Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Urothelial Bladder Carcinoma (Part 3 of a 3-Part Series)

Thursday, March 4, 2021
5:00 PM – 6:15 PM ET

Faculty

Arjun Balar, MD
Elisabeth I Heath, MD
Jonathan E Rosenberg, MD

Moderator

Neil Love, MD

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Faculty

Arjun Balar, MD
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Commercial Support

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seagen Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc and Verastem Inc.

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Dr Balar — Disclosures

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Contracted Research	AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Immunomedics Inc, Janssen Biotech Inc, Merck, Nektar, Pfizer Inc, Seagen Inc

Dr Heath — Disclosures

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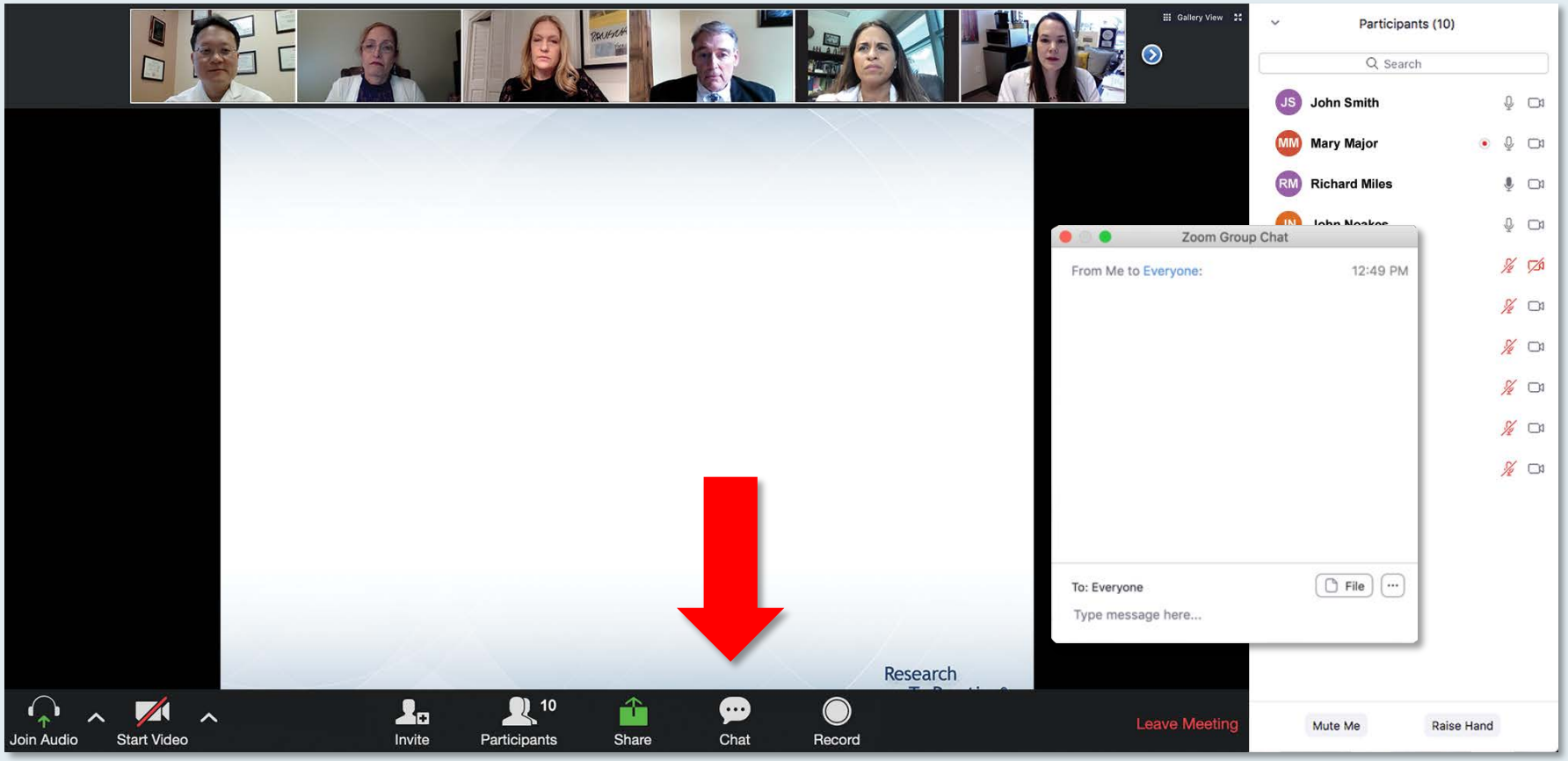
We Encourage Clinicians in Practice to Submit Questions



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Familiarizing Yourself with the Zoom Interface

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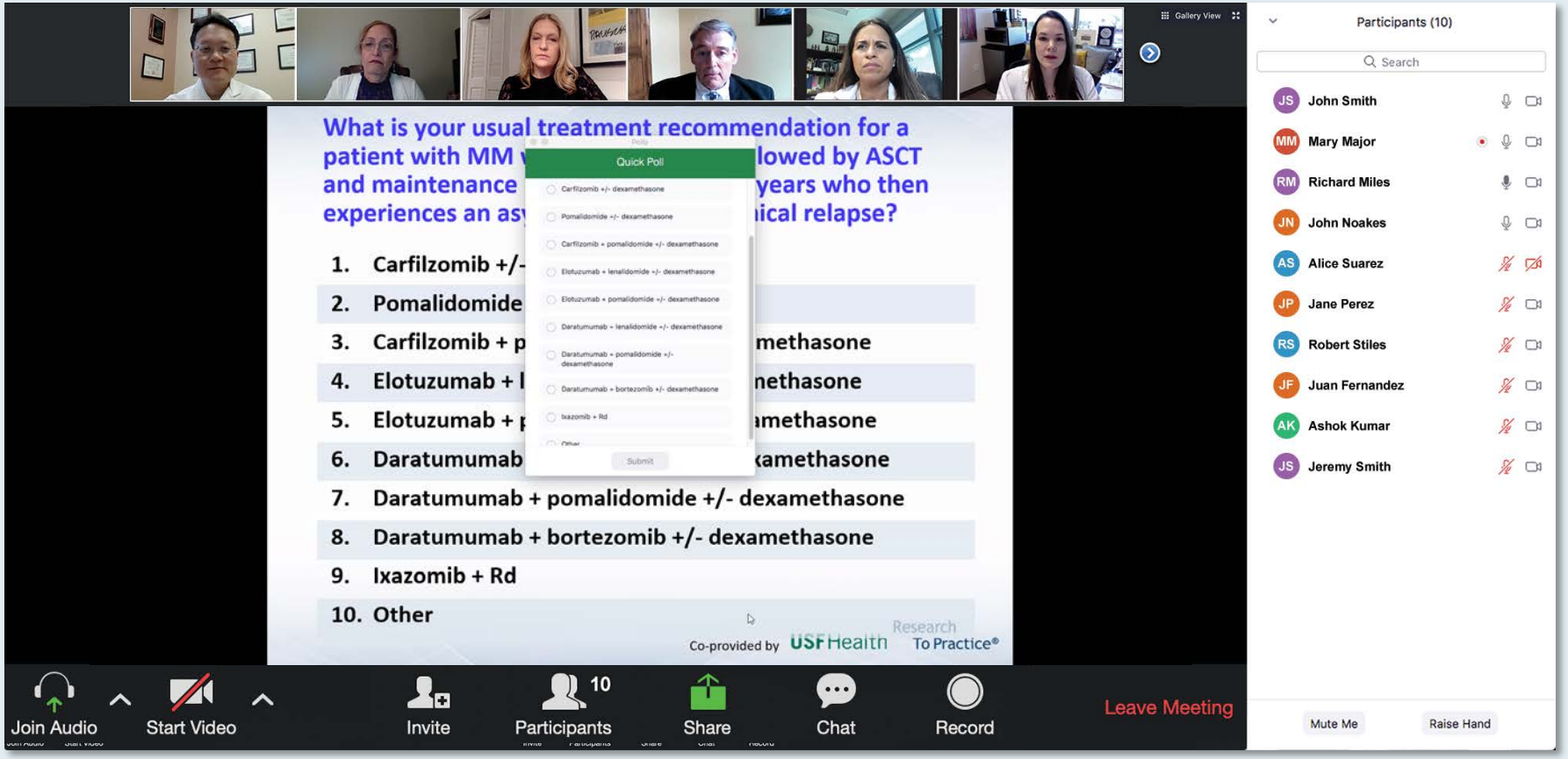

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WITH DR NEIL LOVE

Newly Approved Agents in the Management of Urothelial Bladder Carcinoma

DR MATTHEW GALSKY
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Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium®

Management of HER2-Positive Breast Cancer

Monday, March 8, 2021
5:00 PM – 6:00 PM ET

Faculty

Mark D Pegram, MD

Moderator

Neil Love, MD

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Data + Perspectives: Investigators Discuss the Effects of Emerging Research on the Care of Patients with Acute Myeloid Leukemia

Wednesday, March 10, 2021
7:00 PM – 8:00 PM ET

Faculty

Alexander Perl, MD
Eunice S Wang, MD

Moderator

Neil Love, MD

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Meet The Professor

Management of Chronic Lymphocytic Leukemia

Thursday, March 11, 2021
5:00 PM – 6:00 PM ET

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Steven Coutre, MD

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Neil Love, MD

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Dissecting the Decision: Clinical and Nursing Investigators Provide Practical Perspectives on Key Issues in Cancer Care

Part 1 — Acute Myeloid Leukemia

Tuesday, March 16, 2021
5:00 PM – 6:00 PM ET

Faculty

Rhonda Hewitt, MSN, ANP, AOCNP
Mark Levis, MD, PhD

Moderator

Neil Love, MD

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Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

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Part 2 — HER2-Positive Breast Cancer

Thursday, March 18, 2021
5:00 PM – 6:00 PM ET

Faculty

Jamie Carroll, APRN, MSN, CNP
Sara Hurvitz, MD

Moderator

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.

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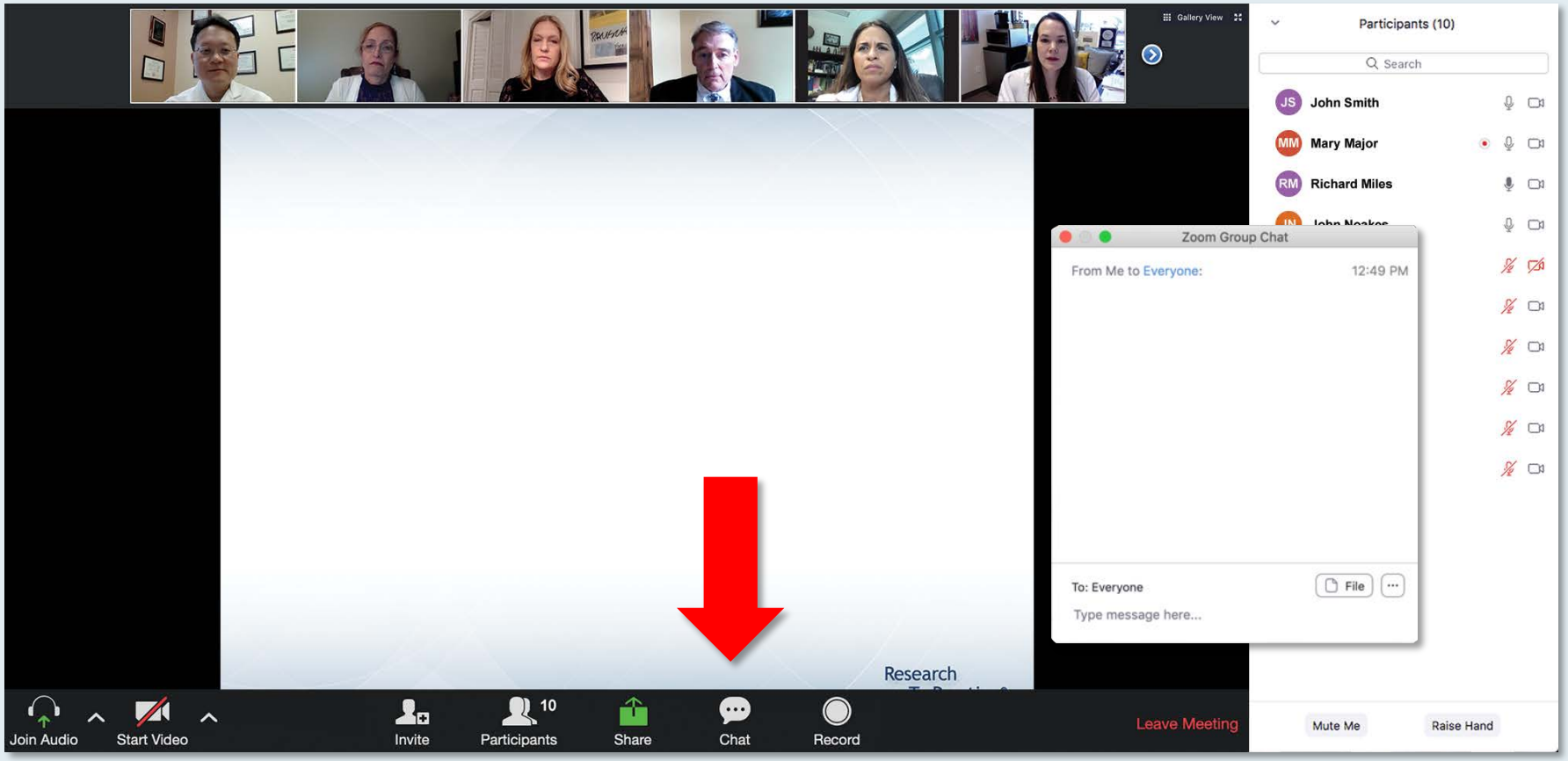

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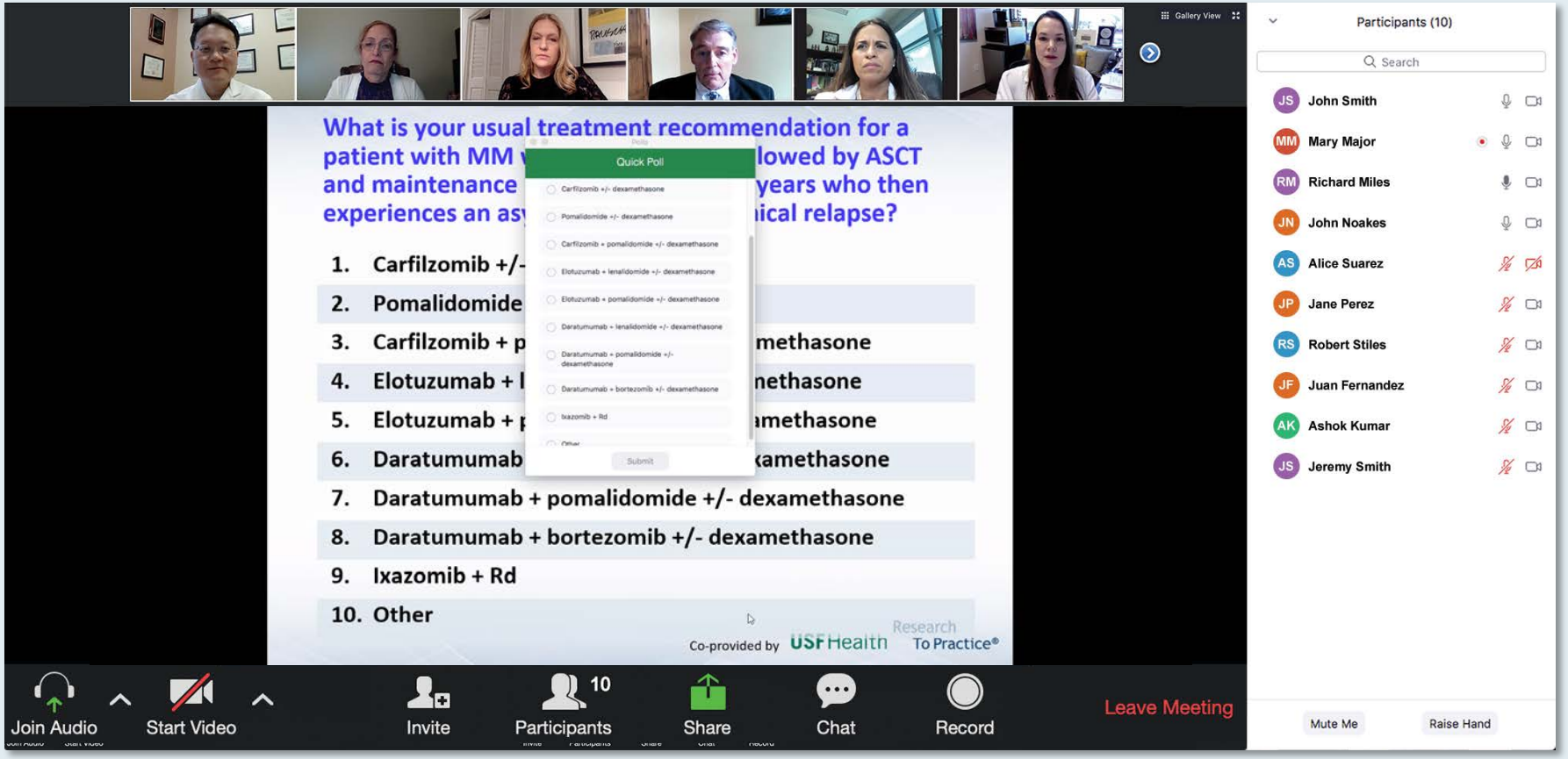

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Syed F Zafar, MD
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Agenda

Module 1 – Case Presentations

- Dr Ma: A 62-year-old woman with Stage IIIA bladder cancer
- Dr Lamar: A 68-year-old woman with cisplatin-ineligible muscle-invasive UBC
- Dr Favaro: A 54-year-old woman with high-grade papillary UBC

Data Review – Non-muscle-invasive bladder cancer; (neo)adjuvant treatment of MIBC

Module 2 – Case Presentations

- Dr Zafar: A 72-year-old man with high-grade UBC – TMB 103 mut/Mb
- Dr Yang: A 77-year-old man with metastatic transitional cell UBC
- Dr Rupard: A 58-year-old man with distal urothelial cell carcinoma of the penis

Data Review – Metastatic disease: Checkpoint inhibitors; enfortumab vedotin

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- Dr Favaro: A 72-year-old man with metastatic UBC – FGFR3 mutation
- Dr Mitchell: Comment – Management of checkpoint inhibitor toxicities

Data Review – Metastatic disease: Erdafitinib; novel agents and strategies

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Case Presentation – Dr Ma: A 62-year-old woman with Stage IIIA bladder cancer

Dr Yanjun Ma

- 9/2020: Presented with Stage IIIA (T3a, N0, M0) carcinoma of the bladder
  - Radical cystectomy; lymph node (8) dissection: negative
- 12/2020: Adjuvant chemotherapy delayed
  - Patient infected with moderate case of COVID-19
- 1/2021: Adjuvant cisplatin/gemcitabine initiated

Questions

- Are there any new developments in the adjuvant curative setting?
- Do the faculty prefer using carboplatin or cisplatin?
- What is their approach for a patient with a GFR of 25 or 30?
- What are their thoughts on moving immune therapy maintenance into the adjuvant setting?

Case Presentation – Dr Lamar: A 68-year-old woman with cisplatin-ineligible muscle-invasive UBC

Dr Zanetta Lamar

- Presented with locally advanced disease
  - Initial assessment: Likelihood of significant response to neoadjuvant chemotherapy low, likely to have positive margins
  - Opted for treatment with concurrent chemoradiation therapy

Questions

- Would the faculty agree or disagree with this approach?
- What is their standard approach for patients with cisplatin-ineligible disease?

Case Presentation – Dr Favaro: A 54-year-old woman with high-grade papillary UBC

Dr Justin Favaro

- Presented with extensive submucosal invasion, high-grade papillary urothelial carcinoma
- Underwent interior pelvic exenteration, vaginal sparing, radical cystectomy
  - Clear margins, 1 positive lymph node, muscle invasive
- Adjuvant dose-dense MVAC → disease relapse 6 months later
- Currently receiving paclitaxel and concurrent radiation therapy
- **Plan:** Order NGS, consider immunotherapy maintenance if high PD-L1 CPS score

Questions

- Despite optimal chemotherapy, many patients with muscle invasive bladder cancer experience disease recurrence: What clinical trials are you most excited about to improve the cure rates in the (neo)adjuvant setting?
- How long would the faculty continue immunotherapy maintenance in a case like this?
- What are their thoughts about administering COVID-19 vaccines concurrently with immunotherapy?

Case Presentation – Dr Balar: A 75-year-old man with high-risk non-muscle-invasive bladder cancer

- 75-year-old man, former 40 pack-year tobacco smoker
  - HTN
  - COPD
- HR NMIBC (CIS) diagnosed in 2015 -> Intravesical BCG induction x 2, maintenance x 2 courses (last 12/2016)
- Recurrent CIS in March 2017
- BCG Unresponsive CIS
- Enrolled to KEYNOTE-057

Case Presentation – Dr Balar: A 75-year-old man with high-risk non-muscle-invasive bladder cancer (continued)

- Pembrolizumab started 5/2017
  - 4 cycles without incident
  - Cystoscopy/cytology @ month 3: normal appearance, normal biopsy and cytology

- Pneumonitis in 4/2018 -> treated with prednisone
- Pembrolizumab stopped

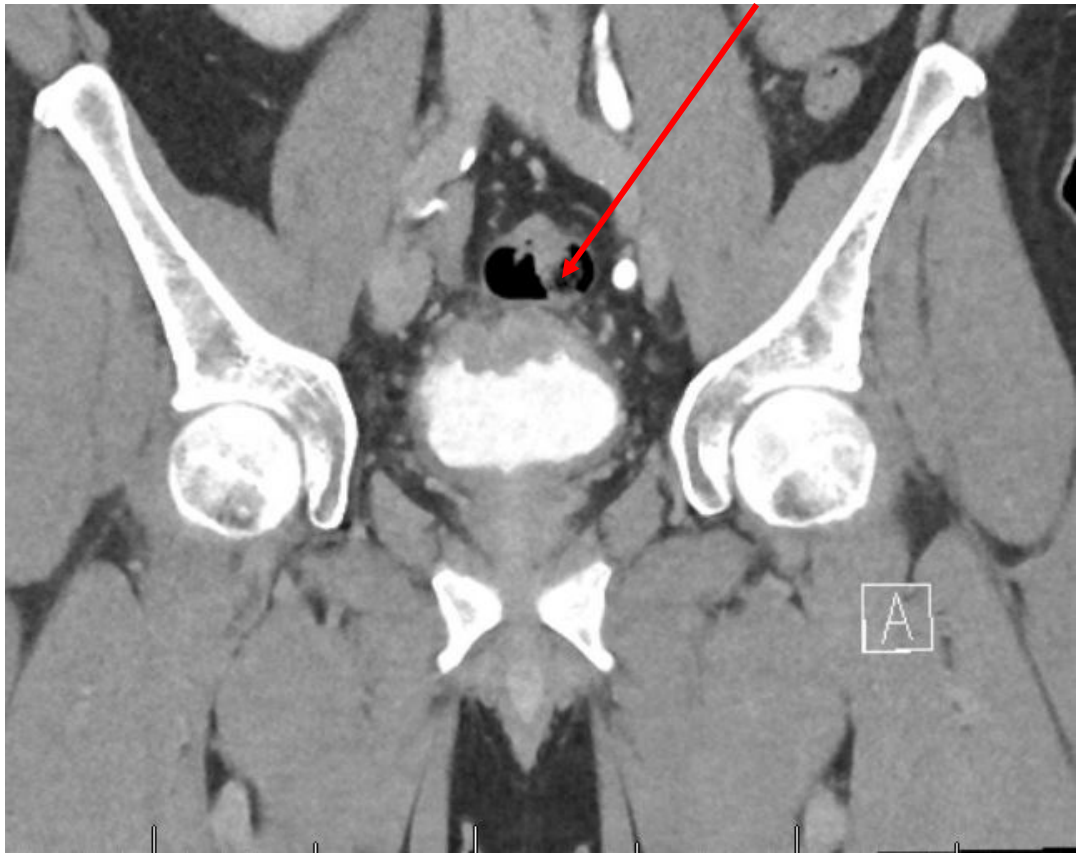
- Last cystoscopy/cytology 2/2021: normal

Case Presentation – Dr Balar: A 73-year-old man with muscle-invasive bladder cancer

- 73-year-old semi-retired photographer, previous heavy smoker
  - HTN
  - Urethral strictures
- Diagnosed with muscle-invasive bladder cancer 4/2019 at the bladder dome

Gemcitabine/Cisplatin x 3 cycles (5/2019 – 6/2019)

Radical Cystectomy 8/2019 (ypT2bN1 HG UC)



Case Presentation – Dr Balar: A 73-year-old man with muscle-invasive bladder cancer (continued)

- High-risk MIBC s/p neoadjuvant chemotherapy and radical cystectomy
  - Risk of relapse >60-70%

- Consented to AMBASSADOR
  - Randomized phase 3 trial of adjuvant pembrolizumab vs observation
  - Randomized to pembrolizumab
  - Tolerated treatment well, remains disease-free as of 12/2020

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

1. Yes
2. No

A 75-year-old patient presents with muscle-invasive UBC with no evidence of distant metastatic disease and a creatinine clearance of 40 mL/min. PD-L1 = 80%. Regulatory and reimbursement issues aside, would you offer this patient neoadjuvant treatment with an anti-PD-1/PD-L1 antibody?

1. Yes
2. No
3. I don’t know

A 65-year-old man receives neoadjuvant dose-dense MVAC for muscle-invasive UBC and undergoes cystectomy, which reveals significant residual disease and a positive pelvic lymph node. PD-L1 = 80%. What adjuvant systemic therapy, if any, would you recommend?

1. None
2. Cisplatin-based chemotherapy
3. Carboplatin-based chemotherapy
4. Anti-PD-1/PD-L1 antibody
5. Other

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FDA Approves Pembrolizumab for BCG-Unresponsive, High-Risk Non-Muscle-Invasive Bladder Cancer

Press Release – January 8, 2020

"The Food and Drug Administration approved pembrolizumab for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Efficacy was investigated in KEYNOTE-057 (NCT02625961), a multicenter, single-arm trial that enrolled 148 patients with high-risk NMIBC, 96 of whom had BCG-unresponsive CIS with or without papillary tumors. Patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression."

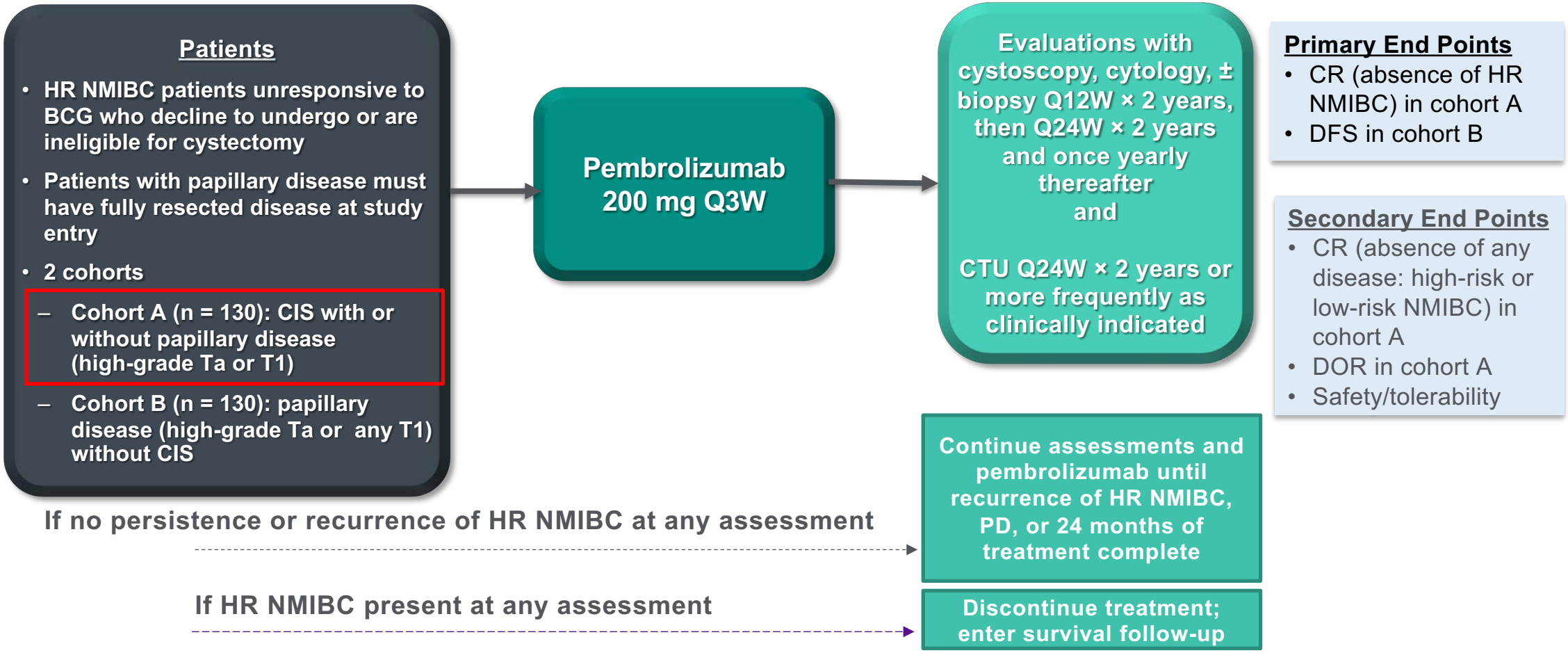
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-bcg-unresponsive-high-risk-non-muscle-invasive-bladder-cancer

Pembrolizumab for the Treatment of Patients with High-Risk (HR) Non-Muscle-Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guérin: Extended Follow-Up of KEYNOTE-057 Cohort A

Balar AV et al.

Genitourinary Cancers Symposium 2021;Abstract 451.

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



Courtesy of Arjun Balar, MD

KEYNOTE-057 Cohort A: Overall Response Rate by Central Review at 3 Months

N = 96	n	%	95% CI
CR	39	40.6	30.7-51.1
Non-CR	56	58.3	47.8-68.3
Persistent[a]	40	41.7	31.7-52.2
Recurrent[b]	6	6.3	2.3-13.1
NMIBC stage progression[c]	9	9.4	4.4-17.1
Non–bladder malignancy[d]	1	1.0	0.0-5.7
Progression to T2	0	0	NA-NA
Nonevaluable[e]	1	1.0	0.0-5.7

Balar AV et al. Genitourinary Cancers Symposium 2021;Abstract 451.

KEYNOTE-057 Cohort A: Immune-Related Adverse Events

Immune-Mediated AE, n (%)	Cohort A N = 101		
	Any Grade	Grade 1 or 2	Grade 3 or 4
Any	22 (21.8)	19 (18.8)	3 (3.0)
Hypothyroidism	8 (7.9)	8 (7.9)	0
Hyperthyroidism	5 (5.0)	5 (5.0)	0
Pneumonitis	3 (2.0)	3 (3.0)	0
Colitis	2 (2.0)	2 (2.0)	0
Adrenal insufficiency	1 (1.0)	0	1 (1.0)
Autoimmune hepatitis	1 (1.0)	1 (1.0)	0
Autoimmune nephritis	1 (1.0)	1 (1.0)	0
Hypophysitis	1 (1.0)	1 (1.0)	0
Pruritus	1 (1.0)	0	1 (1.0)
Type 1 diabetes mellitus	1 (1.0)	0	1 (1.0)
Uveitis	1 (1.0)	1 (1.0)	0

Balar AV et al. Genitourinary Cancers Symposium 2021;Abstract 451.

Phase 3 Trials of PD-1/PD-L1 Inhibitors in NMIBC

Primary endpoint: CR

KEYNOTE-676 (NCT03711032)[1]; N = ≈550

- High-risk NMIBC persistent or recurrent after BCG induction and following cytoscopy/ transurethral resection
- ECOG PS ≤2

R → Pembrolizumab + BCG

R → BCG

Primary endpoint: DFS

POTOMAC (NCT03528694)[2]; N = ≈975

- High-risk NMIBC previously resected and naïve to BCG and cancer immunotherapy

R → Durvalumab + BCG (induction and maintenance)

R → Durvalumab + BCG (induction only)

R → BCG

Primary endpoint: RFS

ALBAN (NCT03799835)[3]; N = 614

- High-risk NMIBC previously resected and naïve to BCG
- Tumor tissue available for PD-L1 assay

R → BCG × 1 y

R → BCG + atezolizumab every 3 wk × 1 y

1. https://clinicaltrials.gov/ct2/show/NCT03711032. Accessed February 7, 2020. 2. https://clinicaltrials.gov/ct2/show/NCT03528694. Accessed February 7, 2020.
3. https://clinicaltrials.gov/ct2/show/NCT03799835. Accessed February 7, 2020.

Courtesy of Arjun Balar, MD

Nivolumab Significantly Improves DFS as Adjuvant Therapy for High-Risk Muscle-Invasive Urothelial Carcinoma in the Phase III CheckMate 274 Trial

Press Release – September 24, 2020

In an interim analysis, CheckMate 274, a pivotal Phase III trial evaluating nivolumab after surgery in patients with high-risk, muscle-invasive urothelial carcinoma, has met its primary endpoints of improving disease-free survival (DFS) versus placebo both in all randomized patients and in patients whose tumor cells express PD-L1 ≥1%.

CheckMate 274 is the first and only Phase III trial in which immunotherapy has reduced the risk of relapse in the adjuvant setting for these patients. The safety profile of nivolumab was consistent with previously reported studies in solid tumors.

The company plans to complete a full evaluation of the CheckMate 274 data, work with investigators to present the results at an upcoming medical conference and submit the data to health authorities. The CheckMate 274 trial will continue as planned to allow for future analyses of secondary endpoints, including overall survival and disease-specific survival.

https://news.bms.com/news/corporate-financial/2020/Opdivo-nivolumab-Significantly-Improves-Disease-Free-Survival-vs.-Placebo-as-Adjuvant-Therapy-for-Patients-with-High-Risk-Muscle-Invasive-Urothelial-Carcinoma-in-Phase-3-CheckMate--274-Trial/default.aspx

First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab versus placebo in patients who underwent radical surgery for high-risk muscle-invasive urothelial carcinoma

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Abstract Number 391

CheckMate 274: Study Design

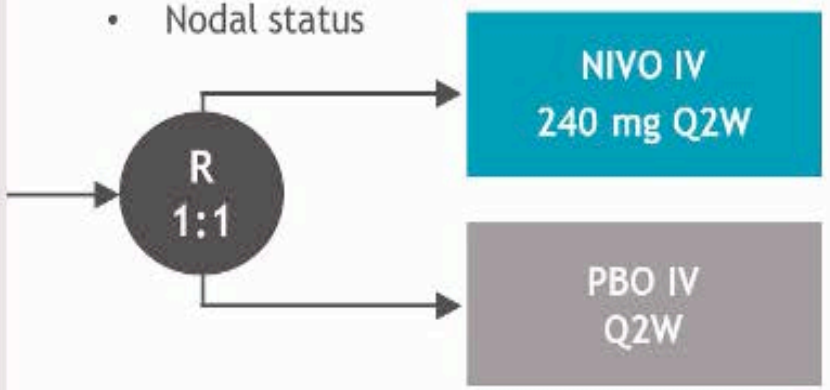
N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors:

- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status



Treat for up to 1 year of adjuvant therapy

Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

Bajorin DF et al. Genitourinary Cancers Symposium 2021;Abstract 391.

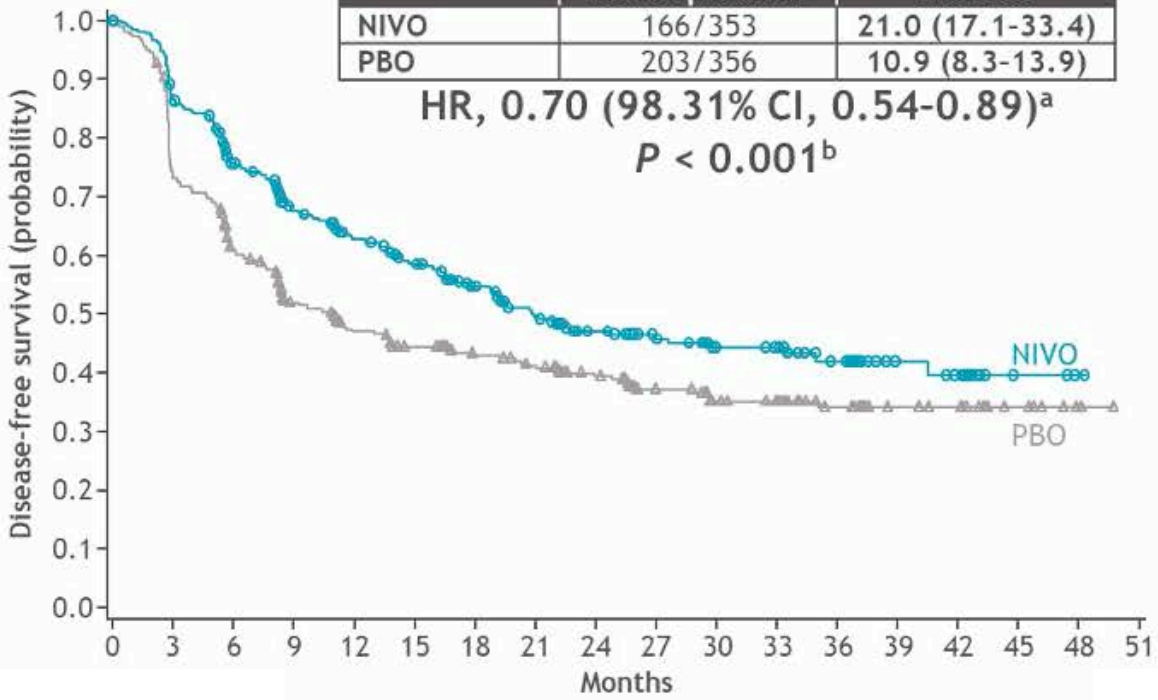
CheckMate 274: Disease-Free Survival (Primary Endpoint)

ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	166/353	21.0 (17.1-33.4)
PBO	203/356	10.9 (8.3-13.9)

HR, 0.70 (98.31% CI, 0.54-0.89)[a]

P < 0.001[b]

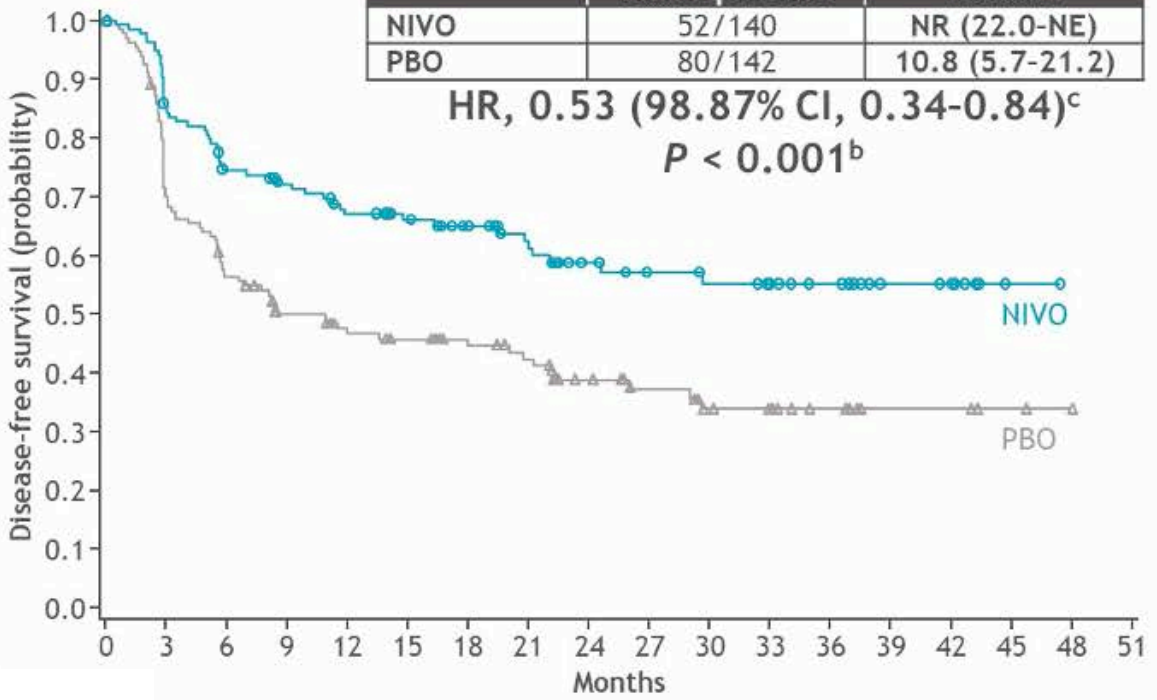


PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	52/140	NR (22.0-NE)
PBO	80/142	10.8 (5.7-21.2)

HR, 0.53 (98.87% CI, 0.34-0.84)[c]

P < 0.001[b]



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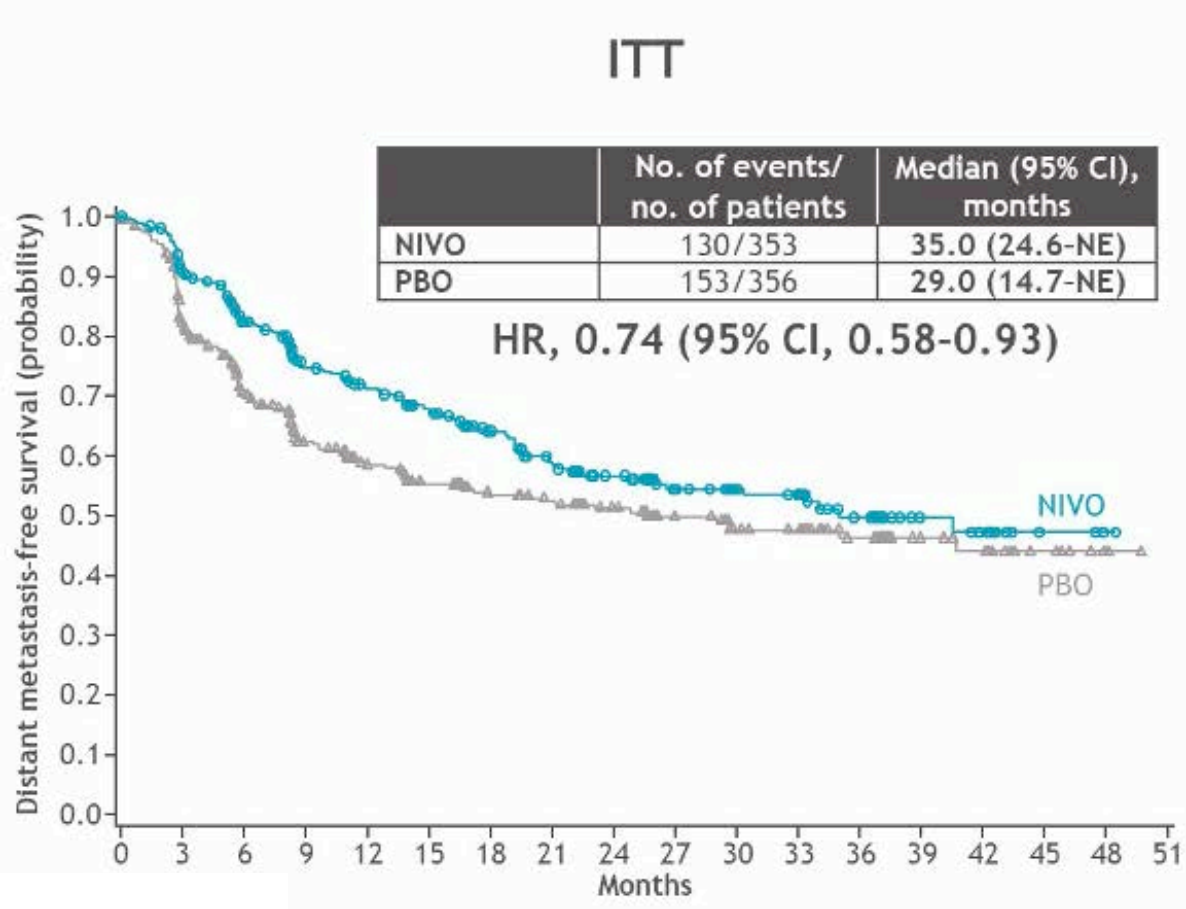
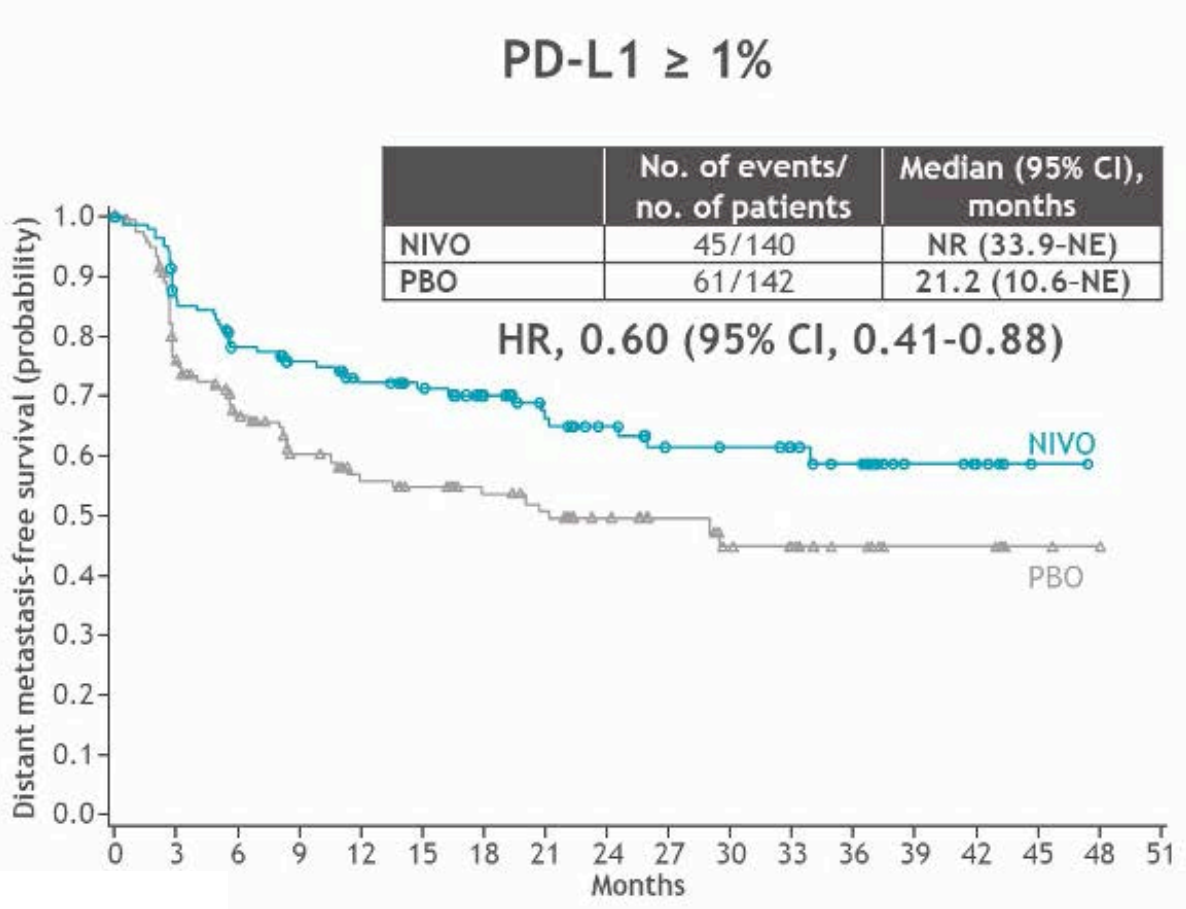
CheckMate 274: Distant Metastasis-Free Survival





Bajorin DF et al. Genitourinary Cancers Symposium 2021;Abstract 391.

RTP RESEARCH TO PRACTICE

Neoadjuvant checkpoint inhibition in patients with MIBC

- **October 2020 update**

	PURE-01	ABACUS	NABUCCO	HOG GU14-188		BLASST	DUTRENEO	MDACC
Treatment	**Pembrolizumab** (PURE-01)	**Atezolizumab** (ABACUS)	**Ipilimumab > Ipi/Nivolumab > Nivo** (NABUCCO)	**Pembrolizumab-GEM/CIS** (HOG GU14-188)	**Pembrolizumab-GEM** (HOG GU14-188)	**Nivolumab-GC** (BLASST)	**Durva/Treme** (DUTRENEO)	Durva/Treme (MDACC)
Reference	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[9]
Sample size	114	88	24	43	37	41	23	28
cT2-stage	54% (CT+mpMRI)	73%	0	47%	43.2	90%	78.2%	43%
cN+ stage	0 (but 6% PET+)	0	42%	0	0	3%	8.7%	0
pT0N0 rate	**37%**	**31%**	**46%**	**44.4%**	**45.2%**	**34%**	**34.8%**	**37.5%**
pT≤1N0 rate	55%		58%	61.1%	51.6%	66%	56.5%	58%
1-y RFS	91% (85-98) [EFS: 87%] [8]	79% (95%CI: 67-87)	92%	2-y: 66%	67%	n.a.	n.a.	82.8%
Biomarkers	PD-L1+ (TMB) Immune-gene signatures	Pre-existing T-cell activation+ (CD8/GZMB, tGE8-high)	PD-L1+; DDR-GA; TLS signature	none	none	Immune-gene signatures	Pre-selected with 18-gene IFN-γ signature	TLS signature

References:
1. Necchi A, et al. *Eur Urol*. 2020;77:439-446; 2. Powles, T, et al. *Nat Med*. 2019;25:1706-1714; 3. van Dijk N, et al. *Nat Med*. 2020. (Epub ahead of print); 4. Holmes CJ, et al. ASCO 2020; 5. Kaimakliotis HZ, et al. ASCO 2020; 6. Gupta S, et al. GU-ASCO 2020; 7. Grande E, et al. ASCO 2020; 8. Bandini M, et al. *Ann Oncol*. 2020 (Epub ahead of print); 9. Gao J, et al. *Nat Med*. 2020. (Epub ahead of print)

Andrea Necchi ESMO 2020

Courtesy of Arjun Balar, MD

Several Neoadjuvant Immunotherapy Trials Are Ongoing

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

1. https://clinicaltrials.gov/ct2/show/NCT03732677. 2. https://clinicaltrials.gov/ct2/show/NCT03661320. 3. https://clinicaltrials.gov/ct2/show/NCT03924895.
4. https://clinicaltrials.gov/ct2/show/NCT03924856. 5. https://clinicaltrials.gov/ct2/show/NCT04209114.

Courtesy of Arjun Balar, MD

Agenda

Module 1 – Case Presentations

- Dr Ma: A 62-year-old woman with Stage IIIA bladder cancer
- Dr Lamar: A 68-year-old woman with cisplatin-ineligible muscle-invasive UBC
- Dr Favaro: A 54-year-old woman with high-grade papillary UBC

Data Review – Non-muscle-invasive bladder cancer; (neo)adjuvant treatment of MIBC

Module 2 – Case Presentations

- Dr Zafar: A 72-year-old man with high-grade UBC – TMB 103 mut/Mb
- Dr Yang: A 77-year-old man with metastatic transitional cell UBC
- Dr Rupard: A 58-year-old man with distal urothelial cell carcinoma of the penis

Data Review – Metastatic disease: Checkpoint inhibitors; enfortumab vedotin

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- Dr Favaro: A 72-year-old man with metastatic UBC – FGFR3 mutation
- Dr Mitchell: Comment – Management of checkpoint inhibitor toxicities

Data Review – Metastatic disease: Erdafitinib; novel agents and strategies

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Case Presentation – Dr Zafar: A 72-year-old man with high-grade UBC – TMB 103 mut/Mb

Dr Syed Zafar

- History of renal transcript
- 1/2020: Patient noted increased urinary frequency
  - Did not immediately seek medical attention due to COVID-19 pandemic
- 6/2020: Cysto-uretoroscopy: Left-side bladder inflammation, left posterior mass
- 7/2020: Cystoscopy with TURBT: Pathology consistent with high-grade urothelial carcinoma
- NGS: TMB = 103 mut/Mb | MSI stable | PD-L1 CPS = 5
- Currently undergoing treatment with carboplatin/gemcitabine

Questions

- How would the faculty approach the next line or lines of therapy if this patient experiences disease progression?

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Case Presentation – Dr Zafar: A 72-year-old man with high-grade UBC – TMB 103 mut/Mb

Dr Syed Zafar

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
TMB	Seq	DNA-Tumor	High, 103 mut/Mb	BENEFIT	pembrolizumab	Level 1

* Biomarker reporting classification: Level 1 - highest level of clinical evidence and/or biomarker association included on the drug label; Level 2 - strong evidence of clinical significance and is endorsed by standard clinical guidelines; Level 3 - potential clinical significance (3A - evidence exists in patient's tumor type, 3B - evidence exists in another tumor type).

Important Note

This PD-L1 CPS is not sufficient for use of pembrolizumab in the front-line locally advanced or metastatic setting for patients still eligible to receive any platinum-based therapy. Front-line use of pembrolizumab is FDA approved for the treatment of locally advanced or metastatic bladder cancer for patients with a PD-L1 CPS≥10 who are not eligible for cisplatin-containing chemotherapy, or for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. CPS is calculated as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total viable tumor cells, multiplied by 100.

TMB-High status should only be used to guide pembrolizumab treatment when no satisfactory alternative treatment options are available.

Cancer Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
MSI	Seq	DNA-Tumor	Stable
Mismatch Repair Status	IHC	Protein	Proficient
NTRK1/2/3	Seq	RNA-Tumor	Fusion Not Detected
ATM	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 9 | p.E390***

Biomarker	Method	Analyte	Result
FGFR2	Seq	RNA-Tumor	Fusion Not Detected
		DNA-Tumor	Mutation Not Detected
FGFR3	Seq	RNA-Tumor	Fusion Not Detected
PD-L1 (22c3)	IHC	Protein	Negative, CPS: 5
PD-L1 (SP142)	IHC	Protein	Negative, IC: 1%

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Case Presentation – Dr Yang: A 77-year-old man with metastatic transitional cell UBC

Dr John Yang

- Presented with metastatic urothelial cancer, transitional cell carcinoma
  - Disease in bladder, R kidney, para-aortic and mediastinal lymph nodes
- Initially treated with carboplatin/gemcitabine x 3
  - Complicated by fatigue, neutropenia, and thrombocytopenia
- 8/28/2020: CT revealed improvement in disease burden
  - However, patient had difficulty tolerating single agent gemcitabine
  - Chemotherapy stopped
- Treated with avelumab
  - Developed allergic reaction to treatment and agent held
- Subsequently treated with pembrolizumab → disease progression

Question

- How would the faculty approach the next line of therapy for this patient?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Rosenberg: A 59-year-old woman with metastatic bladder cancer and an FGFR3 mutation

59 yo woman initially presented with T1 bladder cancer s/p BCG, then developed metastatic disease 1 year later to lymph nodes.

She was treated with gemcitabine and cisplatin with a partial response.

She was observed after 6 cycles of treatment but developed progressive disease 8 months later.

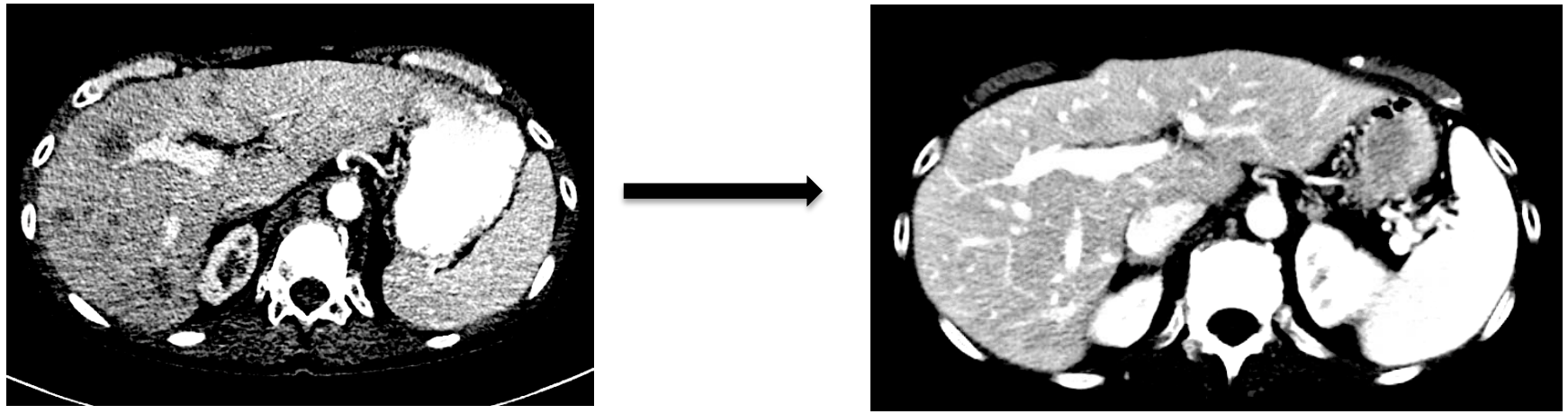
Mutation profiling showed an FGFR3 mutation and she was referred for a trial of a checkpoint inhibitor and an FGFR inhibitor. She developed rapidly progressive disease after 2 months of therapy.

She developed back and RUQ pain and was found to have large liver metastases and multiple new sclerotic lumbar spine lesions as well as enlarged lymph nodes.

Case Presentation – Dr Rosenberg: A 59-year-old woman with metastatic bladder cancer and an FGFR3 mutation (continued)

Pt was treated with enfortumab vedotin. After 1 cycle, pain disappeared and she was no longer requiring opiates.

Imaging after 2 months showed dramatic regression of liver metastases and sclerosis of bone metastases consistent with treatment response.



Pt continued on therapy for 2 years. Treatment was complicated by grade 2 neuropathy managed with dose holding and dose reduction, along with physical and occupational therapy, with reduction to grade 1.

She experienced disease progression after 2 years.

Case Presentation – Dr Rupard: A 58-year-old man with distal urothelial cell carcinoma of the penis – Part 1

Dr Erik Rupard

- History of urinary retention for approximately 1 year
  - Lesion developed near the meatus of his penis
- Biopsy: Urothelial cell carcinoma of the penis
  - Metastases in inguinal and iliac lymph nodes
- Incredible but short-lived response to cisplatin/gemcitabine
- Response to single-agent nivolumab, also short-lived
- Again experienced disease progression following radiation therapy
  - Patient considering hospice

Case Presentation – Dr Rupard: A 58-year-old man with distal urothelial cell carcinoma of the penis – Part 2

Dr Erik Rupard

- History of urinary retention for approximately 1 year
  - Lesion developed near the meatus of his penis
- Biopsy: Urothelial cell carcinoma of the penis
  - Metastases in inguinal and iliac lymph nodes
- Incredible but short-lived response to cisplatin/gemcitabine
- Response to single-agent nivolumab, also short-lived
- Again experienced disease progression following radiation therapy
  - Patient considering hospice

Questions

- How often do the faculty see penile cancers?
- What are their thoughts on treating cancers for which the patients feel a great deal of shame?

What would be your preferred first-line treatment regimen for a 65-year-old patient with metastatic UBC?

1. Cisplatin/gemcitabine
2. Carboplatin/gemcitabine
3. PD-1/PD-L1 monotherapy
4. Test PD-L1 level and administer anti-PD-1/PD-L1 monotherapy if PD-L1 positive
5. Cisplatin/gemcitabine → maintenance avelumab
6. Carboplatin/gemcitabine → maintenance avelumab
7. Platinum-based chemotherapy → other anti-PD-1 maintenance
8. Other

What would you generally recommend for a patient who experiences disease recurrence in the liver 9 months after cystectomy and adjuvant chemotherapy for muscle-invasive UBC (FGFR wild type)?

1. Other chemotherapy
2. Anti-PD-1/PD-L1 antibody
3. Nivolumab/ipilimumab
4. Enfortumab vedotin
5. Other

What would you generally recommend as second-line therapy for an 80-year-old patient with FGFR wild-type UBC metastatic to the liver whose disease progresses on first-line pembrolizumab?

1. Chemotherapy
2. Nivolumab/ipilimumab
3. Enfortumab vedotin
4. Other

Regulatory and reimbursement issues aside, would you administer pembrolizumab in combination with enfortumab vedotin to a patient with metastatic UBC outside of a protocol setting?

1. No
2. Yes, in the first line
3. Yes, in the second line or beyond
4. I am not familiar with this regimen

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FDA Approves Avelumab for Urothelial Carcinoma Maintenance Treatment

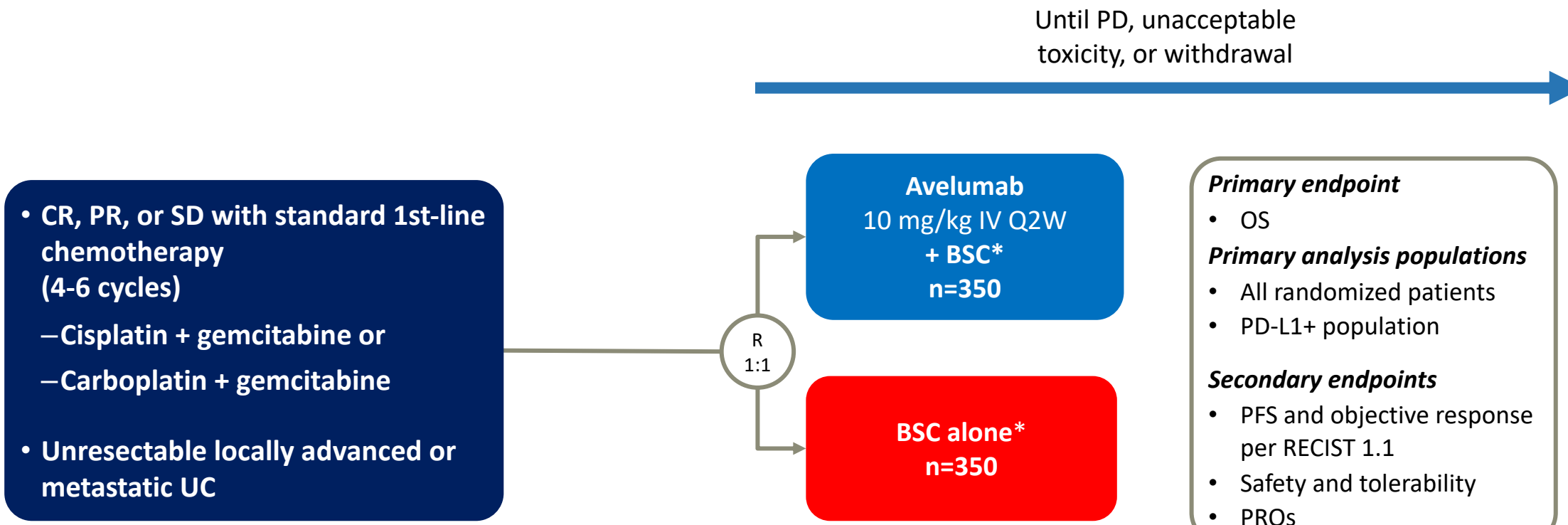
Press Release – June 30, 2020

"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.

Efficacy of avelumab for maintenance treatment of UC was investigated in the JAVELIN Bladder 100 trial (NCT02603432), a randomized, multi-center, open-label trial that enrolled 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma that had not progressed with four to six cycles of first-line platinum-containing chemotherapy. Patients were randomized (1:1) to receive either avelumab intravenously every 2 weeks plus best supportive care (BSC) or BSC alone. Treatment was initiated within 4-10 weeks after last chemotherapy dose."

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

JAVELIN Bladder 100 study design (NCT02603432)



Stratification

- Best response to 1st-line chemo (CR or PR vs SD)
- Metastatic site (visceral vs non-visceral)

PD-L1+ status using SP263 assay, 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

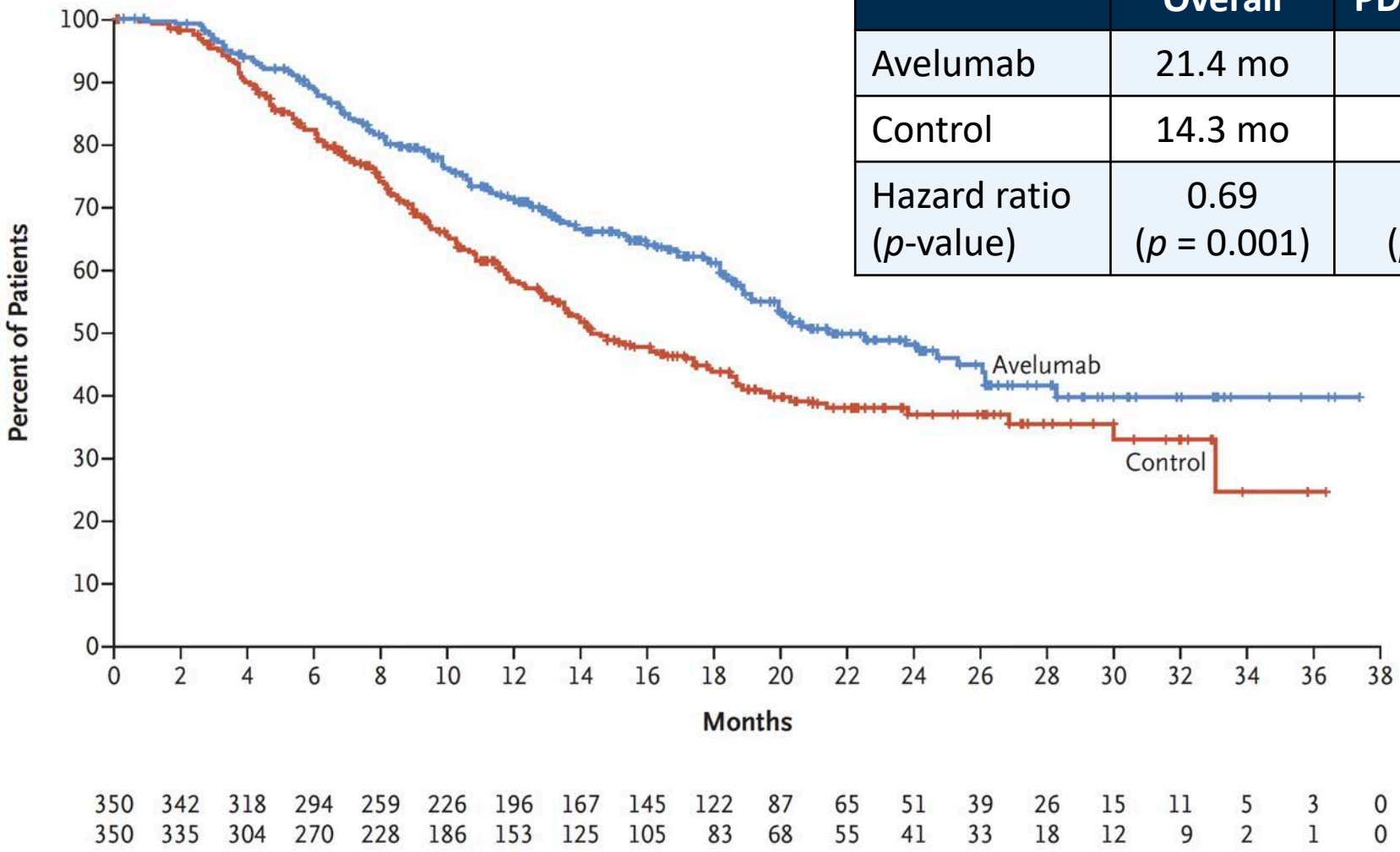
Courtesy of Jonathan E Rosenberg, MD

Memorial Sloan Kettering Cancer Center

Adapted from Powles et al. ASCO 2020

JAVELIN Bladder 100 Primary Endpoint: Overall Survival

	Overall	PD-L1-positive
Avelumab	21.4 mo	NE
Control	14.3 mo	17.1 mo
Hazard ratio (*p*-value)	0.69 (*p* = 0.001)	0.56 (*p* < 0.001)



Powles T et al. *N Engl J Med* 2020;383:1218-30.

Current standard for first-line therapy

- First-line standard remains cisplatin-based chemotherapy in eligible patients

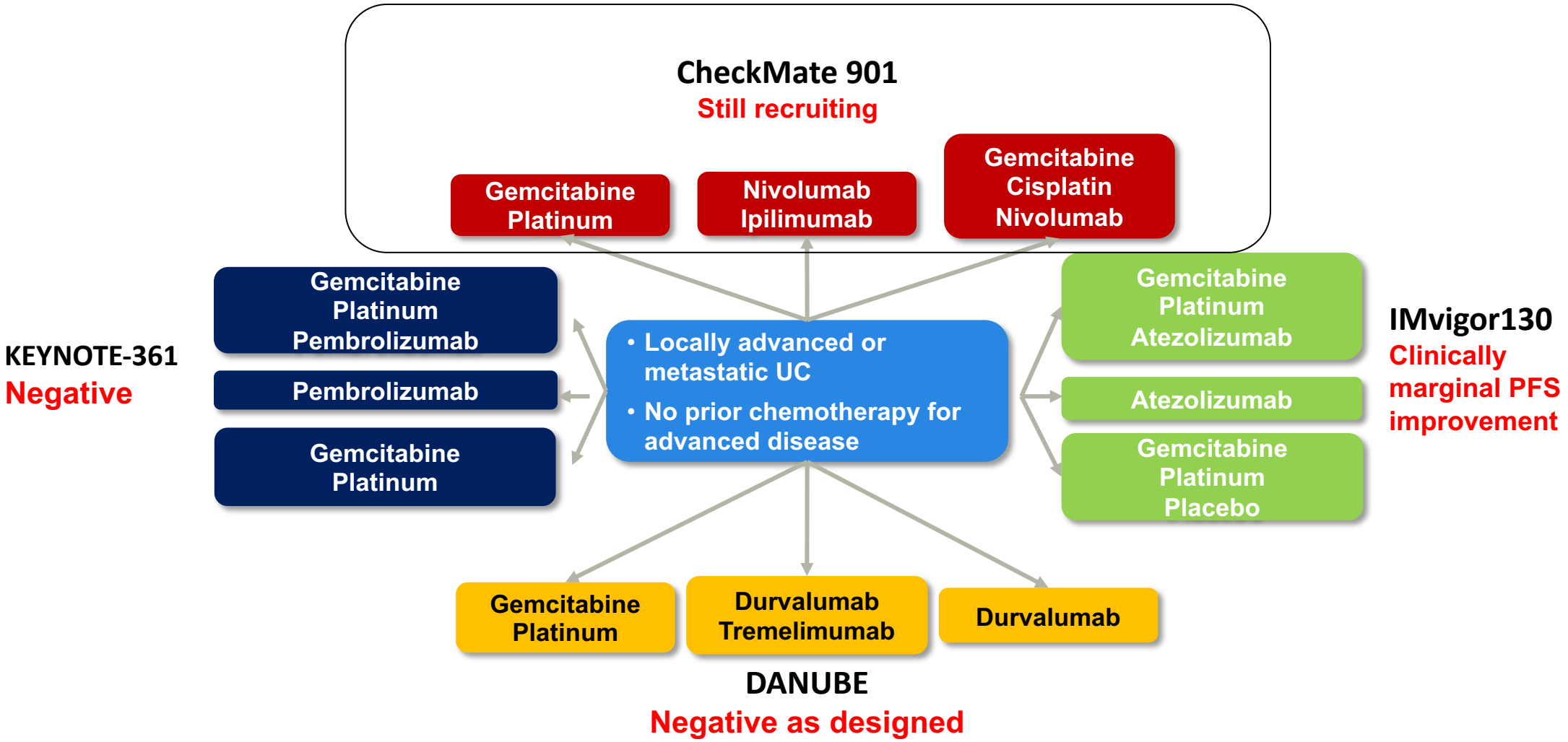
- Pembrolizumab or atezolizumab are FDA approved for PD-L1+ cisplatin-ineligible patients
  - IC 2/3 by SP142 (atezolizumab)
  - CPS ≥10% (pembrolizumab)

- Pembrolizumab and atezolizumab are also approved for platinum-ineligible patients regardless of PD-L1 status

- Less than 50% of patients who progress on first-line therapy receive 2nd-line treatment, and may partly explain results of JAVELIN Bladder 100
  - Early immunotherapy treatment improves outcomes

Courtesy of Jonathan E Rosenberg, MD

First-line metastatic UC trials have started to read out



Courtesy of Jonathan E Rosenberg, MD

Memorial Sloan Kettering Cancer Center

Voluntary Withdrawal of Durvalumab Indication for Advanced Bladder Cancer in the United States

Press Release – February 22, 2021

"The voluntary withdrawal of the durvalumab indication in the US for previously treated adult patients with locally advanced or metastatic bladder cancer [was announced today]. This decision was made in consultation with the Food and Drug Administration (FDA).

In May 2017, durvalumab was granted accelerated approval in the US based on promising tumor response rates and duration of response data from Study 1108, a Phase I/II trial that evaluated the safety and efficacy of durvalumab in advanced solid tumors, including previously treated bladder cancer. Continued approval was contingent on results from the DANUBE Phase III trial in the 1st-line metastatic bladder cancer setting, which did not meet its primary endpoints in 2020. The withdrawal is aligned with FDA guidance for evaluating indications with accelerated approvals that did not meet post-marketing requirements, as part of a broader industry-wide evaluation. This withdrawal does not impact the indication outside the US and does not impact other approved durvalumab indications within or outside the US."

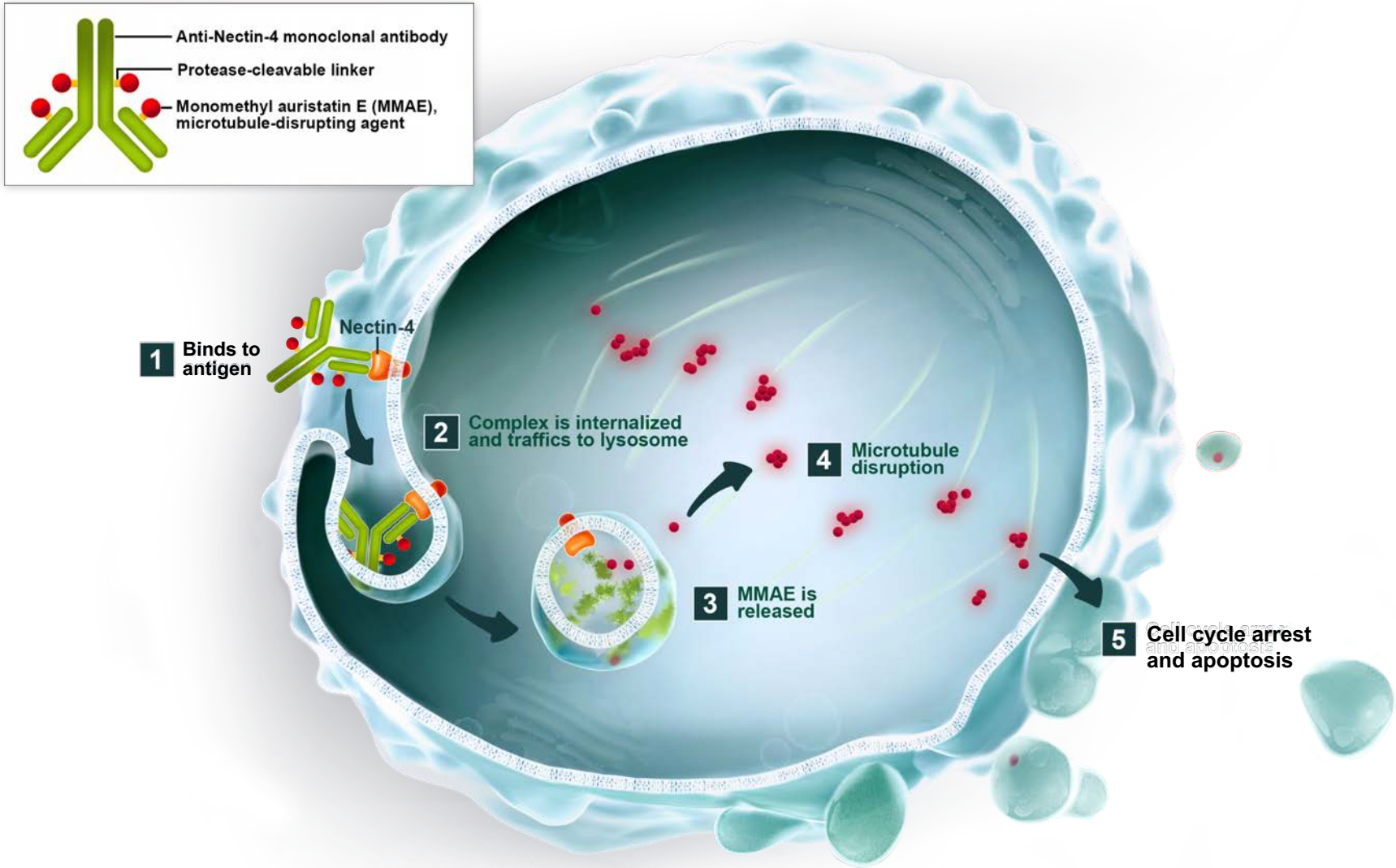
https://www.astrazeneca.com/media-centre/press-releases/2021/voluntary-withdrawal-imfinzi-us-bladder-indication.html

EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors (NCT03219333)

Arjun V. Balar, Bradley McGregor, Jonathan Rosenberg, Michiel S. van der Heijden, Se Hoon Park, Jae Lyun Lee, Michael R. Harrison, Elisabeth I. Heath, Mark N. Stein, Yohann Loriot, Andrea Necchi, Joyce Steinberg, Shang-Ying Liang, Eric Kim, Janet Trowbridge, Mary Campbell, Daniel P. Petrylak, and Evan Y. Yu

Abstract 394

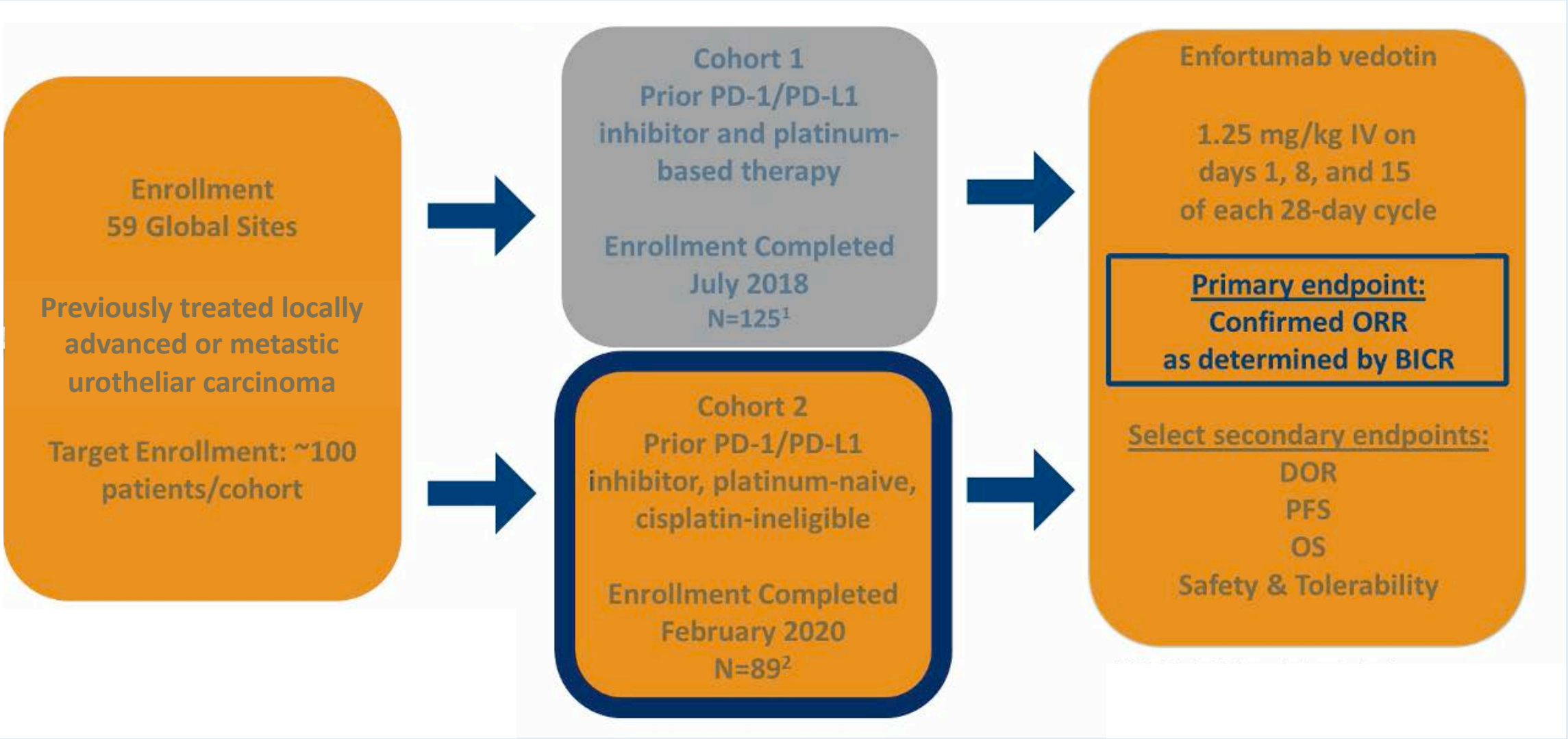
Enfortumab Vedotin: Nectin-4 Targeted Therapy



Courtesy of Jonathan E Rosenberg, MD

Memorial Sloan Kettering Cancer Center

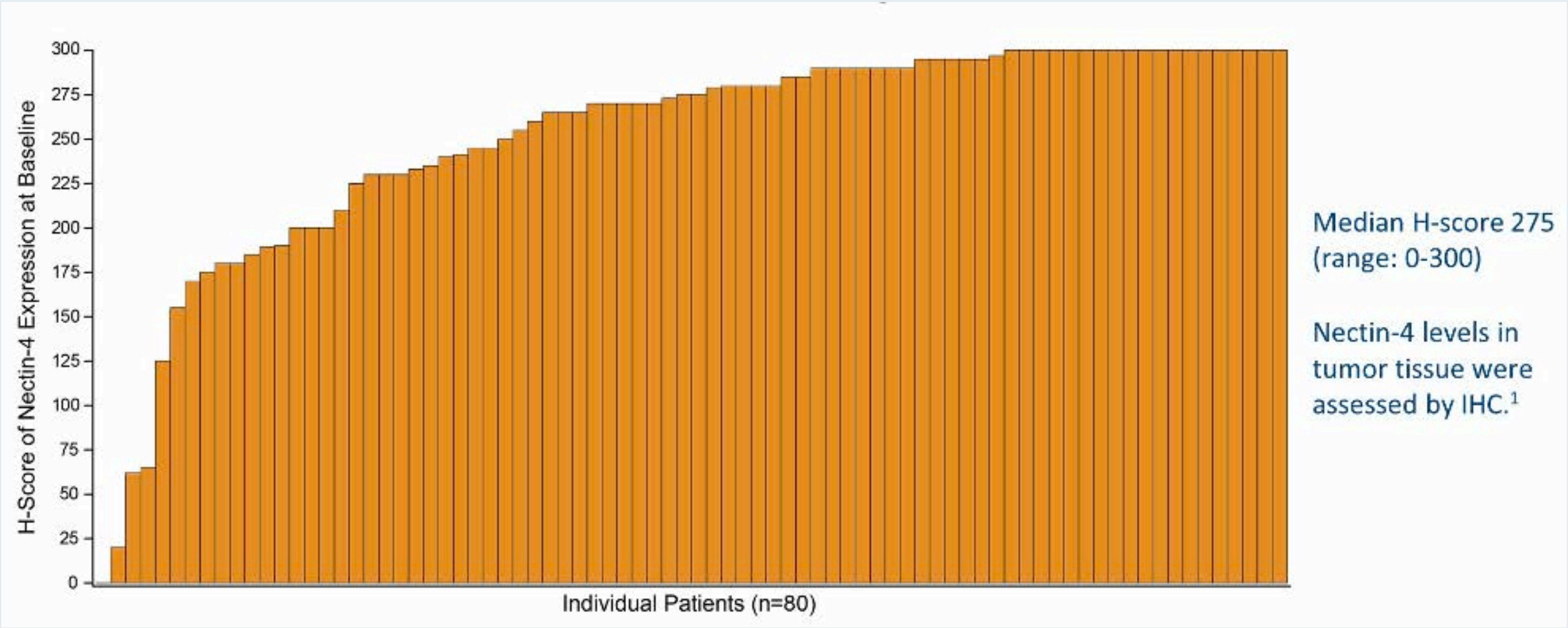
EV-201: Pivotal Phase II Trial Design



Balar AV et al. Genitourinary Cancers Symposium 2021;Abstract 394.

RTP RESEARCH TO PRACTICE

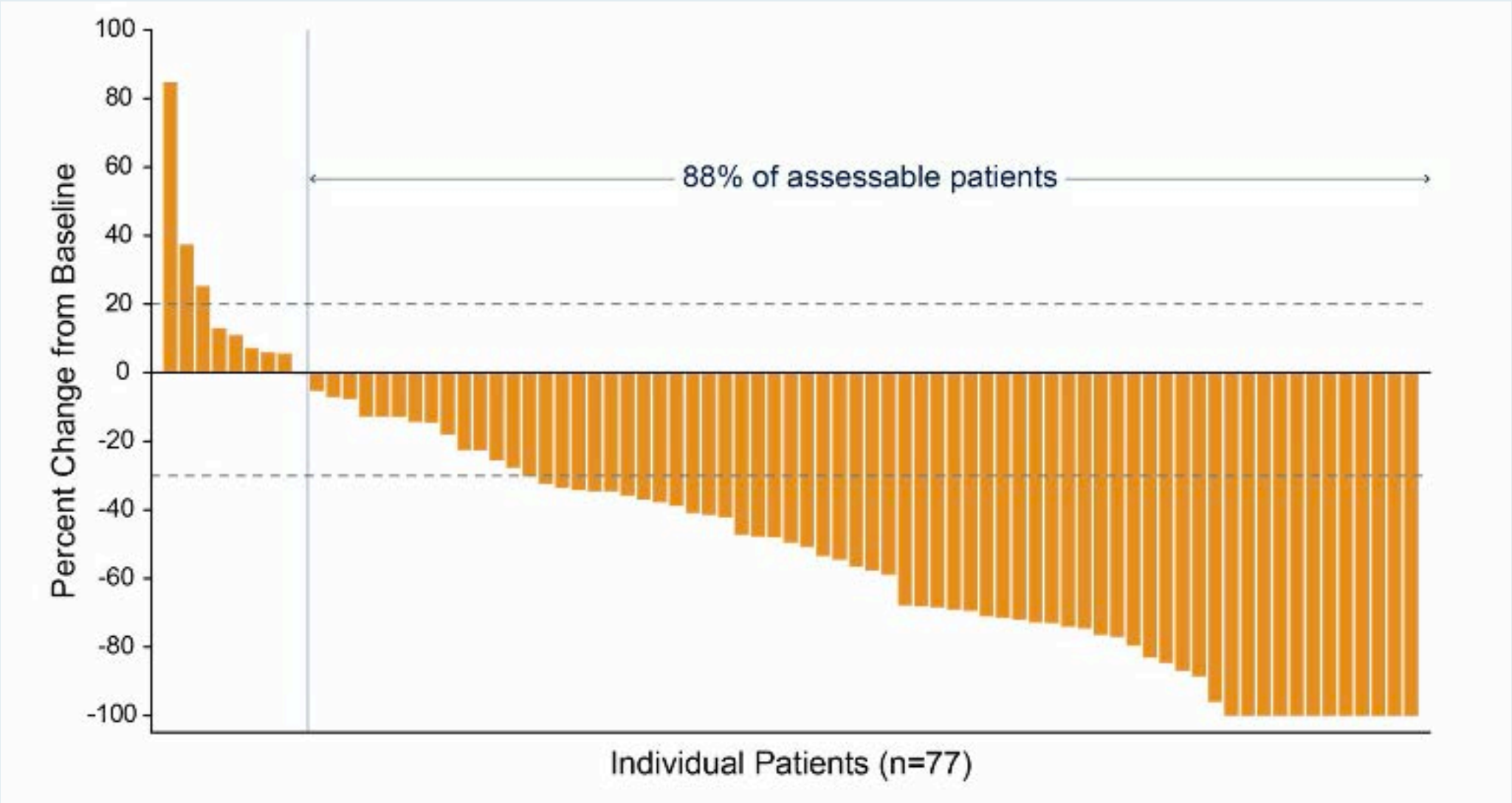
EV-201 Cohort 2: Nectin-4 Expression



Balar AV et al. Genitourinary Cancers Symposium 2021;Abstract 394.

RTP RESEARCH TO PRACTICE

EV-201 Cohort 2: Change in Tumor Measurements per BICR



Balar AV et al. Genitourinary Cancers Symposium 2021;Abstract 394.

RTP RESEARCH TO PRACTICE

EV-201 Cohort 2: Best Overall Response per BICR

ORR per RECIST v 1.1 assessed by BICR	Patients (N=89) %
Confirmed ORR, 95% CI[1]	52 (40.8, 62.4)
Best overall response[2]	
Confirmed complete response	20
Confirmed partial response	31
Stable disease	30
Progressive disease	9
Not evaluable[3]	9

Balar AV et al. Genitourinary Cancers Symposium 2021;Abstract 394.

EV-201 Cohort 2: Treatment-Related Adverse Events of Special Interest

Skin Reactions
61% any grade, 17% ≥Grade 3
Median Onset = 0.5 months[2]
% resolution/improvement[3] = 80%

- No Grade 5 events, 1 Grade 4 event
- 13 patients with severe cutaneous adverse reactions[4]
  - Most ≤Grade 2, no Grade 4 or 5 events
  - 4 patients with Grade 3 events: stomatitis, skin exfoliation, dermatitis bullous, dermatitis exfoliative generalised
  - 1 discontinuation due to severe cutaneous adverse reaction

Peripheral Neuropathy
54% any grade, 8% ≥Grade 3
Median Onset = 2.4 months
% resolution/improvement[3] = 56%

- PN rate was similar in patients with and without pre-existing PN (53% vs 54%)

Hyperglycemia
10% any grade, 6% ≥Grade 3
Median Onset = 0.5 months[2]
% resolution/improvement[3] = 89%

- Higher rate of HG in patients with pre-existing HG than those without pre-existing HG (20% vs. 7%)
- Higher rate of HG in patients with BMI ≥30 kg/m^2 than those with BMI <30 kg/m^2 (23% vs. 8%)

Balar AV et al. Genitourinary Cancers Symposium 2021;Abstract 394.

Primary Results of EV-301: A Phase 3 Trial of Enfortumab Vedotin vs Chemotherapy in Patients With Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

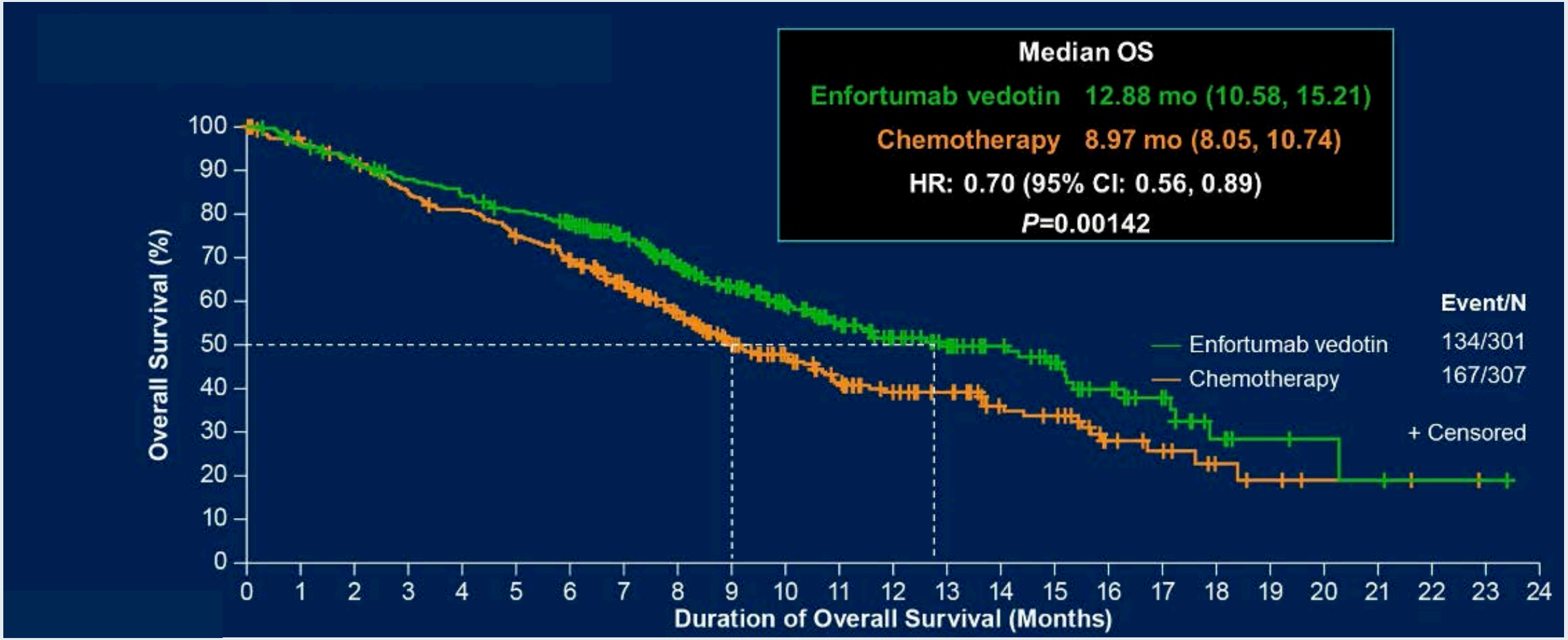
Thomas Powles, MD[1a]; Jonathan E Rosenberg, MD[2a]; Guru P Sonpavde, MD[3]; Yohann Loriot, MD, PhD[4]; Ignacio Durán, MD, PhD[5]; Jae-Lyun Lee, MD, PhD[6]; Nobuaki Matsubara, MD[7]; Christof Vulsteke, MD, PhD[8]; Chunzhang Wu, PhD[9]; Mary Campbell, MD[10]; Maria Matsangou, MBChB, MD[9]; Daniel P Petrylak, MD[11]

[1]Barts Cancer Centre, Queen Mary University of London, London, United Kingdom; [2]Memorial Sloan Kettering Cancer Center, New York City, NY, USA; [3]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [4]Gustave Roussy, Université Paris-Saclay, Villejuif, France; [5]Hospital Universitario Marques de Valdecilla, IDIVAL, Cantabria, Spain; [6]Asan Medical Center and University of Ulsan College of Medicine, Seoul, South Korea; [7]National Cancer Center Hospital East, Chiba, Japan; [8]Center for Oncological Research (CORE), University of Antwerp, Integrated Cancer Center Ghent, Ghent, Belgium; [9]Astellas Pharma, Inc., Northbrook, IL, USA; [10]Seagen Inc., Bothell, WA, USA; [11]Smilow Cancer Center, Yale School of Medicine, New Haven, CT, USA

[a]Dual first authorship; Drs. Powles and Rosenberg contributed equally to this presentation.

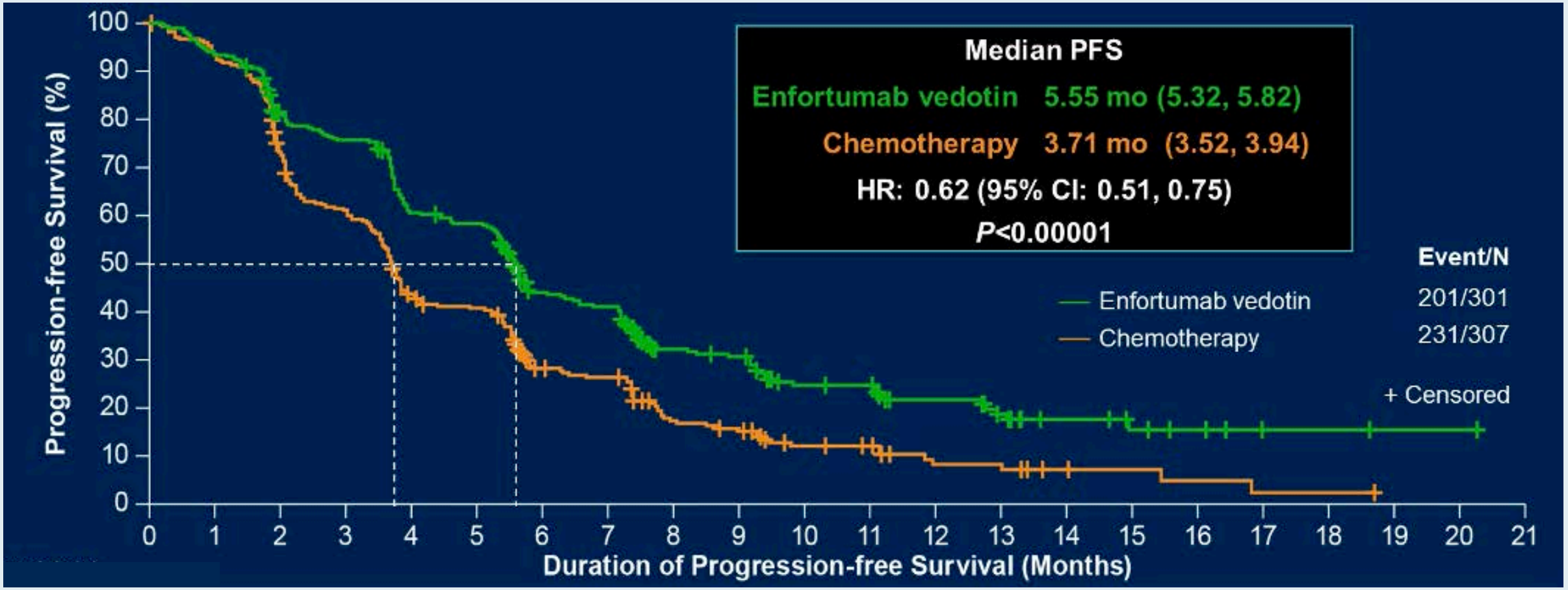
Abstract 393

EV-301: Overall Survival



Powles T and Rosenberg J et al. Genitourinary Cancers Symposium 2021;Abstract 393.

EV-301: Progression-Free Survival



Powles T and Rosenberg J et al. Genitourinary Cancers Symposium 2021;Abstract 393.

RTP RESEARCH TO PRACTICE

EV-301: Randomized phase III trial of EV vs dealers choice chemotherapy (taxane or vinflunine)

- Enfortumab vedotin significantly improved overall survival compared to chemotherapy
  - 30% reduction in risk of death (Hazard Ratio [HR]=0.70; [95% Confidence Interval (CI): 0.56, 0.89]; p=0.001).
- Enfortumab vedotin also significantly improved PFS, a secondary endpoint
  - 39% reduction in risk of disease progression or death (HR=0.61 [95% CI: 0.50, 0.75]; p<0.00001).

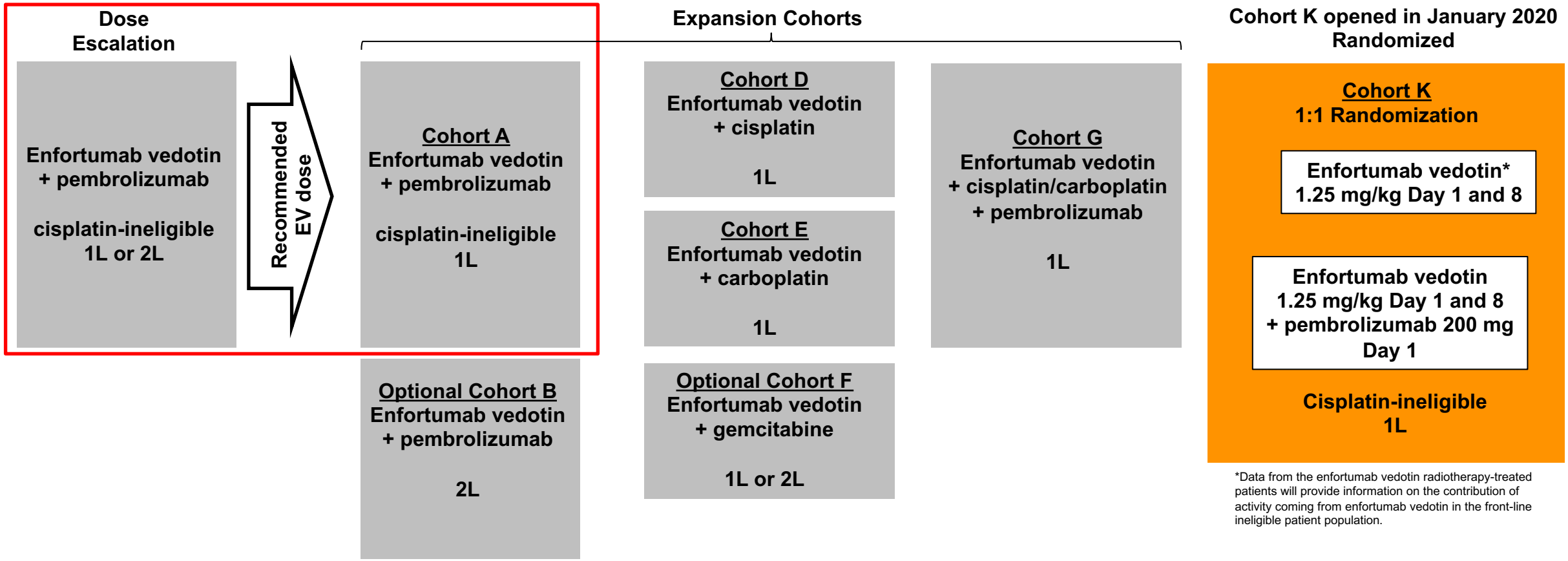
Press release, September 18, 2020

- FDA approved for platinum- and IO-previously treated patients
- Randomized phase III EV-301 shows improved overall survival compared to conventional chemotherapy
- First-line studies are ongoing alone and in combination with pembrolizumab

Courtesy of Jonathan E Rosenberg, MD

EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC

EV-103 Study Design for Locally Advanced or Metastatic Urothelial Carcinima (la/mUC) Cohorts



*Data from the enfortumab vedotin radiotherapy-treated patients will provide information on the contribution of activity coming from enfortumab vedotin in the front-line ineligible patient population.

NCT03288545

Hoimes CJ et al. ESMO 2019. Hoimes CJ et al. J Clin Oncol 37, 2019 (suppl; abstr TPS4593).
Goldberg H. UroToday Conference Highlights 2020.

Courtesy of Elisabeth I Heath, MD

EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC

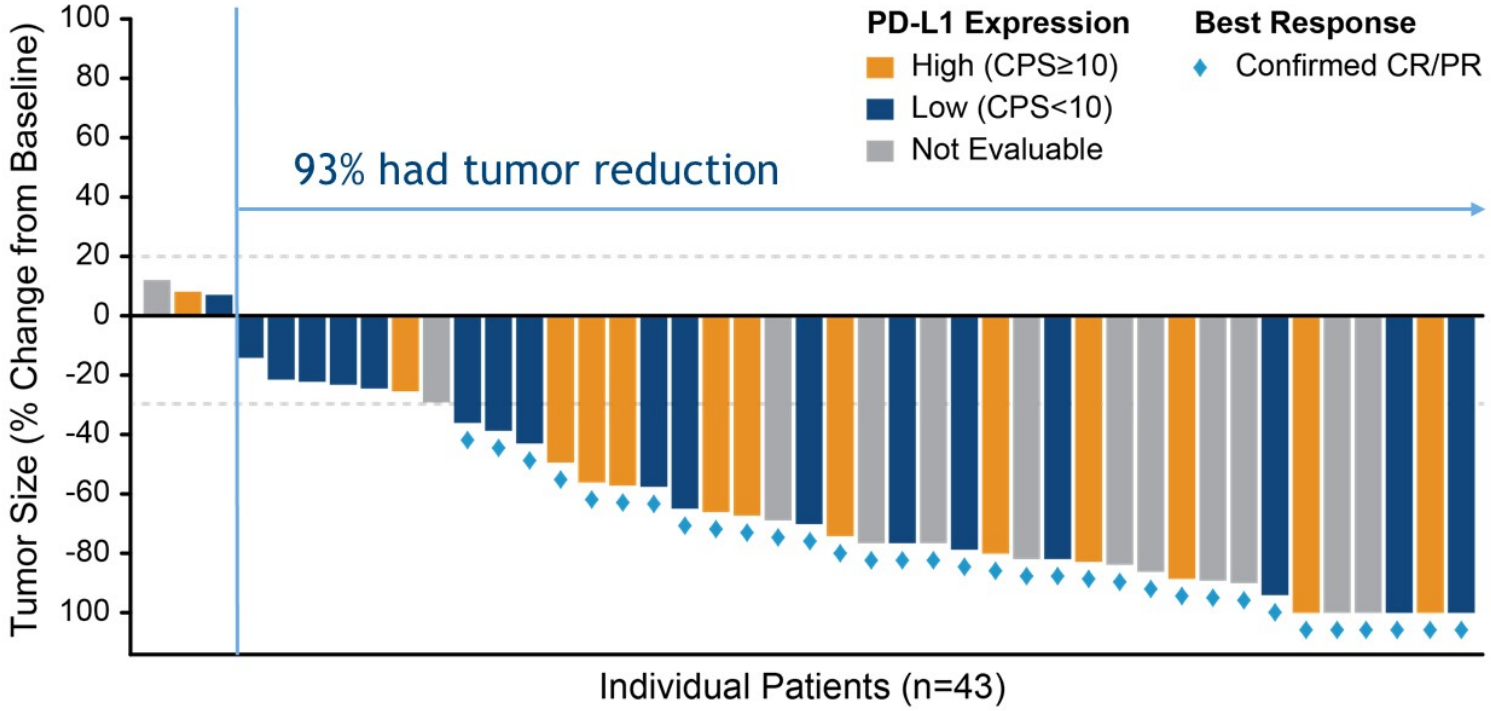
- Results:
  - Objective Response Rate (ORR) = 71%
  - Complete Response Rate (CR) = 13%
  - Stable Disease (SD) = 22%
- Treatment-emergent adverse events:
  - Fatigue = 49%, 9% ≥ Grade 3
  - Diarrhea = 40%, 4% ≥ Grade 3
  - Rash = 27%, 7% ≥ Grade 3
  - Peripheral neuropathy = 47%, 4% ≥ Grade 3

Food and Drug Administration (FDA) Granted Breakthrough Therapy Designation on February 18, 2020

Hoimes CJ et al. ESMO 2019.

Courtesy of Elisabeth I Heath, MD

EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC



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.

NCT03288545

Rosenberg JE at al. J Clin Oncol 38, 2020 (suppl 6; abstr 441). Rosenberg JE at al. J Clin Oncol 38, 2020 (suppl; abstr 5044).

Courtesy of Elisabeth I Heath, MD

EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC

- Results (median follow-up 11.5 months):
  - ORR= 73.3%
    - ORR in patients with liver metastasis = 53.5%
    - ORR by PD-L1 Expression
      - High: 78.6%
      - Low: 63.2%
  - Complete Response Rate = 15.6%
  - Partial Response Rate = 57.8%
  - Stable Disease = 20%
- Median Progression Free Survival (PFS) = 12.3 months (95% CI 7.98,-)
- Median Overall Survival (OS) = not reached
- Median Overall Survival (OS) at 12 months = 81.6%

Rosenberg JE et al. J Clin Oncol 38, 2020 (suppl 6; abstr 441). Rosenberg JE at al. J Clin Oncol 38, 2020 (suppl; abstr 5044).

Courtesy of Elisabeth I Heath, MD

Agenda

Module 1 – Case Presentations

- Dr Ma: A 62-year-old woman with Stage IIIA bladder cancer
- Dr Lamar: A 68-year-old woman with cisplatin-ineligible muscle-invasive UBC
- Dr Favaro: A 54-year-old woman with high-grade papillary UBC

Data Review – Non-muscle-invasive bladder cancer; (neo)adjuvant treatment of MIBC

Module 2 – Case Presentations

- Dr Zafar: A 72-year-old man with high-grade UBC – TMB 103 mut/Mb
- Dr Yang: A 77-year-old man with metastatic transitional cell UBC
- Dr Rupard: A 58-year-old man with distal urothelial cell carcinoma of the penis

Data Review – Metastatic disease: Checkpoint inhibitors; enfortumab vedotin

Module 3 – Case Presentations

- Dr Favaro: A 72-year-old man with metastatic UBC – FGFR3 mutation
- Dr Mitchell: Comment – Management of checkpoint inhibitor toxicities

Data Review – Metastatic disease: Erdafitinib; novel agents and strategies

Case Presentation – Dr Favaro: A 72-year-old man with metastatic UBC – FGFR3 mutation, CPS 1, TMB 10 mut/Mb

Dr Justin Favaro

- Presented with a 5-cm bladder tumor, 1 area of metastasis to a right inguinal lymph node and a secondary solitary bone metastasis
- 1st line: Cisplatin/gemcitabine x 6 and RT to right inguinal node → disease progression
- 2nd line: Pembrolizumab → disease progression
- 3rd line: Erdafitinib – Fared well ~4 months but developed retinal edema
  - Treatment stopped
- 4th line: Enfortumab vedotin – Treated ~4 months but developed infected right inguinal node
  - Currently off treatment with wound vac

Questions

- Would the faculty consider putting this patient back on an FGFR inhibitor given his history of central serous retinopathy?

RTP RESEARCH TO PRACTICE

Practical challenges in community hospitals in recognizing and managing checkpoint inhibitor-associated toxicities

Dr William Mitchell

RTP
RESEARCH
TO PRACTICE

Case Presentation – Dr Heath: A 67-year-old man with metastatic bladder cancer and an FGFR3 mutation

- 67 year old Pakistani male with 6 month history of gross hematuria and flank pain
- Workup revealed T2N0 upper tract tumor
- Completed nephroureterectomy
- In year 3, patient developed persistent right knee pain
- Imaging confirmed metastatic lesion in right distal femur
- Biopsy confirmed metastatic urothelial cancer
- Genomic profiling showed FGFR3 alteration
- Underwent radiation therapy to right distal femur with major improvement in pain
- Received 8 cycles of gemcitabine/cisplatin and then progressed with new liver lesions
- Started erdafitinib with mild hyperphosphatemia
- Clinical trial with sitravatinib upon progression

What would you generally recommend for a patient who experiences disease recurrence in the liver 9 months after cystectomy and adjuvant chemotherapy for muscle-invasive UBC who is found to have an FGFR3 mutation?

1. Other chemotherapy
2. Anti-PD-1/PD-L1 antibody
3. Nivolumab/ipilimumab
4. Erdafitinib
5. Enfortumab vedotin
6. Other

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

1. Enfortumab vedotin → erdafitinib
2. Erdafitinib → enfortumab vedotin

RTP RESEARCH TO PRACTICE

For which of the following adverse events is the risk increased with erdafitinib?

1. Ocular toxicity
2. Hyperphosphatemia
3. Both 1 and 2
4. Neither 1 nor 2
5. I don’t know

Agenda

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RTP
RESEARCH
TO PRACTICE

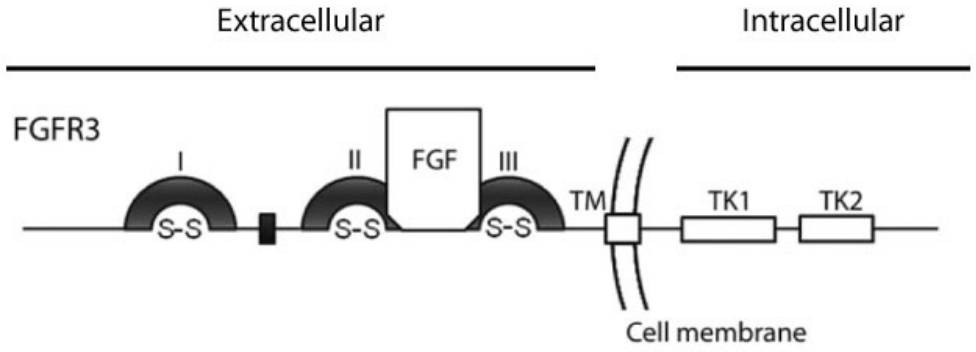
Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma (mUC): Long-Term Outcomes in BLC2001

Siefker-Radtke AO et al.
ASCO 2020;Abstract 5015.

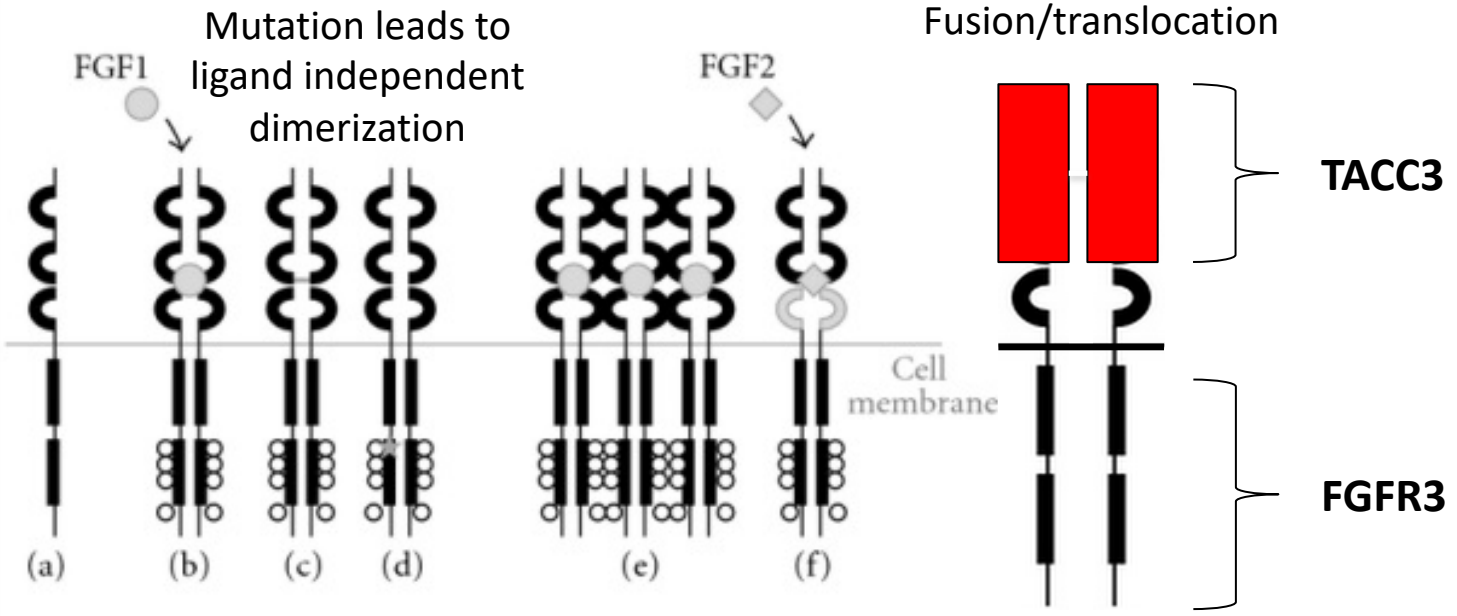
Fibroblast Growth Factor Receptor 3 is a therapeutic target in mUC

- Mutation frequency in non-invasive disease is >50% in Stage 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



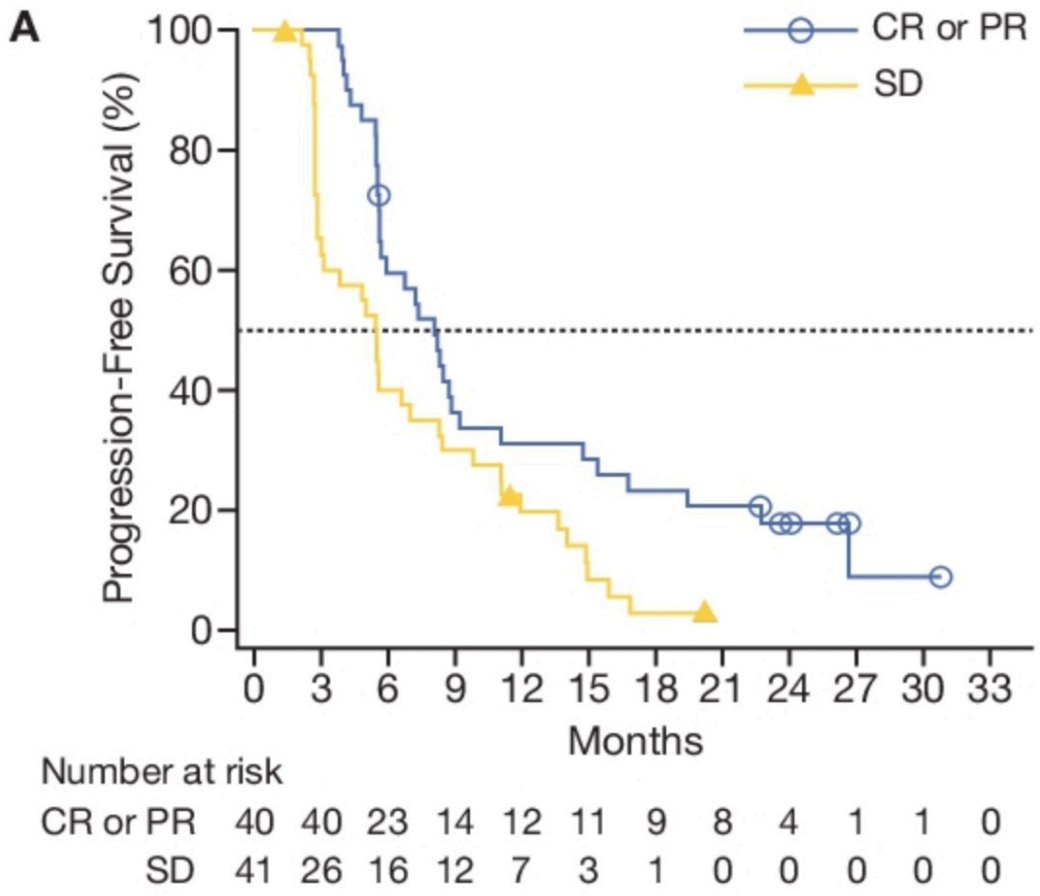
Overexpression

Courtesy of Jonathan E Rosenberg, MD

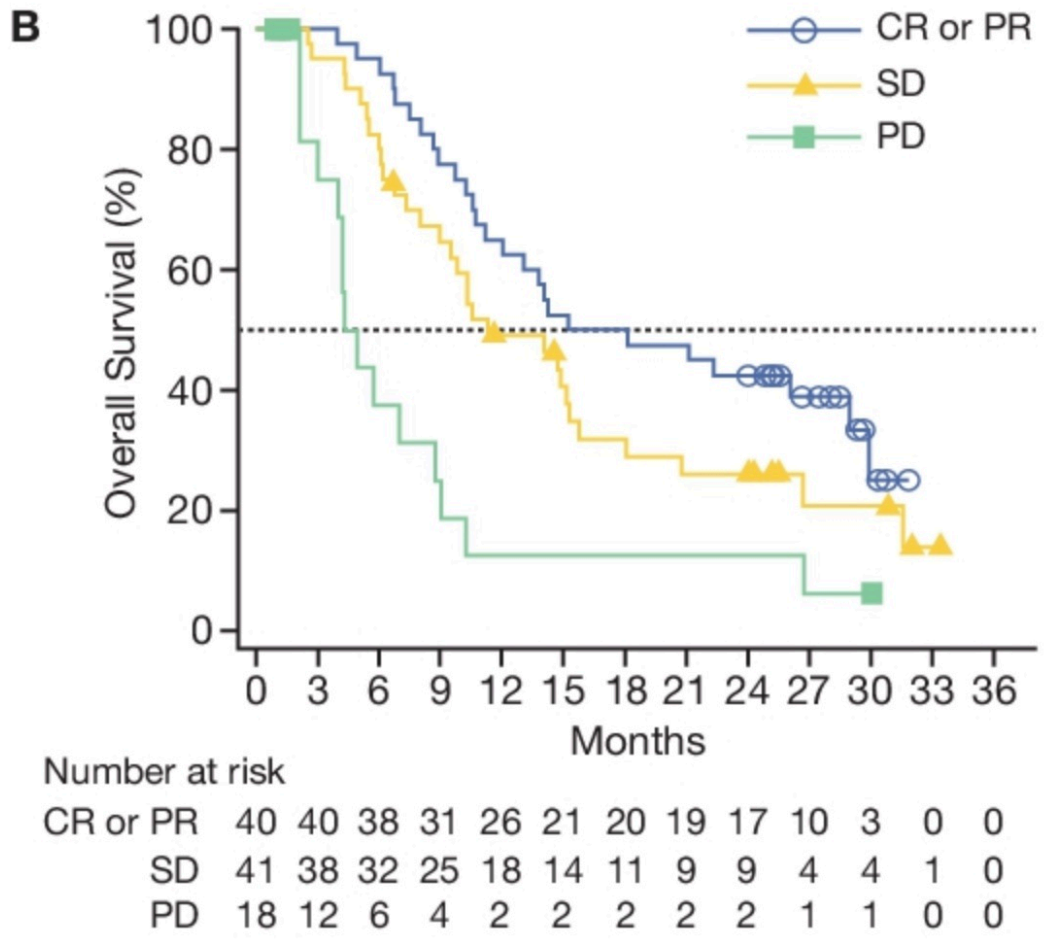
Memorial Sloan Kettering Cancer Center

BLC2001: Survival

Median PFS: 5.5 months



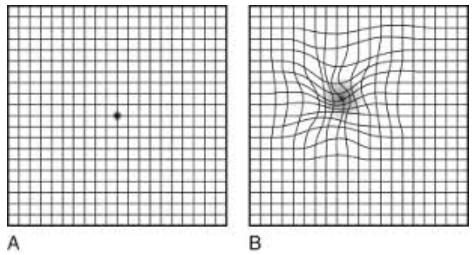
Median OS: 11.3 months



Siefker-Radtke AO et al. ASCO 2020;Abstract 5015.

BLC2001: Toxicity of erdafitinib

- 55% of patients required dose reductions
- 41% of patients were able to escalate to 9mg 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 serious 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

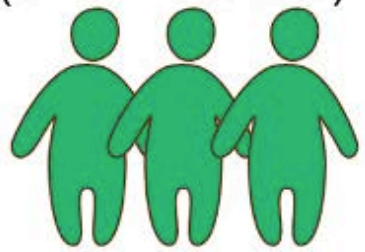
Are FGFR3 Alterations Associated with Resistance to PD-1/PD-L1 Blockade in Large Clinical Trial Cohorts?

Phase 2
(IMvigor 210)

N = 274

18% mFGFR

Phase 2
(*Checkmate 275*)



N = 139

11% mFGFR

Objective Response Rate

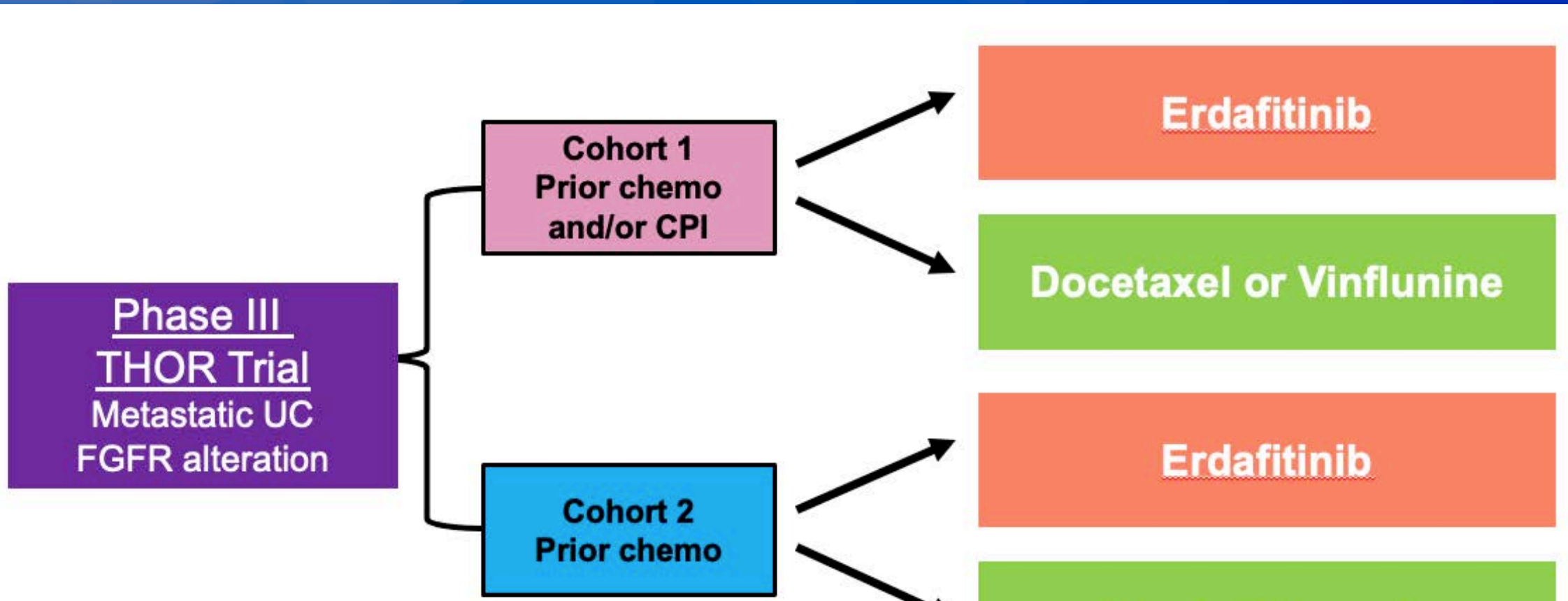
Wild type	**21% (95% CI: 16%, 27%)**
Mutant	**24% (95% CI: 14%, 39%)**

Wild type	**21% (95% CI: 15%, 29%)**
Mutant	**21% (95% CI: 15%, 29%)**

Wang, European Urology, 2019

Courtesy of Matthew Galsky, MD

Ongoing Phase III THOR Trial Design



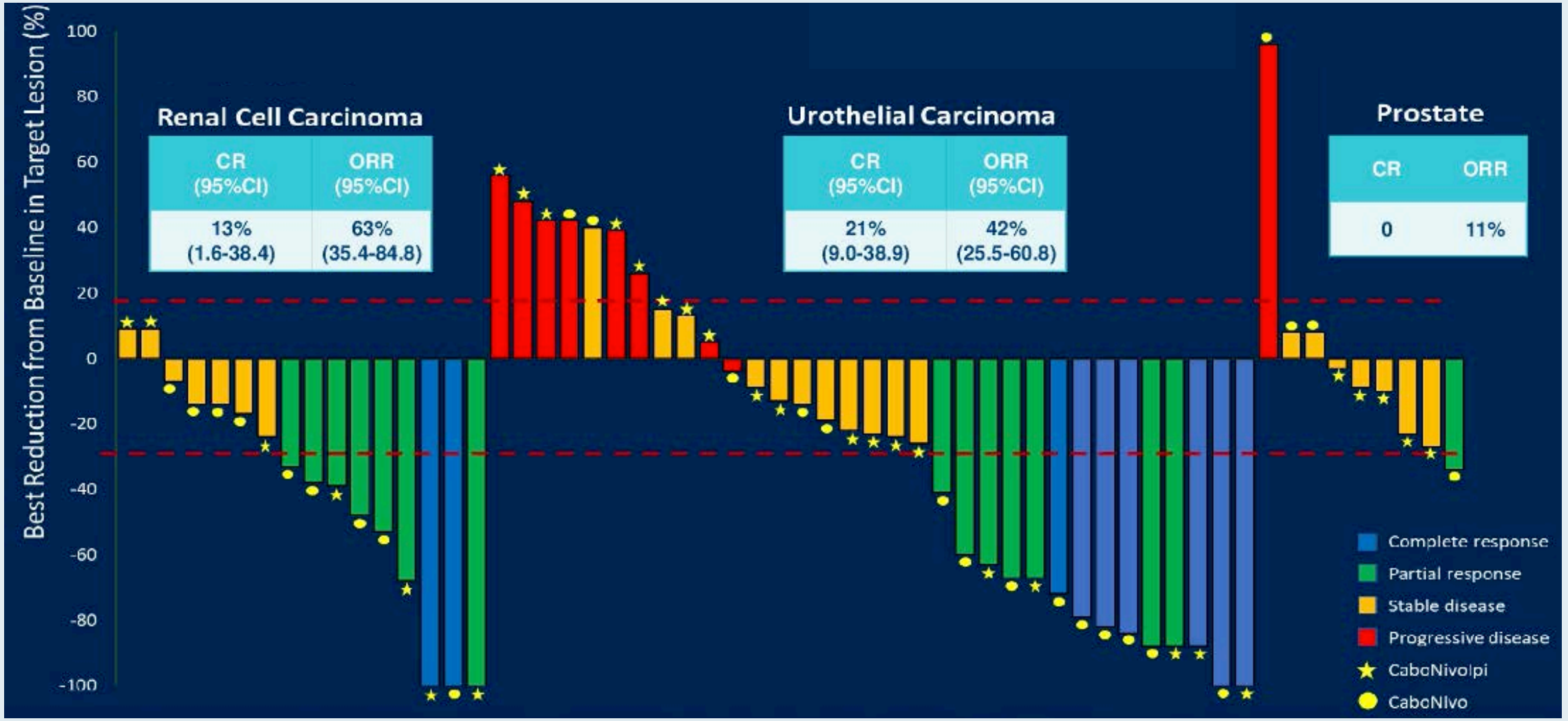
Primary endpoint: Overall survival
Secondary endpoints include progression-free survival, response, safety, change in disease severity and quality of life

Final Results from a Phase 1 Trial and Expansion Cohorts of Cabozantinib and Nivolumab (CaboNivo) Alone or With Ipilimumab (CaboNivoIpi) for Metastatic Genitourinary Tumors

Andrea B. Apolo, Daniel M. Girardi, Scot A. Niglio, Rosa Nadal, Lisa Ley, Lisa M. Cordes, Seth M. Steinberg, Rene Costello, Jane Trepel, Sunmin Lee, Min-Jung Lee, Liang Cao, Mohammad Bagheri, Heather J. Chalfin, Donald P. Bottaro, Biren Saraiya, Sumanta K. Pal, David Quinn, Primo N. Lara, Amir Mortazavi

Abstract ID: 3 (324681)

Reduction in Tumor Size by Tumor Type with Cabo/Nivo or Cabo/Nivo/Ipi

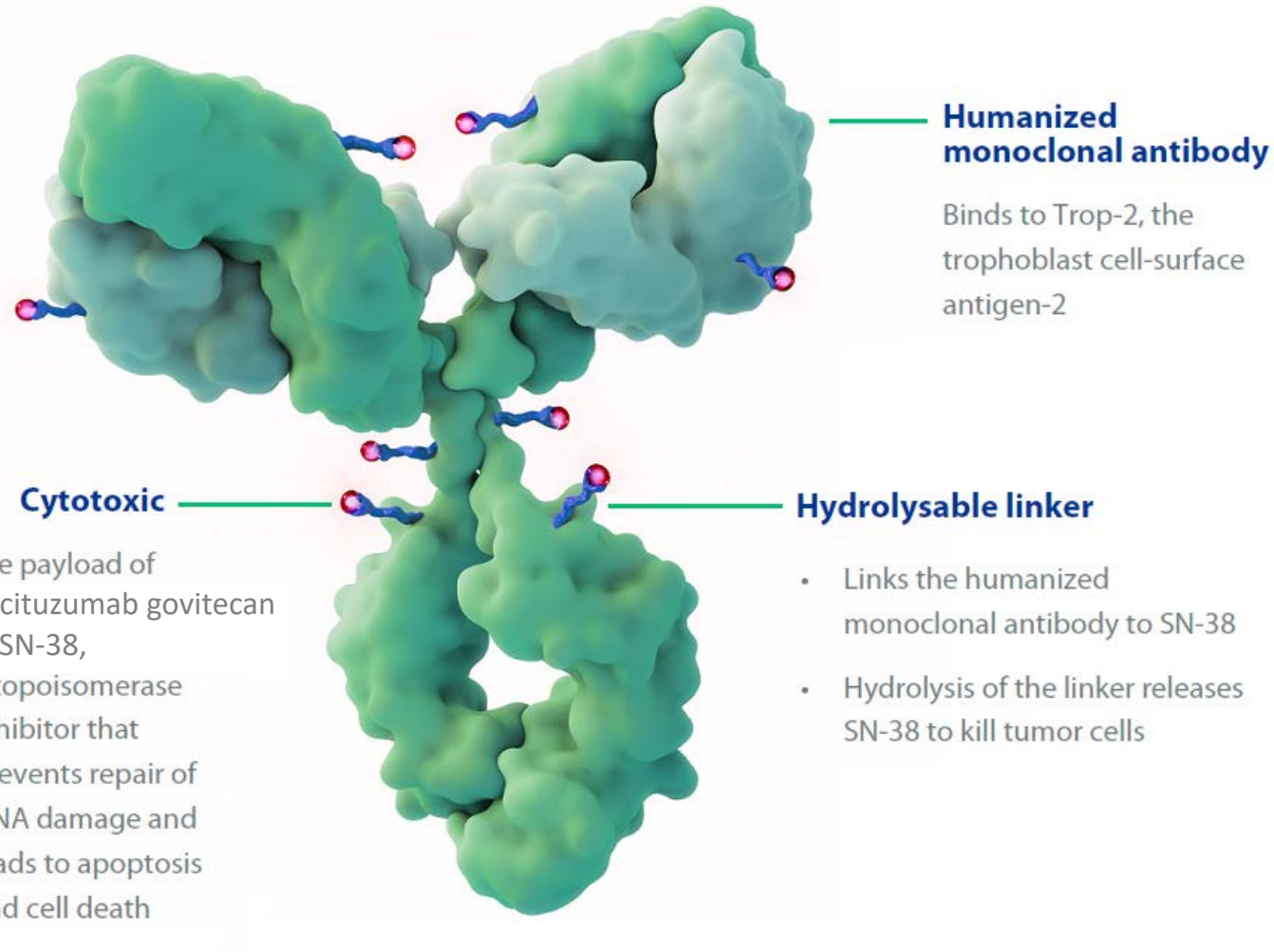


Apolo AB et al. Genitourinary Cancers Symposium 2021;Abstract 3.

RTP RESEARCH TO PRACTICE

Sacituzumab Govitecan

- Trop-2-directed antibody drug conjugate
- Site specific conjugate of irinotecan active metabolite (SN-38) to humanized monoclonal antibody against trophoblastic cell-surface antigen-2 (Trop-2)
- Trop-2 is a cell surface glycoprotein expressed in urothelial cancers



Courtesy of Elisabeth I Heath, MD

Sacituzumab Govitecan

- TROPHY-U-01: Phase 2 trial with multiple cohorts
- Cohort 1: post platinum-based chemotherapy and immune checkpoint inhibitor (113 pts)
  - ORR: 27% (with 76% of patients with reduction in tumor size)
  - Median PFS: 5.4 months
  - Median OS: 10.5 months
- FDA Fast Track Designation for urothelial cancer: April 9, 2020

ADVERSE EVENT	ALL GRADES (%)	GRADE 3 (%)	GRADE 4 (%)
Neutropenia	46	22	12
Febrile Neutropenia	10	7	3
Diarrhea	65	9	1
Fatigue	50	4	0

Loriot Y et al. Annals of Oncology 31(2020);S1156.

NCT03547973

Courtesy of Elisabeth I Heath, MD

Additional Sacituzumab Govitecan Clinical Trials

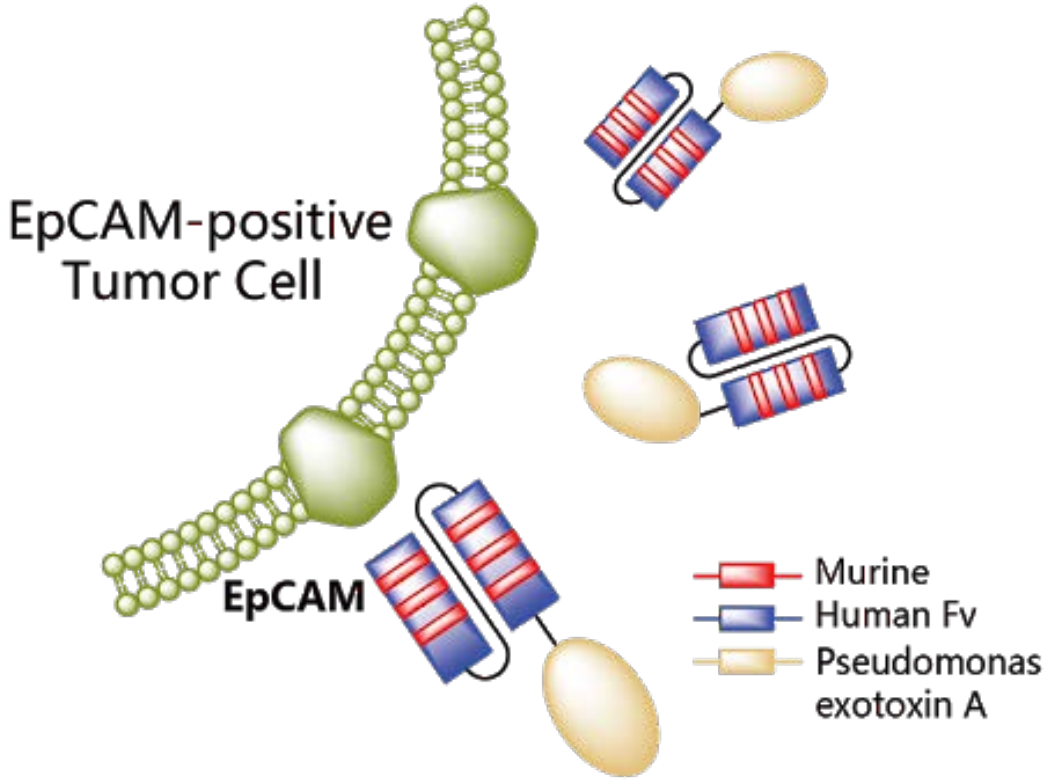
- TROPHY-U-01
  - Cohort 2: cisplatin-ineligible and one prior immune checkpoint inhibitor
  - Cohort 3: progressed after platinum-based chemotherapy and no immune checkpoint inhibitor
- TROPiCS-04
  - Phase III trial: SG versus taxane in post platinum-based chemotherapy, post PD-(L)1 antibody therapy
- MORPHEUS mUC
  - Phase I/II trial: SG plus atezolizumab in post platinum-based chemotherapy
- SEASTAR
  - Phase I/II trial: SG plus rucaparib in urothelial carcinoma with DNA repair deficiency

NCT01928394, NCT04527991, NCT03869190, NCT03992131

Courtesy of Elisabeth I Heath, MD

Oportuzumab Monatox

- Antibody-drug conjugate of humanized scFv monoclonal antibody fragments that bind to epithelial cell adhesion molecule (EpCAM) and a portion of pseudomonas exotoxin A
- VISTA-3: Phase III of VB4-845 in non-muscle invasive bladder cancer previously treated with BCG
- FDA Fast Track Designation August 16, 2018



https://www.pharmacodia.com/yaodu/html/v1/biologics/f9d81ff01aec9a8625983fe8f5c382f0.html#onlineretailersOuBiologys

NCT02449239

Courtesy of Elisabeth I Heath, MD

Disitamab Vedotin (RC48)

- HER2-directed antibody drug conjugate
- Recombinant humanized anti-HER2 monoclonal antibody-MMAE Conjugate
- Phase II:
  - 43 patients
  - HER2 IHC 2+ or 3+
  - Received at least one systemic chemotherapy
  - 86% had visceral metastasis
  - 33% had two prior lines of treatment
- ORR: 60.5%
- Median PFS: not reached
- Treatment related AEs (All Grades)
  - Leukopenia (51%)
  - Neutropenia (37%)
  - Fatigue (35%)

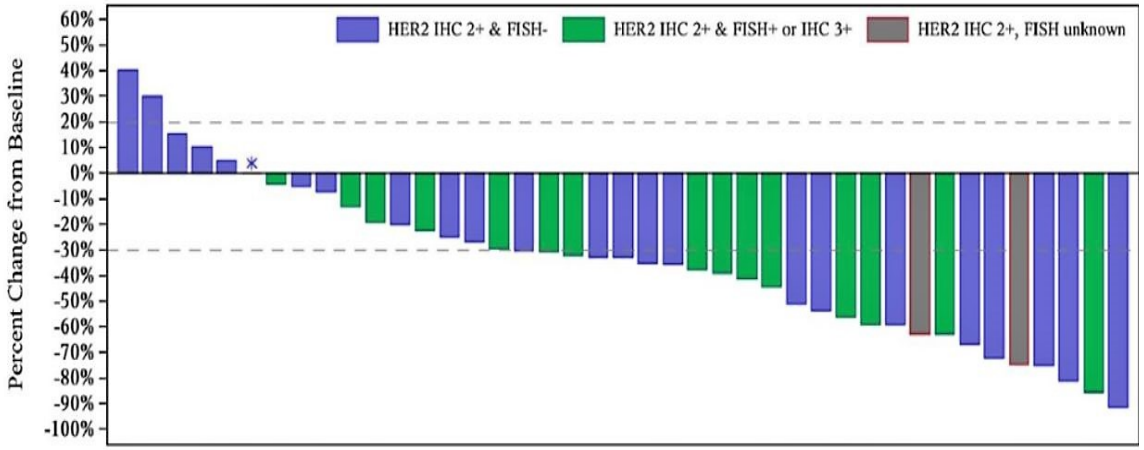
Sheng et al. DOI: 10.1200/JCO.2019.37.15_suppl.4509 *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 4509-4509.

NCT03507166

Courtesy of Elisabeth I Heath, MD

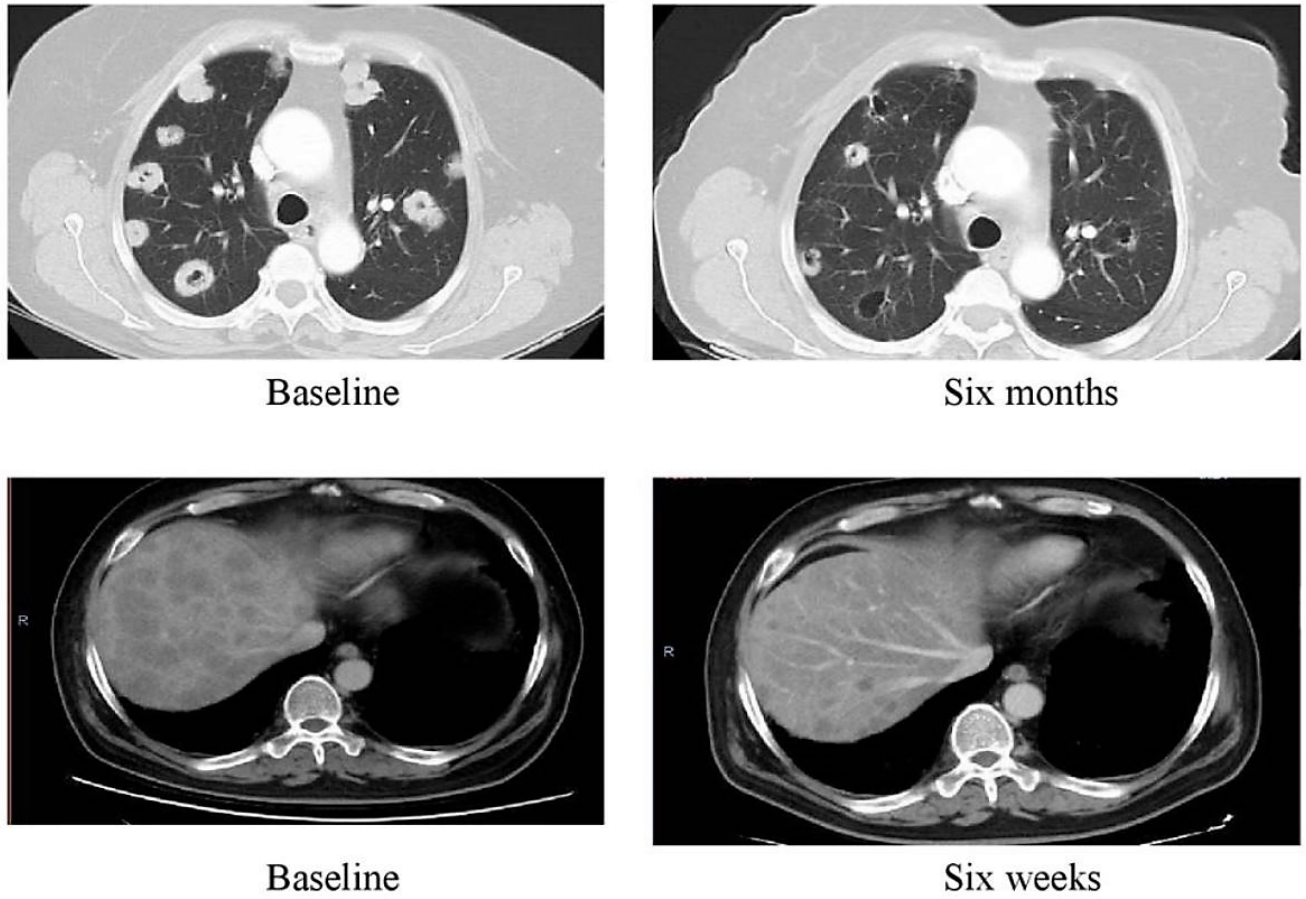
Disitamab Vedotin (RC48)

Figure 3. Best Change of Target lesion from Baseline



Note: * means percent change from baseline of target lesion is 0%

Figure 3. CT Images of Two Patients



Baseline | Six months

Baseline | Six weeks

FDA Fast Track Designation on September 25, 2020

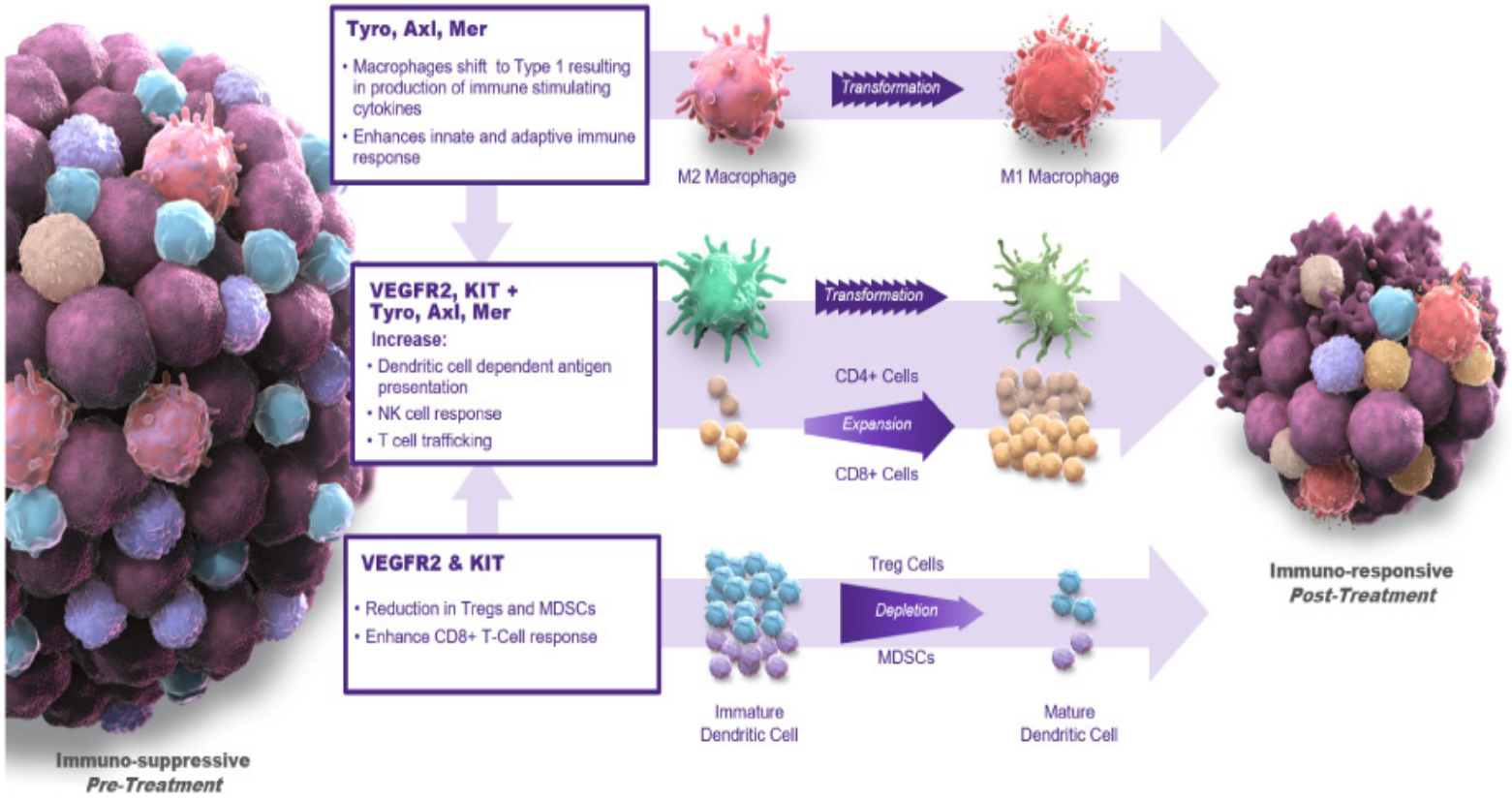
NCT03507166

Sheng et al. DOI: 10.1200/JCO.2019.37.15_suppl.4509 *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 4509-4509.

Courtesy of Elisabeth I Heath, MD

Sitravatinib

- Receptor tyrosine kinase
- Involved in creating immunosuppressive tumor microenvironment
- Sitravatinib targets TAM family (TYRO3, AXL, and MER), VEGFR2, and KIT



https://www.mirati.com/pipeline/sitravatinib/

Courtesy of Elisabeth I Heath, MD

Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium®

Management of HER2-Positive Breast Cancer

Monday, March 8, 2021
5:00 PM – 6:00 PM ET

Faculty

Mark D Pegram, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.