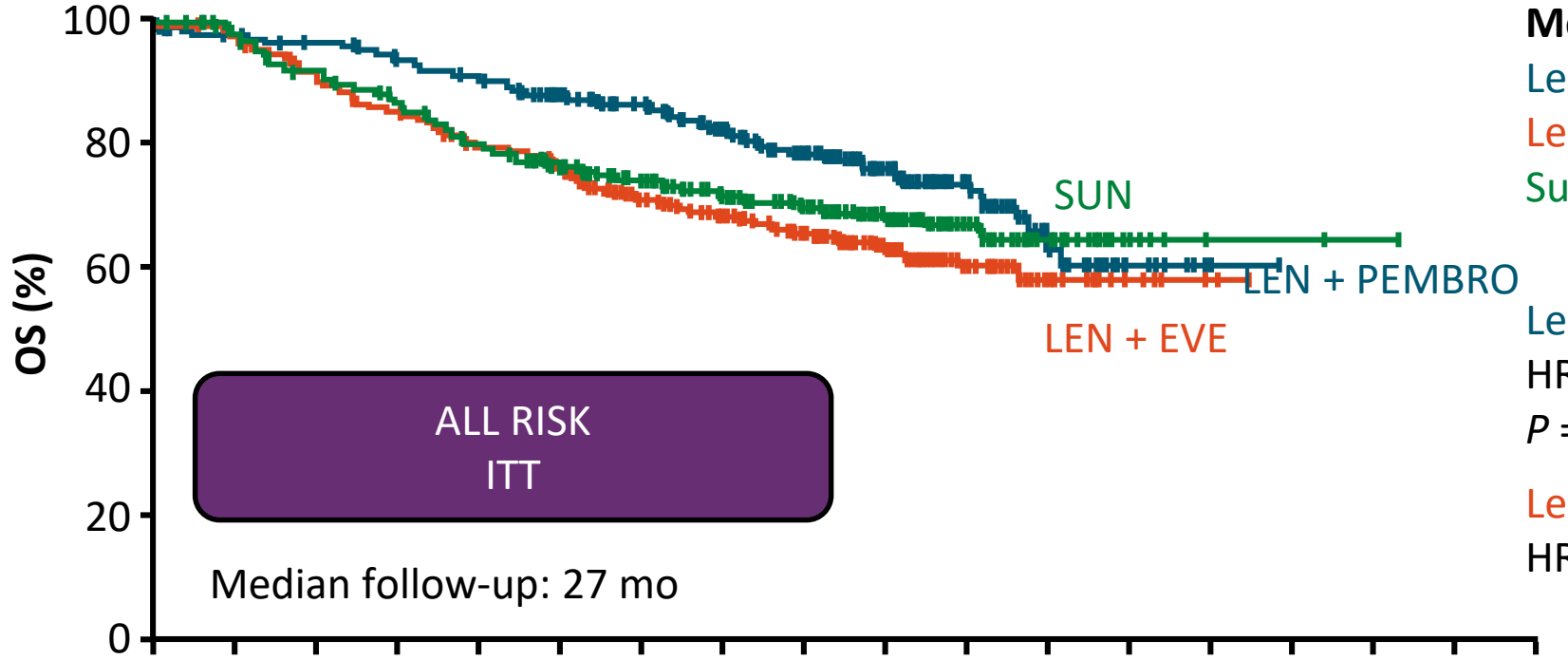
Sunitinib NR (28.4-NE)

HR: 0.94 (95% CI: 0.46-1.92)

Patients at Risk, n												
Nivo + Cabo	74	74	70	68	67	64	55	39	24	15	3	0
Sunitinib	72	70	68	67	62	61	54	38	20	8	1	0

Apolo AB, et al. ASCO GU 2021. Abstract 4553.

1L Lenvatinib + Pembrolizumab or Everolimus vs Sunitinib in Advanced RCC



Patients at Risk, n	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
	Mo																	
Len + Pembro	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0			
Len + Eve	357	346	321	299	277	246	205	183	154	109	46	22	8	2	0			
Sunitinib	357	332	307	289	264	236	207	186	169	112	60	25	7	2	2	1	0	

Median OS, Mo (95% CI)

Len + Pembro	NR (33.6-NE)
Len + Eve	NR (NE)
Sunitinib	NR (NE)

Len + Pembro vs Sunitinib:
HR: 0.66 (95% CI: 0.49-0.88; *P* = .005)

Len + Eve vs Sunitinib:
HR: 1.15 (95% CI: 0.88-1.50; *P* = .3)

Motzer RJ, et al. *N Engl J Med*. 2021;384(14):1289-1300.

1L: Efficacy of Ipilimumab + Nivolumab

CheckMate 214	N = 1096
Randomized, open-label, phase 3 trial; 423 and 416 patients had intermediate or poor risk, respectively	
Arms	Ipi/Nivo → Nivo (n = 547) vs sunitinib (n = 535)*
18-month OS rate (ITT) **Favorable-Risk Group**	75% (95% CI, 70-78) vs 60% (95% CI, 55-65) 88% vs 93%
Median PFS **Favorable-Risk Group**	11.6 mo vs 8.4 mo; HR 0.82; *P* = .03 (prespecified 0.009) 15.3 mo and 25.1 mo; HR, 2.18; 99.1% CI, 1.29-3.68; *P* < .001
ORR (ITT) **Favorable-Risk Group**	42% vs 27%, *P* < 0.001 29% and 52%; *P* < 0.001

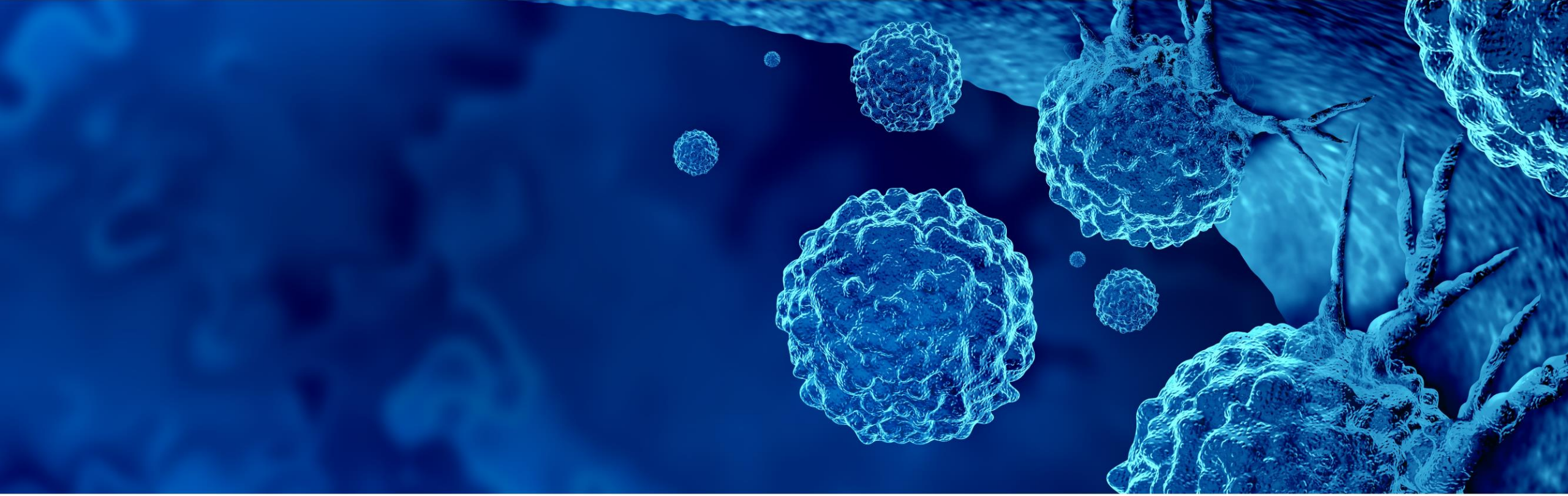
**Note that 1082 patients received treatment.*

Motzer RJ, et al. *N Engl J Med*. 2018;378(14):1277-1290.

Sequencing of Treatment in mRCC

- **First line:** therapeutic landscape rapidly evolving with approval of ipilimumab + nivolumab and VEGF TKIs + IO
- **Second line:** guided by strength of evidence, toxicity profile, comorbidities, patient and physician preference, and financial concerns
- With multitude of possible therapeutic sequences, a definitive resolution is unlikely
- Molecular biomarkers to select for efficacy and toxicity are not ready for prime time, but will hopefully make precision medicine possible
  - More challenging with combination regimens
- ***Clinical trials should be offered for every line since cure is unlikely with current therapy!***

mRCC, metastatic renal cell carcinoma; PD-1, programmed cell death protein-1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.



Management of irAEs

The Evolving Role of Immunotherapy
in the Treatment of Genitourinary Cancers

Immune-Related AEs (irAEs)

- Immune checkpoint inhibitors (ICIs) introduce the potential for transformative, durable responses in multiple malignancies
- ICIs also introduce the potential for toxicity
- irAEs
  - **Activation of immune system that can "target" host tissues/organs**
  - **Can mimic (or flare) preexisting autoimmune conditions**
  - **Pathophysiology is not well understood**
  - **Treatment involves immunosuppressive agents**

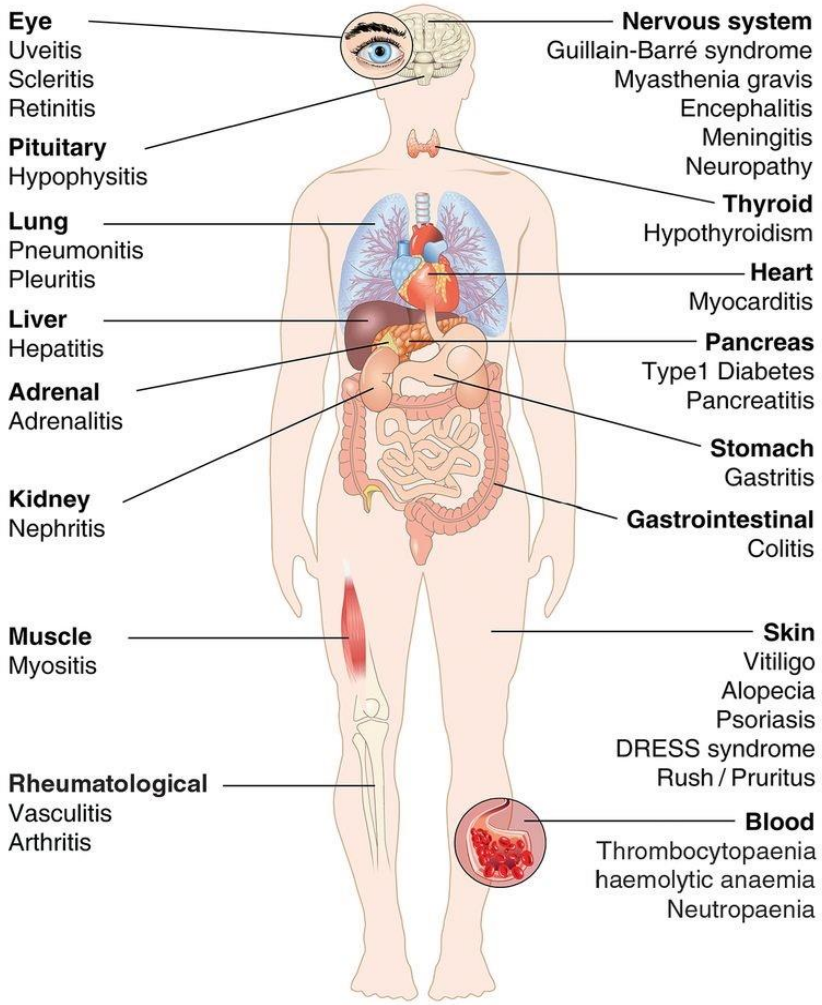
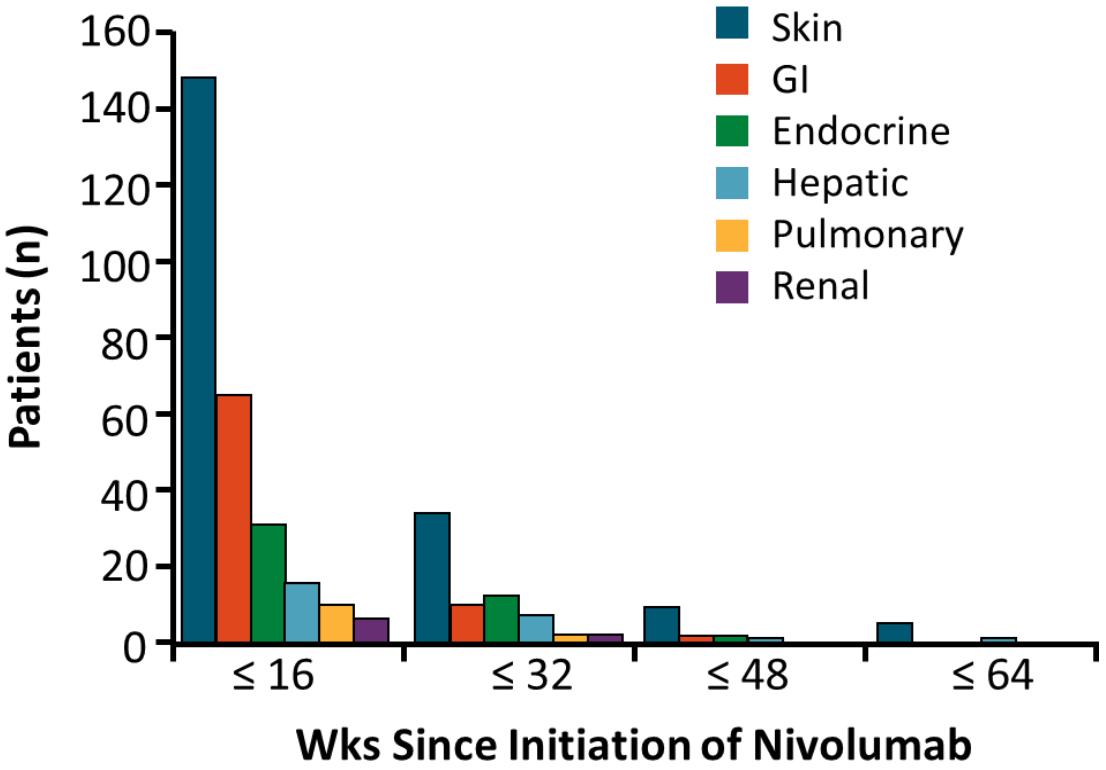
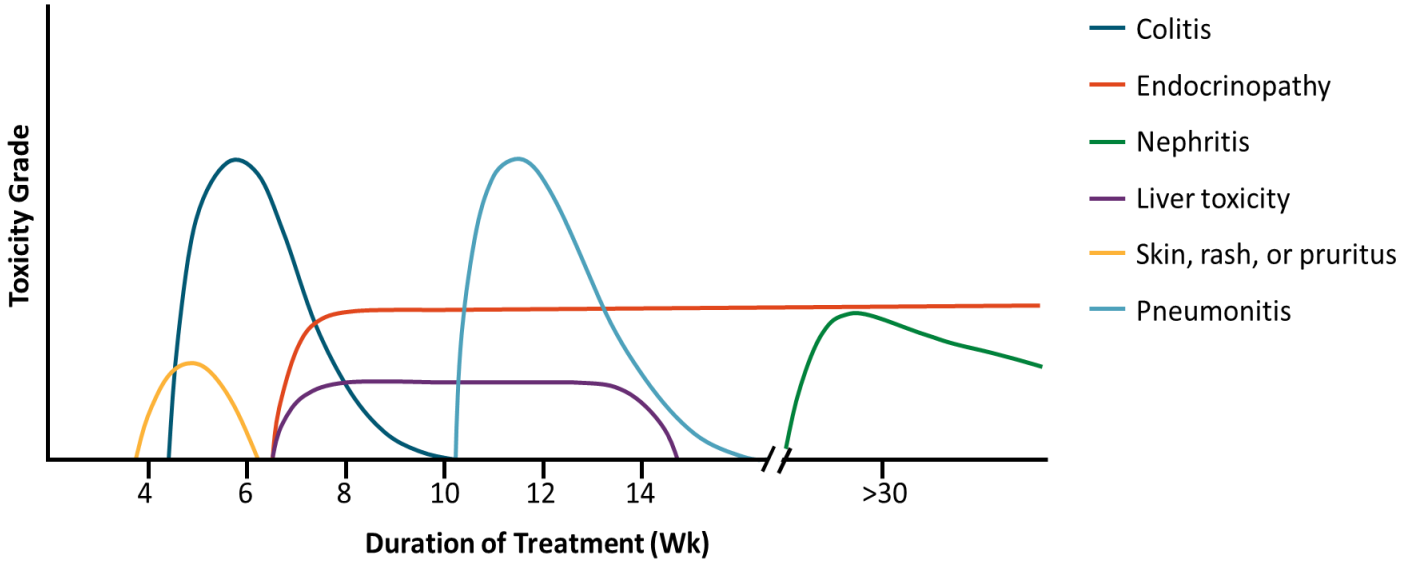


Figure republished from Varricchi G, et al. *ESMO Open*. 2017;2(4):e000247, under the terms of a Creative Commons Attribution NonCommercial (CC By-NC 4.0) license.

Onset of irAEs





Weber JS, et al. *J Clin Oncol*. 2017;35(7):785-792; Petrylak DP. *Clin Genitourin Cancer*. 2017;15(3S):S3-S17; Martins F. *Nat Rev Clin Oncol*. 2019:16;563-580.

PD-1/PD-L1 Education Principles

Prior to Start

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

Patient Instructions

- Notify healthcare professionals (HCPs) of new signs and symptoms
  - Fatigue, rash, cough, shortness of breath, muscle pain, weight loss, etc
- Symptoms should be monitored for a long time, even after therapy completion
- Medication changes, vaccines, etc

Adverse Effect Management

- Review medications for drug-drug interactions (DDIs)
- Symptomatic management for mild-to-moderate irAEs
  - Best supportive care and workup
  - Steroids may be needed
  - Hormone substitution as needed
  - May delay therapy until recovery/ improvement
- Severe irAEs
  - Discontinue treatment
  - Steroids and other immunosuppressants
  - Hospitalization may be required
  - Expert consultation

PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

NCCN. Management of immunotherapy-related toxicities. V3.2021. www.nccn.org. Accessed July 23, 2021.

General Management of irAEs

- **Corticosteroids remain cornerstone of care for irAEs**
  - Resolved most irAEs 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 (ie, 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 mo)
  - Infliximab 5 mg/kg once every 2 wks can be used
- **Endocrine AEs**
  - Hormonal replacement as needed

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 1-2 days	Discontinue and may consider resuming therapy based on risk/benefit*
4	Systemic steroids	If no response to steroids after 1-2 days	Discontinue

CTCAE, Common Terminology Criteria for Adverse Events.
**Doses are either given or held; there are no dose reductions.*

Petrylak DP. *Clin Genitourin Cancer*. 2017;15(3S):S3-S17; Weber JS, et al. *J Clin Oncol*. 2012;30(21):2691-2697; Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-1768.

ICI + TKI Adverse Events

Immunotherapy

- Neurologic
- Eye
- Respiratory
- Endocrine
- Cardiovascular
- Liver
- Pancreas
- GI
- Renal
- Skin
- Musculoskeletal

VEGFR Inhibitor Therapy

- Diarrhea
- Hypertension
- Fatigue
- Anorexia
- Nausea
- Dysphonia
- HFS
- Hypothyroidism
- LFT elevation
- Proteinuria
- Thrombotic events

GI, gastrointestinal; HFS, hand-foot syndrome; ICI, immune checkpoint inhibitor; LFT, liver function test; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

Guidance on Evaluation and Management of Combination AEs

- Timing of AE onset:
  - Axitinib dosed BID (short half-life)
  - ICIs dosed every 2-4 wks (long half-life)
  - Axitinib can be interrupted to assess if the AE resolves
    - If AE occurs during a treatment cycle, only option is axitinib dose interruption
    - If AE occurs prior to beginning a cycle, may interrupt both
  - If AE does not resolve after holding axitinib, irAEs should be considered
- When reviewing the long list of potential AEs with patients, note that nobody gets all of them, but we cannot predict which ones a given patient will experience
  - Communication is key
  - See patient within 3-4 wks of starting treatment to detect emerging AEs early
- Severity of AE:
  - If AE is severe, life-threatening or rapidly worsening, hold both and initiate corticosteroids and supportive care

Rini BI, et al. *N Engl J Med*. 2019;380(12):1116-1127; Motzer RJ, et al. *N Engl J Med*. 2019;380(12):1103-1115.

Thank you!