Thank you for joining us.
The program will commence momentarily.

Meet The Professors

Nurse and Physician Investigators Discuss Existing and Emerging Treatment Strategies for Patients with Bladder Cancer

Thursday, July 30, 2020

5:00 PM – 6:00 PM ET

Faculty

Anastassia Daskalova, NP

Peter H O'Donnell, MD

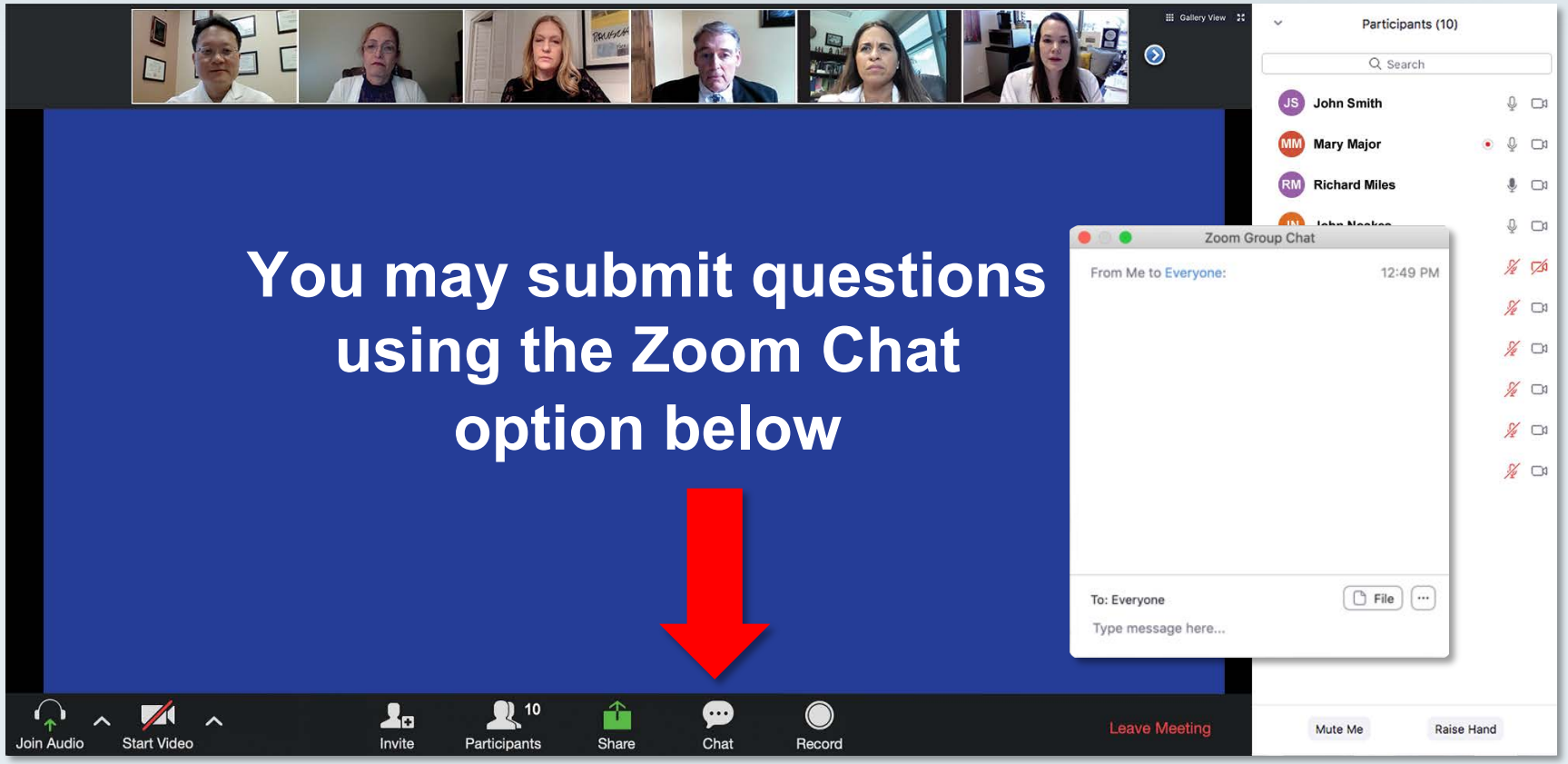
Moderator

Neil Love, MD

Jointly provided by USF Health

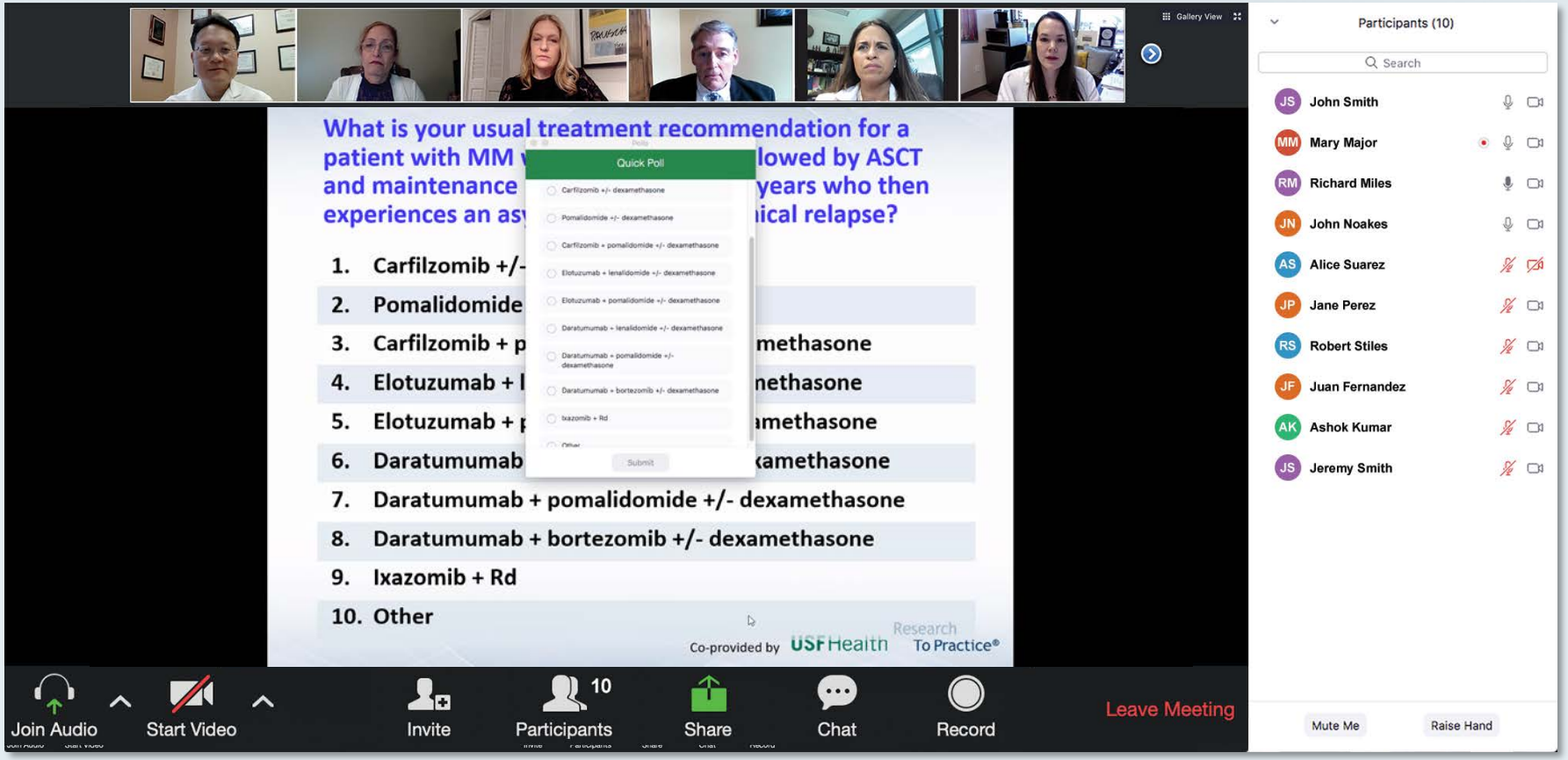
RTP RESEARCH TO PRACTICE

Dr Love and Faculty Encourage You to Ask Questions



Feel free to submit questions **now before** the program commences and **throughout the program.**

Familiarizing yourself with the Zoom interface
How to answer poll questions



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Ms Daskalova — Disclosures

No financial interests or affiliations to disclose.

Dr O’Donnell — Disclosures

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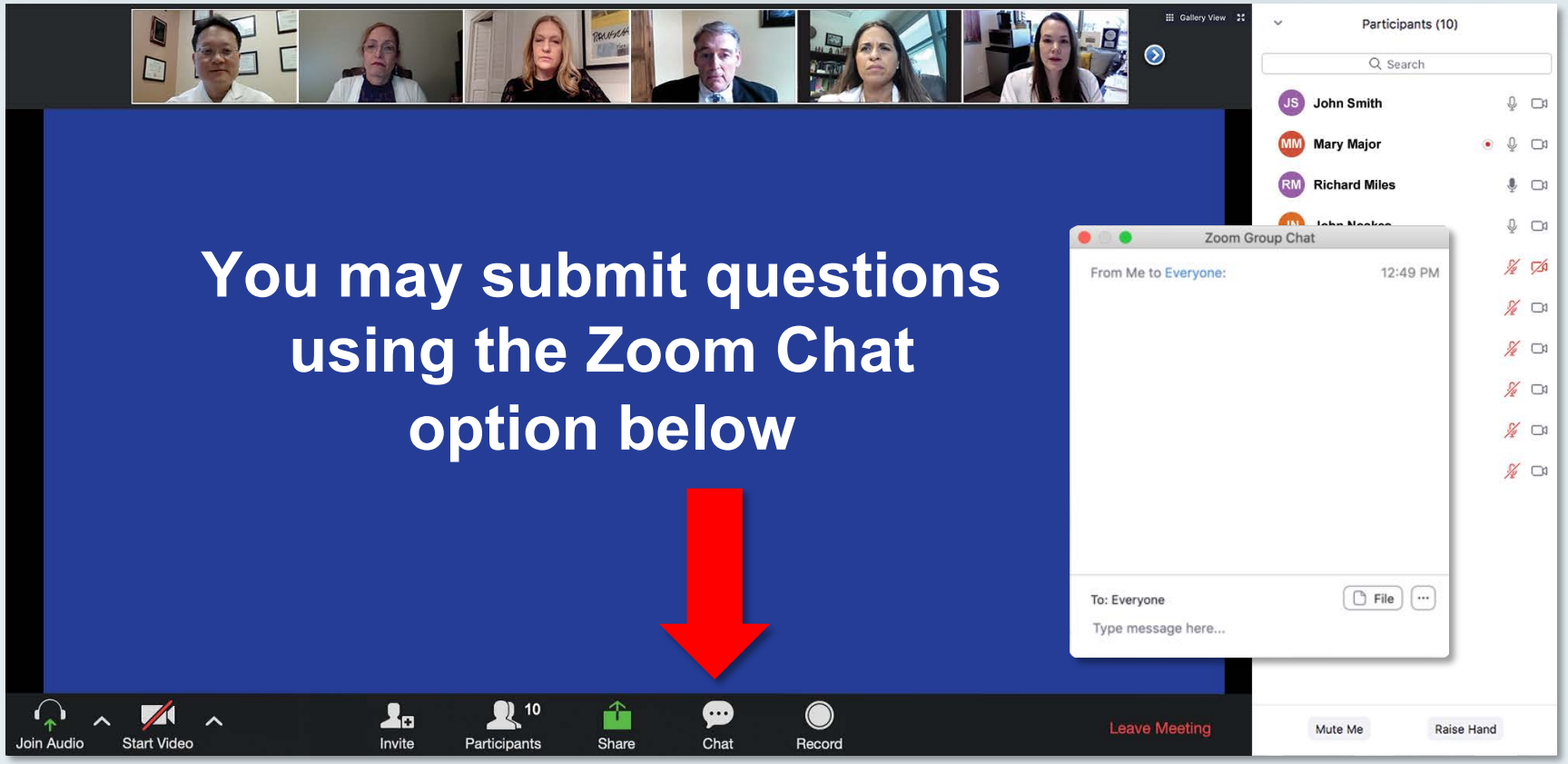

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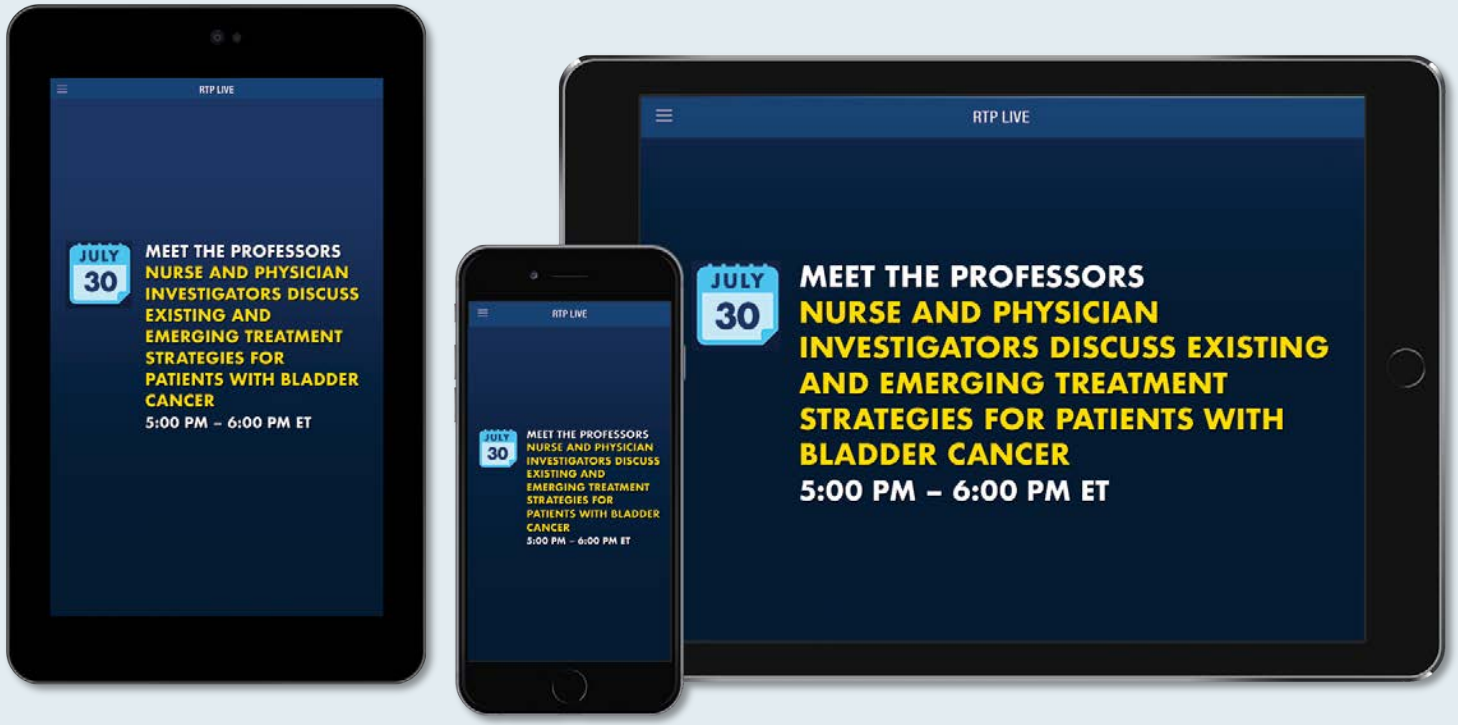

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RTP RESEARCH TO PRACTICE

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Key Decisions in Bladder Cancer and Where New Agents and Strategies Fit In

Case 1: A 62-year-old man with metastatic UBC

- Neoadjuvant therapy versus surgery
- Management of BCG-unresponsive disease
- Choice of first-line therapy
- Management of checkpoint inhibitor associated toxicities

Case 2: An 80-year-old woman with metastatic UBC

- Second-line treatment options
- Clinical activity and adverse event profile of erdafitinib
- Mechanisms of action, risks and benefits of enfortumab vedotin

Case 3: A 95-year-old man with non-muscle-invasive UBC

- Selection of therapy for BCG-unresponsive disease

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- Selection of therapy for BCG-unresponsive disease

Case Presentation: A 62-year-old man with metastatic UBC

Special Considerations

- Current 2 PPD smoker, presents with hematuria
- Diagnosed with 4-cm T3N1M0 MIUBC
- Bartender, concerned about availability of work; recently separated from partner prior to diagnosis
- 2 adult children who work and attend college

Decision 1: Neoadjuvant therapy, cystectomy or clinical trial?

- Neoadjuvant dose-dense MVAC administered; residual disease at surgery
- 8 months later, presents with bone pain; bone and lung metastases with RT to rib mets
- PD-L1 = 65%

Decision 2: Choice of systemic therapy or clinical trial?

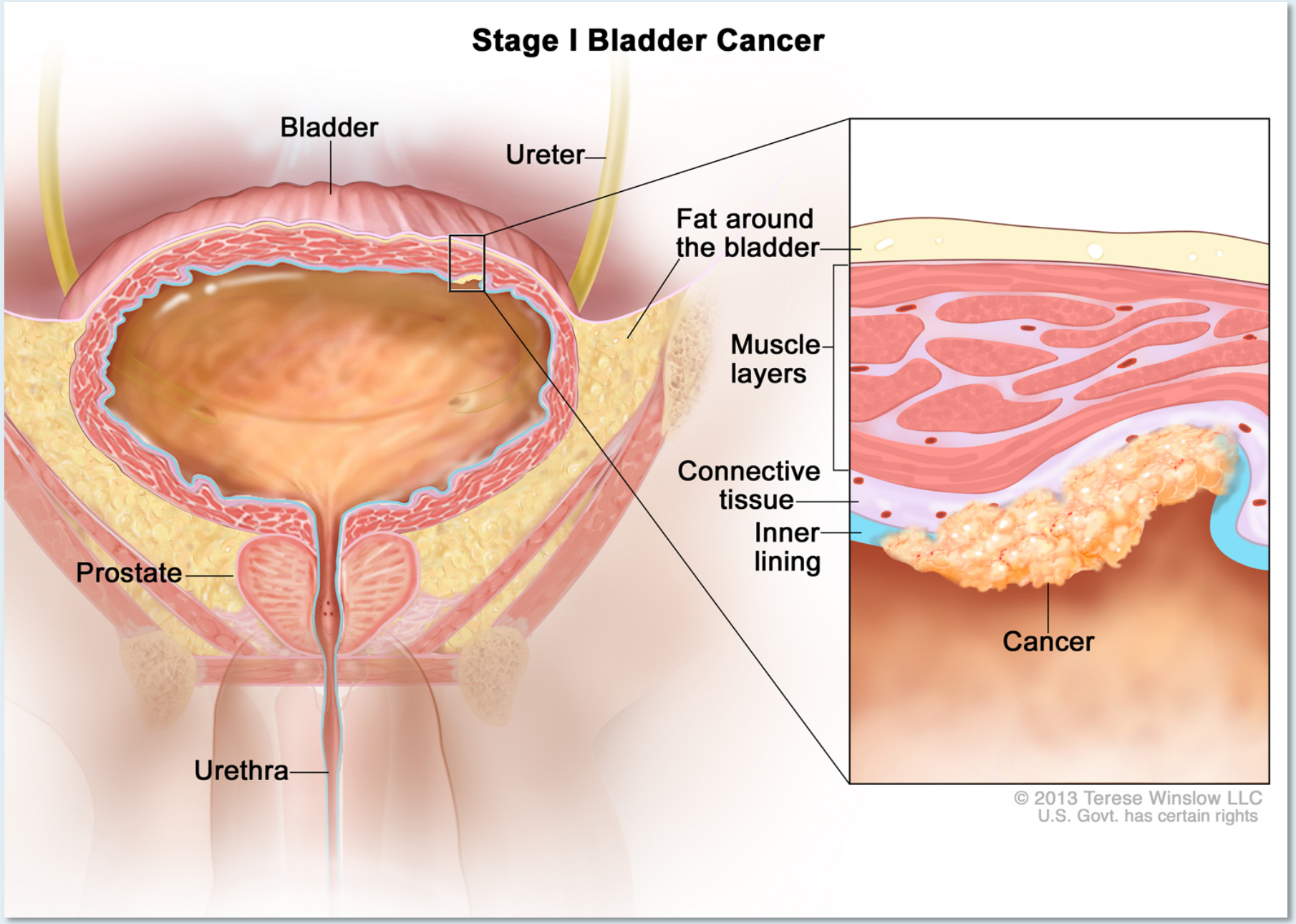
- Receives checkpoint inhibitor with rapid objective response; feels better
- 8 months later, presents with dyspnea and cough

Decision 3: Management of pneumonitis in patient treated with checkpoint inhibitor

Overview of Bladder Cancer

- Patient profile
  - Median age at diagnosis: 73 years
  - 76% male
  - Smoking is the most well-established risk factor (47% of all cases in the US)
- Natural history
  - Non-muscle-invasive
  - Muscle-invasive
  - Metastatic
- Cystectomy and ileal conduit/stoma management
- Neoadjuvant and adjuvant chemotherapy

ACS Cancer Facts & Figures 2020; www.cancer.org.



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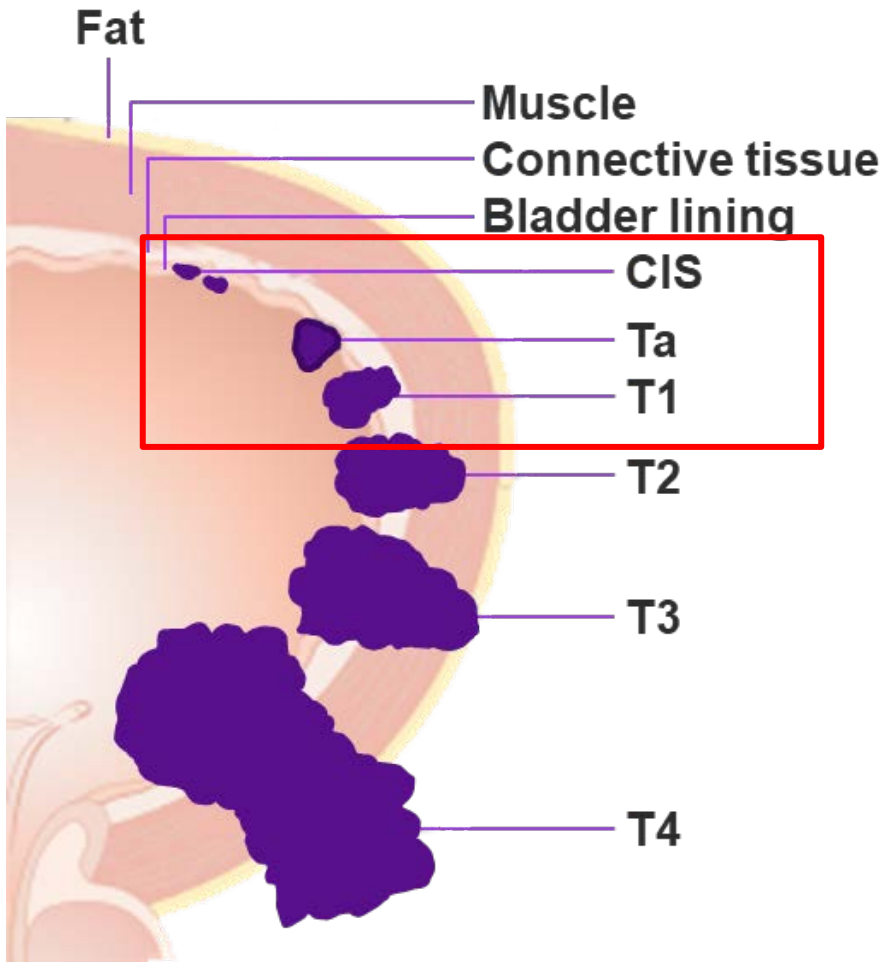
High-Risk Non–Muscle-Invasive BC

- High-risk (HR) NMIBC is defined as any carcinoma in situ (CIS), T1 tumor, and/or high-grade Ta tumor
- Standard-of-care therapy for HR NMIBC is TURBT and intravesical Bacillus Calmette-Guérin (BCG)
  - Although there is a high rate of complete response (70%) to initial therapy, most patients with high-risk disease do not maintain response
    - 30% of patients experience recurrence within 1 year
    - 40% of patients at high risk progress to muscle-invasive disease
    - 20%-30% of patients progress to metastatic disease
- BCG unresponsive disease – standard of care is cystectomy
- With the lack of a suitable comparator, single-arm designs testing novel agents are thought to be acceptable in the BCG-unresponsive population
- World-wide BCG shortage



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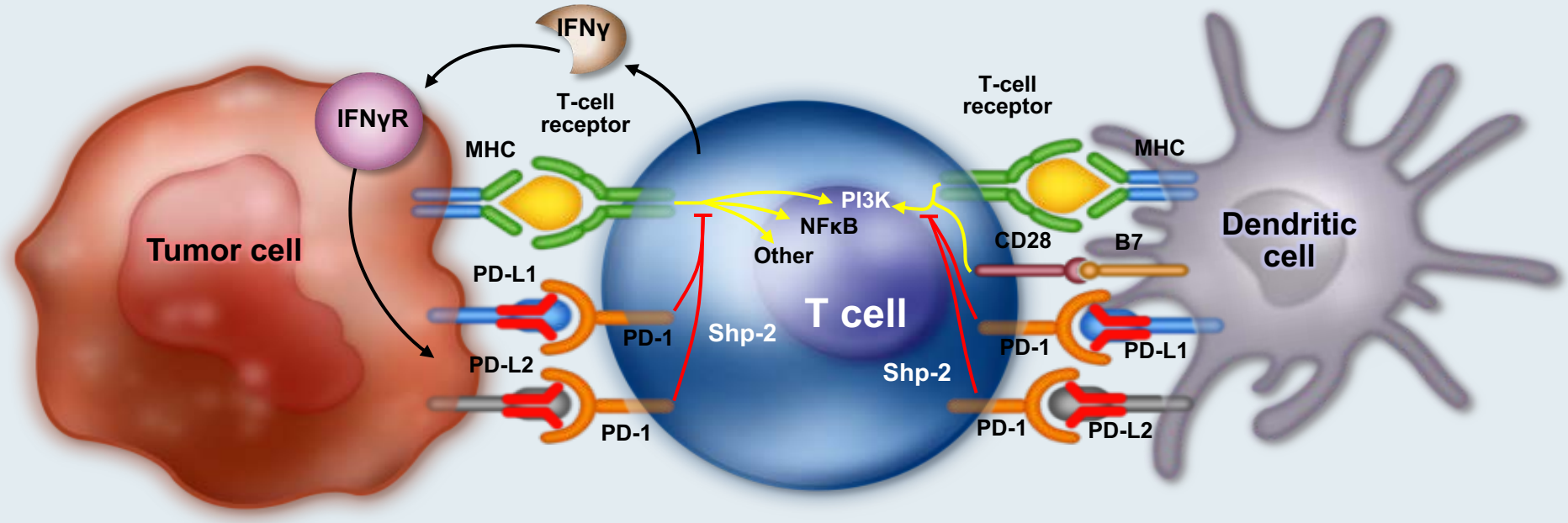
NYU Langone Health

Courtesy of Arjun V. Balar, MD

Anti-PD-1/PD-L1 Antibodies: Mechanism of Action

- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function
  - Anti-PD-1 antibodies bind PD-1 receptors on T cells and disrupt negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function
  - Anti-PD-L1 antibodies bind PD-L1 receptors



Current Treatment Paradigms Metastatic Urothelial Ca

- Cisplatin eligible
  - gem/cis
- Cisplatin ineligible
  - immunotherapy (pembro or atezo) if PD-L1+
  - gem/carbo
- Chemotherapy unfit
  - immunotherapy (pembro or atezo)
- Platinum refractory
  - 5 immunotherapies (pembro level 1 evidence)

Courtesy of Peter H O'Donnell, MD

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

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

- **Pembrolizumab is indicated for the treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and *whose tumors express PD-L1 (CPS ≥10)* as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status**

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

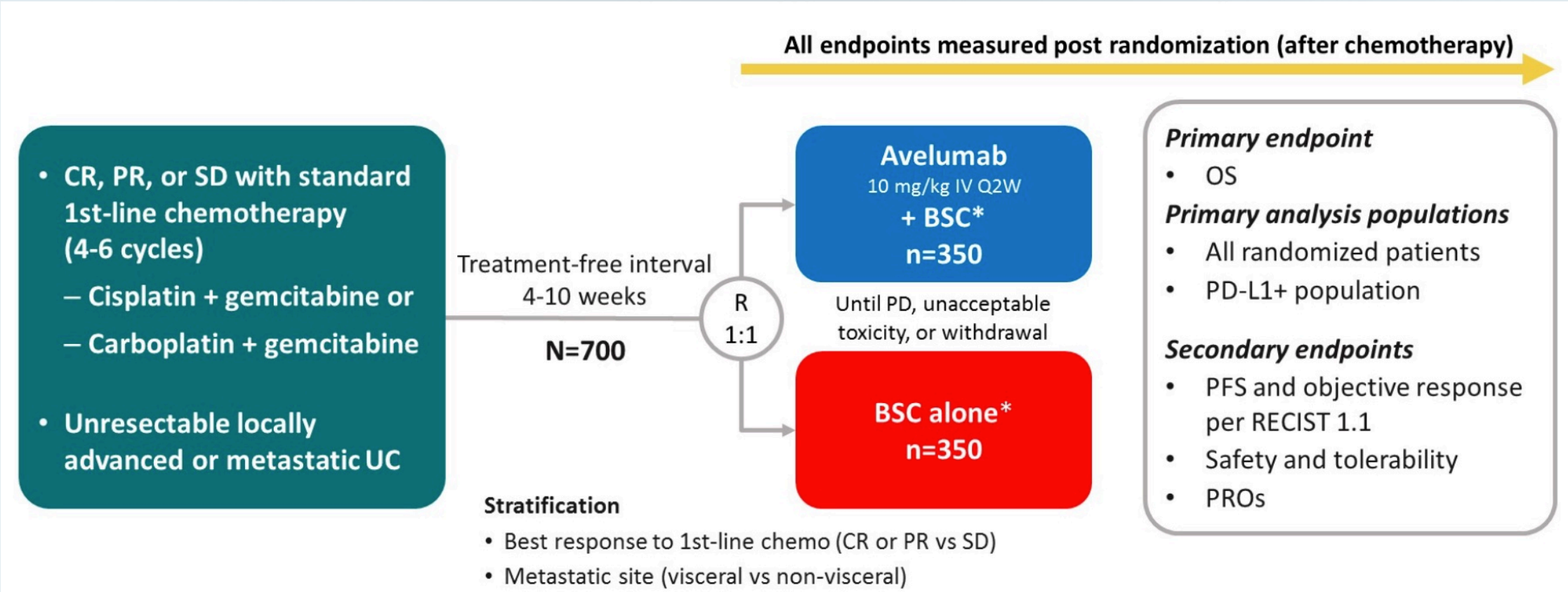
Courtesy of Arjun V. Balar, MD

Maintenance Avelumab + Best Supportive Care (BSC) versus BSC Alone After Platinum-Based First-Line (1L) Chemotherapy in Advanced Urothelial Carcinoma (UC): JAVELIN Bladder 100 Phase III Interim Analysis

Powles T et al.

ASCO 2020;Abstract LBA1 (Plenary)

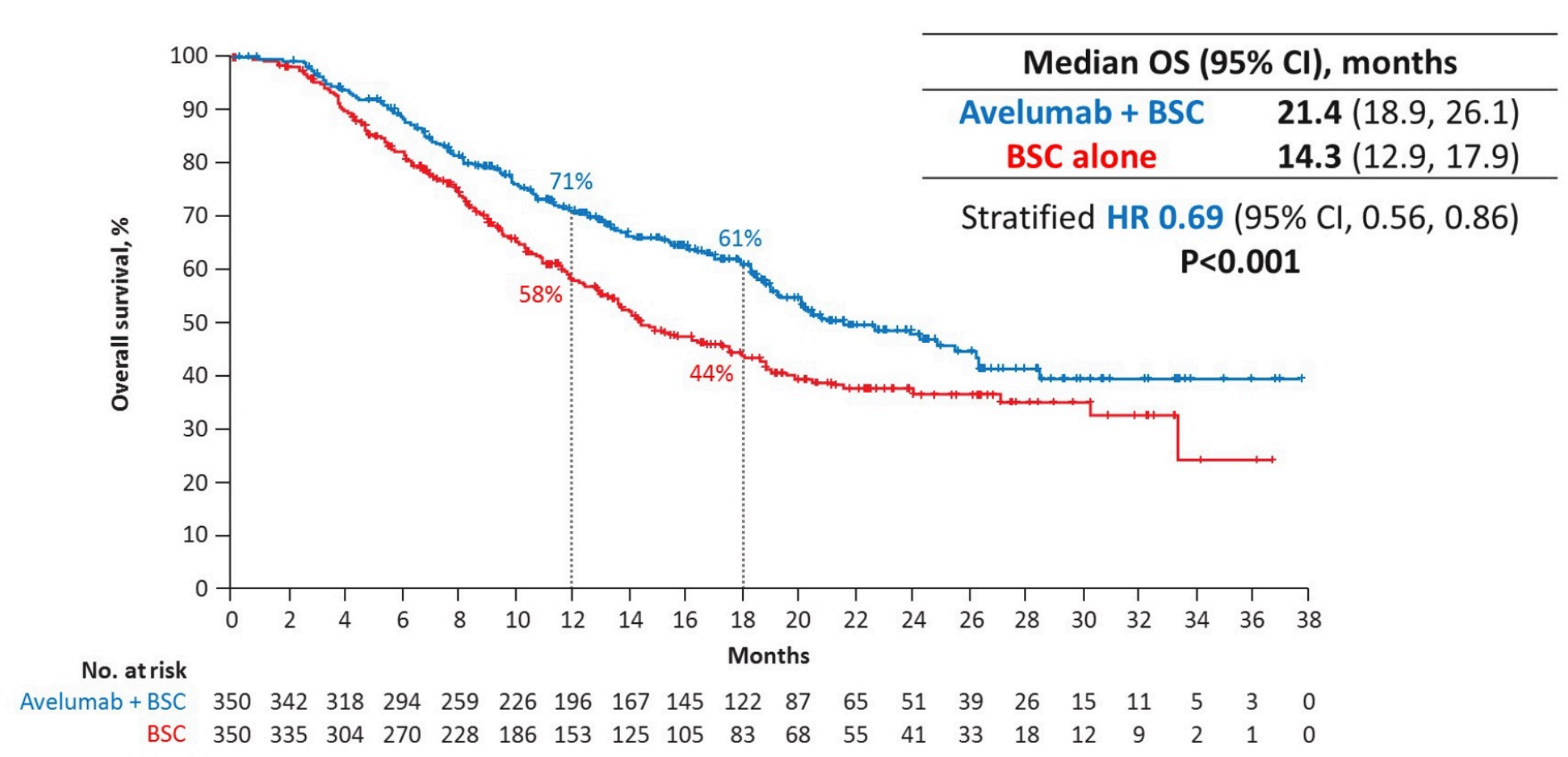
JAVELIN Bladder 100 Phase III Study Schema



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, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

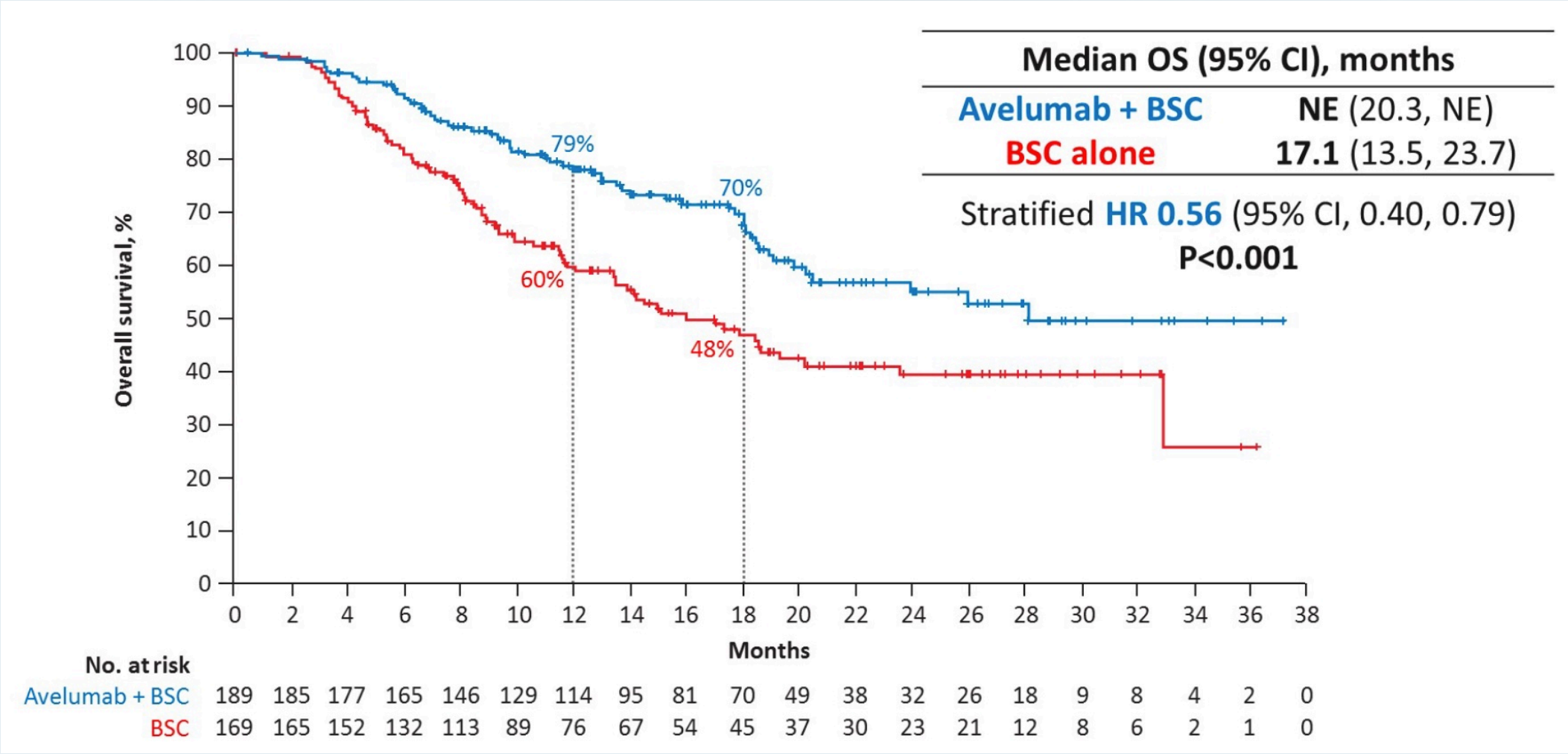
Powles T et al. ASCO 2020;Abstract LBA1.

JAVELIN Bladder 100: OS in the Overall Population



Powles T et al. ASCO 2020;Abstract LBA1.

JAVELIN Bladder 100: OS in the PD-L1+ Population

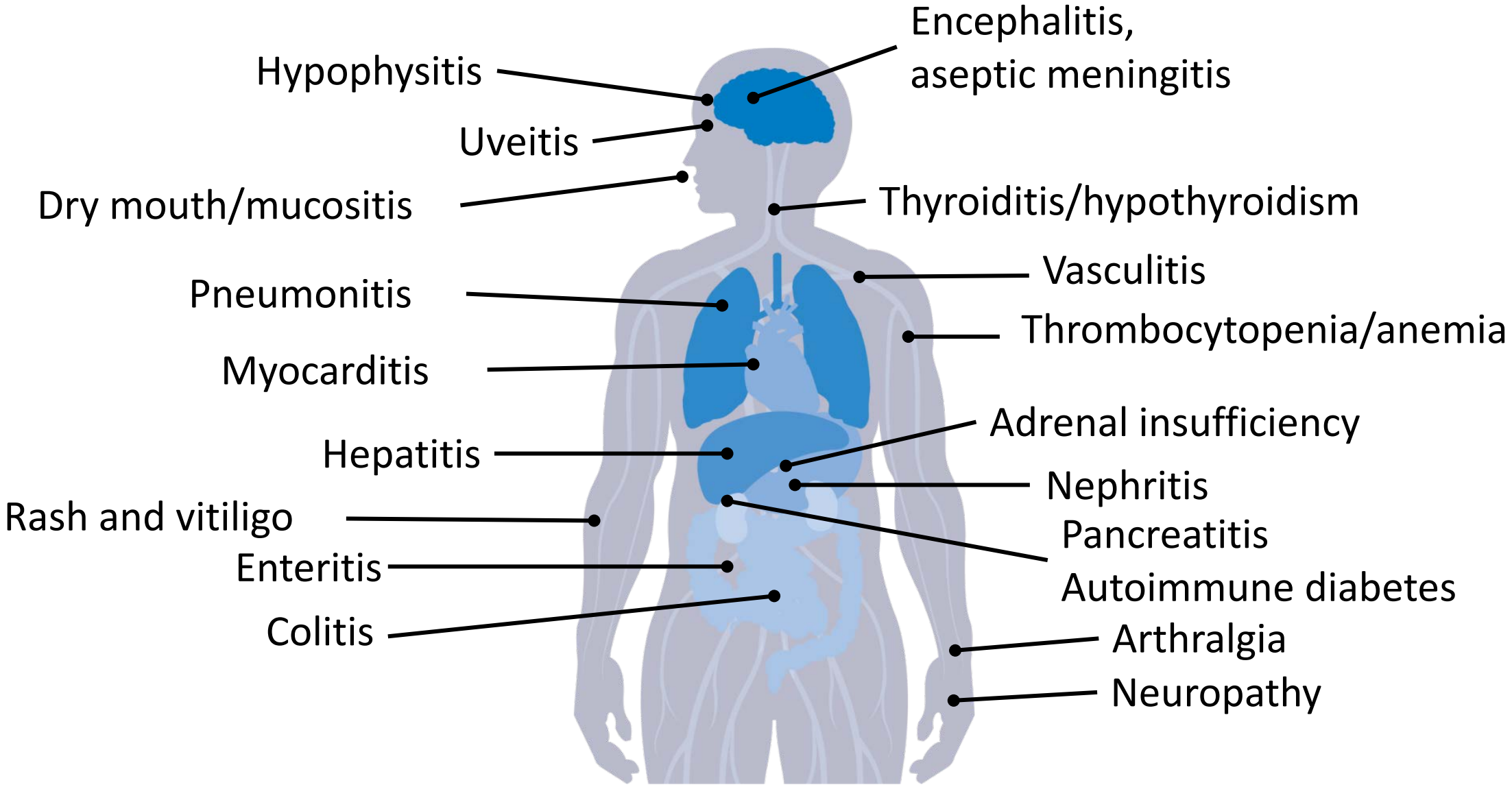


Powles T et al. ASCO 2020;Abstract LBA1.

FDA-Approved Anti-PD-1/PD-L1 Antibodies for Patients with Progressive Metastatic UBC

Agent	Initial approval date
Atezolizumab (PD-L1)	May 2016
Nivolumab (PD-1)	February 2017
Durvalumab (PD-L1)	May 2017
Avelumab (PD-L1)	May 2017
Pembrolizumab (PD-1)	May 2017

The Constellation of irAEs



Courtesy of Arjun V. Balar, MD

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Case 3: A 95-year-old man with non-muscle-invasive UBC

- Selection of therapy for BCG-unresponsive disease

Case Presentation: An 80-year-old woman with metastatic UBC

Special Considerations

- Presents with hematuria; diagnosed with 3-cm T2N1M1b UBC
  - Bone and nodal metastases
- Quit smoking 40 years ago; reduced hearing
- Cr Cl 40 mL/min; PD-L1-positive
- Lives alone in area with high number of COVID-19 cases
  - Concerned about risk of infection and cancer care being compromised due to impact of COVID-19 on resources
- Extensive degenerative joint disease; 2 hip replacements

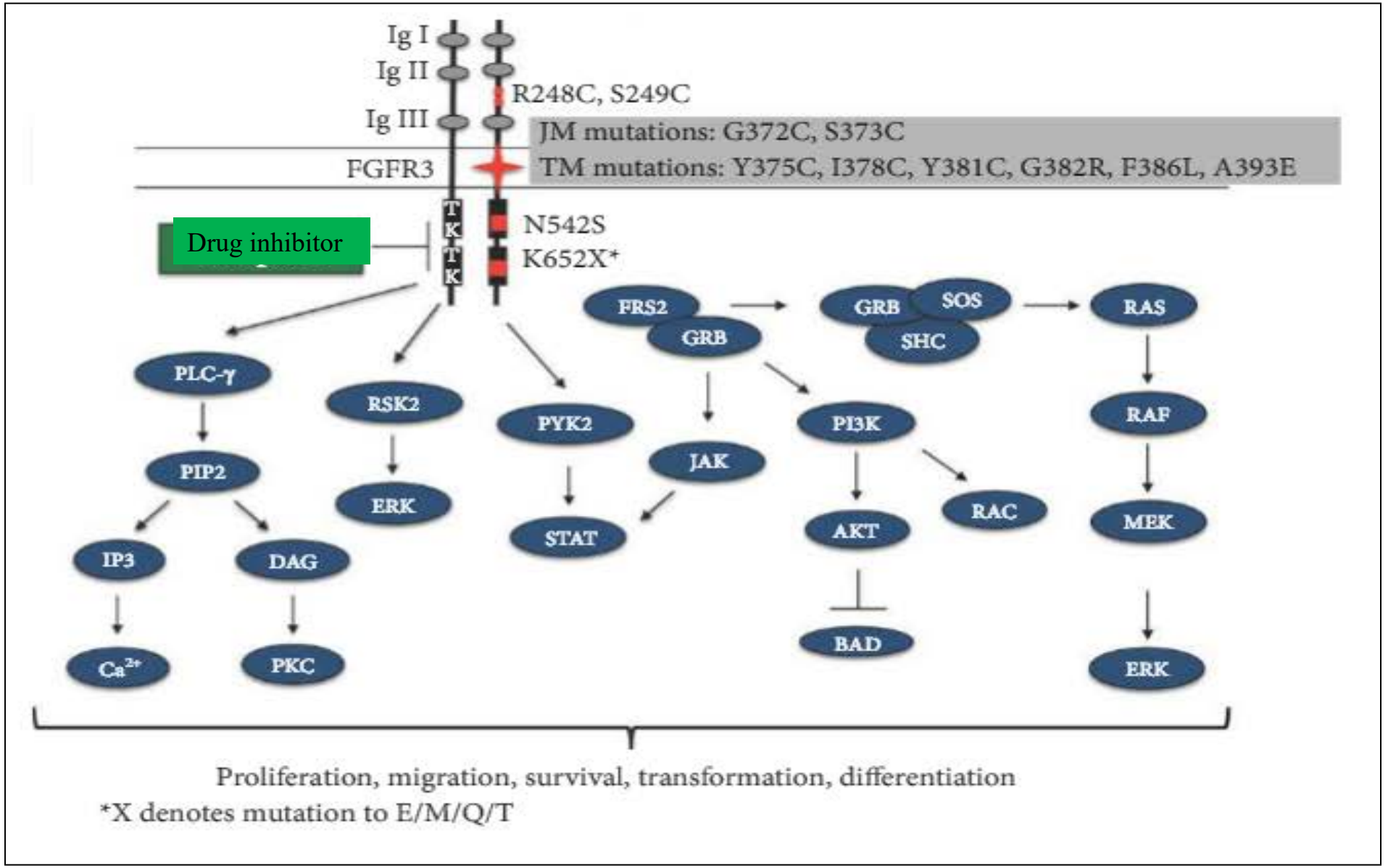
Decision 1: First-line treatment?

- Pembrolizumab initiated and tolerated well, but symptomatic disease progression after 4 months
- Found to have an FGFR3 gene mutation

Decision 2: Second-line treatment?

- Erdafitinib or enfortumab vedotin

FGFR Inhibition



Courtesy of Peter H O'Donnell, MD

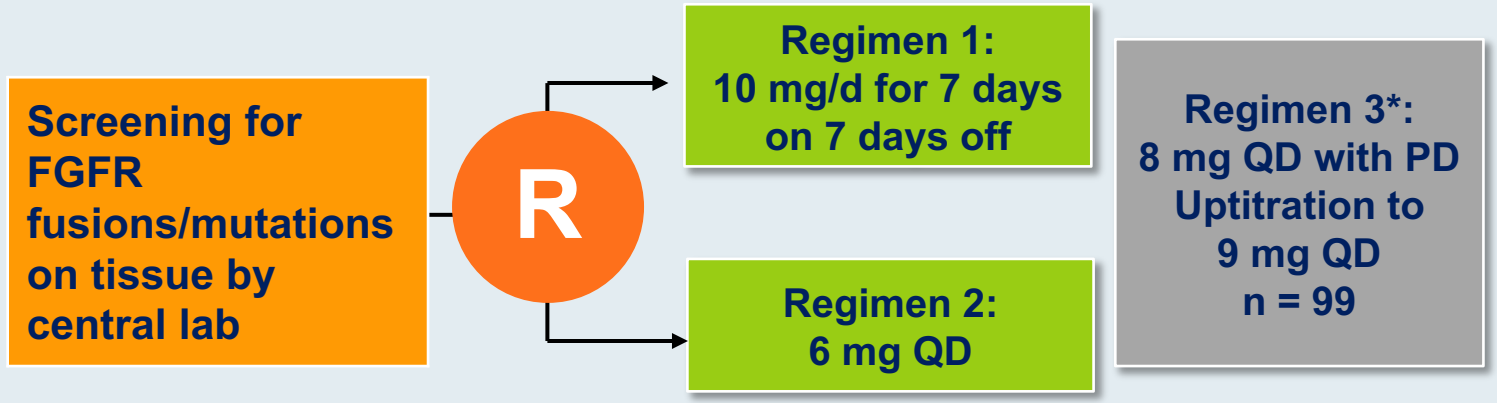
modified from Sethakorn and O'Donnell, BJUI (2016)

BLC2001: A Phase II Study of the Oral Pan-FGFR (1-4) Inhibitor Erdafitinib

Actual enrollment: 239

Eligibility

- Metastatic or unresectable locally advanced UC
- Prior ICI allowed
- Progression on ≥1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo OR
- Chemo-naïve: cisplatin ineligible per protocol criteria†



Primary endpoint: Objective response rate

* Dose uptitration if ≥5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs
† Ineligibility for cisplatin: impaired renal function or peripheral neuropathy

Siefker-Radtke AO et al. *Proc ASCO* 2018;Abstract 4503; www.clinicaltrials.gov; Accessed May 24, 2019 (NCT02365597).

Erdafitinib FDA Approval

- Accelerated approval for patients with locally advanced or metastatic urothelial carcinoma, with susceptible FGFR3 or FGFR2 genetic alterations, that has progressed during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (Apr 2019)

Courtesy of Peter H O'Donnell, MD

Erdafitinib - Toxicities

Most Common Treatment-Related AEs (TRAEs)

Reported in >20% of patients	8 mg continuous dose (n = 99)	
Patients with TRAEs, n (%)	**Any grade**	**Grade 3**
Hyperphosphatemia	72 (73)	2 (2)
Stomatitis	54 (55)	9 (9)
Dry mouth	43 (43)	0
Diarrhea	37 (37)	4 (4)
Dysgeusia	35 (35)	1 (1)
Dry skin	32 (32)	0
Alopecia	27 (27)	0
Decreased appetite	25 (25)	0
Hand-foot syndrome	22 (22)	5 (5)
Fatigue	21 (21)	2 (2)

Most were grade 1 or 2

There were no grade 4 or 5 TRAEs

Serious TRAEs were reported in 9 patients (9%); none was reported in more than 1 patient

Siefker-Radtke AO et al. ASCO 2018;Abstract 4503.

Courtesy of Peter H O'Donnell, MD

Erdafitinib – Key Toxicities

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Disorders

Erdafitinib can cause ocular disorders, including central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) resulting in visual field defect.

CSR/RPED was reported in 25% of patients treated with Erdafitinib, with a median time to first onset of 50 days. Grade 3 CSR/RPED, involving central field of vision, was reported in 3% of patients. CSR/RPED resolved in 13% of patients and was ongoing in 13% of patients at the study cutoff. CSR/RPED led to dose interruptions and reductions in 9% and 14% of patients, respectively and 3% of patients discontinued Erdafitinib.

Dry eye symptoms occurred in 28% of patients during treatment with Erdafitinib and were Grade 3 in 6% of patients. All patients should receive dry eye prophylaxis with ocular demulcents as needed.

Perform monthly ophthalmological examinations during the first 4 months of treatment and every 3 months afterwards, and urgently at any time for visual symptoms. Ophthalmological examination should include assessment of visual acuity, slit lamp examination, fundoscopy, and optical coherence tomography.

Withhold Erdafitinib when CSR occurs and permanently discontinue if it does not resolve within 4 weeks or if Grade 4 in severity. For ocular adverse reactions, follow the dose modification guidelines [*see Dosage and Administration (2.3)*].

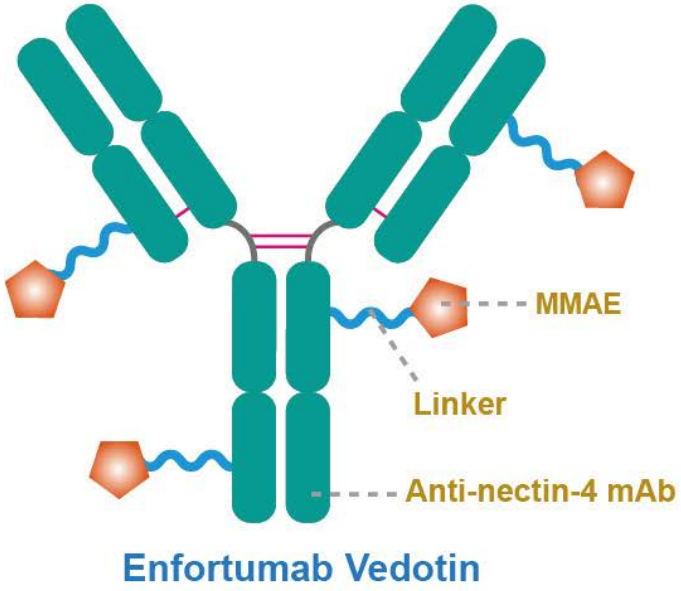
5.2 Hyperphosphatemia

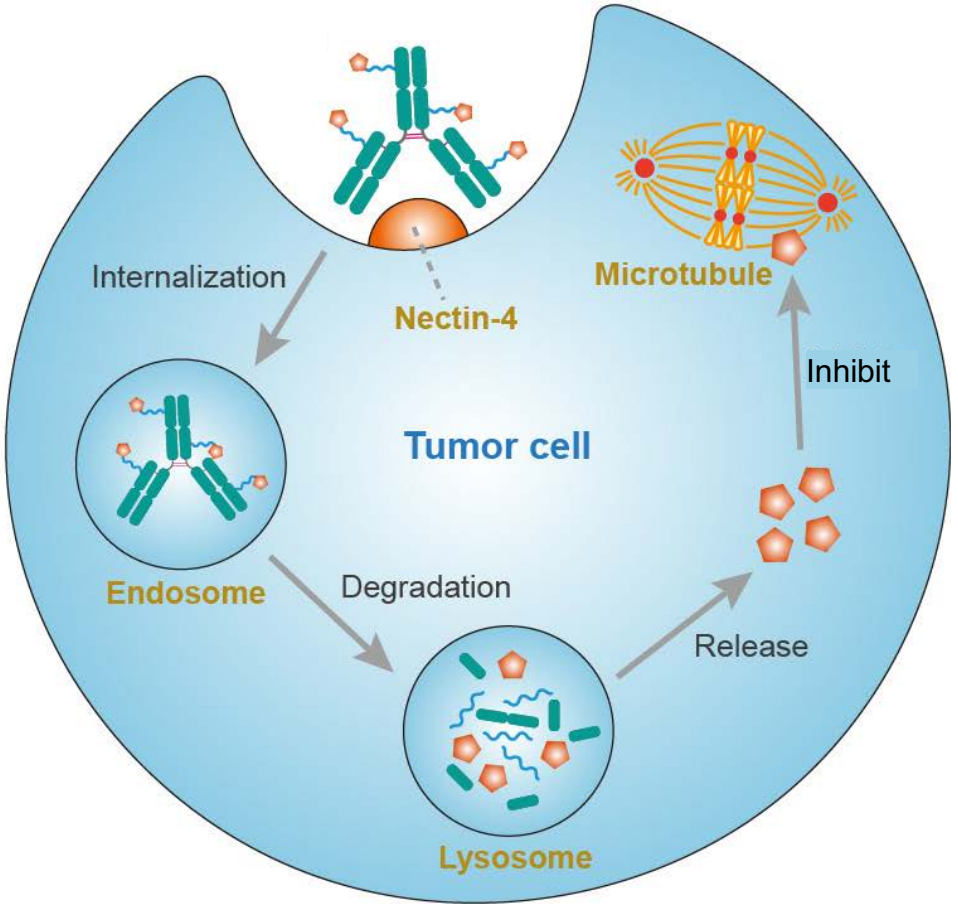
Increases in phosphate levels are a pharmacodynamic effect of Erdafitinib [*see Pharmacodynamics (12.2)].* Hyperphosphatemia was reported as adverse reaction in 76% of patients treated with Erdafitinib. The median onset time for any grade event of hyperphosphatemia was 20 days (range: 8 –116) after initiating Erdafitinib. Thirty-two percent of patients received phosphate binders during treatment with Erdafitinib.

Courtesy of Peter H O'Donnell, MD

erdafitinib FDA label

Enfortumab Vedotin
Proposed Mechanism of Action





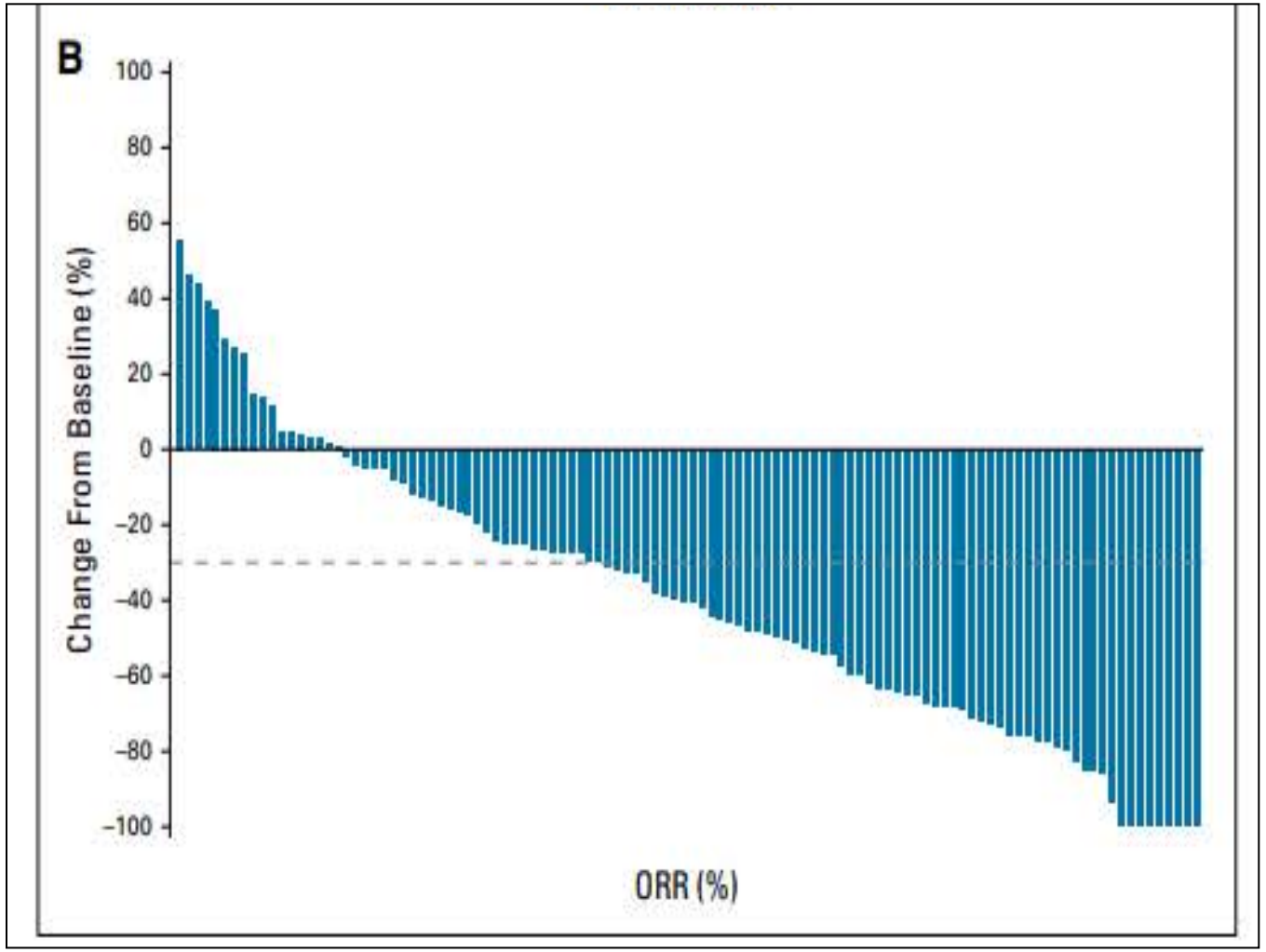
Courtesy of Peter H O'Donnell, MD

MMAE = monomethyl auristatin E

figure adapted from creativebiolabs.net

Enfortumab Efficacy Data

- 44% ORR
  - ➢ 12% CR
  - ➢ 32% PR
- 84% of evaluable patients showed tumor reduction
- Median DOR = 7.6 mos
- Median PFS = 5.8 mos
- Median OS = 11.7 mos



Efficacy data mirror those from phase I study of n=155 UC patients

Courtesy of Peter H O'Donnell, MD

Rosenberg et al., JCO (2019)
Rosenberg et al., JCO (2020)

FDA Approval of EV

- For adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting (Dec 18, 2019)

Courtesy of Peter H O'Donnell, MD

fda.gov

EV - Tolerability

Variable	Patients (N = 125)	
Any adverse event	125 (100)	
Treatment-related adverse events	117 (94)	
Grade ≥ 3 treatment-related adverse events	68 (54)	
Treatment-related serious adverse events	24 (19)	
Treatment-related adverse events resulting in treatment discontinuation	15 (12)	
Treatment-related adverse events leading to death*	0 (0)	
Treatment-related adverse events occurring in ≥ 20% (preferred term)	Any Grade	Grade ≥ 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	0
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	0
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Rash maculopapular	27 (22)	5 (4)
Weight decreased	28 (22)	1 (1)
Dry skin	28 (22)	0

NOTE. Data are presented as No. (%).

*There were no treatment-related deaths during the 30-day safety reporting period. One death as a result of interstitial lung disease that occurred outside the safety reporting period was reported as treatment related.

Courtesy of Peter H O'Donnell, MD

Rosenberg et al., JCO (2019)

Enfortumab – Key Toxicities

EV-201: Cohort 1 Treatment-Related Adverse Events of Interest

Peripheral neuropathy: 50% any grade, 3% ≥Grade 3

- No Grade 4 events
- Sensory events most common (44%, all patients)
- Of patients with peripheral neuropathy at enrollment, 48% did not worsen
- 76% had resolution or events ongoing at Grade 1 at last follow-up

Rash: 48% any grade, 12% ≥Grade 3

- No Grade 4 events
- 1 case of Grade 3 Stevens-Johnson Syndrome was reported by the investigator
- 93% resolution or improvement at last follow-up
- Of those with ongoing rash, most (75%) were Grade 1

Hyperglycemia: 11% any grade, 6% ≥Grade 3

- 68% of patients with pre-existing hyperglycemia did not develop a treatment-related event
- 1 Grade 4 event, resolved, no need for ongoing medication
- 71% resolution or improvement at last follow-up

Courtesy of Peter H O'Donnell, MD

adapted from Petrylak et al., presented at ASCO 2019

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- Selection of therapy for BCG-unresponsive disease

Case Presentation: A 95-year-old man with NMIUBC

Special Considerations

- Noninvasive UBC for 11 years
  - BCG
  - Intravesicular chemotherapy
- History of coronary artery disease
- Does not want further surgeries
- Due to concerns about COVID infection, is seen for initial consult by telemedicine
- Pembrolizumab x 3 cycles
  - Follow-up cystoscopy shows stable disease

Sulfi Ibrahim, MD

Thank you for joining us!

CNE (NCPD) credit information will be emailed to each participant tomorrow morning.