The Current and Future Role of Immune Checkpoint Inhibitors and Other Novel Therapies in Urothelial Bladder Cancer

Thursday, July 9, 2020

5:00 PM – 6:00 PM ET

Faculty

Arjun Balar, MD

Siamak Daneshmand, MD

Ashish M Kamat, MD, MBBS

Jonathan E Rosenberg, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

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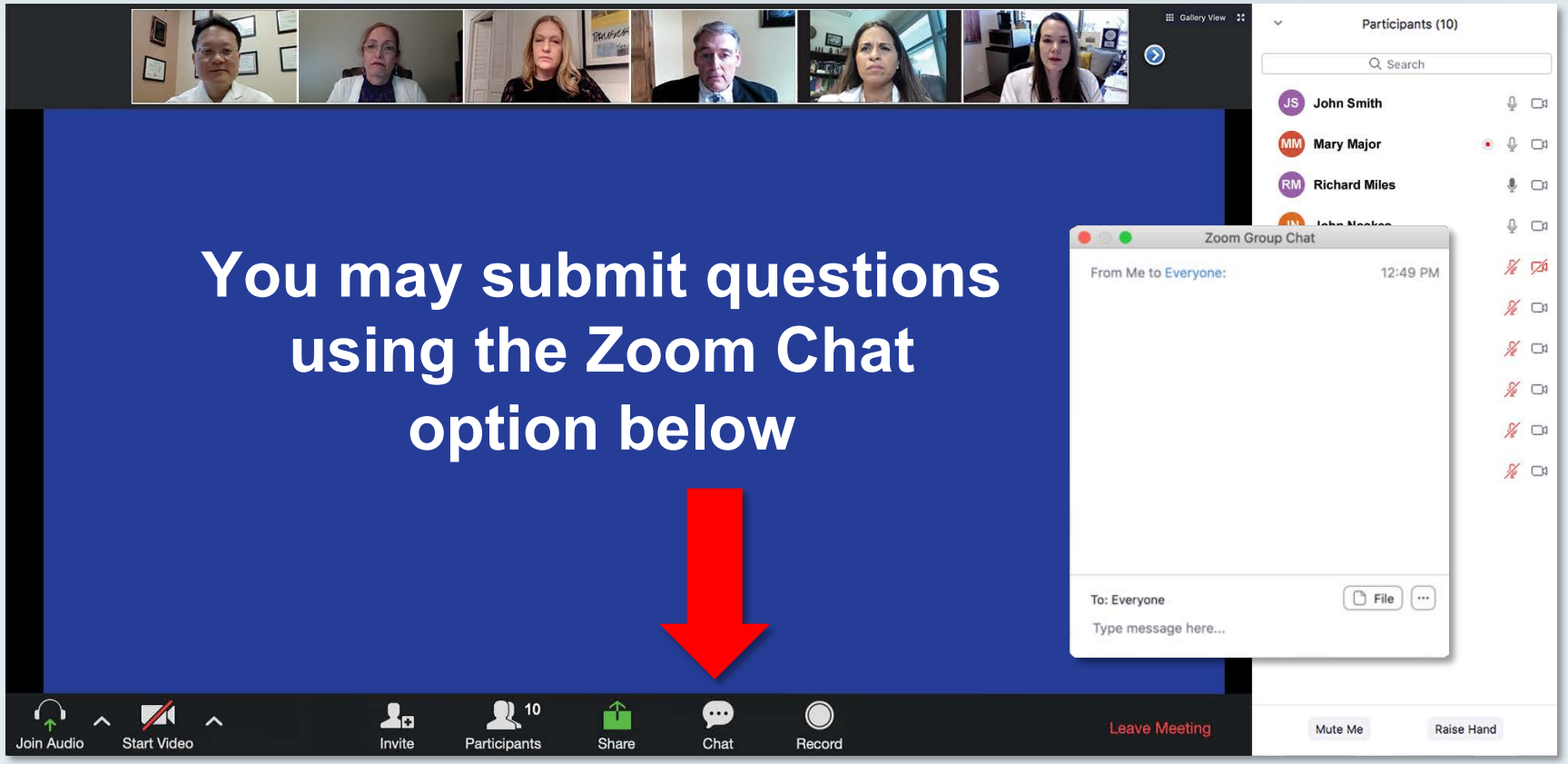
Dr Love and Faculty Encourage You to Ask Questions



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

Key Questions and Emerging Research in the Management of Multiple Myeloma

Monday, July 13, 2020
5:00 PM – 6:00 PM ET

Faculty

Shaji K Kumar, MD
Noopur Raje, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Meet The Professors

Clinical Investigators Discuss Existing and Emerging Treatment Strategies for Patients with Ovarian, Cervical and Endometrial Cancer

Tuesday, July 14, 2020

12:00 PM – 1:00 PM ET

Faculty

Michael J Birrer, MD, PhD
Kathleen Moore, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Recent Advances in Medical Oncology: Targeted Therapy for Lung Cancer

Wednesday, July 15, 2020

5:00 PM – 6:30 PM ET

Faculty

Alexander E Drilon, MD
Professor Solange Peters, MD, PhD
Suresh S Ramalingam, MD

Moderator

Neil Love, MD

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WITH DR NEIL LOVE

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The Current and Future Role of Immune Checkpoint Inhibitors and Other Novel Therapies in Urothelial Bladder Cancer

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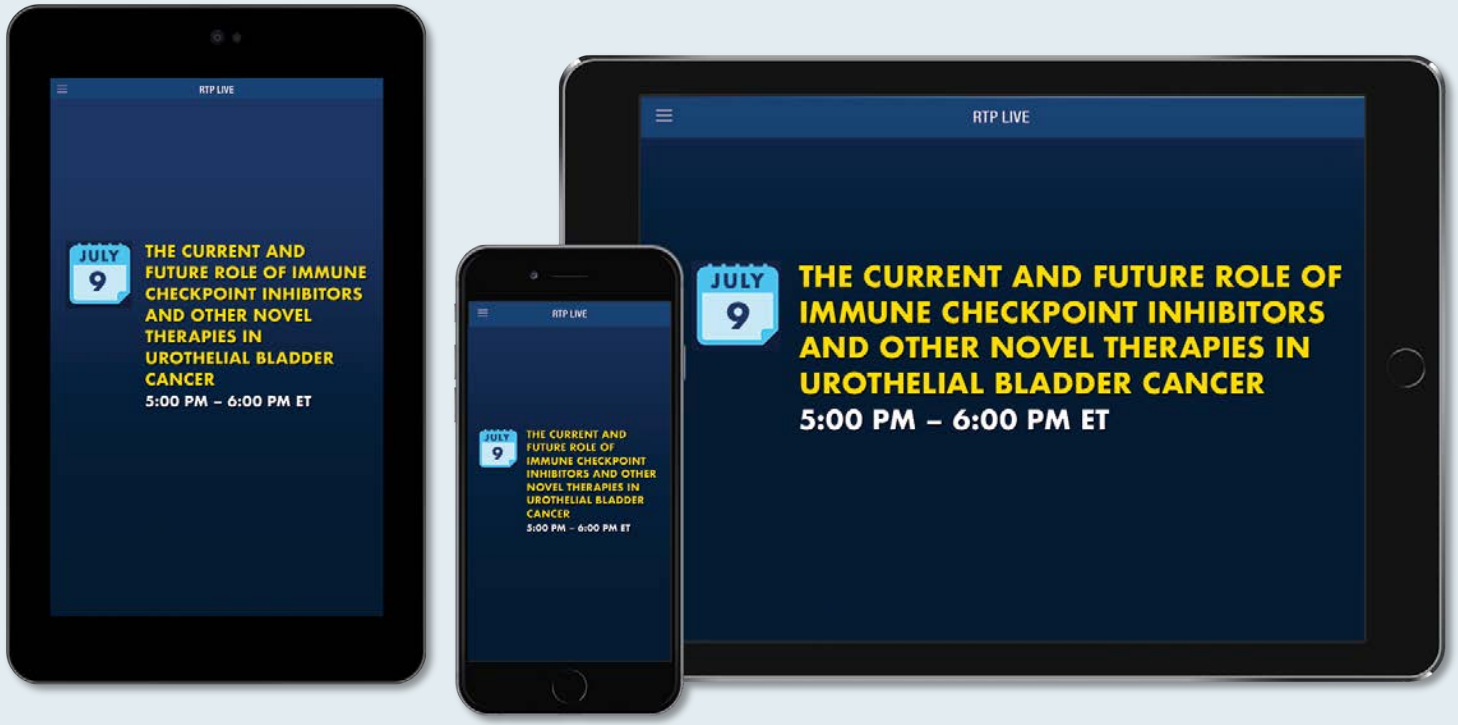


Agenda

MODULE 1: Immune Checkpoint Inhibitors for Non-Muscle-Invasive Urothelial Bladder Cancer (UBC)

MODULE 2: Immune Checkpoint Inhibitors as Neoadjuvant/ Adjuvant Therapy for Muscle-Invasive UBC

MODULE 3: Immune Checkpoint Inhibitors in Advanced UBC

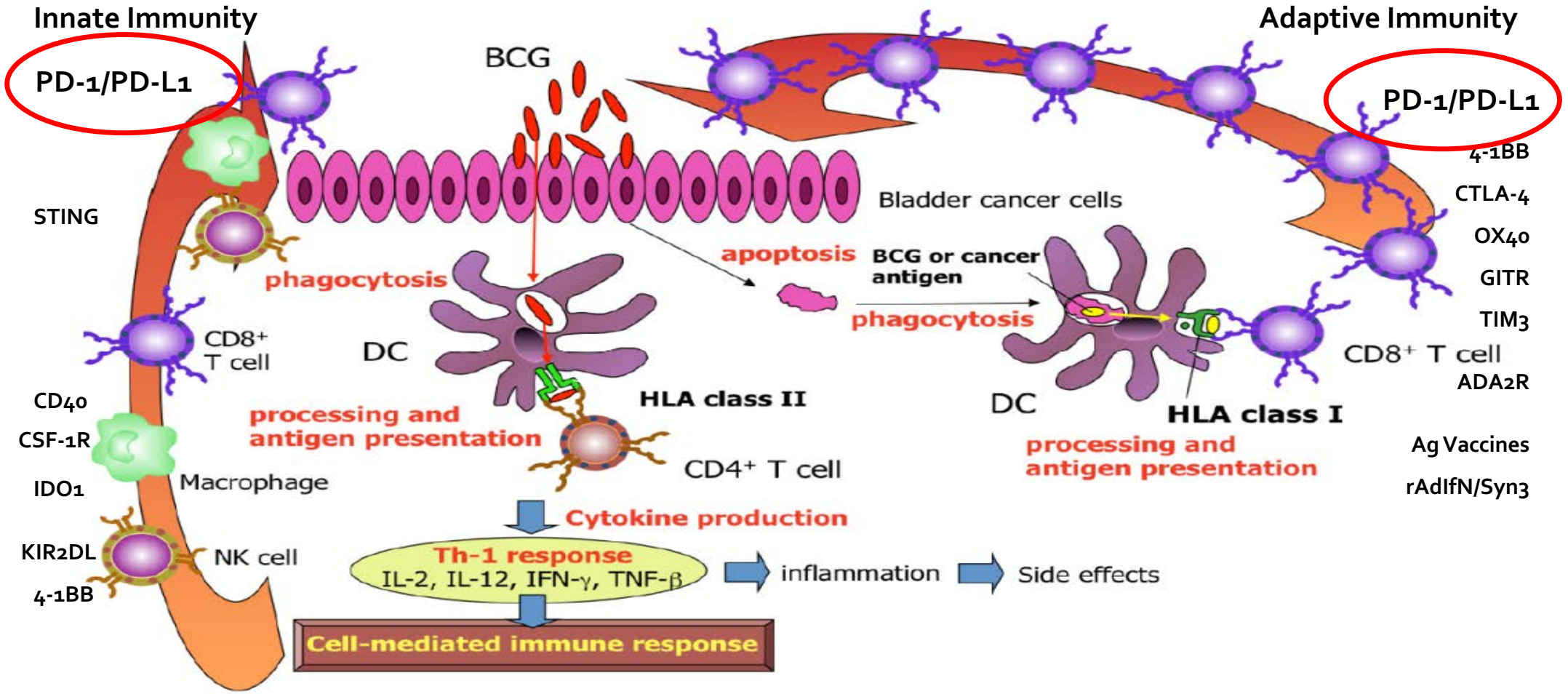
MODULE 4: Current and Future Roles of Recently FDA-Approved Novel Therapies

MODULE 1: Immune Checkpoint Inhibitors for Non-Muscle-Invasive Urothelial Bladder Cancer (UBC) — Dr Kamat

- Clinical data supporting FDA approval of pembrolizumab for BCG-unresponsive NMIBC
- SWOG 1605: Atezolizumab in high-risk, BCG-unresponsive NMIBC
- Case: 68-year-old man with NMIBC
- Case: 62-year-old woman with NMIBC

Courtesy of Ashish M Kamat, MD, MBBS

BCG: Mechanism of Action



Kitamura H et al, Cancers 2011;3:3055-72

Shelley MD et al, Cochrane Database of Systemic Reviews 2006;2:1-29

Slide: Noah Hahn

Courtesy of Ashish M Kamat, MD, MBBS

~ 1.2 Million Doses of BCG used globally for Bladder Cancer

BCG Failure: ~ 30% at 1 yr; ~ 40% at 2-3 yrs

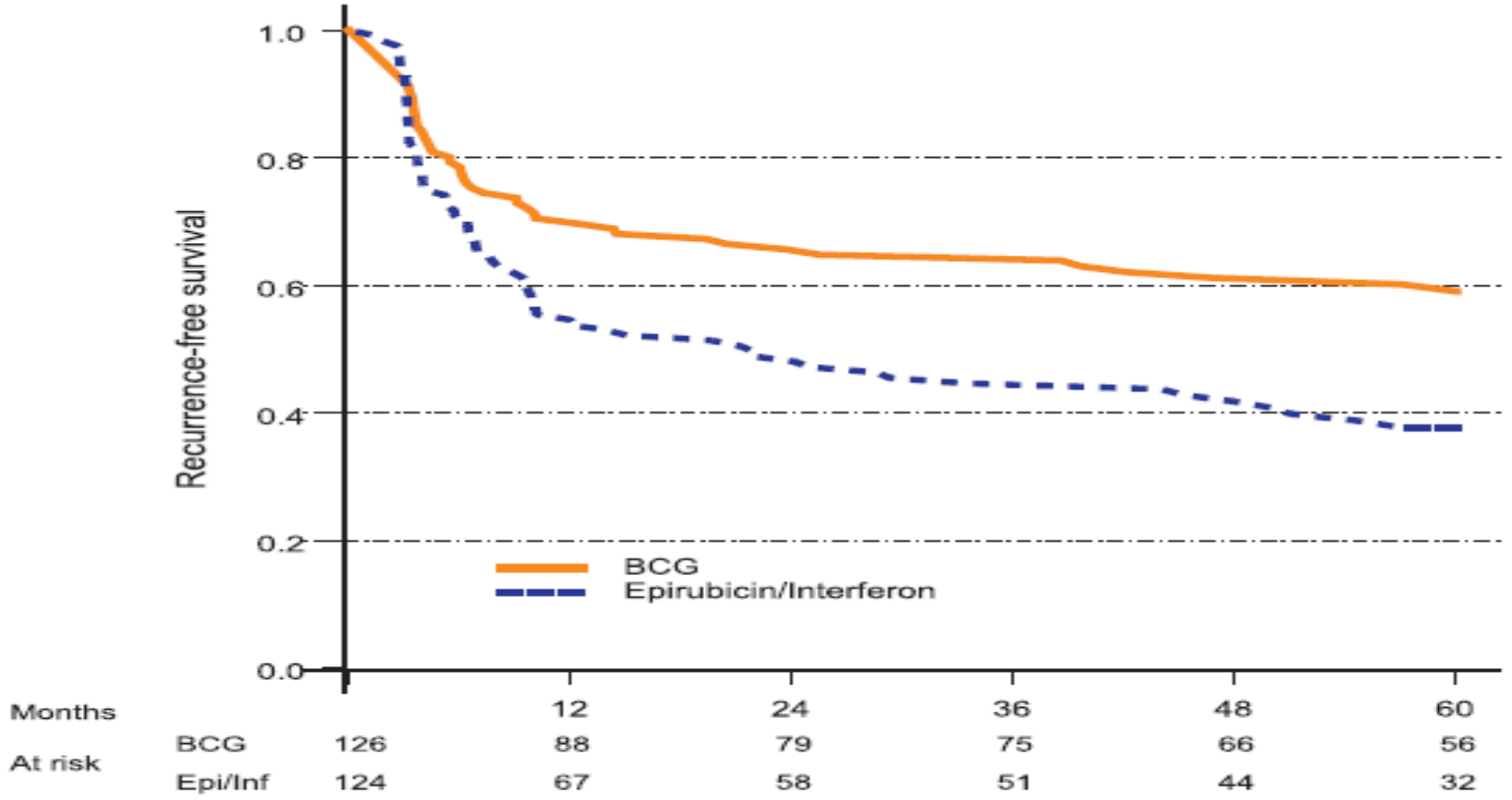


Figure 3. RFS according to randomization arm ($p = 0.001$)

Hemdan et al. J Urol 2014; 191: 1244. Courtesy of Ashish M Kamat, MD, MBBS

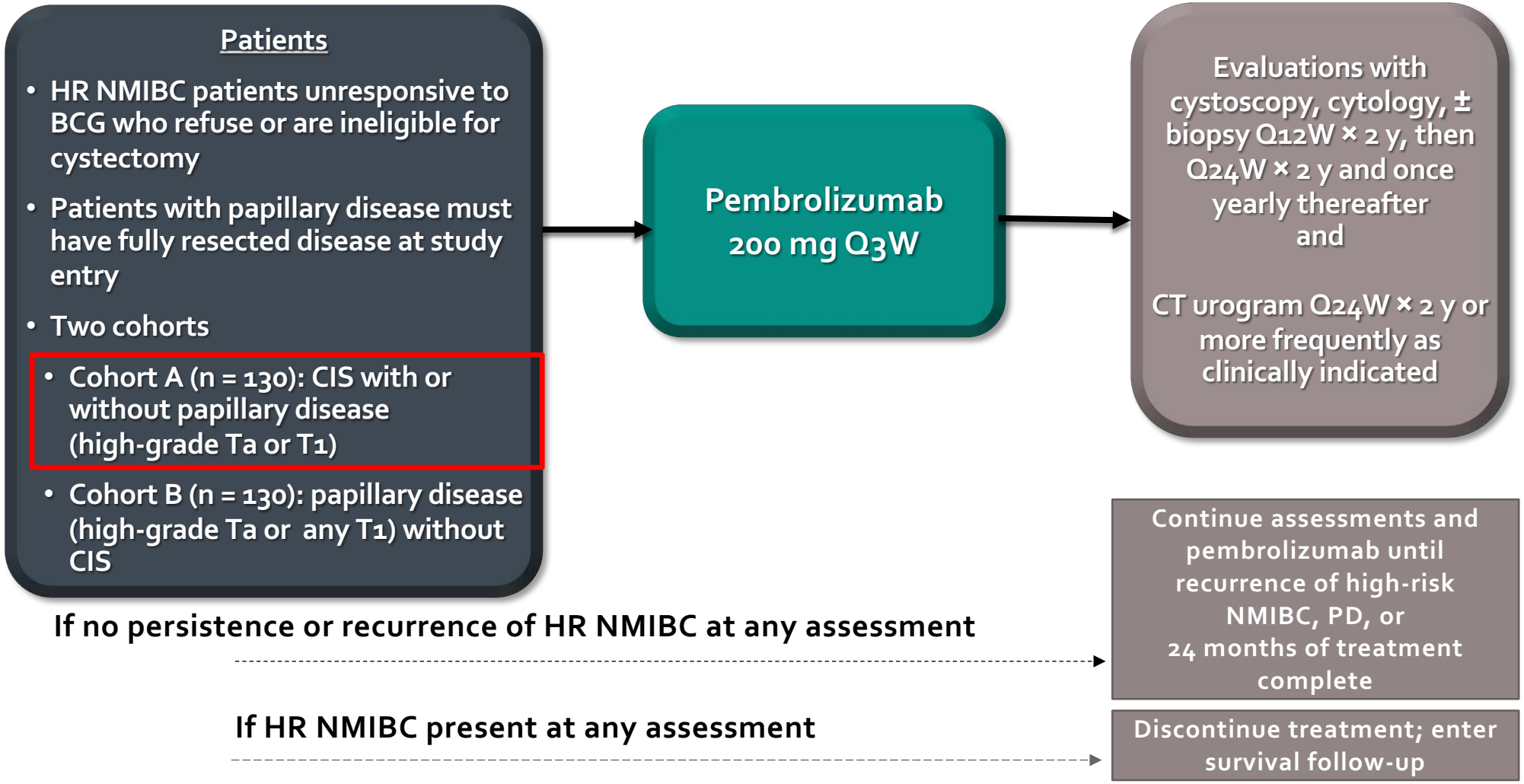
Classification of BCG Failure

BCG refractory:	Persistent HG disease at 6 months despite adequate BCG. Also includes any stage/grade progression by 3 months after iBCG cycle (i.e., T1HG at 3 months after initial Ta, or CIS).
BCG relapsing:	Recurrence of HG disease after achieving a disease-free state at 6 months following adequate BCG. Previously been subdivided based on time to recurrence after stopping BCG (i.e., early [< 12 months], intermediate [1-2 years] or late [> 24 months])
BCG intolerant:	Disease persistence due to inability to receive adequate BCG* due to toxicity.
BCG unresponsive:	BCG refractory + BCG relapsing disease (within 6- 12 months of last BCG exposure) Meant to denote a subgroup of patients at highest risk of recurrence and progression for whom additional BCG therapy is not a feasible option. These patients can be considered for single arm studies.

* For clinical trials, adequate BCG therapy is when a patient has received at least 5 of 6 induction instillations and at least 1 maintenance (2 of 3 instillations) in a 6-month period.

Kamat AM, et al. *J Clin Oncol.* 2016;34(16):1935-44.

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



Primary End Points
- CR (absence of HR NMIBC) in Cohort A
- DFS in Cohort B

Secondary End Points
- CR (absence of any disease – high-risk or low-risk NMIBC) in cohort A
- DOR in cohort A
- Safety/tolerability

ASCO 2019

Courtesy of Ashish M Kamat, MD, MBBS

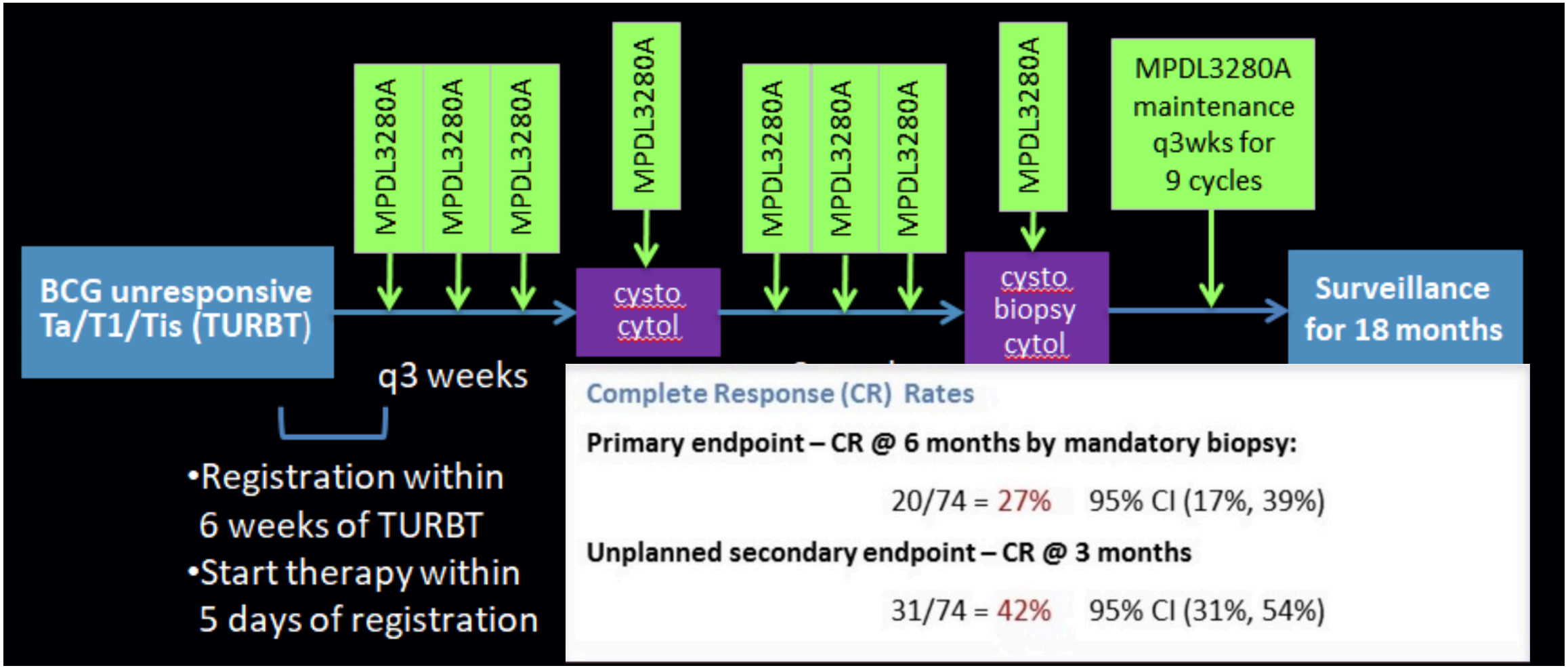
New FDA Approval in NMIBC

January 8, 2020

Pembrolizumab is approved for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for, or who have elected not to undergo, cystectomy

FDA Prescribing Information.

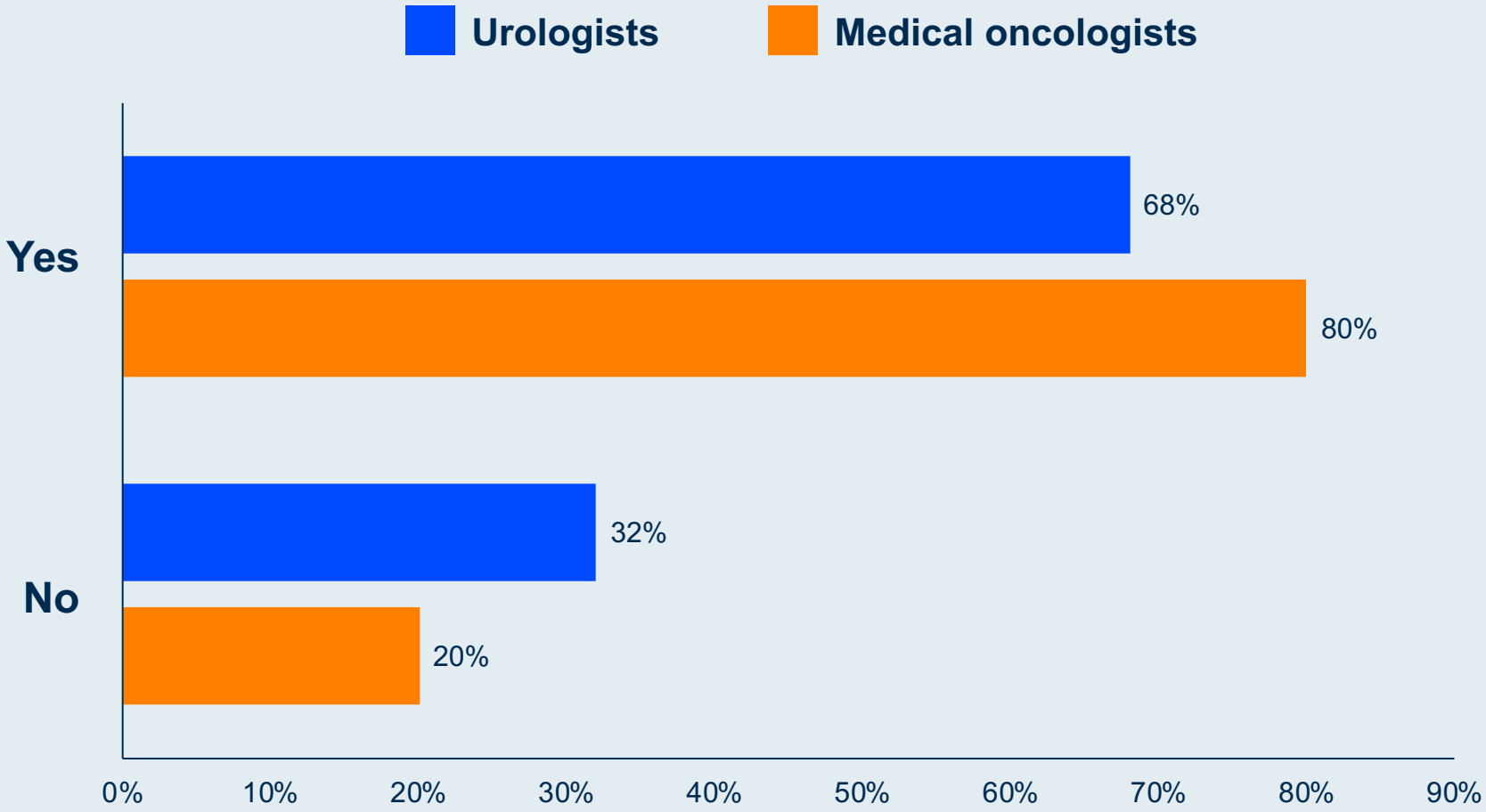
SWOG-S1605: Atezolizumab (MPDL3280A) in BCG Unresponsive High Risk NMIBC



PI: Black, Singh: ASCO 2020

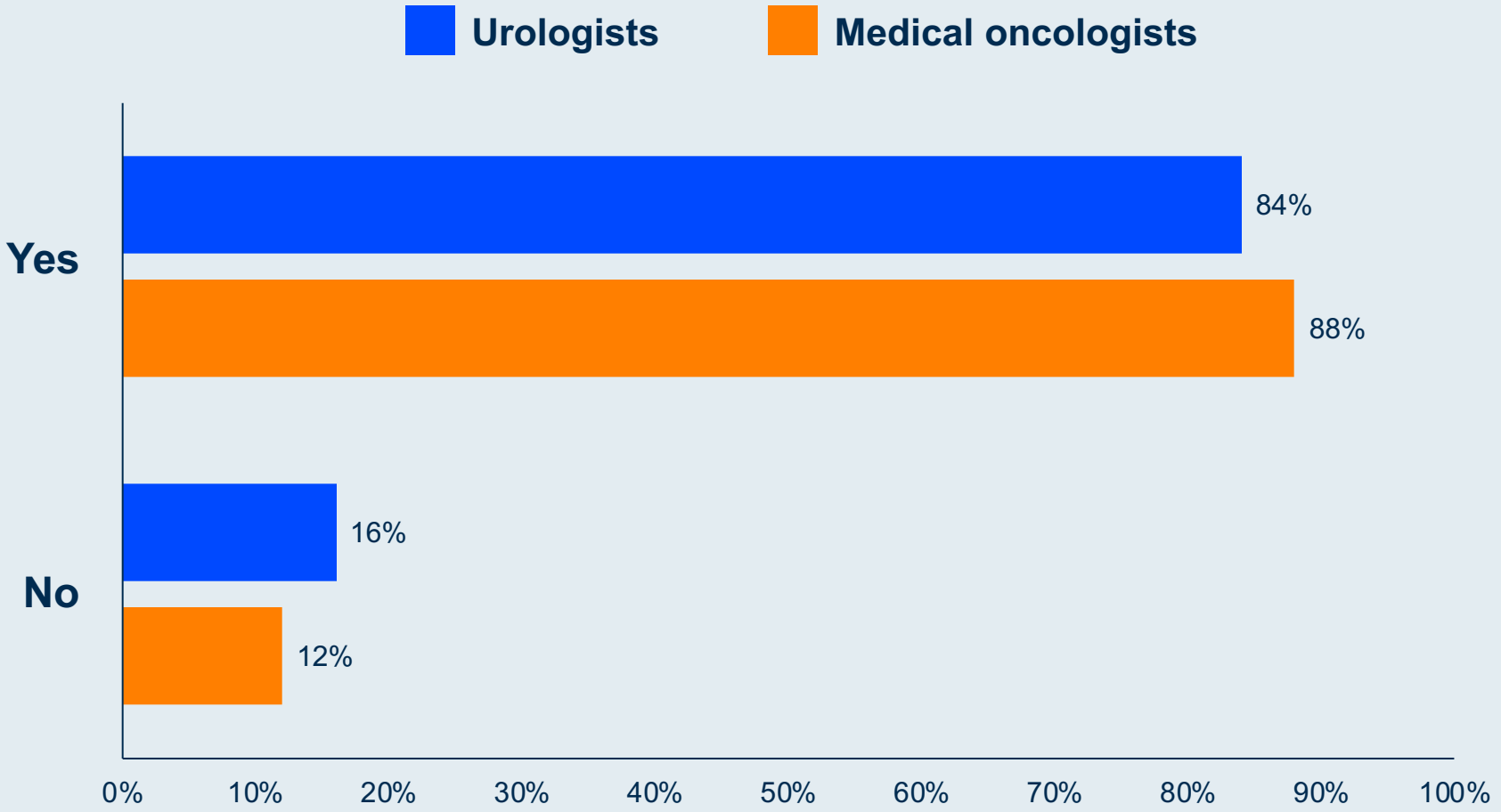
Courtesy of Ashish M Kamat, MD, MBBS

Would you generally offer/recommend pembrolizumab to a **50-year-old otherwise healthy** patient with BCG-unresponsive non-muscle-invasive urothelial bladder cancer (UBC)?



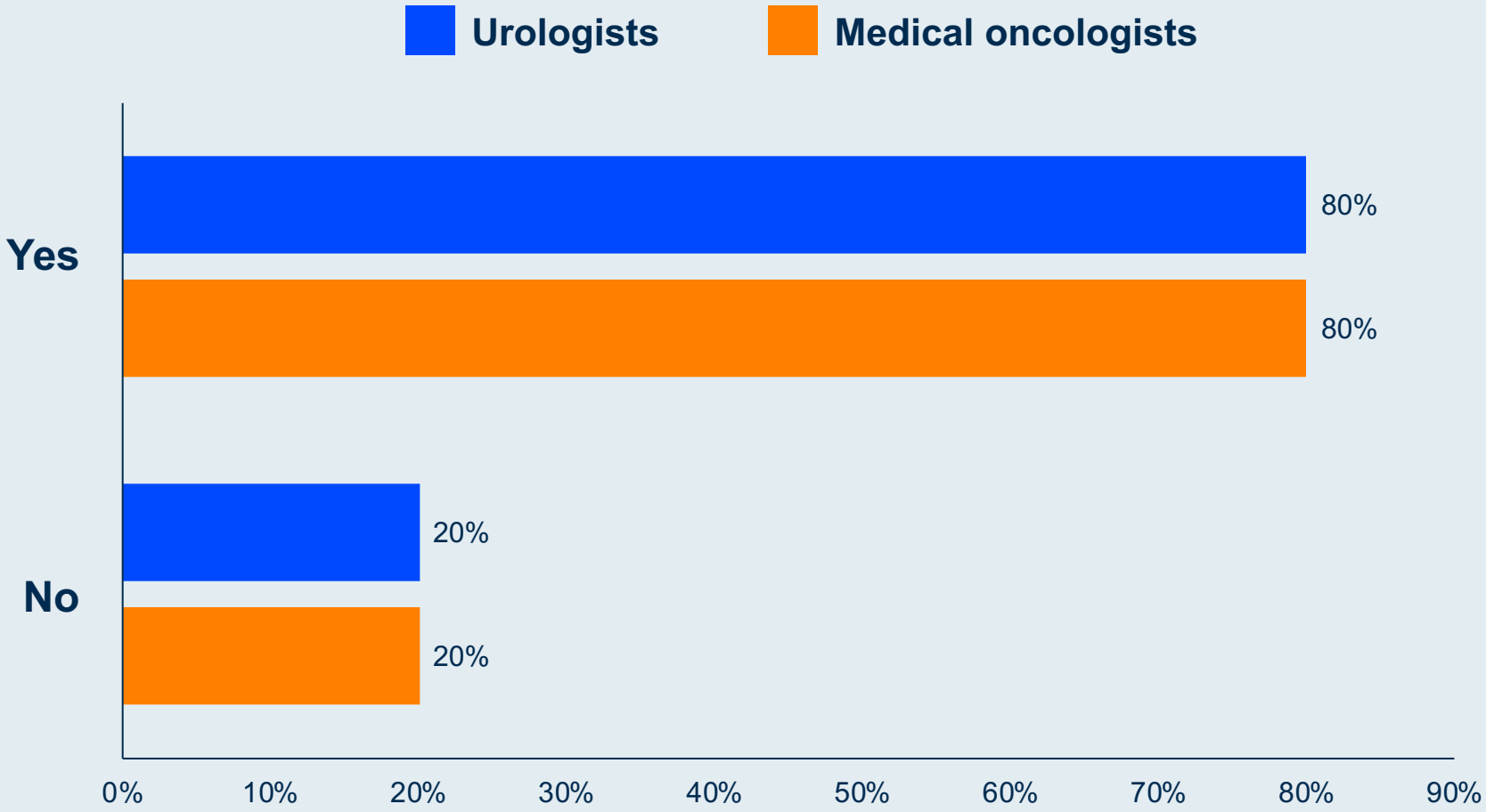
Survey of 25 US-based medical oncologists and 25 US-based urologists, July 2020.

Would you generally offer/recommend pembrolizumab to a 70-year-old patient with BCG-unresponsive non-muscle-invasive UBC and minor comorbidities?



Survey of 25 US-based medical oncologists and 25 US-based urologists, July 2020.

Would you generally offer/recommend pembrolizumab to an 80-year-old patient with BCG-unresponsive non-muscle-invasive UBC and significant comorbidities?



Survey of 25 US-based medical oncologists and 25 US-based urologists, July 2020.

Optimal candidates for pembrolizumab in high-risk non-muscle-invasive UBC

A 68-year-old man undergoes TURBT: pT1 high-grade UBC + CIS. Second resection: pTis. BCG is started. Cystoscopy after 3 months: 0.3-cm papillary tumor. Blue light-aided TURBT: pTa low-grade UBC. What would you recommend?

a. Continue BCG maintenance
b. Stop BCG
c. I don’t know

Case Presentation – Dr Kamat: 68-Year-Old Man with NMIBC

- 68-year-old man
- Has history of confirmed pTa low-grade bladder cancer 6 yrs ago
- Stopped surveillance, now with hematuria
- Medical history: diabetes type II, ECOG PS 0

Case Presentation – Dr Kamat: 68-Year-Old Man with NMIBC (cont)

- Initial workup: Cysto and CTU

- TURBT: pT1 high-grade + CIS
- Second resection: pTis

- Treatment with BCG started

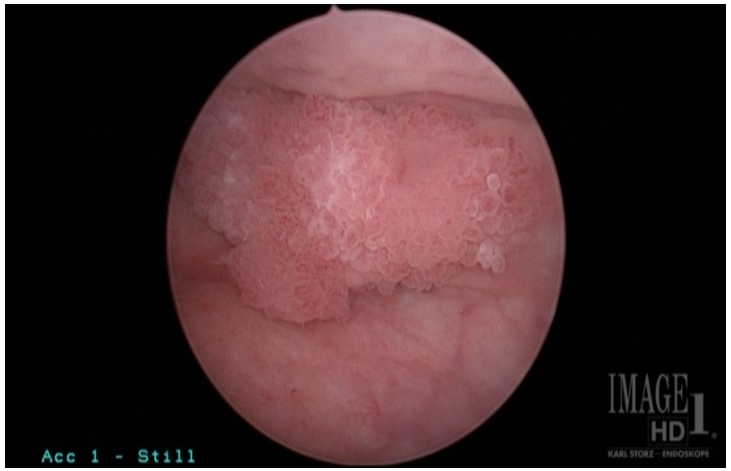
- Follow-up
- Cystoscopy after 3 months: 0.3 cm papillary tumor
- Blue light aided TURBT: confirms pTa low grade

Case Presentation – Dr Kamat: 68-Year-Old Man with NMIBC (cont)

- Options?
- LG recurrence on BCG therapy is not considered a failure in this case
- Continued on BCG maintenance therapy; finished 3 yr maintenance
- Currently NED 7 yrs out

Case Presentation – Dr Kamat: 62-Year-Old Woman with NMIBC

- Healthy Lady (62 yr old), gross hematuria work-up
  - CTU etc (imaging) negative
  - 1 cm tumors, high posterior wall
  - TURBT done – high grade T1 disease, muscle present, not involved



Case Presentation – Dr Kamat: 62-Year-Old Woman with NMIBC (cont)

- Undergoes reTUR – no residual tumor
- Has a discussion of options and selects BCG therapy
- Patient undergoes induction BCG, full dose, x 6 weeks
- 3 month evaluation – NED on cysto/cytology
  - Receives maintenance BCG
- 6 mos – positive cytology, cystoscopy negative
- Blue light showed patchy areas of tumor
  - Biopsy performed: path showed CIS
- All pathology reviewed by second pathologist and confirmed

Case Presentation – Dr Kamat: 62-Year-Old Woman with NMIBC (cont)

- Mentions she cannot undergo cystectomy on religious grounds

- Options?

Case Presentation – Dr Kamat: 62-Year-Old Woman with NMIBC (cont)

- Patient counselled on options
- Given the T1Hg and CIS, elected to undergo Pembro treatment

- 3 mos evaluation – negative cytology and cystoscopy

- Early days, yet

MODULE 2: Immune Checkpoint Inhibitors as Neoadjuvant/ Adjuvant Therapy for Muscle-Invasive UBC — Dr Daneshmand

- Anti-PD-1/PD-L1 antibodies in the neoadjuvant (PURE-01, ABACUS) and adjuvant (IMvigor010) settings
- Ongoing trials evaluating anti-PD-1/PD-L1 antibodies in early disease settings
- Case: A 77-year-old woman with MIBC

Neoadjuvant Systemic Treatment of Breast Cancer

Path CR > 50%, neoadjuvant preferred

- ER-negative, HER2-negative (triple-negative, [TNBC])
- HER2-positive: Post-op T-DM1

Low path CR; Surgery usually first

- ER-positive, HER2-negative

Key Current Question: Addition of IO to neoadjuvant chemotherapy for TNBC

Outcomes with Cystectomy

- 5yr & 10yr DSS for ≤T2N0M0 **60-85%**
- 5yr DSS for extravesical (T3) disease **50%**
- Node-positive disease who have undergone a thorough lymph node dissection: **25-30%**
- Surgical factors influencing outcome:
  - soft tissue margin
  - extent of lymph node dissection

Courtesy of Siamak Daneshmand, MD

USC Institute of Urology

Adjuvant Chemotherapy

- Offered to patients at high-risk for disease recurrence:
  - Positive lymph nodes (pN+)
  - T3b/T4 disease

- Value of adjuvant chemotherapy has not been definitely proven

- Several adjuvant chemotherapy trials have been conducted but they have been challenged by poor accrual and failure to reach predetermined end-points.

Courtesy of Siamak Daneshmand, MD

USC Institute of Urology

Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials

- **945 patients included in 9 randomized trials**
- **OS: pooled HR (9 trials) 0.77 (95%CI 0.59–0.99; p=0.049)**
- **DFS: pooled HR (7 trials) 0.66 (95%CI 0.45–0.91; p=0.014)**
- **DFS benefit more apparent in nodal metastasis (p=0.010)**

LIMITATIONS

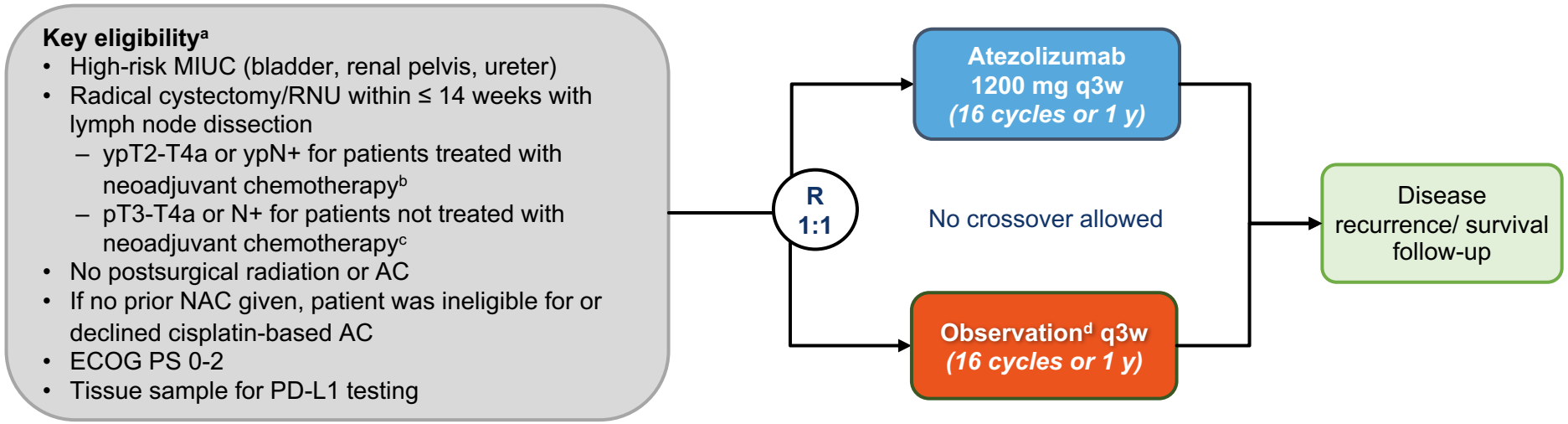
- **Smaller size/flawed individual trials**
- **Variation in eligibility criteria in individual trial, lack of individual patient data**

Slide Courtesy of Dr. Petros Grivas

Courtesy of Siamak Daneshmand, MD

Leow JJ, Eur Urol. 2014;66(1):42-54

IMvigor010 Study Design

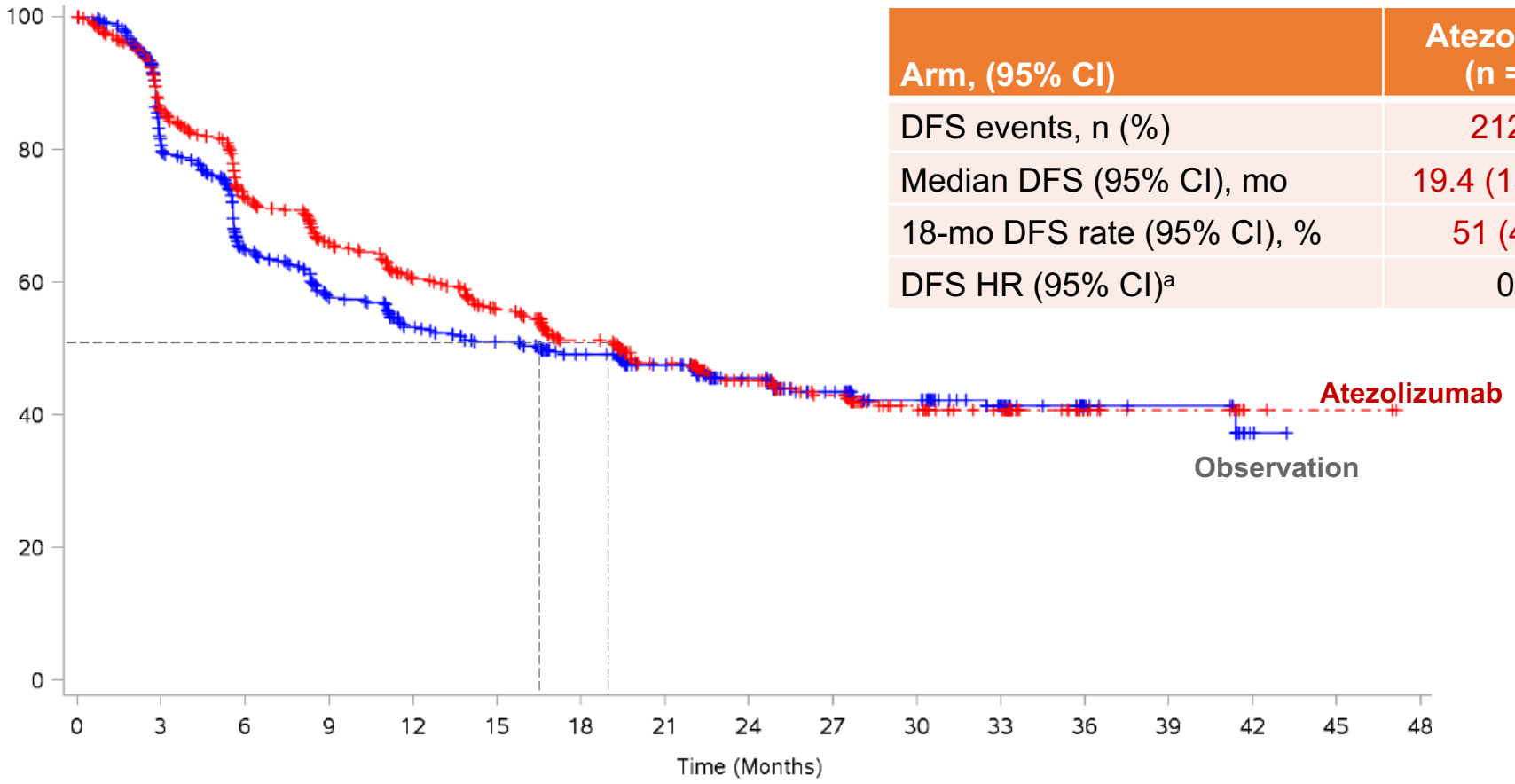


AC, adjuvant chemotherapy; MIUC, muscle-invasive UC; NAC, neoadjuvant chemotherapy; RNU, radical nephroureterectomy; UTUC, upper-tract UC. [a] Protocol amendments broadened eligibility to all-comer patients (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression IC ≥ 5% of tumor area per VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). Tumor staging for patients with UTUC: [b] ypT2-4 or ypN+ and [c] pT3-4 or pN+. [d] Alternating clinic visits and phone calls. [e] VENTANA SP142 assay.

Courtesy of Siamak Daneshmand, MD

Hussain MHA et al. ASCO 2020;Abstract 5000.

DFS in ITT Population



Arm, (95% CI)	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 (95% CI: 0.74, 1.08)	

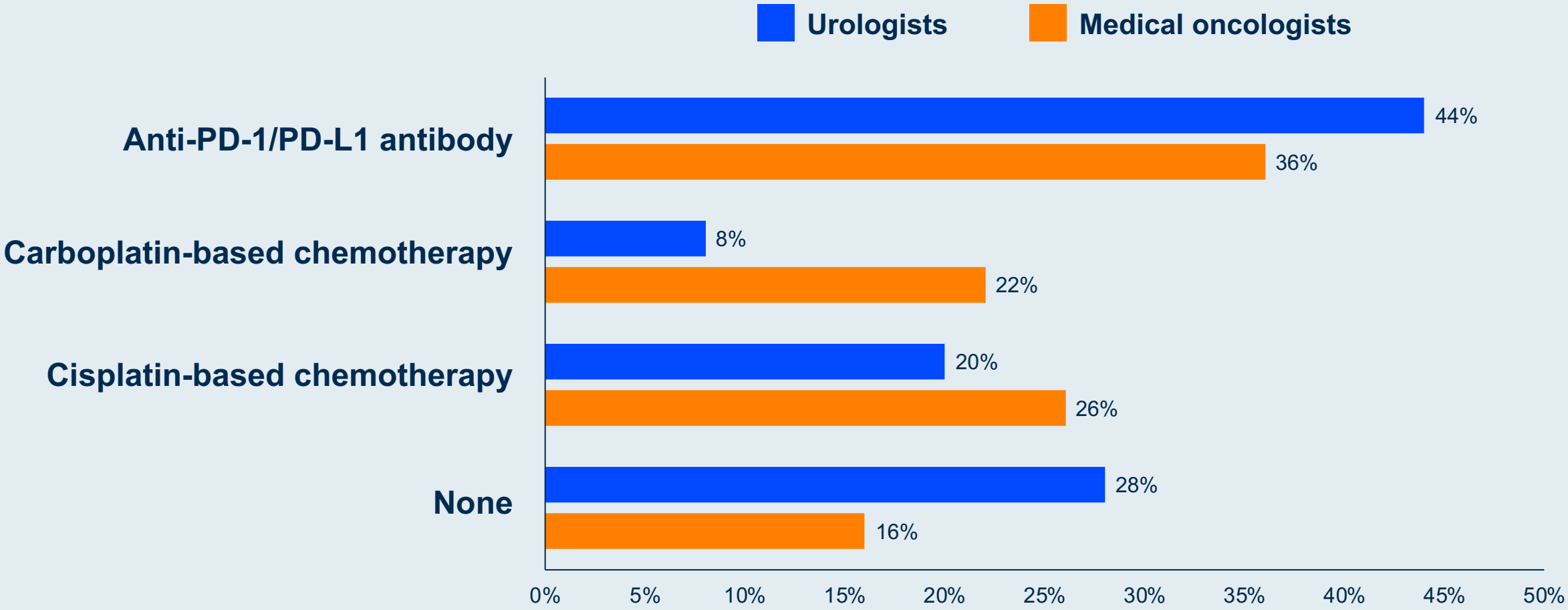
Data cut-off: November 30, 2019. Median follow-up: 21.9 mo.

[a] Stratified by post-resection tumor stage, nodal status and PD-L1 status.

Courtesy of Siamak Daneshmand, MD

Hussain MHA et al. ASCO 2020;Abstract 5000.

A 65-year-old man begins neoadjuvant dose-dense MVAC for muscle-invasive UBC but discontinues therapy after 2 cycles due to significant difficulty tolerating therapy, including a decline in creatinine clearance to 45 mL/min. The patient undergoes cystectomy, which reveals significant residual disease and a positive pelvic lymph node. PD-L1 = 20%. What adjuvant systemic therapy, if any, would you recommend?



Survey of 25 US-based medical oncologists and 25 US-based urologists, July 2020.

A 77-year-old woman is s/p cystectomy for pT3aN0M0 UBC. Would you recommend adjuvant chemotherapy?

a. Yes
b. No
c. I don’t know

Case Presentation – Dr Daneshmand: A 77-Year-Old Woman with MIBC

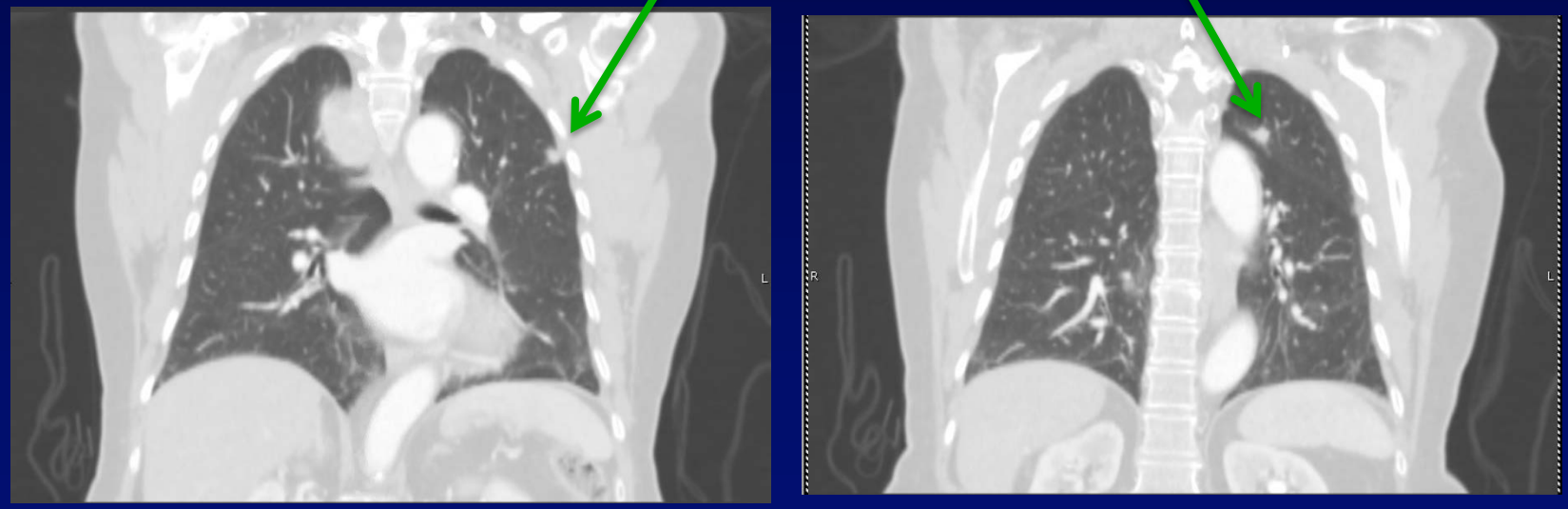
- 77yo female underwent TURBT on 8/27/2014 with pathology revealing squamous cell carcinoma (pure).
- Oct 2014 → Anterior Pelvic Exent/ePLND/ileal conduit
- Path: HG UC with Squamous diff (20%), pT3aN0(0/43)M0
- Completed 4 cycles of Gem/Cis in 3/2015

Courtesy of Sia Daneshmand, MD

USC Institute of Urology

Case Presentation – Dr Daneshmand: A 77-Year-Old Woman with MIBC (cont)

18 months later – August 2016
LUL Lung Nodule x 2



Biopsy: Metastatic UC
No other site of disease

Courtesy of Sia Daneshmand, MD

USC Institute of Urology

Case Presentation – Dr Daneshmand: A 77-Year-Old Woman with MIBC (cont)

- Underwent SBRT in two fractions Oct-Nov 2016
- Treated with **atezolizumab** on 11/15/2016
- Developed pneumonitis 5/22/2017
- Treated with Steroids and Tx discontinued
- CT 6/30/2020: NED

Courtesy of Sia Daneshmand, MD

USC Institute of Urology

MODULE 3: Immune Checkpoint Inhibitors in Advanced UBC — Dr Balar

- Pembrolizumab and atezolizumab as first-line treatment of metastatic UBC (mUBC)
- FDA approval of avelumab as first-line maintenance (JAVELIN Bladder 100)
- Available data with anti-PD-1/PD-L1 antibodies combined with other systemic therapies in mUBC
- Case: 70-year-old man with metastatic urothelial cancer
- Case: 78-year-old man with metastatic urothelial cancer

Major changes to locally advanced/metastatic UC treatment paradigm since 2016

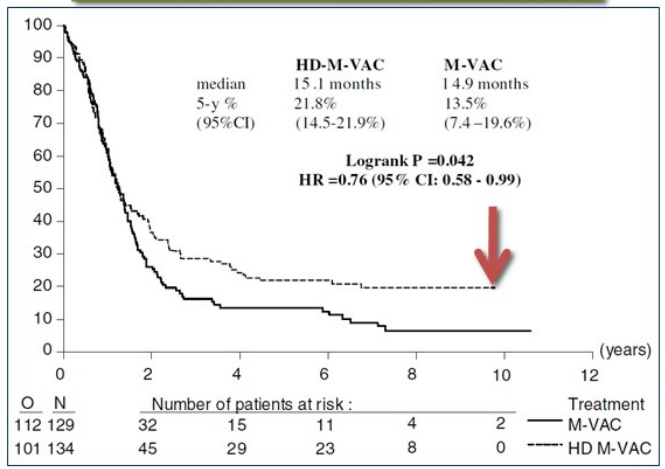
- First-line therapy remains platinum-based combination chemotherapy for most patients
- Immunotherapy in first-line setting for cisplatin-ineligible patients with PD-L1-high tumors
- Maintenance immunotherapy to become standard following chemotherapy
- Two novel agents approved in 2019
  - Erdafitinib targeting FGFR pathway alterations
  - Enfortumab vedotin antibody-drug conjugate targeting Nectin-4

Courtesy of Jonathan E Rosenberg, MD

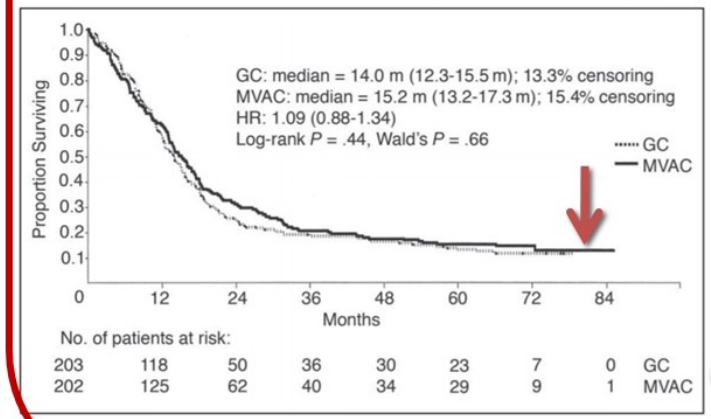
Chemotherapy - before the checkpoint era
Note the "tail" on the curve for cisplatin

Cisplatin Eligible

Dose Dense MVAC
ORR 72%
CR 25%
mOS 15.1 mo

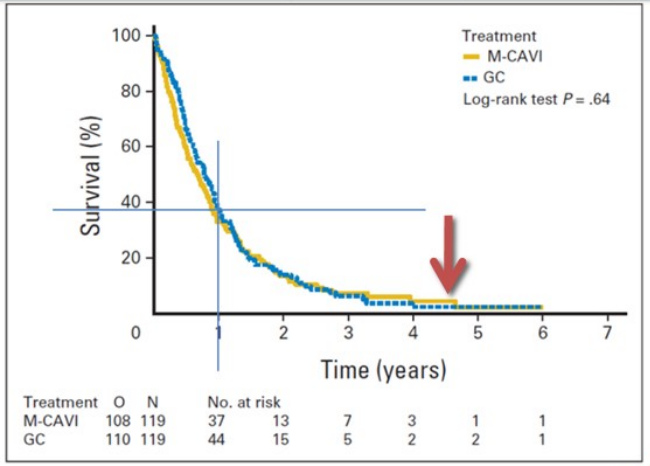


Gemcitabine Cisplatin
ORR 49%
CR 12 %
mOS 14 mo



Cisplatin Ineligible

Gemcitabine Carboplatin
ORR 36%
CR 3%
mOS 9.3 mo



1. von der Maase H, et al. J Clin Oncol. 2005. PMID: 16034041
2. Sternberg CN, et al. EORTC 30924. Eur J Cancer. 2006 PMID: 16330205
3. De Santis M, et al. EORTC 30986. J Clin Oncol. 2011. PMID: 19786668

Presented By Elizabeth Plimack at TBD

Regulatory Updates for Anti-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

KEYNOTE-361: BREAKING NEWS!

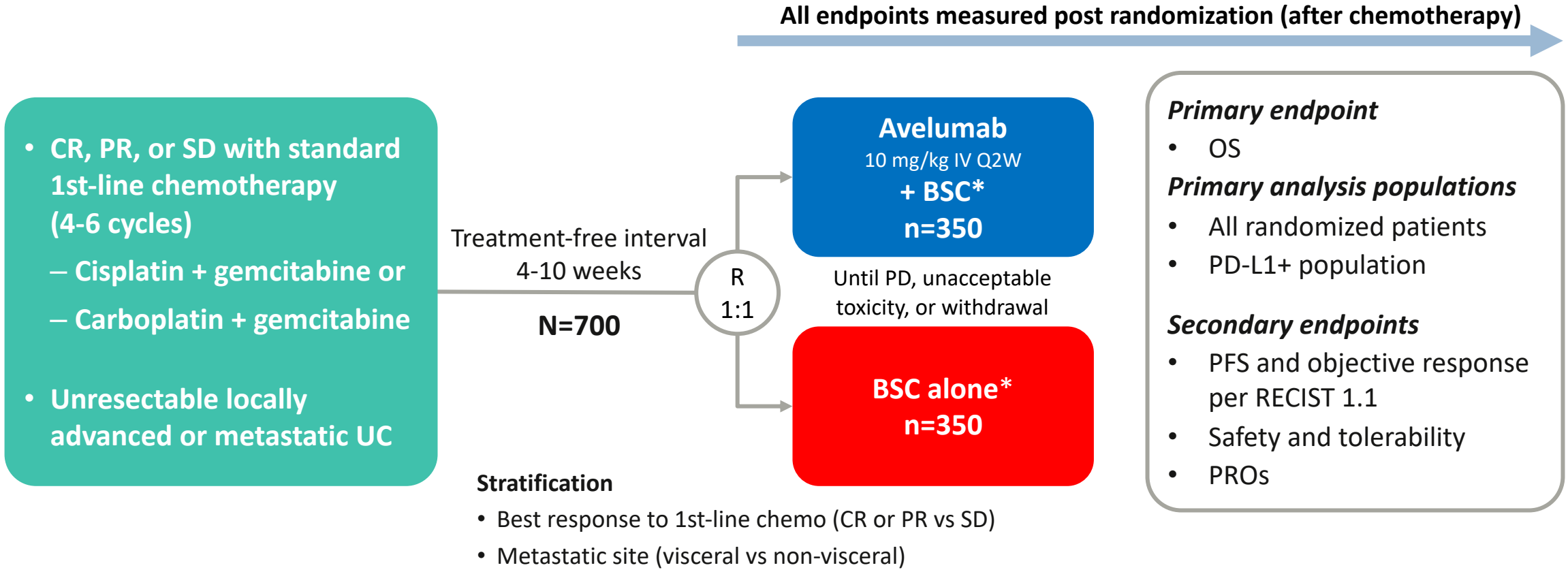
Update on Phase 3 KEYNOTE-361 Trial Evaluating Pembrolizumab as Monotherapy and in Combination with Chemotherapy in Patients with Advanced or Metastatic Urothelial Carcinoma

June 09, 2020

KENILWORTH, N.J. --(BUSINESS WIRE)-- The Phase 3 KEYNOTE-361 trial evaluating pembrolizumab, an anti-PD-1 therapy, in combination with chemotherapy for the first-line treatment of patients with advanced or metastatic urothelial carcinoma (bladder cancer) did not meet its pre-specified dual primary endpoints of overall survival (OS) or progression-free survival (PFS), compared with standard of care chemotherapy. In the final analysis of the study, there was an improvement in OS and PFS for patients treated with pembrolizumab in combination with chemotherapy (cisplatin or carboplatin plus gemcitabine) compared to chemotherapy alone; however, these results did not meet statistical significance per the pre-specified statistical plan. The monotherapy arm of the study was not formally tested, since superiority was not reached for OS or PFS in the pembrolizumab combination arm. The safety profile of pembrolizumab in this trial was consistent with previously reported studies, and no new safety were identified. Results will be presented at an upcoming medical meeting and will be discussed with regulatory authorities.

Courtesy of Arjun V Balar, MD

JAVELIN Bladder 100 study design (NCT02603432)



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

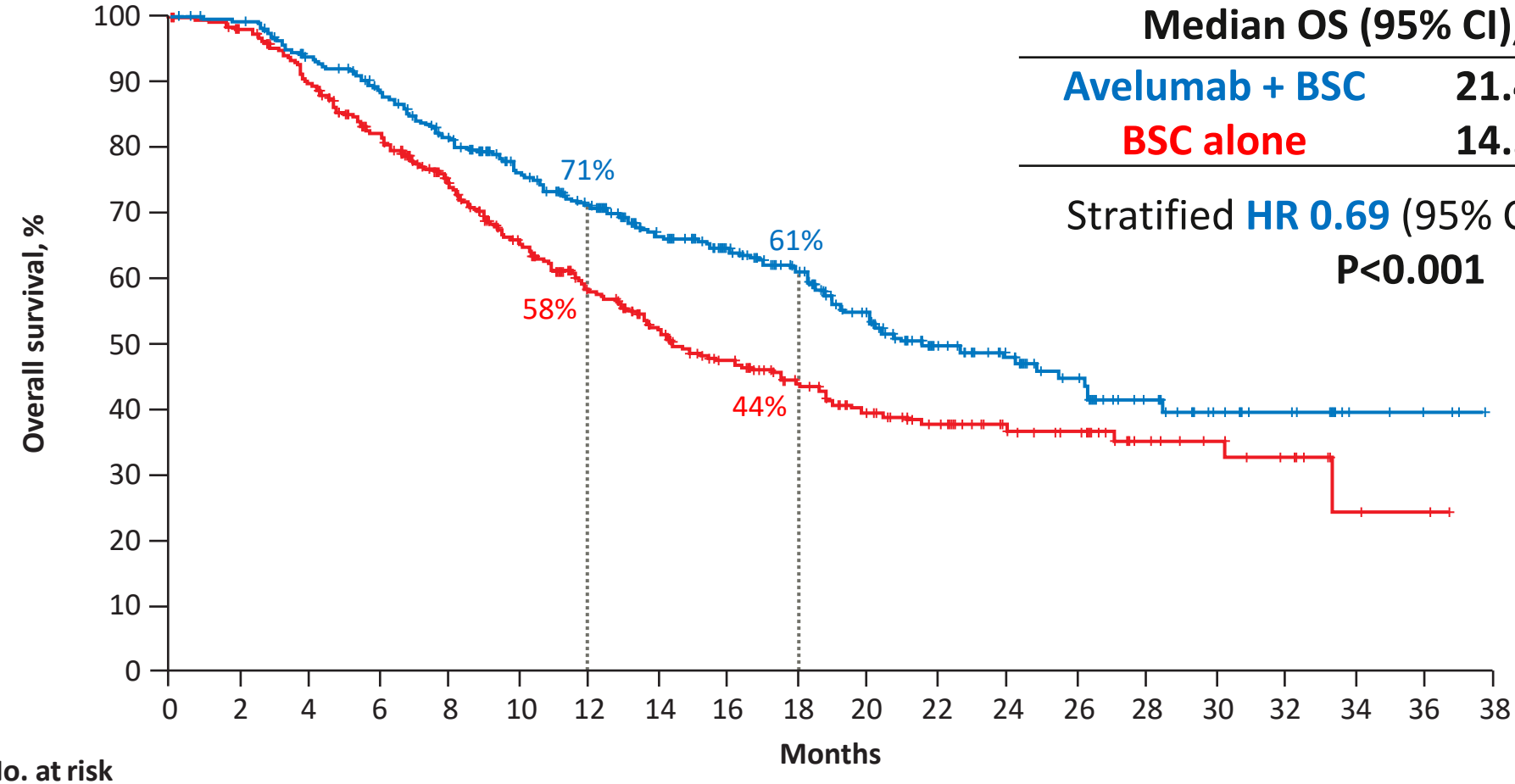
BSC, best supportive care; **CR,** complete response; **IV,** intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W,** every 2 weeks; **R**, randomization; **RECIST 1.1,** Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

Powles T et al. ASCO 2020;Abstract LBA1.

Courtesy of Arjun V Balar, MD

JAVELIN Bladder 100: OS in the overall population



Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

Stratified **HR 0.69** (95% CI, 0.56, 0.86)

P<0.001

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

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

Powles T et al. ASCO 2020;Abstract LBA1.

Courtesy of Arjun V Balar, MD

FDA approves avelumab for urothelial carcinoma maintenance treatment

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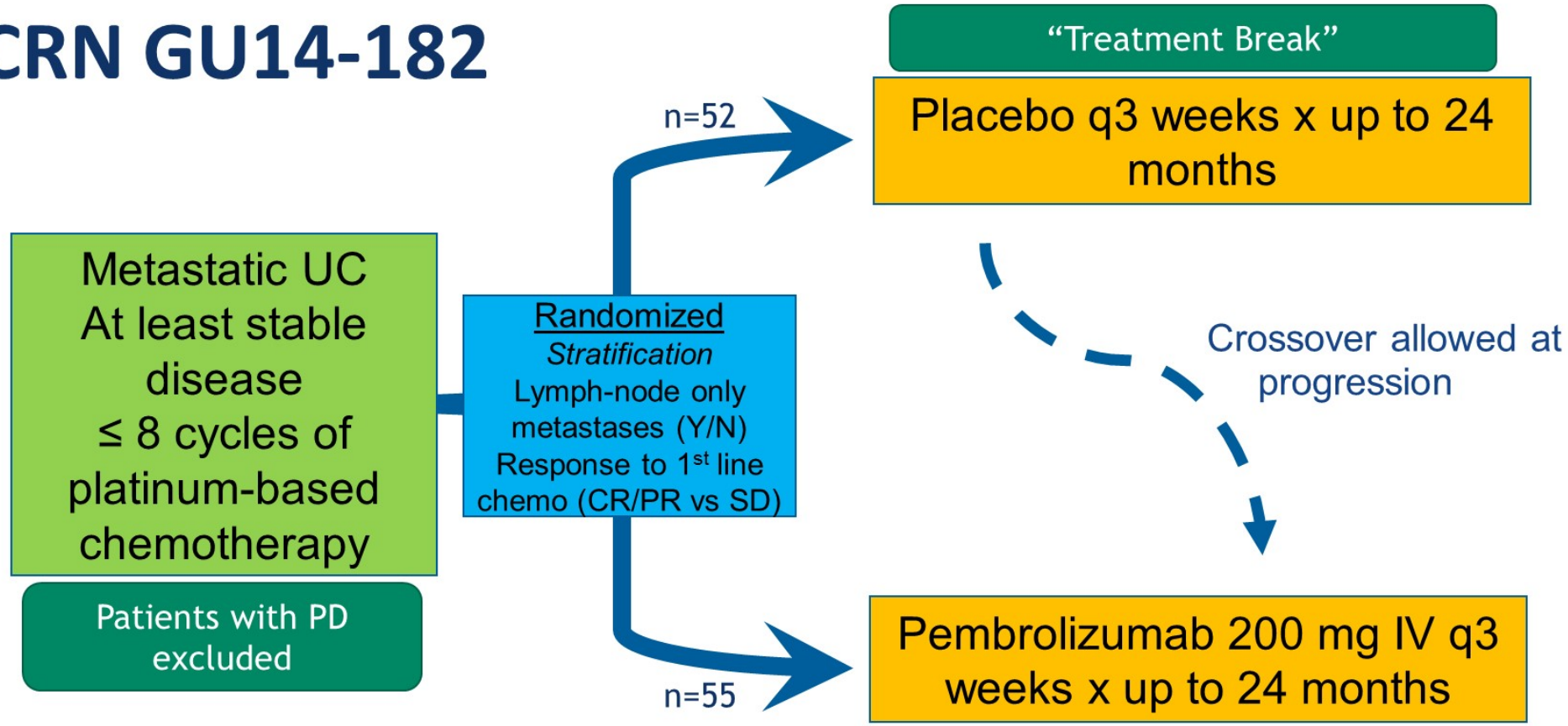
On June 30, 2020, the Food and Drug Administration approved avelumab for maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line-platinum containing chemotherapy.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-avelumab-urothelial-carcinoma-maintenance-treatment

Courtesy of Arjun V Balar, MD

Switch maintenance in mUC: Phase II trial HCRN GU14-182

HCRN GU14-182



1. Galsky, et al. ASCO 2019

Presented By Elizabeth Plimack at TBD

JAVELIN Bladder 100 Subsequent Therapy

Subsequent anticancer therapy

	Overall population*		Subgroup who discontinued study therapy due to PD	
	Avelumab + BSC (N=350)	BSC alone (N=350)	Avelumab + BSC (N=189)	BSC alone (N=263)
Any subsequent therapy, %	**42.3**	**61.7**	**70.4**	**75.3**
PD-L1/PD-1 inhibitor	**6.3**	**43.7**	**9.0**	**52.9**
Fibroblast growth factor receptor inhibitor	2.6	2.3	4.8	3.0
Any other drug	40.0	34.0	67.2	41.8

All percentages were calculated using the denominator of all patients in the treatment arm within each population; some patients received >1 category of subsequent therapy
*All randomized patients, including patients who had discontinued study therapy and those remaining on study therapy

- OS was prolonged with avelumab 1L maintenance despite frequent use of subsequent PD-L1/PD-1 inhibitors in the BSC alone arm

JAVELIN 100

- Crossover was not allowed, yet among those with PD in the control arm, 52.9% received a subsequent PD-L1/PD1 inhibitor

HCRN GU14-182

- A similar proportion [51.9%] crossed over within the study
  - An additional 10% received other further treatment off study, which could have included a PD-L1/PD1 inhibitor

1. Powles et al, ACSCO 2020
2. Galsky MD, et al. Journal of Clinical Oncology. PMID: 32271672

Presented By Elizabeth Plimack at TBD

Post platinum, is switch maintenance checkpoint inhibition preferred over a treatment break followed by second line?

For most patients, yes

- Longer OS with switch maintenance
- Delay in PFS is meaningful – particularly if progression is symptomatic
- Not all patients will be caught by the second line safety net

However:

- If you can guarantee a patient access to second line checkpoint after a treatment break (crossover) their survival may not be impacted
- Some patients will have durable response to platinum and not require checkpoint for months if at all. These patients will be overtreated.

JAVELIN 100 ushers In two paradigm shifts in the treatment of metastatic urothelial cancer

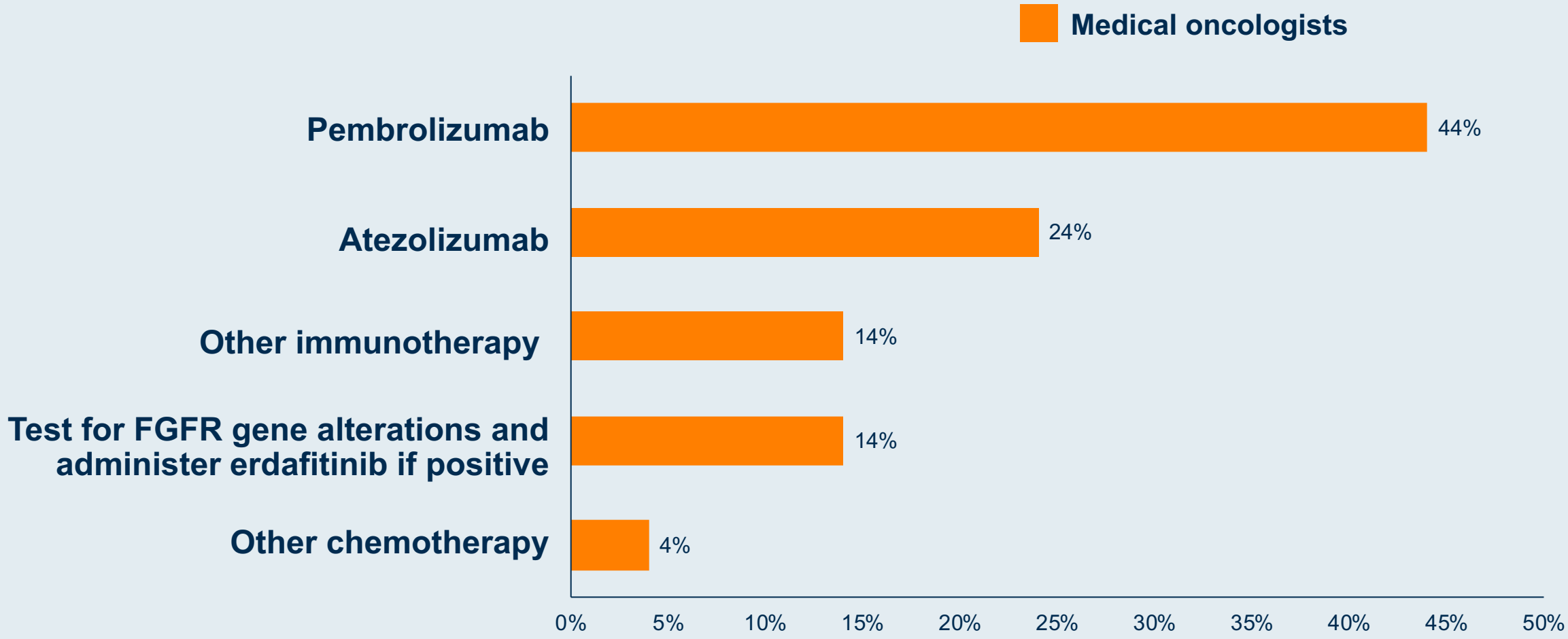
FIRST LINE: Platinum based chemotherapy is best initial therapy

- Highest ORR
- “Tail on the curve” with durable treatment free survival for some
- Sets patient up for best OS to subsequent checkpoint inhibitor
- Does not require PDL1 testing for treatment selection
- Unlikely that a non-responder to platinum would have benefited from first line checkpoint inhibition

POST PLATINUM: Switch maintenance is preferred over treatment break as timing for next line checkpoint inhibitor in patients with SD or response

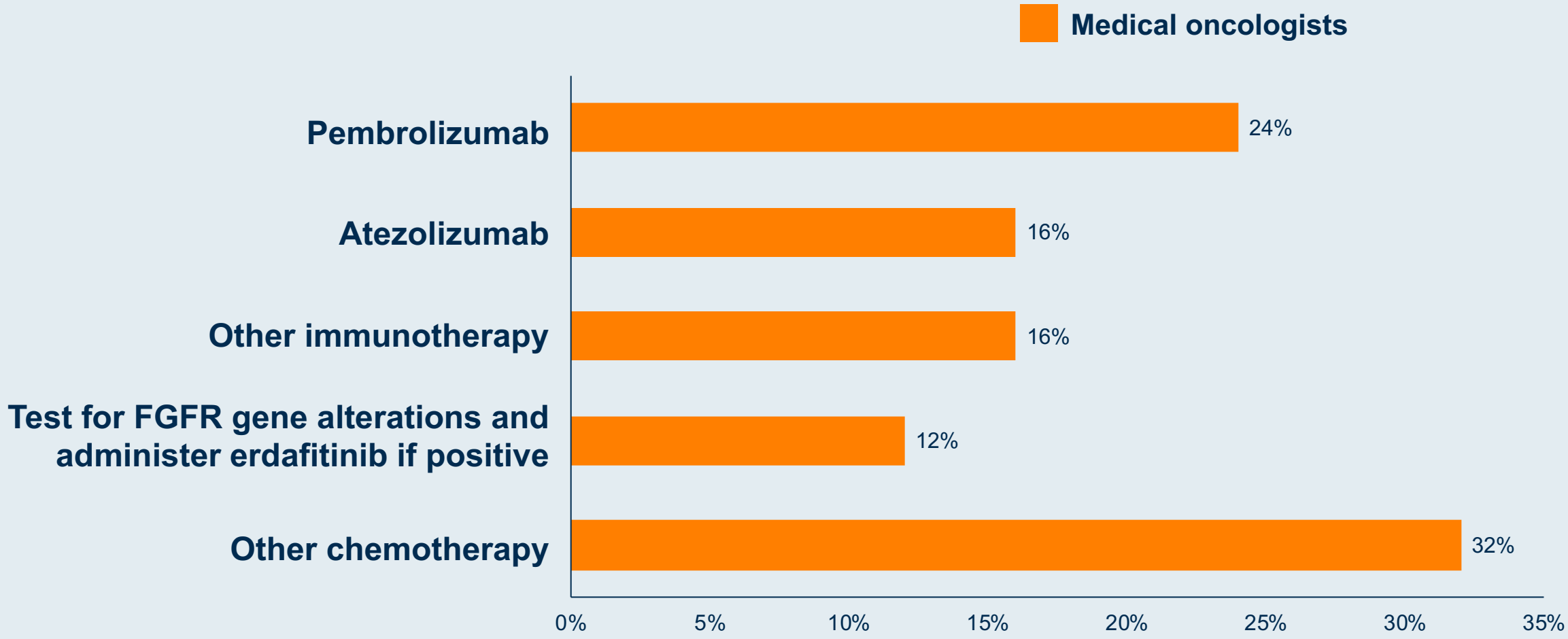
- Delays progression of disease and potentially symptoms
- Overall survival can be similar, only if access to second line checkpoint is guaranteed

What would you generally recommend for a patient who experiences disease recurrence 9 months after cystectomy and adjuvant chemotherapy for muscle-invasive UBC?



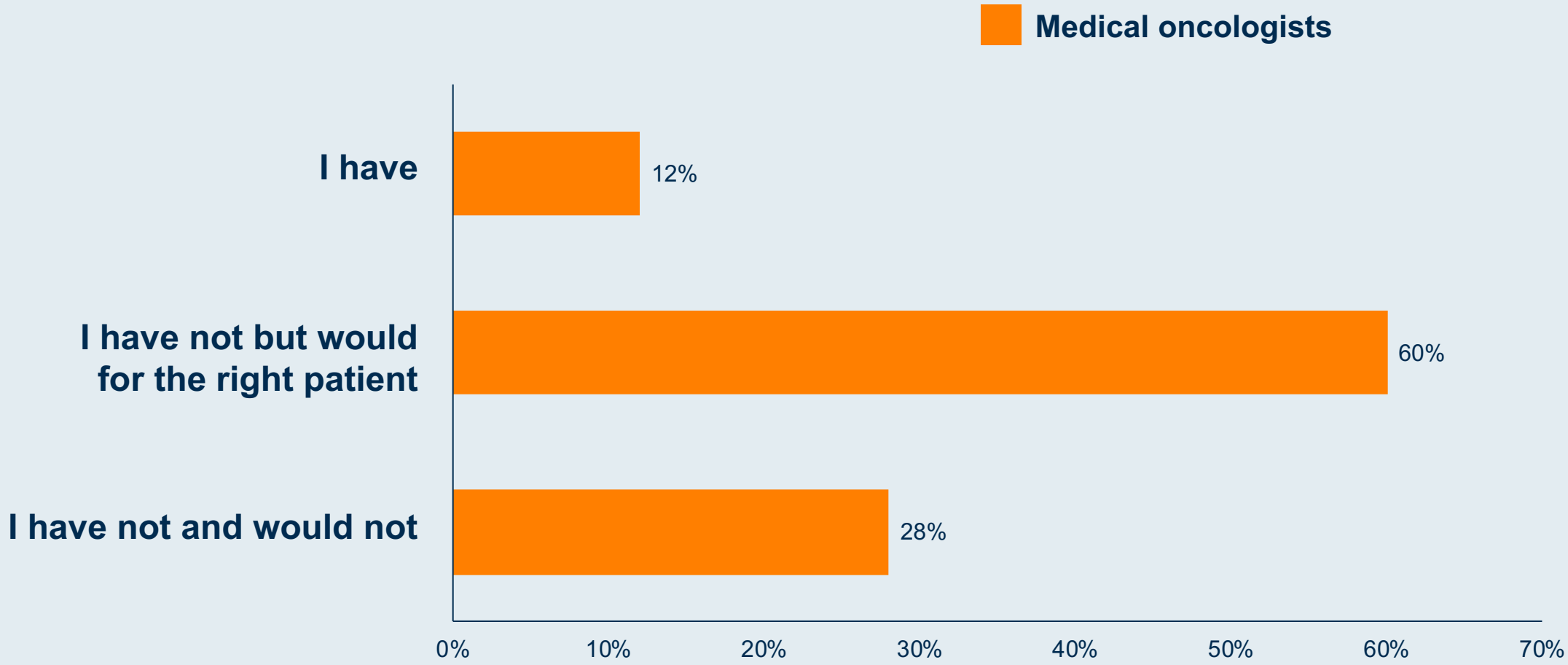
Survey of 25 US-based medical oncologists, July 2020.

What would you generally recommend for a patient who experiences disease recurrence 18 months after cystectomy and adjuvant chemotherapy for muscle-invasive UBC?



Survey of 25 US-based medical oncologists, July 2020.

Have you discontinued or would you discontinue anti-PD-1/ PD-L1 antibody therapy for a patient with metastatic UBC who is experiencing a durable response?



Survey of 25 US-based medical oncologists, July 2020.

Regulatory and reimbursement issues aside, would you administer anti-PD-1/PD-L1 antibody maintenance to a 70-year-old man with mUBC and a creatinine of 1.9 who achieves a partial response to first-line carboplatin/gemcitabine?

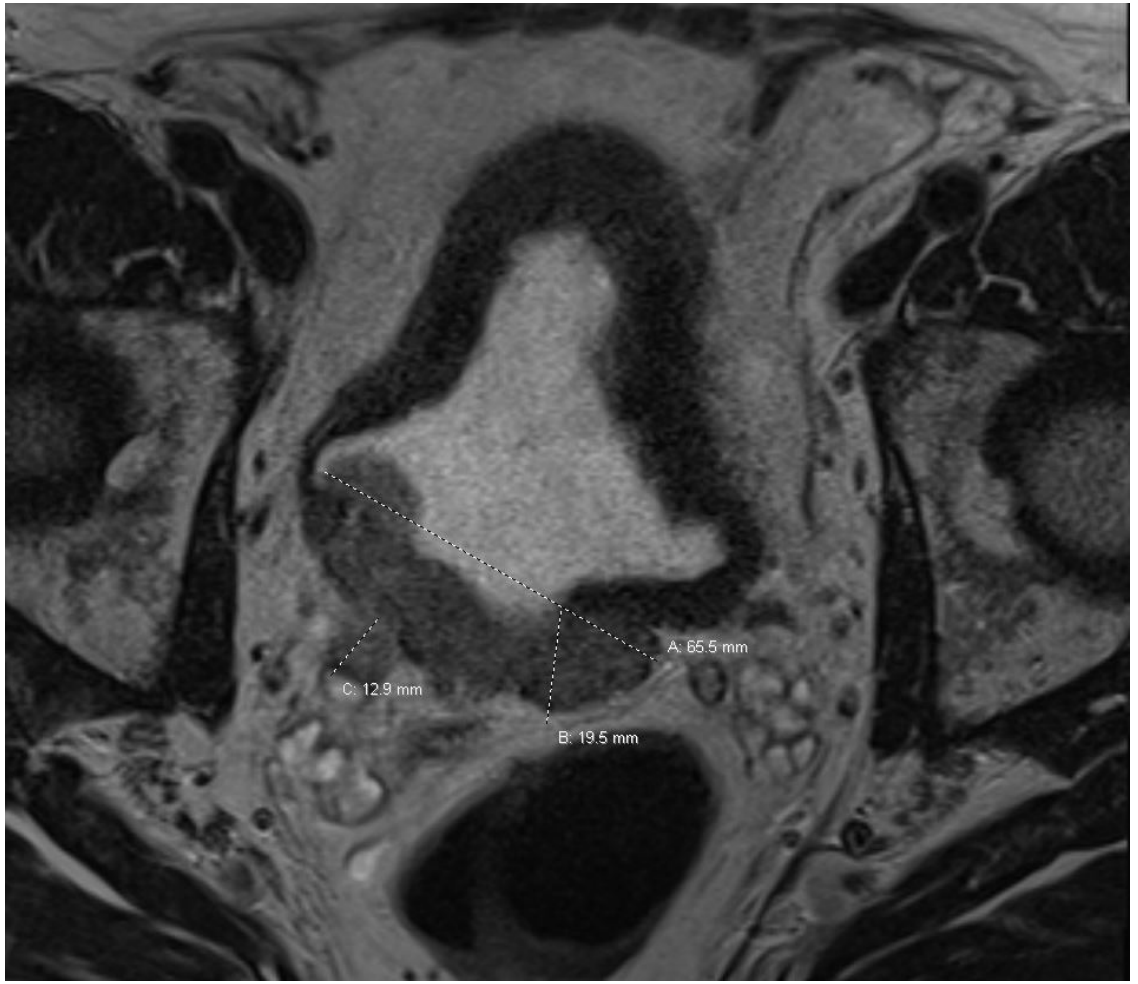
a. Yes, avelumab
b. Yes, pembrolizumab
c. Yes, other
d. No
e. I don’t know

In general, how often do you believe pembrolizumab should be administered?

a. Every 3 weeks
b. Every 6 weeks
c. I don’t know

Case Presentation – Dr Balar: 70-Year-Old Man with Metastatic Urothelial Cancer

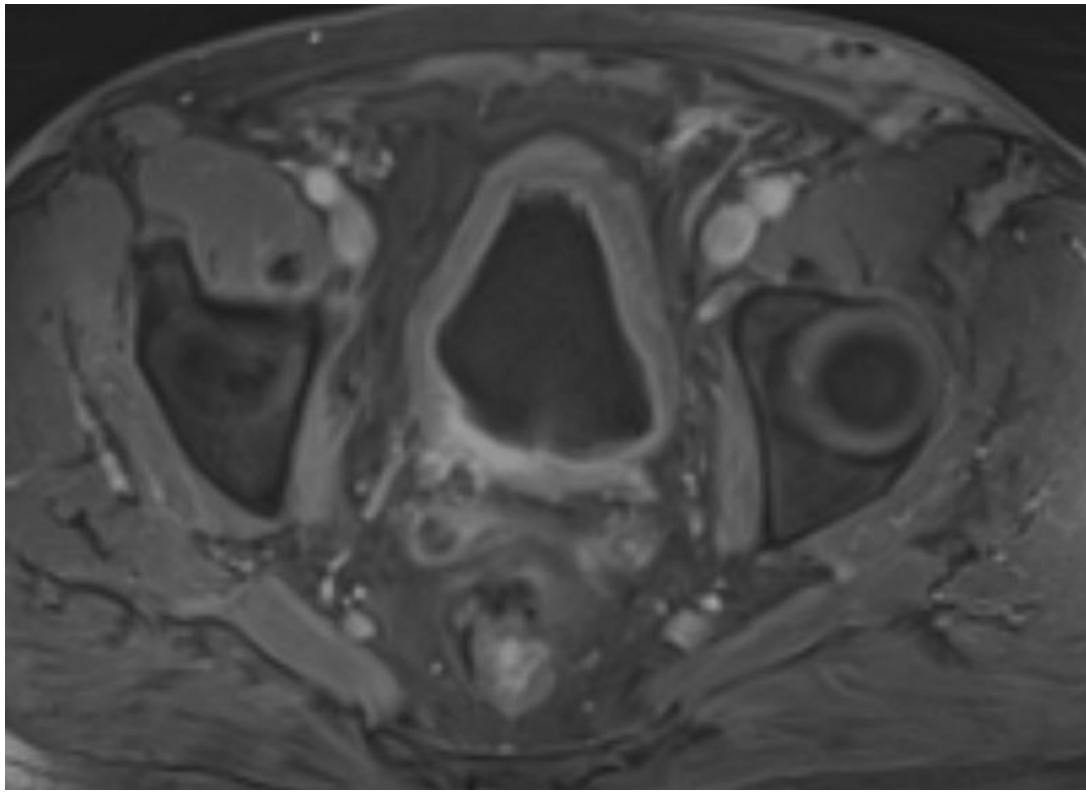
- 70 year old man, former smoker and hypothyroidism presented to NYU ED on 11/11/2018 c/o right flank pain.
  - Found to have atrophic left kidney and AKI due to right sided hydronephrosis from a large bladder mass
  - 11/20/2018 Cytoscopy/TURBT: large papillary/sessile mass obscuring right UO
    - Pathology: muscle-invasive urothelial cancer
    - Right ureteral stent
  - 11/21/2018 MRI AP with contrast: 5.4 cm posterolateral bladder wall mass, no metastatic disease
  - 12/19/2018 Hgb 13.2; creatinine 0.90, normal LFTs
  - ECOG PS 0



Courtesy of Arjun V Balar, MD

Case Presentation – Dr Balar: 70-Year-Old Man with Metastatic Urothelial Cancer (cont)

- Counseled about treatment options, refuses radical cystectomy, interested in bladder preservation therapy
  - Enrolled to NYU S15-00220 phase II study of pembrolizumab
    - Anti-PD-1 added to Trimodal bladder preservation therapy (Maximal TURBT followed by Hypofractionated radiation therapy and twice weekly gemcitabine)
    - Receives treatment between 1/25/2019 through 4/22/2019
  - 6/24/2019 Post-treatment cystoscopy/TUR of tumor bed
    - no residual carcinoma; normal urine cytology
  - 6/21/2019 CT Chest/MR Urogram:
    - Previous bladder tumor no longer visualized, mucosal enhancement consistent with treatment effect
    - No metastatic disease



Courtesy of Arjun V Balar, MD

Case Presentation – Dr Balar: 70-Year-Old Man with Metastatic Urothelial Cancer (cont)

- On surveillance doing well
- 1/3/2020 MRI AP: New metastatic retroperitoneal lymph nodes, largest 4.9 x 2.1 cm in left para-aortic region; normal bladder but progressive right ureteral stricture
  - Creatinine: 1.90, ECOG PS 0
  - Treated with Gemcitabine and Carboplatin x 6 cycles (2/6/2020 through 5/27/2020)
    - 6/24/2020 MRI AP: Moderate response in RP adenopathy (largest 2.5 x 1.8 cm), no new metastases
    - ECOG PS remains 0
- What's the next step?
  - Treatment break or maintenance immunotherapy?

Courtesy of Arjun V Balar, MD

Case Presentation – Dr Balar: 78-Year-Old Man with Metastatic Urothelial Cancer

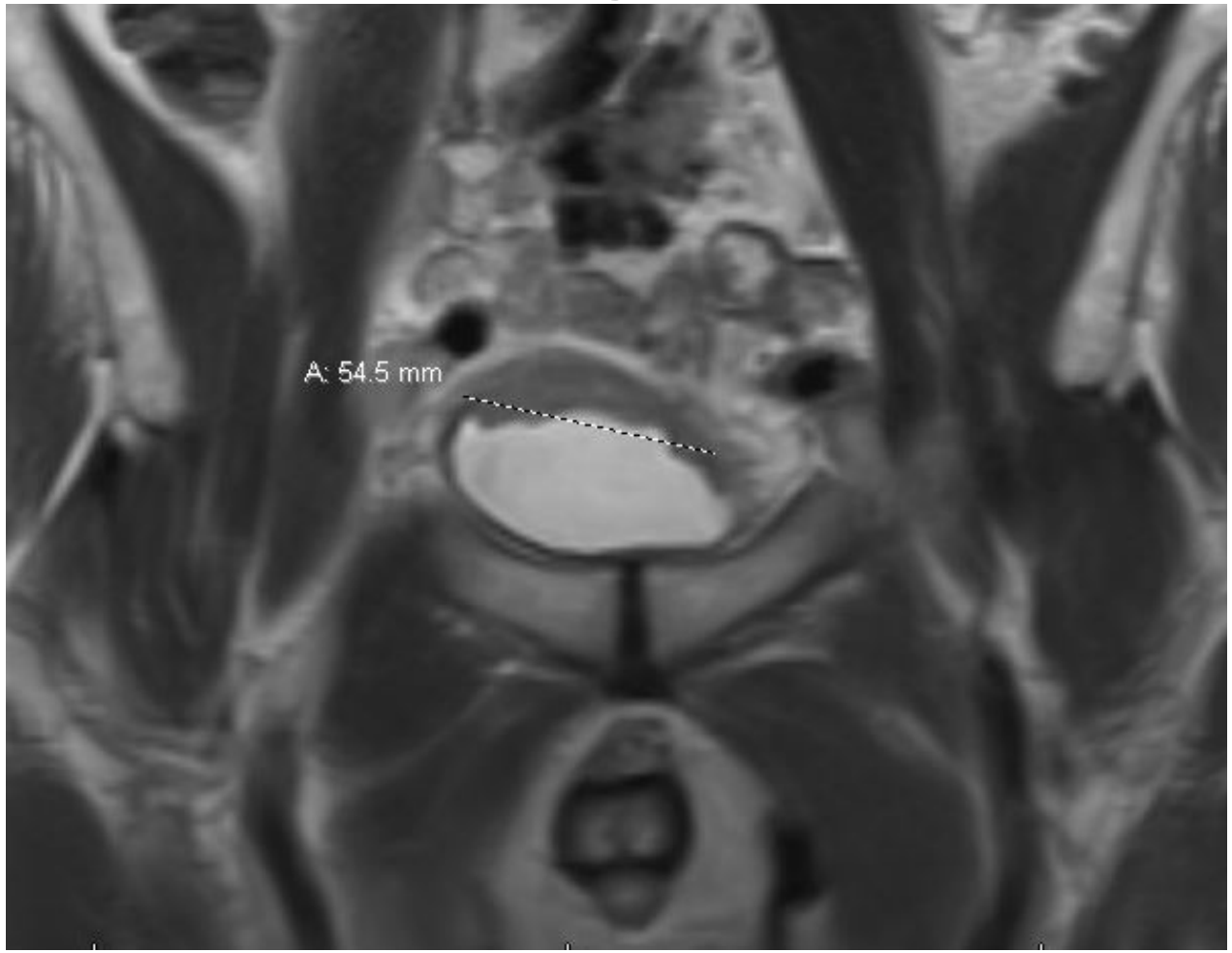
- 78 year old practicing psychologist
- PMH: Low-risk Prostate Cancer on AS and BPH
- Presented with gross hematuria in October 2018; CT AP confirmed a large bladder mass
- 11/26/2018 Cystoscopy/TURBT: 6 cm mass posterior wall/bladder dome
  - Muscle-invasive urothelial cancer

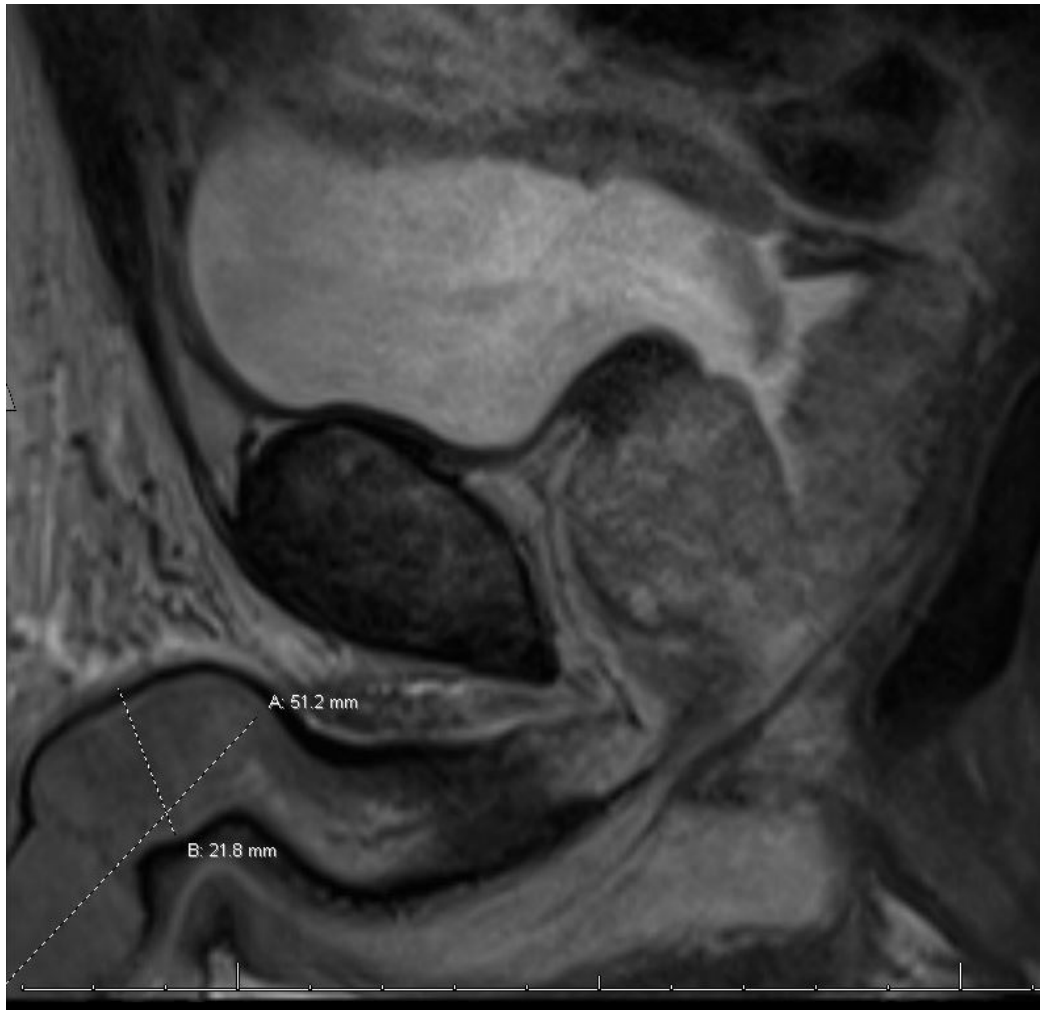
- Referred to medical oncology in 12/20/2018 he reported feeling generally well (ECOG PS 0), however at the end of the visit, he incidentally reported mass-like thickening and rigidity of his penis

Courtesy of Arjun V Balar, MD

Case Presentation – Dr Balar: 78-Year-Old Man (cont)

- **12/21/2018 MR Urogram:**





- **12/26/2018 FNA of Penile Mass:** Malignant cells consistent with metastatic urothelial cancer

Courtesy of Arjun V Balar, MD

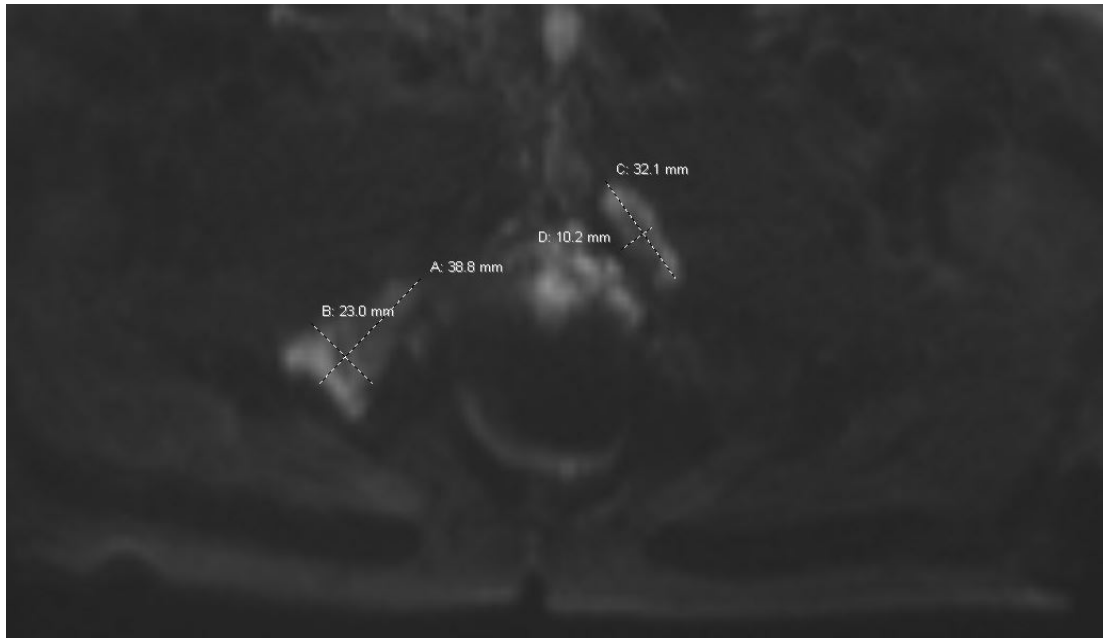
Case Presentation – Dr Balar: 78-Year-Old Man with Metastatic Urothelial Cancer (cont)

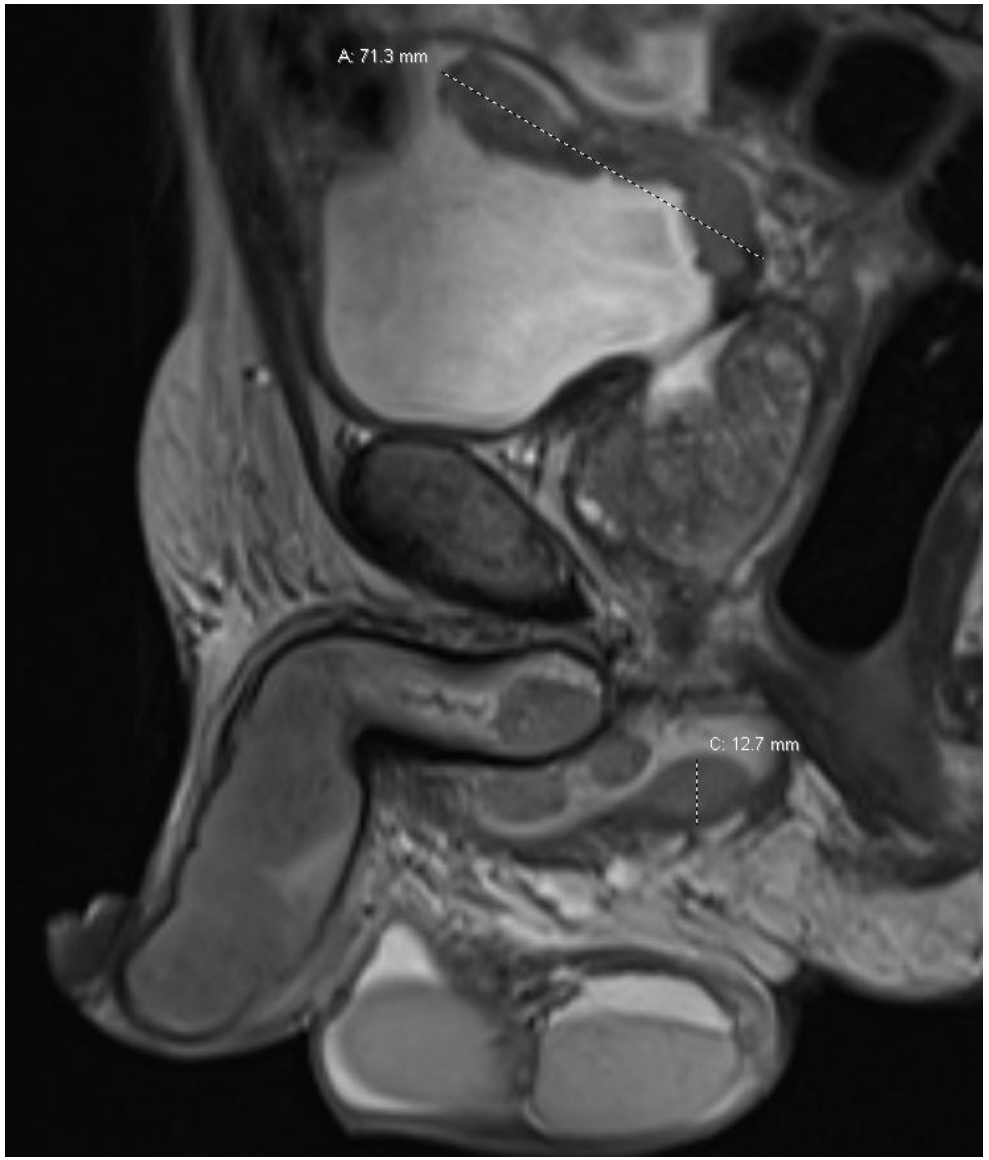
- ECOG PS 0
- 12/24/2018 Labs: Hgb 11.8; Cr 1.00, normal LFTs
- Treatment Discussion:
  - Cisplatin-based chemotherapy
  - Adamant about avoiding chemotherapy
  - Interested only in “natural treatments”
    - Willing to accept immunotherapy as a “natural treatment”
- 12/2018 TURBT tissue tested for PD-L1
  - CPS 50% (clone 22C3)

Courtesy of Arjun V Balar, MD

Case Presentation – Dr Balar: 78-Year-Old Man (cont)

- Multiple visits/treatment discussions
- Begins single agent pembrolizumab on 1/14/2019 and receives a total of 3 cycles
  - Penile mass less firm, urinating normally after 2nd cycle, complicated by fatigue
- 3/14/2019 CT/MRI: POD, new/increasing penile lesions, new bone metastases, new and increasing sub-cm pulmonary nodules





Courtesy of Arjun V Balar, MD

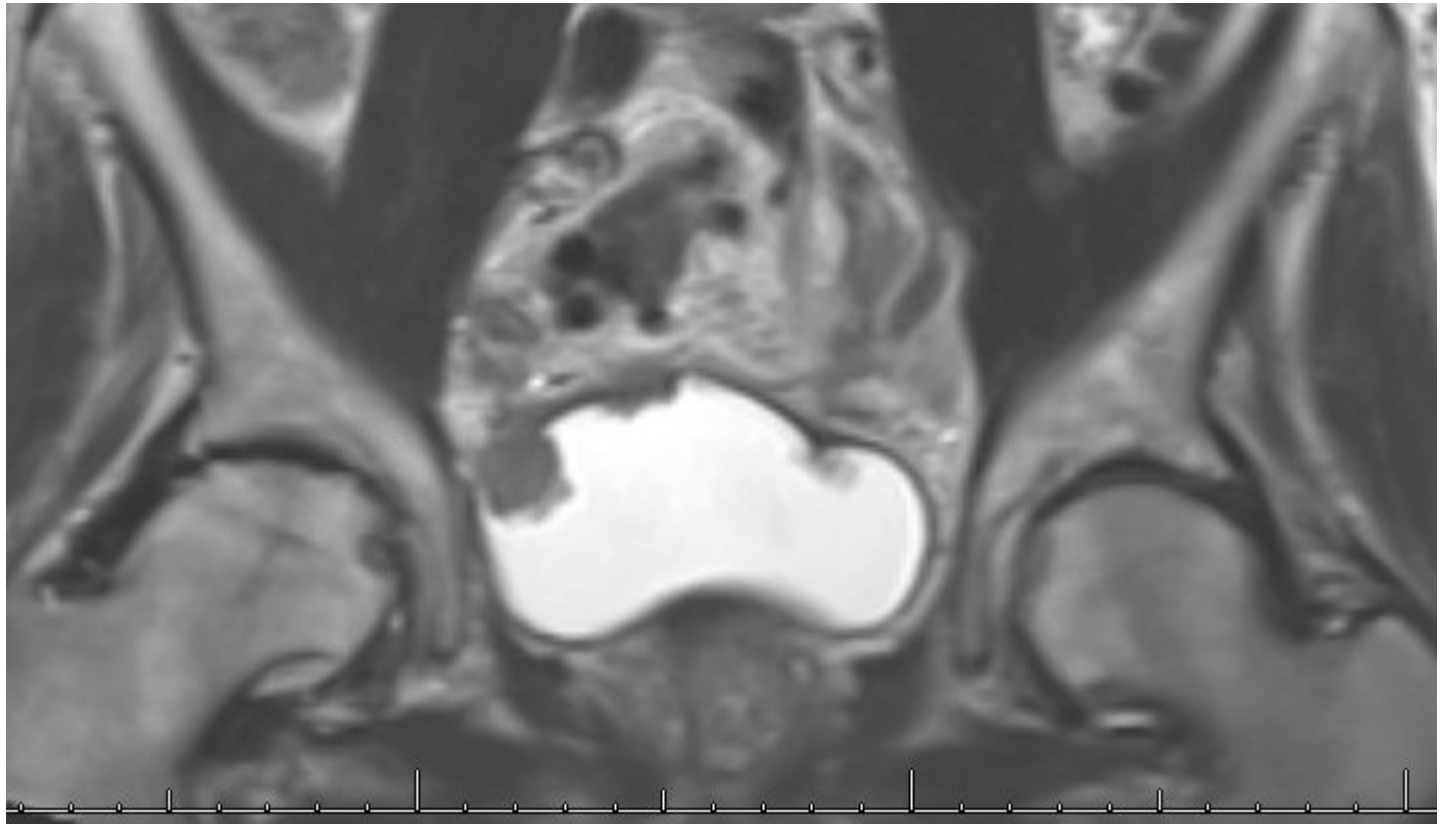
Case Presentation – Dr Balar: 78-Year-Old Man with Metastatic Urothelial Cancer (cont)

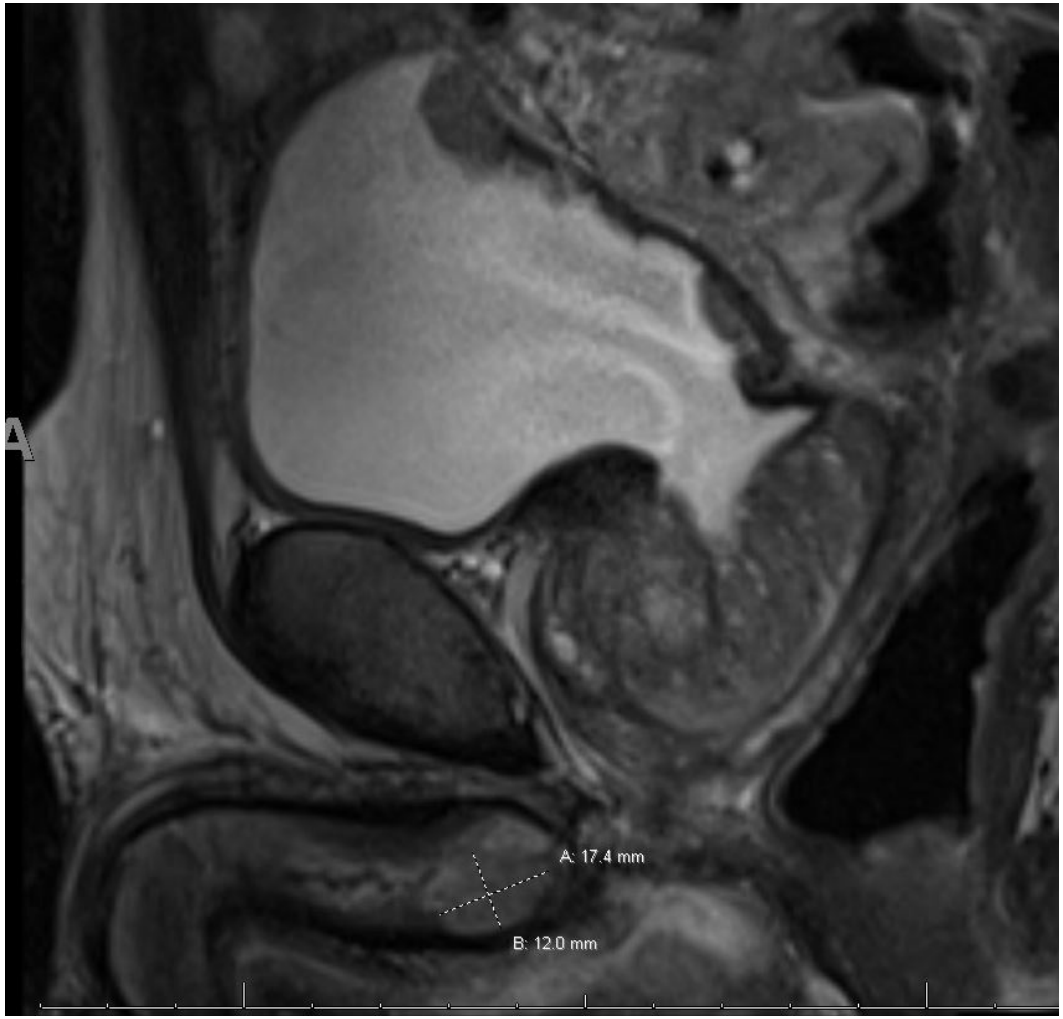
- Despite imaging, patient feels very well, urinating normally, no symptoms concerning for disease progression
- Refuses further treatment with pembrolizumab (last dose 2/25/2019), still unwilling to consider chemotherapy
- 4/17/2019 CT Chest and MRI Urogram: continued progression in bladder mass, mild increase in penile lesions, stable osseous metastases, some lung nodules smaller
- Despite continued progression, refuses further evaluation/interventions since he feels so well.

Courtesy of Arjun V Balar, MD

Case Presentation – Dr Balar: 78-Year-Old Man (cont)

- 6/5/2019 MRI Urogram: decreasing bladder, penile and pelvic nodal metastases, stable bone





Courtesy of Arjun V Balar, MD

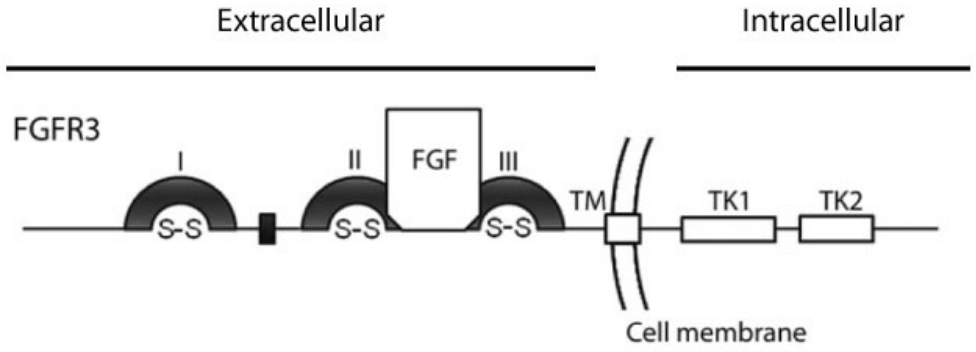
MODULE 4: Current and Future Roles of Recently FDA-Approved Novel Therapies — Dr Rosenberg

- Clinical research data leading to FDA approvals of erdafitinib and enfortumab vedotin
- Adverse event profiles of erdafitinib and enfortumab vedotin; monitoring and management strategies
- FDA Breakthrough Therapy: Enfortumab vedotin combined with pembrolizumab
- Case: 74-year-old man with mUBC
- Case: 74-year-old woman with mUBC

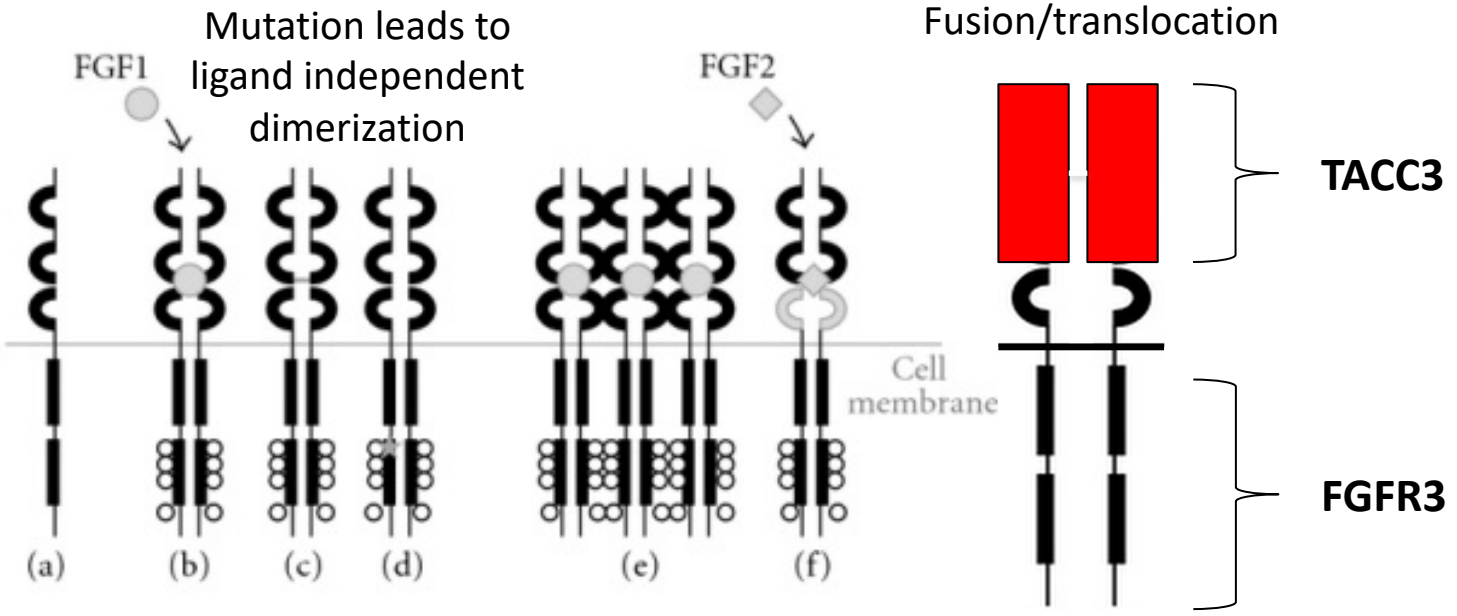
Fibroblast Growth Factor Receptor 3 is a therapeutic target in mUC

- Mutation frequency in non-invasive disease is >50% in Ta tumors
- Mutations and fusions are less common in advanced UC
  - Mutation 5-15%
  - Fusion 3-5% using NGS

FGFR3 signals via PI3K, PKC, RAS/MAP kinase pathways



FGFR3 activation can occur by mutation, overexpression or gene fusion



Overexpression

Courtesy of Jonathan E Rosenberg, MD

Memorial Sloan Kettering Cancer Center

Erdafitinib is the first targeted therapy approved for advanced bladder cancer

- Accelerated approval April 12, 2019
- Indicated in tumors with FGFR3 or FGFR2 alterations
  - Progression during or following prior platinum-containing chemotherapy
- Dosing:
  - 8 mg daily
  - Increase to 9 mg daily if serum phosphorus level is <5.5 mg/dL (and no ocular disorders or ≥ grade 2 toxicity) at days 14-21 of therapy
  - Continue until disease progression or unacceptable toxicity occurs
  - Monthly ophthalmologic exams x 4 then q3 months

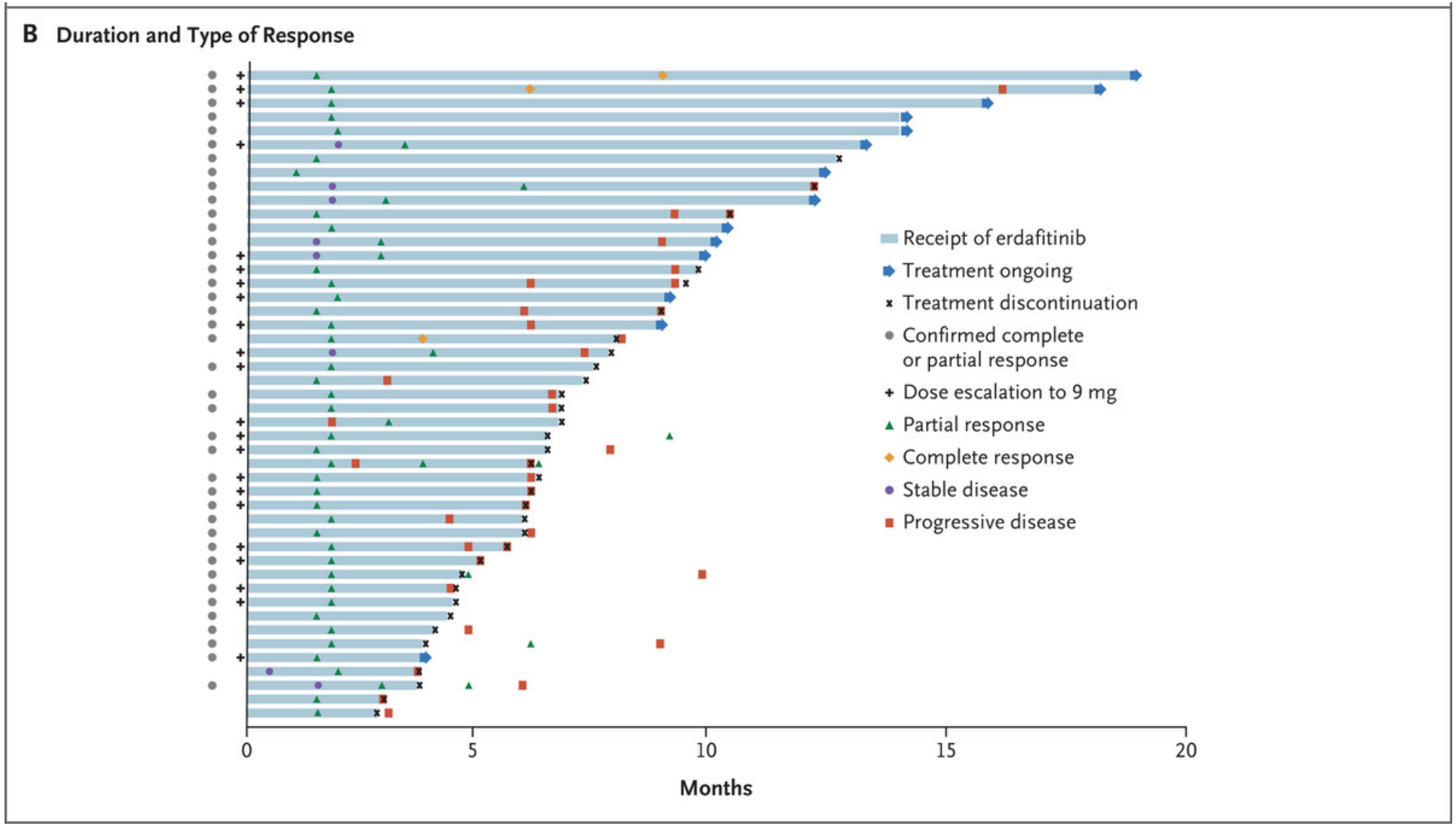
Courtesy of Jonathan E Rosenberg, MD

Phase II BLC2001 Trial

- Enrolled 99 patients with FGFR 1-3 alterations
- 88% had prior chemotherapy, 22% prior immunotherapy
- 12% had no prior systemic therapy
- Majority had visceral metastases
- Objective response rate 40% with 3% CR rate (per investigator)
  - Median TTR 1.4 months
  - Median DOR 5.6 months
- 5/12 patients without prior therapy responded (not FDA approved population)

- Y Loriot et al. N Engl J Med 2019;381:338-348. Courtesy of Jonathan E Rosenberg, MD

Some patients treated with erdafitinib have responses >1 year

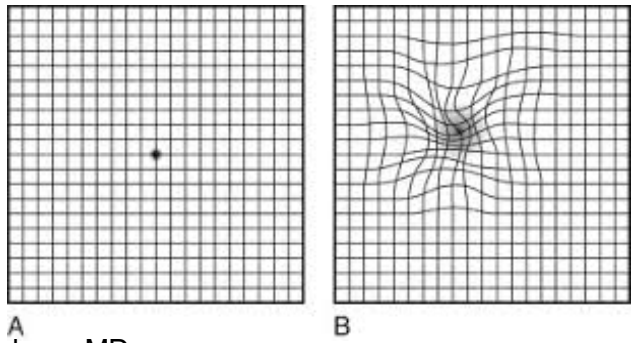


- Y Loriot et al. N Engl J Med 2019;381:338-348. Courtesy of Jonathan E Rosenberg, MD

Memorial Sloan Kettering Cancer Center

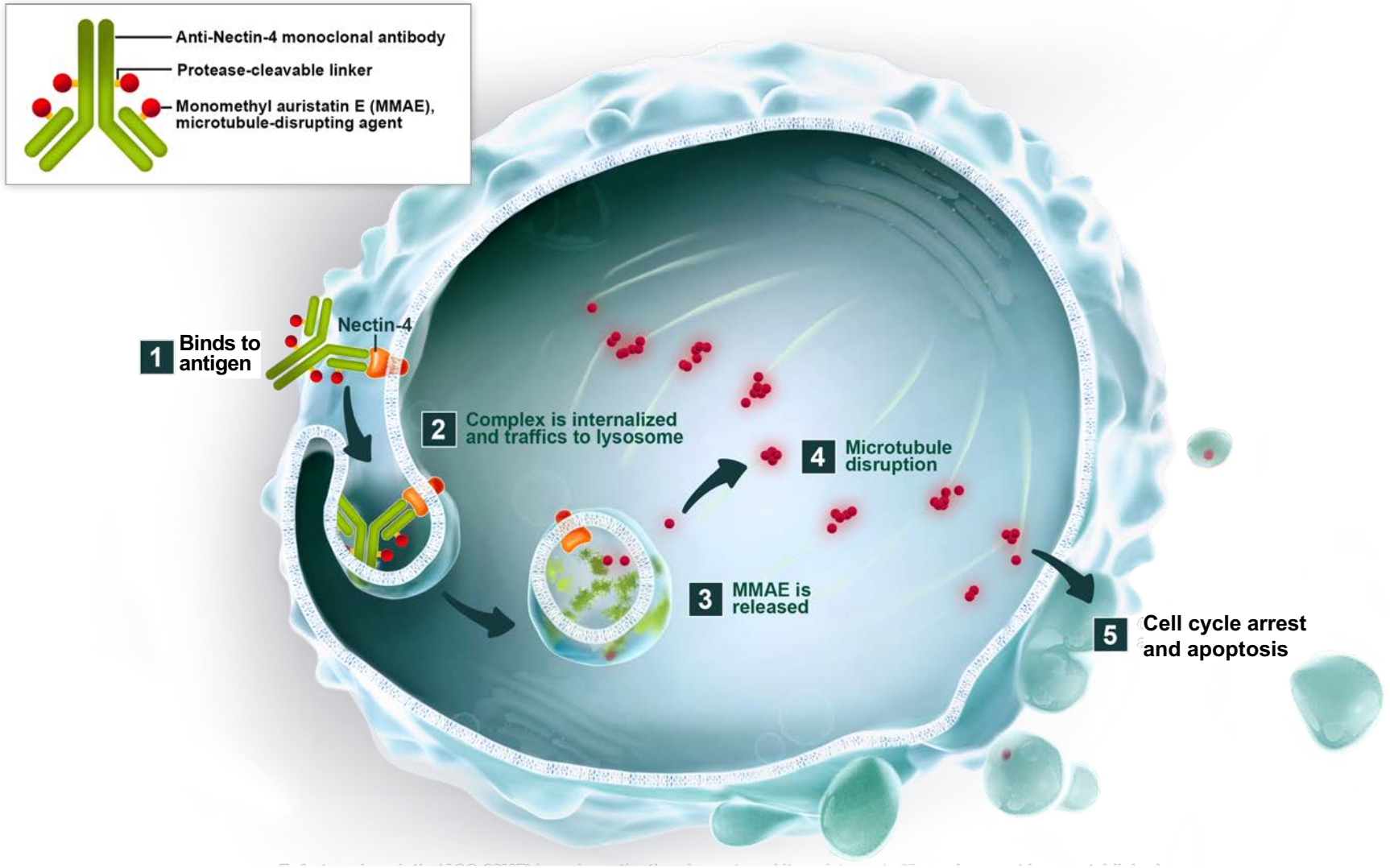
BLC2001: Toxicity of erdafitinib

- 55% of patients required dose reductions
- 41% of patients were able to escalate to 9 mg daily
- 59% required subsequent dose reductions
- 46% of patients had grade 3 or higher AE attributable to treatment
- Most common toxicities are hyperphosphatemia (on-target effect), stomatitis, and diarrhea
- Central serous retinopathy in 21% of patients, 3% grade 3
  - Generally reversible
  - Amsler grid testing



- Y Loriot et al. N Engl J Med 2019;381:338-348. Courtesy of Jonathan E Rosenberg, MD

Enfortumab Vedotin: Nectin-4 Targeted Therapy



Courtesy of Jonathan E Rosenberg, MD

Memorial Sloan Kettering Cancer Center

Phase II EV-201 Trial: Enfortumab Vedotin has high antitumor activity in refractory patients

- Single arm phase II study in mUC patients previously treated with platinum-based chemotherapy and immunotherapy
- ORR 44%
  - Similar to phase I data
- 12% complete responses
- Responses seen in patients with liver metastases
- Median TTR is 1.8 months
- Median DOR is 7.6 months

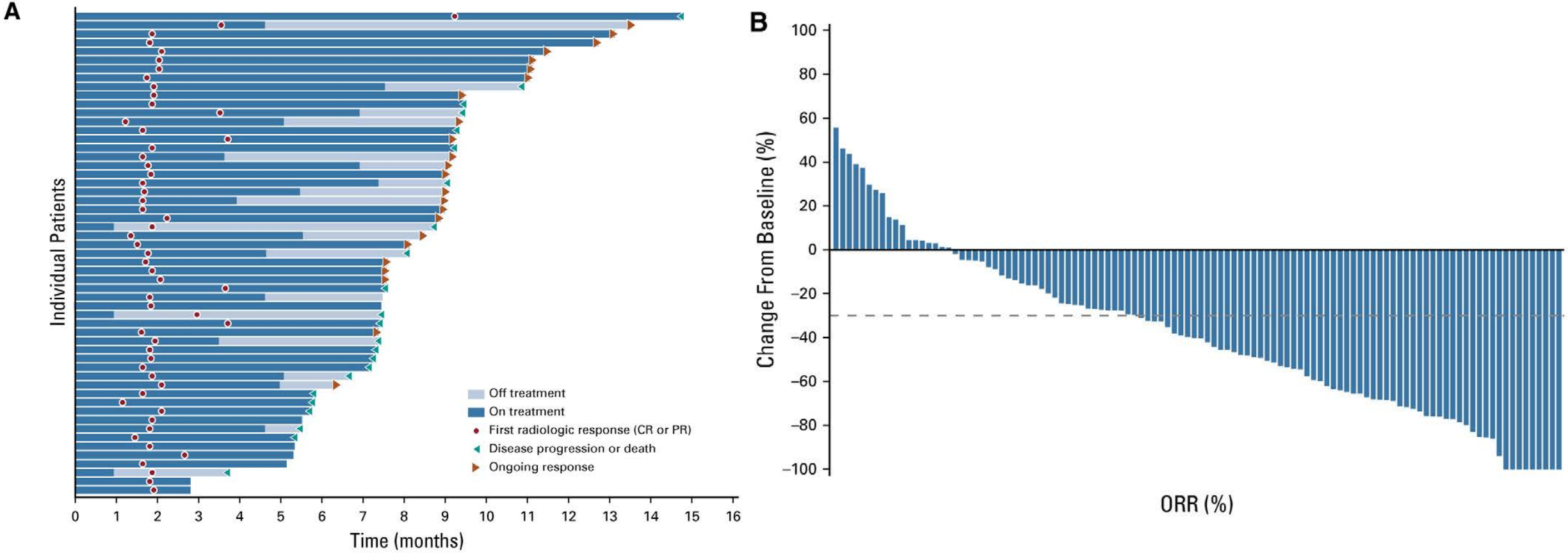
Response	Patients (N = 125)
Objective response rate	55 (44)
95% CI*	35.1 to 53.2
Best overall response†	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable‡	12 (10)

Courtesy of Jonathan E Rosenberg, MD

Rosenberg et al. J Clin Oncol. 2019; 29; 2592-2600

Memorial Sloan Kettering Cancer Center

EV-201: Majority of patients have tumor reduction, many responses ongoing



Courtesy of Jonathan E Rosenberg, MD

Rosenberg et al. J Clin Oncol. 2019; 29; 2592-2600

Memorial Sloan Kettering Cancer Center

EV-201: Common Enfortumab Vedotin toxicities include fatigue, rash, neuropathy

TABLE 3. Summary of Adverse Events in Patients Receiving Enfortumab Vedotin

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 Jonathan E Rosenberg, MD

Rosenberg et al. J Clin Oncol. 2019; 29; 2592-2600

Enfortumab vedotin in mUC

- FDA approved for platinum- and IO-previously treated patients
- Based on high ORR, front-line testing is being explored
- Preclinical and clinical data with MMAE (cytotoxic payload of EV) suggest it may lead to immunogenic cell death
- EV-103 is a multi-cohort Phase I/II trial testing EV combinations in mUC

Courtesy of Jonathan E Rosenberg, MD

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

Locally Advanced or Metastatic Urothelial Carcinoma

Dose Escalation[1]

enfortumab vedotin + pembrolizumab

cisplatin-ineligible

(n=5)

Dose Expansion Cohort A

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: adverse events (AEs), lab abnormalities

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

Rosenberg, et al. GU Cancers Symposium 2020

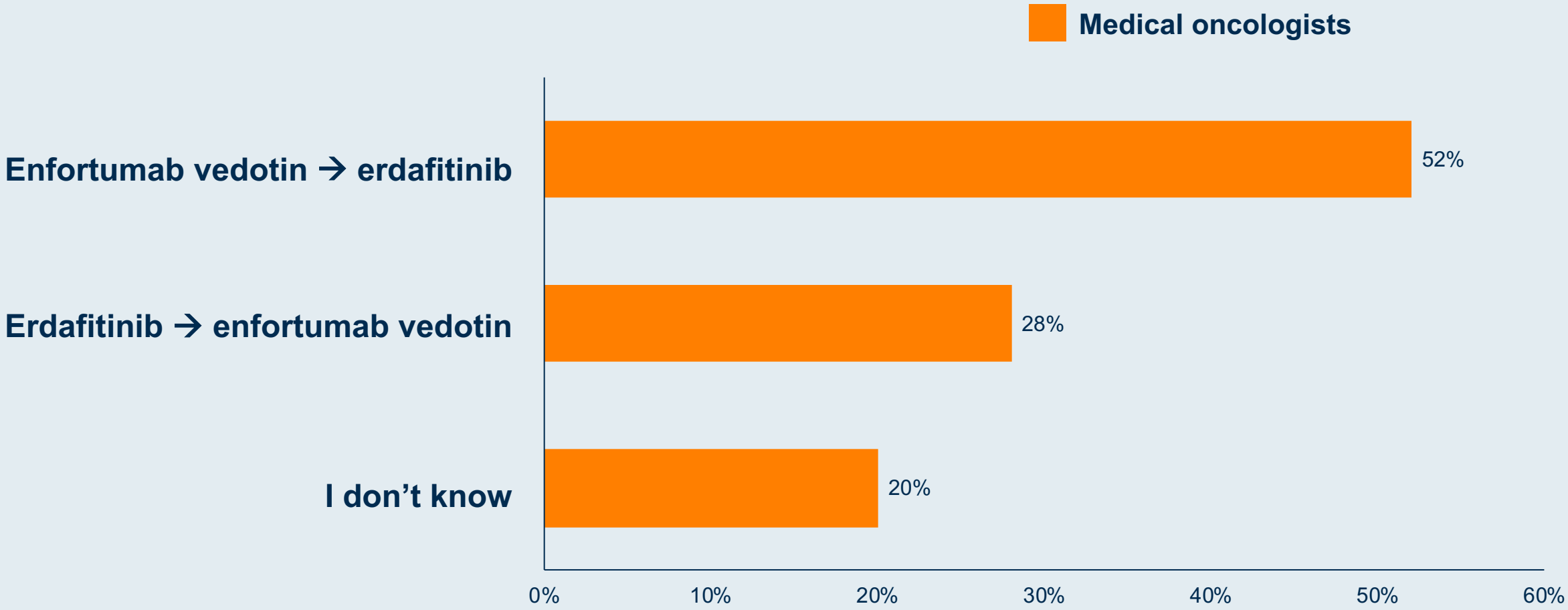
[1] Not included in the current analysis: Three 1L pts treated with EV 1 mg/kg + pembrolizumab 200 mg and two 2L pts treated with EV 1.25 mg/kg + pembrolizumab 200 mg

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

Courtesy of Jonathan E Rosenberg, MD

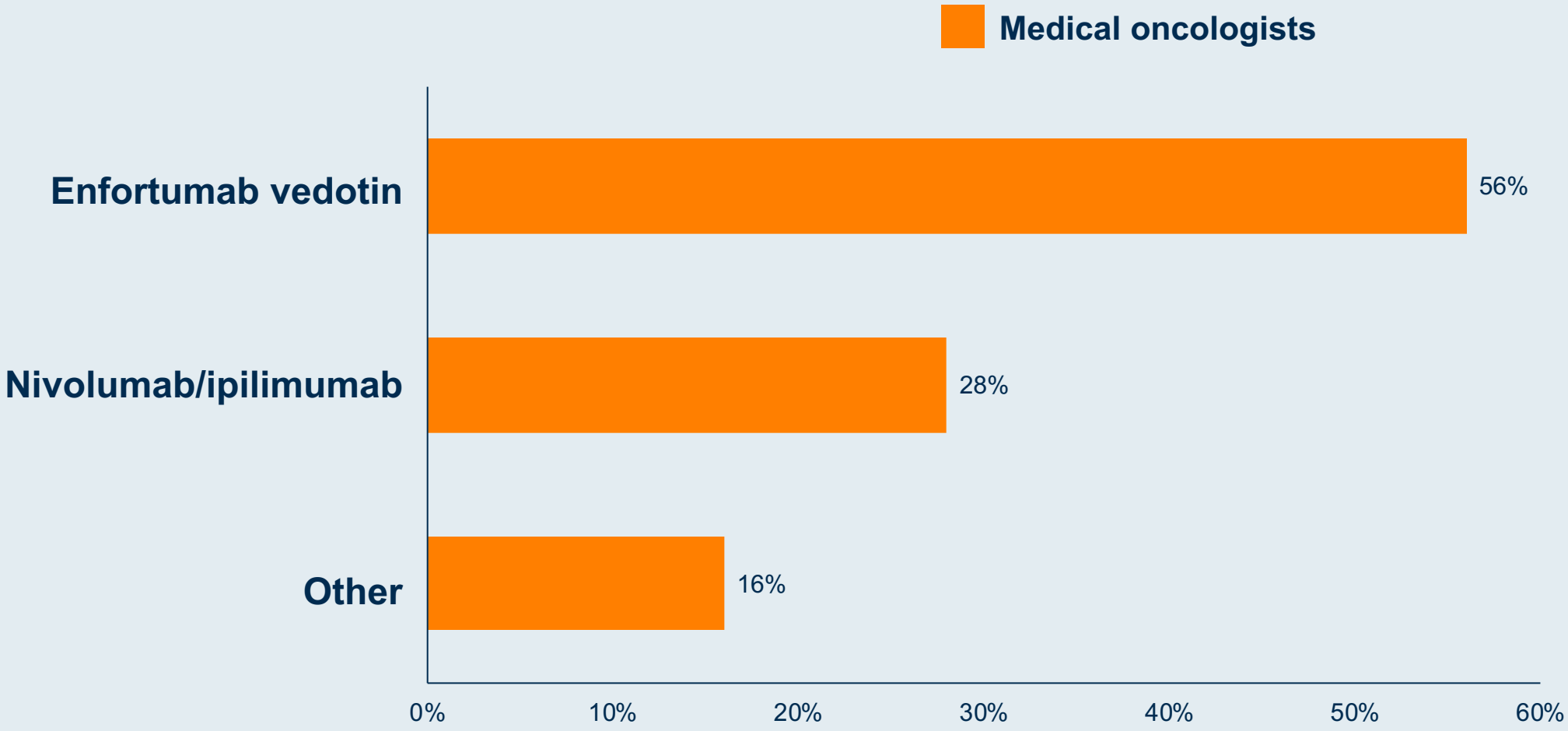
Memorial Sloan Kettering Cancer Center

How would you generally sequence enfortumab vedotin and erdafitinib for a patient with metastatic UBC who is eligible to receive both agents?



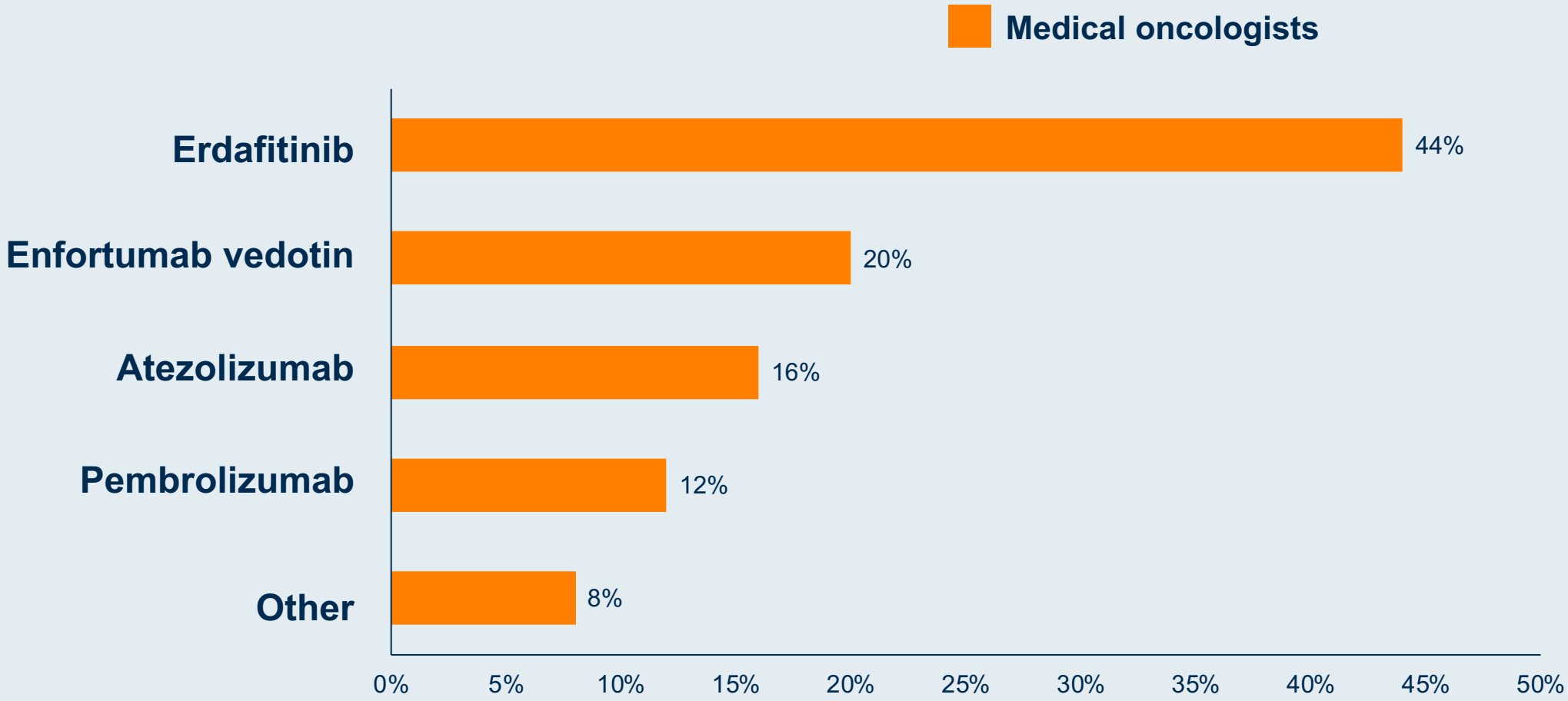
Survey of 25 US-based medical oncologists, July 2020.

What would you generally recommend for a patient with FGFR wild-type UBC metastatic to the liver who receives first-line cisplatin/gemcitabine followed by maintenance avelumab and experiences disease progression during the maintenance avelumab?



Survey of 25 US-based medical oncologists, July 2020.

What would you generally recommend as second-line therapy for a patient with UBC metastatic to the liver who receives first-line cisplatin/gemcitabine but experiences disease progression and is found to have an FGFR3 mutation?



Survey of 25 US-based medical oncologists, July 2020.

In a patient with progressive metastatic UBC with an FGFR genetic alteration, would you generally administer erdafitinib prior to enfortumab vedotin?

a. Yes
b. No, I would administer enfortumab vedotin first
c. I don’t know

Case Presentation – Dr Rosenberg: 74-Year-Old Man with mUBC

- 74 yo man with h/o muscle invasive bladder cancer s/p cystectomy in 2017
- Relapse 1 year later with lung nodules and received gem/carbo
- PD 2 months after completing 6 cycles of therapy (stable disease best response)
- Received pembrolizumab with best response as stable disease for 6 months then PD in pelvis
- Severe pelvic pain requiring high doses of opiates due to tumor invading pelvic sidewall
- **Enrolled on trial of enfortumab vedotin.**
- Pain relief by c1d15. Course complicated by grade 1 neuropathy and grade 2 rash including blistering rash on ankles. Managed with topical corticosteroids and silver sulfadiazine with improvement.
- **Treated for 9 months with partial response in measurable disease**
- POD in sacrum with severe pain. Radiotherapy administered for palliation. Pt resumed therapy with EV as other disease was stable. However, imaging 3 months later showed progression in liver. Pt's condition deteriorated significantly and he died 8 weeks later without receiving additional systemic therapy.

Case Presentation – Dr Rosenberg: 74-Year-Old Woman with mUBC

- 74 yo woman with renal insufficiency s/p RC with progression of disease 1 year later in lung and lymph nodes. NGS performed and showed FGFR3 mutation (S249C)
- Pt initially treated with gemcitabine and carboplatin with initial response to therapy. Phosphorus at 2 weeks was 4.6 and so dose was escalated to 9 mg daily.
- 4 weeks later, developed grade 3 stomatitis, and grade 3 fingernail changes. Stomatitis managed with dexamethasone rinses and fingernails treated with oral antibiotics for paronychia.
- Erdafitinib held for 2 weeks, and resumed at 6mg once stomatitis improved and paronychia resolved.
- Scans after 3 months with stable disease overall. Continues on erdafitinib 6 mg dosing with grade 1 stomatitis managed with dexamethasone rinses.

Key Questions and Emerging Research in the Management of Multiple Myeloma

Monday, July 13, 2020
5:00 PM – 6:00 PM ET

Faculty

Shaji K Kumar, MD
Noopur Raje, MD

Moderator

Neil Love, MD

RTP
RESEARCH TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 days.