Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Urothelial Bladder Cancer

Part 2 of a 2-Part CME Satellite Symposium Series in Conjunction with the AUA 2022 Annual Meeting

Friday, May 13, 2022

6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)

Faculty

Matthew D Galsky, MD
Ashish M Kamat, MD, MBBS
Stephen B Williams, MD, MS

Moderator

Sumanta Kumar Pal, MD

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Faculty

Matthew D Galsky, MD
Professor of Medicine
Icahn School of Medicine at Mount Sinai
Co-Leader, Bladder Cancer Center of Excellence
Associate Director, Translational Research
The Tisch Cancer Institute
New York, New York

Stephen B Williams, MD, MS
Medical Director, High Value Care
UTMB Health System
Chief, Division of Urology
Professor (Tenured), Urology and Radiology
Robert Earl Cone Professorship
Director of Urologic Oncology
Director of Urologic Research
Co-Director of the Surgical Outcomes Research Division
The University of Texas Medical Branch
Galveston, Texas

Ashish M Kamat, MD, MBBS
Professor of Urologic Oncology (Surgery)
Wayne B Duddlesten Professor of Cancer Research
Department of Urology
Division of Surgery
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Moderator

Sumanta Kumar Pal, MD
Professor, Department of Medical
Oncology and Therapeutics Research
City of Hope
Duarte, California

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Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Commercial Support

This activity is supported by educational grants from Astellas and Seagen Inc, AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC.

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Dr Galsky — Disclosures

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Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, Merck

Dr Kamat — Disclosures

No relevant conflicts of interest to disclose

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Dr Pal — Disclosures

No relevant conflicts of interest to disclose

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Dr Williams — Disclosures

No relevant conflicts of interest to disclose

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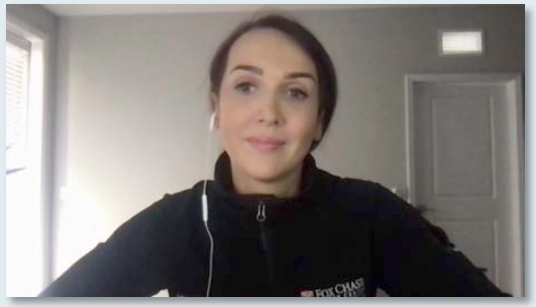
Agenda

MODULE 1: Available Data with and Ongoing Investigation of Novel Agents and Strategies for Non-Muscle-Invasive Bladder Cancer (NMIBC) — Dr Kamat

MODULE 2: Novel Therapeutic Approaches for Muscle-Invasive Bladder Cancer (MIBC) — Dr Williams

MODULE 3: Current and Future Front-Line Management of Metastatic Urothelial Bladder Carcinoma (mUBC) — Dr Galsky

MODULE 4: Selection and Sequencing of Therapy for Relapsed/Refractory mUBC — Dr Pal



Laura Bukavina, MD, MPH
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Sulfi Ibrahim, MD
Reid Health
Richmond, Indiana

Ranju Gupta, MD
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania

Zanetta S Lamar, MD
Florida Cancer Specialists
Naples, Florida

Jason Hafron, MD
Oakland University William Beaumont School of Medicine
West Bloomfield, Michigan

Henna Malik, MD
Texas Oncology
Houston, Texas

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Paul Markowski, MD
Atlantic Health System
Summit, New Jersey

Chris Prakash, MD
Texas Oncology
Paris, Texas

David S Morris, MD
Urology Associates
Nashville, Tennessee

David A Taub, MD, MBA
Lynn Cancer Institute
Baptist Health South Florida
Boca Raton, Florida

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MODULE 1: Available Data with and Ongoing Investigation of Novel Agents and Strategies for Non-Muscle-Invasive Bladder Cancer

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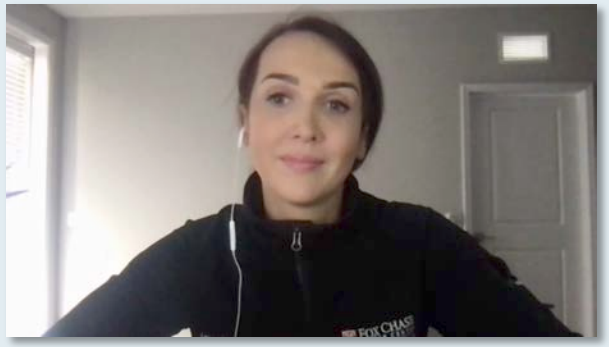
How many patients in your practice with non-muscle-invasive bladder cancer (NMIBC) have been treated with an anti-PD-1/PD-L1 antibody such as pembrolizumab?

1. 0
2. 1
3. 2-5
4. More than 5



Dr Laura Bukavina
Philadelphia, Pennsylvania

A 72-year-old man with persistent NMIBC after multiple therapies

Dr David Taub
Boca Raton, Florida

An 82-year-old woman with high-grade NMIBC

Dr Paul Markowski
Summit, New Jersey

A 70-year-old woman with multiple recurrences of NMIBC involving the ureter – PD-L1: 5%

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What is the age of the oldest patient in your practice who has undergone cystectomy?

1. Younger than 60
2. 60-70
3. 71-80
4. 81-85
5. 86-90
6. 91-95
7. 96-100
8. Older than 100

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Dr David Morris
Nashville, Tennessee

An 88-year-old man with multiple recurrences of FGFR3-positive NMIBC who receives erdafitinib on a clinical trial

Dr David Morris
Nashville, Tennessee

TAR-200: Gemcitabine-releasing intravesicle system

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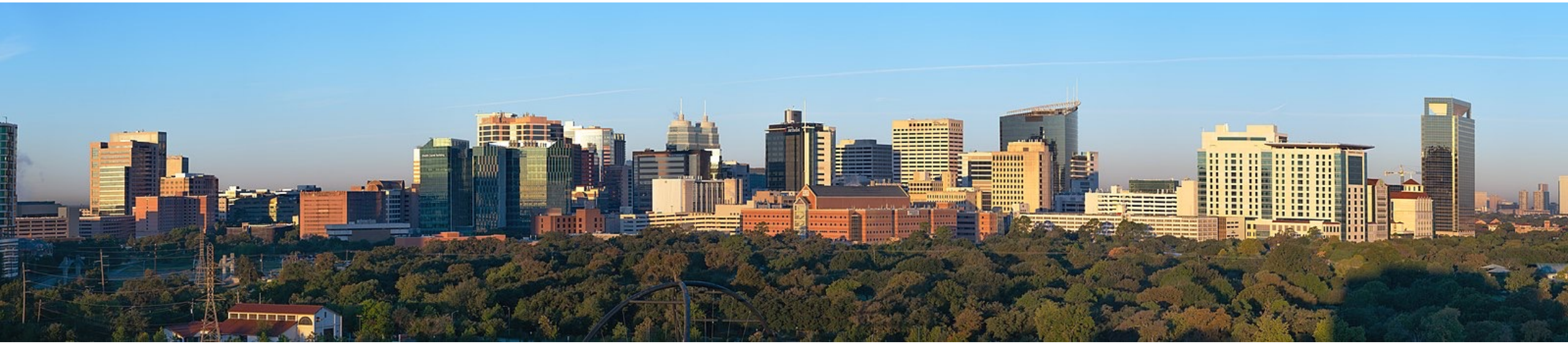


THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

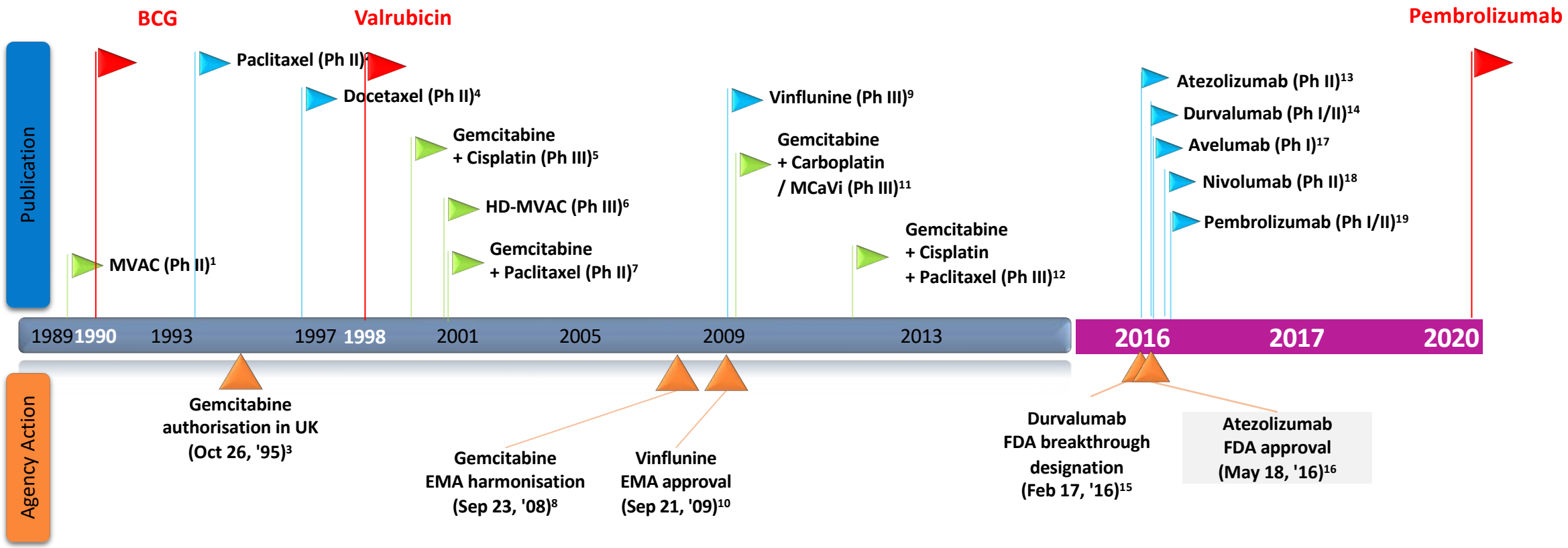
INTERNATIONAL BLADDER CANCER GROUP

Novel Agents and Strategies for Non-Muscle-Invasive Bladder Cancer (NMIBC)

Ashish M. Kamat, MD, MBBS

Professor of Urologic Oncology
Wayne B. Duddlesten Professor of Cancer Research
President, International Bladder Cancer Group (IBCG)
Co-President, International Bladder Cancer Network (IBCN)

Evolution of Therapy for Urothelial Cancer



[1]Sternberg CN, et al. *Cancer.* 1989; [2]Roth BJ, et al. *J Clin Oncol.* 1994; [3]Eli Lilly. SmPC Gemzar® 01-Jul-2014 (www.medicined.org.uk); [4]McCaffrey JA, et al. *J Clin Oncol.* 1997; [5]Von der Maase H, et al. *J Clin Oncol.* 2000; [6]Sternberg CN, et al. *J Clin Oncol.* 2001; [7]Meluch AA, et al. *J Clin Oncol.* 2001; [8]EMA. EMEA/CHMP/512295/2008; 24.09.2018 (www.ema.europa.eu); [9]Bellmunt J, et al. *J Clin Oncol.* 2009; [10]EMA. EMEA/H/C/000983; 2012 (www.ema.europa.eu); [11]De Santis M, et al. *J Clin Oncol.* 2009; [12]Bellmunt J, et al. *J Clin Oncol.* 2012; [13]Rosenberg JE, et al. *Lancet.* 2016; [14]Massard C et al. ASCO 2016: abstract #4502 and oral presentation; [15]AstraZeneca. Press Release 17.02.2016 (access: www.astrazeneca.com); [16]FDA. Press Release 18.05.2016 (access: www.fda.gov); [17]Apolo AB, et al. *J Clin Oncol.* 2016; [18]Galsky MD, et al. ESMO 2016: abstract #LBA31_PR; [19]Balar A, et al. *Ann Oncol.* 2016.

Valrubicin

- FDA approved in 1998 for BCG-refractory CIS in those who are not candidates for cystectomy

- CR at 6 months in 18% of patients

- **2-year DFS only 4%**

Steinberg et al, J Urol, 1998; Dinney et al, Urol Onc, 2013.

Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Arjun V Balar, Ashish M Kamat, Girish S Kulkarni, Edward M Uchio, Joost L Boormans, Mathieu Roumiguié, Laurence E M Krieger, Eric A Singer, Dean F Bajorin, Petros Grivas, Ho Kyung Seo, Hiroyuki Nishiyama, Badrinath R Konety, Haojie Li, Kijoeng Nam, Ekta Kapadia, Tara Frenkl, Ronald de Wit

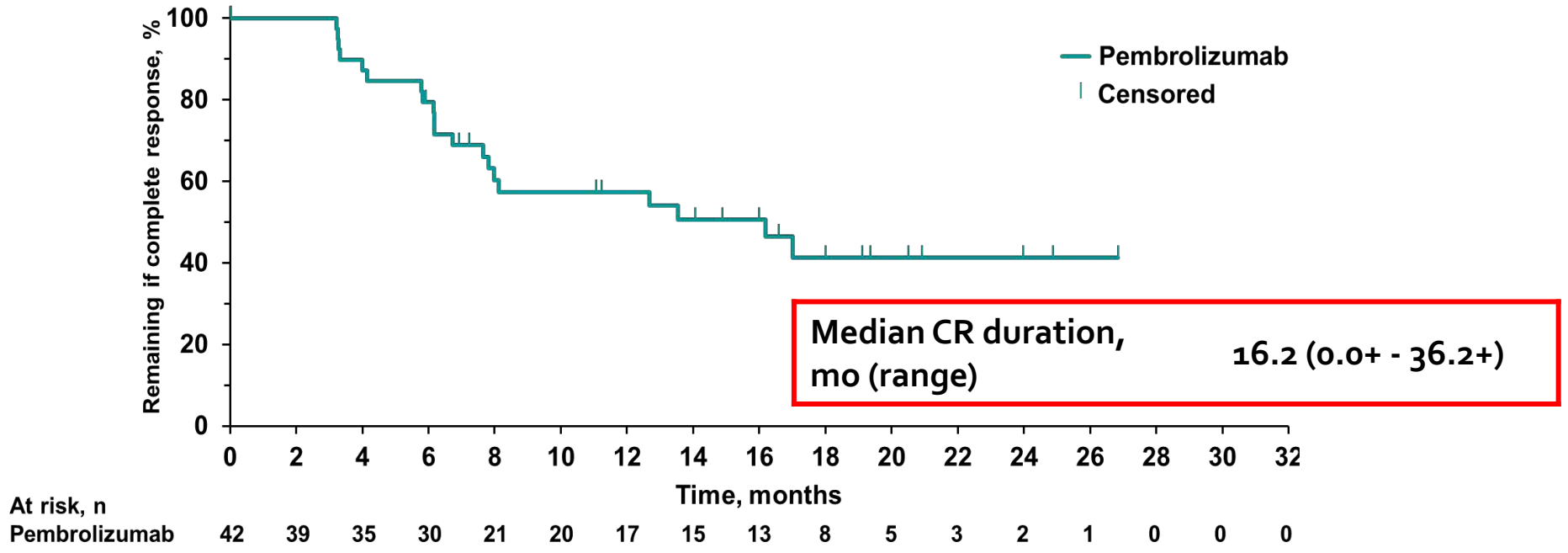
January 8, 2020

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

Lancet Oncology, May 25, 2021

KEYNOTE-057:
BCG Unresponsive CIS Patients Achieving CR with Pembrolizumab

	N=96	
Best response	**n (%)**	**95% CI**
CR	39 (40.6)	30.7, 51.1



CR, complete response. [a]1 month = 30.4367 days. [b]Month 0 = time point when initial CR was achieved.

Updated 2021

Key Baseline Characteristics KN057

Characteristic	N=96
Median age, years (range)	73 (44-92)
<65	30 (31.3)
≥65 to <75	24 (25.0)
≥75 to <85	33 (34.4)
≥85	9 (9.3)
Male, n (%)	81 (84.4)
Female, n (%)	15 (15.6)
Race, n (%)	
White	64 (66.7)
Asian	26 (27.1)
Missing	6 (6.3)
ECOG PS, n (%)	
0	70 (72.9)
1	26 (27.1)

Characteristic	N=97
Median prior BCG instillations, n (range)	12.0 (7.0-45.0)
Tumor pattern at study entry, n (%)	
CIS with T1	12 (12.5)
CIS with high-grade Ta	24 (25.0)
CIS alone	60 (62.5)
PD-L1 status, n (%)	
CPS ≥10	35 (36.5)
CPS <10	56 (58.3)
Not evaluable	5 (5.2)
Reason prior cystectomy not performed, n (%)	
Declined	91 (94.8)
Ineligible	5 (5.2)

Immune-mediated AEs

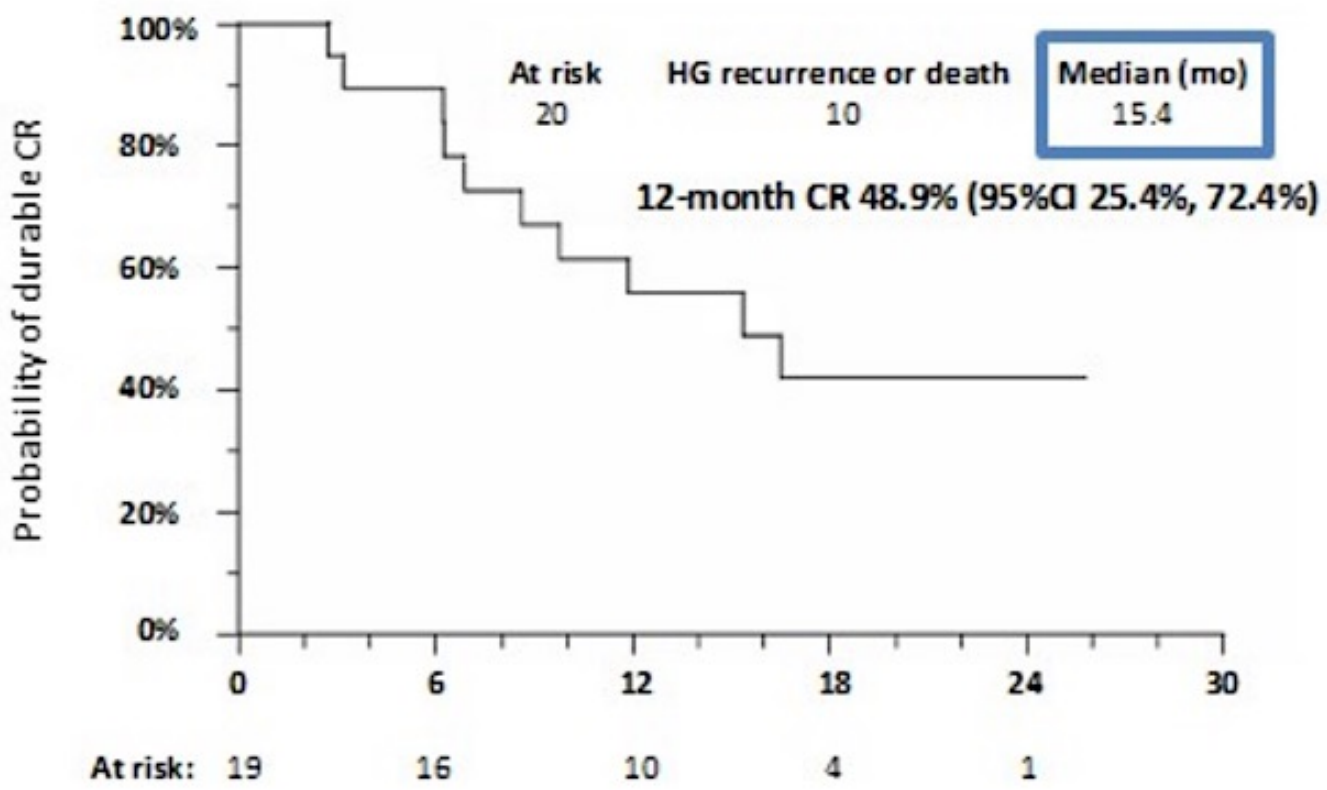
Any Grade and Corresponding Grade 3 or 4[a] Events

Incidence of any-grade immune-mediated AEs, n (%)	N=102
Any	21 (20.6)
Hypothyroidism	8 (7.8)
Hyperthyroidism	5 (4.9)
Pneumonitis	3 (2.9)
Hypophysitis	1 (1.0)
Colitis	1 (1.0)
Adrenal insufficiency	1 (1.0)
Nephritis	1 (1.0)
Severe skin reaction	1 (1.0)
Type 1 diabetes mellitus	1 (1.0)
Uveitis	1 (1.0)
Hepatitis	1 (1.0)

Incidence of grades 3 or 4 immune-mediated AEs, n (%)	N=102
Any	3 (2.9)
Hypothyroidism	0 (0.0)
Hyperthyroidism	0 (0.0)
Pneumonitis	0 (0.0)
Hypophysitis	0 (0.0)
Colitis	0 (0.0)
Adrenal insufficiency	1 (1.0)
Nephritis	0 (0.0)
Severe skin reaction	1 (1.0)
Type 1 diabetes mellitus	1 (1.0)
Uveitis	0 (0.0)
Hepatitis	0 (0.0)

From Balar et al, 2021

SWOG-S1605: Atezolizumab in BCG Unresponsive High Risk NMIBC

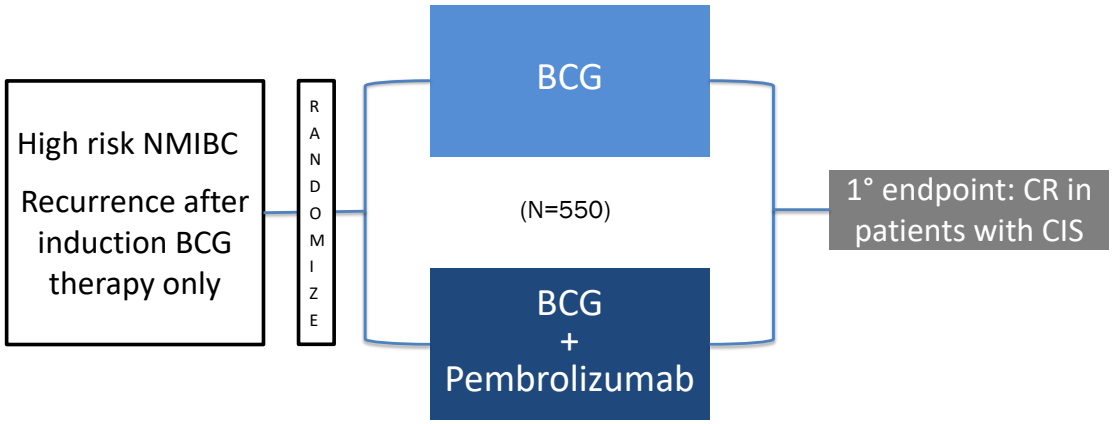


- CR rate at 6 mos: 27% (20/74 patients with CIS)
- KM estimate in patients with 6 month CR
  - 12 months = 48.9% (95% CI 25.4%, 72.4%)
  - 18 months = 17% (90% CI: 9%, 25%)
  - median duration of response was 15.4 months

PI: Black, Singh: ASCO 2021

What's next: Immune Checkpoint Inhibitors for Earlier NMIBC

BCG "Exposed"

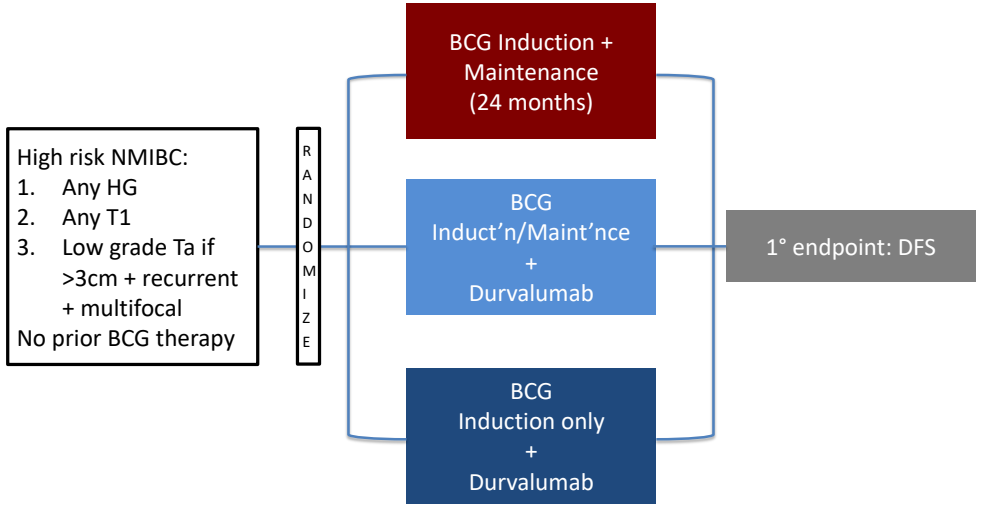


KEYNOTE-676

Similar Trials:

- Checkmate 7G8 with nivolumab
- ADAPT-Bladder durvalumab + RT

BCG Naïve



POTOMAC

Similar Trials:

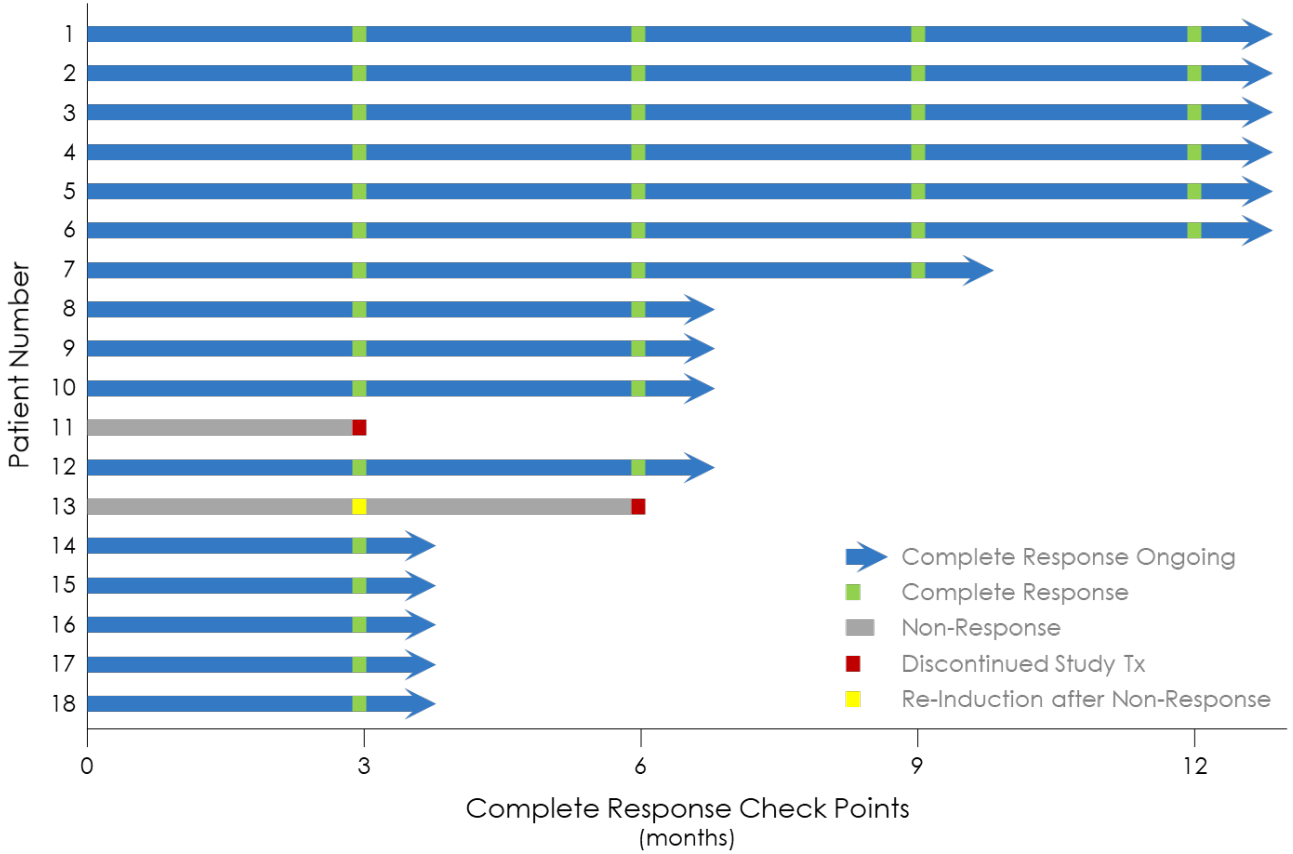
- ALBAN with atezolizumab
- CREST with sasanlimab (subq)

SITC Webinar, 101, Aug 2021 (Slide P. Black)

CORE1: CG0070 + Pembrolizumab Study

Preliminary Results of Combination Therapy in BCG-Unresponsive

Authors: Roger Li, Gary D. Steinberg, Ed Uchio, Paras Shah, Donald Lamm, Trinity Bivalacqua, Vignesh T. Packiam, Ashish M. Kamat, Michael Chisamore, John McAdory, Paola Grandi, Jee-Hyun Kim, and James Burke.



Overall CR Rate:
88.9% (16/18)

CR at 12 Months:
75% (6/8)

Safety profile: consistent with single agent experience for both agents

Primary data readout: 3 mos data all 35 patients August 2022, 12 month May 2023

Nadofaragene Firadenovec: Phase 3, Multi-Center, Open-Label Study

	Carcinoma in situ cohort (n=103)	High-grade Ta or T1 cohort (n=48)	All patients (n=151)
Patients with complete response at month 3*	55 (53·4%; 43·3–63·3)	35 (72·9%; 58·2–84·7)	90 (59·6%; 51·3–67·5)
Duration of complete response† or high-grade recurrence-free survival‡, months	9·69 (9·17–NE)	12·35 (6·67–NE)	7·31 (5·68–11·93)
Patients who were free from high-grade recurrence			
Month 6	42 (40·8%; 31·2–50·9)	30 (62·5%; 47·4–76·0)	72 (47·7%; 39·5–56·0)
Month 9	36 (35·0%; 25·8–45·0)	28 (58·3%; 43·2–72·4)	64 (42·4%; 34·4–50·7)
Month 12	25 (24·3%; 16·4–33·7)	21 (43·8%; 29·5–58·8)	46 (30·5%; 23·2–38·5)

Median duration of HG-RFS was 12.35 months (95% CI: 6.67, NE) in patients with papillary disease
Progression to ≥ MIBC in 8 (5.3%) patients

Boorjian SA, Lancet Oncology, 2021

Nadofaragene Firadenovec

The most common TEAEs were

- instillation site discharge (33.1%),
- fatigue (23.6%),
- bladder spasm (19.7%),
- micturition urgency (17.8%), and
- hematuria (16.6%)

	Grade 1–2	Grade 3	Grade 4–5
Patients with study drug-related adverse events*	103 (66%)	6 (4%)	0
Types of events			
Discharge around the catheter during instillation	39 (25%)	0	0
Fatigue	31 (20%)	0	0
Bladder spasm	24 (15%)	1 (1%)	0
Micturition urgency	22 (14%)	2 (1%)	0
Chills	18 (12%)	0	0
Dysuria	17 (11%)	0	0
Pyrexia	16 (10%)	0	0
Syncope	0	1 (1%)	0
Hypertension	2 (1%)	1 (1%)	0
Urinary incontinence	4 (3%)	1 (1%)	0

Boorjan SA, Lancet Oncology, 2021

QUILT 3.032: N-803 (IL-15 Superagonist Fusion Protein) + BCG
N=81, 58 patients (72%0 with biopsy confirmed CR at 3 or 6 mos

Median Follow Up

20.4 Months

As of May 19, 2021

Median Duration of CR in All Responders

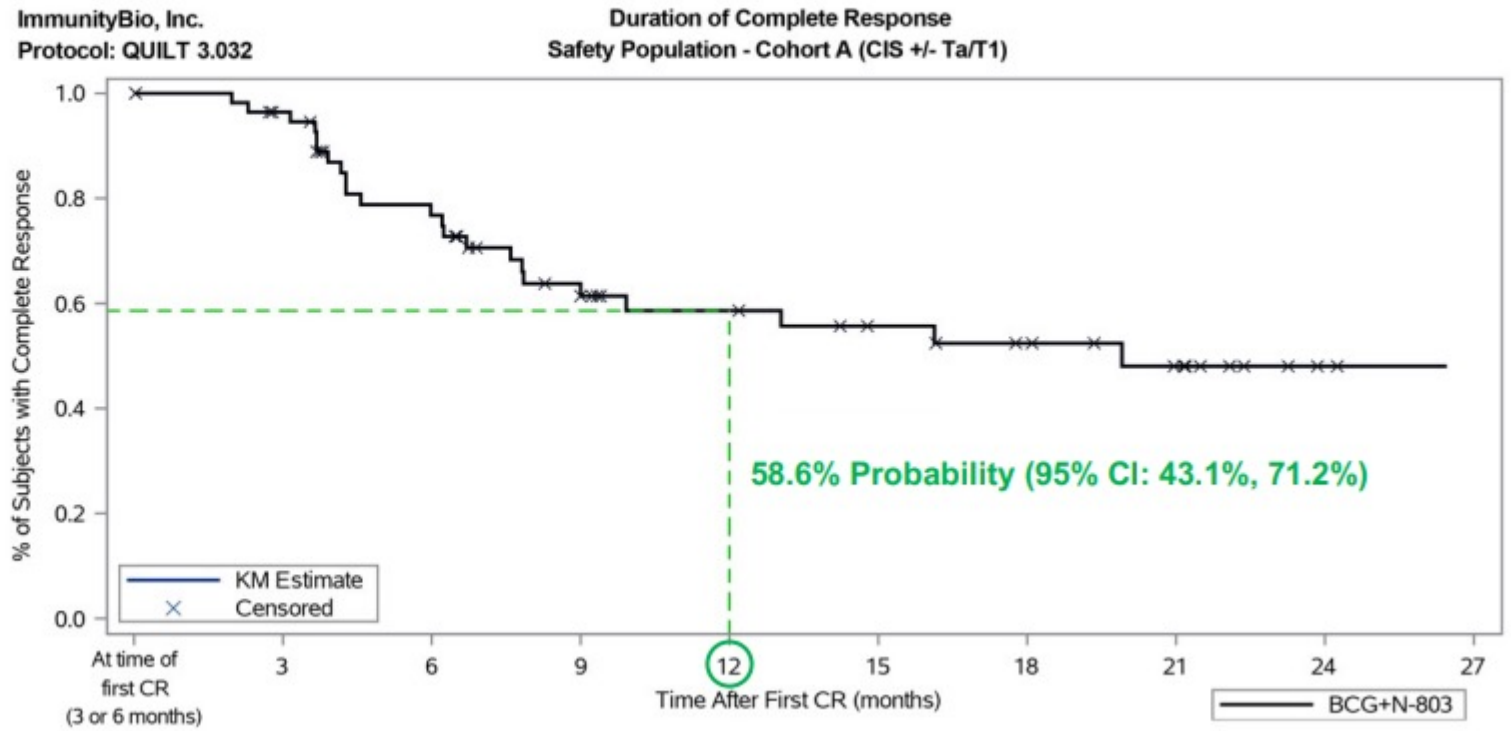
19.9 Months*

95% CI (7.8, Not Reached)

*Kaplan-Meier Estimate

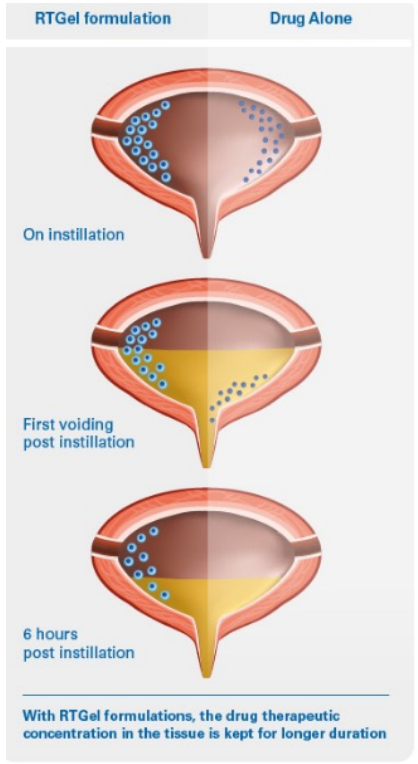
Data cutoff May 19, 2021

58.6% Probability (95% CI: 43.1%, 71.2%) of Duration of CR Greater than 12 Months

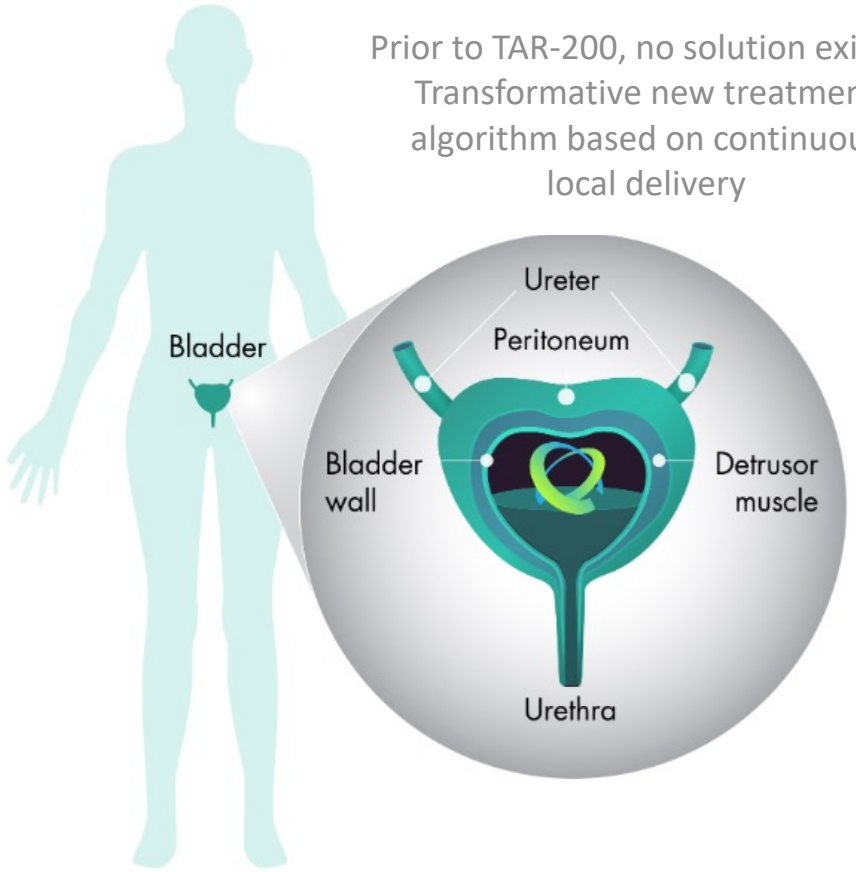


Chamie, AUA 2021

TAR-200



Prior to TAR-200, no solution existed
Transformative new treatment algorithm based on continuous local delivery



Phase 2b – TAR-200 + Cetrelimab NMIBC BCG Un-responsive [BLC2001]

SunRISe-1

Key Eligibility Criteria

- BCG Unresponsive Carcinoma In Situ [CIS]
- Patients Ineligible for or Refusing Radical Cystectomy

Stratification

- Presence or absence of concomitant papillary disease

Randomization [2:1:1; N~200]

COHORT 1 [N~100] → **TAR-200** [225 mg Gemcitabine] Q3W [24 wks.], Quarterly → 2 years **+ CETRELIMAB** 18 Months

COHORT 2 [N~50] → **TAR-200 Alone** [225 mg Gemcitabine] 2 years

COHORT 3 [N~50] → **CETRELIMAB Alone** for 18 Months

Primary Endpoint

- Complete Response [CR] Rate in CIS patients at any time point
  - Assessment via Cystoscopy, Urine Cytology, and Bladder Biopsy

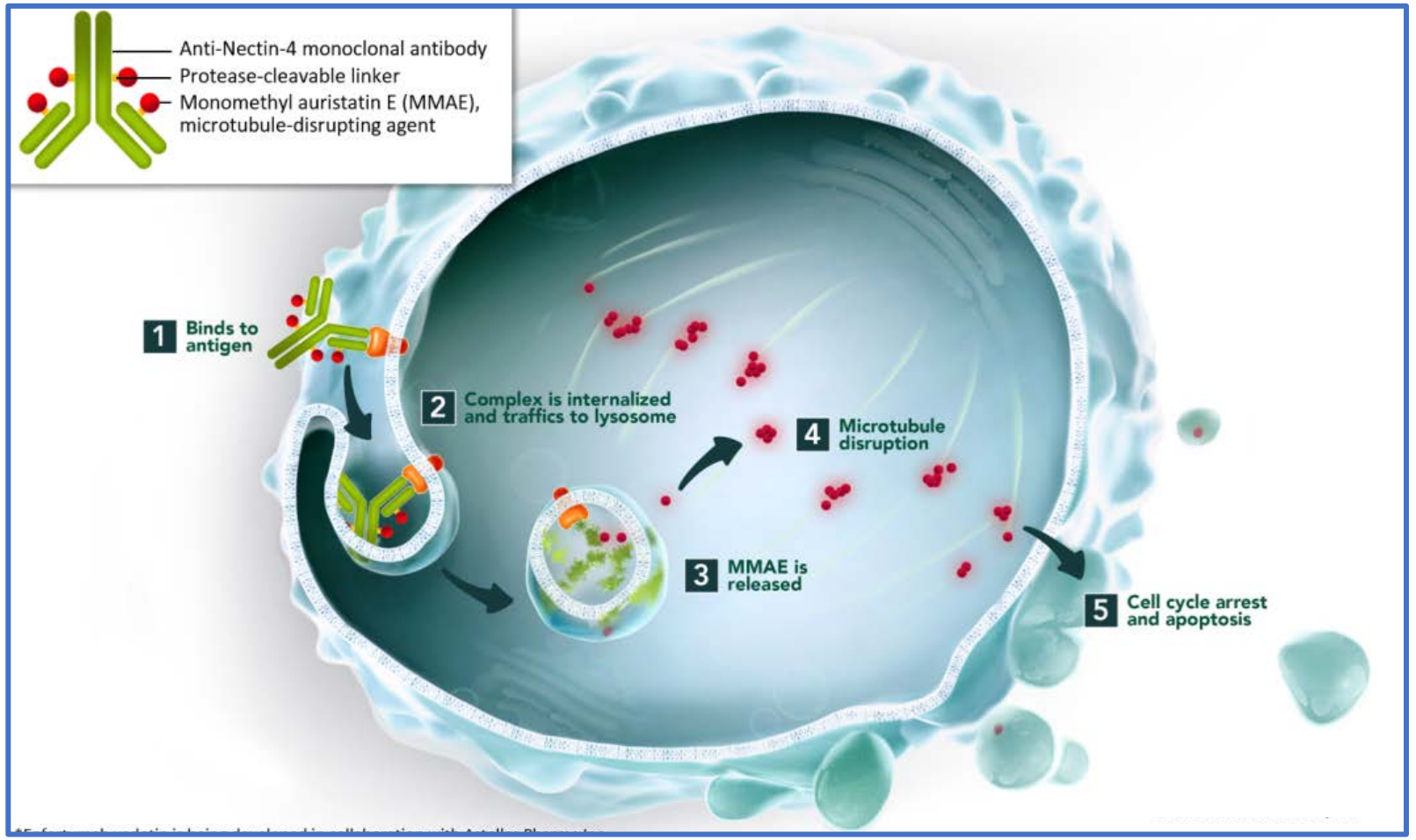
Secondary Endpoints

- Durability of CR at 12 months from Achievement of CR
- Overall Survival [OS] measured as time from cohort assignment to death

Enfortumab Vedotin: Proposed MOA and Target

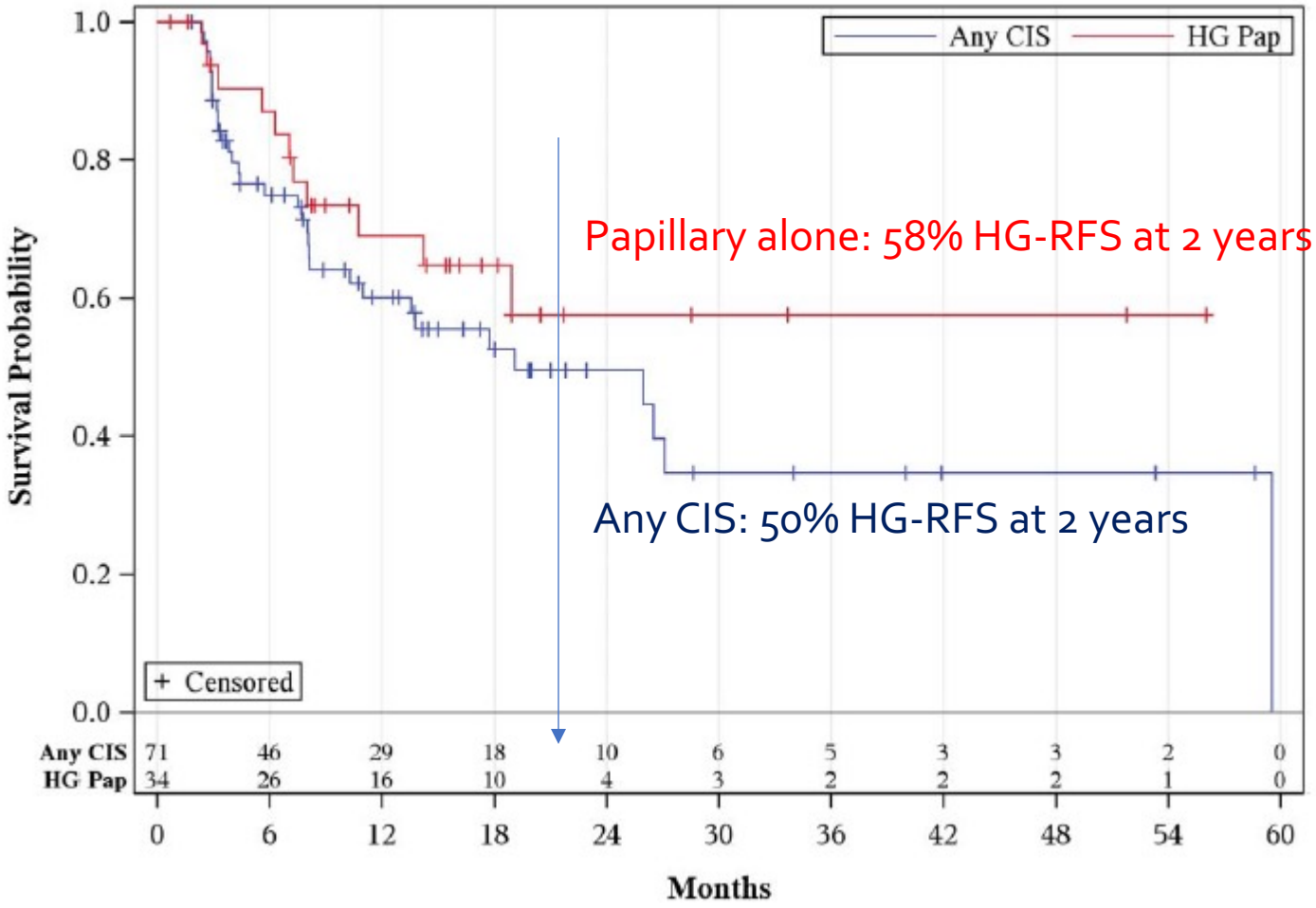
Nectin – 4

- Transmembrane adhesion molecule expressed on skin, urothelium, salivary gland ducts, breast, stomach, esophagus
- Expressed in 83% of UC TMA samples



Multi-Institution Evaluation of Sequential Gemcitabine and Docetaxel as Rescue Therapy for Nonmuscle Invasive Bladder Cancer

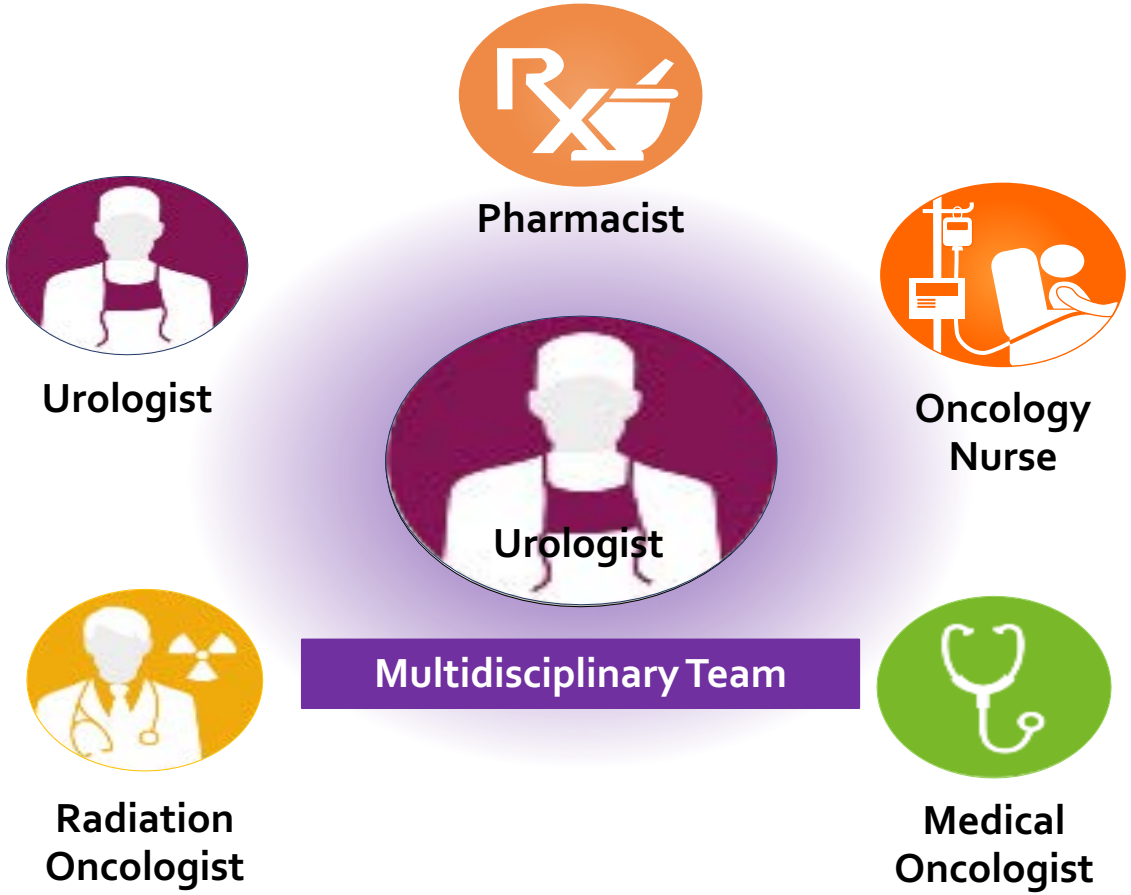
- 276 patients
- **HG RFS: 65% and 52%, at 1 and 2 yr**
- RFS: 60% and 46%, at 1 and 2 yr
- Cystectomy: 15.6%
- 4.0% progression to muscle invasion



High grade bladder recurrence-free survival for **BCG unresponsive cases**

Steinberg, Kamat, O'Donnell et al, J Urol, May 2020

Optimal Management of Bladder Cancer Requires a Multidisciplinary Approach



"Providing the best management for patients with bladder neoplasia relies on close cooperation and teamwork among urologists, oncologists, radiologists, and pathologists"

—2nd International Consultation on Bladder Cancer

"Multidisciplinary input via tumor board discussions and/or directed consultations is critical to the optimal management of patients with bladder cancer"

—ASCO Clinical Practice Guideline Endorsement

Amin MB, et al. *Eur Urol*. 2013; Milowsky MI, et al. *J Clin Oncol*. 2016

MODULE 2: Novel Therapeutic Approaches for Muscle-Invasive Bladder Cancer

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In the past month, approximately how many patients did you see whose primary diagnosis was NMIBC?

1. 0
2. 1
3. 2-5
4. More than 5

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Dr Jason Hafron
West Bloomfield, Michigan

Administration and tolerability of TAR-200

Dr Jason Hafron
West Bloomfield, Michigan

A 76-year-old man with T2 muscle-invasive bladder cancer (MIBC) who discontinues neoadjuvant gemcitabine/cisplatin after acute renal failure

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Regulatory and reimbursement issues aside, would you generally include a checkpoint inhibitor in the initial management of a 66-year-old man with muscle-invasive bladder cancer (MIBC) who is not a candidate for bladder resection due to cardiovascular issues?

1. Yes
2. No

Dr Paul Markowski
Summit, New Jersey

A 66-year-old man with MIBC, PD-L1 >1% and an extensive history of cardiac disease

Dr David Morris
Nashville, Tennessee

A 62-year-old man with high-grade, cT3 FGFR3-positive MIBC

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NOVEL THERAPEUTIC APPROACHES FOR MUSCLE-INVASIVE BLADDER CANCER (MIBC)

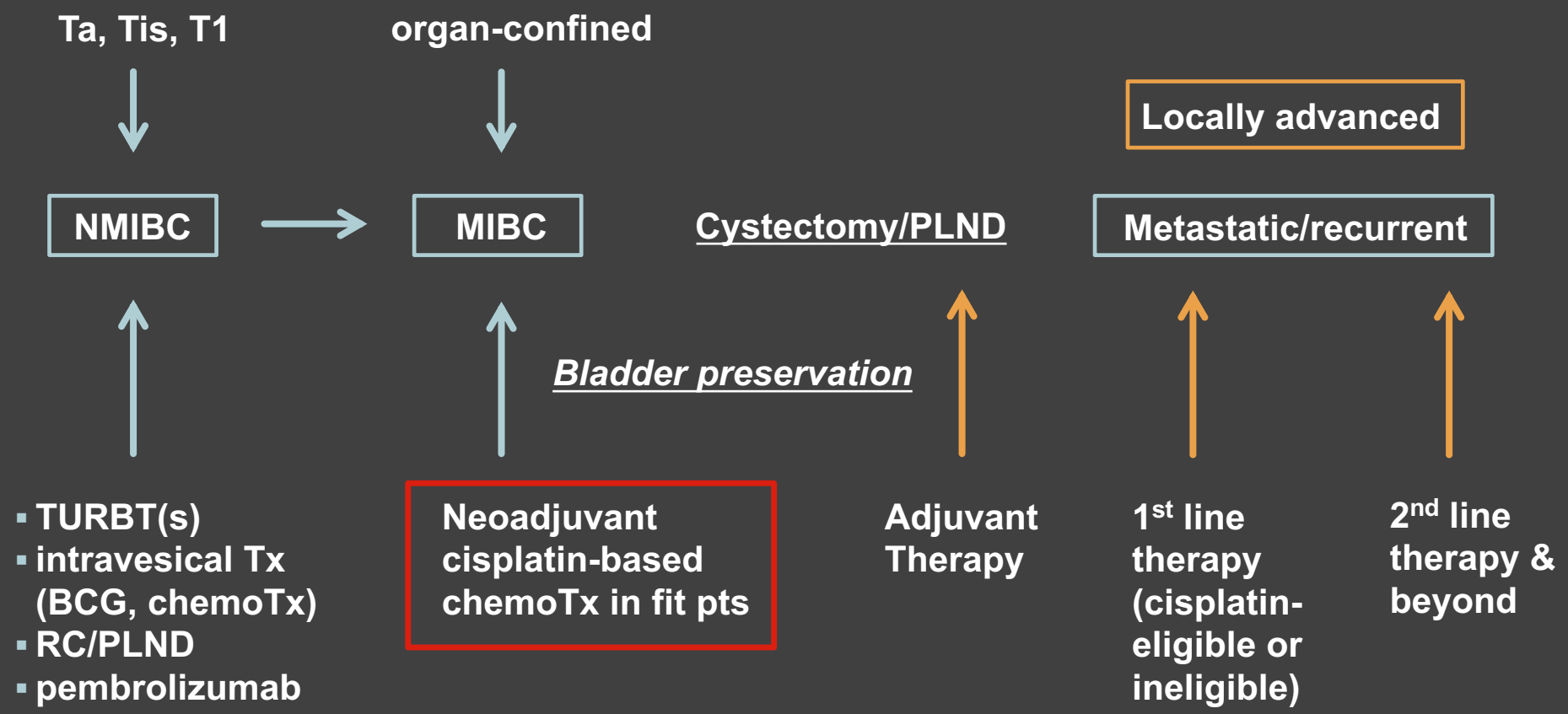
Stephen B. Williams, MD, MBA, MS, FACS

Medical Director for High Value Care, UTMB Health System

Professor (Tenured)
Chief, Division of Urology
The Robert Earl Cone Professorship in Urology
Director of Urologic Oncology
Director of Urologic Research
Co-Director, Surgical Outcomes Research Program
The University of Texas Medical Branch in Galveston, TX

utmb Health

DISEASE / TREATMENT SETTINGS



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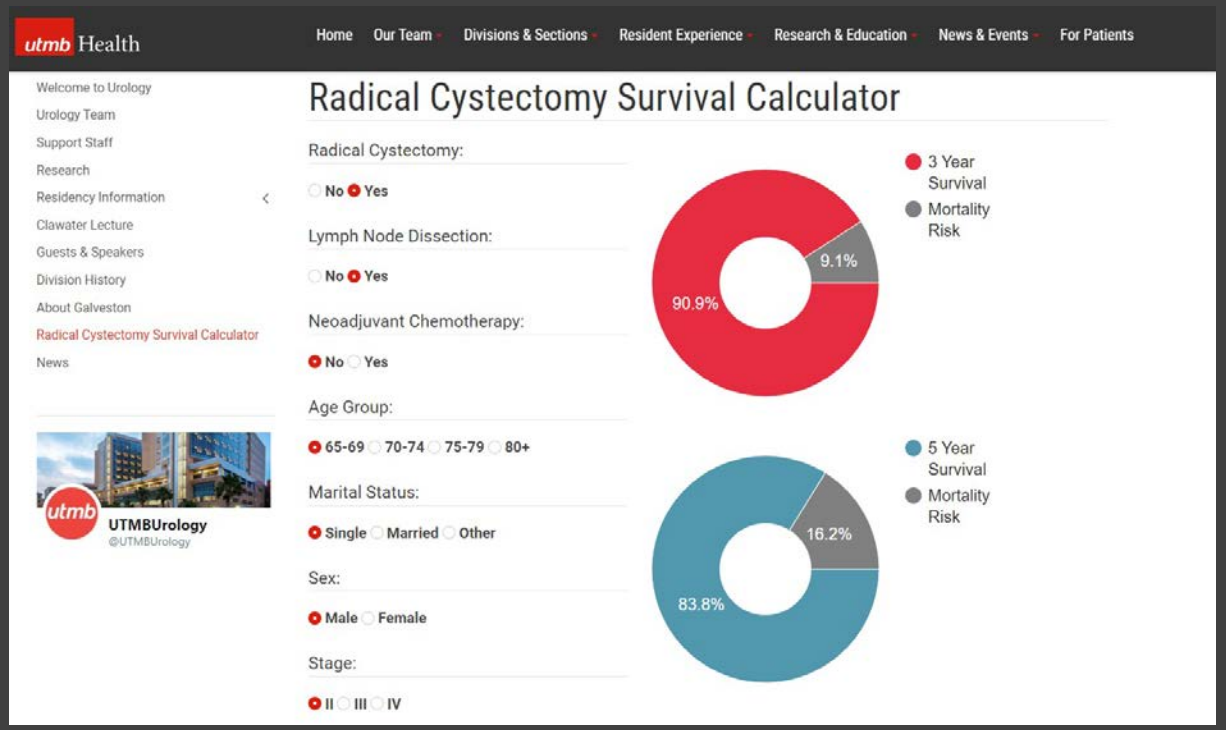
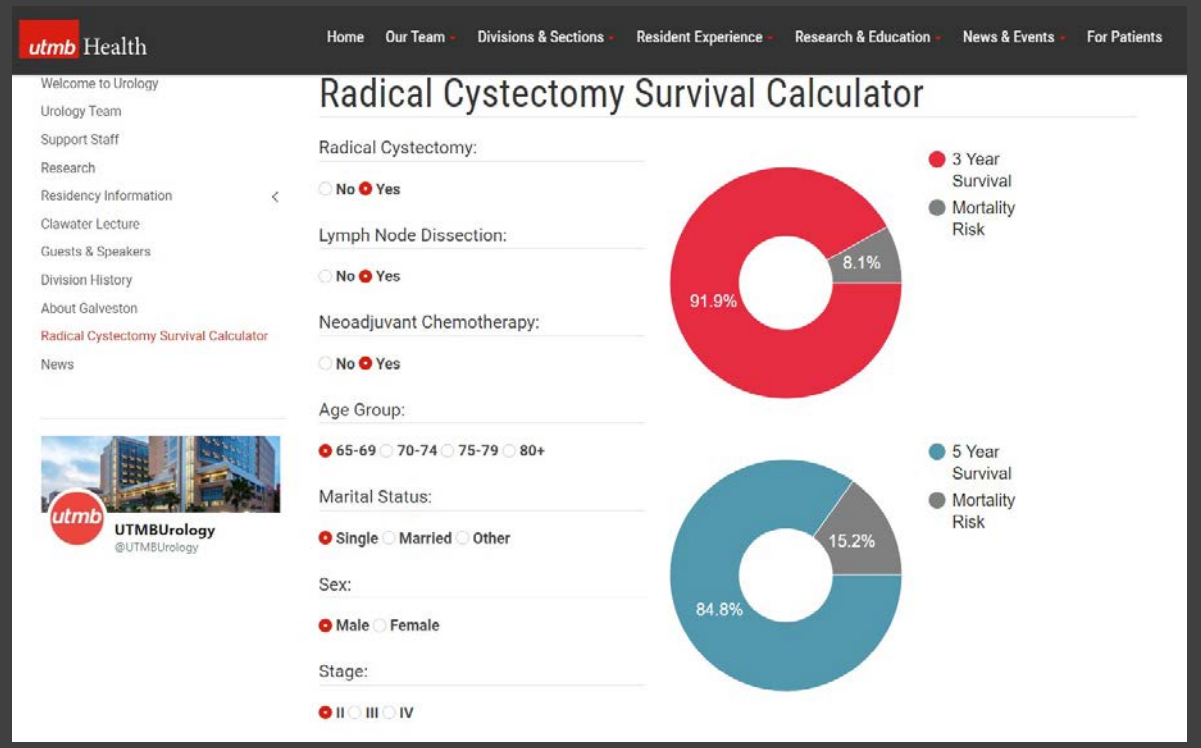
NAC: NEED TO MOVE THE NEEDLE…





https://www.utmb.edu/surgery/divisions-and-sections/urology/radical-cystectomy-survival-calculator

Williams SB et al. Urology. 2017 Dec;110:76-83

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Advantages of neoadjuvant systemic therapy

- Neoadjuvant cisplatin-based chemotherapy improves OS.
- Often better tolerated.
- Potential for maximizing impact on patient outcomes by administering drug at the earliest point in the natural history of the disease.
- Tissue availability from TURBT and RC offers opportunities to study biomarkers of response in clinical trials.
- Surrogate endpoints of responsiveness to therapy (pCR) enable early risk-stratification to select patients who could benefit from additional therapy.

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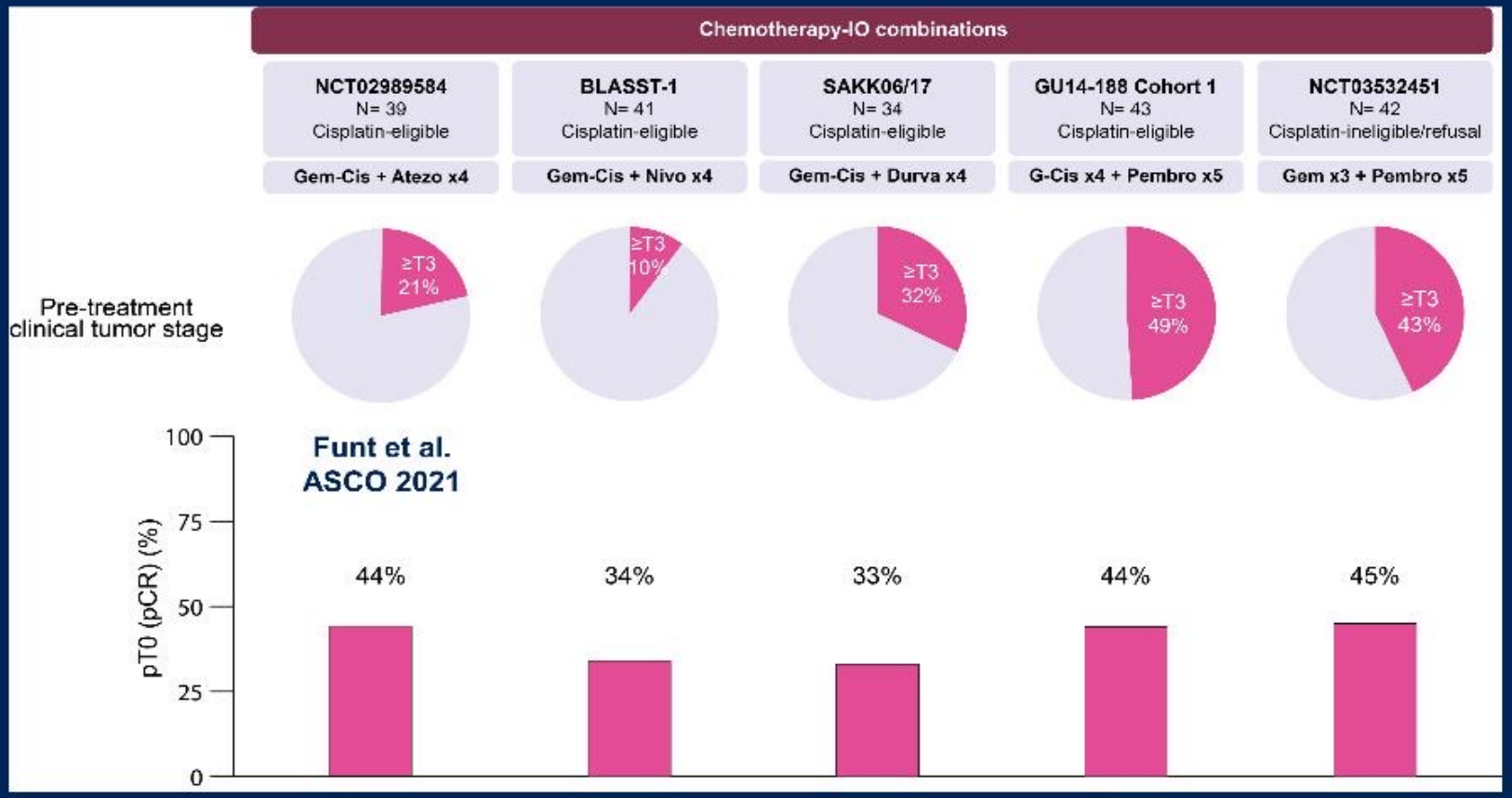
IO-chemotherapy neoadjuvant combinations for MIBC



Presented By: **Bishoy M. Faltas MD**

Figure adapted from:
Rey-C´ardenas et al. Cancer Treatment Reviews, 2021.
Rouanne et al. European Urology Oncology, 2020

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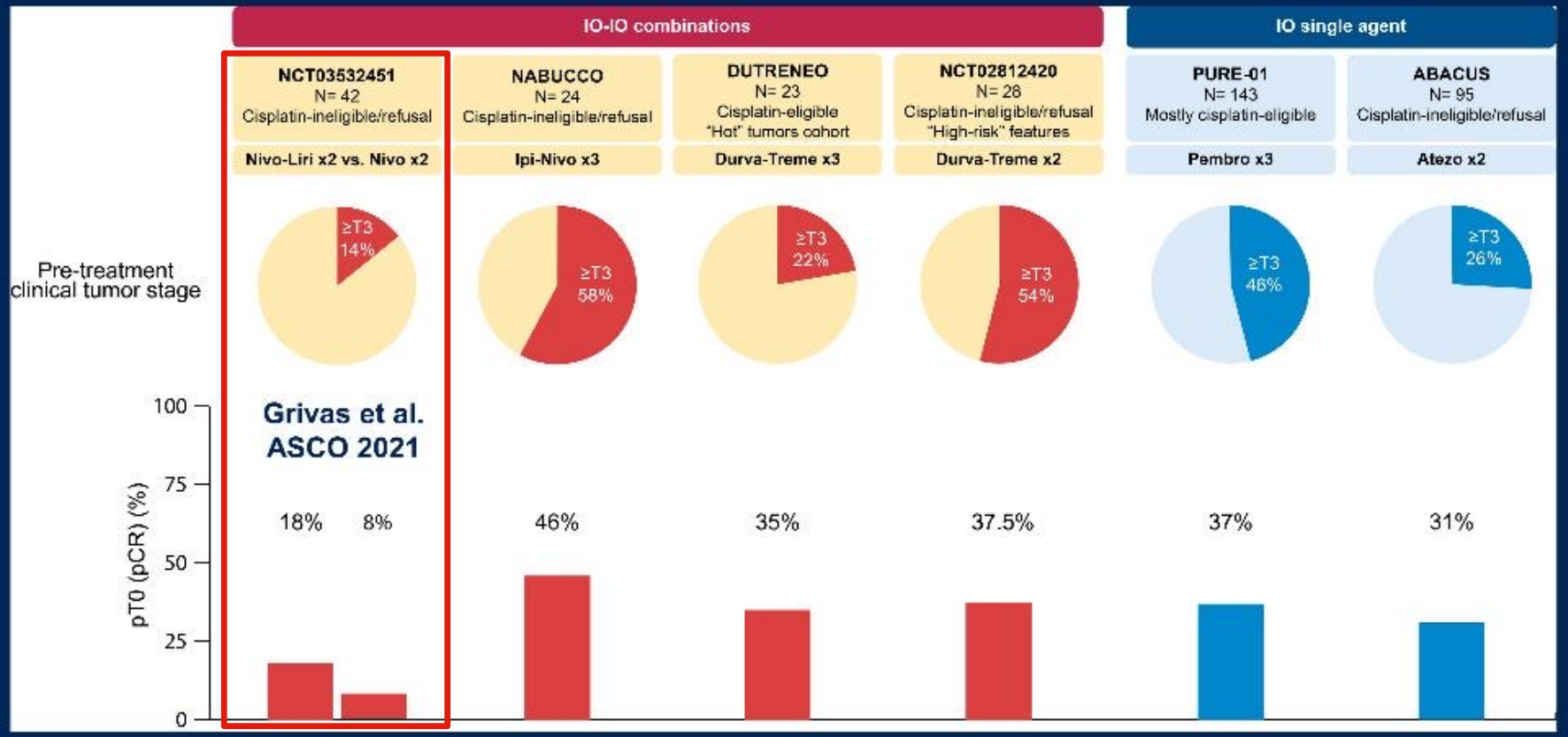
Neoadjuvant IO single agent and combinations for MIBC



Presented By: **Bishoy M. Faltas MD**

Figure adapted from:
Rey-C´ardenas et al. Cancer Treatment Reviews, 2021.
Rouanne et al. European Urology Oncology, 2020

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Phase 2 studies exploring neoadjuvant IO

	PURE-01	ABACUS	NABUCCO			DUTRE NEO	MDACC	PrE0807	MSKCC	
	Pembro	Atezo	Ipi > Ipi/Nivo > Nivo	Ipi3-Nivo1	Ipi1-Nivo3	Durva + Treme	Durva + Treme	Nivo+ Liri	Nivo3	Ipi3-Nivo1
N	143	88	24	15	15	23	28	30	15	15
cT2	49%	73%	0	0	0	78%	43%	87%	54%	46%
cN1-3	0	0	42%	47%	53%	9%	0	3%	0	0
pT0N0	39%	31%	46%	43%	7%	35%	38%	18%	13%	7%
p≤T1	56%		58%	57%	29%	57%	58%	29%	26%	20%
1-yr RFS	87%	79%	92%	NA	NA	NA	83%	NA	77%	68%

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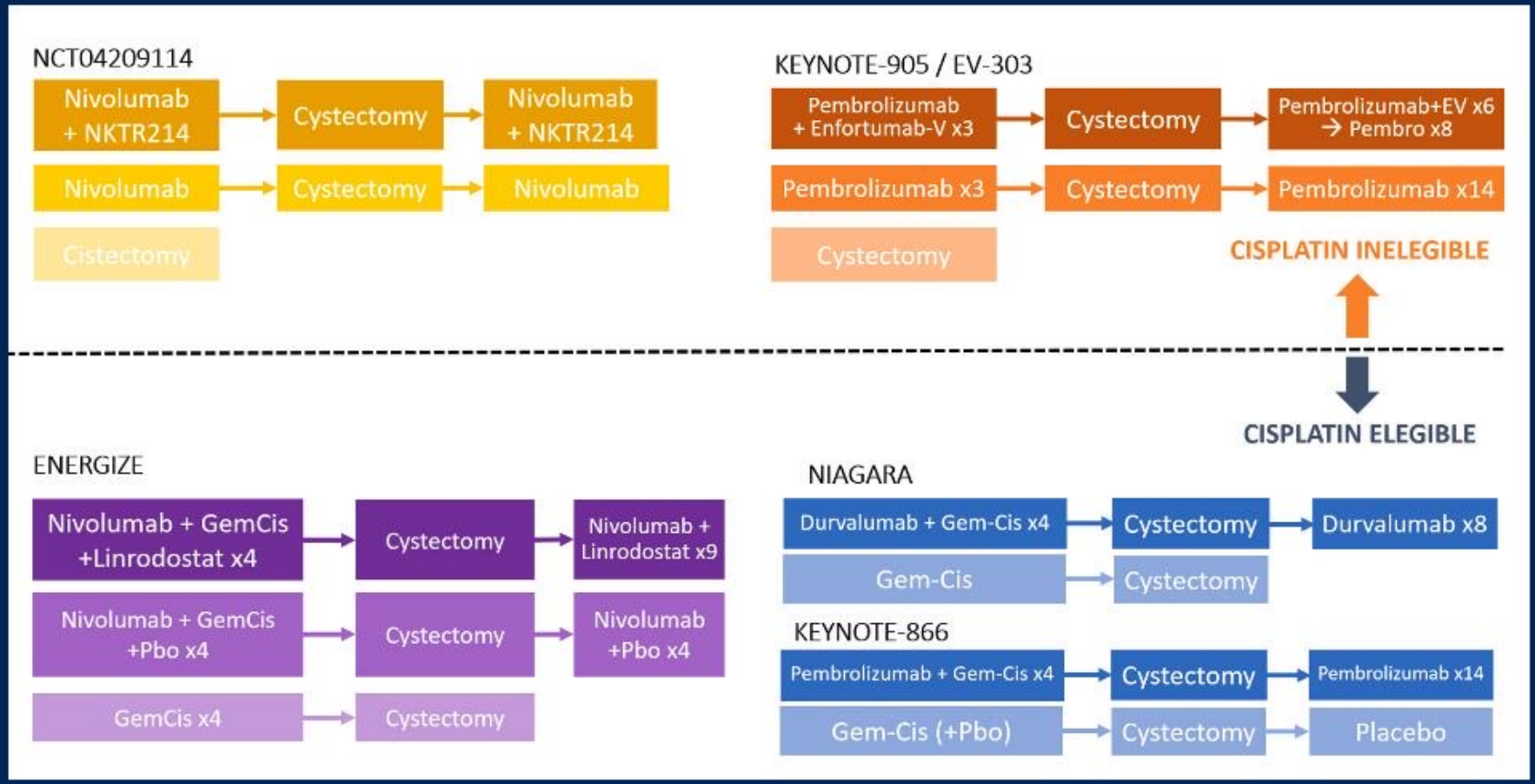
Bandini et al, Ann Oncol, 2020; Powles, Nat Med, 2019; van Dijk, Nat Med, 2019; Van Dorp, Ann Oncol, 2021; Grande, ASCO, 2020; Gao, Nat Med, 2020; Grivas, ASCO, 2021; Guercio, ASCO GU 2022 (Slide use permission: Matt Galsky)

Phase III neoadjuvant IO trials



Presented By: **Bishoy M. Faltas MD**

Rey-C´ardenas et al. Cancer Treatment Reviews, 2021.

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3 trials integrating IO into neoadjuvant regimens

Cisplatin Ineligible			
• Pembrolizumab → Cyst* • Pembro + Enfortumab vedotin → Cyst*	Cyst	T2-4aN0M0	KEYNOTE-905/EV-303 NCT03924895
• Nivolumab → Cyst* • Nivolumab + NKTR-214 → Cyst*	Cyst	T2-4aN0M0	NCT04209114
Cisplatin Eligible			
• Gem/Cis + pembrolizumab → Cyst*	Gem/Cis → Cyst	T2-4aN0M0	KEYNOTE-866 NCT03924856
• Gem/Cis + durvalumab → Cyst*	Gem/Cis → Cyst	T2-4aN0M0	NIAGARA NCT03732677
• Gem/Cis + nivolumab → Cyst* • Gem/Cis + nivolumab ± BMS-986205 → Cyst*	Gem/Cis → Cyst	T2-4aN0M0	ENERGIZE NCT03661320
• Pembro + Enfortumab vedotin → Cyst*	Gem/Cis → Cyst	T2-4aN0M0	KEYNOTE-B15 NCT03661320

*regimen continued in the adjuvant setting

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Key unanswered questions for perioperative immunotherapy

- What is optimal schedule, duration and time to cystectomy with these regimens?
- What are the most accurate surrogate clinical endpoints to predict OS?
- Are IO + chemo , IO + IO , IO + ADCs more effective than single agents in RCTs?
- Can we select patients who will likely benefit from neoadjuvant IO based on a biomarker?
- What is the best sequence of neoadjuvant, adjuvant and maintenance lines of therapy?

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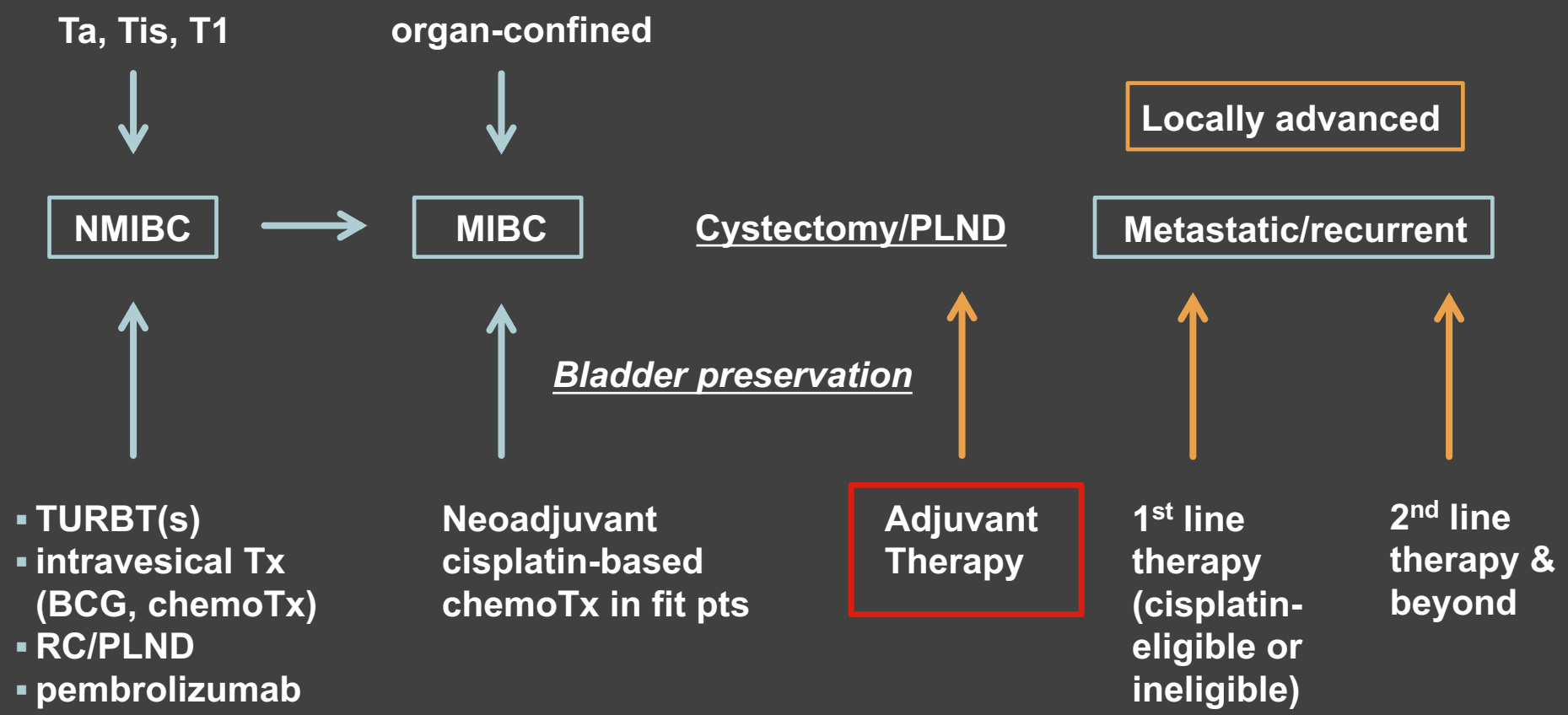
DISEASE / TREATMENT SETTINGS



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VOLUME 34 · NUMBER 8 · MARCH 10, 2016

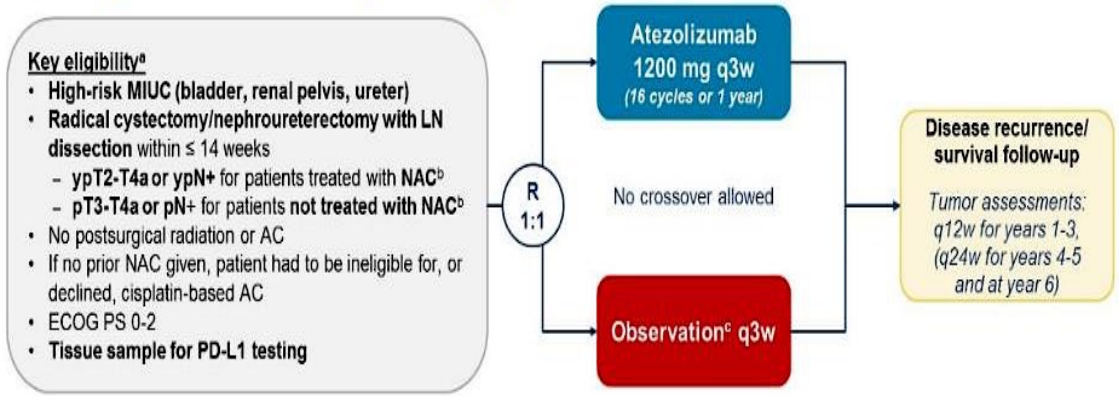
JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Adjuvant Chemotherapy for Bladder Cancer: Using Population-Based Data to Fill a Void of Prospective Evidence

Sumanta K. Pal, *City of Hope Comprehensive Cancer Center, Duarte, CA*
Neeraj Agarwal, *Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*
Petros Grivas, *Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*
Toni Choueiri, *Dana-Farber Cancer Institute, Boston, MA*

IMvigor010 Study Design



AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b] Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c] Alternating clinic visits and phone calls.

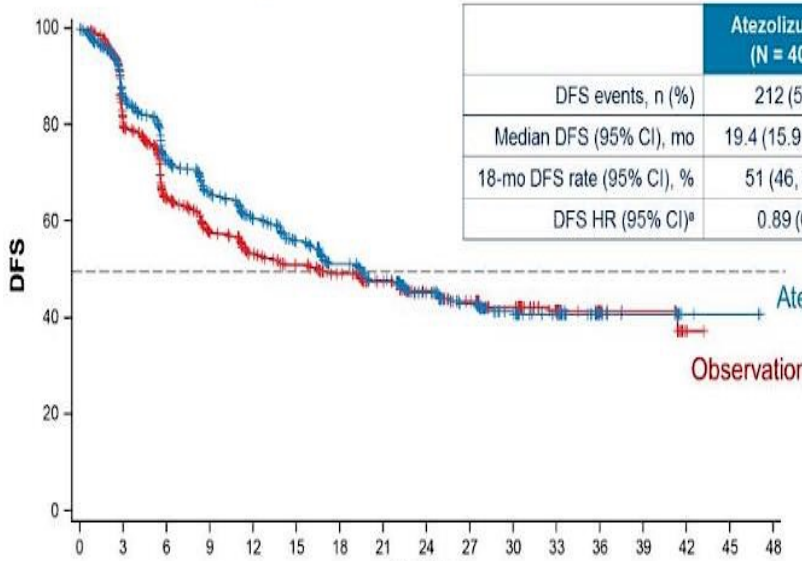
Baseline Characteristics

	Atezolizumab (N = 406)	Observation (N = 403)
Median age, years (range)	67 (31-86)	66 (22-88)
Male, n (%)	**322 (79)**	**316 (78)**
ECOG PS, n (%)		
0	248 (61)	259 (64)
1	142 (35)	130 (32)
2	16 (4)	14 (4)
Primary tumor site, n (%)		
Bladder	**377 (93)**	**378 (94)**
Upper tract (ureter, renal pelvis)	29 (7)	25 (6)
Prior neoadjuvant chemotherapy, n (%)[a]	**196 (48)**	**189 (47)**
Pathologic tumor stage, n (%)[b]		
pT2N0	34 (8)	39 (10)
pT3N0	**124 (31)**	**119 (30)**
pT4N0	**32 (8)**	**33 (8)**
≤pT2-4 and pN+, n (%)[a]	**212 (52)**	**208 (52)**
PD-L1 IHC status, n (%)[c]		
IC0	57 (14)	66 (16)
IC1	152 (37)	138 (34)
IC2	147 (36)	144 (36)
IC3	50 (12)	55 (14)

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Per interactive voice/web response system (IxRS). [b] Per electronic case report form (eCRF). [c] Archival and/or fresh pre-treatment FFPE tumor tissue from all patients (surgical resection or lymph node dissection) were prospectively tested for PD-L1 status per a central laboratory and used as a stratification factor; 119 patients were enrolled using IC2/3 selection, and 690 patients were enrolled under an "all-comer" protocol.

PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Hussain M. IMvigor010 primary analysis [abs 5000]. https://bit.ly/2SKSAD3

DFS in ITT Population

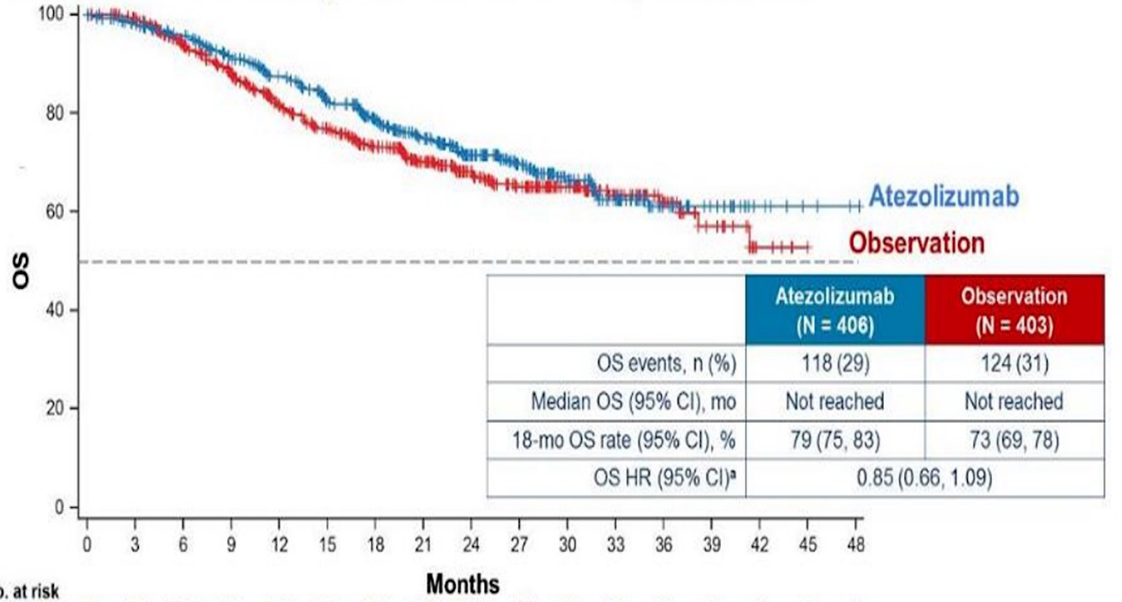


	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

No. at risk																
Atezolizumab	406	332	281	248	223	201	169	142	115	92	67	52	15	10	3	2
Observation	403	305	240	211	188	177	156	131	109	87	67	42	17	12	2	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

Interim OS Analysis in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

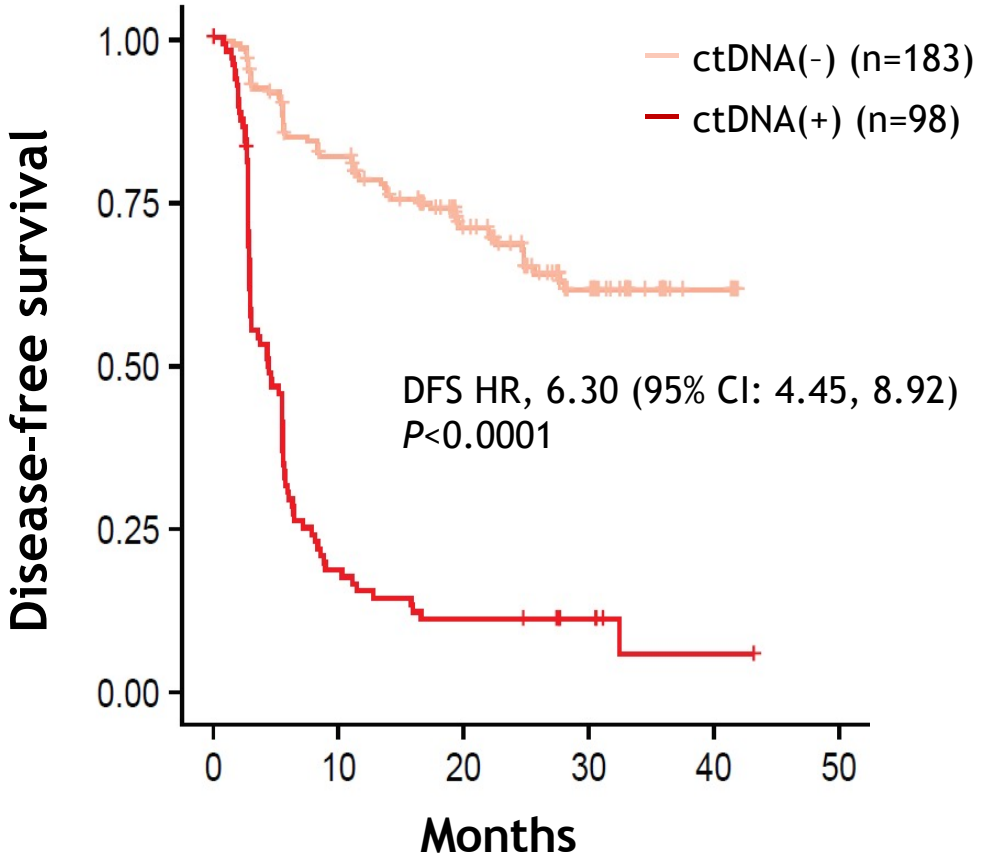
No. at risk																
Atezolizumab	406	383	369	350	328	306	267	229	185	144	100	72	35	22	8	4	2
Observation	403	377	345	318	289	270	235	199	163	134	100	65	36	20	6	1	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%). [a] OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

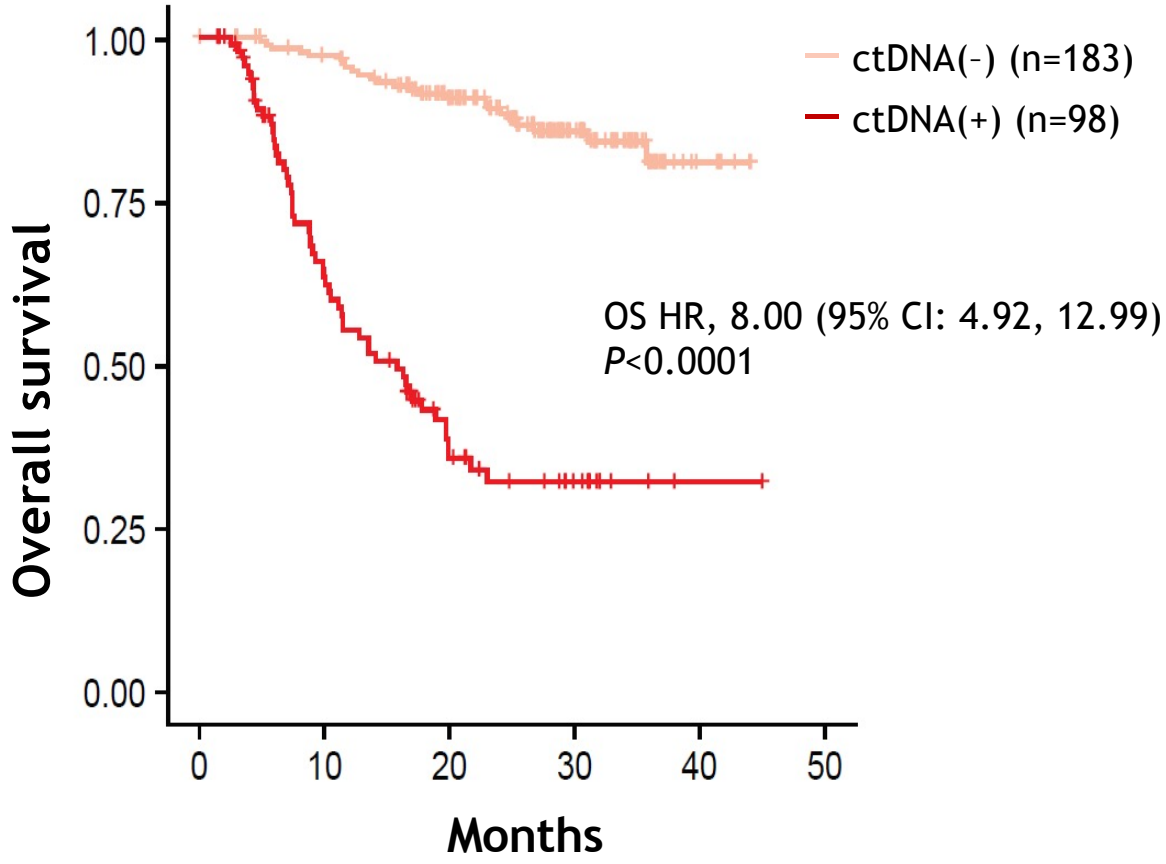
PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Hussain M. IMvigor010 primary analysis [abs 5000]. https://bit.ly/2SKSAD3

CTDNA(+) PORTENDS POOR PROGNOSIS

Observation arm



Observation arm



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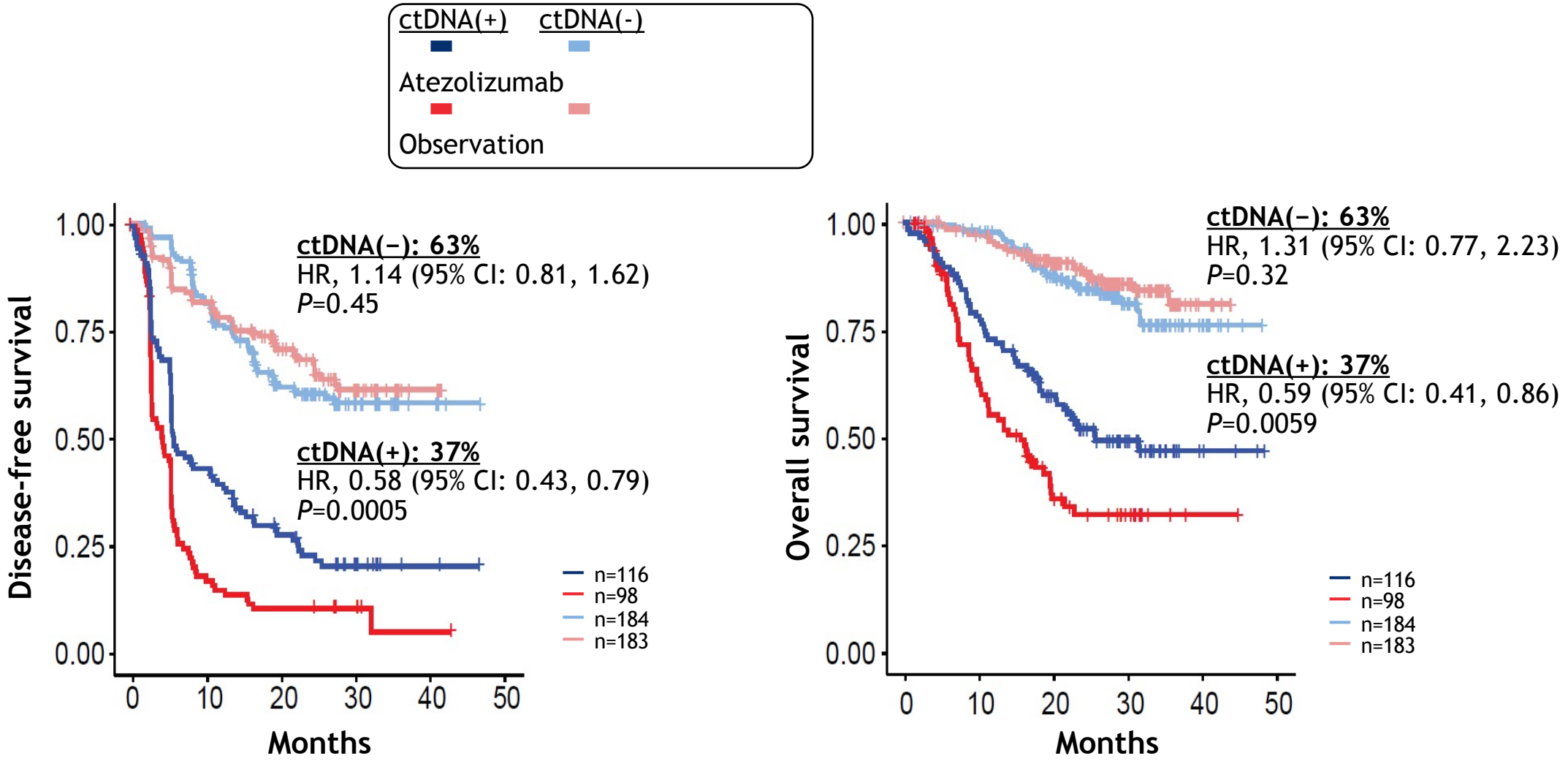
IMvigor010 confirmed the prognostic value of ctDNA status

Powles et al. ESMO IO, 2020

Powles et al. Nature, 2021

CTDNA(+) ASSOCIATED WITH IMPROVED DFS AND OS WITH ATEZOLIZUMAB VS OBSERVATION



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Powles et al. ESMO IO, 2020

Powles et al. Nature, 2021

Study design

- CheckMate 274 is a phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

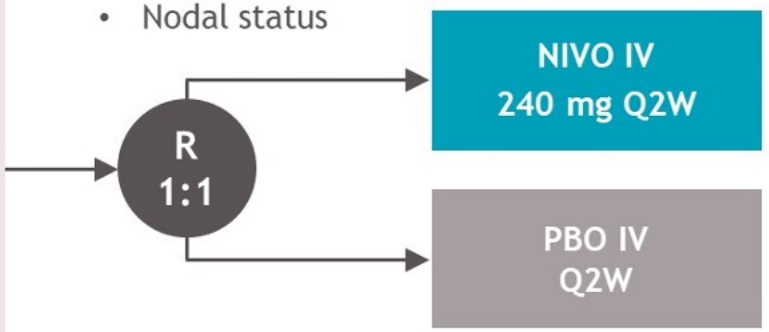
N = 709

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

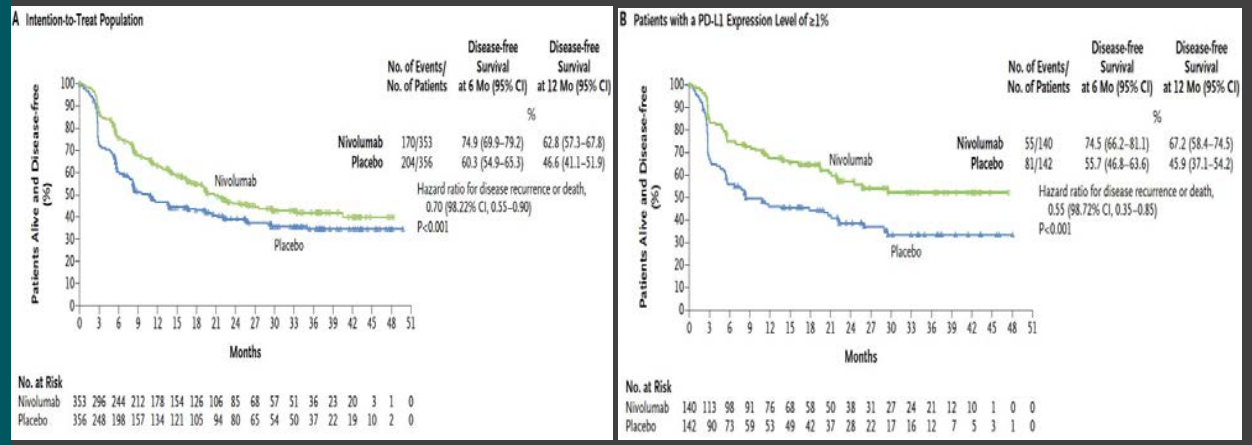
Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

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

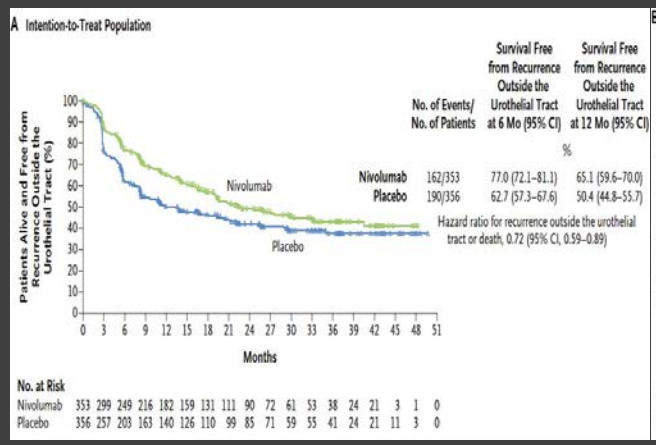
[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IHC, immunohistochemistry; ITT, intent-to-treat; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; R, randomized.

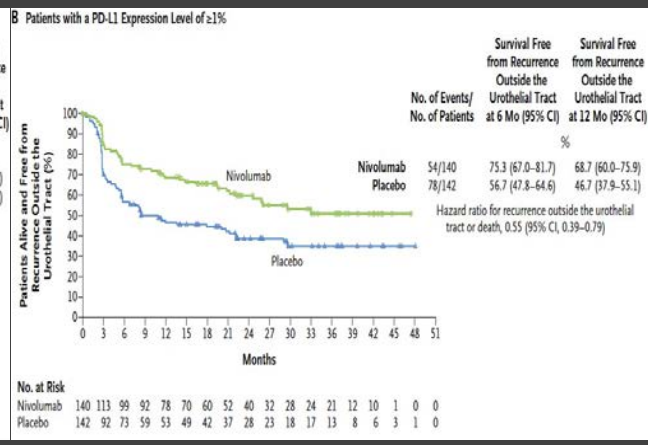
Bajorin DF et al. *N Engl J Med* 2021;384:2102-114.

DISEASE-FREE SURVIVAL

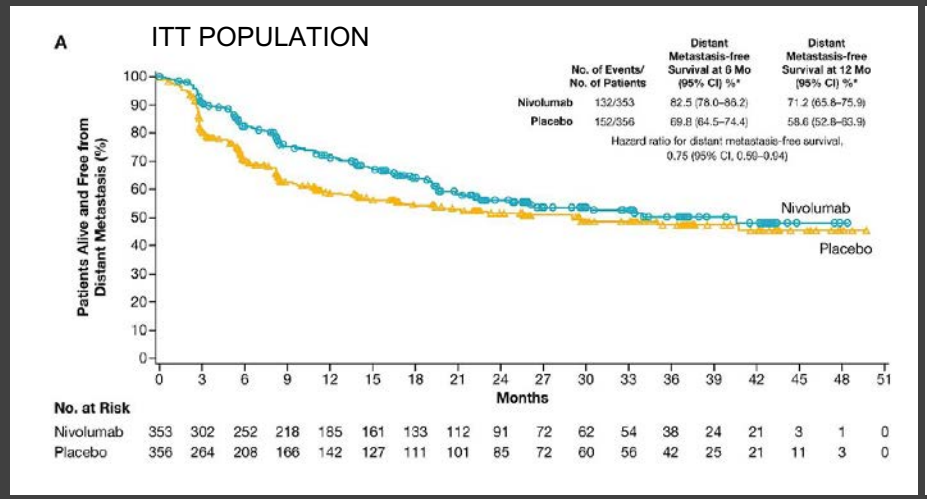


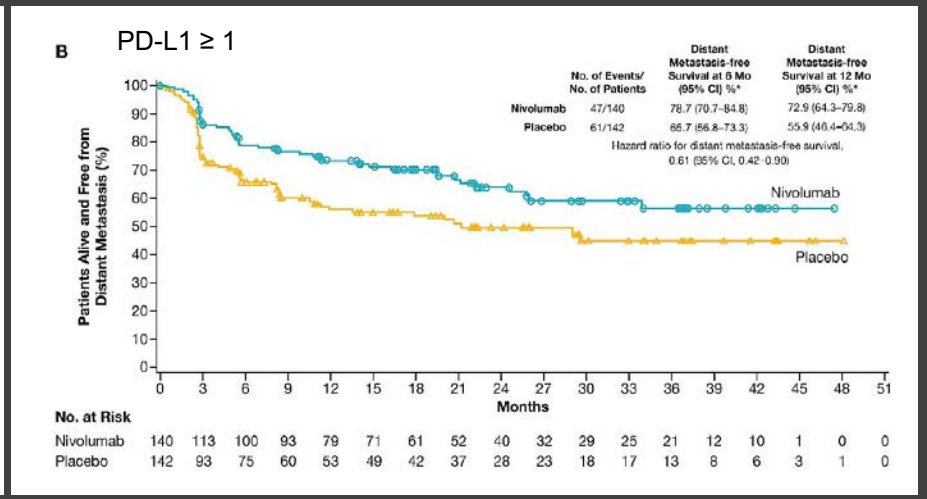
SURVIVAL FREE FROM RECURRENCE OUTSIDE THE UROTHELIAL TRACT





DISTANT METASTASIS-FREE SURVIVAL





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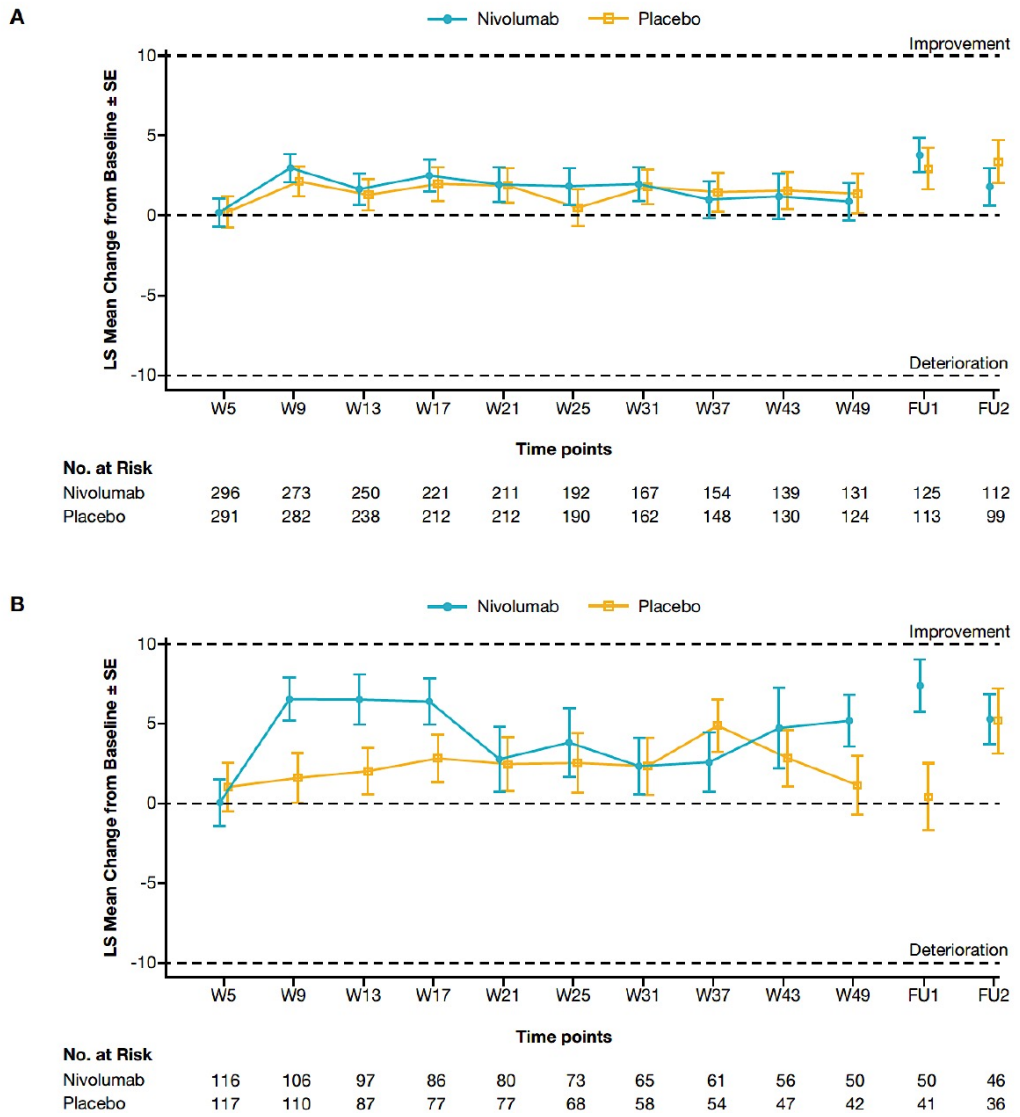
Bajorin DF et al. *N Engl J Med* 2021;384:2102-114.

Table 2. Adverse Events.*

Adverse Event	Nivolumab (N=351)		Placebo (N=348)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Adverse event of any cause	347 (98.9)	150 (42.7)	332 (95.4)	128 (36.8)
Adverse event related to nivolumab or placebo†	272 (77.5)	63 (17.9)	193 (55.5)	25 (7.2)
Pruritus	81 (23.1)	0	40 (11.5)	0
Fatigue	61 (17.4)	1 (0.3)	42 (12.1)	0
Diarrhea	59 (16.8)	3 (0.9)	38 (10.9)	1 (0.3)
Rash	53 (15.1)	2 (0.6)	19 (5.5)	0
Increased lipase level	34 (9.7)	18 (5.1)	20 (5.7)	9 (2.6)
Hypothyroidism	34 (9.7)	0	5 (1.4)	0
Increased amylase level	33 (9.4)	13 (3.7)	20 (5.7)	5 (1.4)
Hyperthyroidism	33 (9.4)	0	3 (0.9)	0
Asthenia	24 (6.8)	2 (0.6)	17 (4.9)	0
Nausea	24 (6.8)	0	13 (3.7)	0
Decreased appetite	20 (5.7)	2 (0.6)	11 (3.2)	0
Increased blood creatinine level	20 (5.7)	1 (0.3)	11 (3.2)	0
Maculopapular rash	19 (5.4)	2 (0.6)	4 (1.1)	0

Figure S3. Mean Change from Baseline in EORTC-QLQC30 Global Health Status Score in All EORTC QLQ-C30 Evaluable Patients (Panel A) and EORTC QLQ-C30 Evaluable Patients with PD-L1 ≥1% (Panel B).



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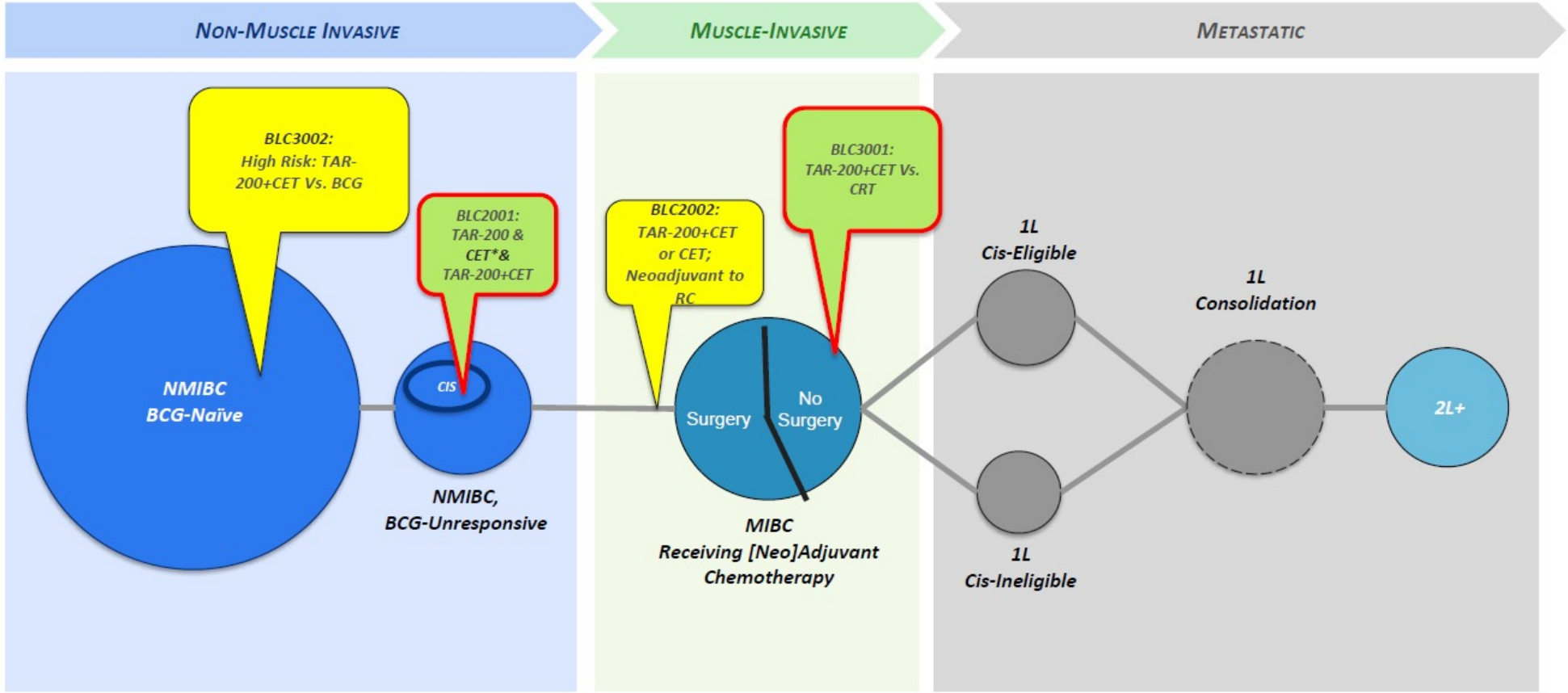
Bajorin DF et al. *N Engl J Med* 2021;384:2102-114.

PARADIGM SHIFT: DELIVERY SYSTEMS ENTER THE ROOM…

SOLUTIONS ACROSS THE BLADDER CANCER SPECTRUM



Note: Size of bubbles roughly represents number of eligible patients

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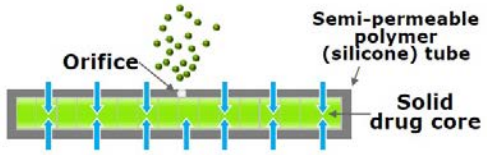
PARADIGM SHIFT: DELIVERY SYSTEMS ENTER THE ROOM…

TARIS® System Allows Controlled Drug Delivery

Example of Delivery: Osmotic Engine

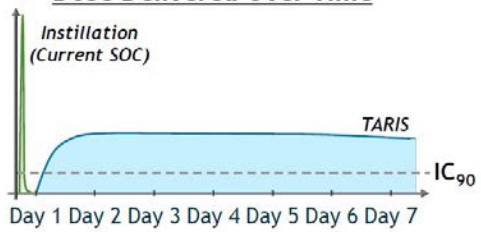


Osmotic pump modulates drug release from internal reservoir

Dose and duration tailored to specific disease states

Rational dosing maximizes intracellular drug potency

Dose Delivered Over Time



Time of Drug Exposure >IC90

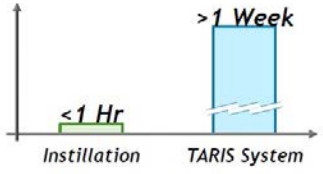
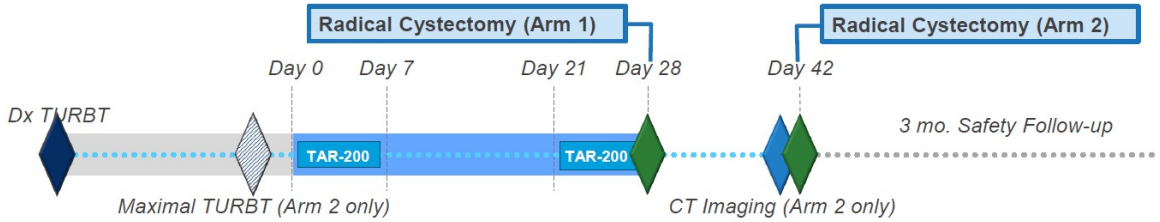


TABLE 3: Pathologic Response in the ITT Population

Response, n/N (%)	Arm 1 (> 3 cm)	Arm 2 (< 3 cm)
Underwent pathology at RC	10/11 (91)[a]	10/12 (83)[b]
Pathologic response	4/10 (40)	6/10 (60)
pCR	1/10 (10)	3/10 (30)
pPR	3/10 (30)	3/10 (30)

[a]1 patient in Arm 1 did not receive either dosing cycle due to an initial unsuccessful insertion attempt. [b]2 patients in Arm 2 discontinued study treatment before the second dosing cycle (1 consent withdrawal, 1 local disease progression).

Proof of Principle: TAR-200-101 in MIBC Neoadjuvant to RC



- Organ-confined, non-metastatic MIBC patients
  - Clinical Staging: cT_2-cT_3 N_{0-1} M_0
- TAR-200 administered neoadjuvant to radical cystectomy
- Status: Complete, 20 patients through cystectomy (10/Arm)

TAR-200 was safe, well tolerated, 50% pCR or pPR

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Daneshmand S et al. *Urol Oncol* 2022;[Online ahead of print].

Phase 3 – TAR-200 + Cetrelimab MIBC [BLC3001]

SunRISe 2

Key Eligibility Criteria

- Patients with muscle-invasive urothelial carcinoma of the bladder [cT2-cT4a N0 M0]
- Not Receiving Radical Cystectomy

Stratification

- Tumor Stage at Randomization [T0, Ta/T1/Tis, or T2-T4a]
- Presence or Absence of Visible Residual Disease

Randomization [1:1; N~550]

Arm 1 [N~275]

TAR-200

[225 mg Gemcitabine] Q3W [18 wks.], Quarterly → 3 years

+ CETRELIMAB

18 months

Arm 2 [N~275]

Chemoradiotherapy

- Cisplatin or Gemcitabine AND
- 55 or 64 Gy External Beam Radiation

~ 4.5 – 6 Weeks

Primary Endpoint

- Bladder Intact Event-Free Survival [BI-EFS] – any MIBC, +N, or M+ disease

Secondary Endpoints

- Metastasis Free Survival
- Overall Survival
- Objective Response Rate at Week 18
- QoL Outcomes Comparing Acute and Long-term Toxicity/Side Effects

utmb Health

Phase 2 – TAR-200 + Cetrelimab
MIBC Neoadjuvant [BLC2002]

SunRISe -4

Key Eligibility Criteria

- Patients with MIBC who are Scheduled for RC [cT2-cT4a N0 M0]
- Patients Ineligible for or Refusing Platinum-Based Neoadjuvant Chemotherapy

Stratification

- T stage: T2-T4a
- Completeness of TURBT: Complete vs. Incomplete <3cm

Randomization [5:3; N~160]

Arm 1 [N~100]
TAR-200
[225 mg Gemcitabine] Q3W [12 wks.]
+ CETRELIMAB 3 Months

Arm 2 [N~60]
CETRELIMAB Alone [360 mg]
For 3 Months

Primary Endpoint

- Assessment of Pathologic Complete Response [pCR] Rate at RC

Secondary Endpoints

- Evaluation of the Safety and Tolerability of TAR-200 in Combination with Cetrelimab
- Compare Recurrence Free Survival [RFS]

"Window of Opportunity" Study to Demonstrate the Activity of Cetrelimab Alone and Cetrelimab in Combination with TAR-200 with respect to **pCR Rates at RC** and the **Potential Subsequent Correlation with Post-Surgical Metastasis-Free Survival**

utmb Health

Meeting Abstract | 2022 ASCO Genitourinary Cancers Symposium

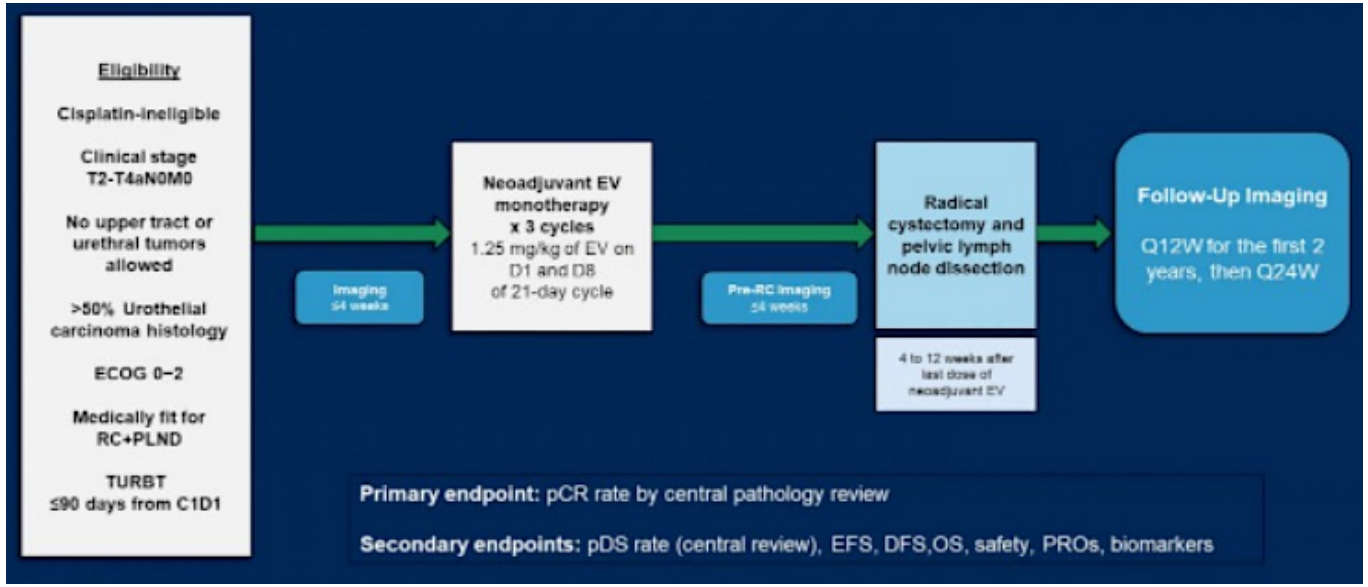
UROTHELIAL CARCINOMA

Study EV-103 Cohort H: Antitumor activity of neoadjuvant treatment with enfortumab vedotin monotherapy in patients (pts) with muscle invasive bladder cancer (MIBC) who are cisplatin-ineligible.

Check for updates

Daniel P. Petrylak, Thomas W. Flaig, Nataliya Mar, Theodore Stewart Gourdin, Sandy Srinivas, Jonathan E. Rosenberg, Maria Guseva, Yao Yu, Sujata Narayanan, Christopher J. Hoimes

Yale Cancer Center, New Haven, CT; University of Colorado Anschutz Medical Campus, Aurora, CO; University of California Irvine, Orange, CA; Hollings Cancer Center, Medical University of South Carolina, Charleston, SC; Stanford University Medical Center, Stanford, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Astellas, Northbrook, IL; Seagen Inc., Bothell, WA; Stanford University Hospital and Clinics, Stanford, CA; Duke Cancer Center, Durham, NC



Enfortumab vedotin (EV) is an antibody-drug conjugate directed to Nectin-4

Cohort H of the EV-103 phase 1b/2 trial (NCT03288545):

- cis-ineligible cT2-T4aN0M0 MIBC RC + PLND eligible.
- 3 cycles of neoadjuvant EV (1.25 mg/kg) on Days 1 and 8 of every 3-week cycle prior to RC+PLND.

utmb Health

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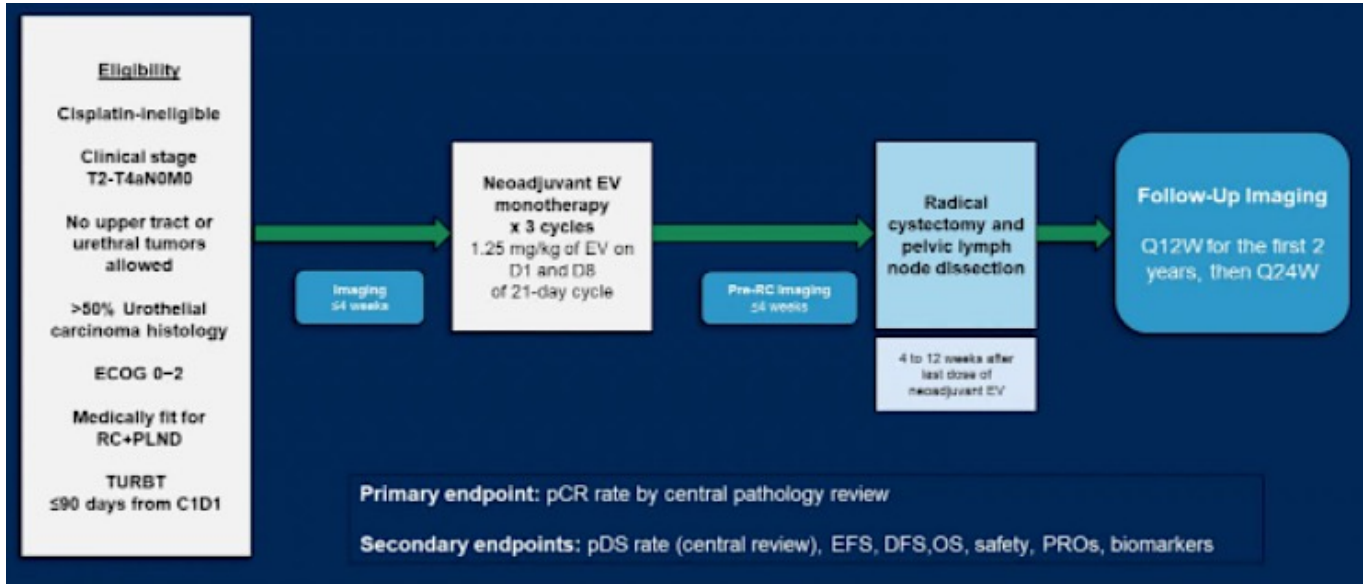
Yale Cancer Center, New Haven, CT; University of Colorado Anschutz Medical Campus, Aurora, CO; University of California Irvine, Orange, CA; Hollings Cancer Center, Medical University of South Carolina, Charleston, SC; Stanford University Medical Center, Stanford, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Astellas, Northbrook, IL; Seagen Inc., Bothell, WA; Stanford University Hospital and Clinics, Stanford, CA; Duke Cancer Center, Durham, NC



Results: 22 pts were treated->21 underwent RC+PLND, and 1 had a partial cystectomy.
-36.4% pCR-> 50% pPR-> well tolerated-> no delay to surgery.

Supports ongoing Phase II and III programs evaluating EV in MIBC.

utmb Health

TOMORROWLAND NO MORE: NOVEL THERAPEUTIC APPROACHES FOR MIBC

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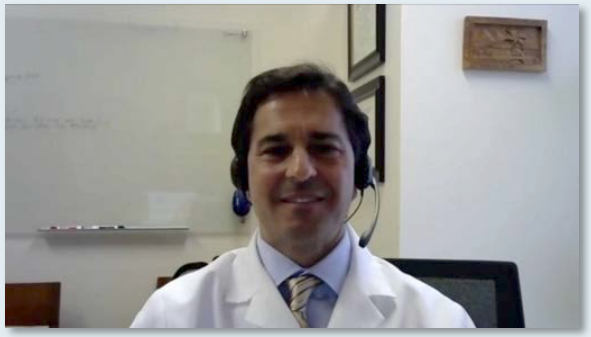
MODULE 3: Current and Future Front-Line Management of Metastatic Urothelial Bladder Carcinoma

For a patient with responding/stable disease after first-line chemotherapy for metastatic urothelial bladder cancer (mUBC), would you generally recommend maintenance therapy with a checkpoint inhibitor?

1. Yes
2. Yes, if PD-L1-positive
3. No



Dr David Taub
Boca Raton, Florida

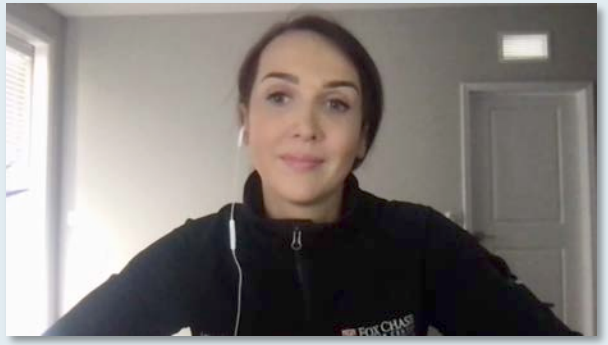
A 75-year-old man with metastatic urothelial bladder cancer (mUBC) who required bilateral percutaneous nephrostomies

Dr Jason Hafron
West Bloomfield, Michigan

A 69-year-old man with mUBC and peritoneal carcinomatosis

The key antitumor mechanism of most antibody-drug conjugates is…

1. Immune-based
2. Antiapoptotic
3. Cytotoxic
4. Kinase inhibition
5. I don’t know



Dr Laura Bukavina
Philadelphia, Pennsylvania

A 73-year-old man with mUBC and recurrence in the bladder while receiving pembrolizumab

Dr Sulfi Ibrahim
Richmond, Indiana

Sequencing immunotherapy and enfortumab vedotin

RTP
RESEARCH
TO PRACTICE

Current and Future Front-Line Management of Metastatic Urothelial Bladder Carcinoma (mUBC)

Matthew D. Galsky, MD

Professor of Medicine

Icahn School of Medicine at Mount Sinai

Associate Director, Translational Research

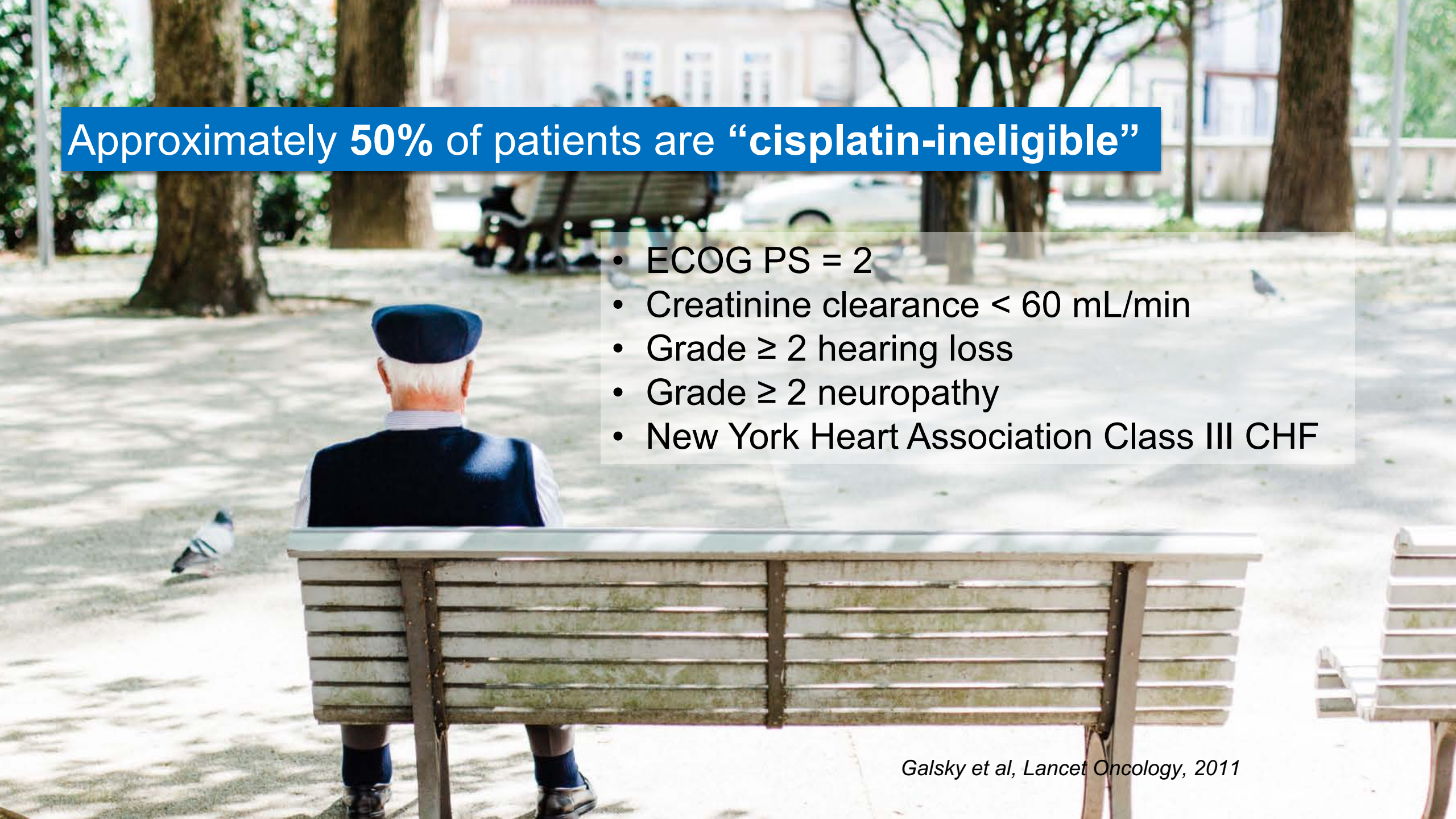
Co-Leader, Cancer Clinical Investigation Program

Tisch Cancer Institute

@MattGalsky

Immune Checkpoint Inhibitors for Locally Advanced and Metastatic UC

Agent	Ab Inhibits	Schedule	Post Platinum	Front-line Cis-Ineligible
Atezolizumab	PD-L1	Q3W	Accelerated	Accelerated
Nivolumab	PD-1	Q2W	Accelerated	--
Durvalumab	PD-L1	Q2W	Accelerated	--
Avelumab	PD-L1	Q2W	Accelerated	--
Pembrolizumab	PD-1	Q3W	Level 1	Accelerated



Approximately **50%** of patients are **"cisplatin-ineligible"**

- ECOG PS = 2
- Creatinine clearance < 60 mL/min
- Grade ≥ 2 hearing loss
- Grade ≥ 2 neuropathy
- New York Heart Association Class III CHF

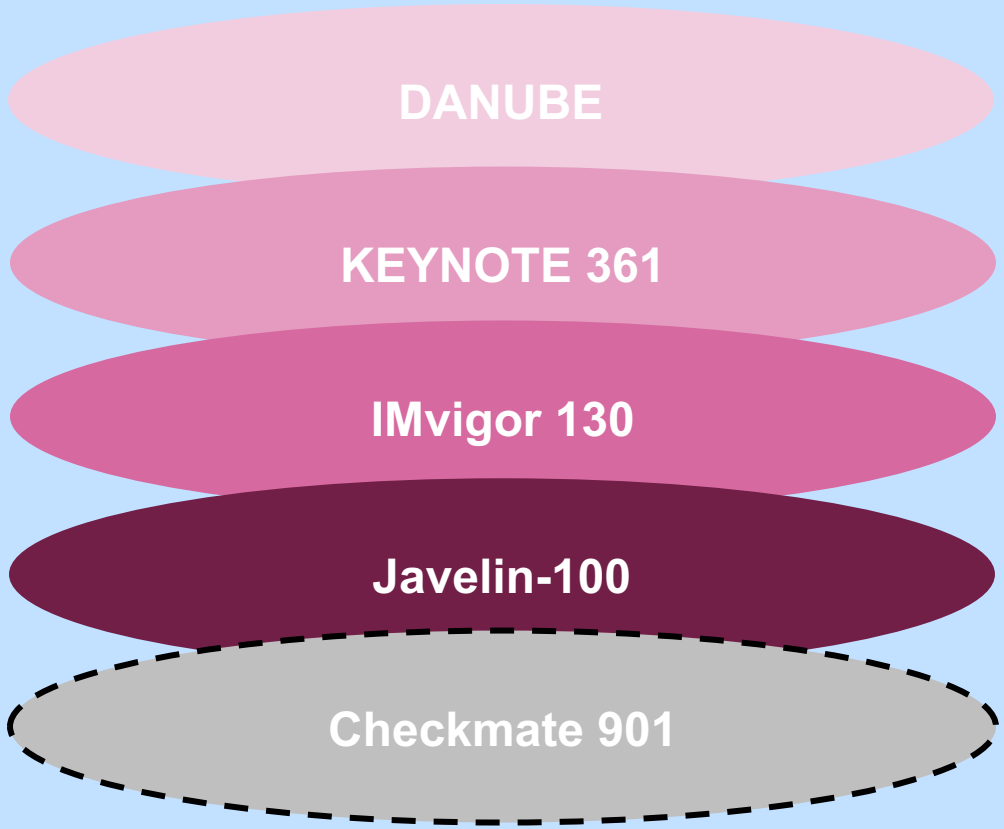
Galsky et al, Lancet Oncology, 2011

Immune Checkpoint Inhibitors for 1st line treatment of Cisplatin-ineligible patients with Metastatic UC

Study[a]	IMvigor210[1] Atezolizumab Phase 2 – Cohort 1	KEYNOTE-052[2] Pembrolizumab Phase 2
Patients, no.	119	370
Study arm	Atezolizumab 1200 mg IV q3w	Pembrolizumab 200 mg IV q3w
Key inclusion criteria	▪ Inoperable la/mUC ▪ No prior treatment for mUC ▪ ECOG PS ≤2 ▪ Cisplatin ineligible	▪ Inoperable la/mUC ▪ No prior chemotherapy for mUC ▪ ECOG PS ≤2 ▪ Cisplatin ineligible
ORR (%)	23	29

1. Balar AV, et al. *Lancet.* 2017;389(10064):67-76. 2. Vuky J, et al. *J Clin Oncol.* 2020;38(23):2658-2666.

A series of randomized clinical trials has recently refined first-line treatment for metastatic urothelial CA



Is there a role for chemo + IO?

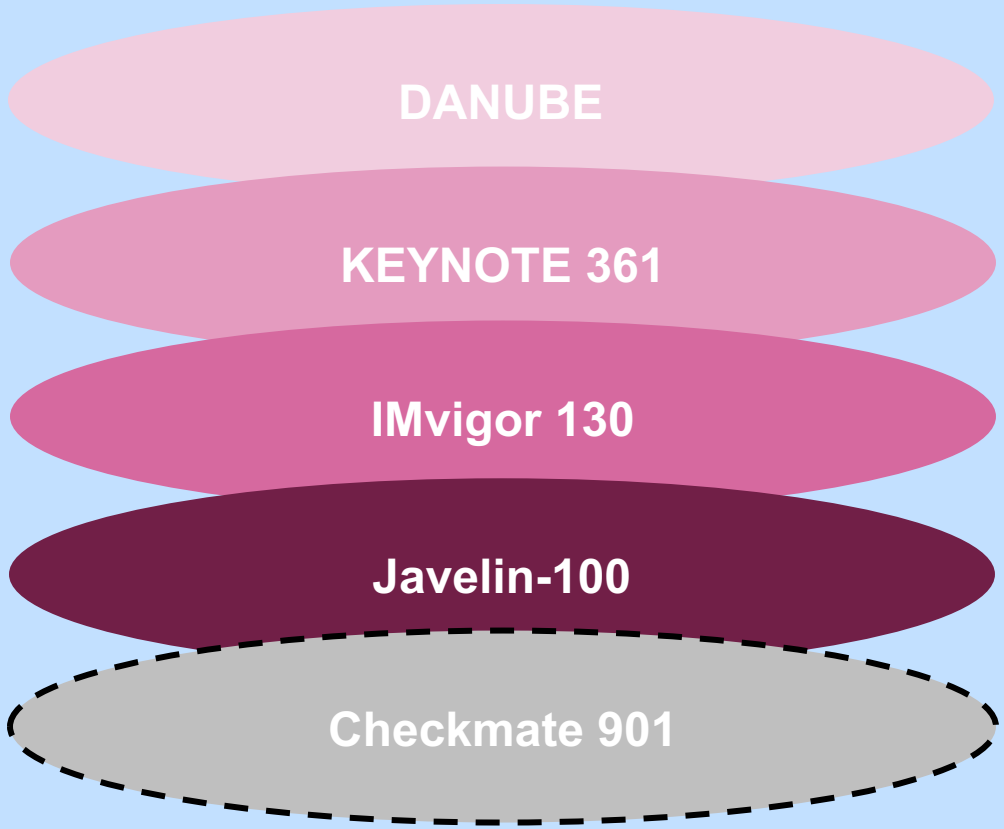
Is there a role for IO alone upfront?

Is there a role for biomarker selection for IO?

Is there a role for "switch maintenance" IO?

Is there a role for IO doublet therapy?

A series of randomized clinical trials has recently refined first-line treatment for metastatic urothelial CA



Is there a role for chemo + IO?

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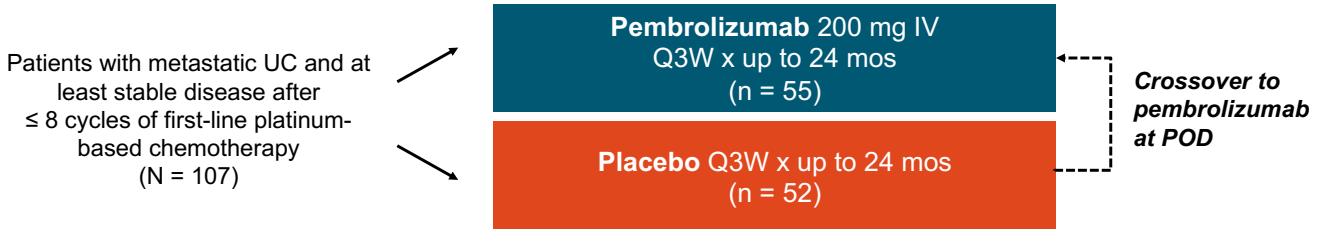
Is there a role for "switch maintenance" IO?

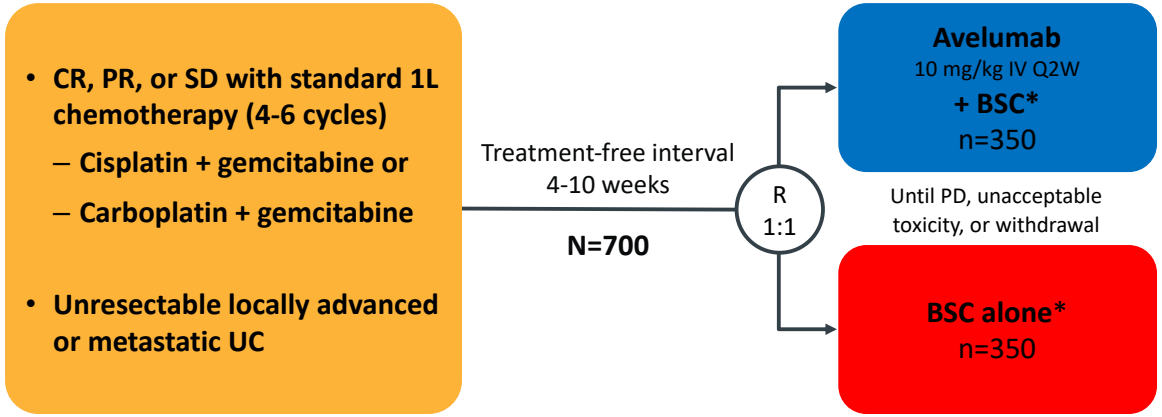
Is there a role for IO doublet therapy?

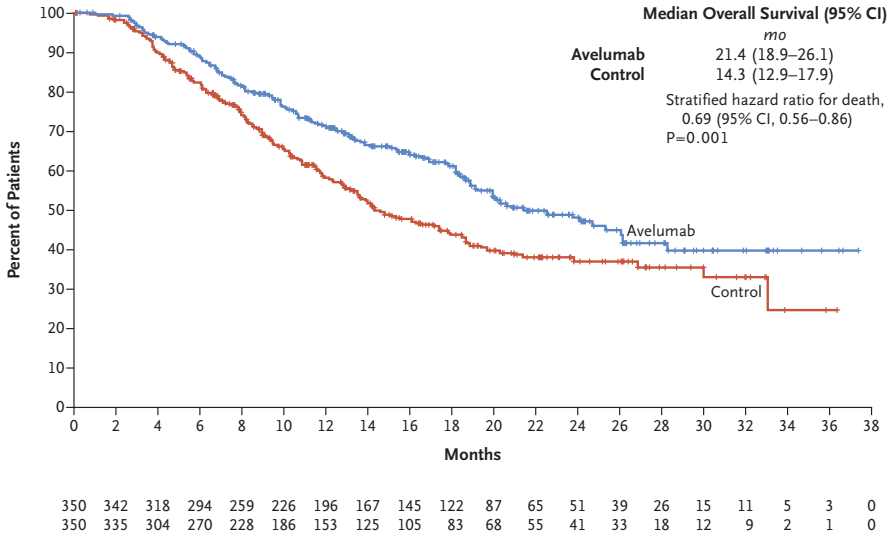
“Switch Maintenance” PD-1/PD-L1 blockade improves outcomes in metastatic UC

HCRN 14-182 Randomized Phase 2



Javelin Bladder-100 Randomized Phase 3



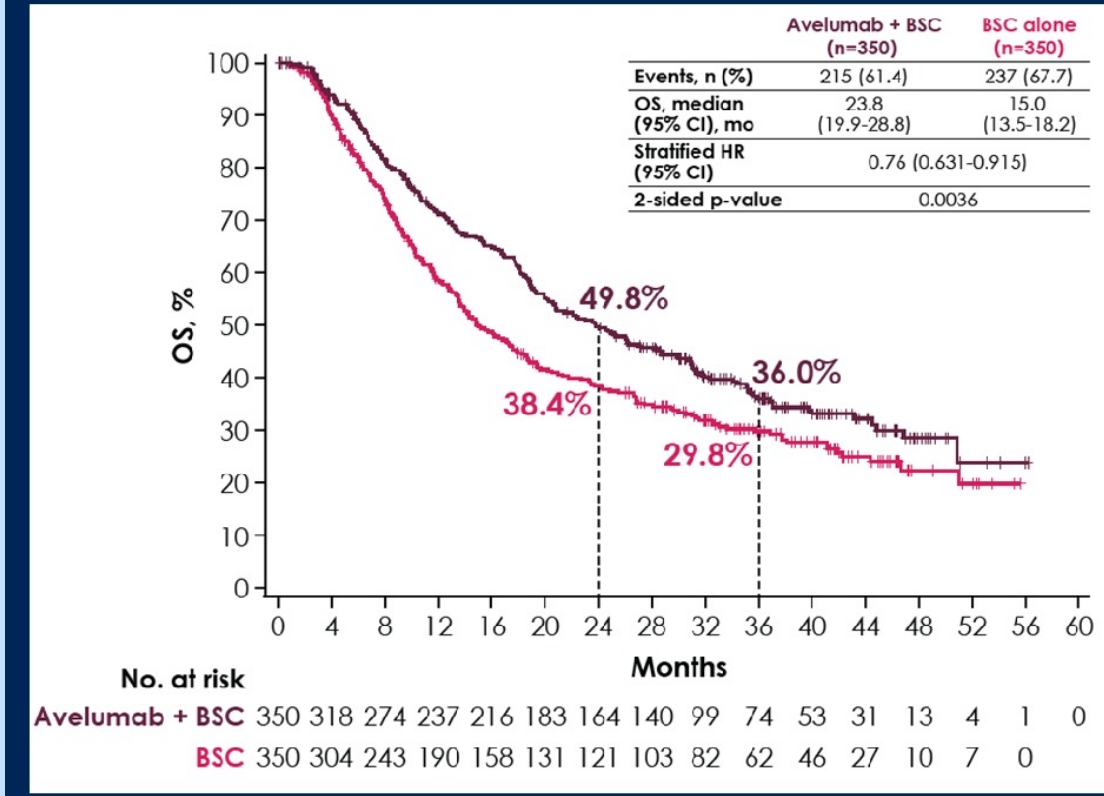


Javelin Bladder-100 Overall Survival

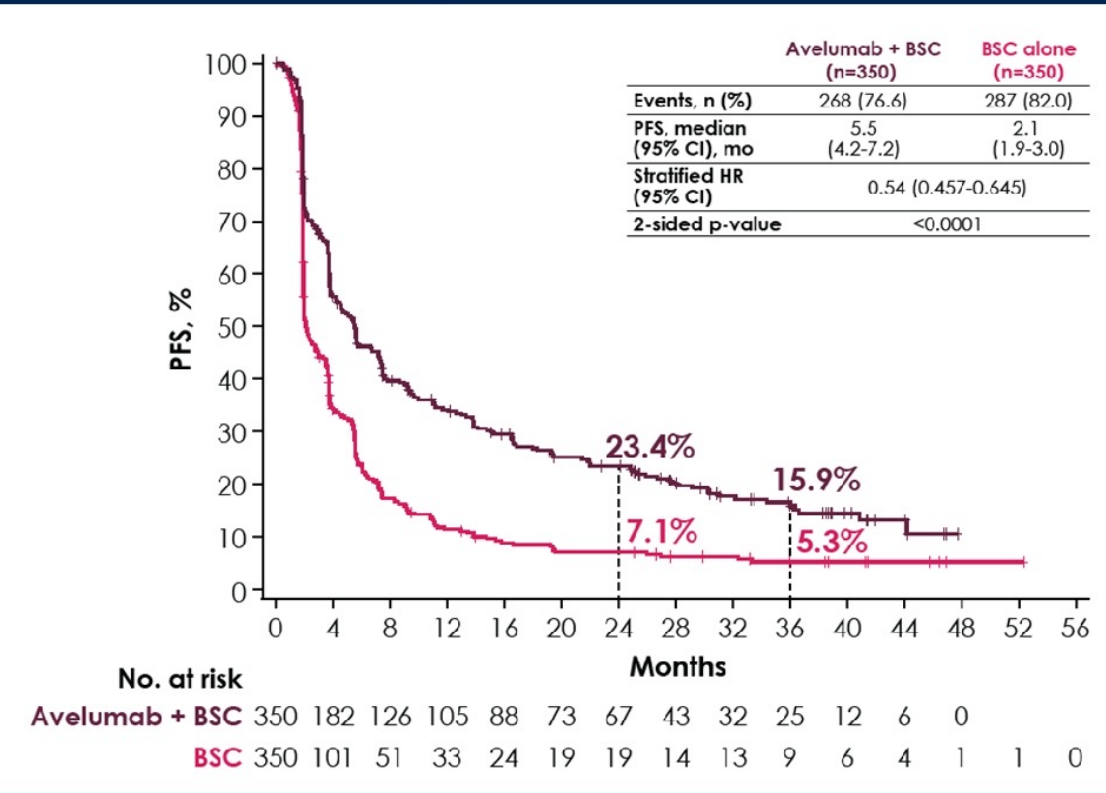
Galsky et al, JCO, 2020
Powles, NEJM, 2020

Long term follow-up of Javelin Bladder 100 (≥ 2 year follow up)

OS



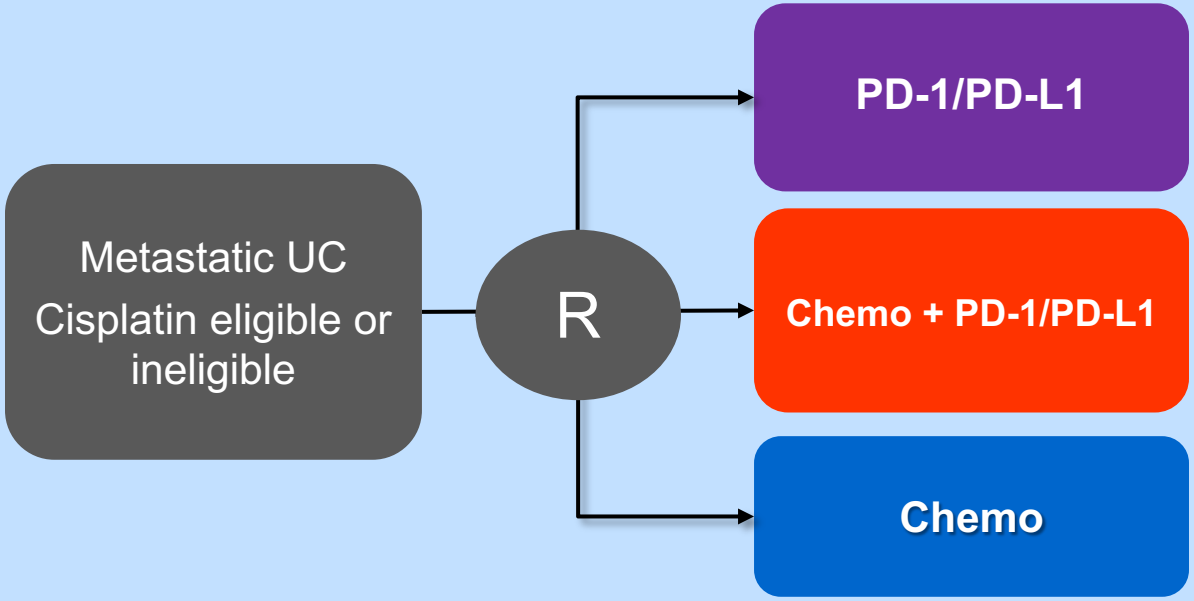
Investigator-assessed PFS



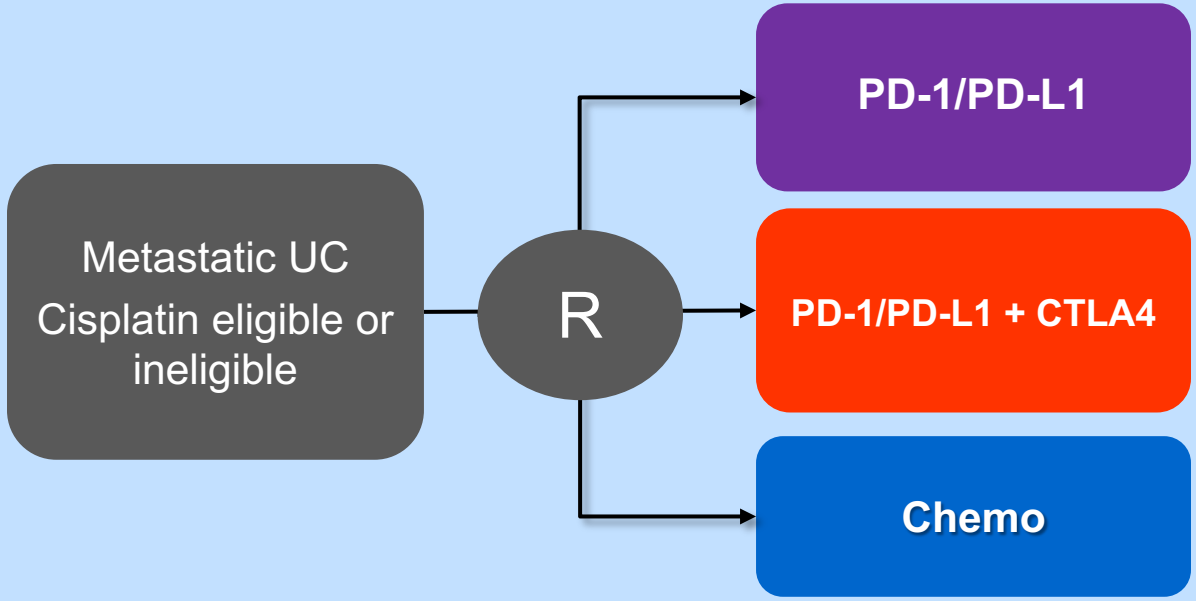
HR, hazard ratio.

Powles et al, ASCO GU 2022 # A487

What is optimal first-line treatment for metastatic UC?

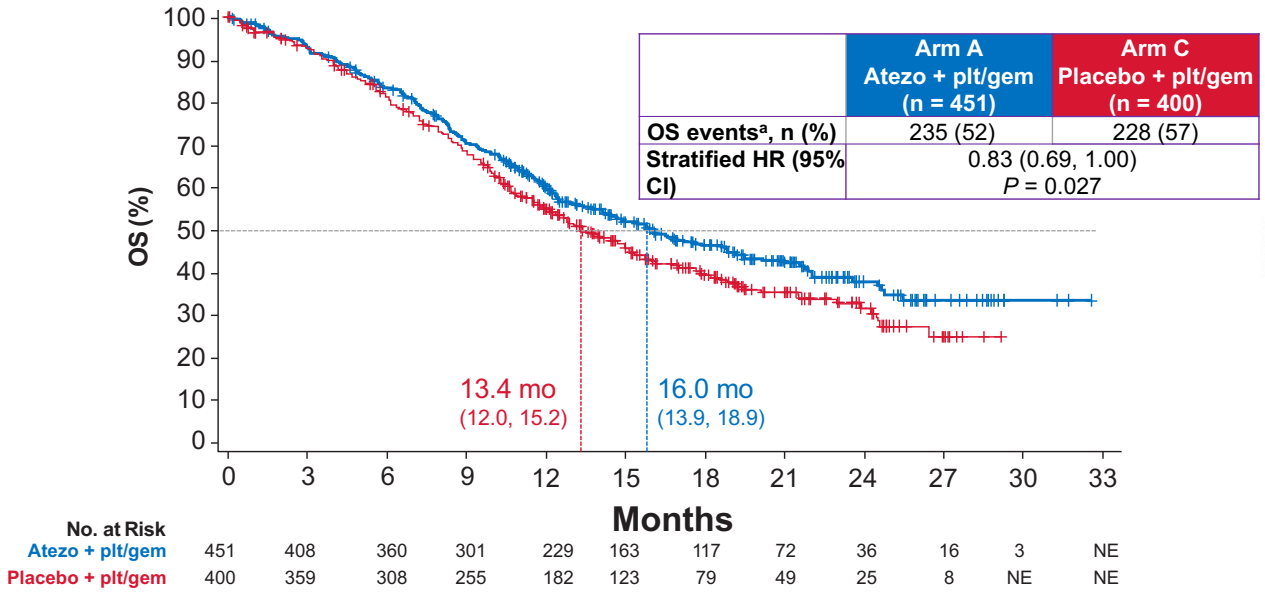


IMvigor 130 ✓
Keynote 361 ✓
Checkmate 901 (substudy)
NILE



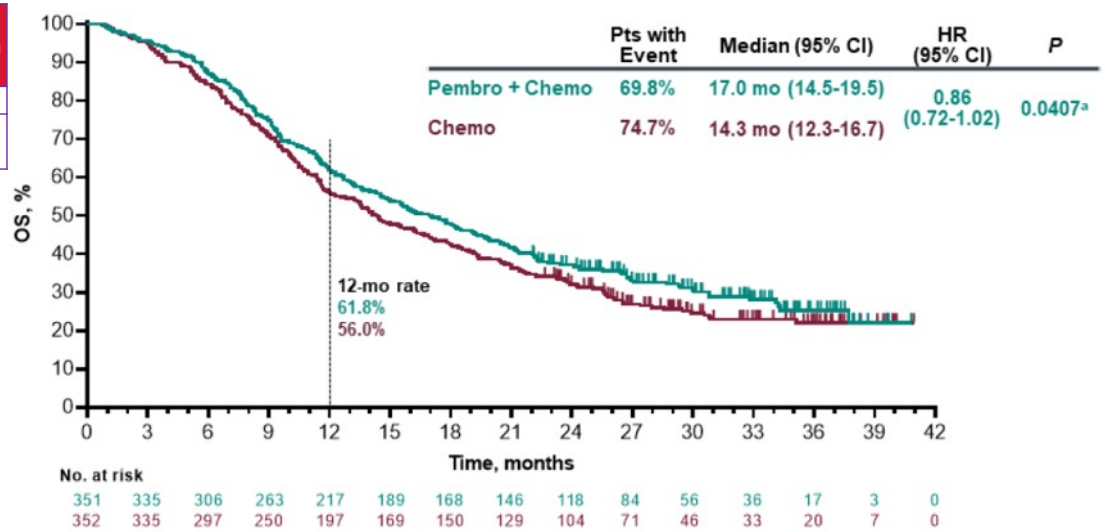
DANUBE ✓
Checkmate 901 (main study)
NILE (sort of…)

Platinum-based chemo + anti-PD-1/PD-L1 leads to non-significant improvements in OS in ITT



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027	

IMvigor 130



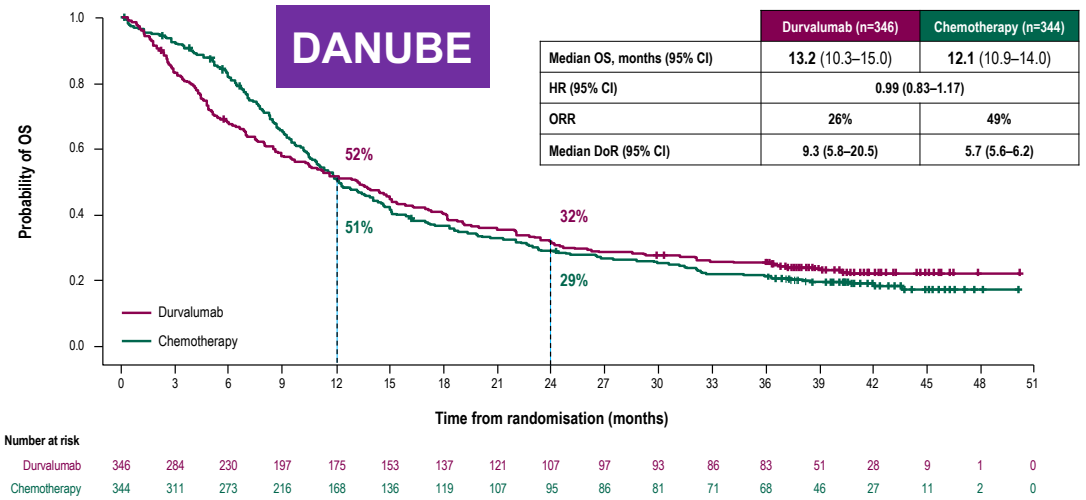
	Pts with Event	Median (95% CI)	HR (95% CI)	*P*
Pembro + Chemo	69.8%	17.0 mo (14.5-19.5)	0.86 (0.72-1.02)	0.0407[a]
Chemo	74.7%	14.3 mo (12.3-16.7)		

Keynote 361

Galsky et al, Lancet, 2020
Alva et al, ESMO, 2020

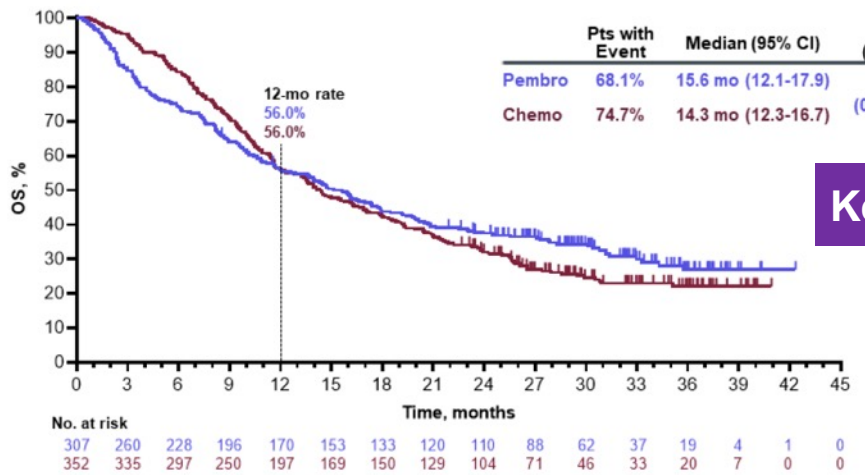
Platinum-based chemo vs anti-PD-1/PD-L1 in ITT populations

DANUBE



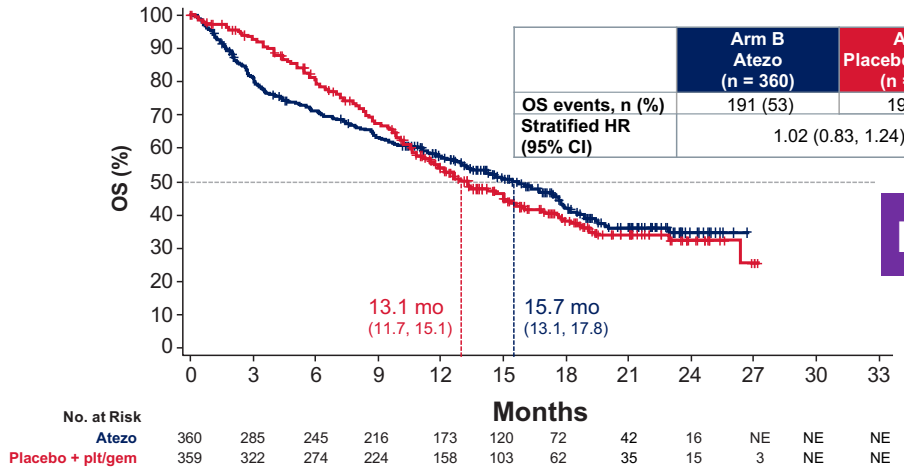
	Durvalumab (n=346)	Chemotherapy (n=344)
Median OS, months (95% CI)	**13.2** (10.3–15.0)	**12.1** (10.9–14.0)
HR (95% CI)	0.99 (0.83–1.17)	
ORR	26%	49%
Median DoR (95% CI)	9.3 (5.8–20.5)	5.7 (5.6–6.2)

Keynote 361



	Pts with Event	Median (95% CI)	HR (95% CI)
Pembro	68.1%	15.6 mo (12.1-17.9)	0.92 (0.77-1.11)
Chemo	74.7%	14.3 mo (12.3-16.7)	

IMVIGOR 130



	Arm B Atezo (n = 360)	Arm C Placebo + plt/gem (n = 359)[a]
OS events, n (%)	191 (53)	198 (55)
Stratified HR (95% CI)	1.02 (0.83, 1.24)	

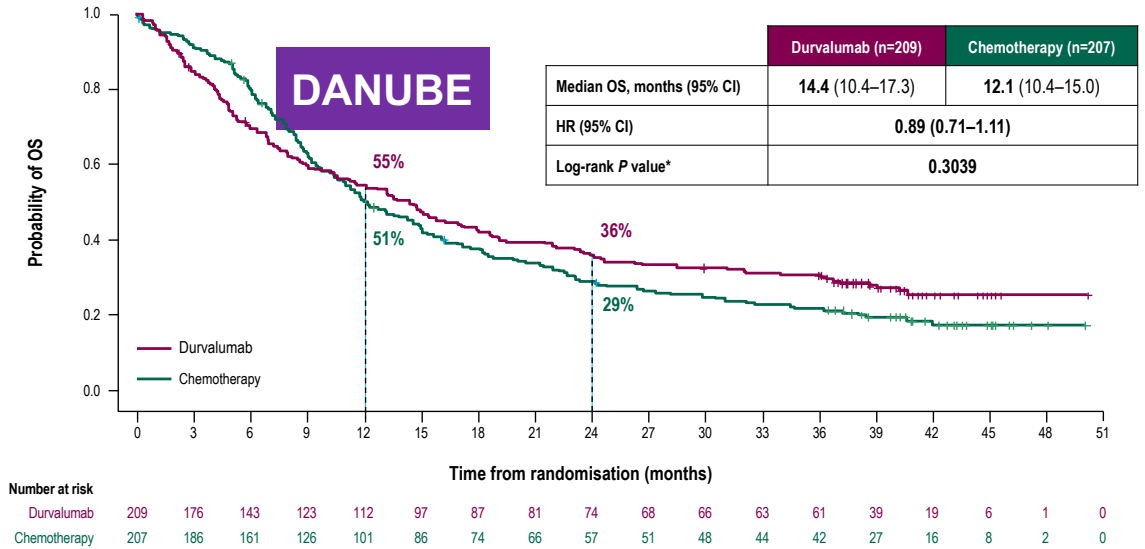
Galsky et al, Lancet, 2020
Alva et al, ESMO, 2020
Powles, Lancet Oncol, 2020

PD-L1 testing…clear as mud?

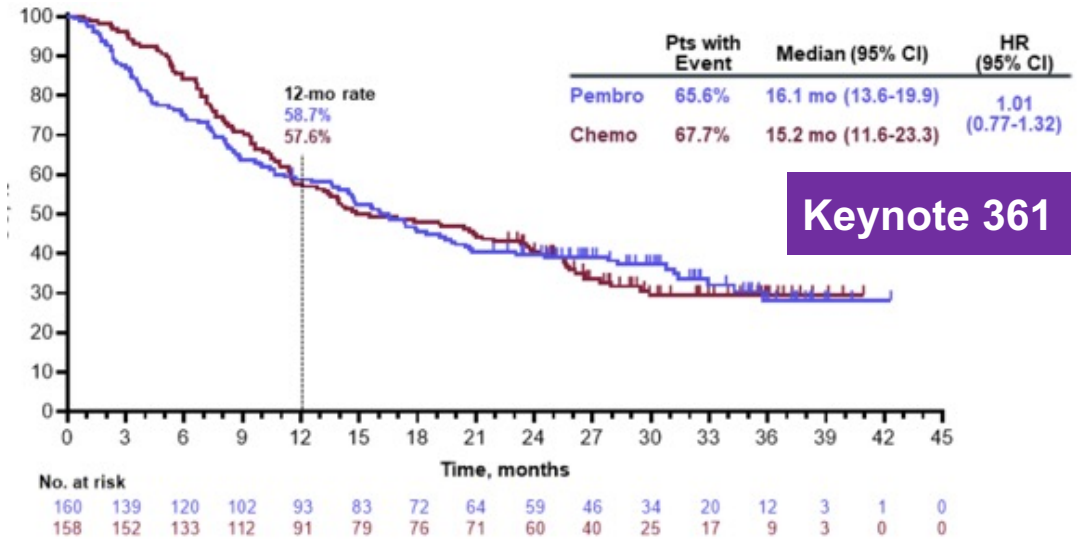
Drug	Biomarker	Scoring
Pembrolizumab	22C3	TC + IC
Atezolizumab	SP142	IC
Nivolumab	28-8	TC
Durvalumab	SP263	TC + IC
Avelumab	73-10	TC + IC

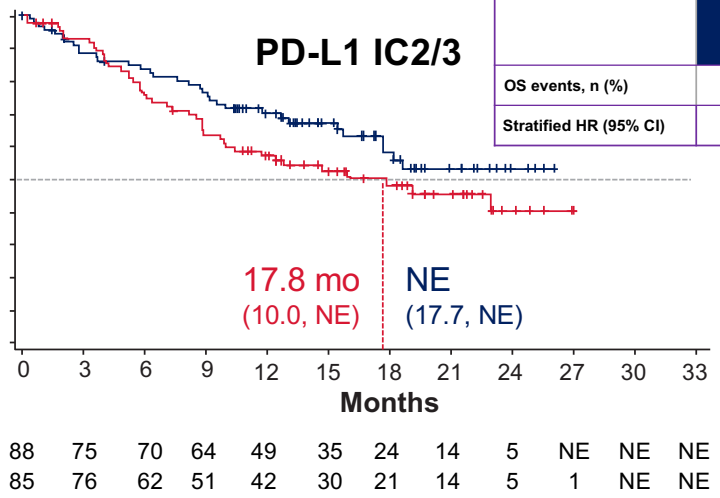
TC, tumor cell; IC, immune cell

Platinum-based chemo vs anti-PD-1/PD-L1 in PD-L1+ populations



	Durvalumab (n=209)	Chemotherapy (n=207)
Median OS, months (95% CI)	**14.4** (10.4–17.3)	**12.1** (10.4–15.0)
HR (95% CI)	**0.89 (0.71–1.11)**	
Log-rank *P* value*	**0.3039**	



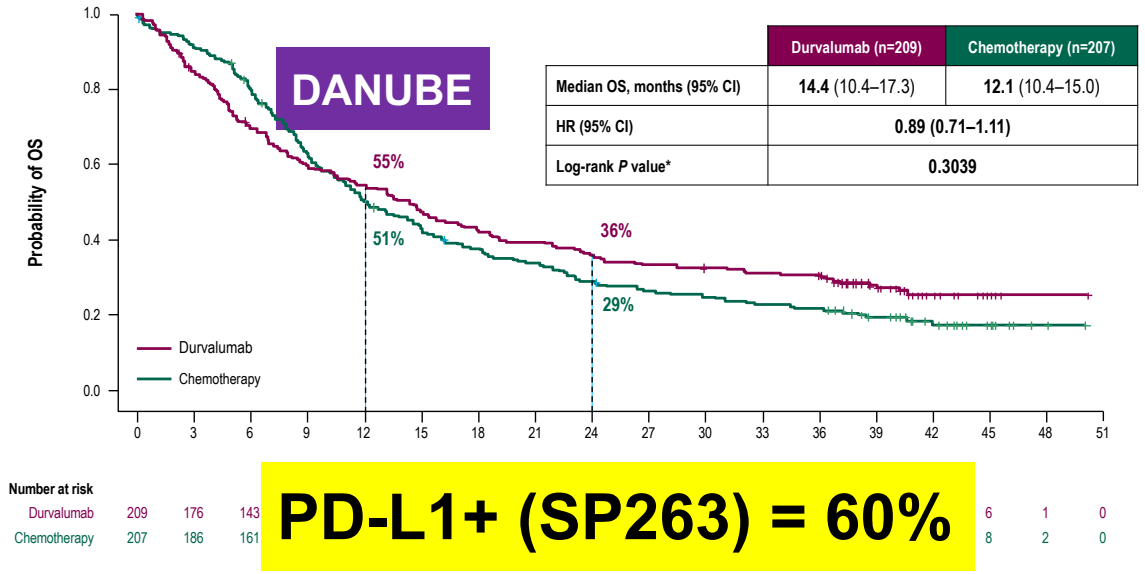


	Arm B Atezo (n = 88)	Arm C Placebo + plt/gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR (95% CI)	0.68 (0.43, 1.08)	

IMVIGOR 130

Galsky et al, Lancet, 2020
Alva et al, ESMO, 2020
Powles, Lancet Oncol, 2020

Platinum-based chemo vs anti-PD-1/PD-L1 in PD-L1+ populations



DANUBE

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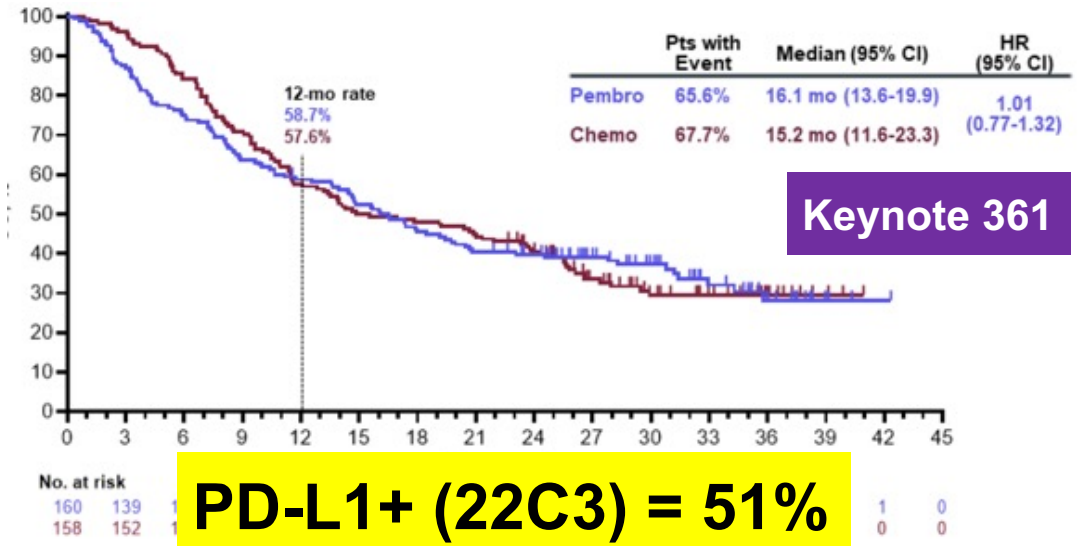
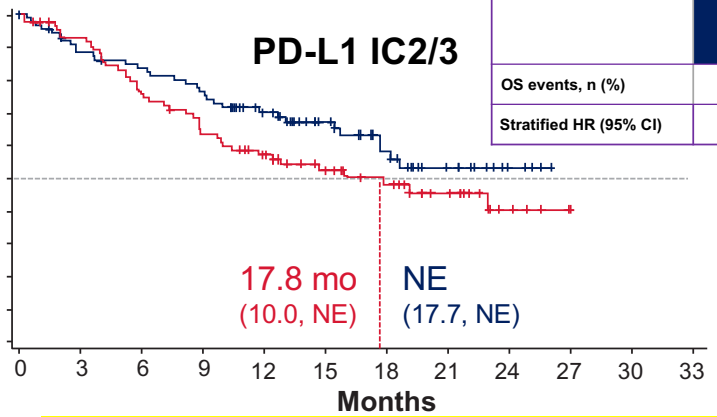
Median OS, months (95% CI)	**14.4** (10.4–17.3)	**12.1** (10.4–15.0)
HR (95% CI)	**0.89 (0.71–1.11)**	
Log-rank *P* value*	**0.3039**	

PD-L1+ (SP263) = 60%



Keynote 361

PD-L1+ (22C3) = 51%



	Arm B Atezo (n = 88)	Arm C Placebo + plt/gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR (95% CI)	0.68 (0.43, 1.08)	

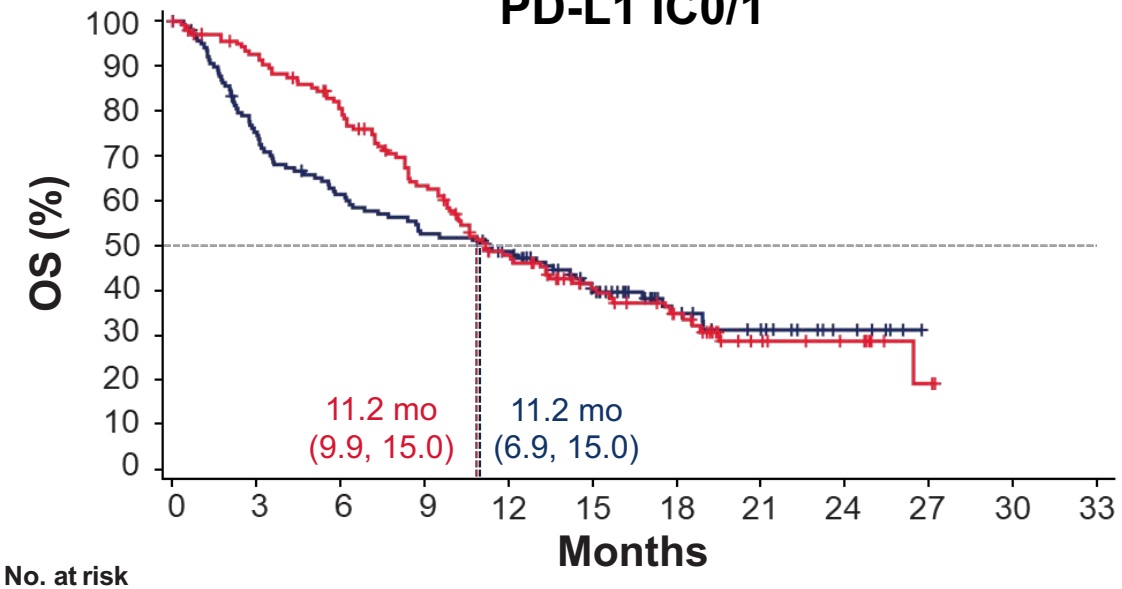
IMVIGOR 130

PD-L1+ (SP142) = 24%

Galsky et al, Lancet, 2020
Alva et al, ESMO, 2020
Powles, Lancet Oncol, 2020

What about the current label (ie, cisplatin ineligible + PD-L1 ”high”)?

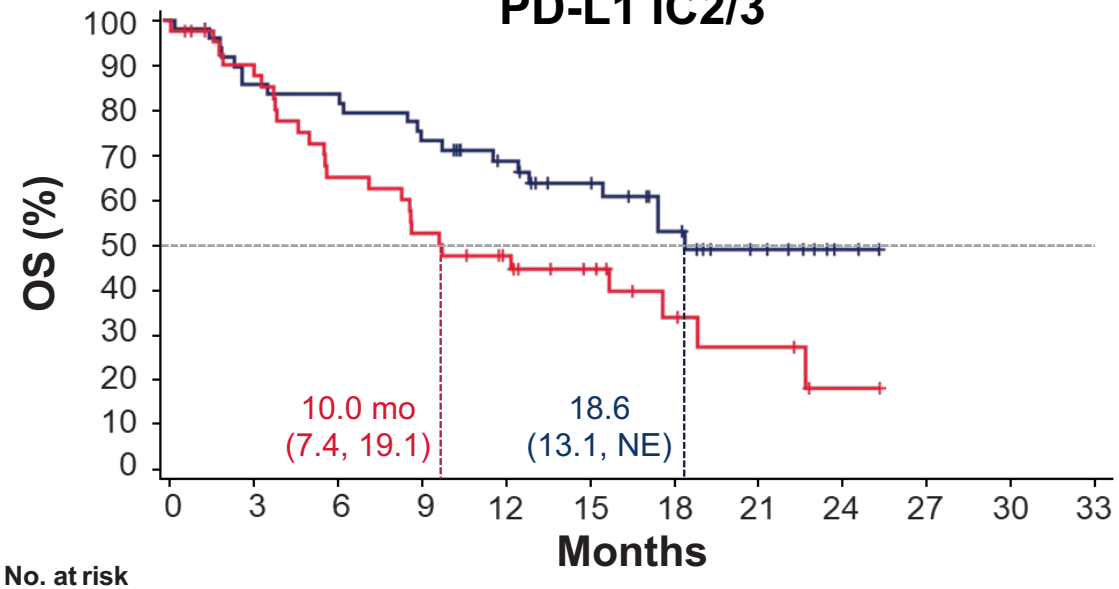
PD-L1 IC0/1



No. at risk												
Atezolizumab	140	103	83	71	60	39	21	14	7	NE	NE	NE
Placebo+plt/gem	140	124	105	80	55	38	26	12	8	2	NE	NE

	Atezolizumab (Arm B) (n=140)	Placebo + plt/gem (Arm C) (n=140)
OS events	85	85
OS HR (95% CI)	1.11 (0.82, 1.51)	
ORR (95% CI), %[a]	16 (10, 23)	42 (34, 51)

PD-L1 IC2/3

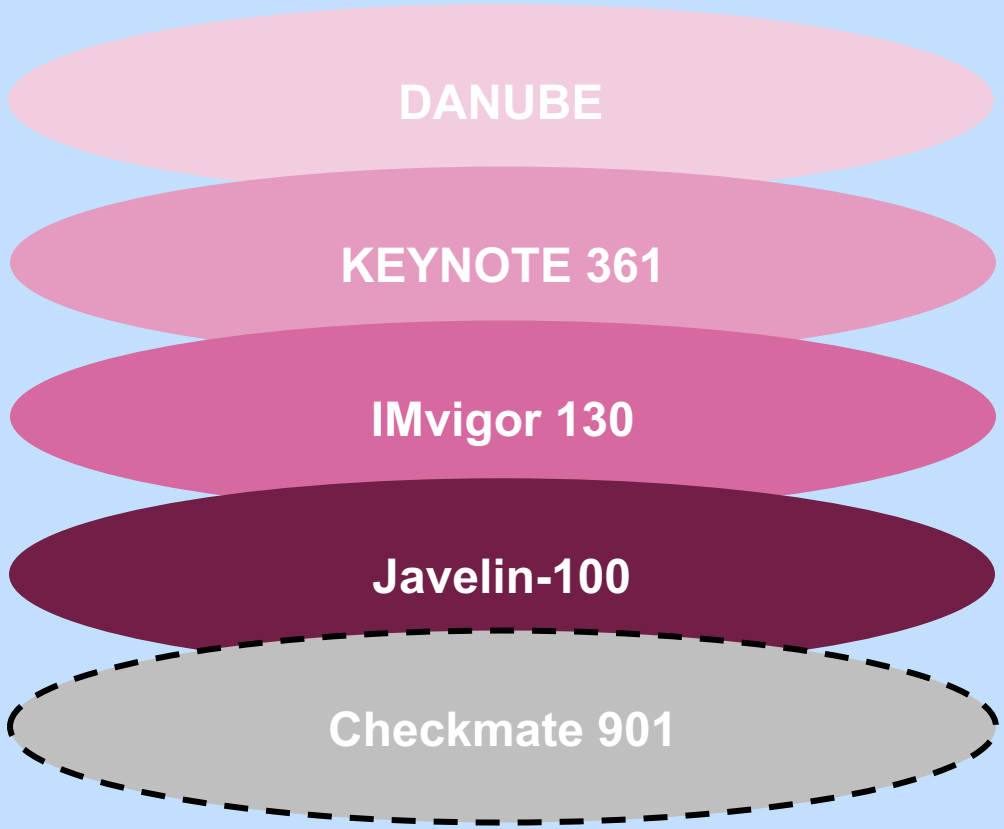


No. at risk												
Atezolizumab	50	42	40	37	28	22	14	8	2	NE	NE	NE
Placebo+plt/gem	43	36	26	21	17	12	6	4	1	NE	NE	NE

	Atezolizumab (Arm B) (n=50)	Placebo + plt/gem (Arm C) (n=43)
OS events	21	26
OS HR (95% CI)	0.53 (0.30, 0.94)	
ORR (95% CI), %	38 (25, 53)	33 (19, 49)

Galsky et al, ASCO GU 21

A series of randomized clinical trials has recently refined first-line treatment for metastatic urothelial CA



Is there a role for chemo + IO?

Is there a role for IO alone upfront?

Is there a role for biomarker selection for IO?

Is there a role for "switch maintenance" IO?

Is there a role for IO doublet therapy?

CheckMate 032: Phase 1/2 Trial of Nivolumab + Ipilimumab

- Pretreated patients with la/mUC (or refused chemotherapy)
- Progressive disease after ≥1 prior platinum-based chemotherapy

NIVO3 (n=78)

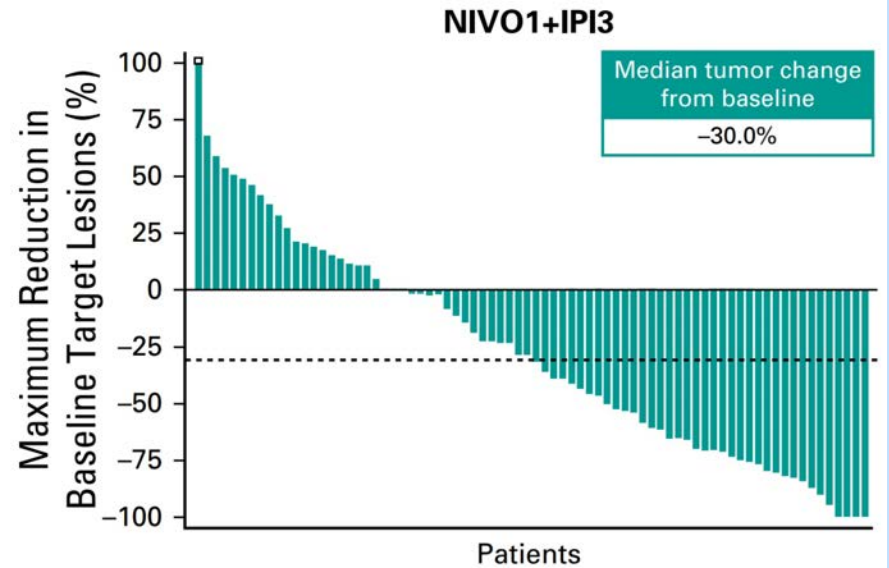
NIVO3 + IPI1 (n=104)

NIVO1 + IPI3 (n=92)

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks x4 doses
followed by nivolumab maintenance

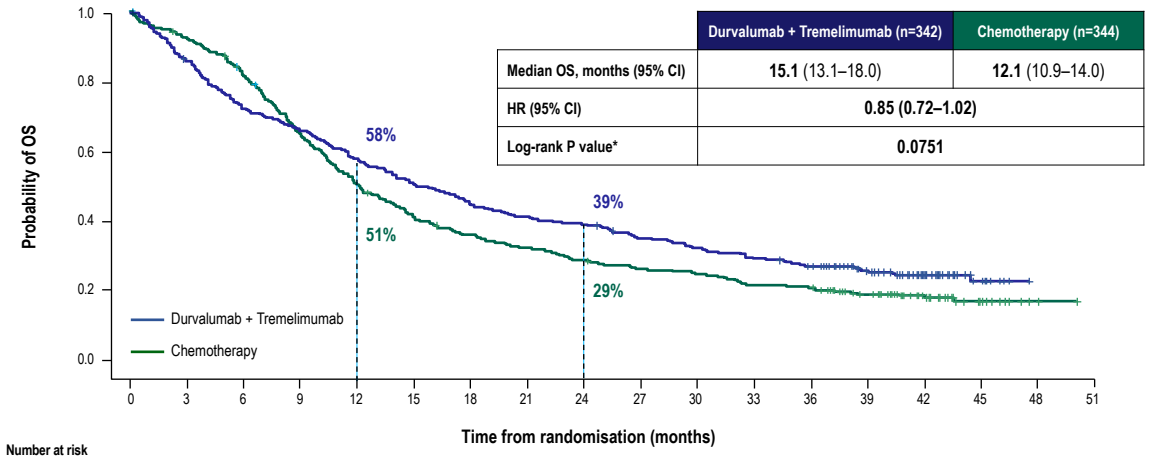
	NIVO1 + IPI3 (n=92)
ORR 95% CI	35 (**38.0%**) (28.1, 48.8)
Complete response	6 (6.5%)
Partial response	29 (31.5%)

Best Tumor Change From Baseline in Target Lesion per Investigator[1]



Sharma et al, JCO, 2019

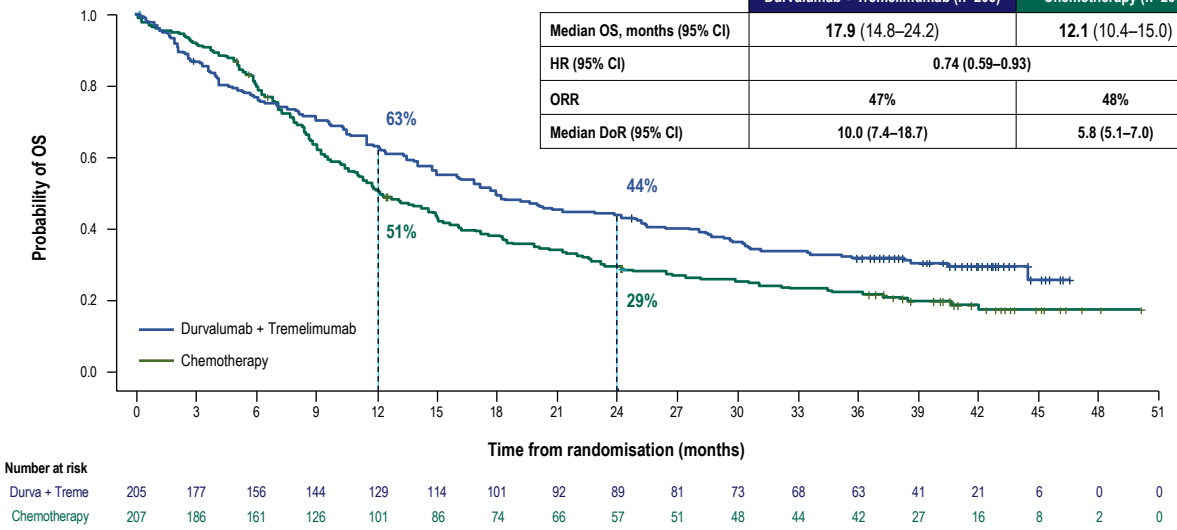
Can anti-CTLA4 + PD-L1 ↑ ORR enough to compete with chemo?



	Durvalumab + Tremelimumab (n=342)	Chemotherapy (n=344)
Median OS, months (95% CI)	**15.1** (13.1–18.0)	**12.1** (10.9–14.0)
HR (95% CI)	**0.85 (0.72–1.02)**	
Log-rank P value*	**0.0751**	

DANUBE (ITT)

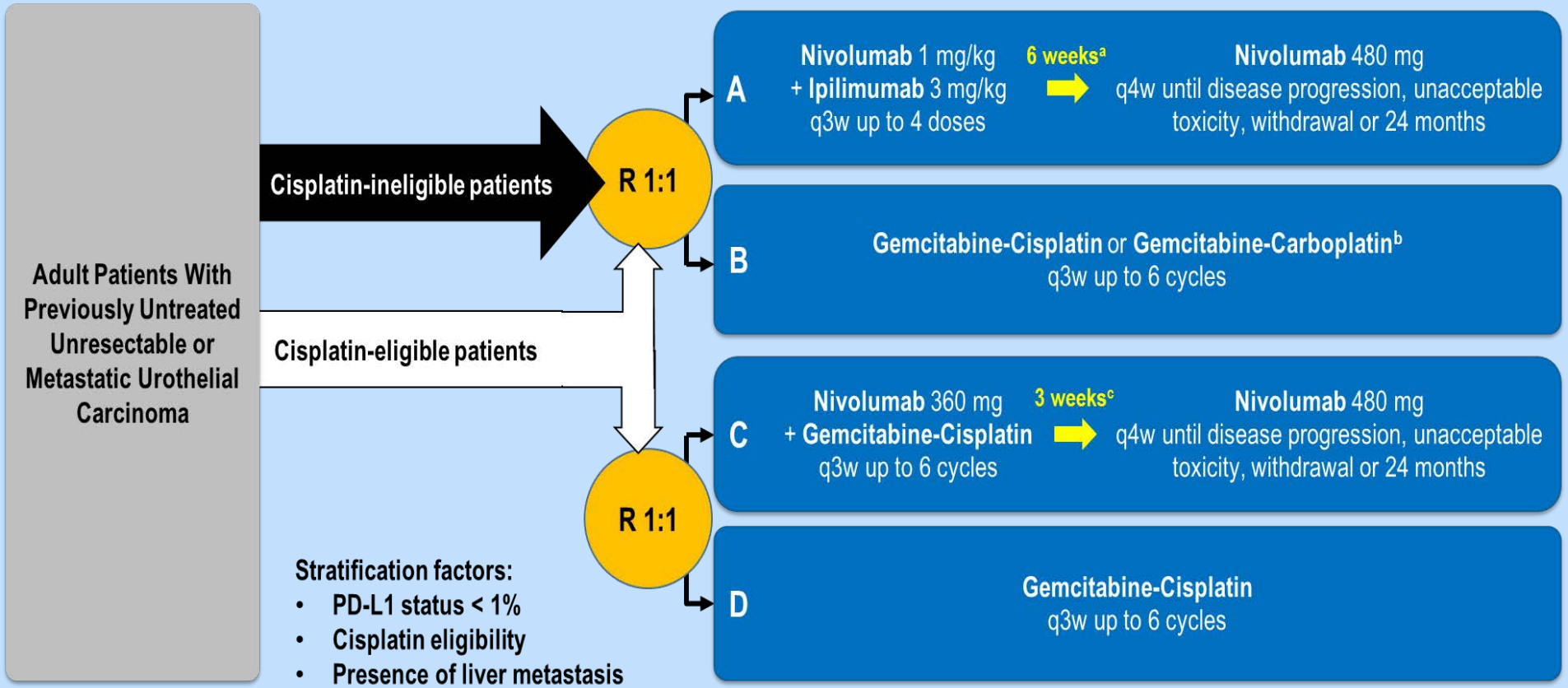
DANUBE (PD-L1+)



	Durvalumab + Tremelimumab (n=205)	Chemotherapy (n=207)
Median OS, months (95% CI)	**17.9** (14.8–24.2)	**12.1** (10.4–15.0)
HR (95% CI)	**0.74 (0.59–0.93)**	
ORR	**47%**	**48%**
Median DoR (95% CI)	**10.0 (7.4–18.7)**	**5.8 (5.1–7.0)**

Powles, Lancet Oncol, 2020

Checkmate 901 Trial



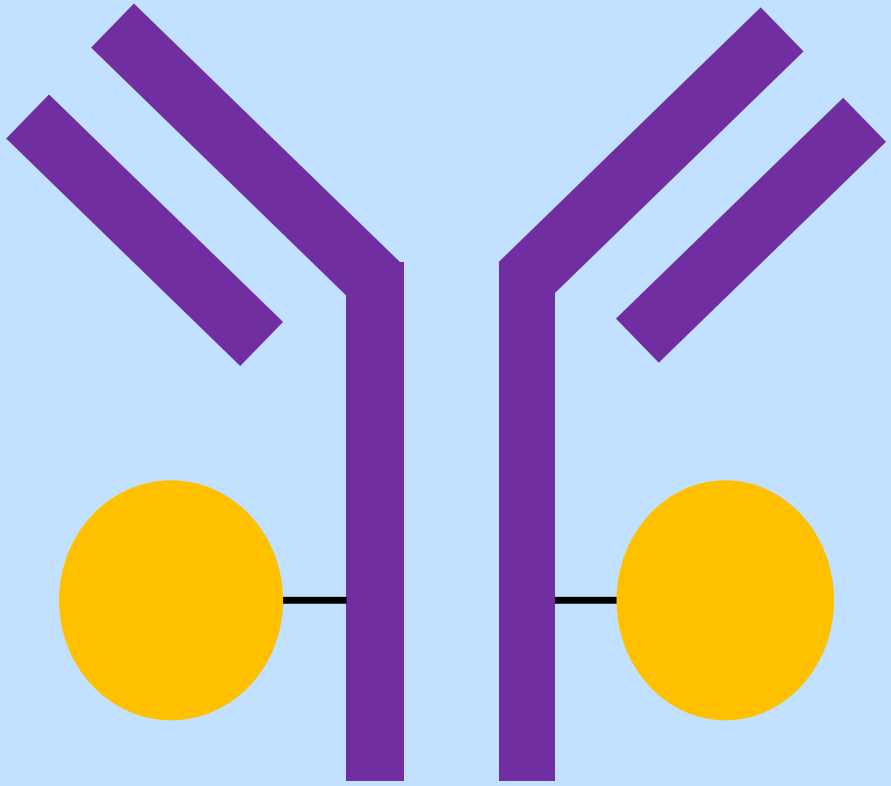
How can we further improve PD-1/PD-L1 blockade?

Move treatment earlier

Combination regimens

Biomarkers

Antibody-drug conjugates are changing UC treatment landscape



1. Antigen
2. Payload
3. Linker

Enfortumab Vedotin

Target: Nectin-4, a type 1 transmembrane cell adhesion molecule overexpressed in epithelial cancers

Linker: Protease cleavable

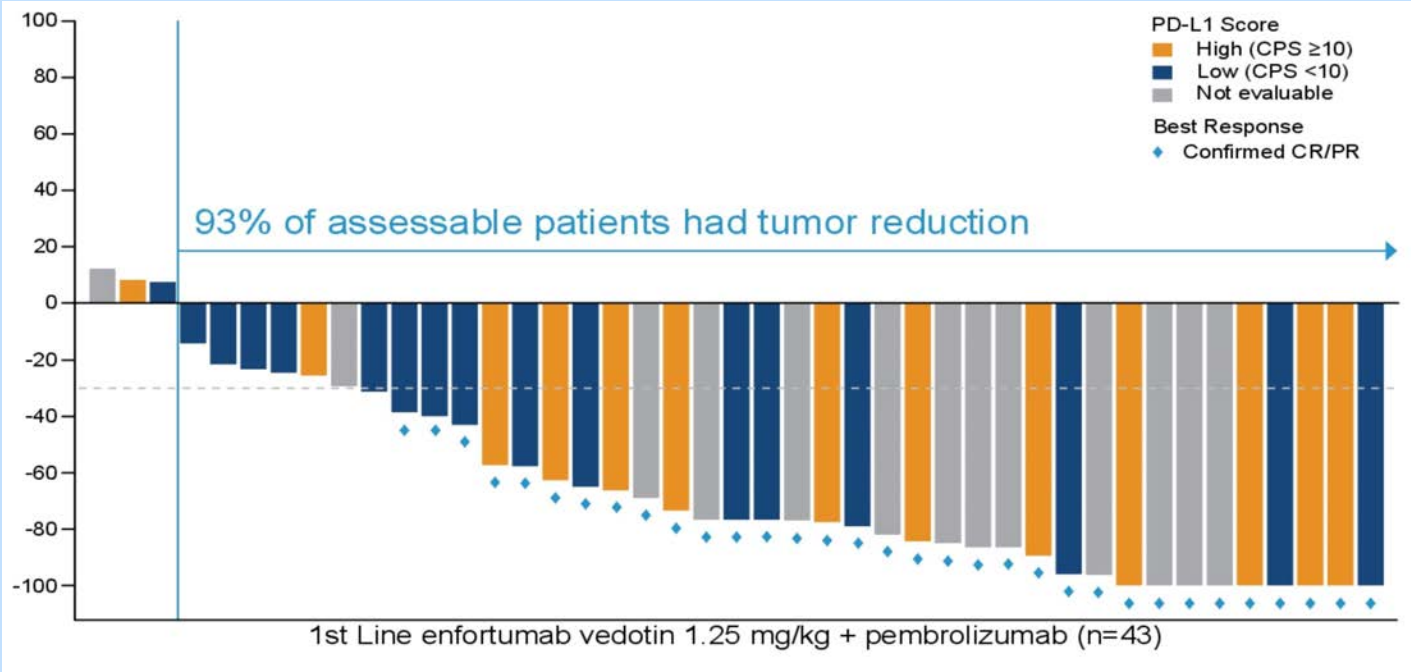
Payload: MMAE

EV + Pembrolizumab in cisplatin-ineligible patients with metastatic urothelial cancer

EV 1.25 mg/kg days 1 and 8
of a 3-week cycle
+
Pembrolizumab 200 mg on day 1
of a 3-week cycle

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

Median DOR =25.6 mo



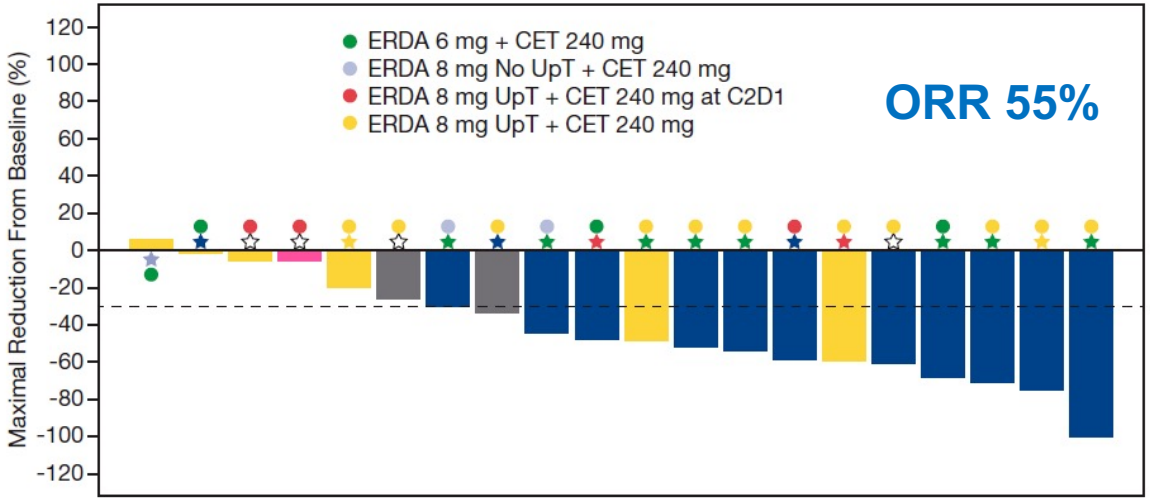
Friedlander, ASCO 2021

FGFR3 mutations in urothelial cancer

- Hotspot mutations in 15-25% invasive
- Enriched in upper tract disease
- Not definitively associated with ICB resistance
- Small molecule TKIs with ORR ~40%

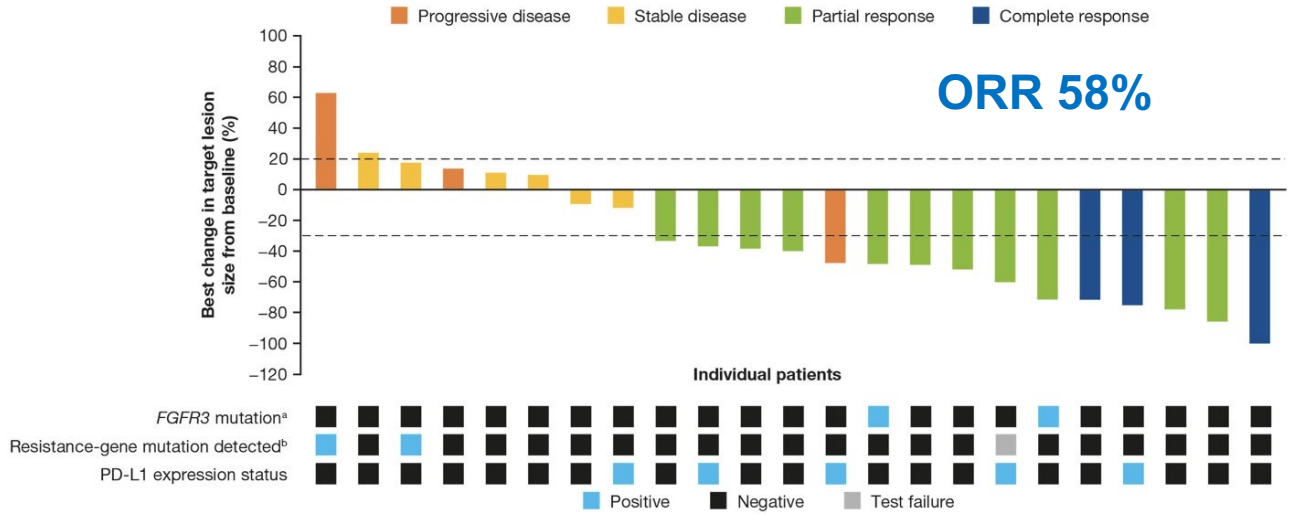
FGFR3 inhibition plus PD-1/PD-L1 blockade

Erdafitinib plus cetrelimab



Phase 2 NORSE trial at ESMO 2021 (n=19)
ORR 68%

Rogaratinib in combination with atezolizumab



Siefker-Radke, ESMO, 2020; Rosenberg, ASCO, 2021; Powles, ESMO, 2021

MODULE 4: Selection and Sequencing of Therapy for Relapsed/Refractory Urothelial Bladder Carcinoma

Current first-line treatment of metastatic disease frequently involves the use of chemotherapy in combination with a checkpoint inhibitor in which of the following tumor types?

1. Non-small cell lung cancer
2. Head and neck cancer
3. Esophageal cancer
4. Cervical cancer
5. Triple-negative breast cancer
6. All of the above
7. I don’t know

Dr Zanetta Lamar
Naples, Florida

A 68-year-old man with mUBC whose disease progressed after 4 years of nivolumab/ipilimumab

Dr Sulfi Ibrahim
Richmond, Indiana

A 70-year-old woman with mUBC and PD-L1 30% with enfortumab vedotin-associated dermatologic toxicity

RTP
RESEARCH
TO PRACTICE

What would you generally recommend as second-line therapy for a patient with mUBC with an FGFR somatic mutation whose disease progresses while he is receiving avelumab maintenance after first-line chemotherapy?

1. Enfortumab vedotin
2. Erdafitinib
3. Sacituzumab govitecan
4. Other

Dr Chris Prakash
Paris, Texas

A 58-year-old man with mUBC and an FGFR mutation

Dr Henna Malik
Houston, Texas

An 84-year-old woman with NMIBC and an FGFR2 mutation

Dr Ranju Gupta
Bethlehem, Pennsylvania

A 67-year-old man with mUBC who receives sacituzumab govitecan

RTP
RESEARCH
TO PRACTICE

Selection and Sequencing of Therapy for Relapsed/Refractory mUBC

Sumanta Kumar Pal, MD

Professor, Department of Medical Oncology and Therapeutics Research
City of Hope
Duarte, California

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

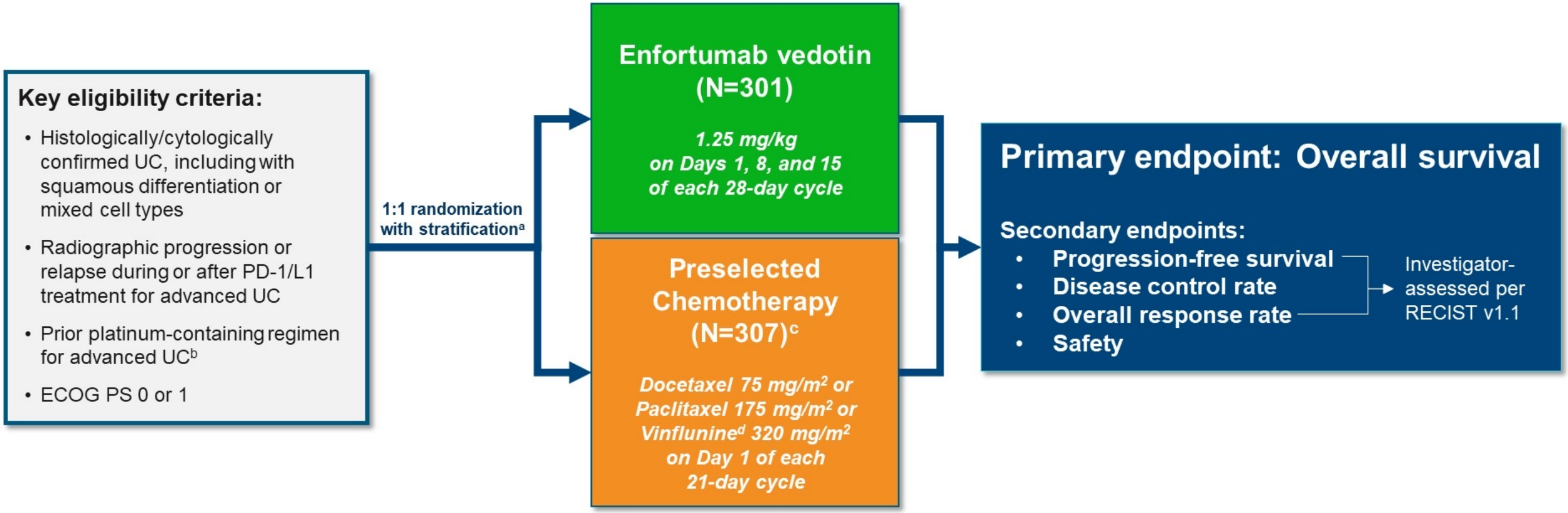
Thomas Powles, MD[1a]; Jonathan E Rosenberg, MD[2a]; Guru P Sonpavde, MD[3]; Yohann Loriot, MD, PhD[4]; Ignacio Durán, MD, PhD[5]; Jae-Lyun Lee, MD, PhD[6]; Nobuaki Matsubara, MD[7]; Christof Vulsteke, MD, PhD[8]; Chunzhang Wu, PhD[9]; Mary Campbell, MD[10]; Maria Matsangou, MBChB, MD[9]; Daniel P Petrylak,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

PRESENTED AT: Genitourinary Cancers Symposium

EV-301 Open-Label Phase 3 Trial Design



[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.

Overall Survival

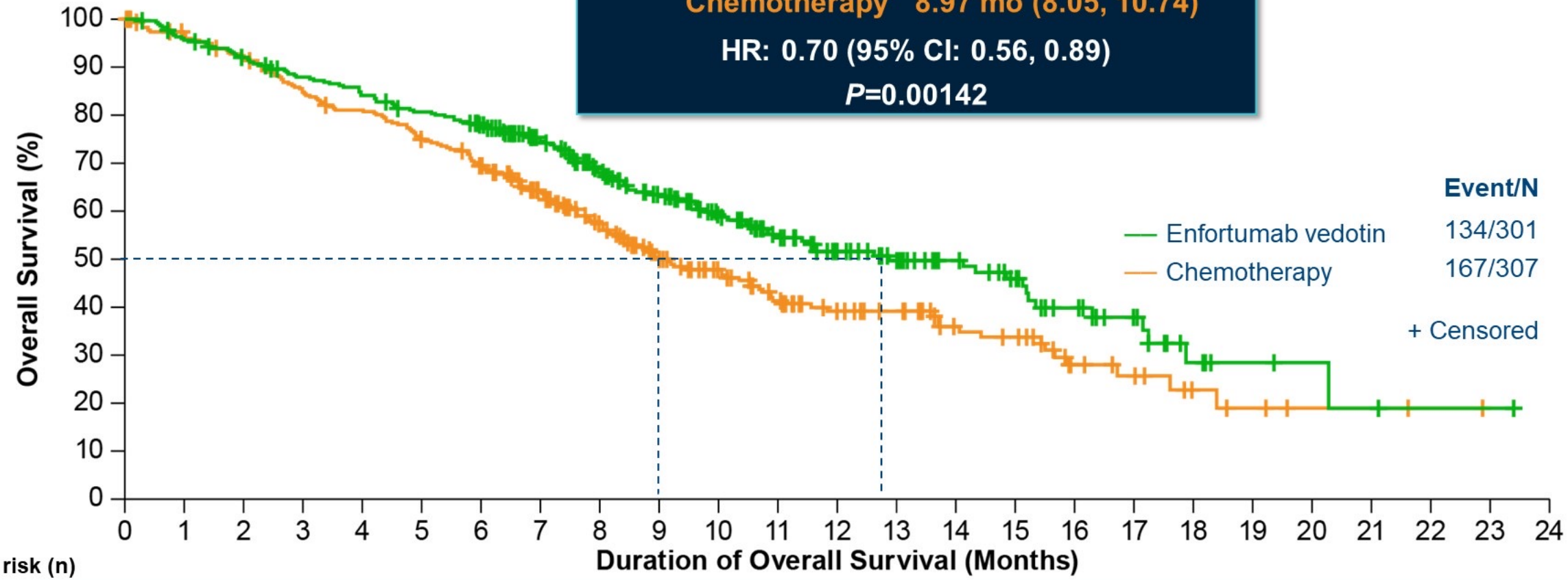
Median OS

Enfortumab vedotin 12.88 mo (10.58, 15.21)

Chemotherapy 8.97 mo (8.05, 10.74)

HR: 0.70 (95% CI: 0.56, 0.89)

***P*=0.00142**



Patients at risk (n)

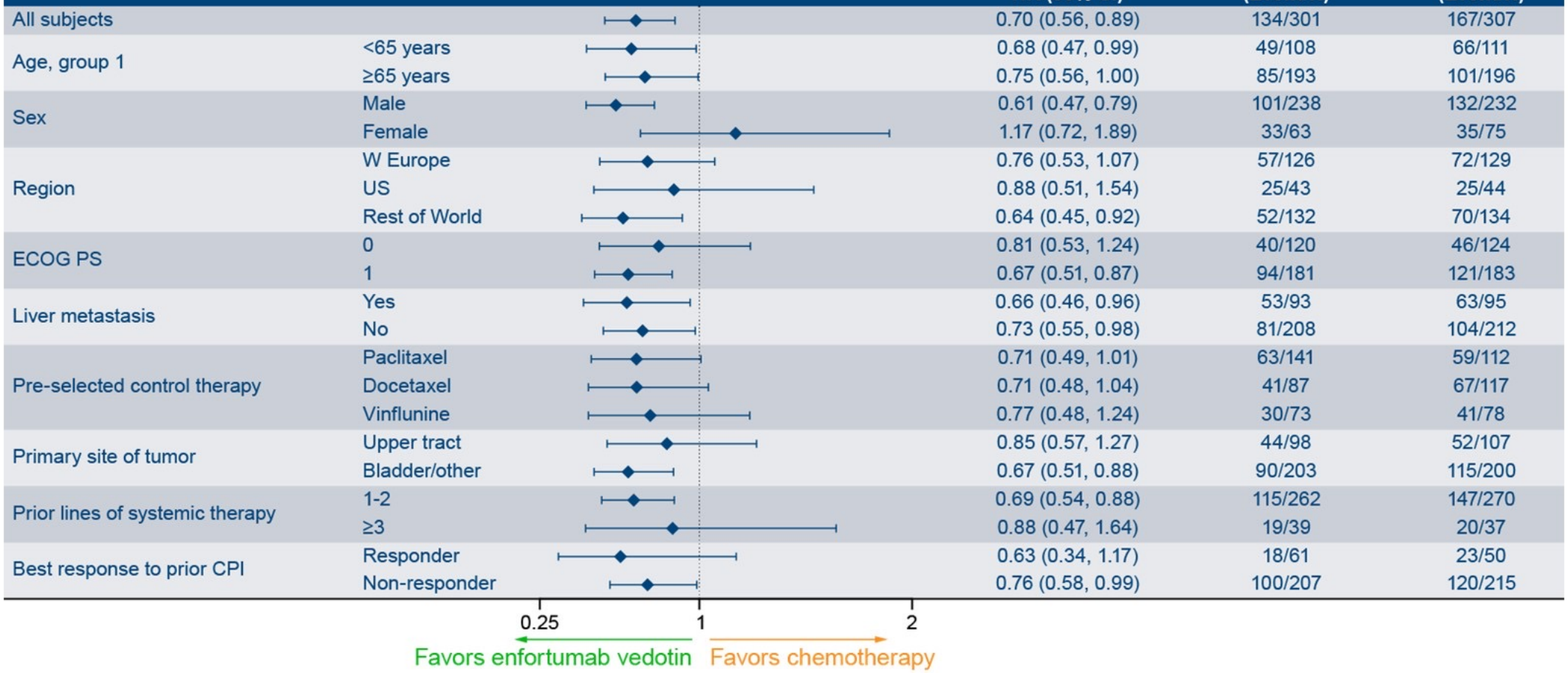
Enfortumab vedotin	301	286	272	257	246	234	222	190	158	130	105	85	63	52	42	33	23	15	7	4	3	2	1	1	0
Chemotherapy	307	288	274	250	238	219	198	163	131	101	84	66	51	44	32	29	16	11	6	4	2	2	1	0	0

Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off: July 15, 2020

Overall Survival: Subgroup Analyses

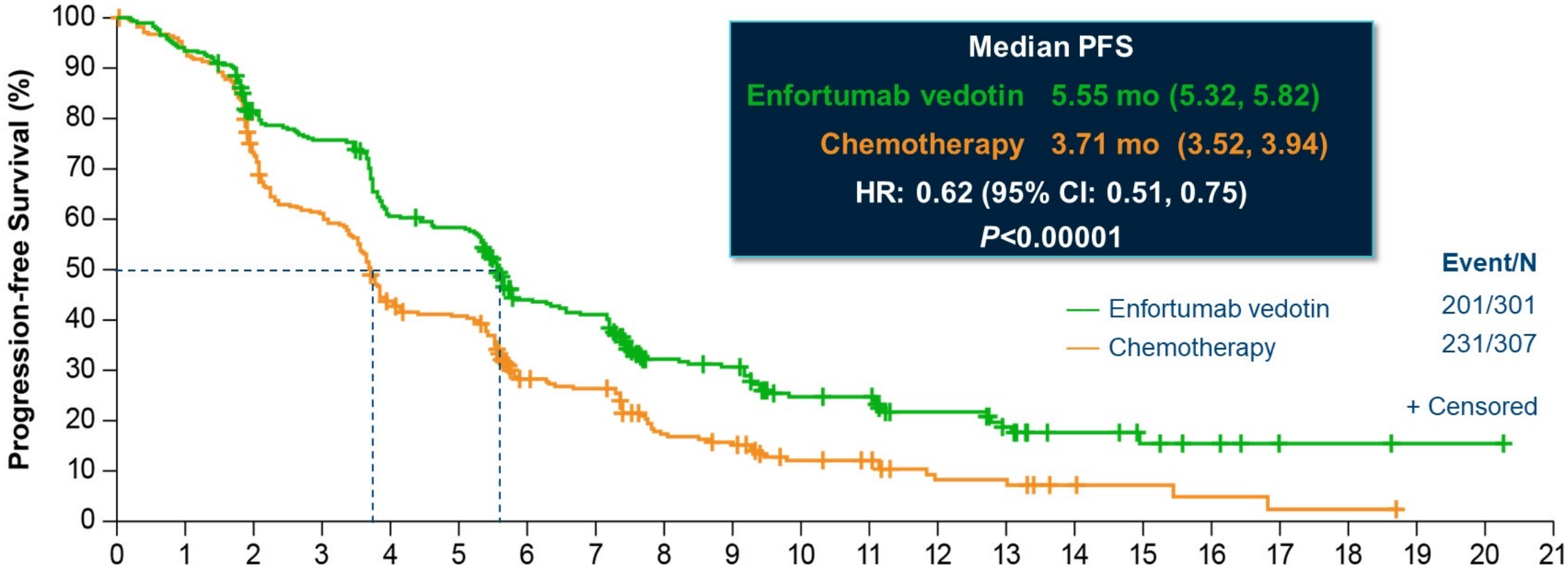
		HR (95% CI)	Enfortumab vedotin (Event/N)	Chemotherapy (Event/N)
All subjects		0.70 (0.56, 0.89)	134/301	167/307
Age, group 1	<65 years	0.68 (0.47, 0.99)	49/108	66/111
	≥65 years	0.75 (0.56, 1.00)	85/193	101/196
Sex	Male	0.61 (0.47, 0.79)	101/238	132/232
	Female	1.17 (0.72, 1.89)	33/63	35/75
Region	W Europe	0.76 (0.53, 1.07)	57/126	72/129
	US	0.88 (0.51, 1.54)	25/43	25/44
	Rest of World	0.64 (0.45, 0.92)	52/132	70/134
ECOG PS	0	0.81 (0.53, 1.24)	40/120	46/124
	1	0.67 (0.51, 0.87)	94/181	121/183
Liver metastasis	Yes	0.66 (0.46, 0.96)	53/93	63/95
	No	0.73 (0.55, 0.98)	81/208	104/212
Pre-selected control therapy	Paclitaxel	0.71 (0.49, 1.01)	63/141	59/112
	Docetaxel	0.71 (0.48, 1.04)	41/87	67/117
	Vinflunine	0.77 (0.48, 1.24)	30/73	41/78
Primary site of tumor	Upper tract	0.85 (0.57, 1.27)	44/98	52/107
	Bladder/other	0.67 (0.51, 0.88)	90/203	115/200
Prior lines of systemic therapy	1-2	0.69 (0.54, 0.88)	115/262	147/270
	≥3	0.88 (0.47, 1.64)	19/39	20/37
Best response to prior CPI	Responder	0.63 (0.34, 1.17)	18/61	23/50
	Non-responder	0.76 (0.58, 0.99)	100/207	120/215



Abbreviations: CI, confidence interval; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; US, United States; W, western.

Data cut-off: July 15, 2020

Progression-free Survival

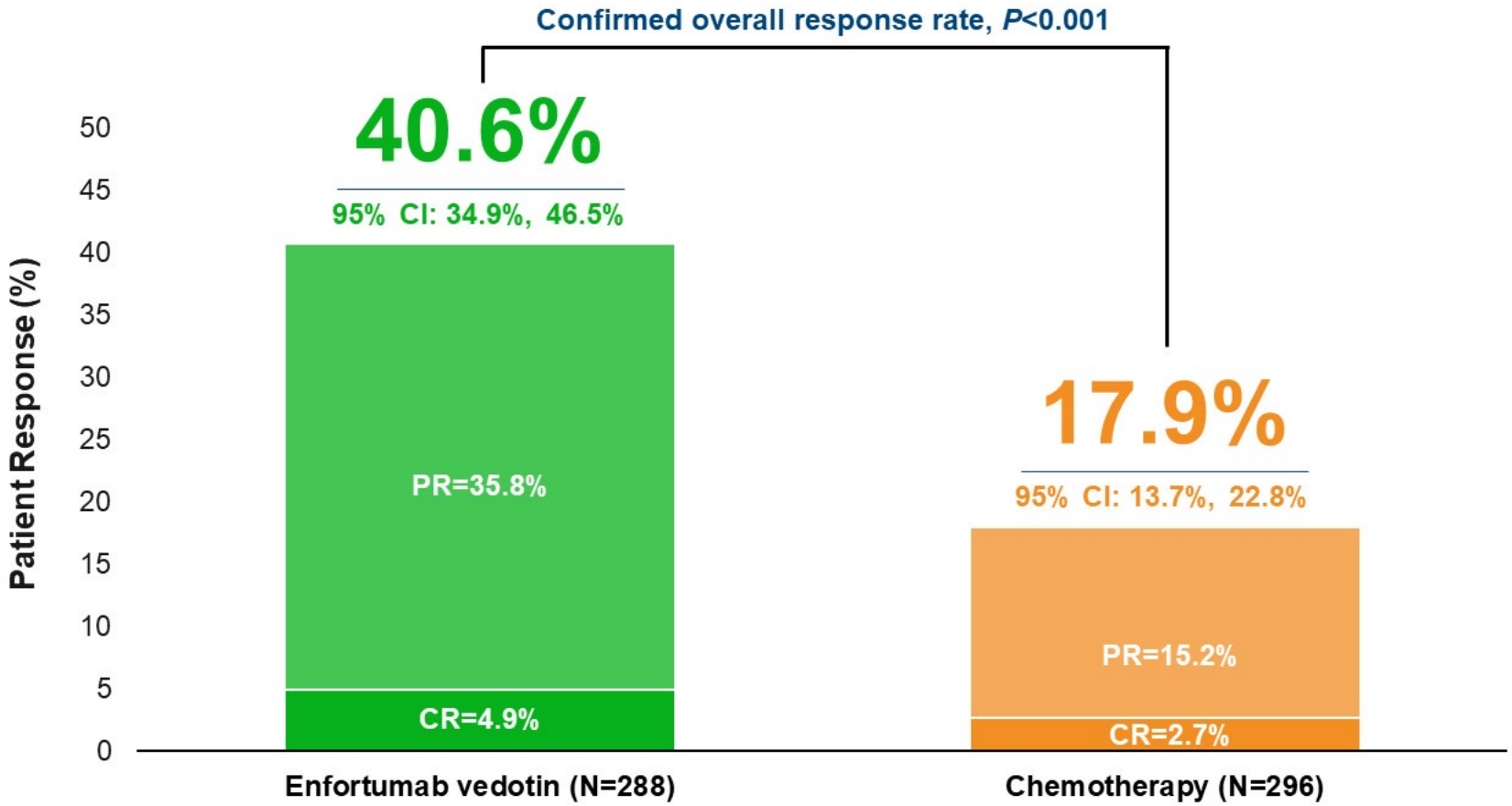


Patients at risk (n)																						
Enfortumab vedotin	301	269	224	208	165	158	102	95	60	56	38	36	23	17	11	7	5	2	2	1	1	0
Chemotherapy	307	259	200	166	116	107	62	57	33	29	18	16	8	8	4	3	2	1	0	0	0	0

Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Data cut-off: July 15, 2020

Investigator-Assessed Overall Response



Disease control rate,[a] % (95% CI)	71.9 (66.3, 77.0)	53.4 (47.5, 59.2)	*P*<0.001

Evaluated in the response-evaluable population. Response is as assessed by the investigator per RECIST v1.1.
[a]Indicates the proportion of patients who had a best overall response of confirmed CR, PR, or SD (at least 7 weeks); enfortumab vedotin vs chemotherapy.
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Data cut-off: July 15, 2020

Treatment-Related Adverse Events

Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any adverse event	**94%**	**51%**	**92%**	**50%**
Alopecia	45%	0	36%	0
Peripheral sensory neuropathy	34%	3%	21%	2%
Pruritus	32%	1%	4%	0
Fatigue	31%	6%	23%	4%
Decreased appetite	31%	3%	23%	2%
Diarrhea	24%	3%	16%	2%
Dysgeusia	24%	0	7%	0
Nausea	23%	1%	22%	1%
Rash maculopapular	16%	7%	2%	0
Anemia	12%	3%	20%	8%
Neutrophil count decreased	10%	6%	17%	13%
Neutropenia	7%	5%	8%	6%
White blood cell decreased	5%	1%	11%	7%
Febrile neutropenia	1%	1%	5%	5%
Serious adverse events[a]	23%	-	23%	-
Leading to treatment withdrawal	14%	-	11%	-

TRAEs leading to death, excluding disease progression, occurred in 7 patients (2.4%) treated with EV and 3 (1.0%) treated with chemotherapy.

Evaluated in the safety population; displaying adverse events (AEs) occurring in ≥20% or grade ≥3 AEs occurring in ≥5% of patients in either treatment group. Dashes indicate 'not applicable.'
Treatment-related AEs are events with a reasonable possibility of relationship to treatment (investigator-assessed) or missing relationship and are not time-adjusted.
This slide contains updated data in the chemotherapy arm to adjust for compounded rounding.
[a]AEs that were deemed "serious" in the view of the investigator or sponsor and based upon predefined criteria.
Abbreviations: AE, adverse event; EV, enfortumab vedotin; TRAEs, treatment-related adverse events.

Data cut-off: July 15, 2020

Adverse Events of Special Interest

Treatment-Related Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Skin Reactions[a]	**47%**	**15%**	**16%**	**1%**
Rash	44%	15%	10%	0[c]
Severe cutaneous adverse reactions[b]	20%	5%	8%	1%
Peripheral neuropathy	**46%**	**5%**	**31%**	**2%**
Sensory events	44%	4%	30%	2%
Motor events	7%	2%	2%	0
Hyperglycemia	**6%**	**4%**	**0[c]**	**0**

The majority of TRAEs of special interest were mild-to-moderate in severity.

Evaluated in the safety population; displaying selected TRAEs of special interest to EV. Differences between AE rates in current and prior slide may be due to preferred term groupings. TRAE are events with a reasonable possibility of relationship to study treatment as assessed by the investigator or missing relationship.

[a]Encompasses rash and severe cutaneous adverse reactions.

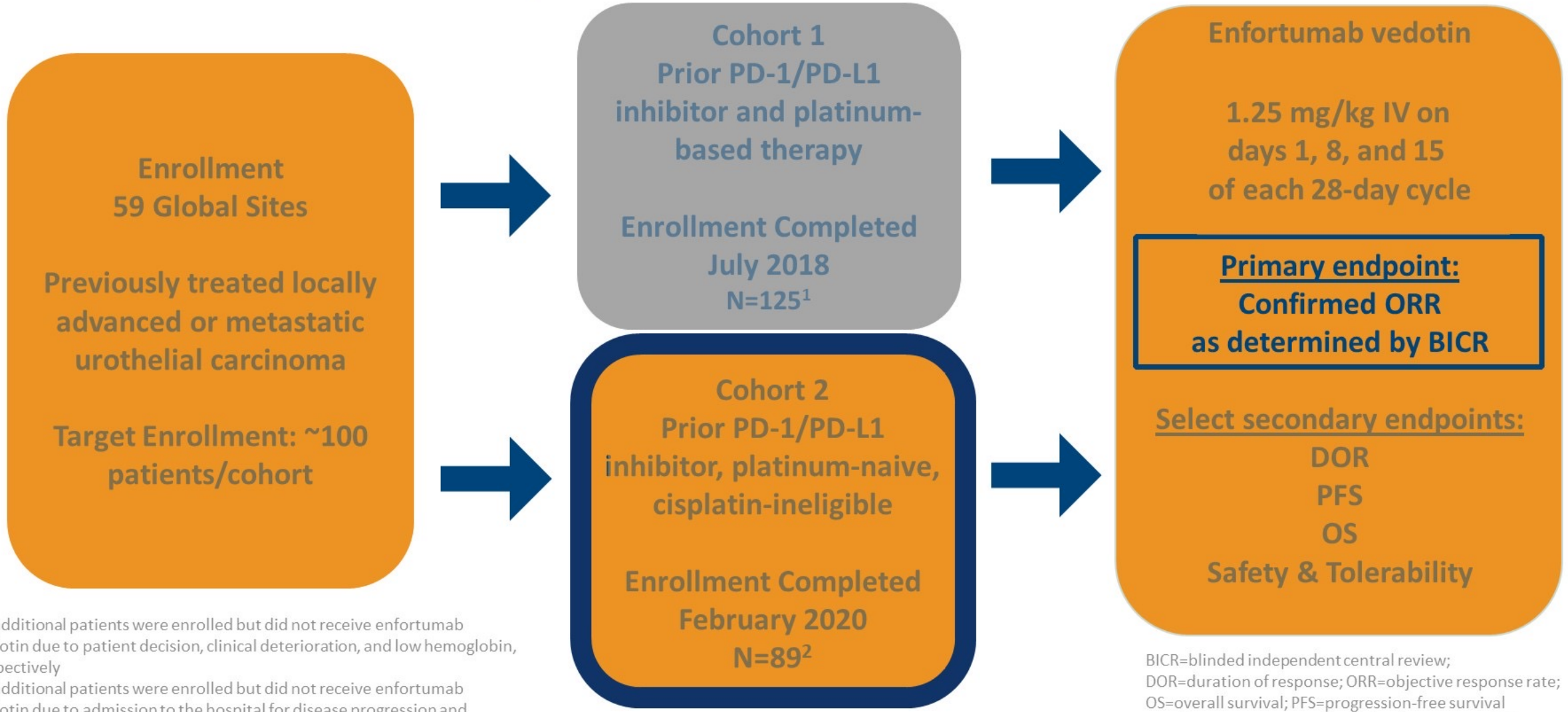
[b]Severe cutaneous adverse reactions included the following (by Preferred Term): stomatitis, drug eruption, conjunctivitis, blister, dermatitis bullous, skin exfoliation, erythema multiforme, exfoliative rash, fixed eruption, mouth ulceration, pemphigus, and toxic skin eruption.

[c]One patient had the TRAE that is listed.

Abbreviations: EV, enfortumab vedotin; TRAE, treatment-related adverse event.

Data cut-off: July 15, 2020

EV-201: Non-Comparative, Pivotal Phase 2 Trial



[1]3 additional patients were enrolled but did not receive enfortumab vedotin due to patient decision, clinical deterioration, and low hemoglobin, respectively

[2]2 additional patients were enrolled but did not receive enfortumab vedotin due to admission to the hospital for disease progression and hospice care, respectively

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival PD-1/PD-L1=programmed cell death protein 1 inhibitor, programmed death-ligand 1 inhibitor

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

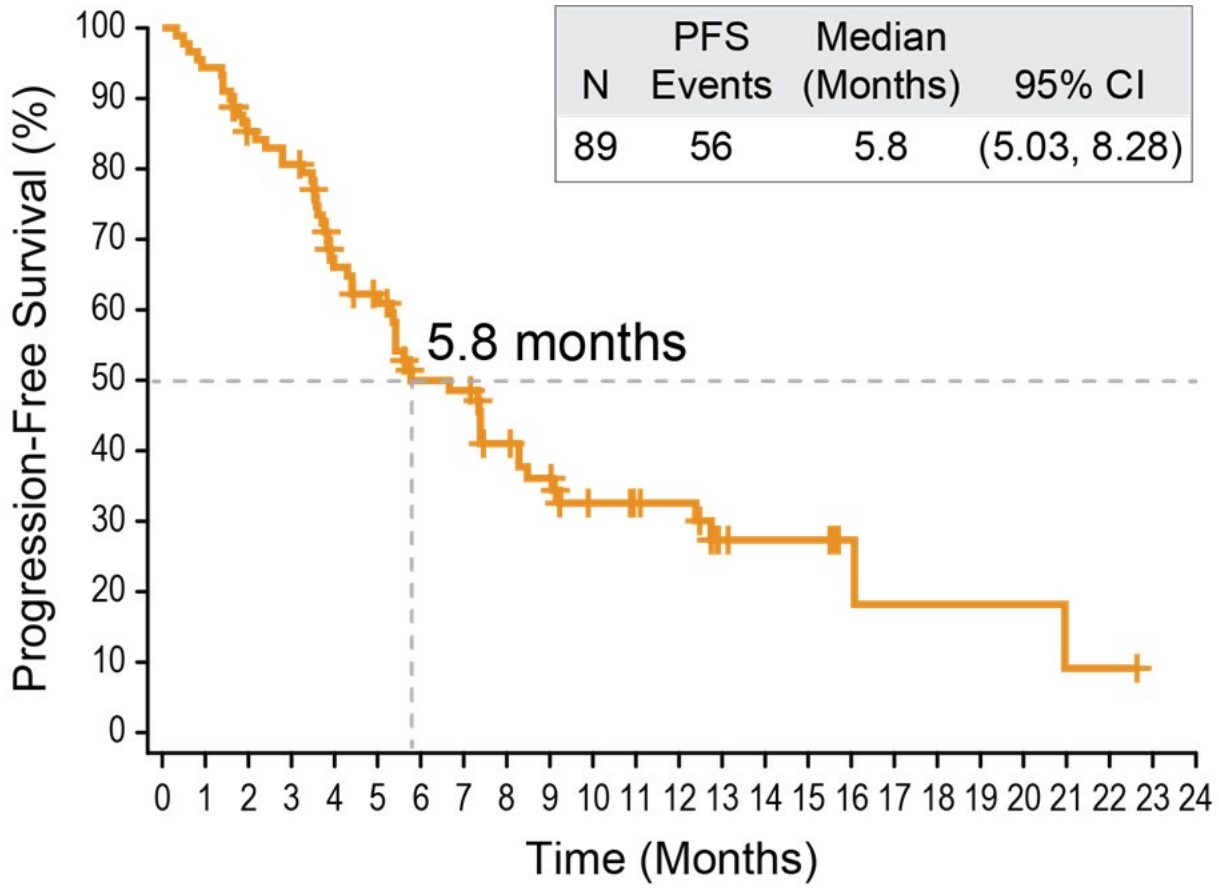
ORR = Objective Response Rate; RECIST = Response Evaluation Criteria in Solid Tumors; BICR = Blinded Independent Central Review

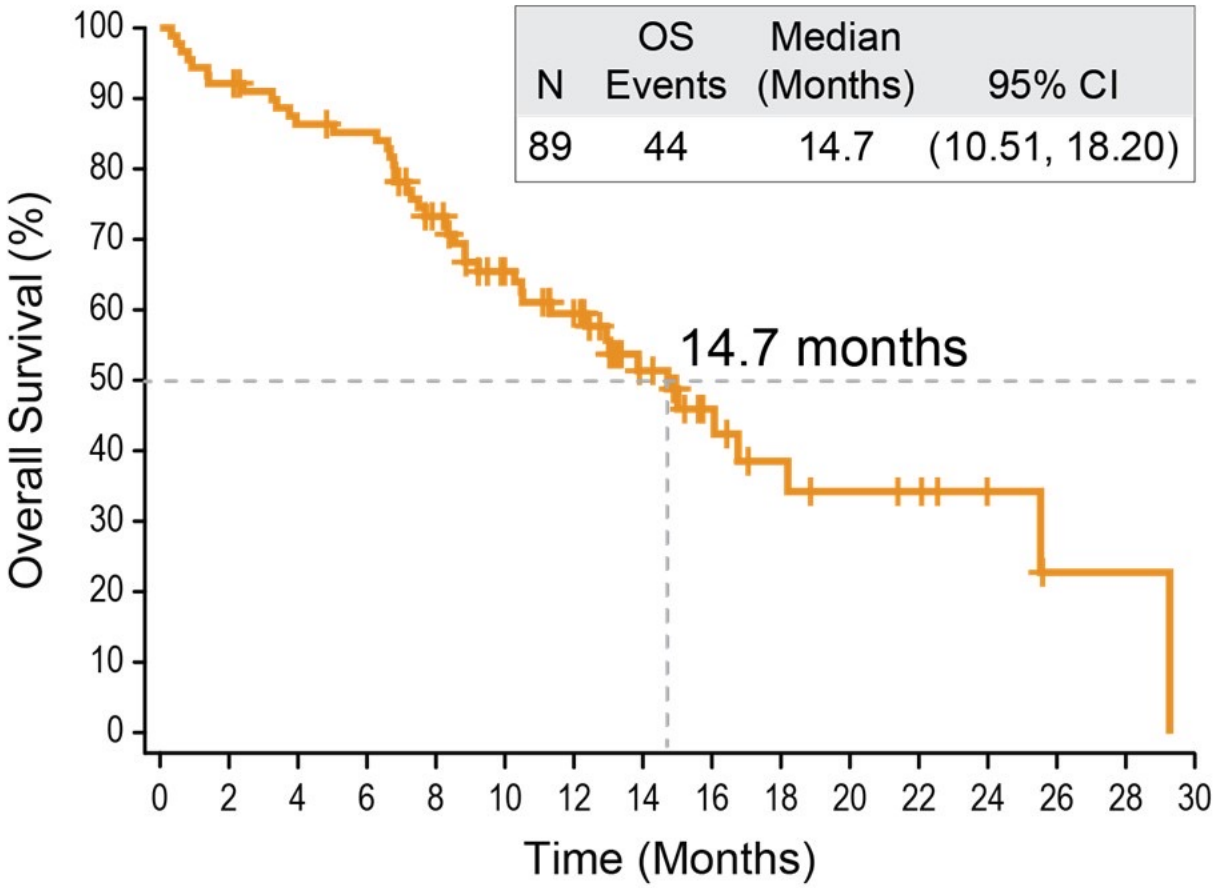
[1]CI = Confidence Interval, Computed using the Clopper-Pearson method

[2]Best overall response according to RECIST v1.1. Complete response and partial response were confirmed with repeat scans ≥28 days after initial response.

[3]Includes five subjects who did not have response assessment post-baseline, two subjects whose post-baseline assessment did not meet the minimum interval requirement for stable disease, and one subject whose response cannot be assessed due to incomplete anatomy.

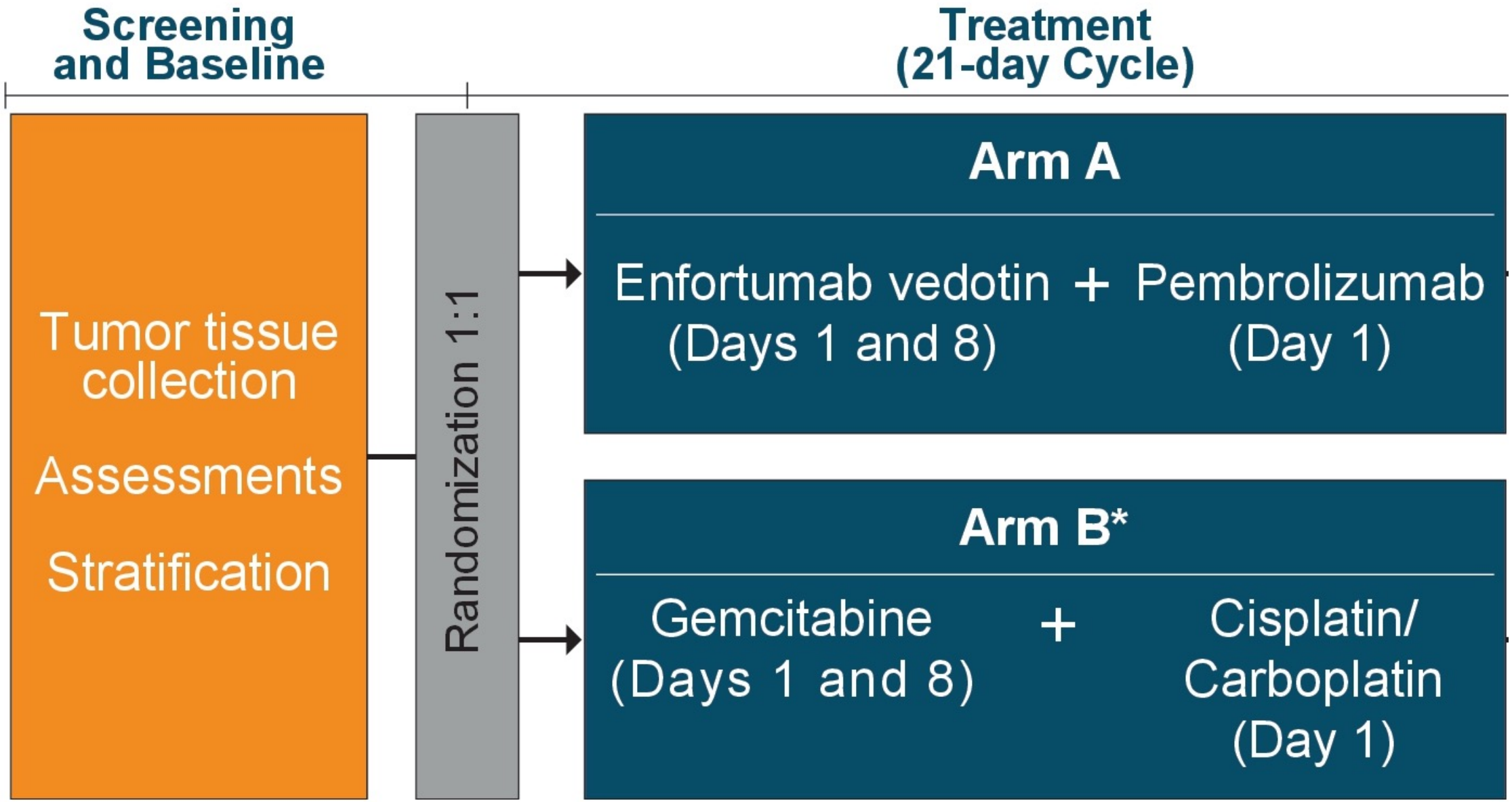
EV-201 Cohort 2: Progression-Free Survival and Overall Survival



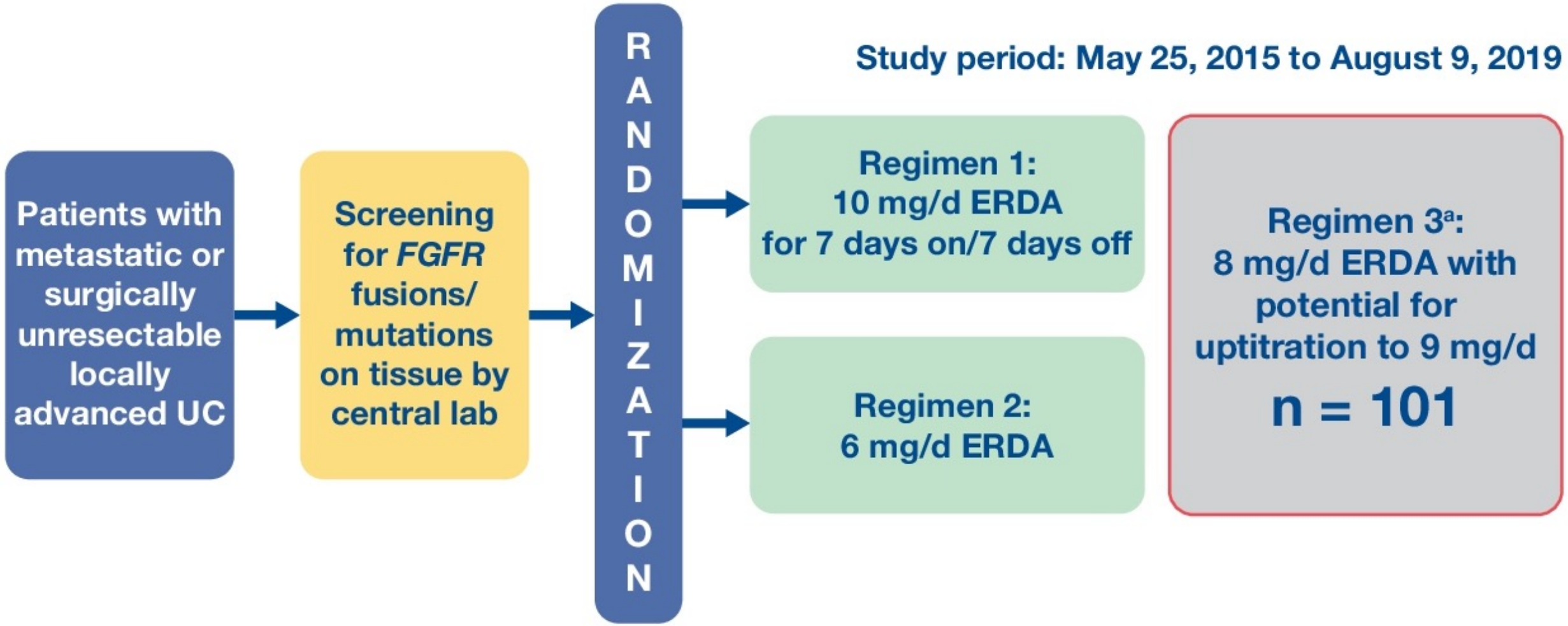


Median follow-up: 13.4 months

EV-302/Keynote-A39 Study Design



Erdafitinib in locally advanced or metastatic urothelial carcinoma (mUC): Long-term outcomes in BLC2001.



[a]Dose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.

Siefker-Radtke *et al* ASCO 2020 (Abstr 5015)

Table 1. Baseline Characteristics

Patients, n (%)		ERDA 8 mg/d UpT n = 101[a]
Age, median (range), years		67 (36-87)
ECOG PS	0 1 2	51 (50) 43 (43) 7 (7)
Pretreatment	Progressed or relapsed after chemo Chemo naive Prior immunotherapy	89 (88) 12 (12) 24 (24)
Number of lines of prior treatment	0 1 2 ≥ 3	10 (10) 48 (48) 28 (28) 15 (15)
Visceral metastases	Present Absent	78 (77) 23 (23)
Hemoglobin level, g/dL	≥ 10 < 10	86 (85) 15 (15)
Tumor location	Upper tract Lower tract	25 (25) 76 (75)
Creatinine clearance rate	< 60 mL/min ≥ 60 mL/min	53 (52) 48 (48)

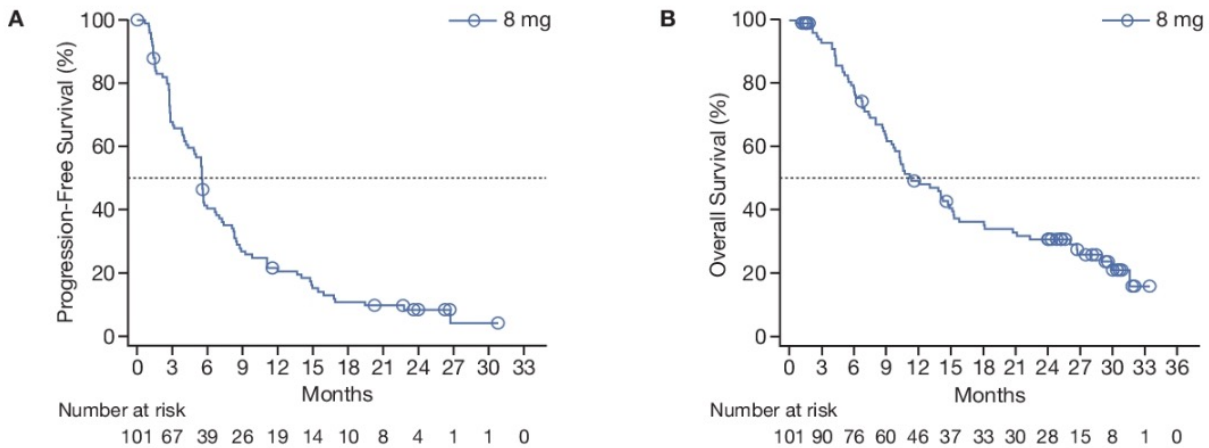
[a]2 patients were added to the 8 mg daily regimen since the cutoff date for the primary analysis (March 15, 2018).

Siefker-Radtke *et al* ASCO 2020 (Abstr 5015)

Efficacy

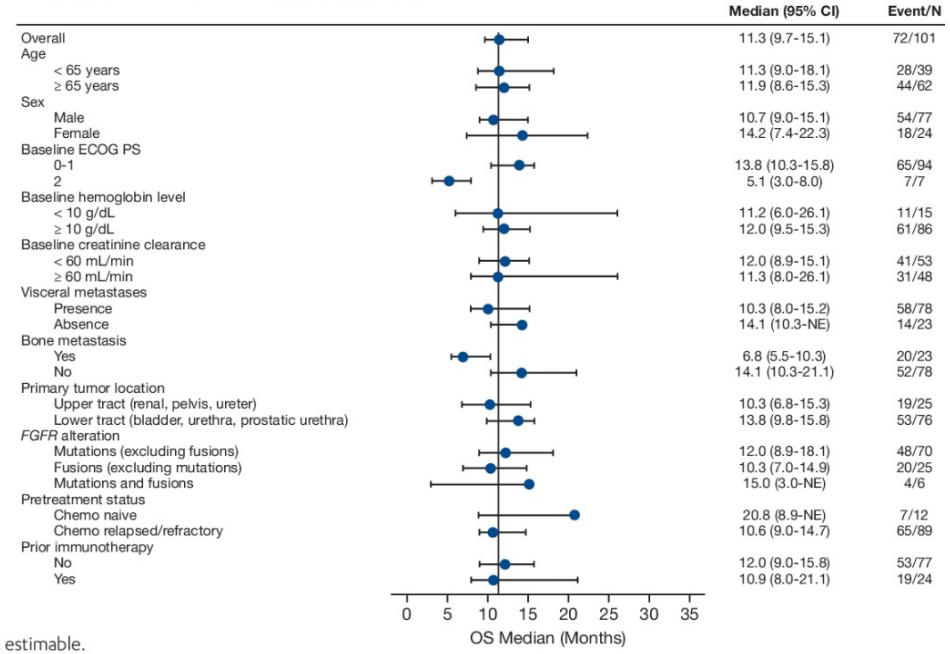
- At final analysis, the confirmed investigator-assessed ORR was 40% (95% confidence interval [CI], 30%-49%) among all patients, consistent with the 40% ORR (95% CI, 31%-50%) at the time of primary analysis.[3]
- Confirmed ORR was 39% (95% CI, 29%-50%) for the treated chemo-relapsed/refractory (R/R) population.
- Median DOR was 6.0 (95% CI, 4.2-7.5) months and independent of age, sex, and most baseline characteristics, eg, hemoglobin level and renal function; 31% of responders had DOR ≥ 12 months.
- Median PFS was 5.5 months (95% CI, 4.0-6.0) for all treated patients (Figure 2A), and:
  - 5.5 months (95% CI, 4.0-5.7 months) for treated chemo-R/R patients
  - 5.7 months (95% CI, 4.9-8.3 months) for patients with prior immunotherapy
  - 5.5 months (95% CI, 2.8-6.0), 5.5 months (95% CI, 2.7-8.3), and 5.7 months (95% CI, 4.0-9.2), among patients with 1, 2, and 3 prior lines of therapy, respectively

Figure 2. A) Progression-Free Survival[a] and B) Overall Survival



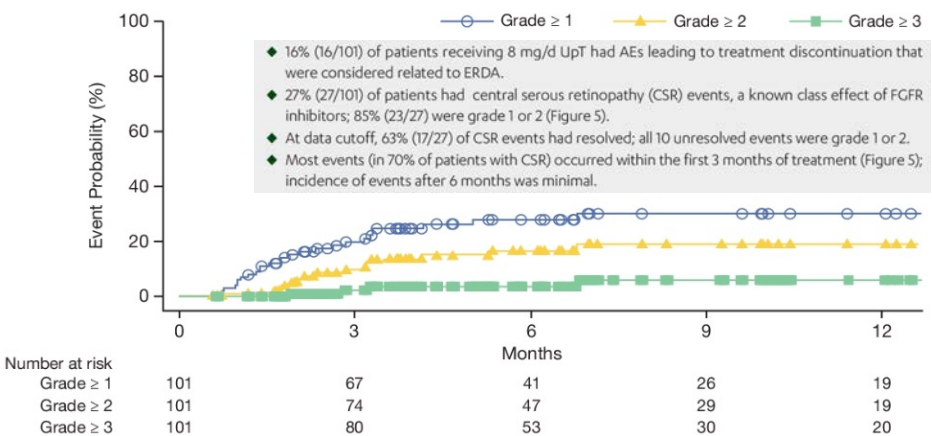
[a]By investigator assessment.

Figure 4. Forest Plot of OS by Subgroup



NE, not estimable.

Figure 5. Central Serous Retinopathy

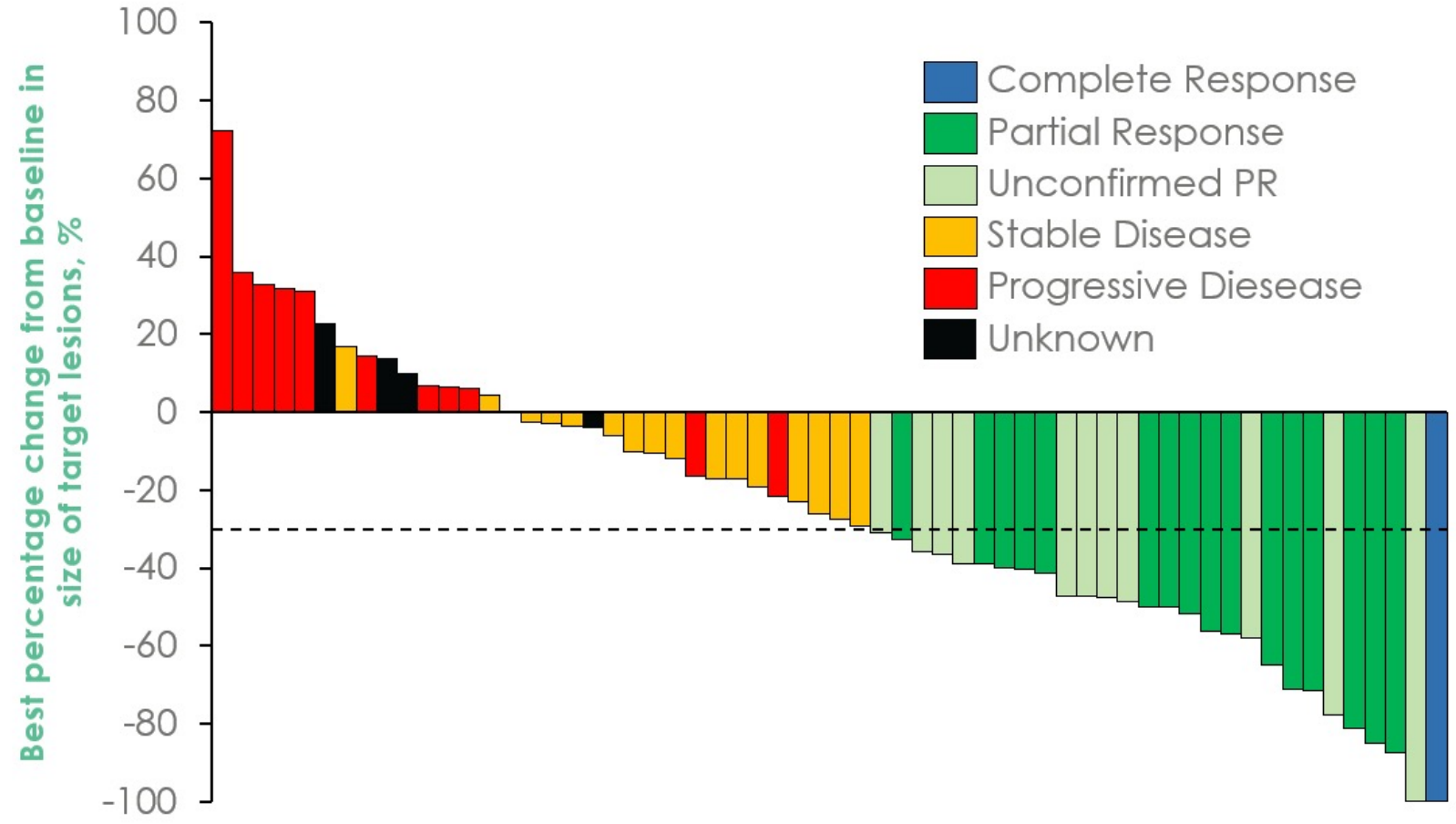


Three patients had grade 3 CSR events that resolved or lessened in severity to grade 1 following dose reduction or interruption in 2 patients and no dose modification in another patient, and 1 patient had grade 3 detachment of retinal pigment epithelium, which initially resolved but then recurred as a grade 2 event following dose reduction (ultimately leading to discontinuation of ERDA in this patient).

Siefker-Radtke *et al* ASCO 2020 (Abstr 5015)

Infigratinib: FGFR3 inhibitor

Phase 1 expansion cohort advanced urothelial carcinoma with FGFR GAs (N=67)



25% confirmed ORR

42% BOR (including unconfirmed responses)

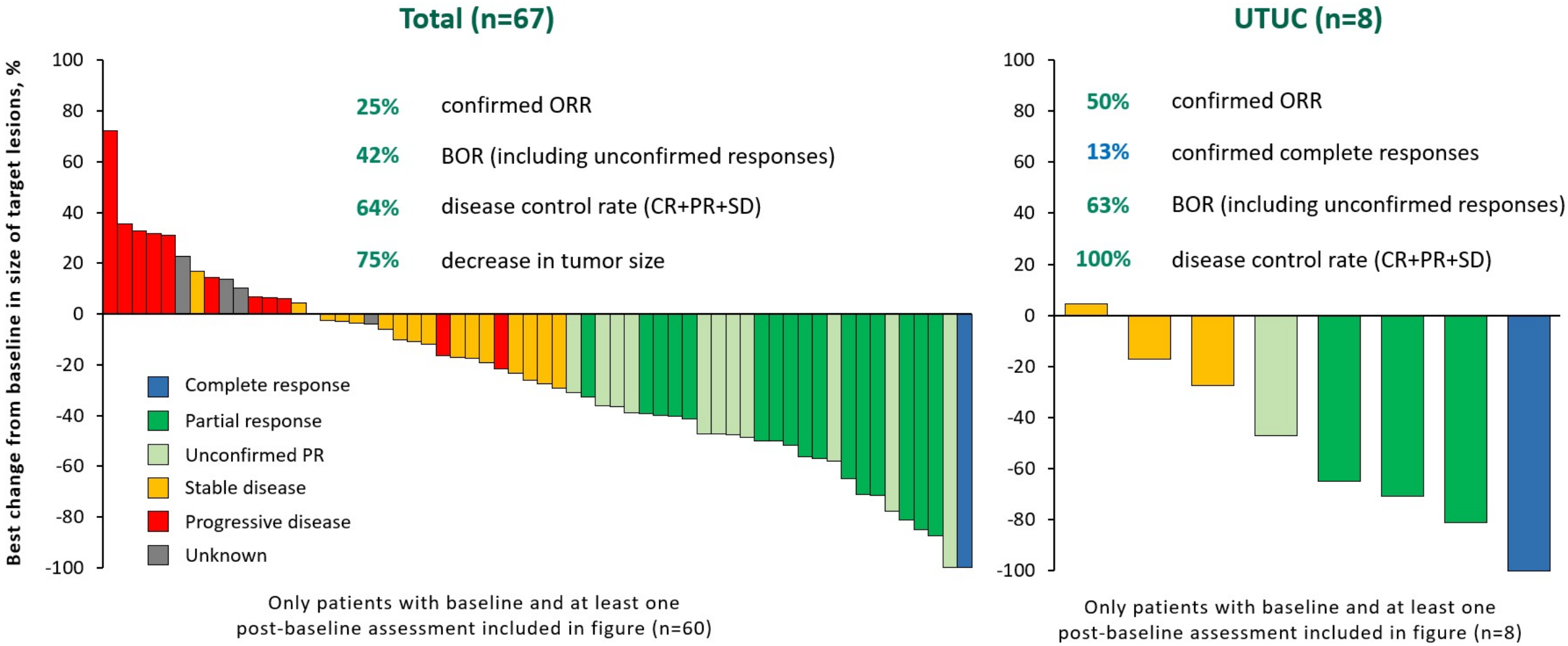
64% disease control rate (CR+PR+SD)

75% decrease in tumor size

Only patients with baseline and at least one post-baseline assessment included in figure (N=60)

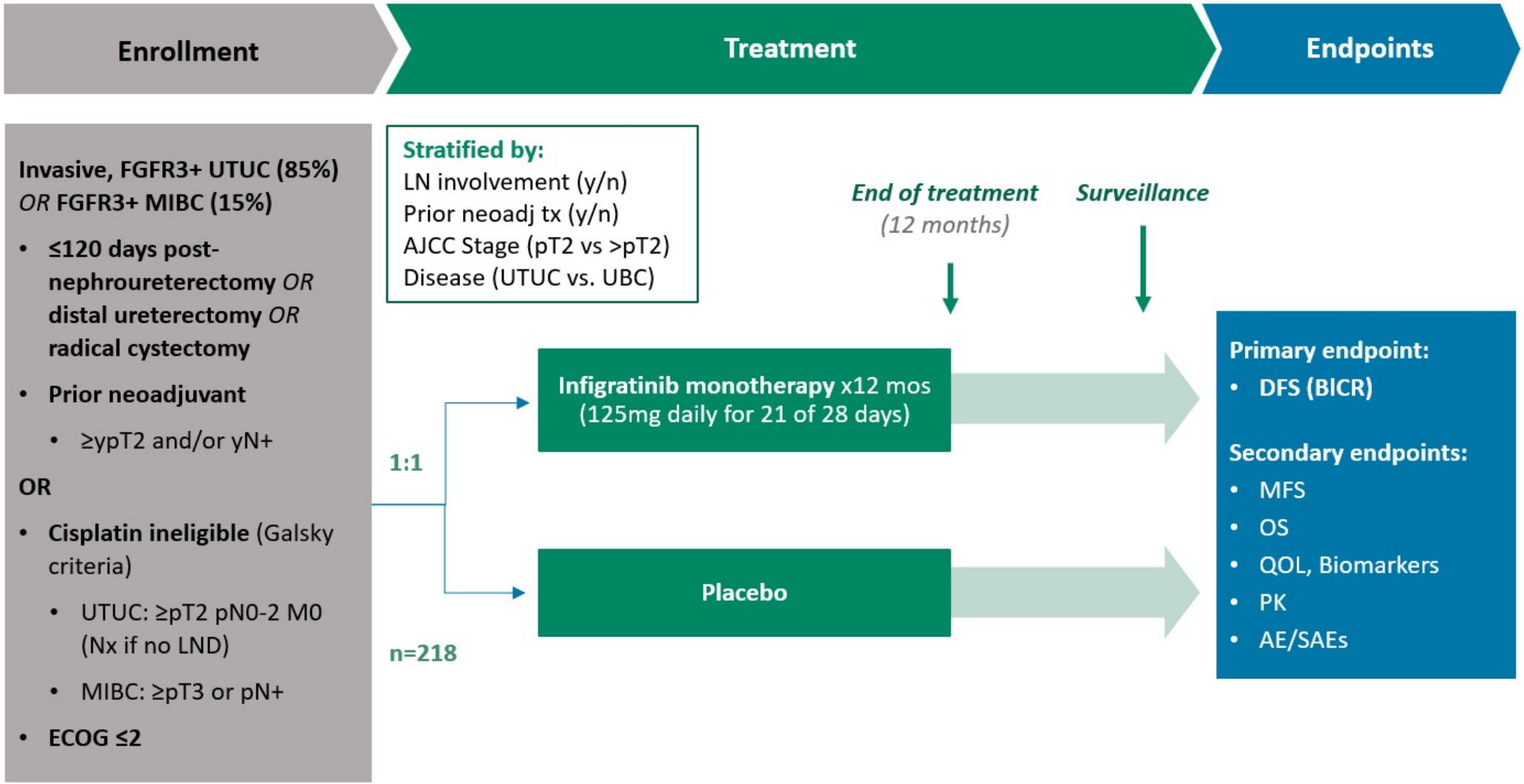
Pal, Sumanta K., Jonathan E. Rosenberg, Jean H. Hoffman-Censits, Raanan Berger, David I. Quinn, Matthew D. Galsky, Juergen Wolf, et al. "Efficacy of BGJ398, a Fibroblast Growth Factor Receptor 1-3 Inhibitor, in Patients with Previously Treated Advanced Urothelial Carcinoma with FGFR3 Alterations." *Cancer Discovery* 8, no. 7 (July 2018): 812–21. https://doi.org/10.1158/2159-8290.CD-18-0229.

Responses seen in urothelial patients



Pal, Sumanta K., Siamak Daneshmand, Surena F. Matin, Yohann Loriot, Srikala S. Sridhar, Petros Grivas, Shilpa Gupta, et al. "PROOF 302: A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Infigratinib as Adjuvant Therapy in Patients with Invasive Urothelial Carcinoma Harboring FGFR3 Alterations." *Journal of Clinical Oncology* 38, no. 6_suppl (February 20, 2020): TPS600–TPS600. https://doi.org/10.1200/JCO.2020.38.6_suppl.TPS600.

PROOF 302: adjuvant infigratinib vs. placebo for invasive urothelial carcinoma with susceptible *FGFR3* alterations



Pal, Sumanta K., Siamak Daneshmand, Surena F. Matin, Yohann Loriot, Srikala S. Sridhar, Petros Grivas, Shilpa Gupta, et al. "PROOF 302: A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Infigratinib as Adjuvant Therapy in Patients with Invasive Urothelial Carcinoma Harboring FGFR3 Alterations." *Journal of Clinical Oncology* 38, no. 6_suppl (February 20, 2020): TPS600–TPS600. https://doi.org/10.1200/JCO.2020.38.6_suppl.TPS600.

original reports

TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors

Scott T. Tagawa, MD, MS[1]; Arjun V. Balar, MD[2]; Daniel P. Petrylak, MD[3]; Arash Rezazadeh Kalebasty, MD[4]; Yohann Loriot, MD, PhD[5]; Aude Fléchon, MD, PhD[6]; Rohit K. Jain, MD[7]; Neeraj Agarwal, MD[8]; Manojkumar Bupathi, MD, MS[9]; Philippe Barthelemy, MD, PhD[10]; Philippe Beuzeboc, MD, PhD[11]; Phillip Palmbos, MD, PhD[12]; Christos E. Kyriakopoulos, MD[13]; Damien Pouessel, MD, PhD[14]; Cora N. Sternberg, MD[1]; Quan Hong, MD[15]; Trishna Goswami, MD[15]; Loretta M. Itri, MD[15]; and Petros Grivas, MD, PhD[16]

ASCO

Journal of Clinical Oncology®

2474 Volume 39, Issue 22

TABLE 1. Patient Demographics

Characteristic
Age, median (range), years
≥ 75, No. (%)
Male, No. (%)
Race, No. (%)
White
Black
Asian
Other
Not reported
ECOG PS, No. (%)
0
1

TABLE 2. Summary of Treatment Efficacy

Variable	(N = 113)
Best response, No. (%)	
CR	6 (5)
PR	25 (22)
SD	38 (34)
PD	21 (19)
Not evaluable	8 (7)
Not assessed[a]	15 (13)
ORR	
No. of patients	31
% patients (95% CI)	27 (19 to 37)
CBR[b]	
No. of patients	42
% patients (95% CI)	37 (28 to 47)
Time to onset of response (months)	
Median	1.6
Range	1.2-2.9

108 (96)
4 (3.5)
1 (0.09)
75 (66)
49 (43)
38 (34)
15 (13)
No. (%)
22 (19.5)
108 (95.6)
36 (31.9)
112 (99)[b]
, No. (%) 113 (100)
89 (79)
24 (21)
10 (8.8)
2 (1.8)
Prior anticancer regimens, median, No. (range) 3.0 (1-8)

Tagawa *et al* JCO 2021

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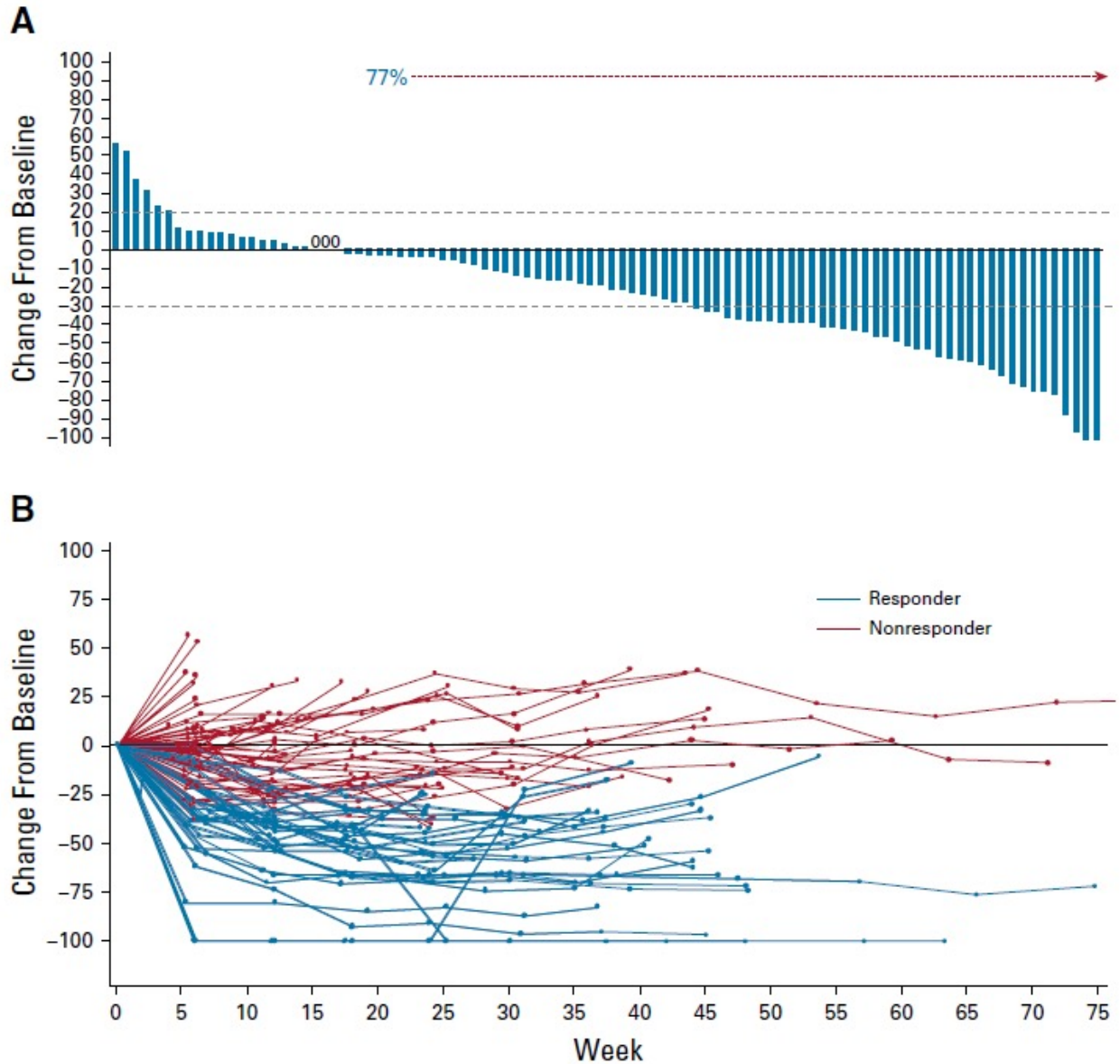
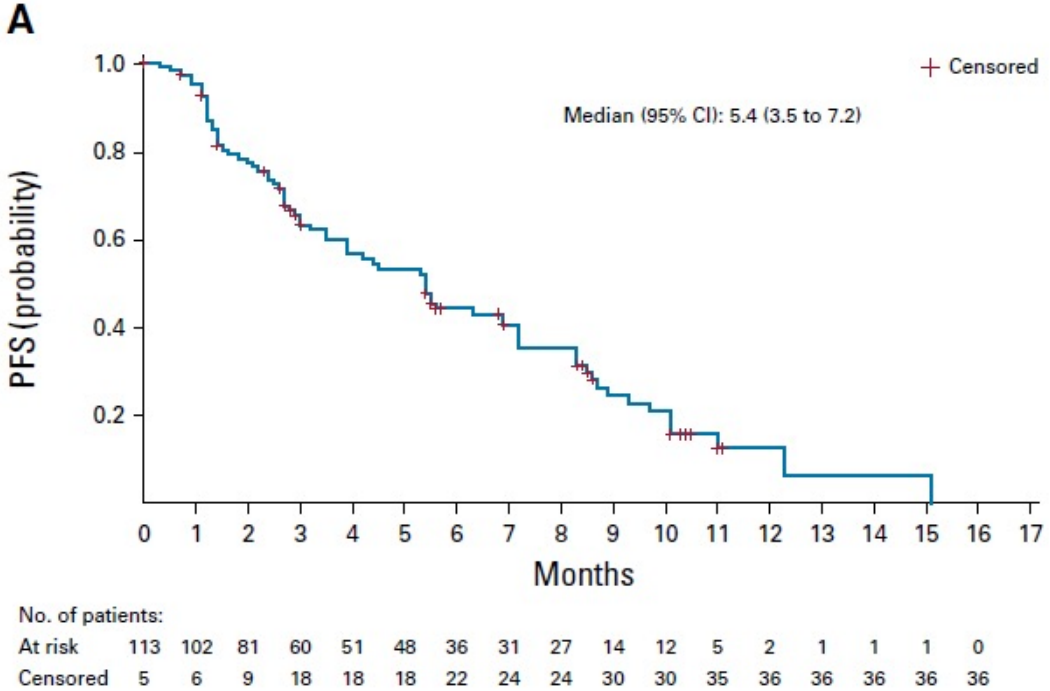
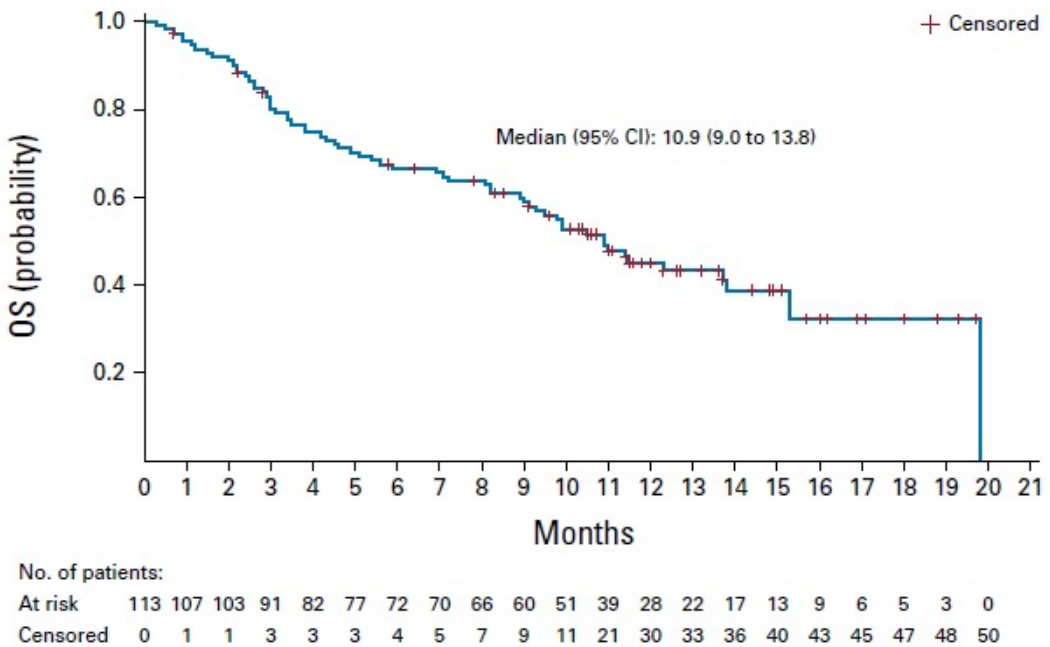


Tagawa *et al* JCO 2021





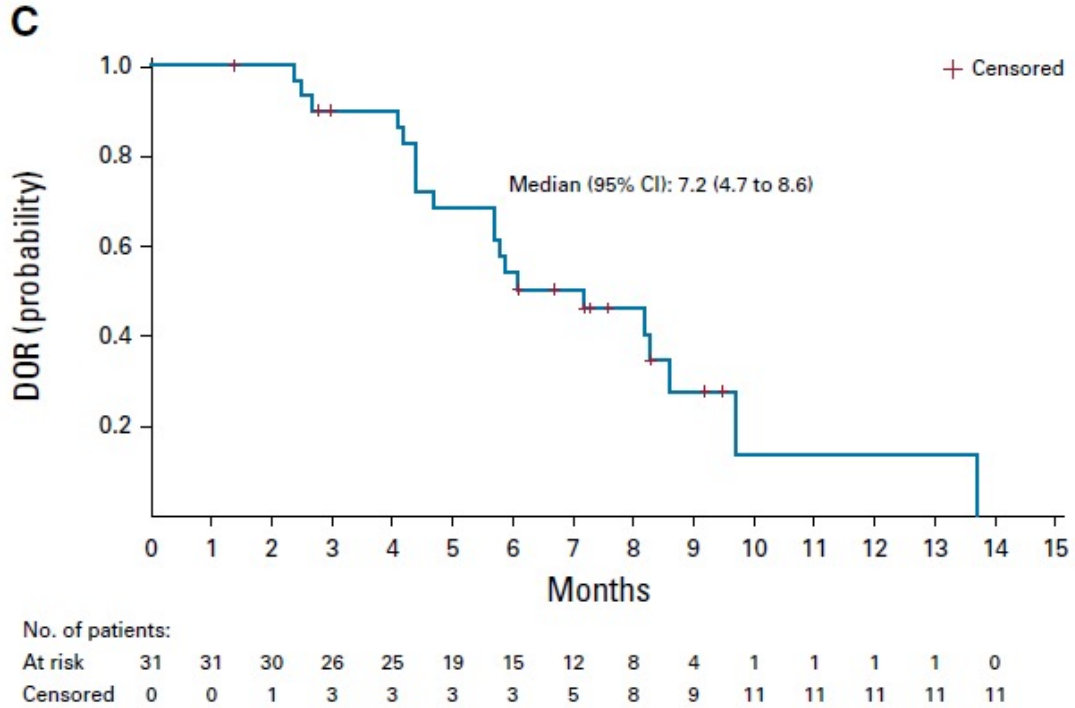


TABLE 3. Most Common TRAEs of Any Grade (Observed in ≥ 20% of Patients) orTRAEs Grade ≥ 3 (Observed in ≥ 5% of Patients) (N = 113)

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	Neutropenia	46	22	12
	Leukopenia	25	12	5
	Anemia	33	14	0
	Lymphopenia	11	5	2
	Febrile neutropenia	10	7	3
GI	Diarrhea	65	9	1
	Nausea	60	4	0
	Vomiting	30	1	0
General disorders and administrative site conditions	Fatigue	52	4	0
Skin and subcutaneous tissue	Alopecia	47	0	0
Metabolism and nutrition	Decreased appetite	36	3	0
Infections and infestations	Urinary tract infection	8	6	0

Tagawa *et al* JCO 2021

TROPHY-U-01 Is a Registrational, Open-Label, Multicohort Phase 2 Trial in Patients With mUC

TROPHY U-01

Cohort 1* (~100 patients): patients with mUC who progressed after prior platinum-based and CPI-based therapies
→ SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 2 (~40 patients): patients with mUC ineligible for platinum-based therapy and who progressed after prior CPI-based therapies
→ SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 3[a] (up to 61 patients): mUC CPI naïve patients who progressed after prior platinum-based therapies
→ SG 10 mg/kg Days 1 and 8, every 21 days + Pembrolizumab 200 mg day 1 every 21 days

Cohort 4 (up to 60 patients): mUC platinum-naïve patients
→ SG Days 1 and 8, every 21 days + Cisplatin[b]

Cohort 5 (up to 60 patients): mUC platinum-naïve patients
→ SG Days 1 and 8, every 21 days + Cisplatin[c] + Avelumab 800 mg every 2 weeks

Continue treatment in the absence of unacceptable toxicity or disease progression

Continue until a maximum of 6 cycles has been completed,[d] disease progression, lack of clinical benefit, toxicity, or withdrawal of consent

→ **Maintenance avelumab (800 mg every 2 weeks) with SG (Days 1 and 8 every 21 days) for those without disease progression**

Primary Endpoint:
Objective response rate by investigator review per RECIST 1.1 criteria

Key Secondary Endpoints:
Safety/tolerability, DOR, PFS, OS

Key Inclusion Criteria: Age ≥18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥30 mL/min,[b,c] adequate hepatic function
Key Exclusion Criteria: Immunodeficiency, active Hepatitis B or C, active secondary malignancy, or active brain metastases

***Accelerated FDA approval for treatment of patients with locally advanced or mUC who previously received platinum-containing chemotherapy and PD-1/L1 inhibitor[1]**

[a]Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. [b]In patients with CrCl ≥60 mL/min; [c]In patients with creatinine clearance 50–60 mL/min. [d]For patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 2 weeks beginning cycle 1, day 1 and every 2 weeks thereafter) followed by SG on days 1 and 8 every 21 days.
CBR, clinical benefit rate; CPI, checkpoint inhibitor; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.
1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

Demographics

TROPHY U-01

	Cohort 3 (N=41)
Male, n (%)	34 (83)
Median age, y (range)	67 (46–86)
Race, n (%)	
White	22 (54)
Other or not reported	19 (46)
ECOG PS 1, n (%)	25 (61)
Baseline Hgb <10 g/dl	5 (12)
Tumor stage at screening, n (%)	
Loco-regional only	9 (22)
Distant metastasis	32 (78)
Site of disease at baseline	
Visceral	28 (68)
Liver metastasis at baseline, n (%)	12 (29)
Non-visceral	13 (32)
Median prior anticancer chemotherapy regimens, (range)	1 (1-2)
≤2 prior anticancer chemotherapy regimen, n (%)	41 (100)
Prior platinum chemotherapy, n (%)	
Cisplatin	28 (68)
Carboplatin	12 (29)

ECOG PS, Eastern Cooperative Oncology Group performance status; Hgb, hemoglobin.

Baseline Disease Characteristics and Prior Therapy

TROPHY U-01

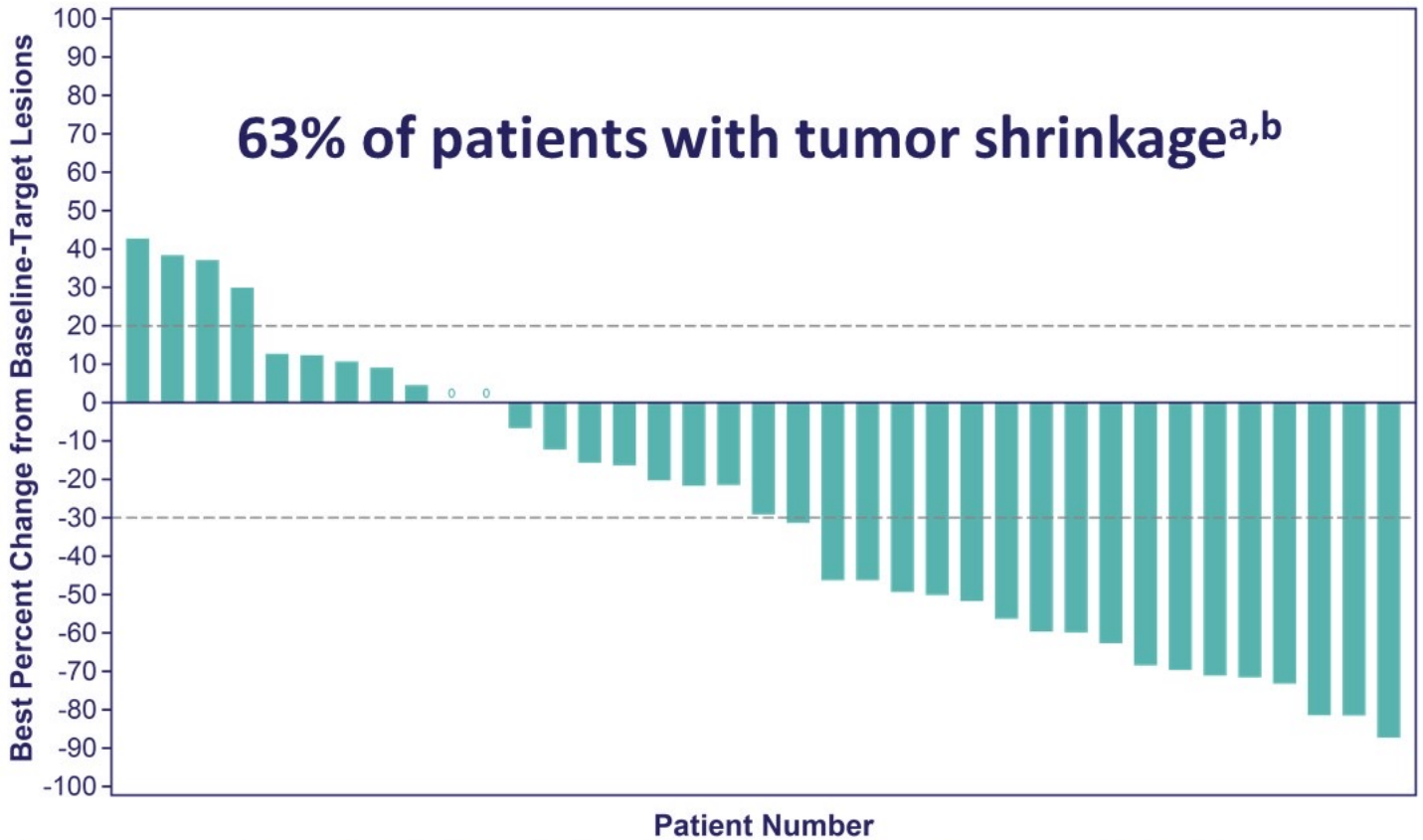
	Cohort 3 (N=41)
Bellmunt risk factor	
0	10 (24)
1	20 (49)
2	11 (27)
Setting of prior systemic therapy, n (%)	
(Neo)adjuvant	20 (49)
Median time from end of most recent prior systemic therapy to screening start date, months	6.8
Metastatic*	21 (51)
Median time from end of most recent prior systemic therapy to screening start date, months	1.6
Best response to prior systemic therapy in metastatic setting¶, n (%)	
Complete response	1 (2)
Partial response	2 (5)
Stable disease	11 (27)
Disease progression	6 (15)

*Makrakis, D et al. 2022 ASCO-GU. Abs ID505; ¶Pending data query for one patient (n=1)

Overall Response and Best % Change From Baseline in Tumor Size

TROPHY U-01

- Median follow-up: 5.8 months (data cutoff date: 2021-09-24)
- Median time to response: 2 months (1.3–2.8; n=14)
- Median DOR not yet reached: N/A (2.80-N/A)
- Median PFS (95% CI), 5.5 months (1.7–NR); median OS, not reached



	Cohort 3[a] (N=41)
Objective response rate (CR + PR), n (%) [95%CI]	**14 (34) [20.1-50.6]**
Objective response rate (CR + PR), evaluable patients, n (%)	14 (38)
Best overall response, n (%)	
CR	1 (2)
PR	13 (32)
SD	11 (27)
SD ≥ 6 months	*4 (10)*
PD	12 (29)
Not assessed	4 (10)
Clinical Benefit Rate (CR + PR + SD), n (%) [95%CI]	25 (61) [44.5-75.8]

[a]Responses assessed by investigator in the intent-to-treat population. [b]Patients without post-baseline assessments are not shown here.
CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

ASCO Genitourinary Cancers Symposium

Primary Analysis From DS8201-A-U105: A Phase 1b, 2-Part, Open-Label Study of Trastuzumab Deruxtecan (T-DXd) With Nivolumab in Patients With HER2-Expressing Urothelial Carcinoma (UC)

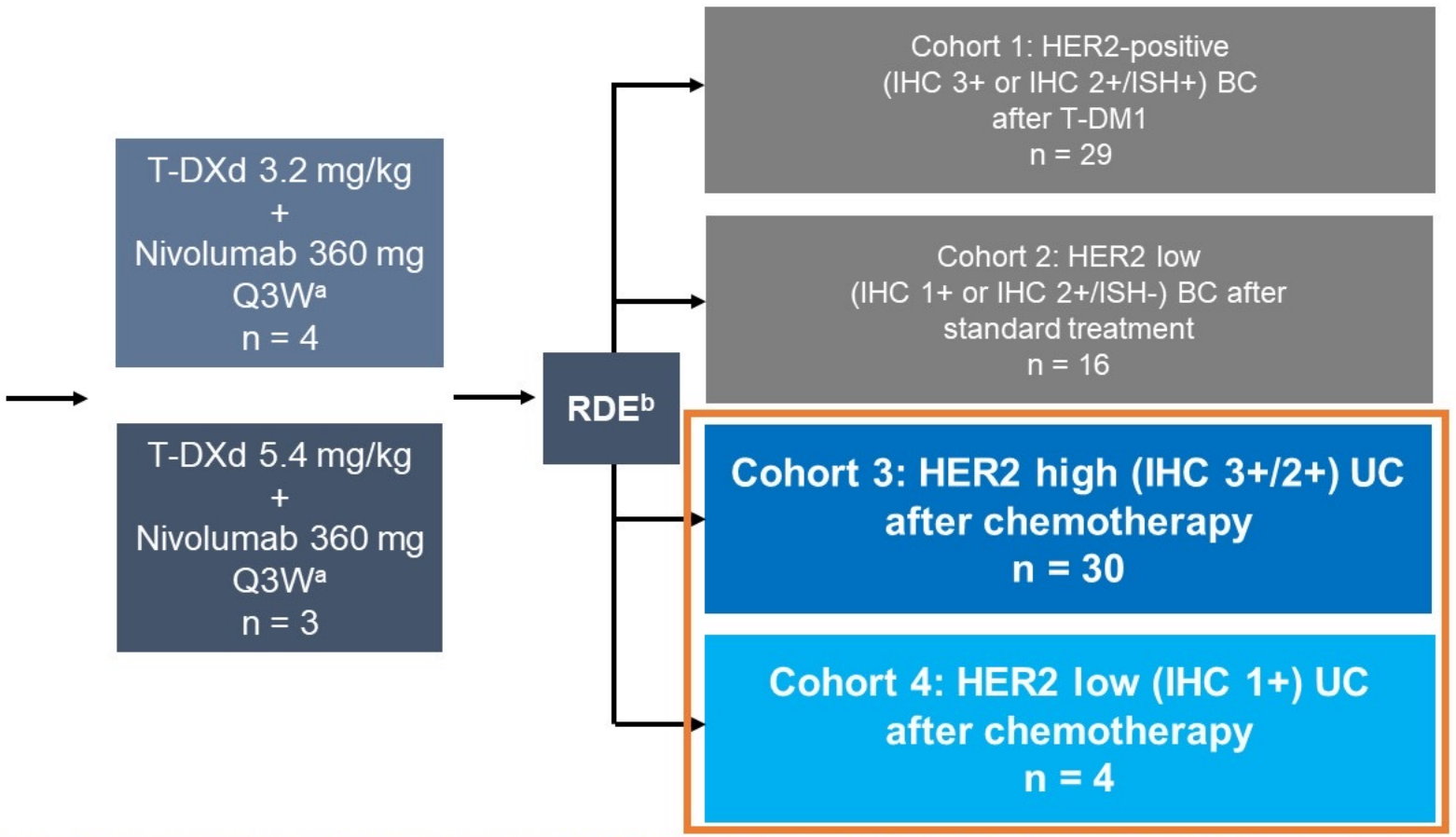
Matthew D. Galsky, Gianluca Del Conte, Silvia Foti, Evan Y. Yu, Jean-Pascal H. Machiels, Bernard Doger, Andrea Necchi, Filippo G. De Braud, Erika P. Hamilton, Audrey Hennequin, Tom Van den Mooter, Philip R. Debruyne, Irene Moreno, Hendrik-Tobias Arkenau, Zenta Tsuchihashi, Fu-Chih Cheng, Bincy Augustine, Ben Cheng, Daniel Barrios, Diana Lüftner

Matthew D. Galsky, MD
Icahn School of Medicine at Mount Sinai, New York, NY

DS8201-A-U105 Study Design

Key Eligibility Criteria

- HER2-expressing advanced/metastatic BC or UC (centrally confirmed)
- ECOG PS 0 or 1
- ≥1 measurable lesion per RECIST v1.1
- No prior T-DXd or I-O
- To be eligible for part 1, patients must meet additional cohort specific criteria of part 2



Primary endpoint
- Part 1: MTD or RDE
- Part 2: ORR[c] by ICR

Secondary endpoints
- DOR by ICR, DCR, PFS by ICR, TTR by ICR, OS, investigator-assessed ORR[c]
- PK/PD
- Safety and tolerability

Exploratory endpoint
- Biomarkers of response[d]

BC, breast cancer; bTMB, blood tumor mutation burden; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; I-O, immuno-oncology; ICR, independent central review; IHC, immunohistochemistry; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; RDE, recommended dose for expansion; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTR, time to response; UC, urothelial carcinoma.

[a]Nivolumab 360 mg Q3W is an approved dose in the United States for certain indications in combination with ipilimumab or fluoropyrimidine- and platinum-containing chemotherapy (Opdivo [nivolumab] prescribing information) and is currently under investigation in monotherapy oncology studies. [b]The RDE for T-DXd was 5.4 mg/kg. [c]ORR was based on RECIST v1.1. [d]Biomarker data (PD-L1 expression by IHC and bTMB) were assessed from baseline archival or new tumor tissue biopsies.

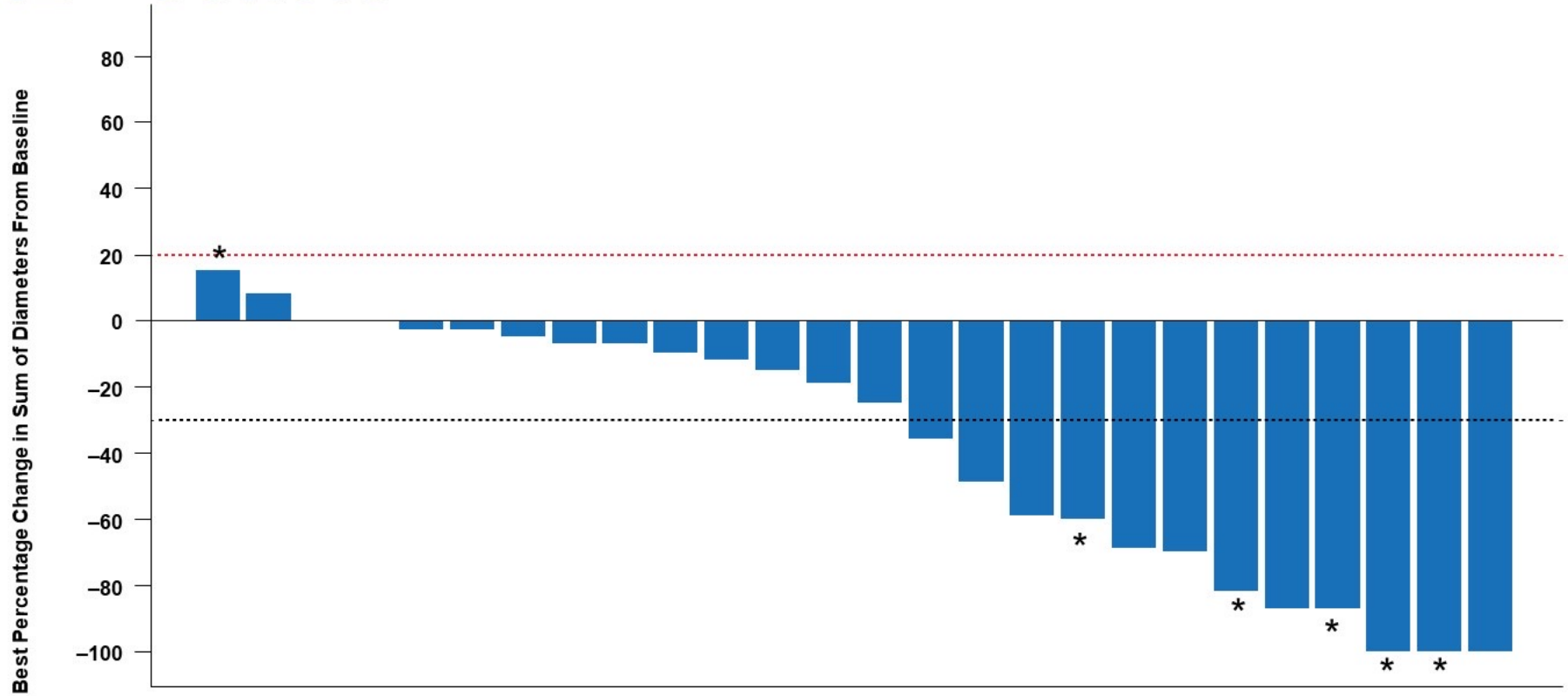
Summary of Efficacy Results in UC Cohorts

	Cohort 3 HER2 IHC 3+/2+ n = 30
Confirmed ORR by ICR (ORR, CR + PR)	
n (%)	**11 (36.7)**
95% CI	(19.9-56.1)
Best overall response, n (%)	
CR	4 (13.3)
PR	7 (23.3)
SD	12 (40.0)
PD	5 (16.7)
NE[a]	2 (6.7)
DOR, median (95% CI), months	13.1 (4.1-NE)
PFS, median (95% CI), months	6.9 (2.7-14.4)
TTR, median (95% CI), months	1.9 (1.2-6.9)
OS, median (95% CI), months	11.0 (7.2-NE)
Treatment duration, median (range), months	
T-DXd	3.9 (1-21)
Nivolumab	4.1 (1-20)

- Data cutoff: July 22, 2021
- In cohort 3:
  - HER2 IHC 3+: 62.5% (5/8) patients had a confirmed objective response, including 2 CR (25%)
  - HER2 IHC 2+: 27.3% (6/22) patients had a confirmed objective response, including 2 CR (9.1%)
- In cohort 4 (HER2 IHC 1+)[b]:
  - 2 patients had a PR
  - 1 patient had SD
  - 1 patient had PD

CR, complete response; DOR, duration of response; ICR, independent central review; NE, nonevaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.
[a]Patients were missing postbaseline scans.
[b]For cohort 4, efficacy endpoints are not summarized because of the small sample size (n = 4).

Best Percentage Change in Tumor Size by ICR in HER2 IHC 3+/2+ Cohort[a]



Cohort 3 HER 3+/2+ (n = 30) (part 2: T-DXd 5.4 mg/kg and nivolumab 360 mg) Best (minimum) percentage change					
n	**Mean**	**SD**	**Median**	**Min**	**Max**
26	–37.8	38.52	–22.0	–100	15

*Cohort 3 patient with HER2 IHC 3+. The line at 20% indicates PD, and the line at −30% indicates a PR.
[a]In cohort 3, 4 patients did not have best percentage change available, of whom 2 were IHC 3+. For cohort 4, efficacy endpoints are not summarized because of the small sample size (n = 4).

Adverse Events of Special Interest: ILD/Pneumonitis and LV Dysfunction

Adjudicated as drug-related ILD/pneumonitis,[a,b] n (%)						
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/Total
Cohort 3 HER2 IHC 3+/2+ n = 30	0	4 (13.3)	1 (3.3)	0	1 (3.3)	6 (20.0)
Cohort 4 HER2 IHC 1+ n = 4	2 (50.0)	0	0	0	0	2 (50.0)
Overall N = 34	2 (5.9)	4 (11.8)[c]	1 (2.9)	0	1 (2.9)	8 (23.5)

- All 8 cases of ILD/pneumonitis occurring before the data cutoff (July 22, 2021) were adjudicated
  - 6 of 8 cases of ILD/pneumonitis were low grade (grade 1/2)
  - Median time to adjudicated onset was 129 days (range, 35-342)

LV dysfunction

- In cohort 3, 1 (3.3%) patient experienced grade 3 LV dysfunction[d]
  - At the time of the AE onset, the patient had already discontinued T-DXd because of progressive disease. Nivolumab was ongoing and was continued until further clinical progression.
- In cohort 4, none of the patients experienced LV dysfunction[d]

ILD, interstitial lung disease; MedDRA, Medical Dictionary of Regulatory Activities.
[a]Cases of potential ILD or pneumonitis were evaluated by an independent adjudication committee that was separate from the response assessment committee. Data shown here are for cases that were deemed drug-related by the adjudication committee. [b]The adjudication committee did not discriminate between T-DXd- and nivolumab-related ILD/pneumonitis. [c]2 grade 1 ILD events by the principal investigator were adjudicated as grade 2. [d]Per Standardized MedDRA Query of Cardiac Failure and of Myocardial Infarction.

Thank you for attending!

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