Oncology Grand Rounds

New Agents and Strategies in Urothelial Bladder Carcinoma

Thursday, June 18, 2020

5:00 PM – 6:30 PM ET

Faculty

Arjun Balar, MD
Anastassia Daskalova, NP
Peter H O'Donnell, MD
Susan K Roethke, CRNP, MSN, ANP-BC, AOCNP

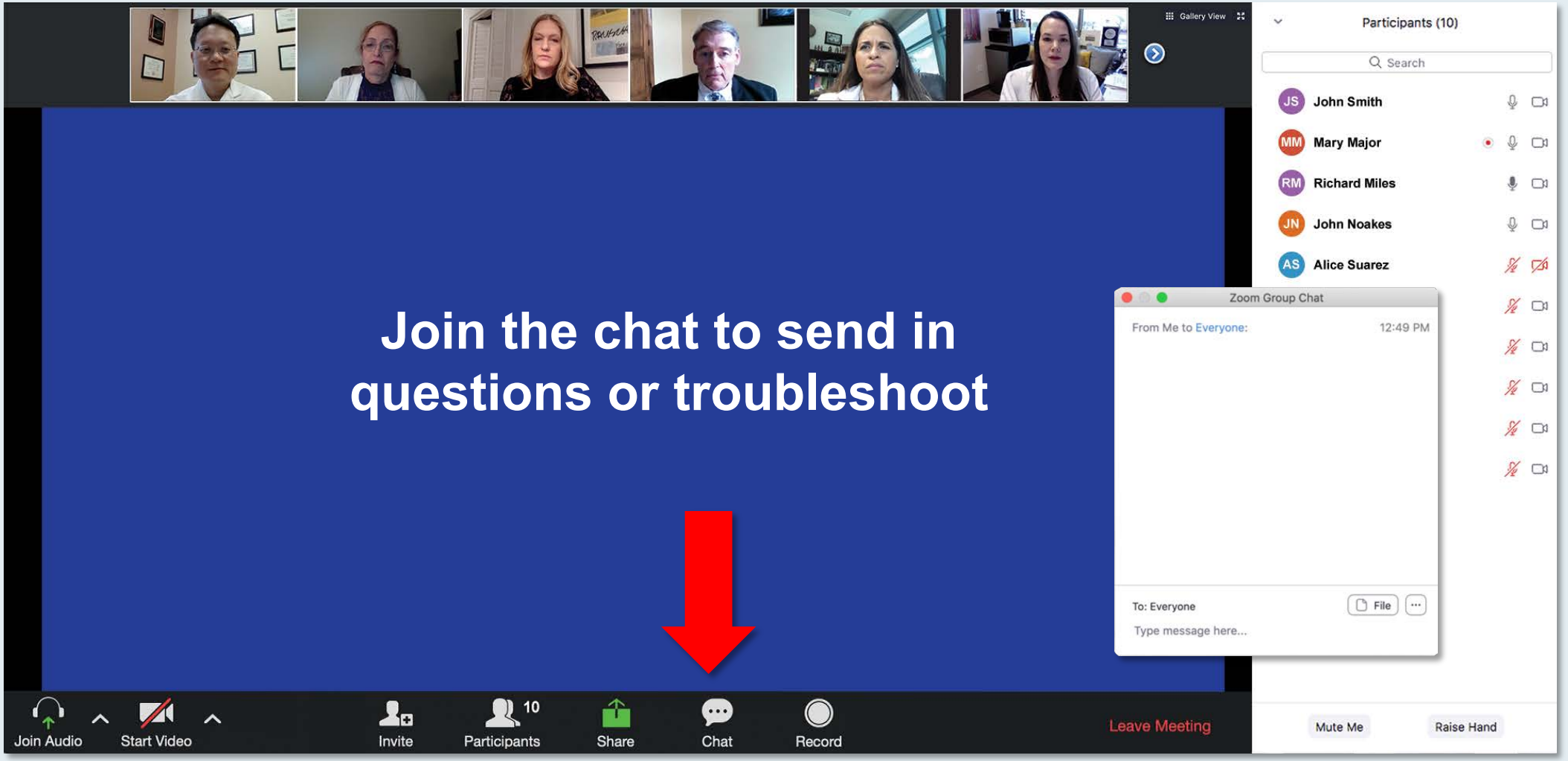
Moderator

Neil Love, MD

Jointly provided by USF Health RTP RESEARCH TO PRACTICE

Familiarizing yourself with the Zoom interface

How to participate in the chat



RTP Live Webinar Nursing Series

Monday	Tuesday	Wednesday	Thursday	Friday
25	26 **Breast Ca** **5:00 PM**	27	28 **GI Ca** **5:00 PM**	29
Jun 1	2 **Lymphoma** **5:00 PM**	3	4 **CLL** **5:00 PM**	5
8	9 **GYN** **5:00 PM**	10	11 **Metastatic Lung Ca** **5:00 PM**	12
15	16 **Locally Advanced Lung Ca** **5:00 PM**	17	18 **Bladder Ca** **5:00 PM**	19
22	23 **CAR-T** **5:00 PM**	24	25 **PARP** **5:00 PM**	26
29	30 **Prostate Ca** **5:00 PM**	Jul 1 9 AM	2	3
6	7	8	9	10

About the Enduring Program

- This webinar is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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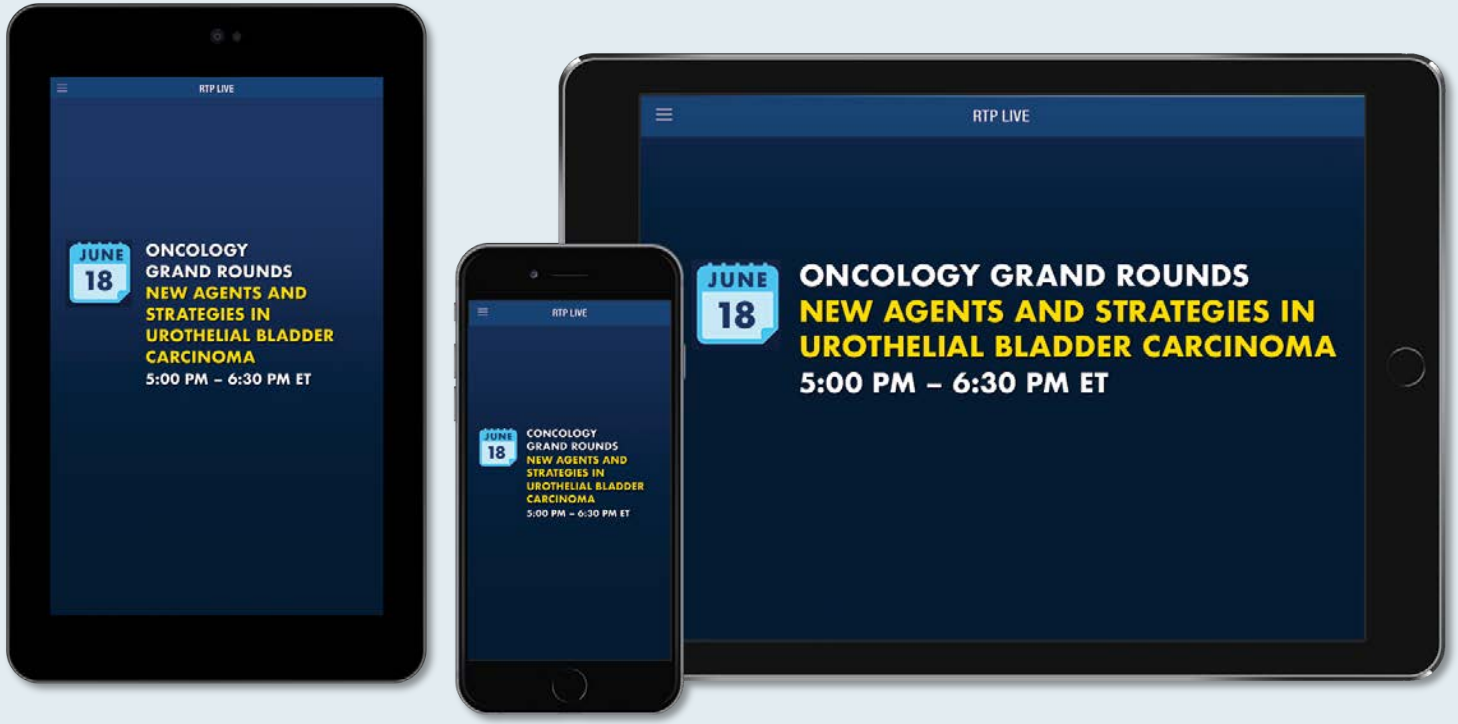

Oncology Grand Rounds

New Agents and Strategies in Chimeric Antigen Receptor T-Cell Therapy

Tuesday, June 23, 2020

5:00 PM – 6:30 PM ET

Faculty

Krishna Komanduri, MD
Nikhil C Munshi, MD
Sattva S Neelapu, MD
Tiffany A Richards, PhD, ANP-BC, AOCNP
Elizabeth Zerante, AGACNP-BC

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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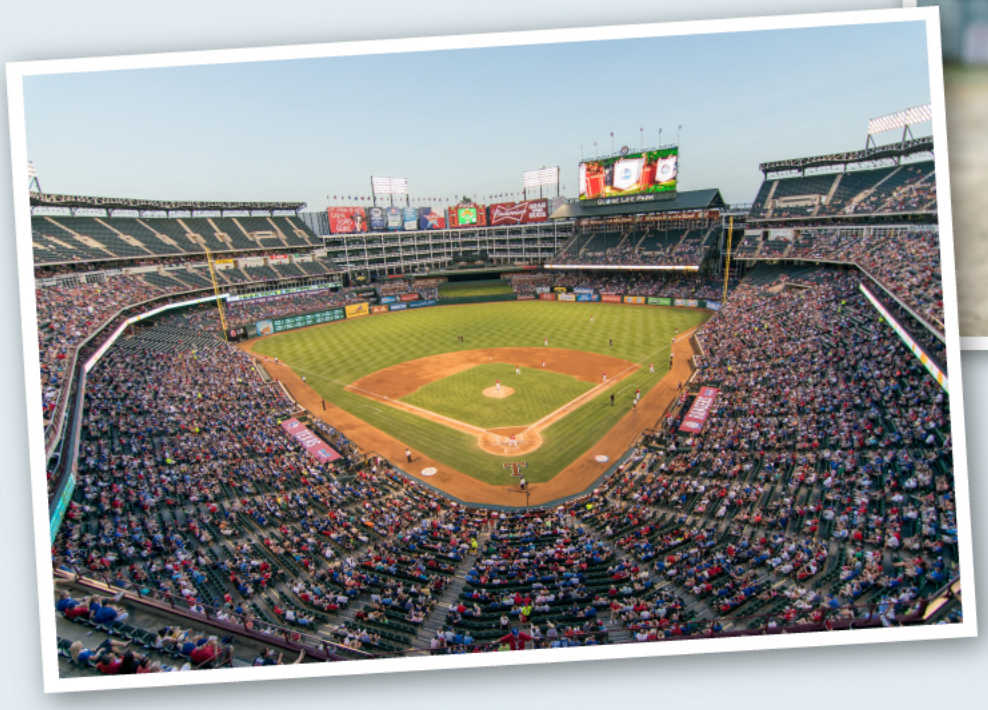
Arjun Balar, MD
NYU Langone Health
New York, New York

Anastassia Daskalova, NP
Genitourinary Oncology, Mount Sinai
New York, New York

Peter H O'Donnell, MD
The University of Chicago
Chicago, Illinois



Susan K Roethke, CRNP, MSN, ANP-BC, AOCNP
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Agenda

Module 1: Overview of Urothelial Bladder Cancer (UBC) Management

Case Presentation: Ms Roethke — 85-year-old widower and retired automotive mechanic

Module 2: Anti-PD-1/PD-L1 Antibodies for Patients with Nonmetastatic UBC

Module 3: Risks and Benefits of Immune Checkpoint Inhibitors in Advanced UBC

Case Presentation: Ms Daskalova — 78-year-old woman with a PMH of cervical cancer

Module 4: Integration of FGFR-Directed Therapy into Current UBC Management Algorithms

Case Presentation: Ms Roethke — 62-year-old auto body repairman

Module 5: Antibody-Drug Conjugates in UBC

Case Presentation: Ms Roethke — 70-year-old married man and retired telephone technician

Module 6: Management of UBC in the Era of COVID-19

Case Presentation: Ms Daskalova — 63-year-old man

Module 1: Overview of Urothelial Bladder Cancer (UBC) Management

When was the last time you encountered a patient with bladder cancer?

a. Within the past week

b. Between 1 week and 1 month ago

c. Between 1 month and 6 months ago

d. Between 6 months and 1 year ago

e. More than 1 year ago

f. I have not encountered a patient with bladder cancer in my practice

Which of the following is the most significant risk factor for the development of bladder cancer?

a. Obesity

b. Smoking

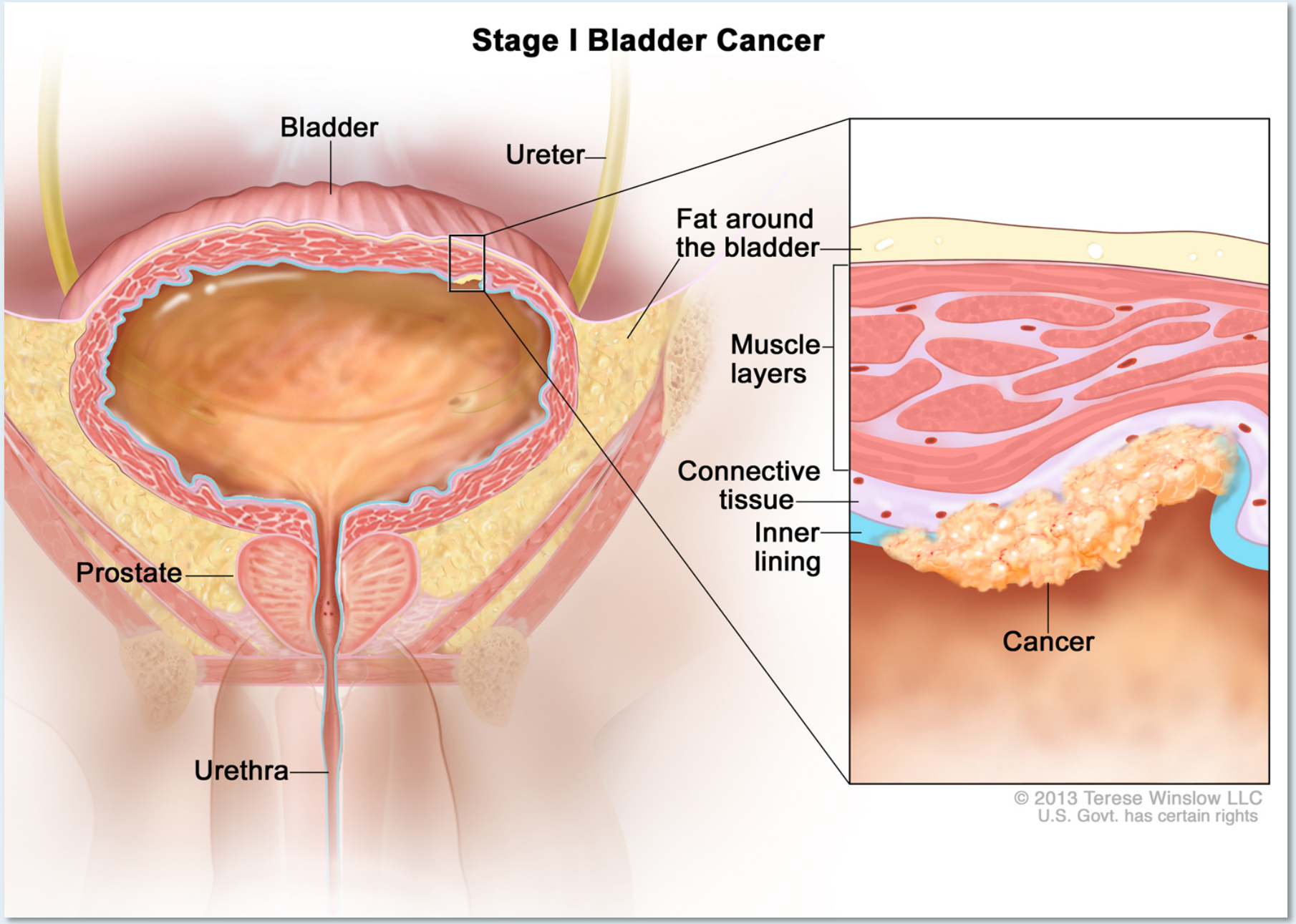
c. Female sex

d. I don’t know

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

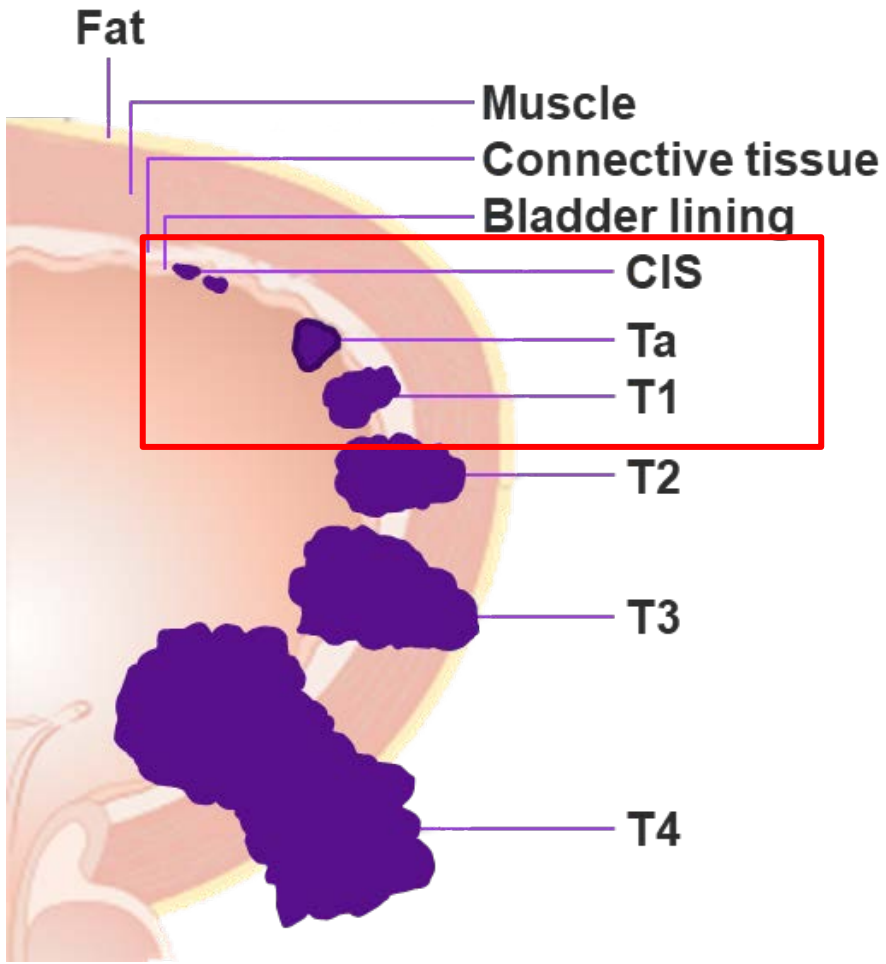
ACS Cancer Facts & Figures 2020; www.cancer.org.



With permission from Terese Winslow LLC

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



Cumberbatch MGK et al. *Eur Urol.* 2018;74:784-795. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): bladder cancer (Version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed January 7, 2019. Hemdan T et al. *J Urol*. 2014;191:1244. Herr HW et al. *Urol Oncol.* 2015;33:108.e1-4. 5. Anastasiadis A et al. *Ther Adv Urol.* 2012;4:13-32. US Department of Health and Human Services. BCG-unresponsive nonmuscle invasive bladder cancer: developing drugs and biologics for treatment—Guidance for industry. February 2018. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm529600.pdf. Accessed February 5, 2019. Babjuk M et al. *Eur Urol.* 2017;71:447-461.

NYU Langone Health

Courtesy of Arjun V. Balar, MD

85-year-old Widower and Prior Smoker with PMH of stage IV CKD, HTN, GERD, Anemia of Chronic Disease and Chronic Back Pain (from the practice of Ms Roethke)

- 5/2019: pT1 multifocal, high-grade invasive urothelial cancer (UC), with gross hematuria and clot retention
  - PCNU due to hydronephrosis at initial TURBT
- 6/2019, 8/2019: Recurrent non-muscle invasive disease → BCT
- 11/2019: Admitted with Hgb: 5.5
  - TURBT: Invasive high-grade UC, with invasion of muscularis propria
- Not eligible for platinum-based chemo due to CKD, hearing loss, frailty
- Molecular testing: PD-L1 CPS: 10
- 12/2019: Pembrolizumab 200mg Q3W x 6
  - Changed to 400mg Q6W during COVID-19 pandemic
  - Imaging: Smaller mass, but not contrast CT
- 5/2020 Cystoscopy to change ureteral stent: No visible tumor

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When was the last time you encountered a patient with bladder cancer receiving an anti-PD-1/PD-L1 antibody?

a. Within the past week

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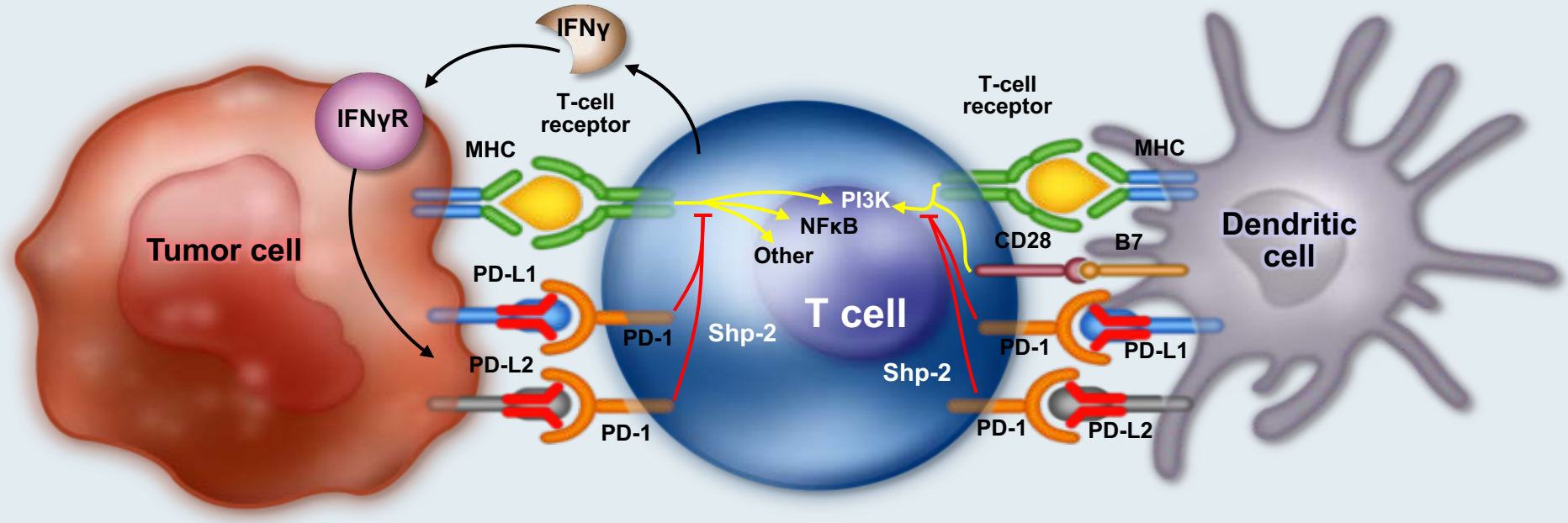
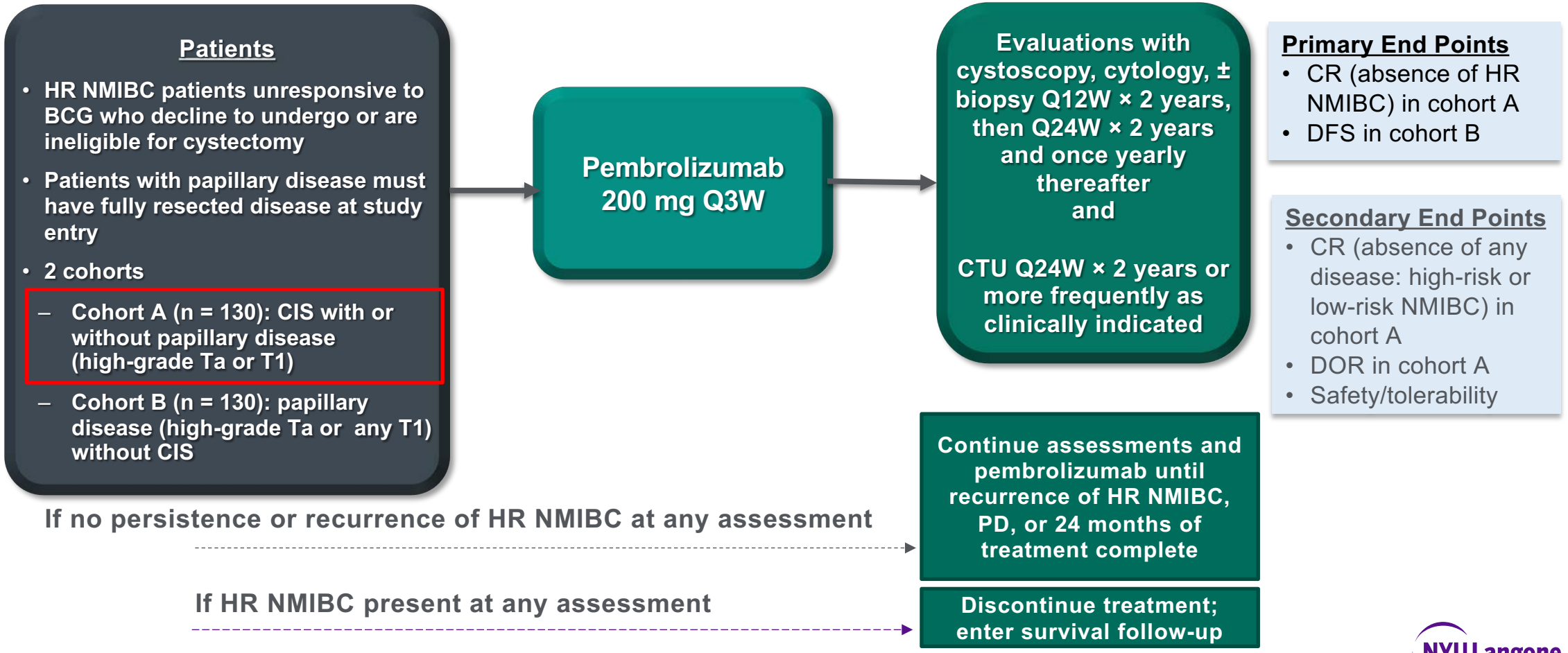
f. I have not encountered a patient with bladder cancer receiving an anti-PD-1/PD-L1 antibody in my practice

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 disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function
  - Anti-PD-L1 antibodies bind PD-L1 receptors



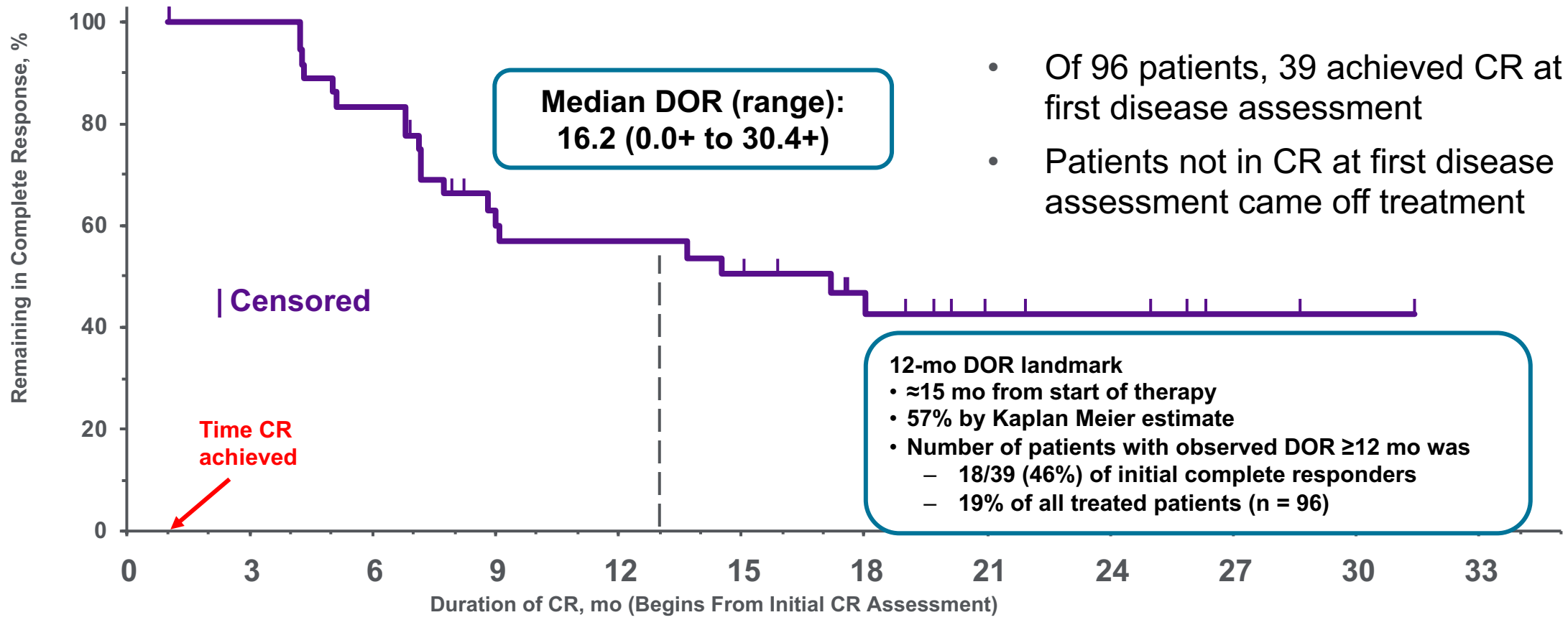
KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



Courtesy of Arjun V. Balar, MD

NYU Langone Health

Duration of Complete Response is Clinically Meaningful



- Of 96 patients, 39 achieved CR at first disease assessment
- Patients not in CR at first disease assessment came off treatment

1. Balar A et al. ASCO GU 2019. Abstract 350. 2. Balar A. FDA ODAC submission 2019.

Courtesy of Arjun V. Balar, MD

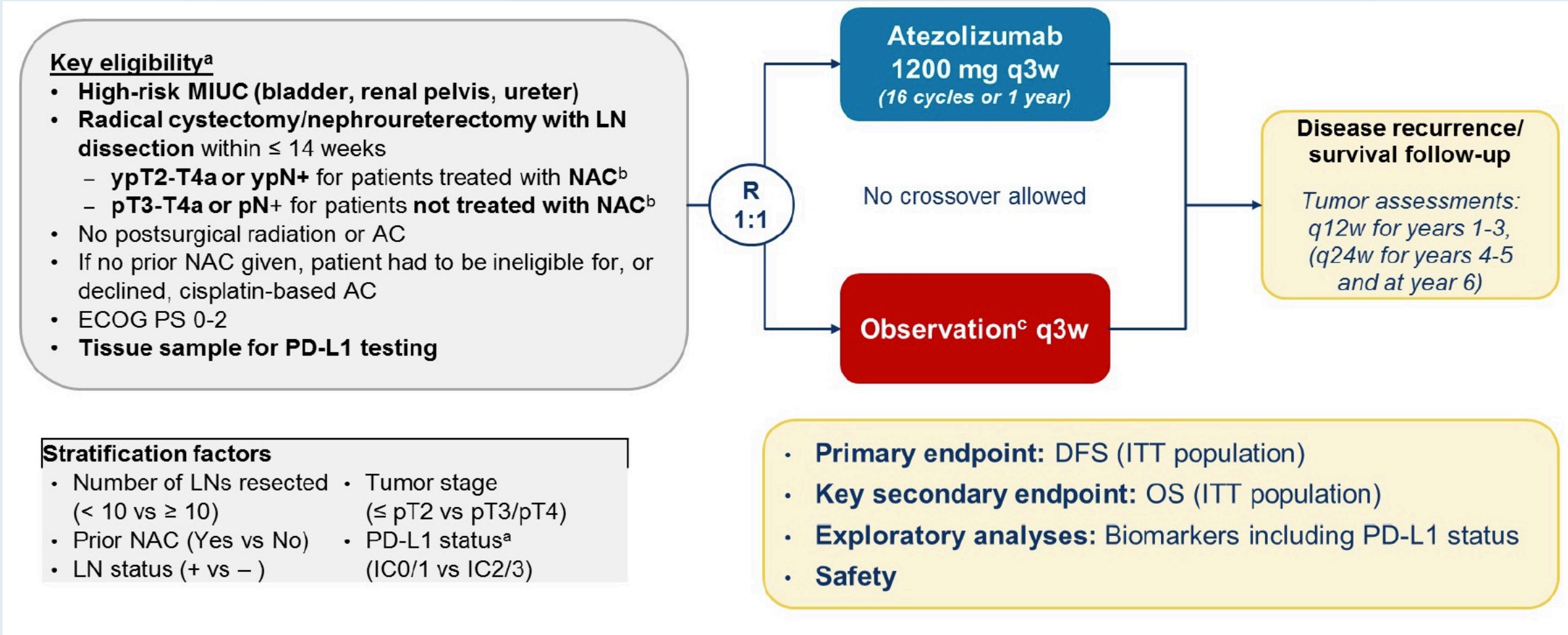
NYU Langone Health

IMvigor010: Primary Analysis from A Phase III Randomized Study of Adjuvant Atezolizumab (Atezo) versus Observation (Obs) in High-Risk Muscle-Invasive Urothelial Carcinoma (MIUC)

Hussain MH et al.

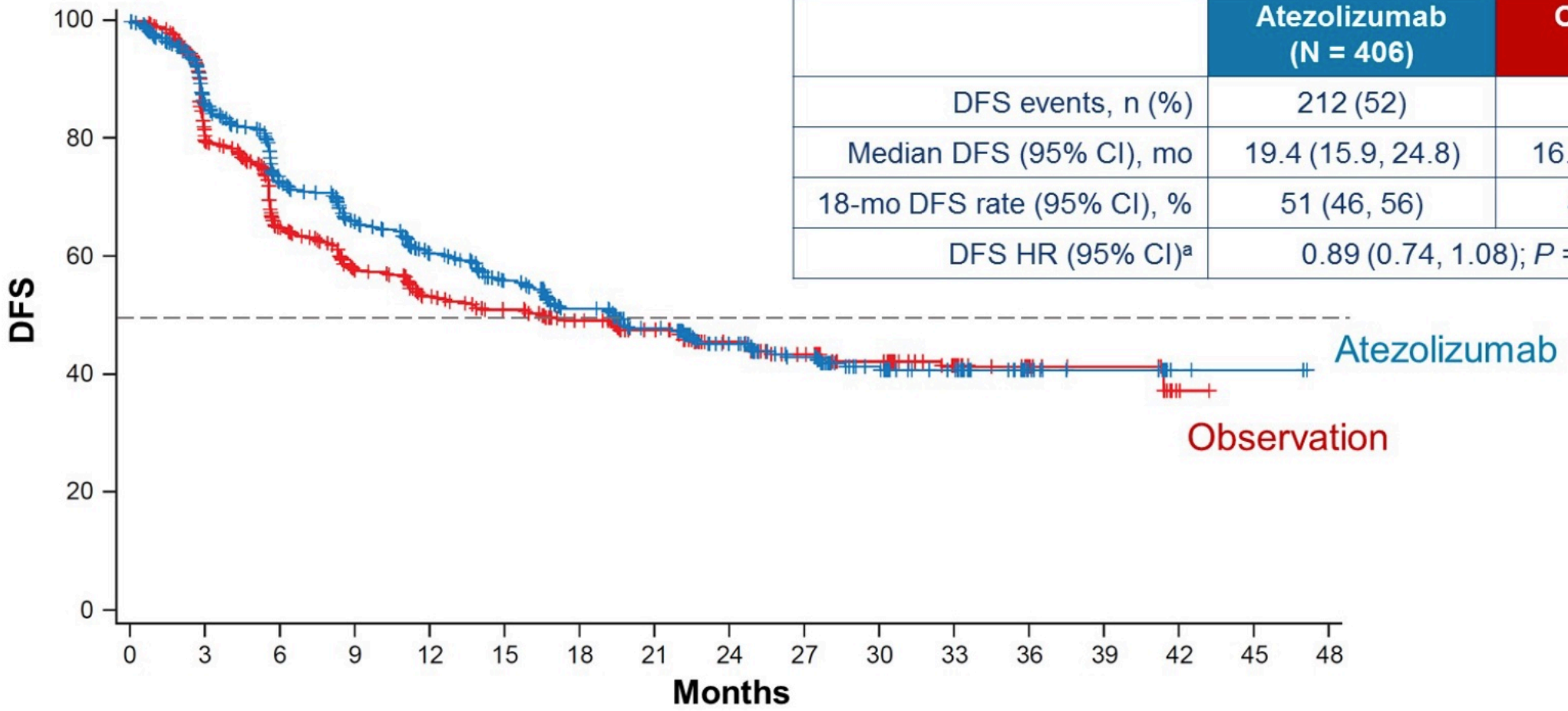
ASCO 2020;Abstract 5000.

IMvigor010 Phase III Trial Schema



Hussain MH et al. ASCO 2020; Abstract 5000.

IMvigor010: Disease-Free Survival (DFS) in ITT Population



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

Hussain MH et al. ASCO 2020; Abstract 5000.

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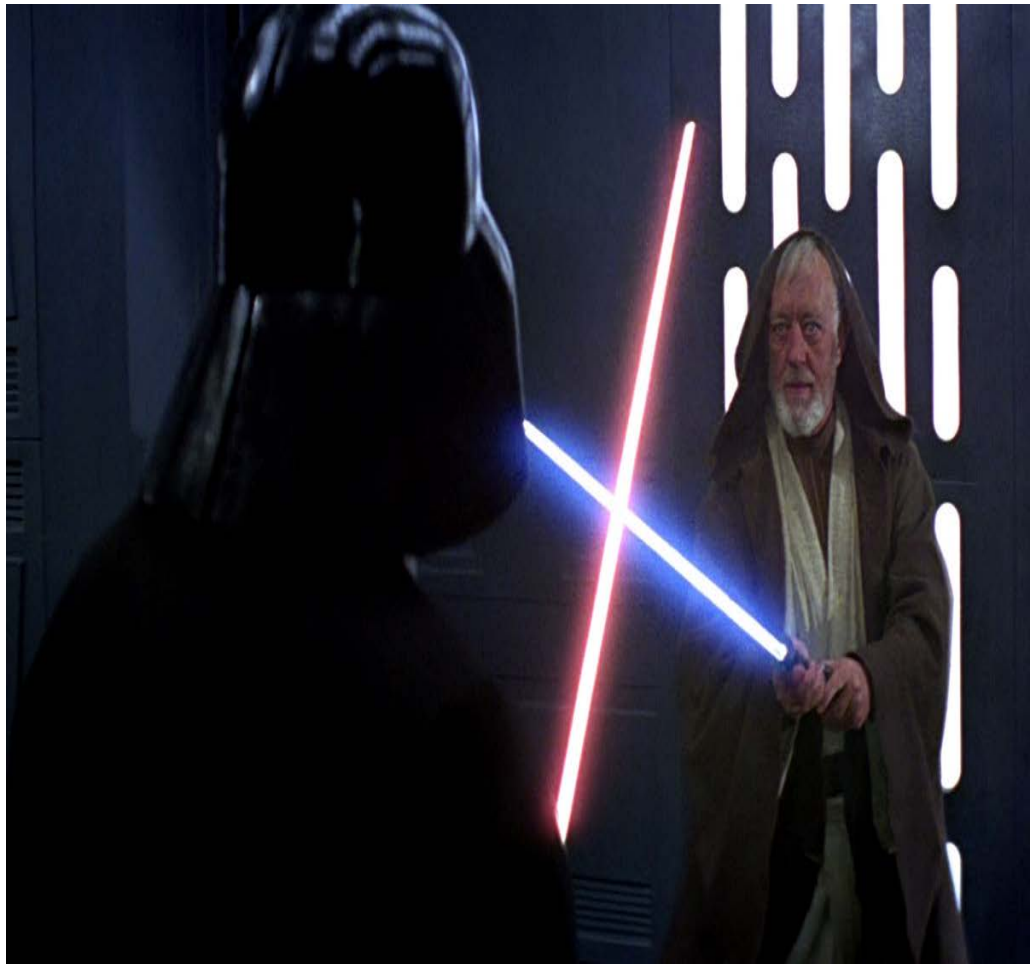
Module 3: Risks and Benefits of Immune Checkpoint Inhibitors in Advanced UBC

A long time ago, in a galaxy far far away?

- 1985 - MVAC reported
- 1997 - Gemcitabine reported to have activity
  - GC found comparable to MVAC in 2000
- Response rates:
  - 50-55% tumor regression
  - additional 33% with stable disease
- Median PFS 7.5 months
- OS 14 months



Courtesy of Peter H O'Donnell, MD

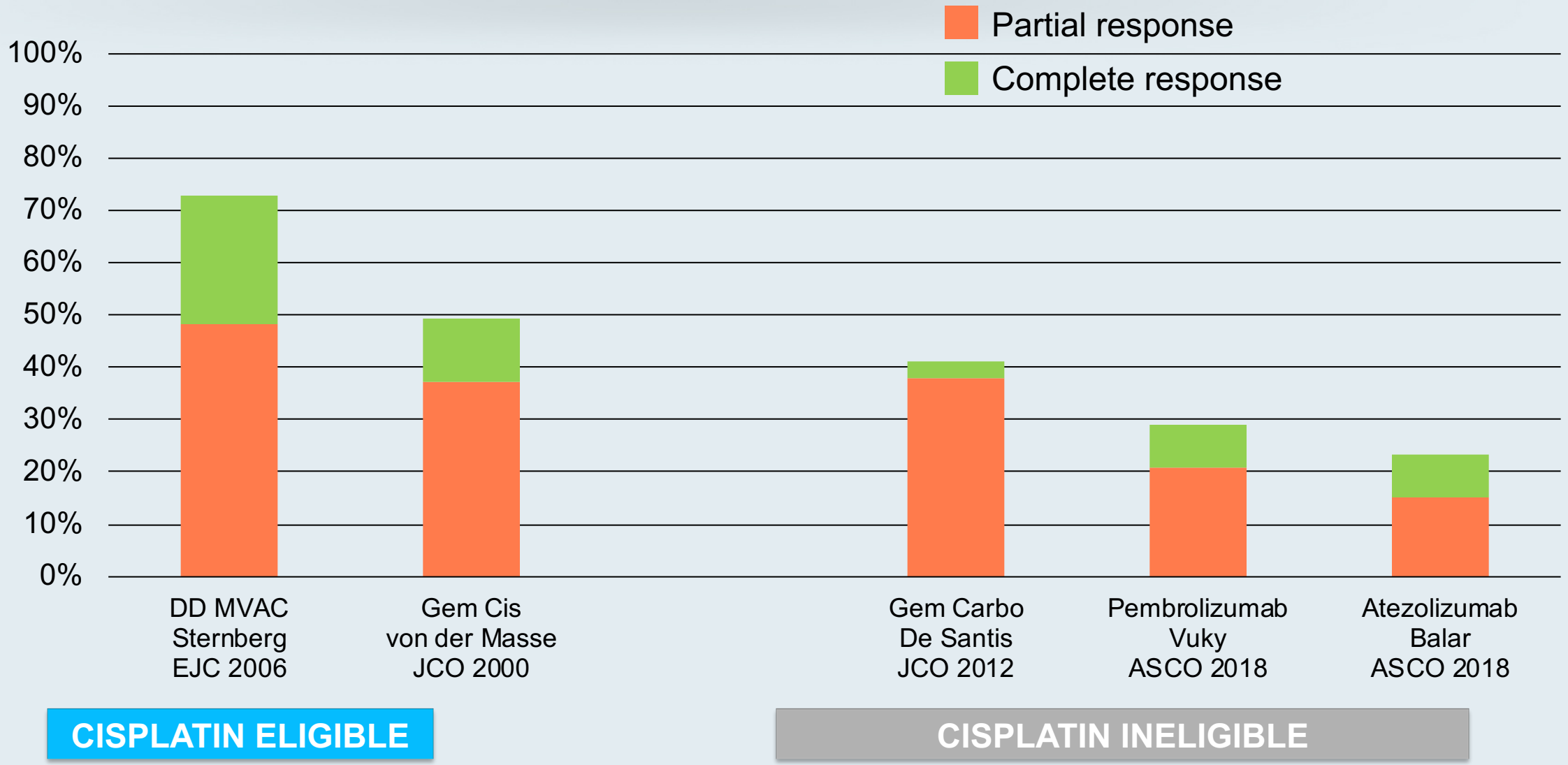
Sternberg et al., J Urol (1985)
Stadler et al., JCO (1997)
von der Maase et al., JCO (2000)

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

Response Rates to First-Line Therapy for Metastatic Urothelial Carcinoma



IMvigor210 Cohort 1 Study Design: First-Line Treatment

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

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

→ **Atezolizumab** 1,200 mg IV every 3 wk until RECIST 1.1 progression

Cohort 2 (n = 310)
Platinum-treated mUC

→ **Atezolizumab** 1,200 mg IV every 3 wk until loss of clinical benefit

Cohort 1: Specific Inclusion Criteria

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

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

Courtesy of Arjun V. Balar, MD

NYU Langone Health

[a] PD-L1 prospectively assessed by a central laboratory, with patients and investigators blinded.

1. Balar A et al. 2016 American Society of Clinical Oncology Annual Meeting (ASCO 2016). Abstract LBA4500. 2. Balar AV et al. *Lancet*. 2017;389:67-76.

KEYNOTE-052: Pembrolizumab as First-Line Therapy for Cisplatin-Ineligible Advanced UC[1]

N = 350

- Advanced urothelial cancer
- No prior chemotherapy for metastatic disease
- ECOG PS 0-2
- Ineligible for cisplatin based on ≥1 of the following
  - CrCl <60 mL/min
  - ECOG PS 2
  - Grade ≥2 neuropathy or hearing loss
  - NYHA class III CHF

→ **Pembrolizumab**
200 mg every 3 wk

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

Demographics

42% were ECOG PS 2
49% aged ≥75 y
85% had visceral metastases
49% had renal impairment

Courtesy of Arjun V. Balar, MD

NYU Langone Health

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

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[1]**

- **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[2]**

Courtesy of Arjun V. Balar, MD

IMvigor130 study design

- **Locally advanced or mUC**
- **No prior systemic therapy in the metastatic setting**
- **ECOG PS ≤ 2**
- **1L platinum-eligible**
- **N = 1200**
- **Randomised 1:1:1**

Arm A
Atezo + platinum/gem ★

Arm B
Atezo monotherapy

Arm C
Placebo + platinum/gem ★

Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 and/or patients with liver metastases)
- Investigator choice of plt/gem (cisplatin + gem or carboplatin + gem)

Co-primary endpoints:
- INV-assessed PFS[a] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

Key secondary endpoints:
- INV-ORR[a] and DOR
- PFS[a] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

[a] per RECIST 1.1.

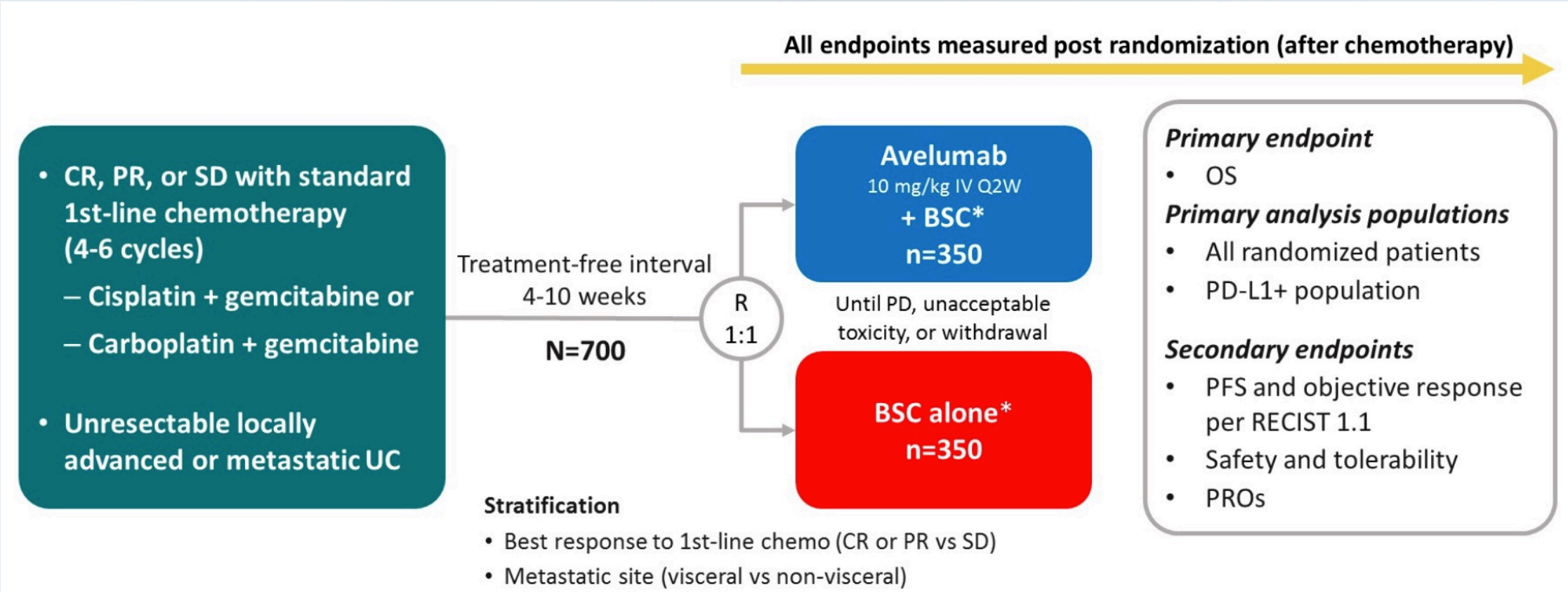
Adapted from Grande et al. ESMO 2019
Courtesy of Jonathan E Rosenberg, MD

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)

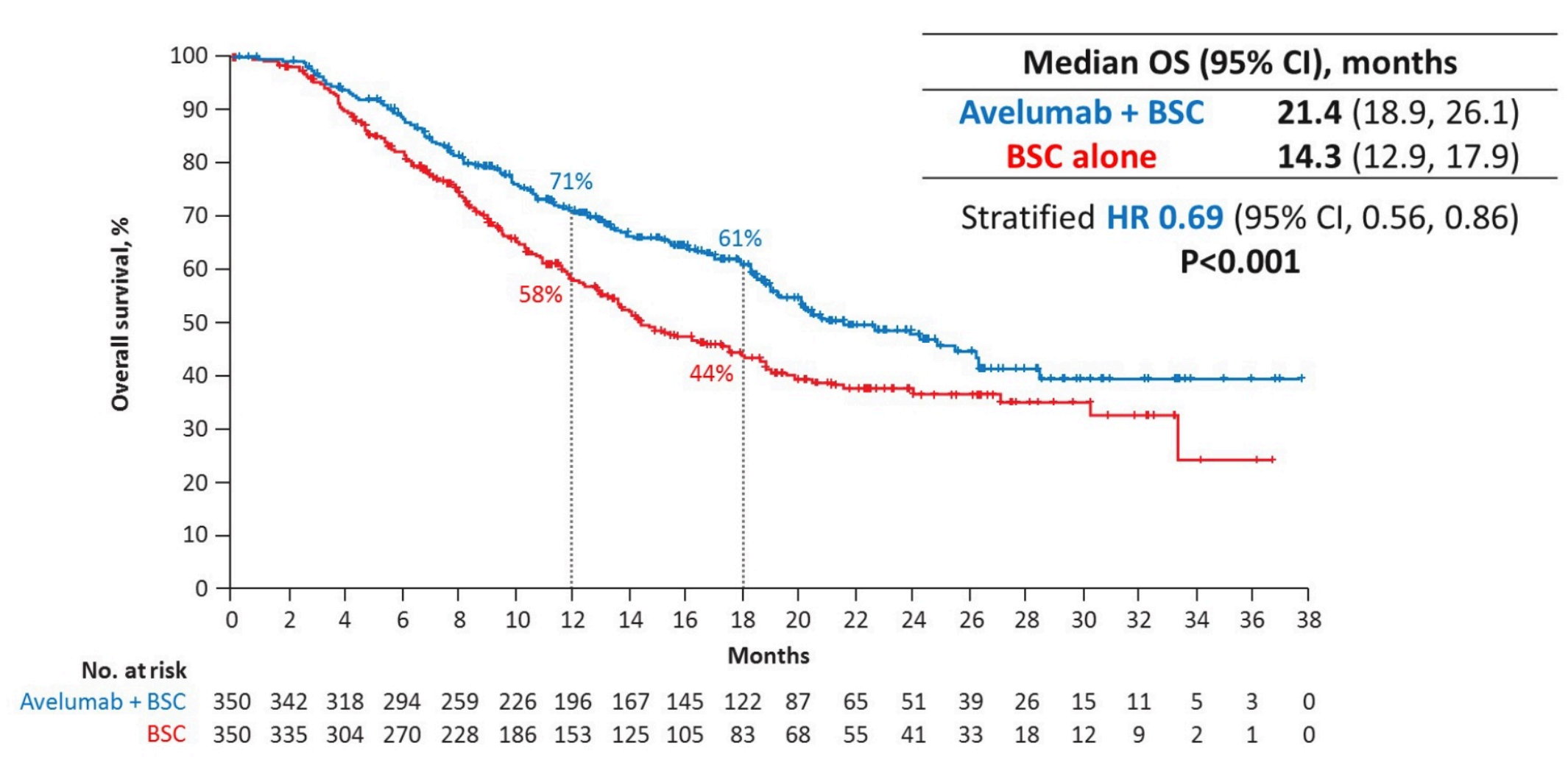
JAVELIN Bladder 100 Phase III Study Schema



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

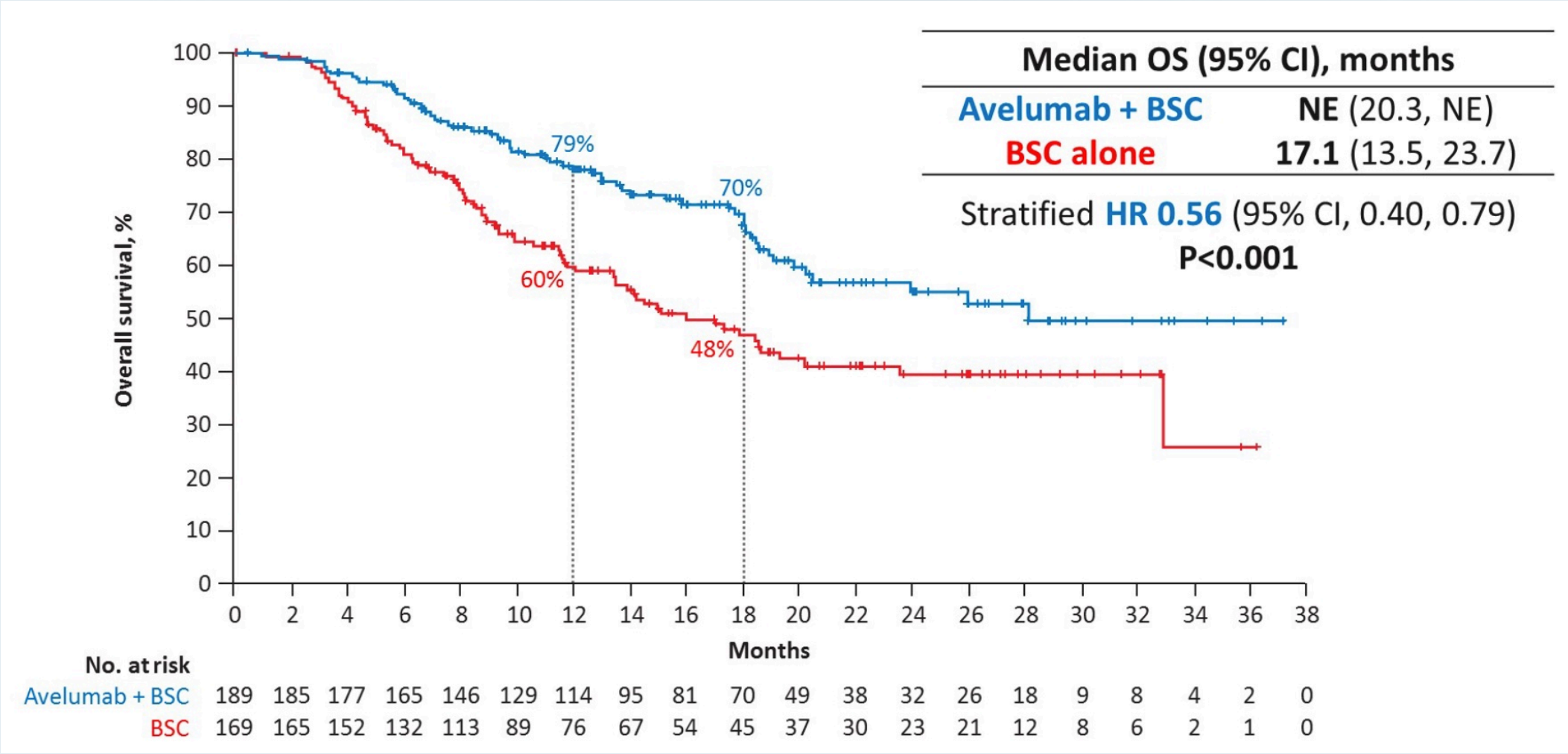
Powles T et al. ASCO 2020;Abstract LBA1.

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

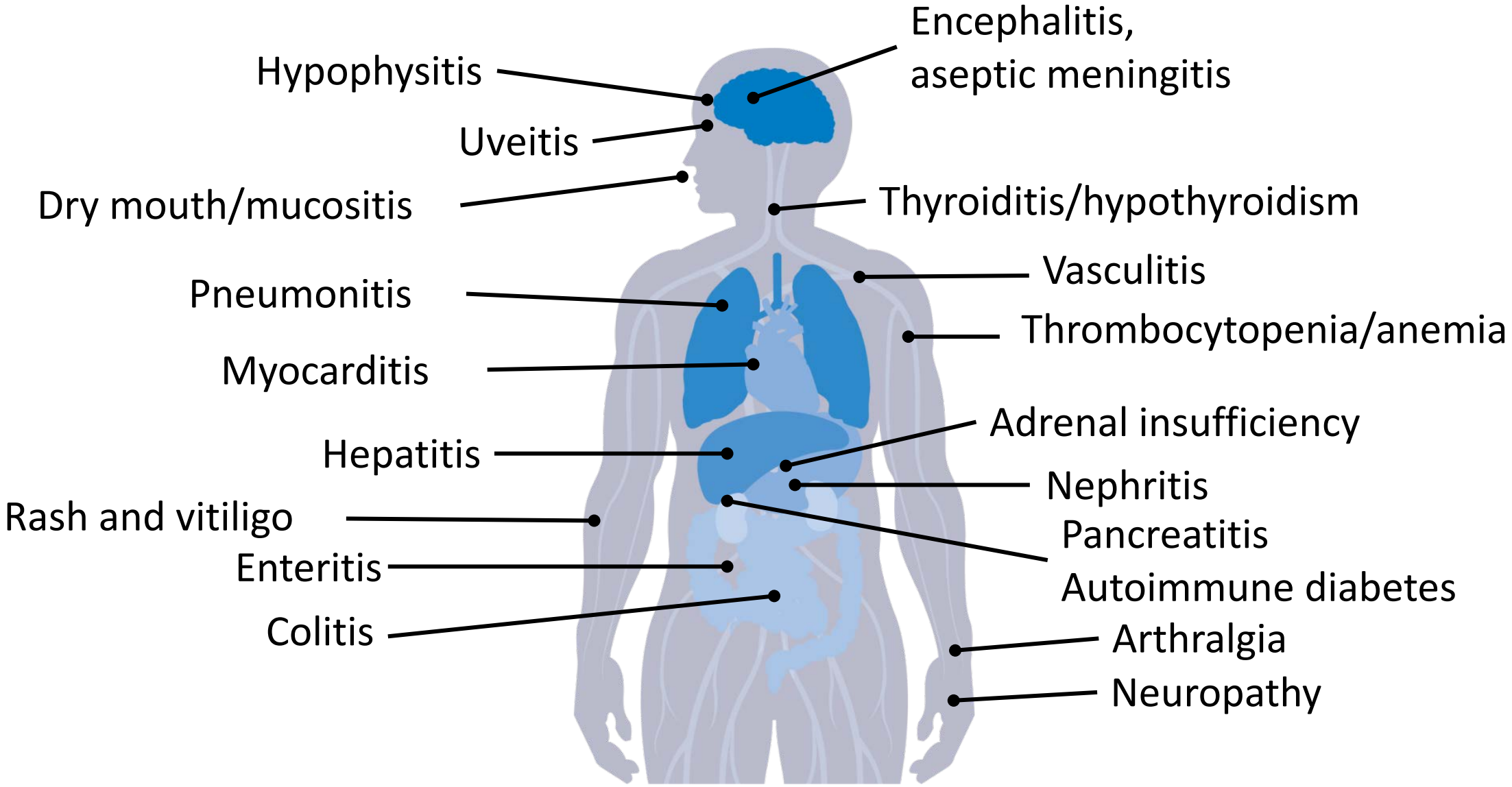


Powles T et al. ASCO 2020;Abstract LBA1.

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

78-year-old woman with a PMH of cervical cancer, controlled HTN (from the practice of Ms Daskalova)

- 4/2019: Urinary urgency, frequency and hematuria past few months
  - CT AP: Bladder wall thickening, no lymphadenopathy or visceral mets
- 5/2019: TURBT: High-grade muscle-invasive urothelial cancer
- 6/2019: Cystectomy (pT4N2 – 8/21 nodes+), with negative margins → pt declines adjuvant therapy, opts for surveillance
- 1/2020: MRI AP and CT chest: Extensive recurrent tumor in cystectomy bed, new liver and lung mets, and retroperitoneal, pelvic and inguinal lymphadenopathy
  - Symptomatic: Pain, fatigue, weight loss, insomnia
- Cisplatin-ineligible based on kidney function (Cr Cl <60 [37])
  - PDL1 status: Low
  - BRCA2 and TP53 mutations
- Carboplatin + gemcitabine x 6 → Significant response
- Plan to enroll on a clinical trial (“as maintenance”) with immunotherapy + personalized vaccine

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When was the last time you encountered a patient with bladder cancer receiving erdafitinib?

a. Within the past week

b. Between 1 week and 1 month ago

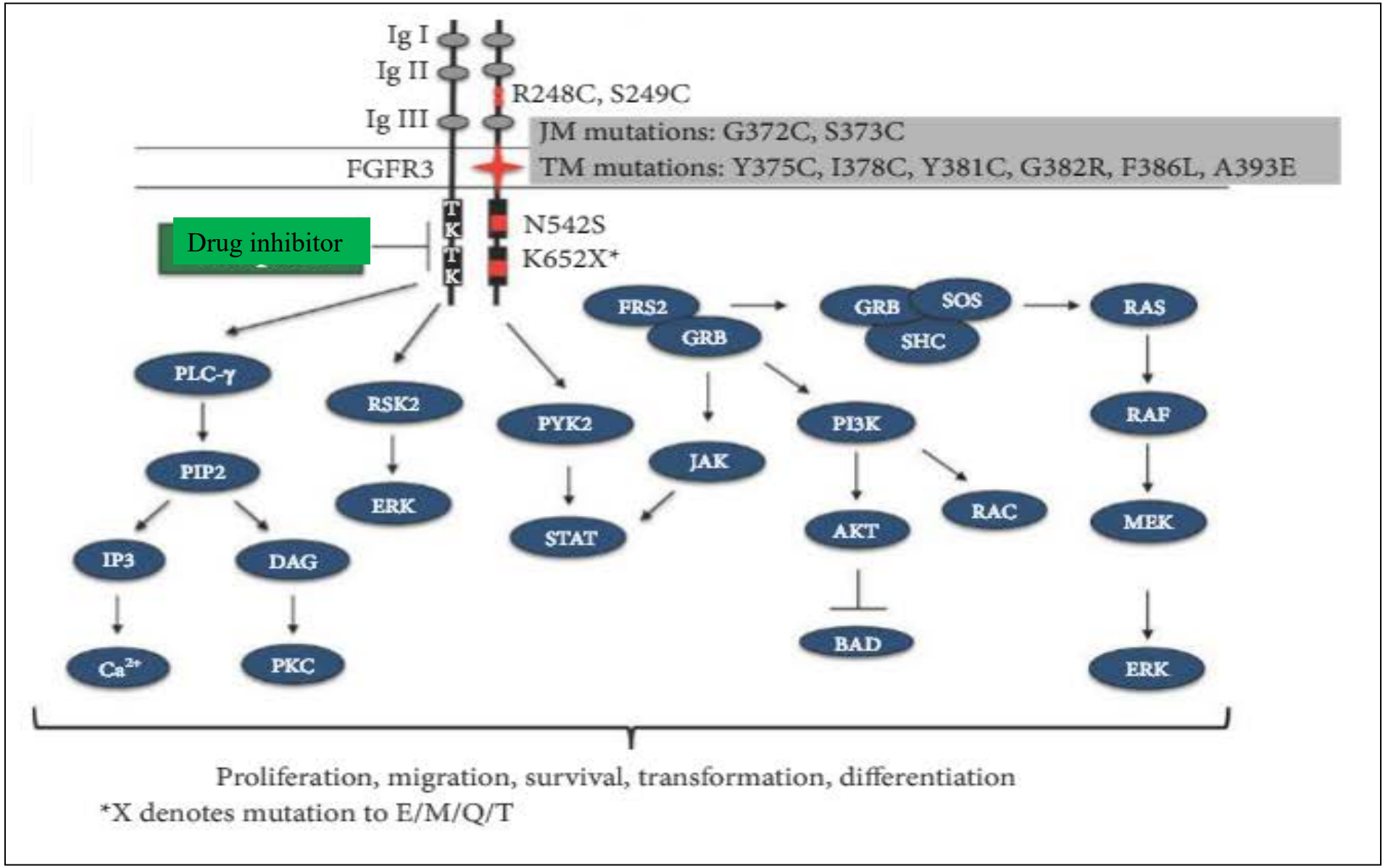
c. Between 1 month and 6 months ago

d. Between 6 months and 1 year ago

e. More than 1 year ago

f. I have not encountered a patient with bladder cancer receiving erdafitinib in my practice

FGFR Inhibition



Courtesy of Peter H O'Donnell, MD

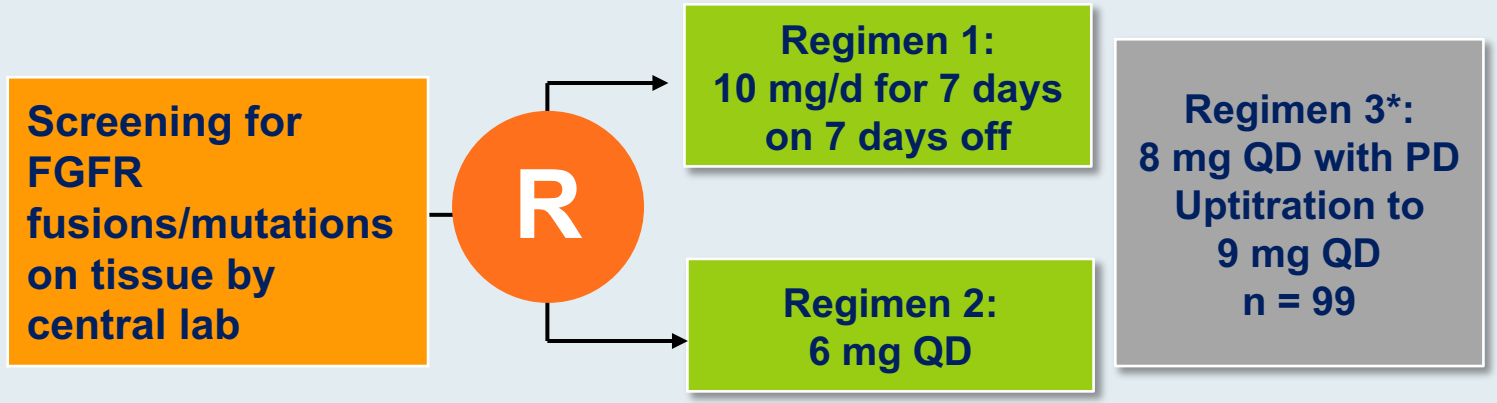
modified from Sethakorn and O'Donnell, BJUI (2016)

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†



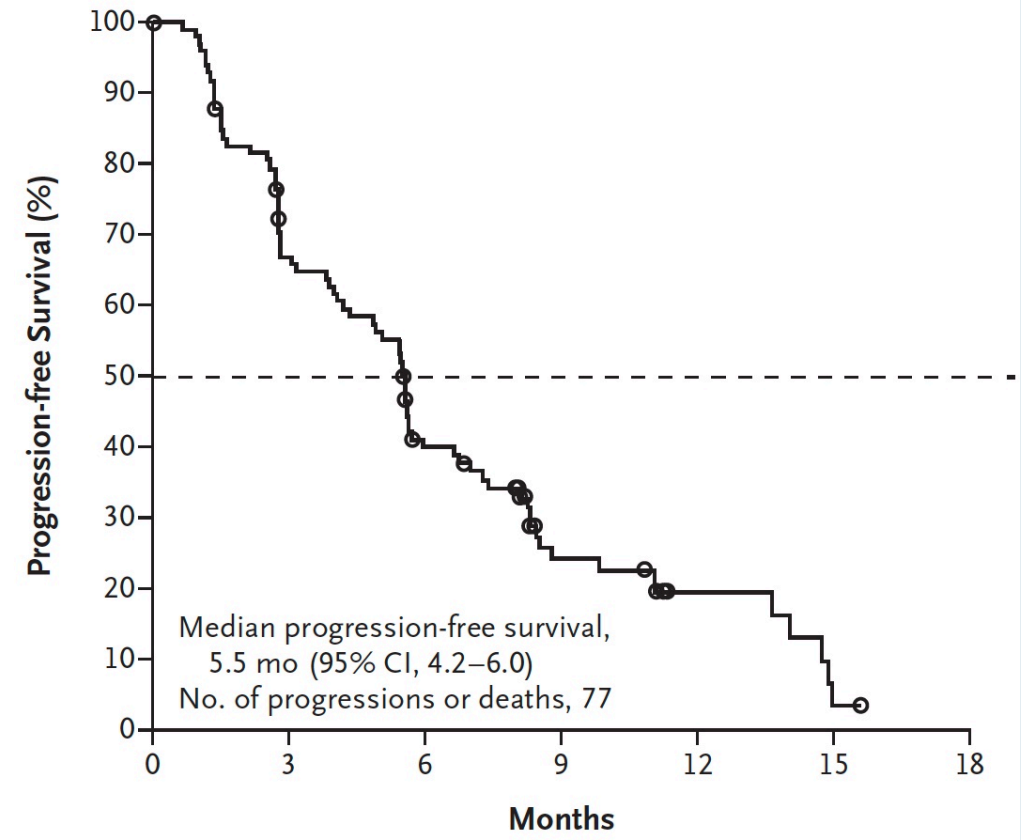
Primary endpoint: Objective response rate

* 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).

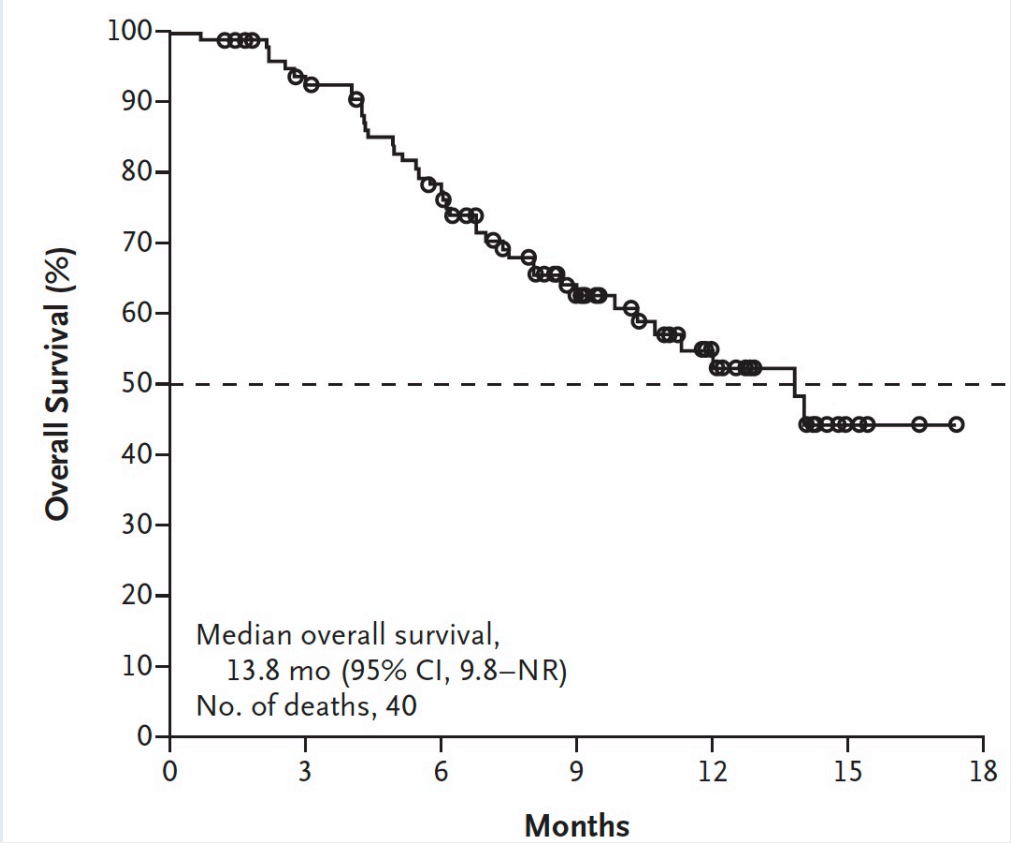
BLC2001: Erdafitinib Efficacy Data

Progression-Free Survival



ORR = 40% (additional 39.4% with SD)

Overall Survival



Duration of Response (median) = 5.6 mo

Loriot Y et al. *N Engl J Med* 2019;381:338-348.

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

Erdafitinib Dosing, and Adjustments

- Recommended starting dose is 8 mg (two 4 mg tablets) orally once daily, with dose increase to 9 mg (three 3 mg tablets) once daily based on serum phosphate levels and tolerability at 14–21 days.
- Assess serum phosphate levels 14–21 days after initiating. Increase erdafitinib to 9 mg once daily if serum phosphate level is <5.5 mg/dl (and there are no ocular disorders or ≥Grade 2 adverse reactions).
- Monitor phosphate levels monthly for hyperphosphatemia.

Table 2: Dose Modifications for Adverse Reactions

Adverse Reaction	Erdafitinib Dose Modification
Hyperphosphatemia	
In all patients, restrict phosphate intake to 600-800 mg daily. If serum phosphate is above 7.0 mg/dL, consider adding an oral phosphate binder until serum phosphate level returns to < 5.5 mg/dL.	
5.6-6.9 mg/dL (1.8-2.3 mmol/L)	Continue Erdafitinib at current dose.
7.0-9.0 mg/dL (2.3-2.9 mmol/L)	Withhold Erdafitinib with weekly reassessments until level returns to < 5.5 mg/dL (or baseline). Then restart Erdafitinib at the same dose level. A dose reduction may be implemented for hyperphosphatemia lasting > 1 week.
> 9.0 mg/dL (> 2.9 mmol/L)	Withhold Erdafitinib with weekly reassessments until level returns to < 5.5 mg/dL (or baseline). Then may restart Erdafitinib at 1 dose level lower.
> 10.0 mg/dL (> 3.2 mmol/L) or significant alteration in baseline renal function or Grade 3 hypercalcemia	Withhold Erdafitinib with weekly reassessments until level returns to < 5.5 mg/dL (or baseline). Then may restart Erdafitinib at 2 dose levels lower.

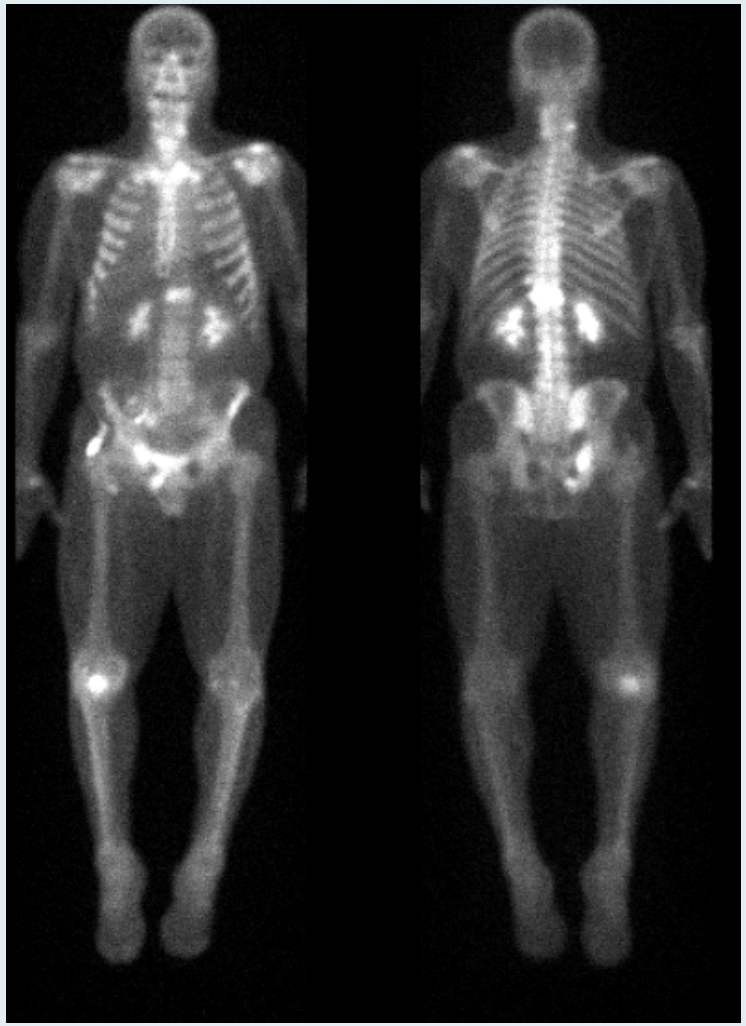
Courtesy of
Peter H O'Donnell, MD

erdafitinib FDA label

62-year-old man with PMH of Anxiety/Depression, Chronic Arthralgias and >30 Years History of Tobacco Use (from the practice of Ms Roethke)

- 3/2019 TURBT: High-grade MIBC, with focal invasion of muscularis propria and high-grade UC of prostatic urethra
- 6/2019: Completed neoadjuvant dose-dense MVAC x 3
- Genomic testing: BRCA1 mutation, FGFR3 mutation
- 7/2019: Radical cystoprostatectomy, b/l pelvic lymph node dissection, creation of ileal conduit
  - Pathology: Residual 5.5-cm bladder tumor, micropapillary type with invasion to perivesical soft tissue, 4+ nodes
  - Wound infection and abcess, distress and anger related to ostomy
- 10/2019 CT: Normal
- 12/2019: New bone metastases (see scan)
- 1/2020: SBRT to T12
- Erdafitinib
  - Transient, mild mouth sores
  - Developed CSR, erdafitinib held until improvement then re-started at reduced dose
- 3/2020: Improvement on bone scan; improvement in pain and general well-being

62-year-old man (from the practice of Ms Roethke)



12/2019: New Bone Mets

- **Intense uptake in T12 vertebral body**
- **Right ischial tuberosity**
- **Right pubic bone**
- **Left iliac bone posteriorly**

Agenda

Module 1: Overview of Urothelial Bladder Cancer (UBC) Management

Case Presentation: Ms Roethke — 85-year-old widower and retired automotive mechanic

Module 2: Anti-PD-1/PD-L1 Antibodies for Patients with Nonmetastatic UBC

Module 3: Risks and Benefits of Immune Checkpoint Inhibitors in Advanced UBC

Case Presentation: Ms Daskalova — 78-year-old woman with a PMH of cervical cancer

Module 4: Integration of FGFR-Directed Therapy into Current UBC Management Algorithms

Case Presentation: Ms Roethke — 62-year-old auto body repairman

Module 5: Antibody-Drug Conjugates in UBC

Case Presentation: Ms Roethke — 70-year-old married man and retired telephone technician

Module 6: Management of UBC in the Era of COVID-19

Case Presentation: Ms Daskalova — 63-year-old man

Module 5: Antibody-Drug Conjugates in UBC

When was the last time you encountered a patient with bladder cancer receiving enfortumab vedotin?

a. Within the past week

b. Between 1 week and 1 month ago

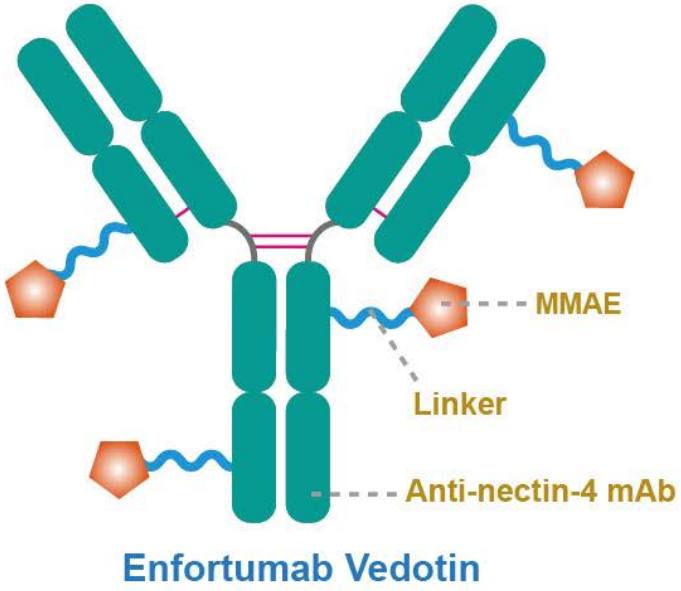
c. Between 1 month and 6 months ago

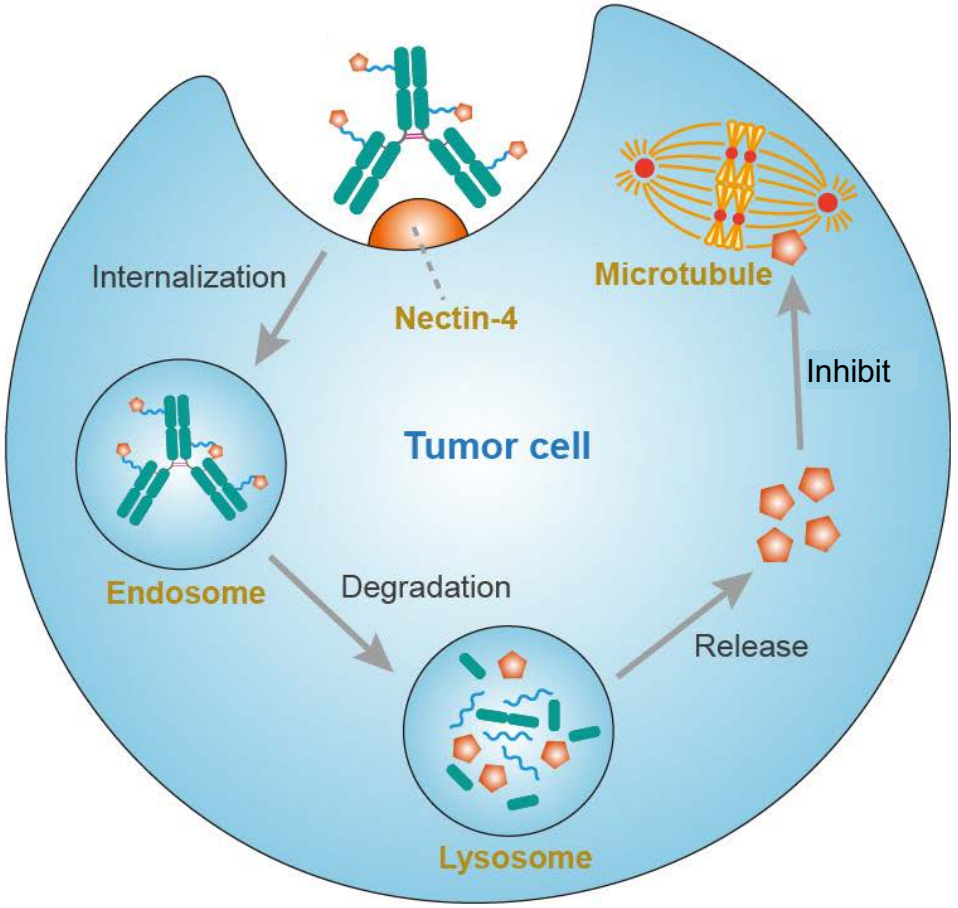
d. Between 6 months and 1 year ago

e. More than 1 year ago

f. I have not encountered a patient with bladder cancer receiving enfortumab vedotin in my practice

Enfortumab Vedotin
Proposed Mechanism of Action



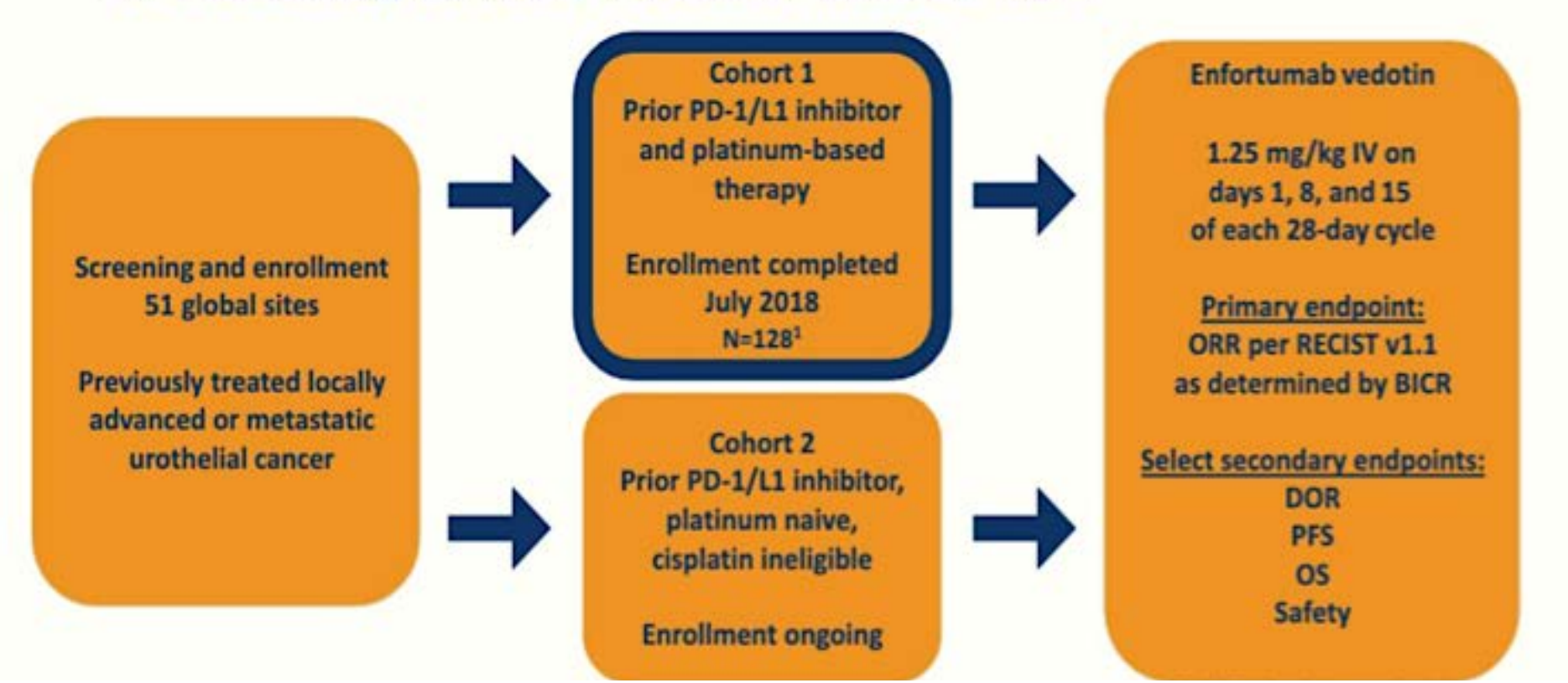


Courtesy of Peter H O'Donnell, MD

MMAE = monomethyl auristatin E

figure adapted from creativebiolabs.net

Enfortumab Phase II Study Design (EV-201)



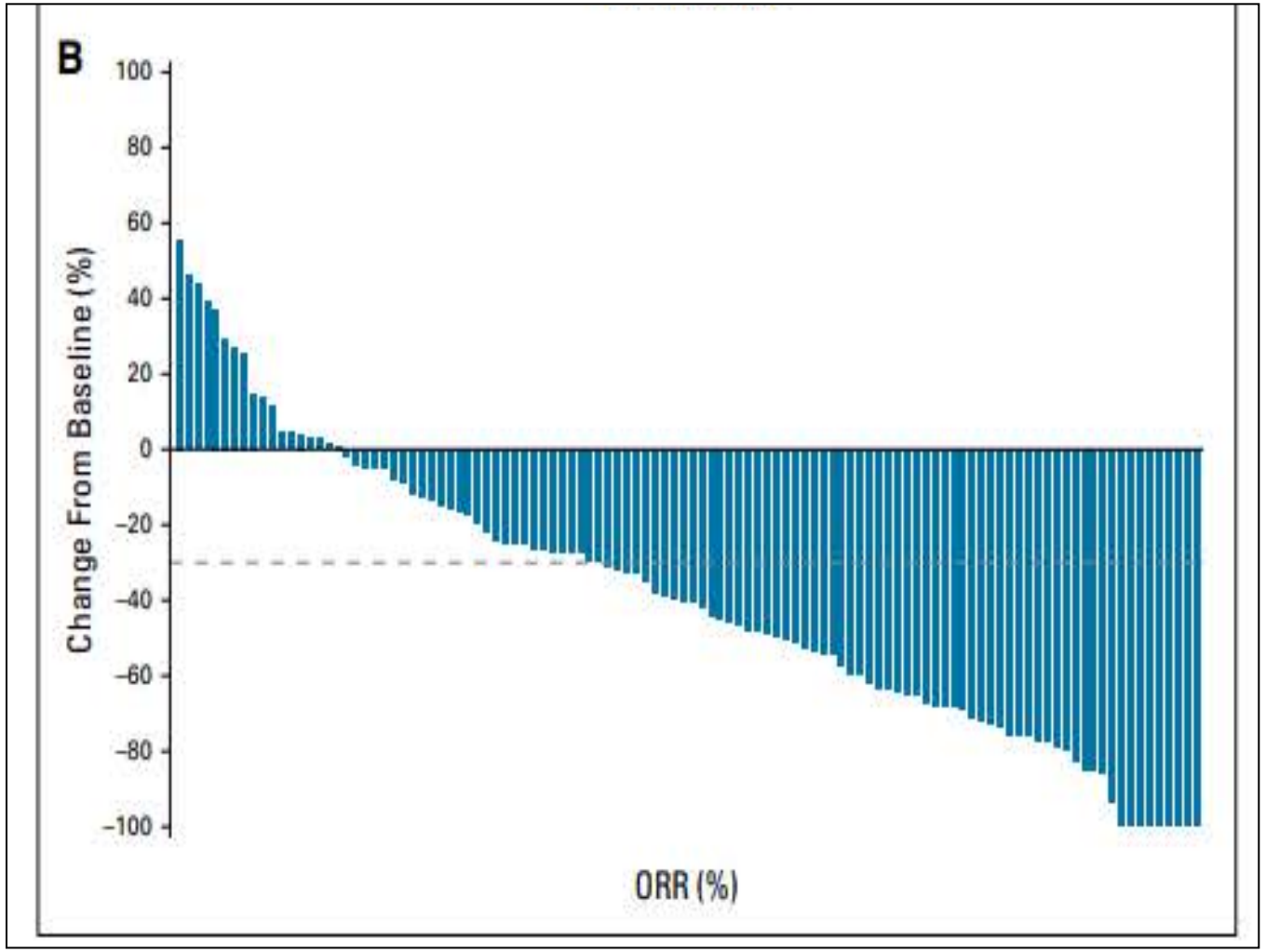
Courtesy of Peter H O'Donnell, MD

ORR=objective response rate
BICR=blinded independent central review
DOR=duration of response

adapted from Petrylak et al., presented at ASCO 2019

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

EV-103 – First-line Cohorts of Enfortumab Vedotin + Pembrolizumab

Enfortumab vedotin 1.25 mg/kg + pembrolizumab (200 mg) in 1L cisplatin-ineligible la/mUC patients (N=45)

Patient Population	Dose Escalation[1]	Dose Expansion Cohort A
Locally Advanced or Metastatic Urothelial Carcinoma	**enfortumab vedotin + pembrolizumab** cisplatin-ineligible (n=5)	**enfortumab vedotin + pembrolizumab** cisplatin-ineligible (n=40)

Dosing: Enfortumab vedotin on days 1 and 8 and pembrolizumab on day 1 of every 3-week cycle

Enfortumab vedotin exposure: Comparable to enfortumab vedotin monotherapy on 4-week schedule (Days 1, 8, and 15)[2]

Primary endpoints: safety and tolerability

Key secondary endpoints: dose-limiting toxicities, ORR, DOR, PFS, OS

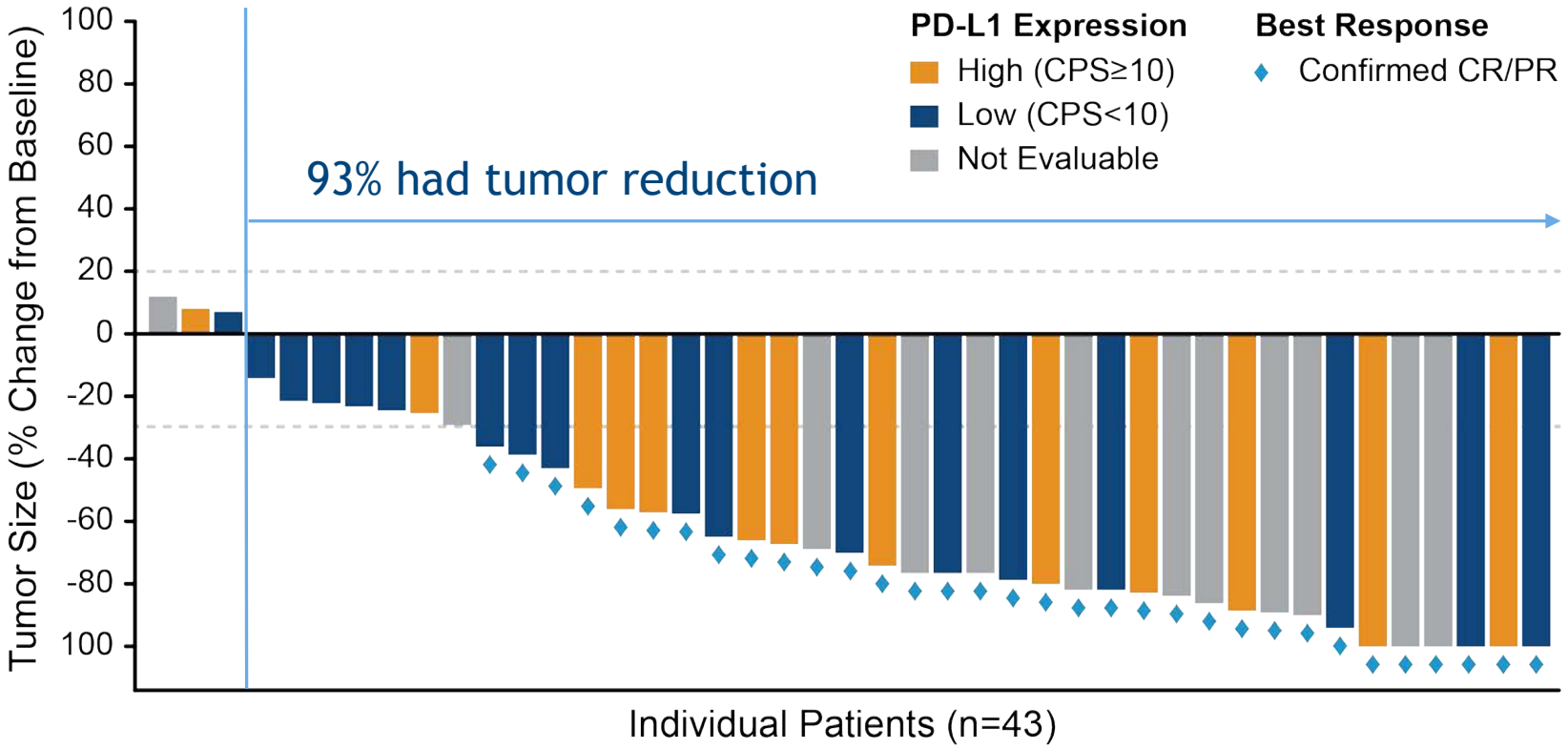
[1] Not included in the current analysis: three 1L patients treated with EV 1 mg/kg + pembrolizumab 200 mg and two 2L patients treated with EV 1.25 mg/kg + pembrolizumab 200 mg

[2] Rosenberg et al. *J Clin Oncol.* 2019;37(29):2592-600.

Courtesy of Daniel P Petrylak, MD

Rosenberg JE et al. GU Cancers Symposium 2020; Abstract 441.

Maximal Target Lesion Reduction by PD-L1 status and Objective Response Rate per Investigator



Confirmed ORR 95% CI	73.3% (33/45) (58.1, 85.4)
Complete response	15.6% (7/45)
Partial response	57.8% (26/45)

Best Overall Response Per RECIST v 1.1 by investigator (N=45)

- Responses observed regardless of PD-L1 expression level

Two patients did not have post-baseline response assessments before end-of-treatment: 1 withdrew consent and 1 died before any post-baseline response assessment. These patients are included in the full analysis set used to calculate ORR, but are not included in the figure above. Horizontal lines at positive 20% and negative 30% denote thresholds for target lesions for disease progression and response, respectively.

Courtesy of Daniel P Petrylak, MD

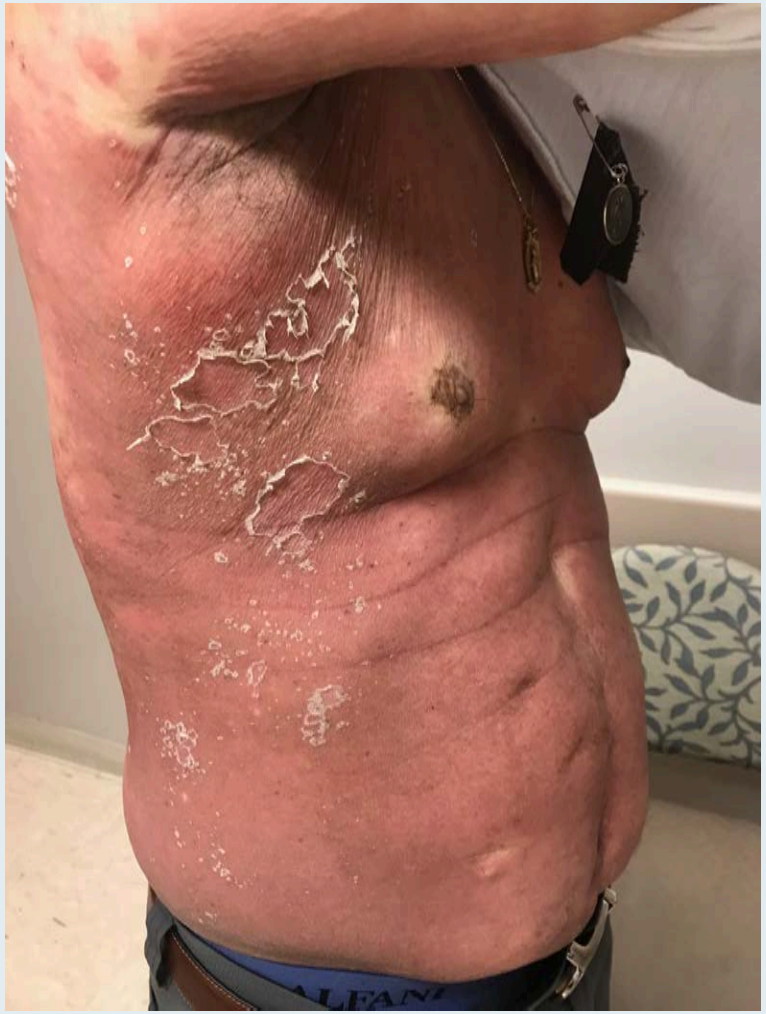
Rosenberg JE et al. GU Cancers Symposium 2020; Abstract 441.

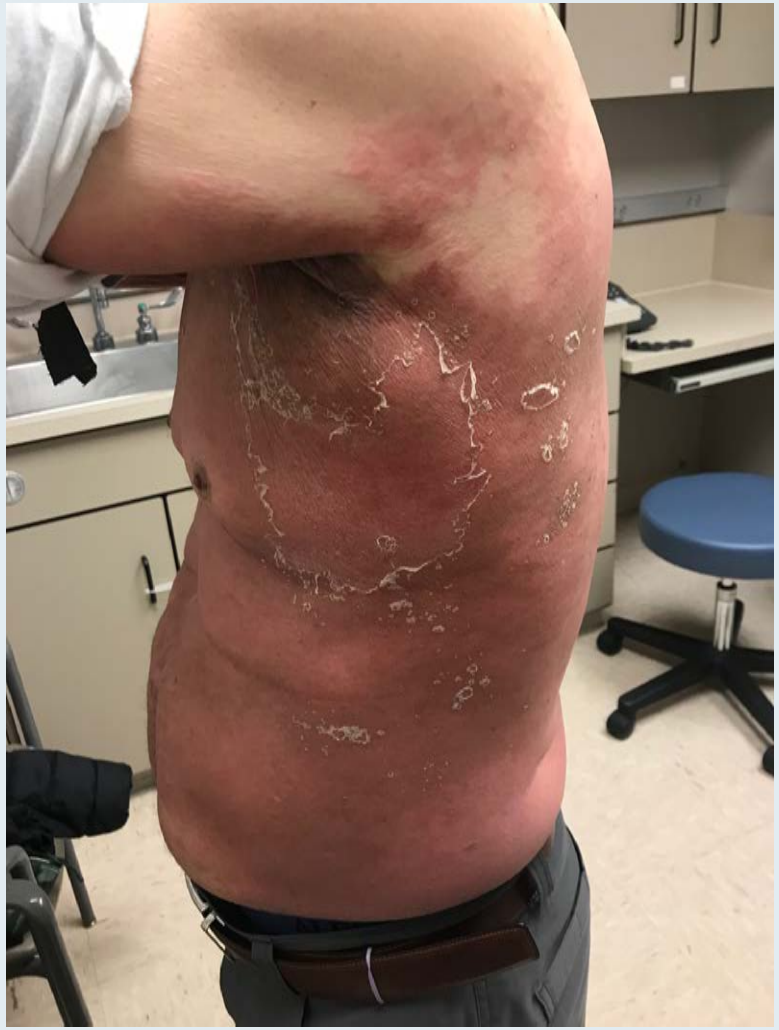
70-year-old man with PMH of CKD, T2DM, HTN, Hyperlipidemia (from the practice of Ms Roethke)

- 1/2017: High-grade UC of right distal ureter
- 3/2017: Completed neoadjuvant MVAC x 3 → 5/2017: R nephroureterectomy
  - Pathology: Residual 1-cm carcinoma invading muscularis, Node-negative
- 6/2017: Rapidly progressive recurrent disease, with gastric outlet obstruction → gastrojejunostomy
  - Pathology: Metastatic UC, marked peritoneal carcinamatosis
- 7/2017: Pembrolizumab 200mg Q3W → remarkable response, no measurable disease
  - 4/2018: Adrenal insufficiency, treatment discontinued
  - Observation x 16 months
- 8/2019: Perirectal recurrence
  - Pembrolizumab resumed but discontinued due to continued tumor growth
- 11-12/2019: SBRT
- 4/2020 CT and MRI: Large mass invading bladder, rectum, seminal vesicles
- Enfortumab vedotin
  - Bright red rash/exfoliative dermatitis -- treatment held -- resolved

70-year-old man (from the practice of Ms Roethke)

Rash/Exfoliative Dermatitis After Starting Enfortumab Vedotin





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Module 6: Management of UBC in the Era of COVID-19

63-year-old man (from the practice of Ms Daskalova)

- Non-muscle-invasive BC → BCG
- 2/2018: Subsequent cystoscopy: Muscle-invasive BC → radical cystoprostatectomy and neobladder creation
  - Pathology: pT2aN0 papillary urothelial carcinoma
- Surveillance
- Second scan: New 1.8-cm lung nodule at the RUL C/W metastatic urothelial cancer
- Gemcitabine plus split-dose cisplatin → worsening kidney function → Gemcitabine + carboplatin (cycles 2-3)
- Restaging imaging: PD
- FGFR tumor mutation
- 1/2019: Pembrolizumab → progressive disease → erdafitinib with good response
- Contracted COVID-19 and passed away

Thank you for joining us!

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