Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Urothelial Bladder Cancer

Thursday, February 22, 2024
5:00 PM – 6:00 PM ET

Faculty

Shilpa Gupta, MD

Thomas Powles, MBBS, MRCP, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Faculty

Shilpa Gupta, MD
Clinical Professor of Medicine
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Director, Genitourinary Oncology Program
Taussig Cancer Institute, Cleveland Clinic
Cleveland, Ohio

Thomas Powles, MBBS, MRCP, MD
Director of Bart's Cancer Institute
Queen Mary University of London
London, United Kingdom

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

RTP Year in Review 2024

Commercial Support

This activity is supported by educational grants from Astellas and Seagen Inc, Bristol Myers Squibb, and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC.

Dr Love — Disclosures

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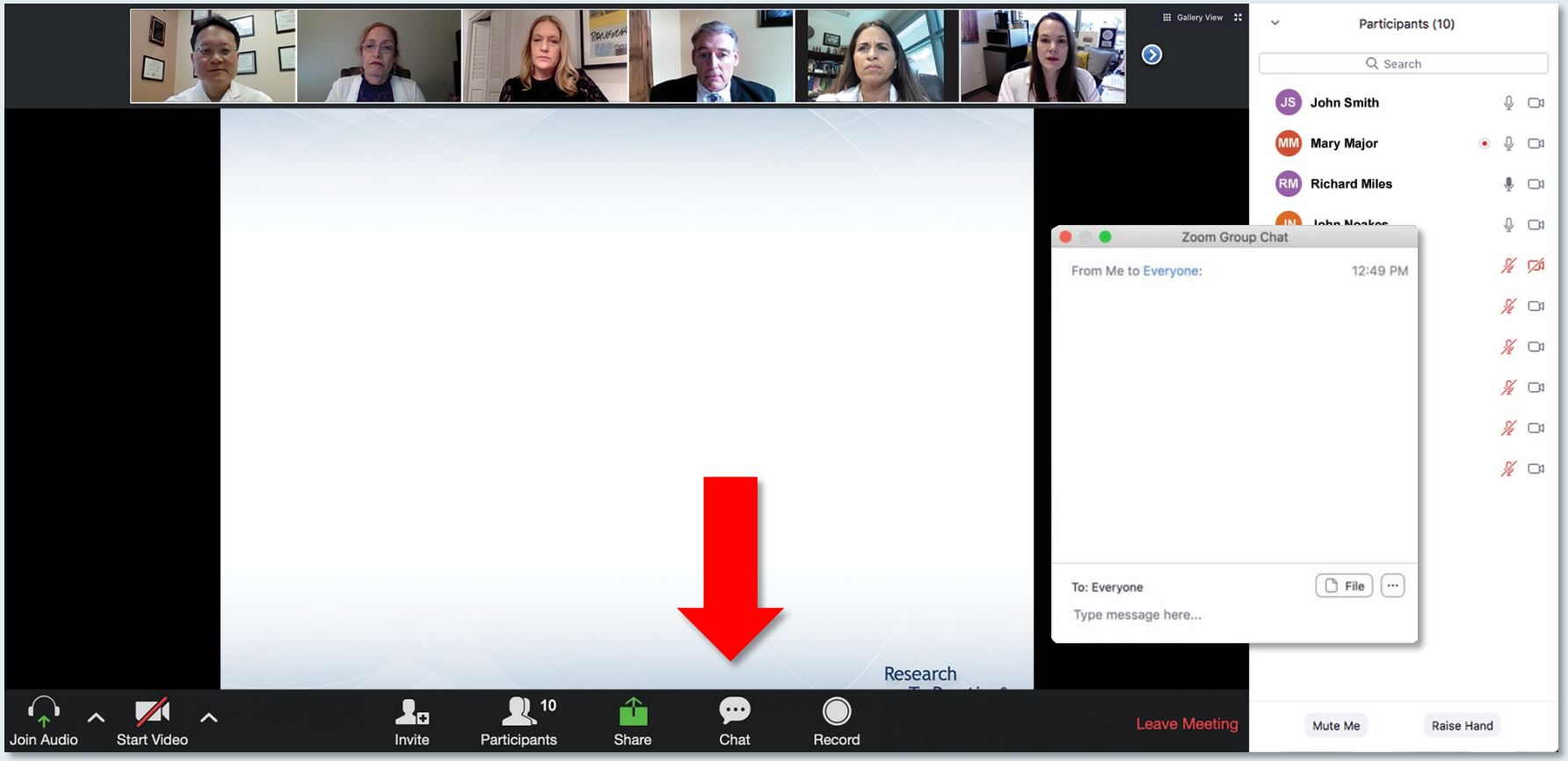
We Encourage Clinicians in Practice to Submit Questions



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

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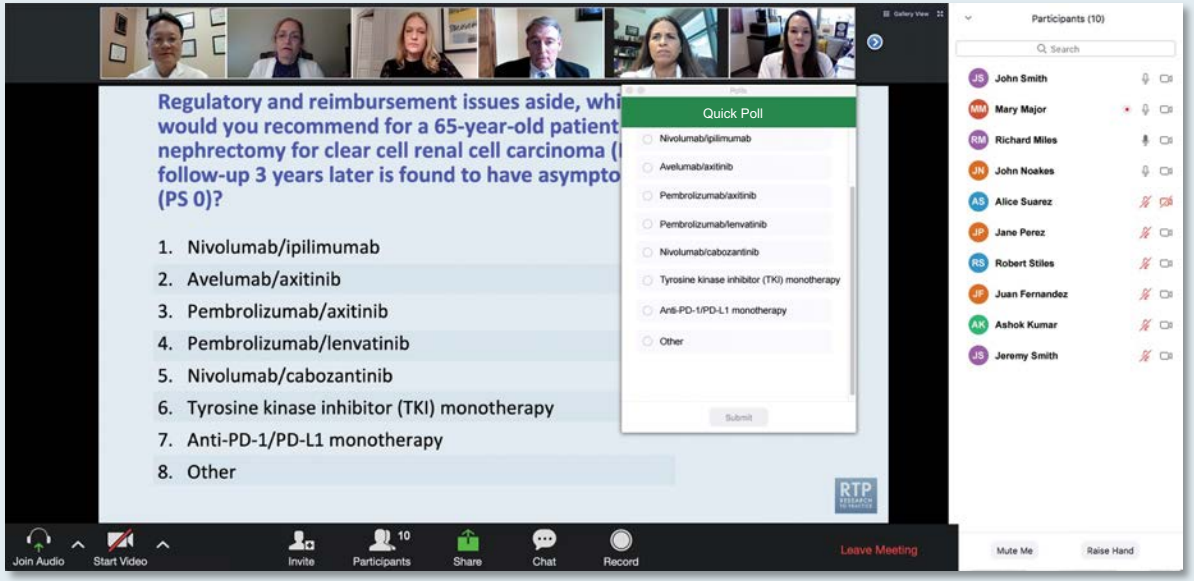

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Special Edition — Key Presentations on Genitourinary Cancers from the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting

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UC SAN DIEGO MOORES CANCER CENTER

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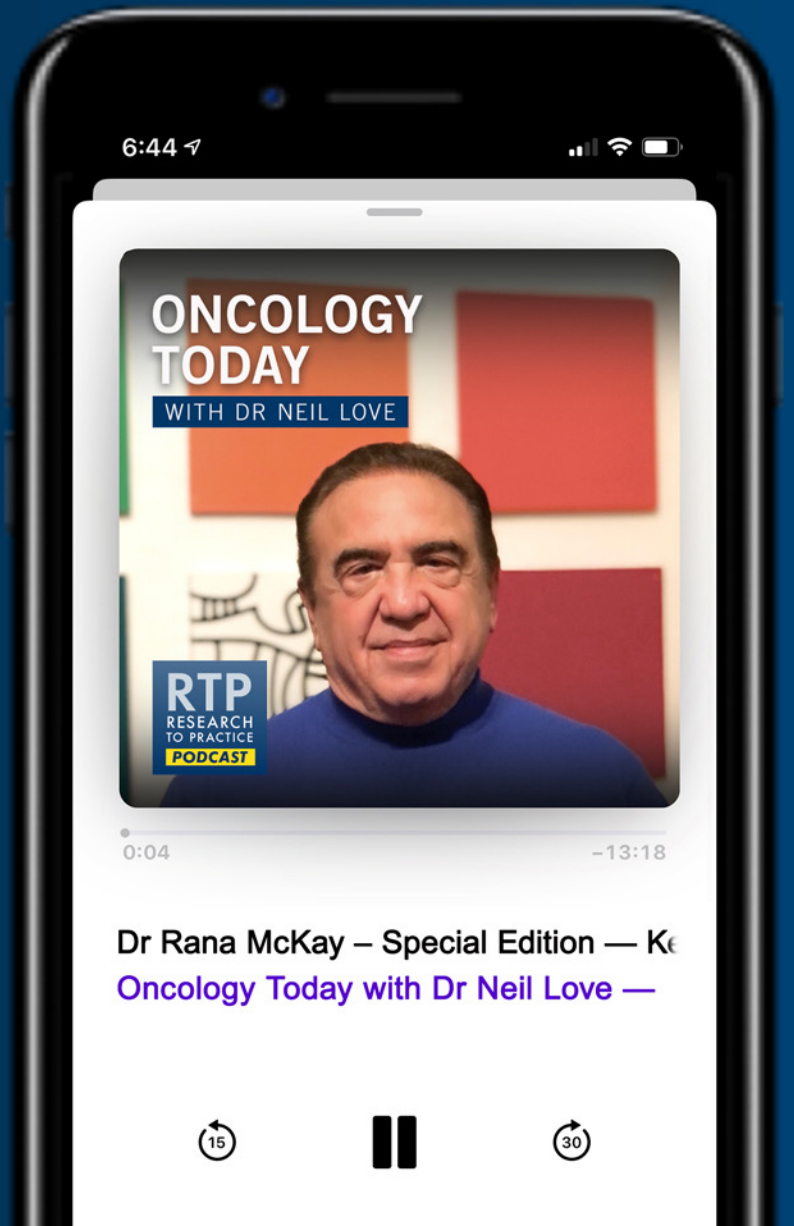

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Prostate Cancer

Wednesday, February 28, 2024
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Faculty

Andrew J Armstrong, MD, ScM

Maha Hussain, MD, FACP, FASCO

Moderator

Neil Love, MD

RTP Year in Review 2024

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Colorectal Cancer

Tuesday, March 5, 2024
5:00 PM – 6:00 PM ET

Faculty

Thierry Andre, MD
Arvind Dasari, MD, MS

Moderator

Neil Love, MD

RTP Year in Review 2024

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Ovarian Cancer

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Monday, March 18, 2024

6:30 AM – 8:00 AM PT (9:30 AM – 11:00 AM ET)

Faculty

Joyce F Liu, MD, MPH

Mansoor Raza Mirza, MD

David M O'Malley, MD

Moderator

Kathleen N Moore, MD, MS

RTP RESEARCH TO PRACTICE

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Endometrial Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

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Meet The Professor

Optimizing the Management of Myelofibrosis

Wednesday, April 3, 2024
5:00 PM – 6:00 PM ET

Faculty

Ruben A Mesa, MD

Moderator

Neil Love, MD

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Agenda

INTRODUCTION: The Cancer-Immunity Cycle

MODULE 1: Nonmetastatic Urothelial Bladder Cancer — Dr Gupta

- Non-Muscle-Invasive Bladder Cancer – Checkpoint Inhibitors
- Non-Muscle-Invasive Bladder Cancer – Intravesical Therapies
- Muscle-Invasive Bladder Cancer – Adjuvant Checkpoint Inhibition
- Muscle-Invasive Bladder Cancer – Enfortumab Vedotin
- Muscle-Invasive Bladder Cancer – TAR-200
- Other Strategies for Localized Urothelial Bladder Cancer

MODULE 2: Metastatic Urothelial Bladder Cancer (mUBC) — Prof Powles

- Checkpoint Inhibition for Previously Untreated mUBC
- Enfortumab Vedotin/Pembrolizumab for Previously Untreated mUBC
- Erdafitinib-Based Therapy for Previously Treated mUBC
- Sacituzumab Govitecan for Previously Treated mUBC
- HER2-Directed Therapies

Thank you for joining us!

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

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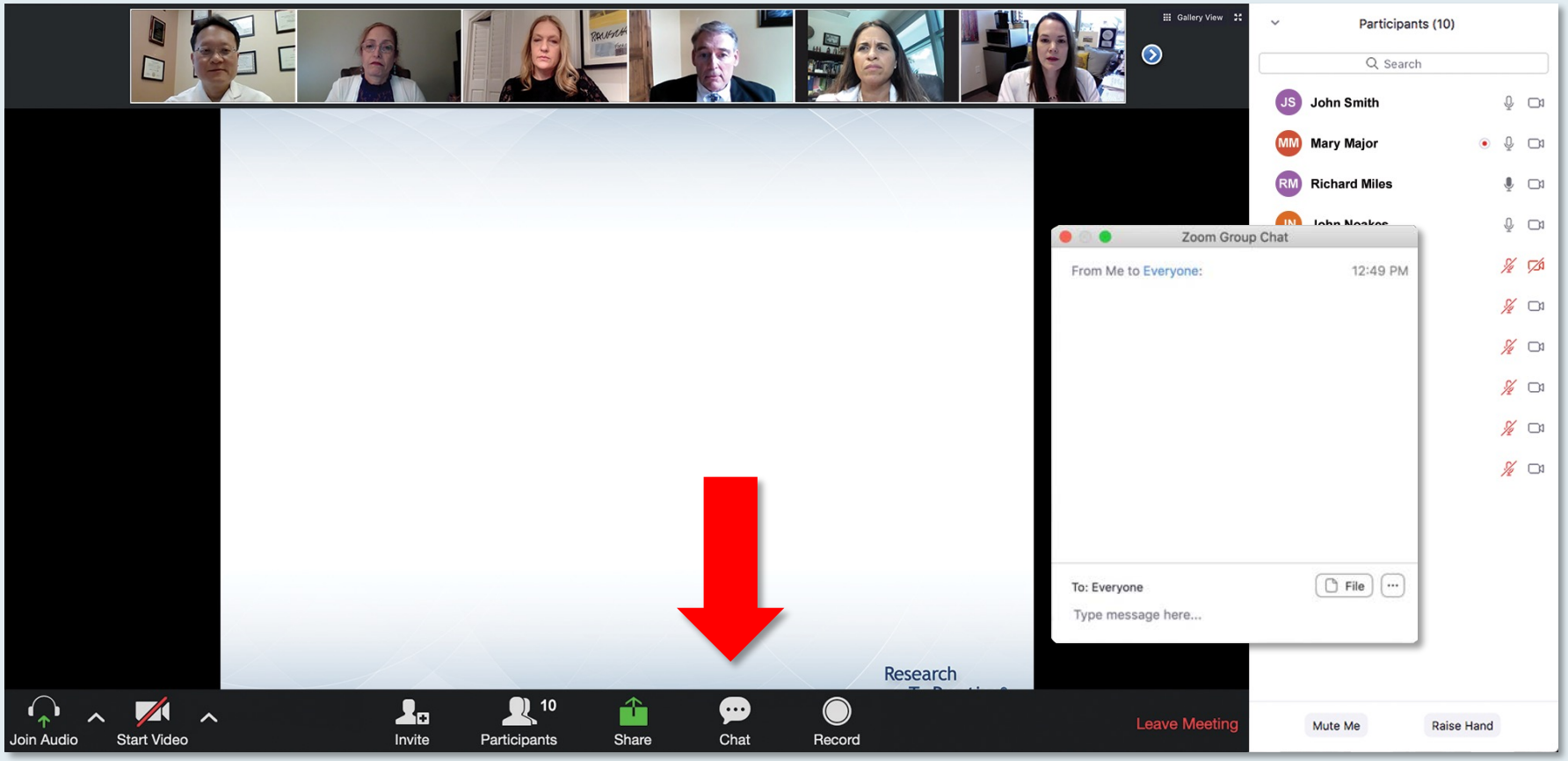

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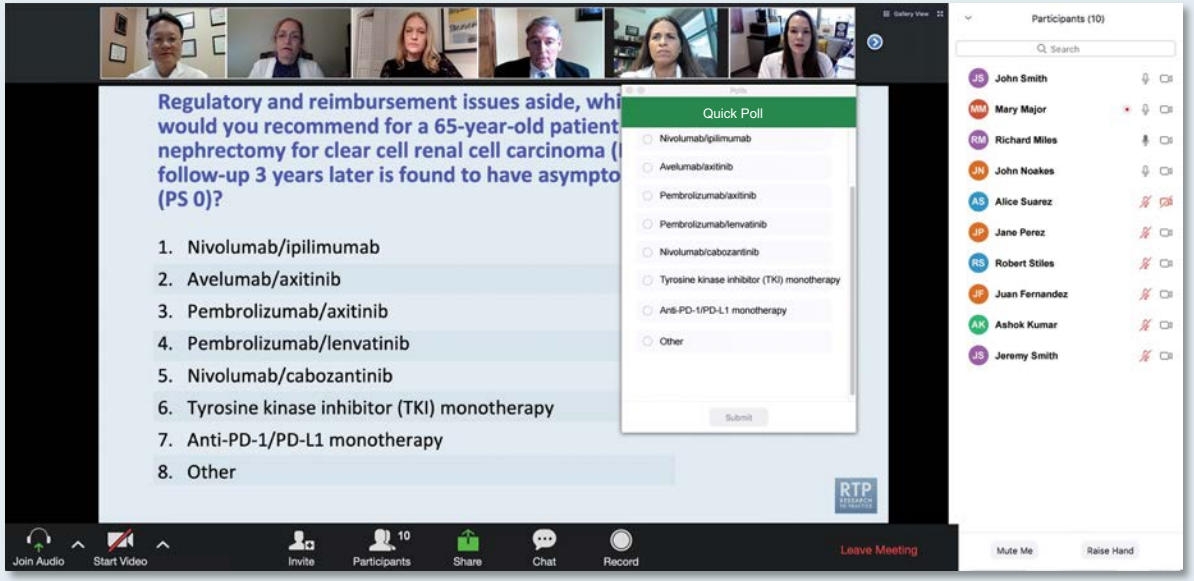

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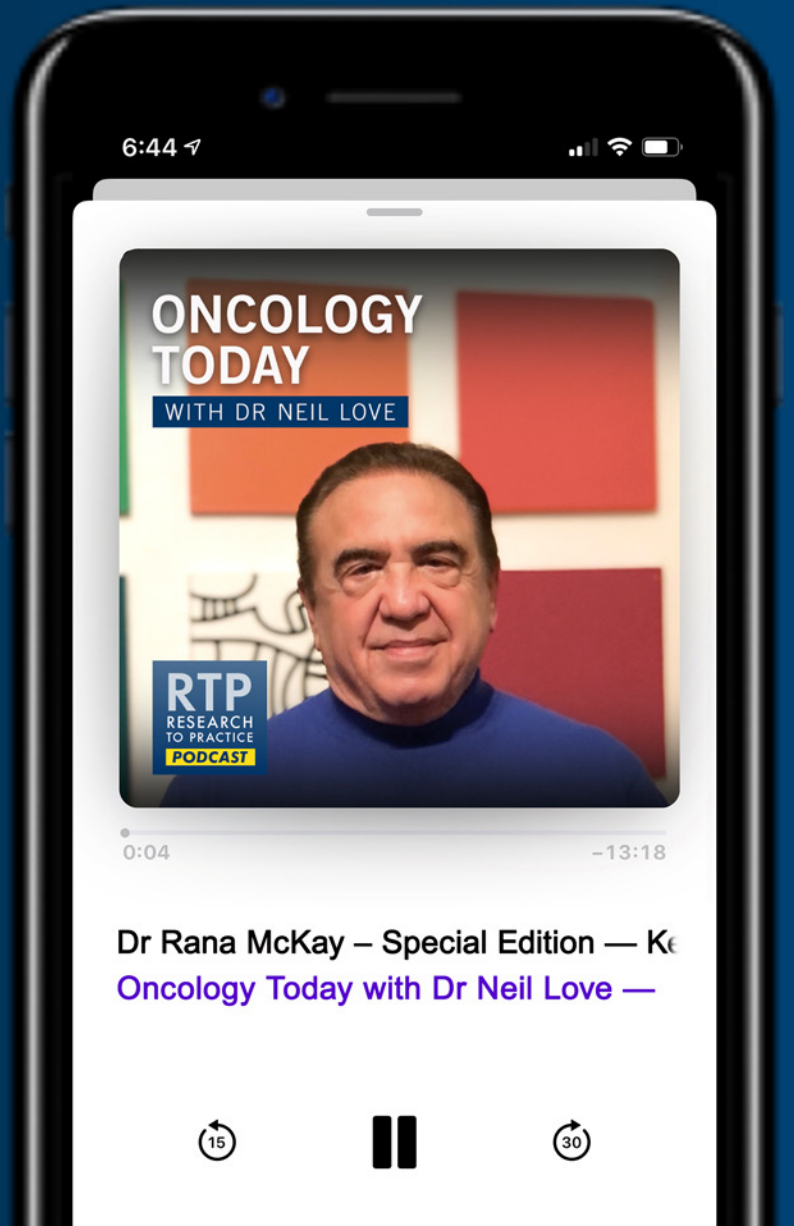

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Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024

6:30 PM – 7:00 PM

Welcome Reception

7:00 PM – 9:00 PM

Keynote Session: ER-Positive Metastatic Breast Cancer

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Special Feature: Clinicians with Breast Cancer

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

7:30 AM – 9:10 AM

Hodgkin and Non-Hodgkin Lymphoma

Ann S LaCasce, MD, MMSc
Matthew Lunning, DO
Kami Maddocks, MD
Andrew D Zelenetz, MD, PhD

9:30 AM – 10:20 AM

Gynecologic Cancers

Bradley J Monk, MD
David M O'Malley, MD

10:20 AM – 11:10 AM

Localized Breast Cancer; SABCS 2023 Review

Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD

11:10 AM – 12:00 PM

Metastatic Breast Cancer, Triple-Negative Breast Cancer, HER2-Positive Breast Cancer; SABCS 2023 Review

Erika Hamilton, MD
Virginia Kaklamani, MD, DSc
Hope S Rugo, MD

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

12:30 PM – 1:20 PM

Prostate Cancer

Emmanuel S Antonarakis, MD

Rana R McKay, MD

1:20 PM – 2:10 PM

Urothelial Bladder Cancer

Matthew D Galsky, MD

Jonathan E Rosenberg, MD

2:10 PM – 3:00 PM

Renal Cell Carcinoma

Eric Jonasch, MD

Brian Rini, MD

3:20 PM – 4:10 PM

Targeted Therapy for Non-Small Cell Lung Cancer

Ibiayi Dagogo-Jack, MD

Helena Yu, MD

4:10 PM – 5:00 PM

Nontargeted Treatments for Lung Cancer

Edward B Garon, MD, MS

Corey J Langer, MD

Third Annual **National General Medical Oncology Summit**

Sunday, March 24, 2024

7:30 AM – 8:20 AM

Multiple Myeloma

Natalie S Callander, MD
Paul G Richardson, MD

8:20 AM – 9:10 AM

Gastroesophageal Cancers

Yelena Y Janjigian, MD
Samuel J Klempner, MD

9:30 AM – 10:20 AM

Hepatobiliary Cancers

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD

10:20 AM – 11:10 AM

Colorectal Cancer

Kristen K Ciombor, MD, MSCI
John Strickler, MD

11:10 AM – 12:00 PM

Pancreatic Cancer

Andrew H Ko, MD
Eileen M O'Reilly, MD

Meet The Professor

Optimizing the Management of Myelofibrosis

Wednesday, April 3, 2024
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Cleveland Clinic

Year in Review — Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Bladder Cancer Edition

Shilpa Gupta, M.D.
Clinical Professor
Cleveland Clinic Lerner College of Medicine at CWRU
Director, Genitourinary Oncology Program
Cleveland Clinic Taussig Cancer Institute

Improving outcomes in urothelial cancer

Thomas Powles

Director of Barts Cancer Center.
Professor of Urology Cancer, Barts Cancer Institute.

Key Data Sets

Shilpa Gupta, MD

- Singer E et al. **Pembrolizumab** (pembro) for patients (pts) with **high-risk non-muscle-invasive** bladder cancer (HR NMIBC) unresponsive to **bacillus Calmette-Guerin (BCG)**: Efficacy and evaluation of subsequent cystectomy from Cohort B of the phase 2 **KEYNOTE-057** study. AUA 2023;Abstract LBA03-08.
- Hahn NM et al. A phase 1 trial of **durvalumab** in combination with bacillus Calmette-Guerin (**BCG**) or external beam **radiation therapy** in patients with BCG-unresponsive **non-muscle-invasive** bladder cancer: The Hoosier Cancer Research Network **GU16-243 ADAPT-BLADDER** study. *Eur Urol* 2023;83(6):486-94.
- Necchi A et al. Results from **SunRISe-1** in patients (pts) with bacillus Calmette–Guérin (**BCG**)-**unresponsive high-risk non–muscle-invasive** bladder cancer (HR NMIBC) receiving **TAR-200** monotherapy. ESMO 2023;Abstract LBA105.
- Catto JWF et al. **Erdafitinib** in **BCG-treated high-risk non-muscle-invasive** bladder cancer. *Ann Oncol* 2024;35(1):98-106.

Key Data Sets

Shilpa Gupta, MD (continued)

- Vliaseca A et al. First safety and efficacy results of the **TAR-210 erdafitinib** (erda) intravesical delivery system in patients (pts) with **non-muscle-invasive** bladder cancer (NMIBC) with select FGFR alterations (alt). ESMO 2023;Abstract LBA104.
- Roupret M et al. A first-in-human trial of **intravesical enfortumab vedotin (EV)**, an antibody-drug conjugate (ADC), in patients with **non-muscle invasive** bladder cancer (NMIBC): Interim results of a phase 1 study (**EV-104**). ASCO 2023;Abstract 4596.
- Milowsky M et al. Results from the **extended follow-up** in patients with **muscle-invasive** bladder cancer in the **CheckMate 274** trial. AUA 2023;Abstract LBA02-08.
- Apolo AB et al. **AMBASSADOR Alliance A031501**: **Phase III** randomized adjuvant study of **pembrolizumab** in **muscle-invasive** and locally advanced urothelial carcinoma (MIUC) vs observation. Genitourinary Cancers Symposium 2024;Abstract LBA531.
- Flaig TW et al. **Study EV-103**: **Neoadjuvant** treatment with **enfortumab vedotin** monotherapy in **cisplatin-ineligible** patients (pts) with **muscle invasive** bladder cancer (MIBC): Updated results for **Cohort H**. ASCO 2023;Abstract 4595.

Key Data Sets

Shilpa Gupta, MD (continued)

- Sridhar S et al. **Study EV-103 cohort L**: **Perioperative** treatment w/**enfortumab vedotin (EV)** monotherapy in cisplatin **(cis)-ineligible** patients (pts) w/ **muscle invasive** bladder cancer (MIBC). ESMO 2023;Abstract 2365MO.
- Tyson MD et al. Safety, tolerability, and preliminary efficacy of **TAR-200** in patients with **muscle-invasive** bladder cancer who refused or were unfit for curative-intent therapy: A phase 1 study. *J Urol* 2023;209(5):890-900.
- Galsky MD et al. **Gemcitabine and cisplatin** plus **nivolumab** as **organ-sparing** treatment for **muscle-invasive** bladder cancer: A phase 2 trial. *Nat Med* 2023;29(11):2825-34.
- Cathomas R et al. Perioperative chemoimmunotherapy with **durvalumab** for **muscle-invasive** urothelial carcinoma: Primary analysis of the single-arm phase II trial **SAKK 06/17**. *J Clin Oncol* 2023;41(33):5131-9.
- Joshi M et al. Concurrent **durvalumab and radiation therapy** (DUART) followed by **adjuvant durvalumab** in patients with localized urothelial cancer of bladder: Results from phase II study, **BTCRC-GU15-023**. *J Immunother Cancer* 2023;11(2):e006551.

Key Data Sets

Thomas Powles, MBBS, MRCP, MD

- Friedlander TW et al. **Enfortumab vedotin (EV)** with or without **pembrolizumab (P)** in patients (pts) who are **cisplatin-ineligible** with **previously untreated** locally advanced or metastatic urothelial cancer (la/mUC): Additional 3-month follow-up on **cohort K** data. ASCO 2023;Abstract 4568.
- Powles TB et al. **EV-302/KEYNOTE-A39**: Open-label, randomized phase III study of **enfortumab vedotin** in combination with **pembrolizumab** (EV+P) vs chemotherapy (chemo) in **previously untreated** locally advanced metastatic urothelial carcinoma (la/mUC). ESMO 2023;Abstract LBA6.
- van der Heijden MS et al. **Enfortumab vedotin (EV)** in combination with **pembrolizumab (P)** versus chemotherapy in **previously untreated** locally advanced metastatic urothelial carcinoma (la/mUC): **Subgroup** analyses results from **EV-302**, a **phase 3** global study. Genitourinary Cancers Symposium 2024;Abstract LBA530.
- van der Heijden MS et al. **Nivolumab** plus **gemcitabine-cisplatin** in advanced urothelial carcinoma. *N Engl J Med* 2023;389(19):1778-89.
- Ozyilkan O et al. Outcomes by complete response to **first-line pembrolizumab** or platinum-based chemotherapy in advanced urothelial carcinoma (UC) in **KEYNOTE-361**. ASCO 2023;Abstract 4513.

Key Data Sets

Thomas Powles, MBBS, MRCP, MD (continued)

- Powles T et al. **Avelumab first-line maintenance** for advanced urothelial carcinoma: Results from the **JAVELIN Bladder 100** trial after ≥2 years of follow-up. *J Clin Oncol* 2023;41(19):3486-92.
- Siefker-Radtke AO et al. **Erdafitinib (ERDA)** vs **ERDA plus cetrelimab** (ERDA+CET) for patients (pts) with metastatic urothelial carcinoma (mUC) and fibroblast growth factor receptor alterations (**FGFRa**): **Final results** from the phase 2 **Norse study**. ASCO 2023;Abstract 4504.
- Rosenberg JE et al. **EV-301** long-term outcomes: 24-month findings from the **phase III** trial of **enfortumab vedotin** versus chemotherapy in patients with previously treated advanced urothelial carcinoma. *Ann Oncol* 2023;34(11):1047-54.
- Loriot Y et al. **Erdafitinib** or chemotherapy in advanced or metastatic urothelial carcinoma. *N Engl J Med* 2023;389(21):1961-71.
- Siefker-Radtke AO et al. **Erdafitinib** versus **pembrolizumab** in pretreated patients with advanced or metastatic urothelial cancer with **select FGFR alterations**: Cohort 2 of the randomized **phase III THOR** trial. *Ann Oncol* 2024;35(1):107-17.

Key Data Sets

Thomas Powles, MBBS, MRCP, MD (continued)

- McGregor BA et al. The **Double Antibody Drug** Conjugate (**DAD**) phase I trial: **Sacituzumab govitecan plus enfortumab vedotin** for metastatic urothelial carcinoma. *Ann Oncol* 2024 January;35(1):91-7.
- Loriot Y et al. Safety analysis by **UGT1A1 status** of **TROPHY-U-01 cohort 1**, a phase 2 study of **sacituzumab govitecan (SG)** in patients (pts) with metastatic urothelial cancer (mUC) who progressed after platinum (PT)-based chemotherapy and a checkpoint inhibitor (CPI). ASCO 2023;Abstract 4514.
- Meric-Bernstam F et al. Efficacy and safety of **trastuzumab deruxtecan** in patients with HER2-expressing solid tumors: Primary results from the **DESTINY-PanTumor02** phase II trial. *J Clin Oncol* 2024;42(1):47-58.
- Sheng X et al. Efficacy and safety of **disitamab vedotin** in patients with human epidermal growth factor receptor 2-positive locally advanced or metastatic urothelial carcinoma: A **combined analysis** of two phase II clinical trials. *J Clin Oncol* 2023;[Online ahead of print].
- Sheng X et al. **Disitamab vedotin**, a novel humanized anti-HER2 antibody-drug conjugate (ADC), combined **with toripalimab** in patients with locally advanced or metastatic urothelial carcinoma: An open-label phase 1b/2 study. ASCO 2023;Abstract 4566.

Agenda

INTRODUCTION: The Cancer-Immunity Cycle

MODULE 1: Nonmetastatic Urothelial Bladder Cancer — Dr Gupta

- Non-Muscle-Invasive Bladder Cancer – Checkpoint Inhibitors
- Non-Muscle-Invasive Bladder Cancer – Intravesical Therapies
- Muscle-Invasive Bladder Cancer – Adjuvant Checkpoint Inhibition
- Muscle-Invasive Bladder Cancer – Enfortumab Vedotin
- Muscle-Invasive Bladder Cancer – TAR-200
- Other Strategies for Localized Urothelial Bladder Cancer

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- Sacituzumab Govitecan for Previously Treated mUBC
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Immunity

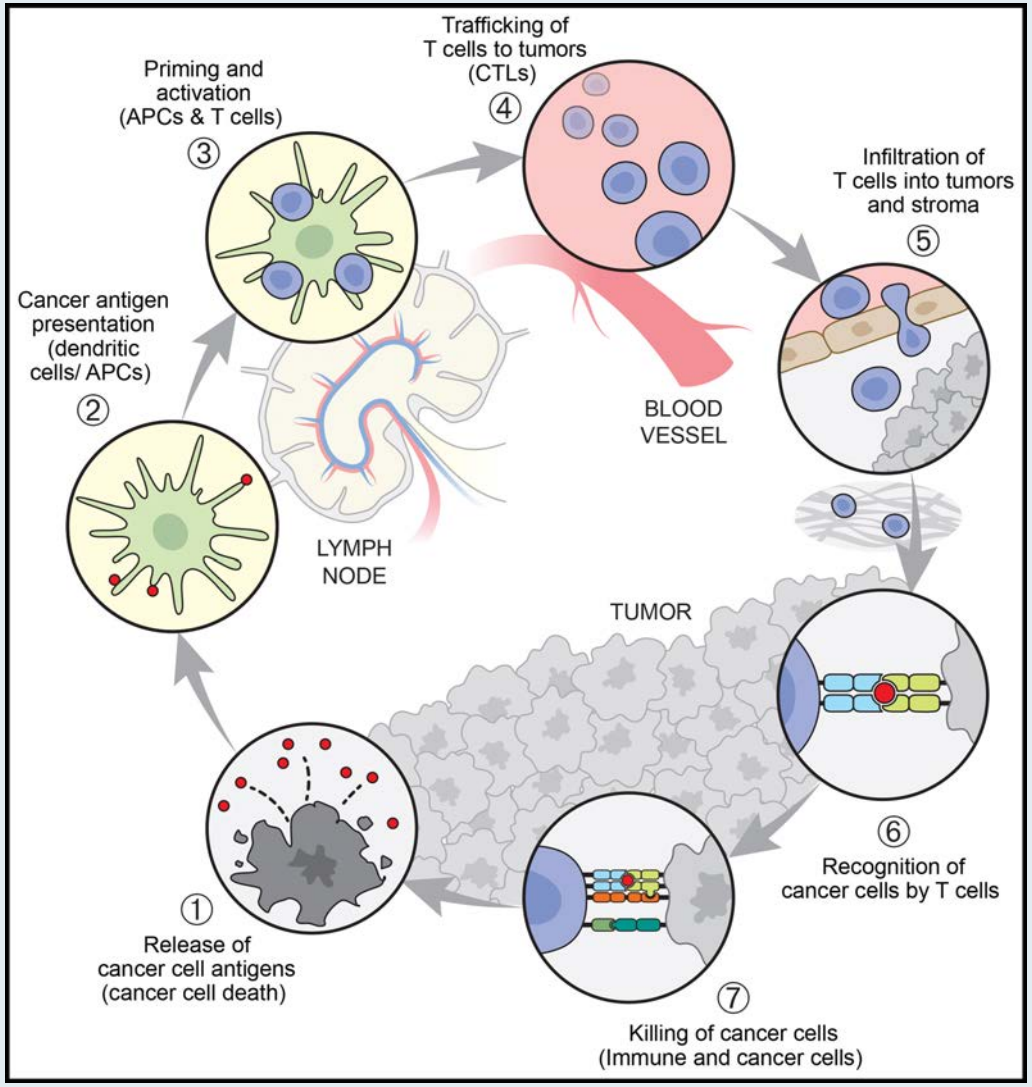
REVIEW | VOLUME 56, ISSUE 10, P2188-2205, OCTOBER 10, 2023

The cancer-immunity cycle: Indication, genotype, and immunotype

Ira Mellman • Daniel S. Chen • Thomas Powles • Shannon J. Turley

Open Access • DOI: https://doi.org/10.1016/j.immuni.2023.09.011 •

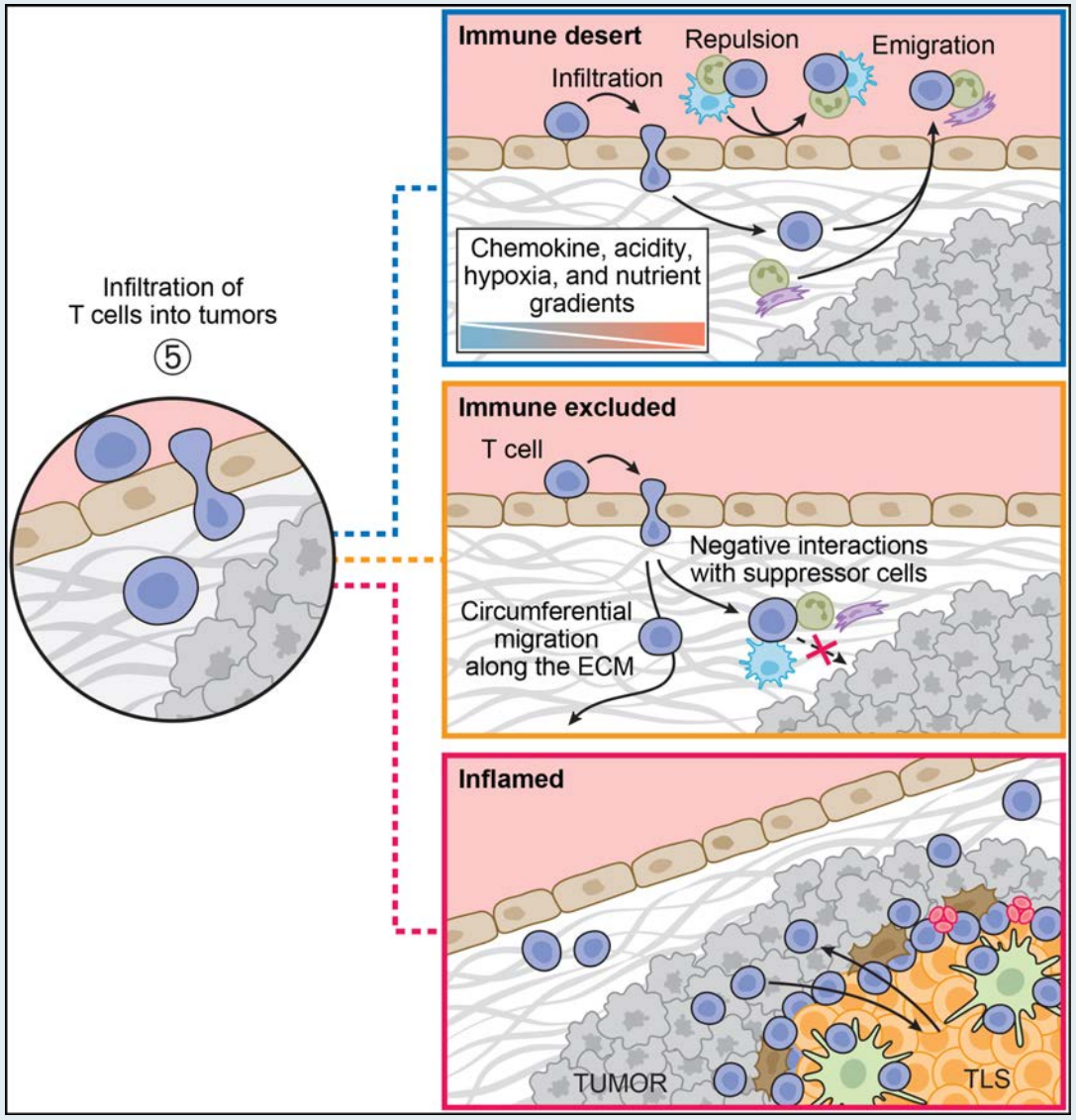
Original Cancer-Immunity Cycle (2013)



Mellman I et al. *Immunity* 2023 October 10;56(10):2188-205.

RTP RESEARCH TO PRACTICE

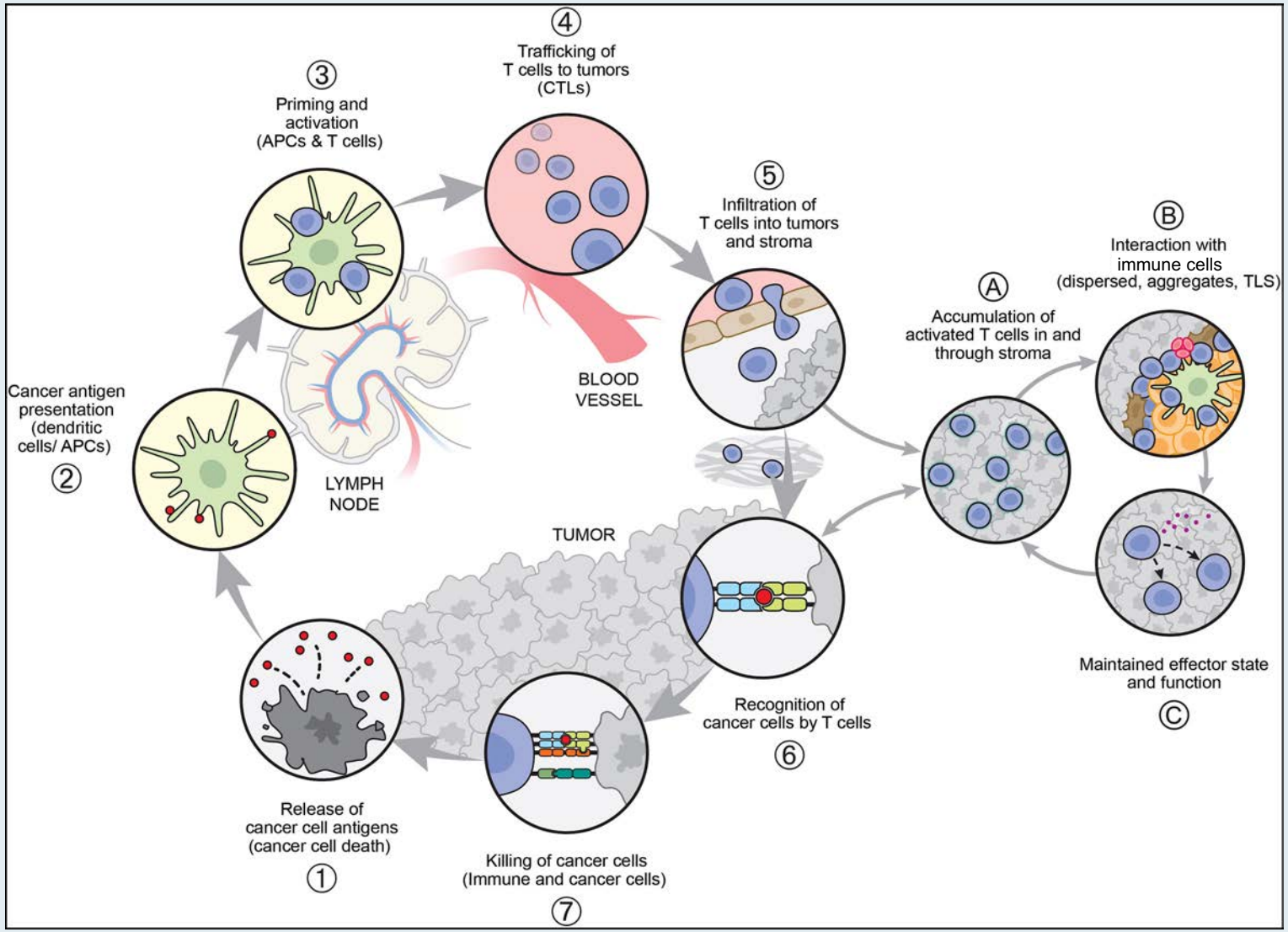
Immunotypes



Mellman I et al. *Immunity* 2023 October 10;56(10):2188-205.

RTP RESEARCH TO PRACTICE

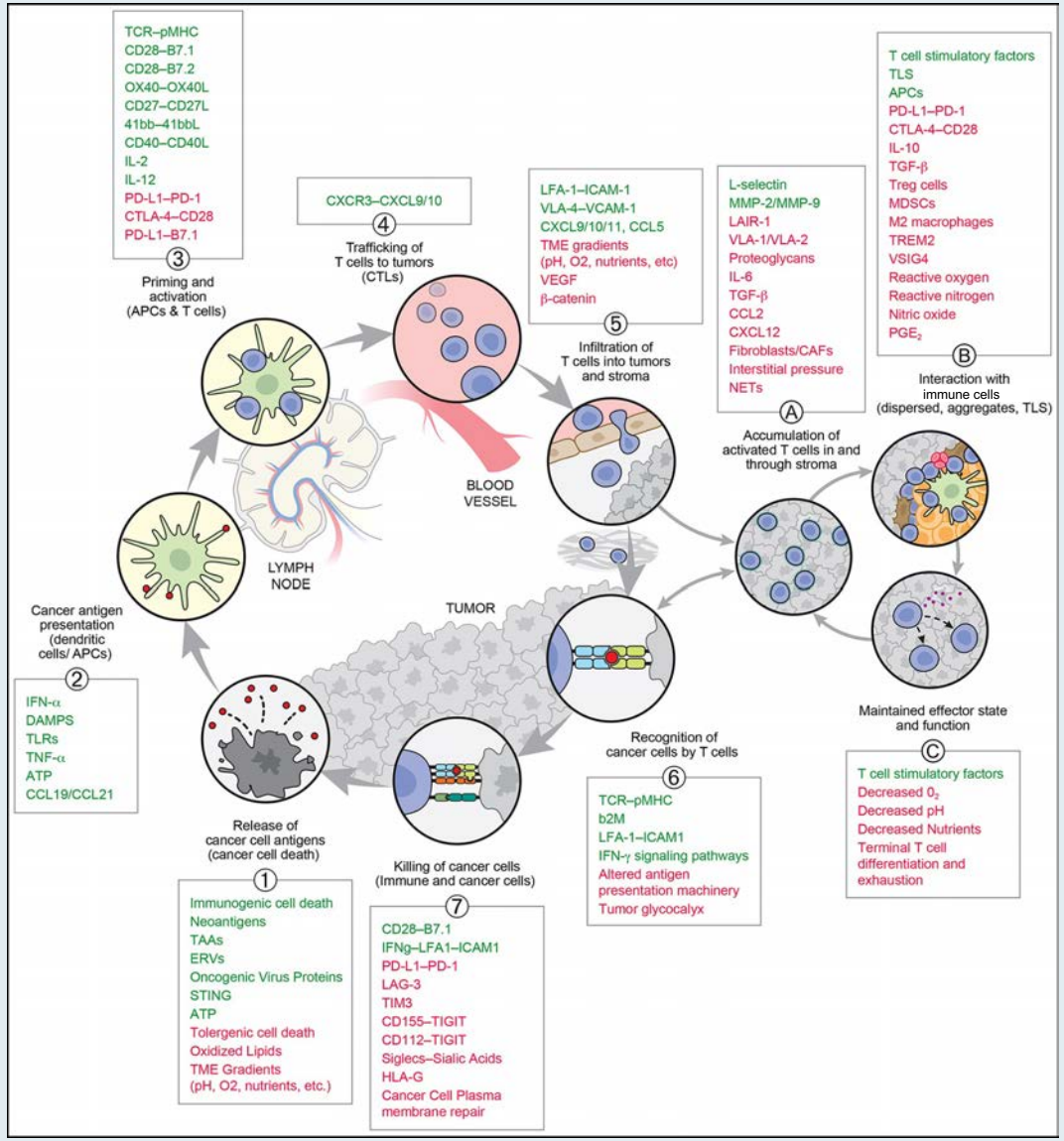
Cancer-Immunity Cycle and TME Cancer-Immunity Cycle



TME = tumor microenvironment

Mellman I et al. *Immunity* 2023 October 10;56(10):2188-205.

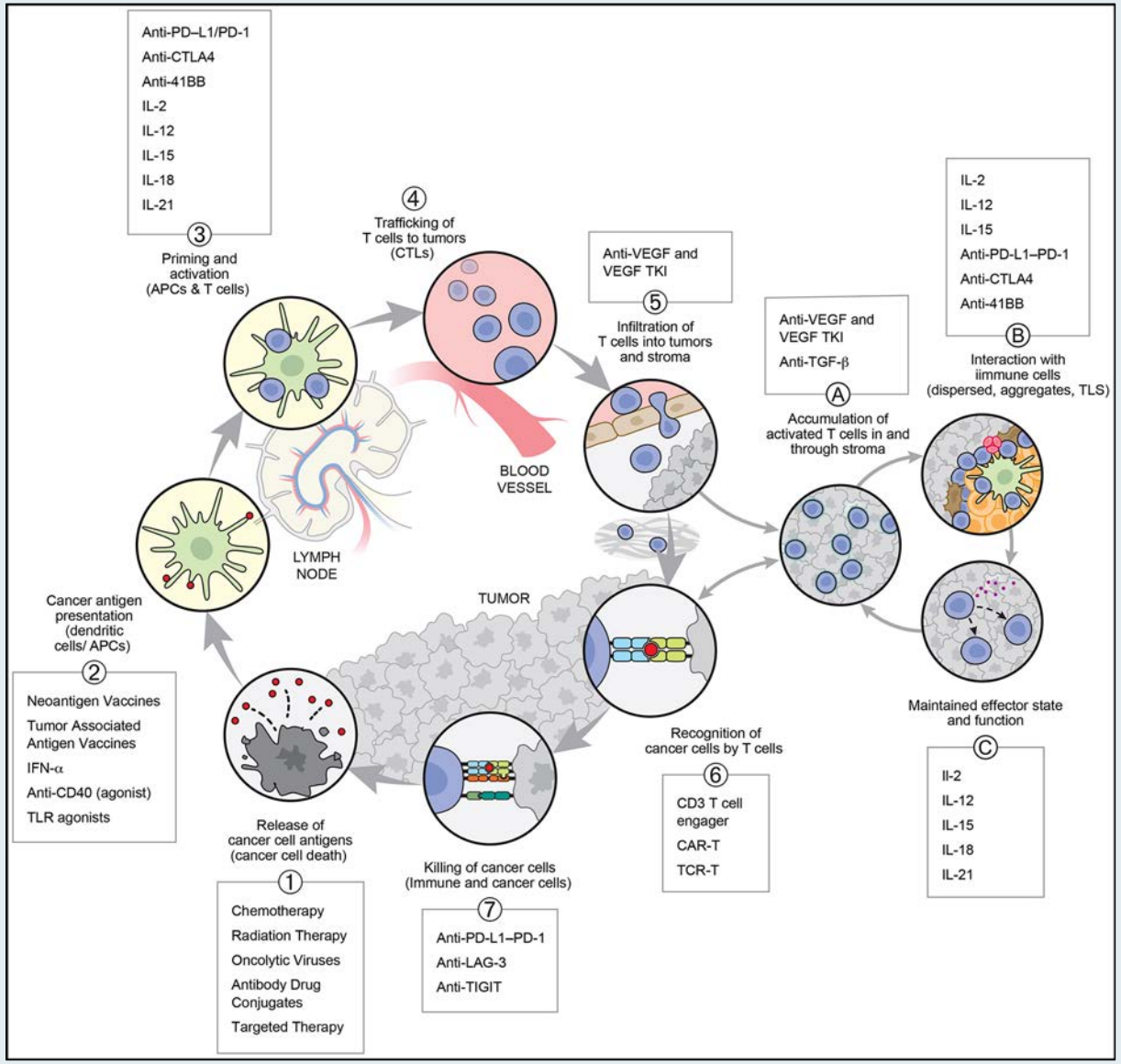
Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle



Mellman I et al. *Immunity* 2023 October 10;56(10):2188-205.

RTP RESEARCH TO PRACTICE

Approved and Selected Therapies That Target the Cancer-Immunity Cycle



Mellman I et al. *Immunity* 2023 October 10;56(10):2188-205.

RTP RESEARCH TO PRACTICE

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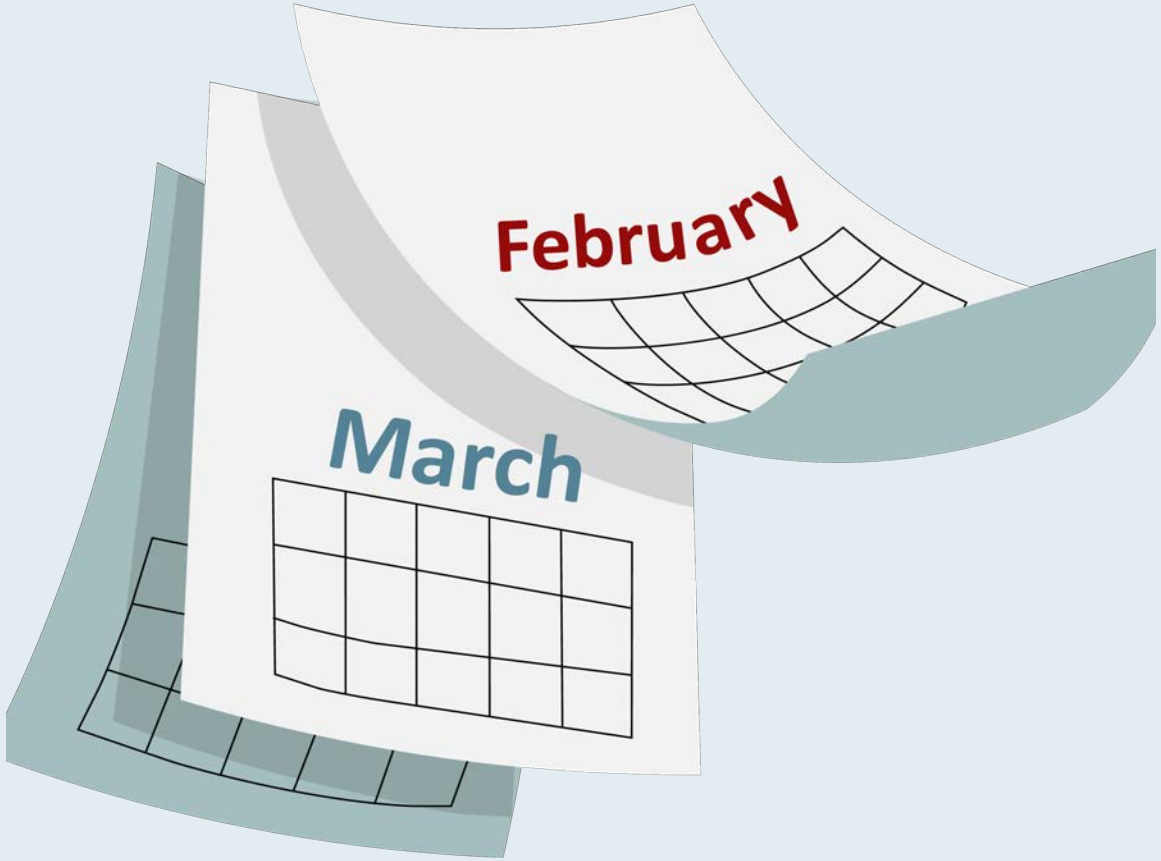
Where we were February 22, 2023

Nonmetastatic Urothelial Bladder Cancer



Addressing Unmet Needs in Non-Metastatic Urothelial Bladder Cancer (UBC)

- Only a third of patients with NMIBC receive intravesical BCG; BCG shortages in the US affects access
- Over 50% of patients with MIBC may not receive curative intent therapy globally
- High risk of recurrence in MIBC despite neoadjuvant cisplatin-based chemotherapy (NAC) and surgery
- 50% of patients deemed ineligible for NAC, 30% refuse NAC
- Radical Cystectomy (RC) has a significant mortality and morbidity and long term negative impact on QOL
- Development of effective, safe, and durable treatment for NMIBC and MIBC as well as bladder sparing treatments is an unmet need

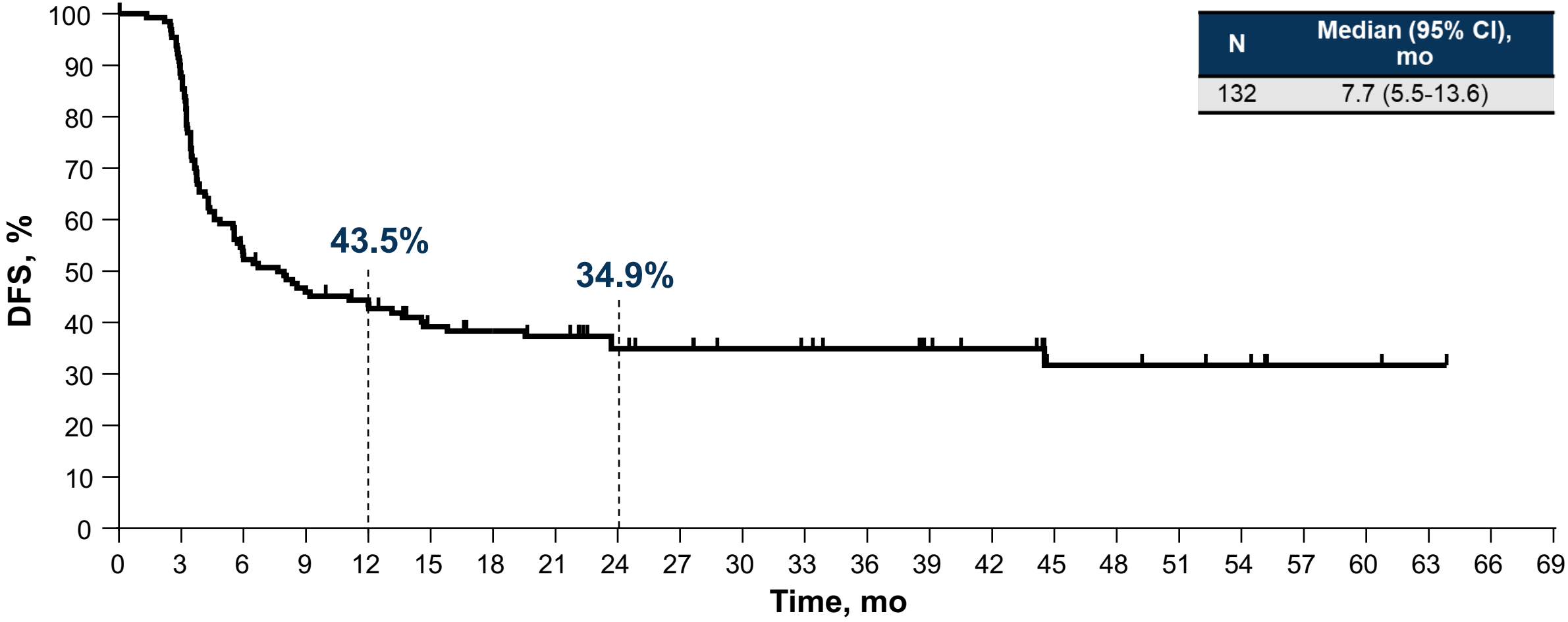
Tyson M et al. JCO 2019, Westergren DO et al. J Urol 2019; Roupret M et al. Eur Urol. 2021, Tan WS et al. Adv Urol 2015, Allareddy V et al. Cancer 2006, Zippe CD et al. Urology 2004

Courtesy of Shilpa Gupta, MD

Non-Muscle-Invasive Bladder Cancer – Checkpoint Inhibitors

- Singer E et al. **Pembrolizumab** (pembro) for patients (pts) with **high-risk non-muscle-invasive** bladder cancer (HR NMIBC) unresponsive to **bacillus Calmette-Guerin (BCG)**: Efficacy and evaluation of subsequent cystectomy from Cohort B of the phase 2 **KEYNOTE-057** study. AUA 2023;Abstract LBA03-08.
- Hahn NM et al. A phase 1 trial of **durvalumab** in combination with bacillus Calmette-Guerin (**BCG**) or external beam **radiation therapy** in patients with BCG-unresponsive **non-muscle-invasive** bladder cancer: The Hoosier Cancer Research Network **GU16-243 ADAPT-BLADDER** study. *Eur Urol* 2023;83(6):486-94.

KEYNOTE-057 Cohort B: Pembrolizumab for Papillary High-Risk NMIBC



N	Median (95% CI), mo
132	7.7 (5.5-13.6)

Median follow-up: 4 months

Singer E et al. AUA 2023;Abstract LBA03-08.

Courtesy of Shilpa Gupta, MD

Durvalumab +/- BCG or with EBRT in patients with BCG-unresponsive NMIBC: HCRN GU16-243 ADAPT-BLADDER Study

Durva q 3w x 8 cycles +/- BCG induction and maintenance

EBRT patients received concurrent EBRT (6 Gy × 3 in cycle 1 only)

Primary endpoint: RP2D for each regimen

Secondary endpoints: Toxicity and CR rates

N=28

Durva (N = 3)

Durva + BCG (N = 13)

Durva + EBRT (N=12)

R2PD: Full-dose Durva, BCG and , full-dose BCG, 6 Gy EBRT

1 Grade 3 TRAE of autoimmune hepatitis

The 3-mo CR: 64% of all patients, 33%, 85%, and 50% of Durva, Durva + BCG, and Durva + EBRT cohorts

12-mo CR: 46% of all patients; 73% of Durva + BCG and 33% of Durva+ EBRT patients.

Hahn NM et al. Eur Urol 2023

Courtesy of Shilpa Gupta, MD

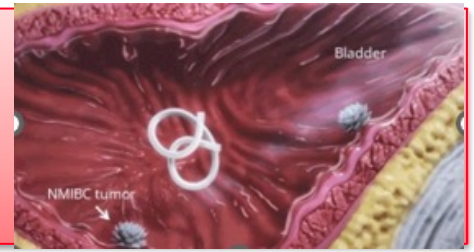
Non-Muscle-Invasive Bladder Cancer – Intravesical Therapies

- Necchi A et al. Results from **SunRISe-1** in patients (pts) with bacillus Calmette–Guérin (**BCG**)-**unresponsive high-risk non-muscle-invasive** bladder cancer (HR NMIBC) receiving **TAR-200** monotherapy. ESMO 2023;Abstract LBA105.
- Catto JWF et al. **Erdafitinib** in **BCG-treated high-risk non-muscle-invasive** bladder cancer. *Ann Oncol* 2024;35(1):98-106.
- Vliaseca A et al. First safety and efficacy results of the **TAR-210 erdafitinib** (erda) intravesical delivery system in patients (pts) with **non-muscle-invasive** bladder cancer (NMIBC) with select FGFR alterations (alt). ESMO 2023;Abstract LBA104.
- Roupret M et al. A first-in-human trial of **intravesical enfortumab vedotin (EV)**, an antibody-drug conjugate (ADC), in patients with **non-muscle invasive** bladder cancer (NMIBC): Interim results of a phase 1 study (**EV-104**). ASCO 2023;Abstract 4596.

TAR-200 Intravesical Drug Delivery System

TAR-200

Intravesical drug delivery system that enables a sustained release of gemcitabine into the bladder, increasing the dwell time of the local drug concentration



Phase 2 SunRISe-1

Key Eligibility Criteria
- BCG-unresponsive high-risk NMIBC
- ECOG PS 0-2
- With or without papillary disease (T1, high-grade Ta)
- Ineligible for or declined RC

2:1:1

R

- **Cohort 1: TAR-200 + cetrelimab** (N = 100) *Cohort closed*
- **Cohort 2: TAR-200[a] (N = 80)**
- **Cohort 3: Cetrelimab (N = 50)** *Cohort closed*

Primary endpoint: Overall CR rate

Key secondary endpoints: DOR, OS, safety

Key Eligibility Criteria
- HR NMIBC papillary disease only (no CIS)

- **Cohort 4: TAR-200[a] (N = 50)**

Primary endpoint: DFS rate

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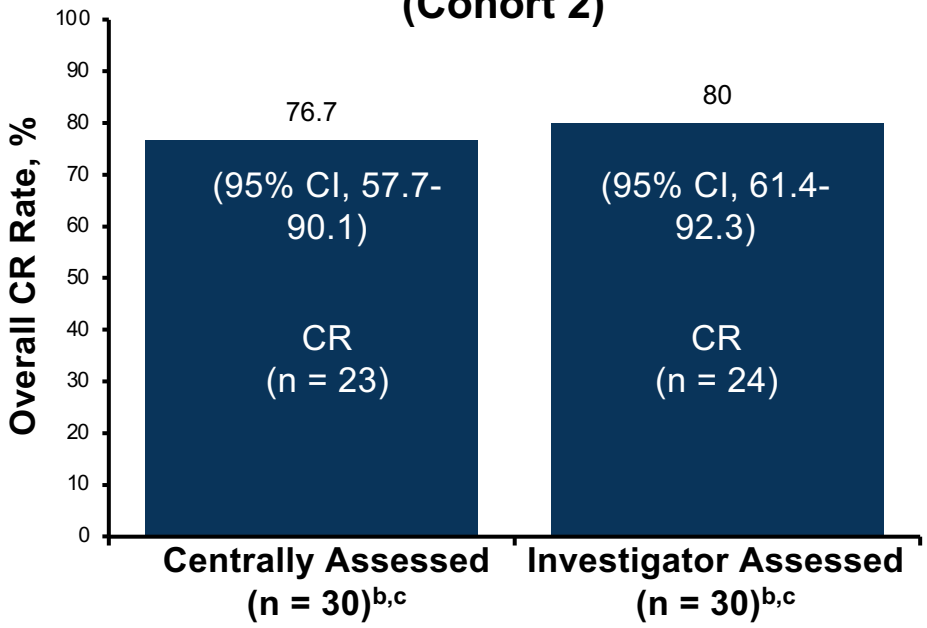
TAR-200 dosing: Q3W (indwelling) for first 24 weeks; then Q12W through Week 96.
Necchi A et al. ESMO 2023. LBA105

Courtesy of Shilpa Gupta, MD

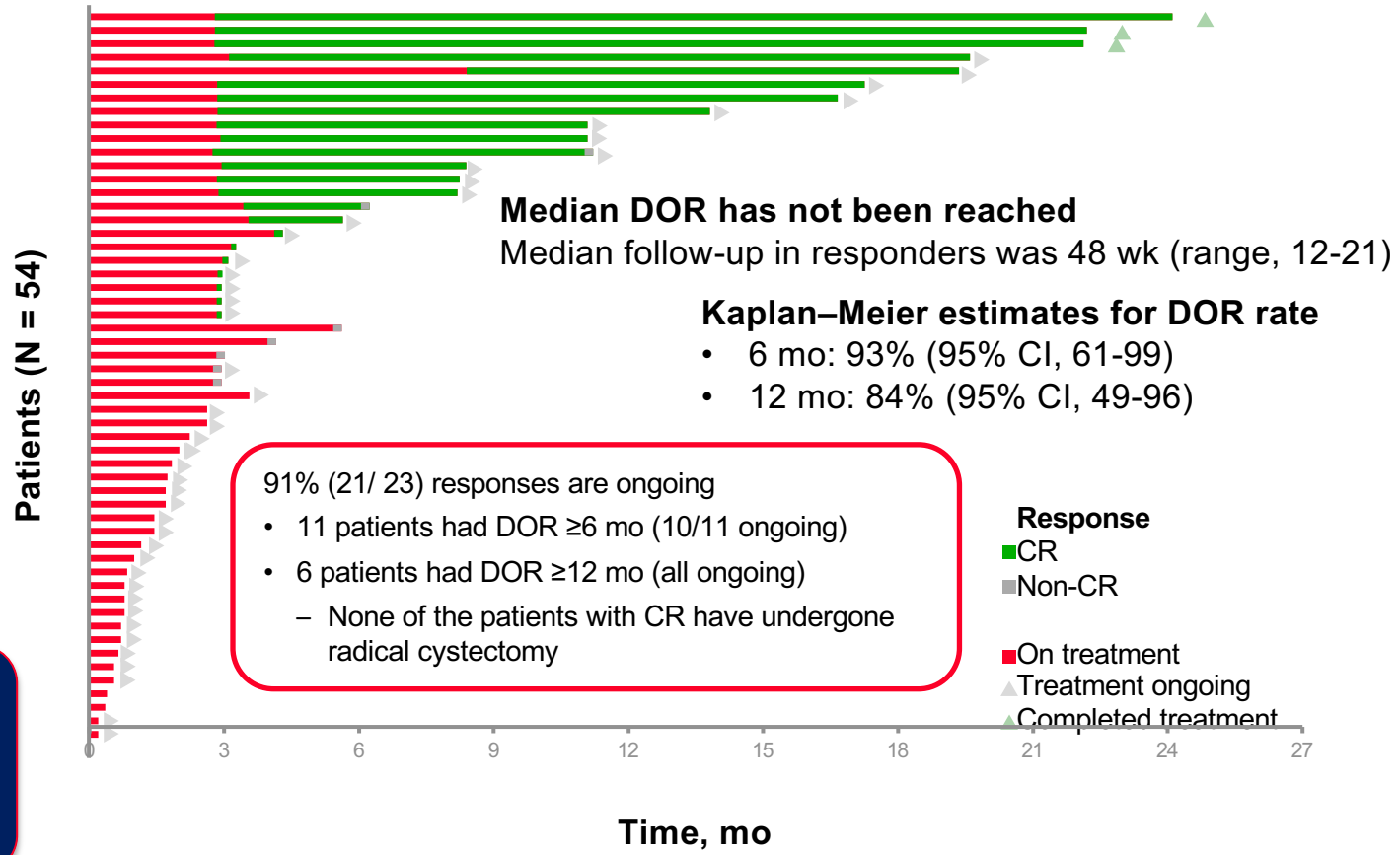
SunRISe-1:BCG-Unresponsive High-Risk NMIBC

CR Rate in Patients With High-Risk NMIBC CIS (Cohort 2)



- TAR-200 was well tolerated—mainly low-grade 1 or 2 AEs, with manageable urinary symptoms
- TAR-200–related SAEs, grade ≥3 AEs, and discontinuations were infrequent

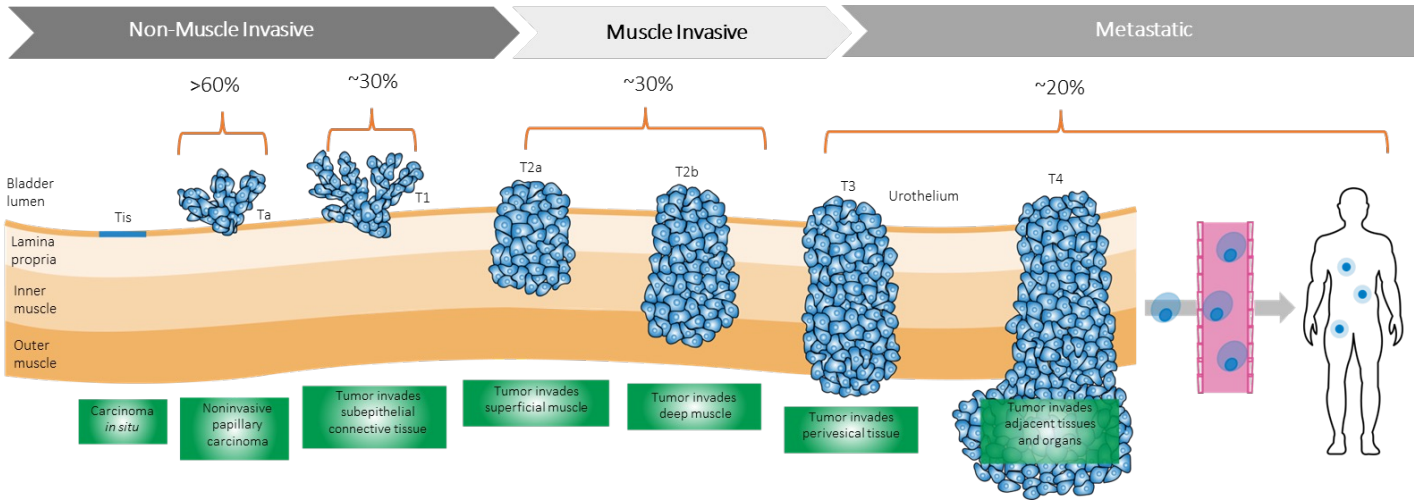
Treatment Duration and Response to TAR-200 Monotherapy



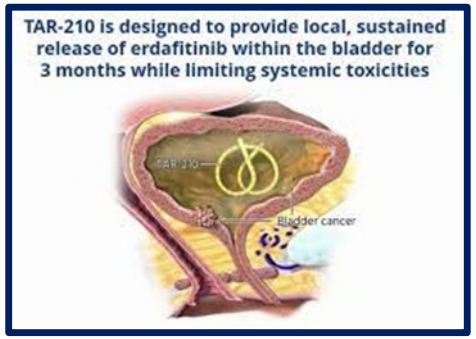
Necchi A et al. ESMO 2023. LBA105

Courtesy of Shilpa Gupta, MD

Targeting FGFR in NMIBC



- FGFR alterations are commonly detected in NMIBC
- ~ 30% patients with high-risk papillary NMIBC have FGFR alterations
- Targeting FGFR in NMIBC is a rational therapeutic approach
  - Systemic erdafitinib
  - Intravesical erdafitinib (TAR 210)



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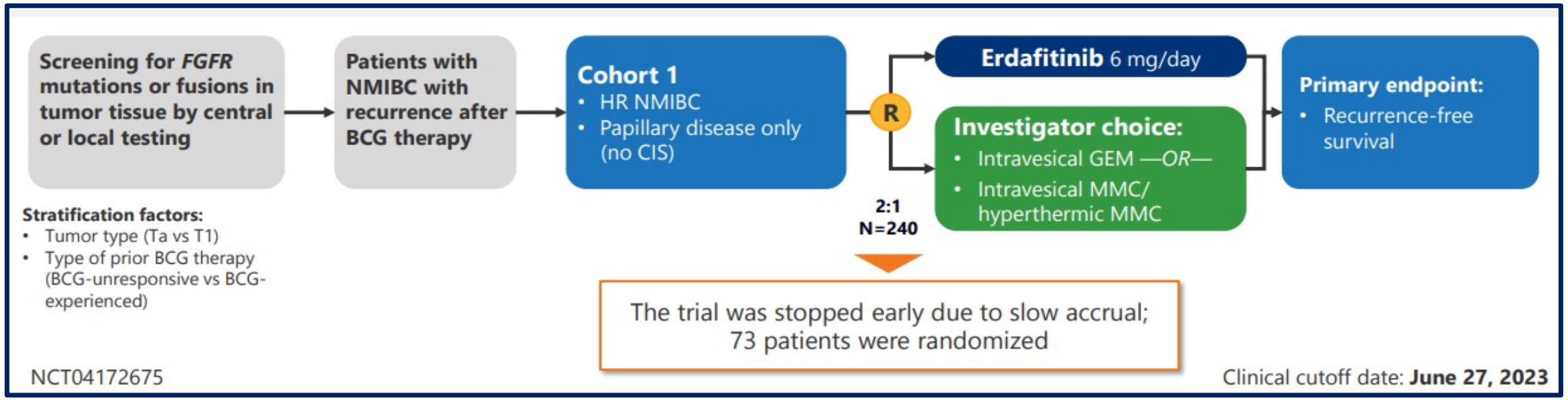
Courtesy of Shilpa Gupta, MD

THOR-2 Cohort 1: Oral Erdafitinib Versus Intravesical Chemotherapy in BCG-Unresponsive High-Risk NMIBC



	Definition
BCG-unresponsive[1]	Patients must meet ≥1 of the following criteria: • Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy • T1 high-grade at the first disease assessment following an induction BCG course Adequate BCG: • ≥5 of 6 full doses of an initial induction course including ≥1 maintenance course (2 of 3 full weekly doses) in a 6-month period —*OR*— • ≥5 of 6 full doses of an initial induction course plus ≥2 of 6 full doses of a second induction course
BCG-experienced	Patients must meet the following criteria: • Recurrent high-grade Ta/T1 disease within 12 months of completion of BCG therapy Prior BCG: • ≥5 of 6 full doses of an initial induction course —*OR*— • ≥5 of 6 full doses of an initial induction course plus ≥1 maintenance course (2 of 3 weekly doses) in a 6-month period. Half doses or one-third doses were allowed during maintenance

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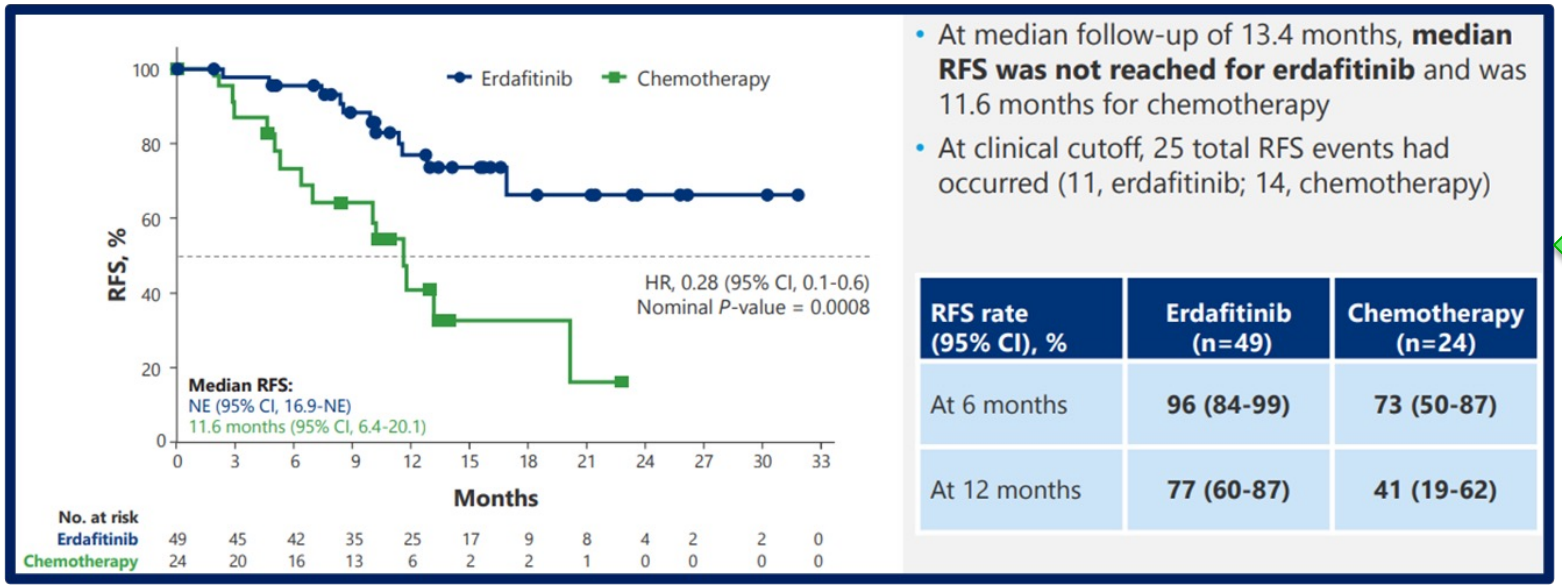
Catto JWF et al. Ann Oncol 2024;35(1):98-106; ESMO 2023.

Courtesy of Shilpa Gupta, MD



- At median follow-up of 13.4 months, **median RFS was not reached for erdafitinib** and was 11.6 months for chemotherapy
- At clinical cutoff, 25 total RFS events had occurred (11, erdafitinib; 14, chemotherapy)

RFS rate (95% CI), %	Erdafitinib (n=49)	Chemotherapy (n=24)
At 6 months	96 (84-99)	73 (50-87)
At 12 months	77 (60-87)	41 (19-62)

Efficacy

Safety

Patients with ≥1 event, n (%)[a]	Erdafitinib (n=49)	
	Any grade	Grade ≥3
Any adverse events of interest	49 (100)	—
Nail toxicity[b]	38 (77.6)	3 (6.1)
Hyperphosphatemia	36 (73.5)	0
Eye toxicities (excluding central serous retinopathy)[c]	29 (59.2)	2 (4.1)
Skin toxicity[d]	25 (51.0)	0
Dry mouth	23 (46.9)	0
Stomatitis	20 (40.8)	5 (10.2)
Central serous retinopathy[e,f]	19 (38.8)	2 (4.1)

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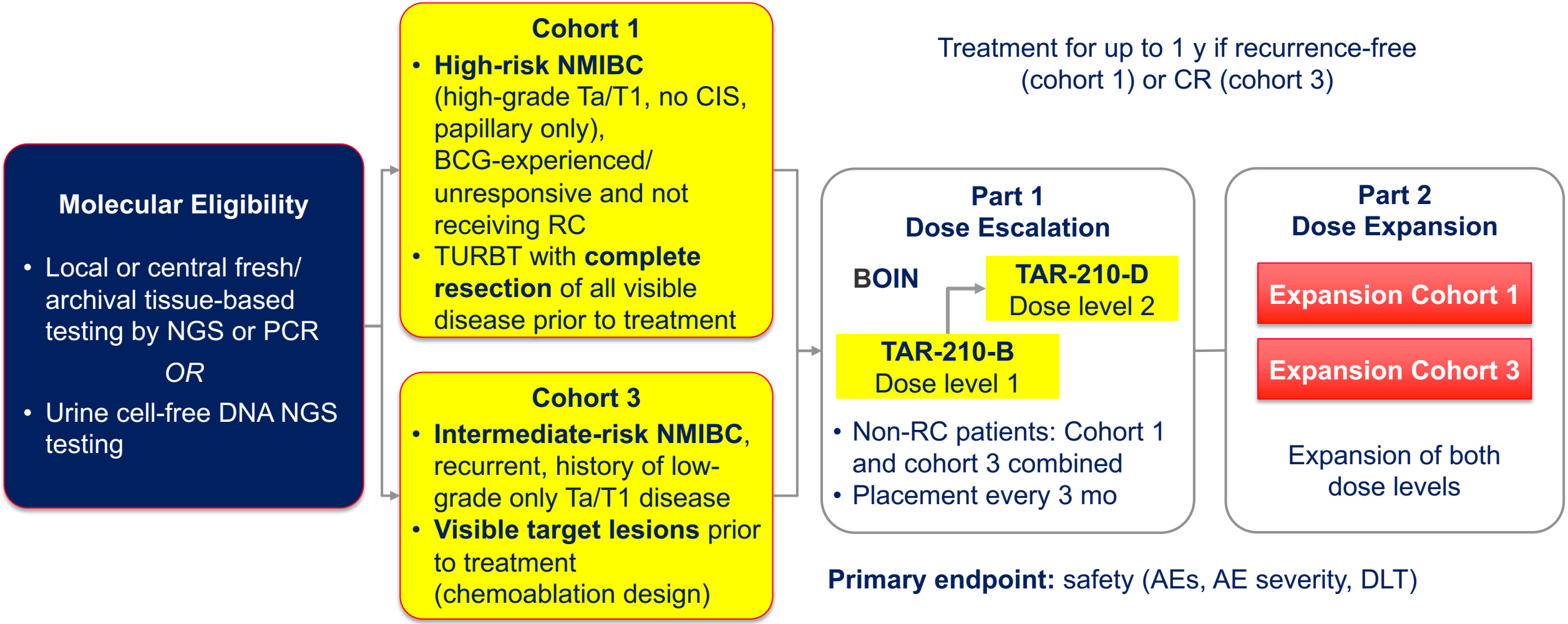
Catto JWF et al. Ann Oncol 2024;35(1):98-106; ESMO 2023.

Courtesy of Shilpa Gupta, MD

TAR-210: Erdafitinib Intravesical Delivery



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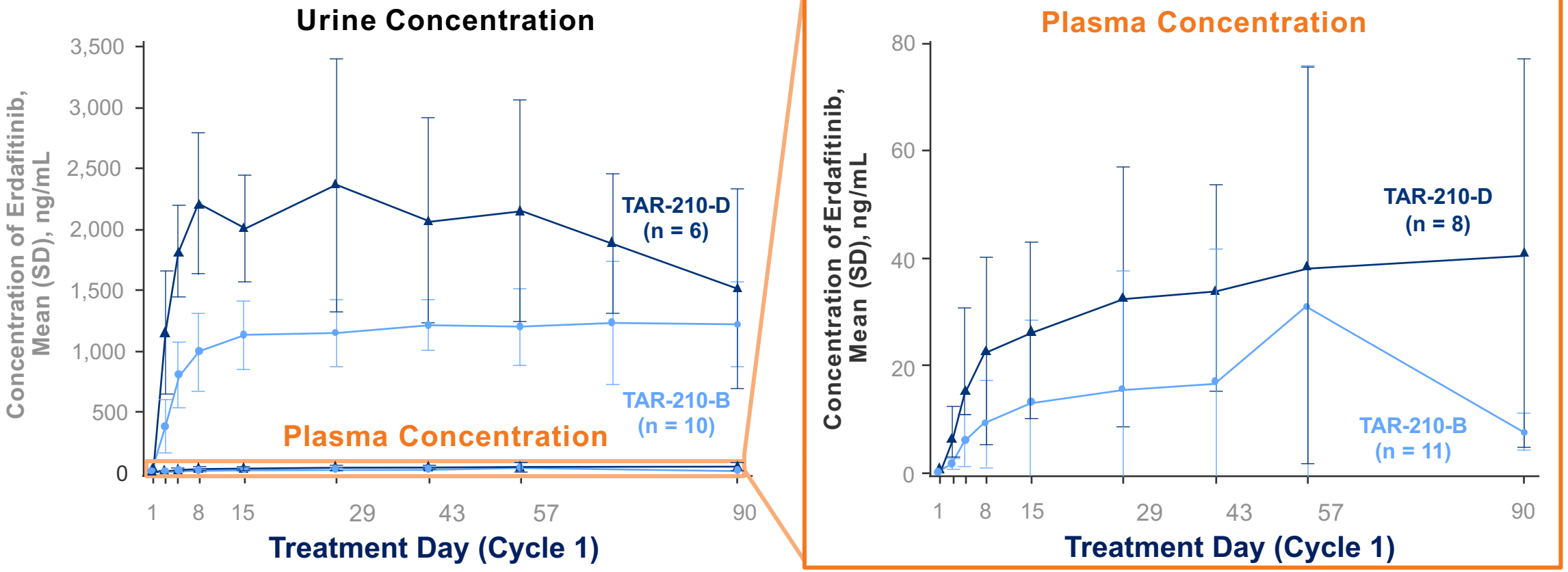
Vilaseca A et al. ESMO 2023. LBA104

Courtesy of Shilpa Gupta, MD

- Steady-state mean plasma concentrations are >50x lower than oral erdafitinib 9 mg daily
- No hyperphosphatemia
- TAR-210 Provides Sustained Erdafitinib Release in Urine Over 90 Days With Very Low Plasma Concentrations



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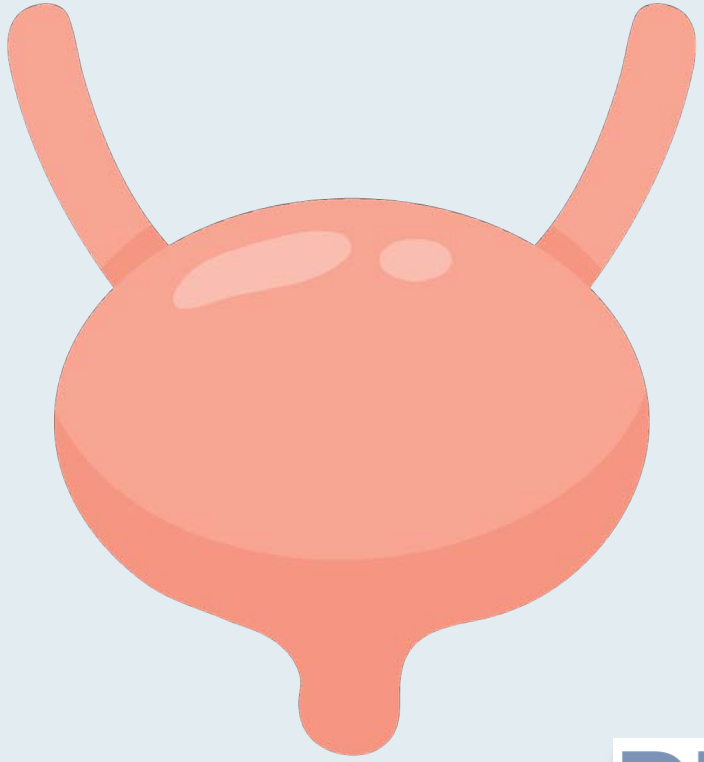
Courtesy of Shilpa Gupta, MD

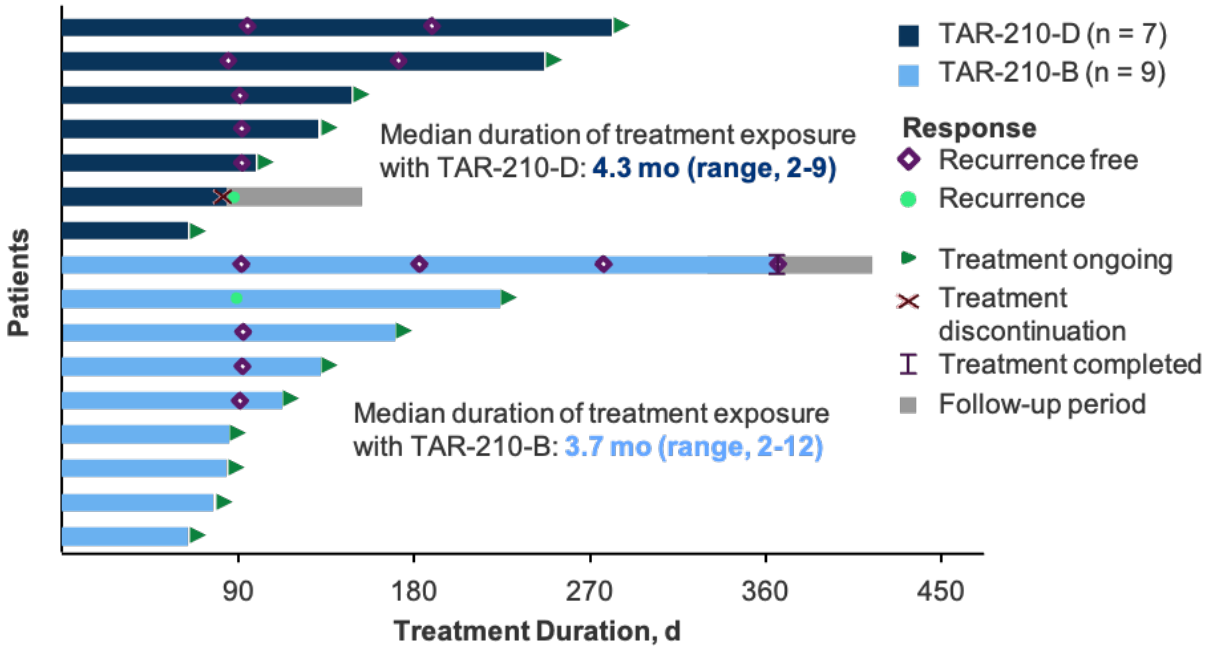
What is the nature of the “blood/bladder barrier” in relation to drug efflux?



TAR-210 Efficacy

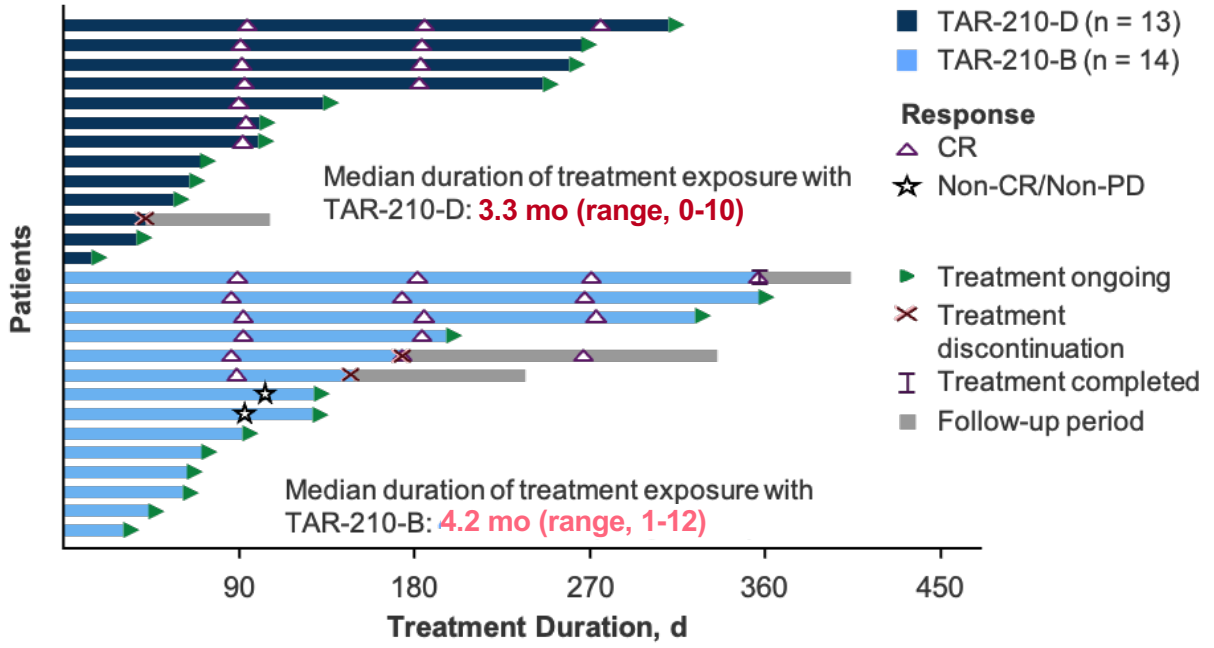
Cohort 1: *FGFR*-Altered High-Risk NMIBC (N = 16)

Primary endpoint: RFS
RFS-82%; median RFS not met



Cohort 3: *FGFR*-Altered Intermediate-Risk NMIBC (N = 27)

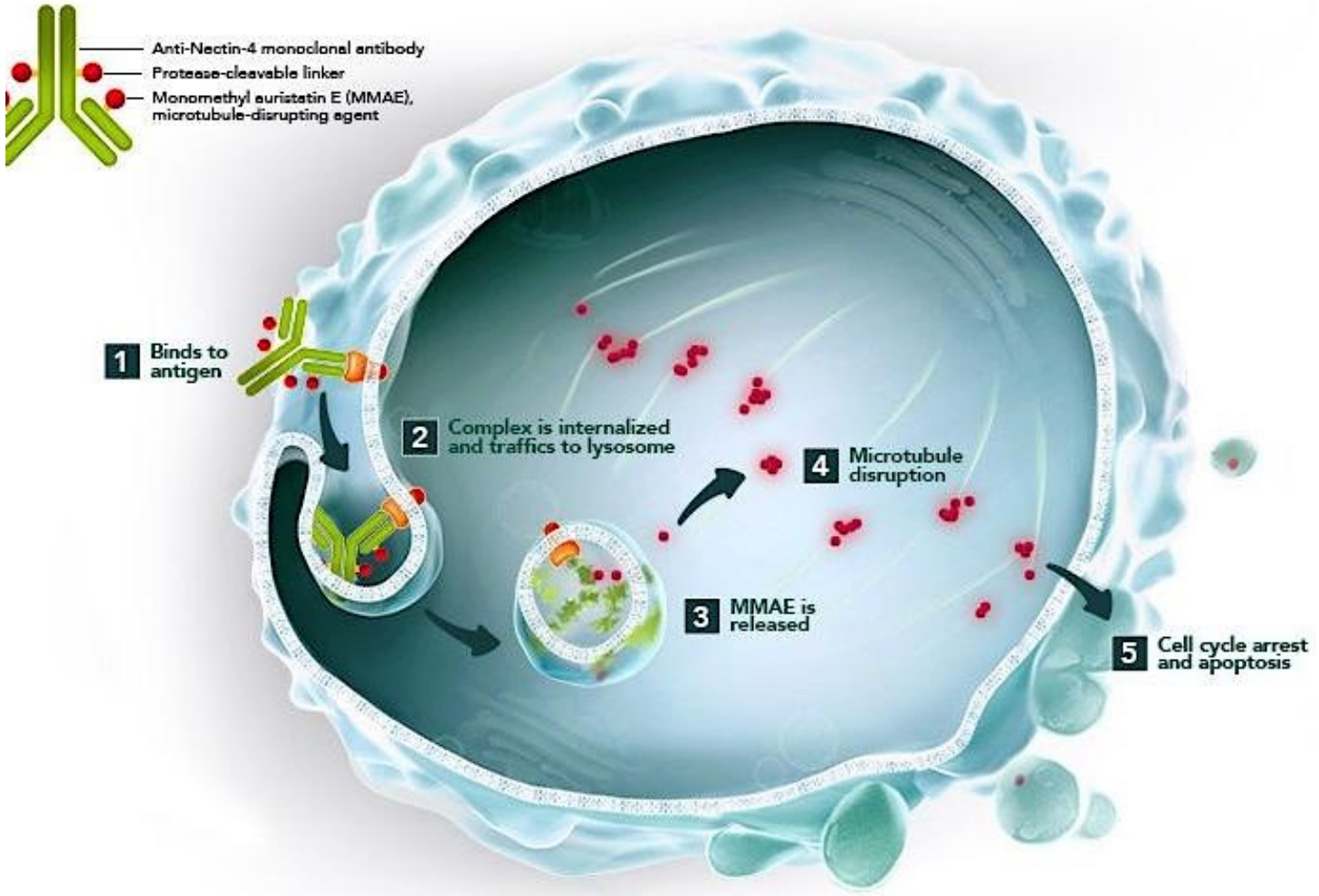
Primary endpoint: CR, DoR
CR- 87%



Vilaseca A et al. ESMO 2023. Abstract LBA104

Courtesy of Shilpa Gupta, MD

Exploiting ADC Enfortumab Vedotin in NMIBC



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Courtesy of Shilpa Gupta, MD

EV-104: Intravesical Enfortumab Vedotin in Patients with NMIBC

EV-104 Study Design

Patient population

Histologically confirmed BCG-unresponsive CIS; with or without papillary disease

Unfit for or "refuse" radical cystectomy

ECOG PS 0-2

Screening TURBT

Month 1-3 | Month 4-12

Induction
Intravesical EV (25 mL) weekly instillation x6 doses

Maintenance
Intravesical EV (25 mL) monthly instillation x9 doses

Follow-up

Survival follow-up

Cystoscopy/cytology Q3 months for 2 years; Q6 months thereafter for 5 years after enrollment

Primary endpoints	• Type, incidence, severity, seriousness, and relatedness of AEs • Type, incidence, and severity of laboratory abnormalities • Incidence of DLTs and cumulative safety per dose level
Key secondary endpoints	• Estimates of selected PK parameters • CR rate at any time on study and CR rates at 3, 6, 12, 18 and 24 months • Duration of CR, PFS, and cystectomy-free survival

EV-104 Dose Escalation Design

- Dose escalation phase aims to identify the MTD or recommended dose of intravesical EV at four dose levels
- Study design optimized to maximize intravesical drug concentration and limit urinary urgency with a 25 mL dose volume
- Approximately 18 patients will be treated across four dosing levels during dose escalation
- Escalation rules are guided by the modified toxicity probability interval design using a Bayesian model for "escalation", "stay", or "de-escalation"
- As of data cutoff (10 February 2023), 6 patients had been enrolled and received EV at the first two dose levels

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Roupret M et al. ASCO 2023

Courtesy of Shilpa Gupta, MD

Summary of Disposition

	EV 125 mg (N=4) n (%)	EV 250 mg (N=2) n (%)
Patients receiving any amount of EV	4 (100.0)	2 (100.0)
Patients on treatment	2 (50.0)	2 (100.0)
Patients off treatment	2 (50.0)	0
Reason for treatment discontinuation		
Completed treatment	1 (25.0)	0
Persistent disease	1 (25.0)	0
Patients on study	4 (100.0)	2 (100.0)

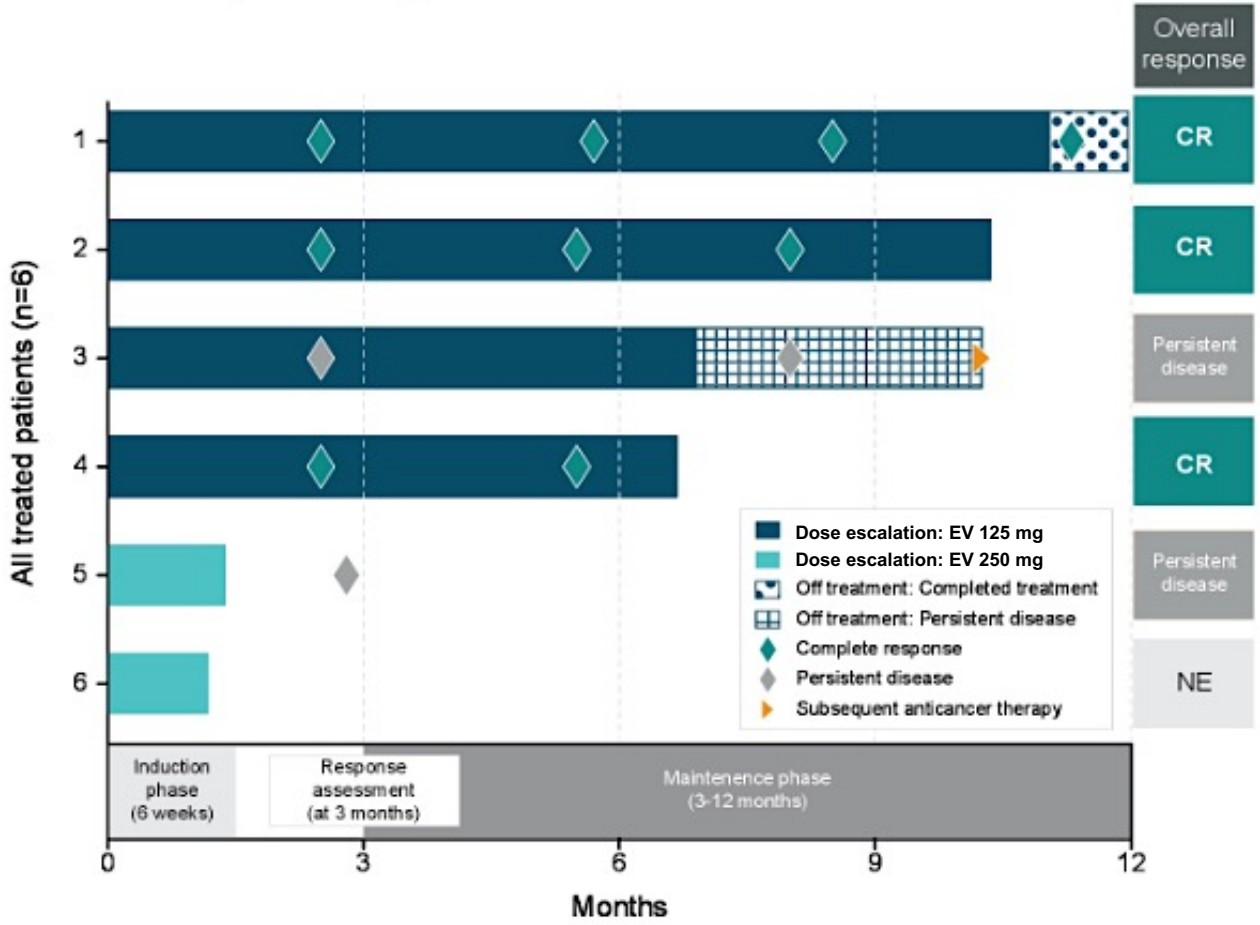
All 6 patients completed the DLT evaluable period.
No DLTs were observed for either 125 mg or 250 mg.

Treatment-Related Adverse Events

TRAEs by preferred term ≥2 of 6 total patients	EV 125 mg (N=4) n (%)		EV 250 mg (N=2) n (%)		Total (N=6) n (%)	
	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2
Patients with any event	2 (50.0)	1 (25.0)	1 (50.0)	1 (50.0)	3 (50.0)	2 (33.3)
Fatigue	2 (50.0)	0	0	1 (50.0)	2 (33.3)	1 (16.7)
Dry eye	2 (50.0)	0	0	0	2 (33.3)	0
Micturition urgency	1 (25.0)	0	1 (50.0)	0	2 (33.3)	0

- No grade ≥3 TRAEs
- No treatment-related SAEs
- No TRAEs leading to dose reduction or discontinuation

Preliminary Efficacy of Intravesical EV



Per protocol, patient 3 (125 mg) with persistent disease at 3 months was allowed to stay on treatment until the 6-month disease assessment

At the time of data cutoff, patient 6 (250 mg) had not yet completed their 3-month evaluation and was considered non-evaluable

- 1 patient at 125mg completed all planned doses of EV
- Of the 5 efficacy-evaluable patients, 3 achieved a CR at the time of the data cutoff

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Courtesy of Shilpa Gupta, MD

Muscle-Invasive Bladder Cancer – Adjuvant Checkpoint Inhibition

- Milowsky M et al. Results from the **extended follow-up** in patients with **muscle-invasive** bladder cancer in the **CheckMate 274** trial. AUA 2023;Abstract LBA02-08.
- Apolo AB et al. **AMBASSADOR Alliance A031501**: **Phase III** randomized adjuvant study of **pembrolizumab** in **muscle-invasive** and locally advanced urothelial carcinoma (MIUC) vs observation. Genitourinary Cancers Symposium 2024;Abstract LBA531.

Adjuvant IO trials in high-risk MIUC

High risk MIUC: if received NAC- ypT2-T4a/ypN+ or pT3-T4a/pN+ if not eligible for or declined adjuvant cisplatin-based chemotherapy

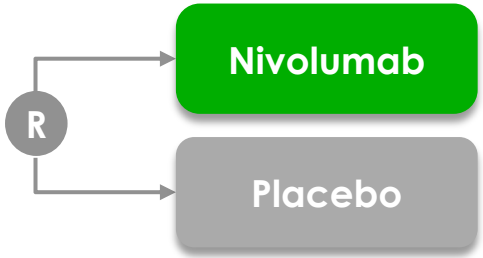
IMvigor010

Primary endpoint:
DFS

Key secondary endpoints:
OS, DSS, distant metastasis-free survival, NUTRFS

No DFS or OS improvement

CheckMate 274



Primary endpoint:
DFS

Key secondary endpoints:
OS, NUTRFS, DSS

DFS Improvement Waiting for OS

AMBASSADOR

Coprimary endpoints:
DFS and OS

Key secondary endpoints:
OS and DFS in PD-L1–positive and PD-L1–negative patients

DFS Improvement

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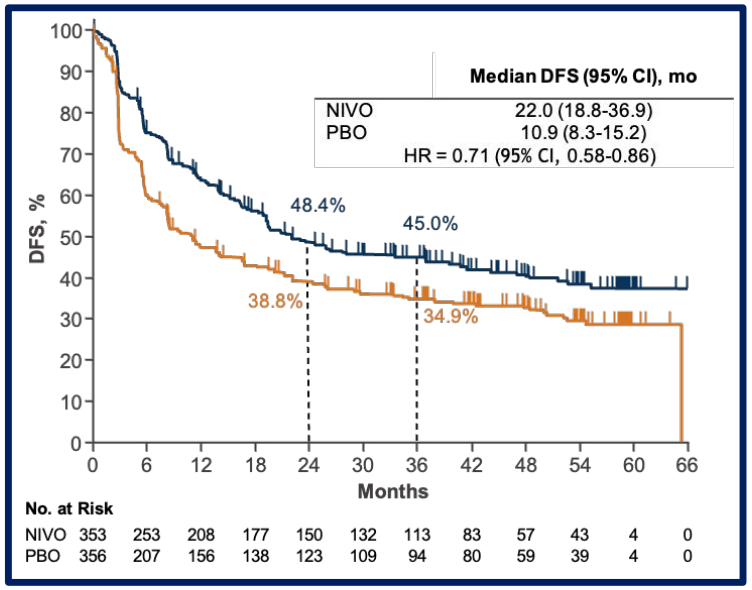
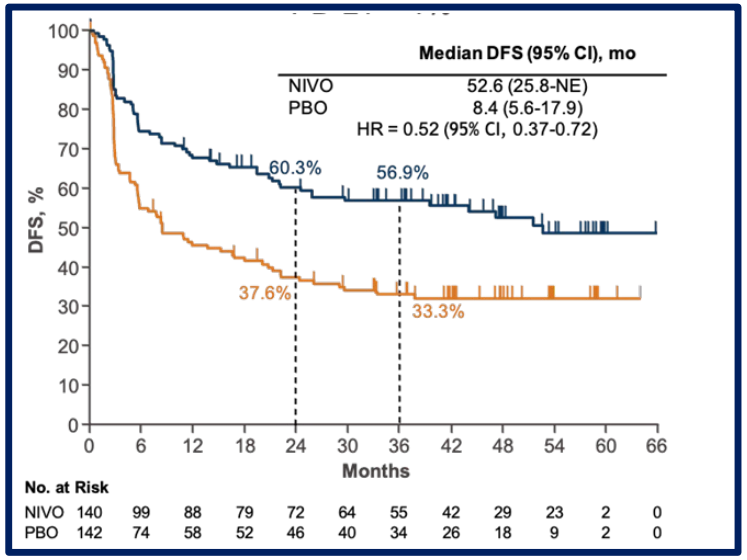
Courtesy of Shilpa Gupta, MD

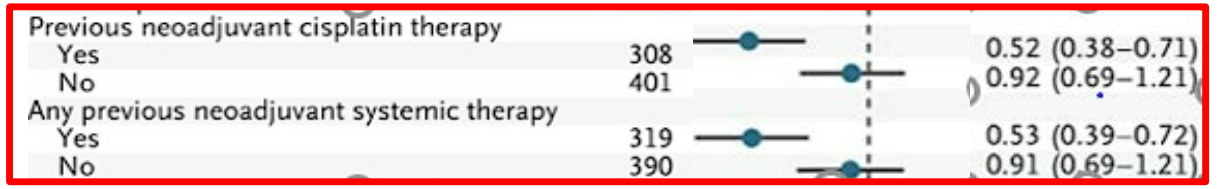
CheckMate 274 Extended Follow-up

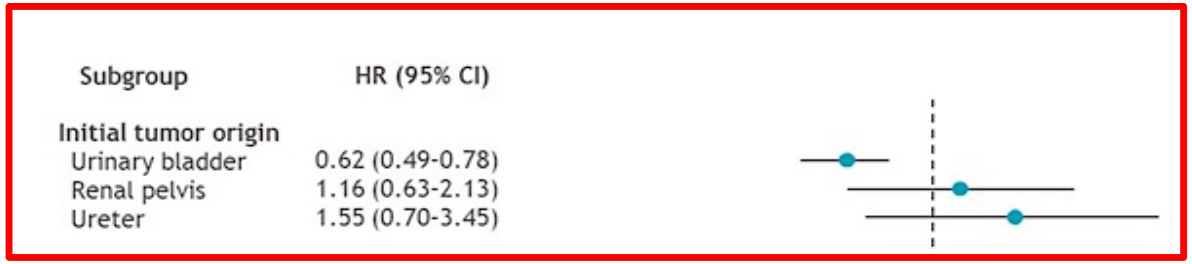
ITT

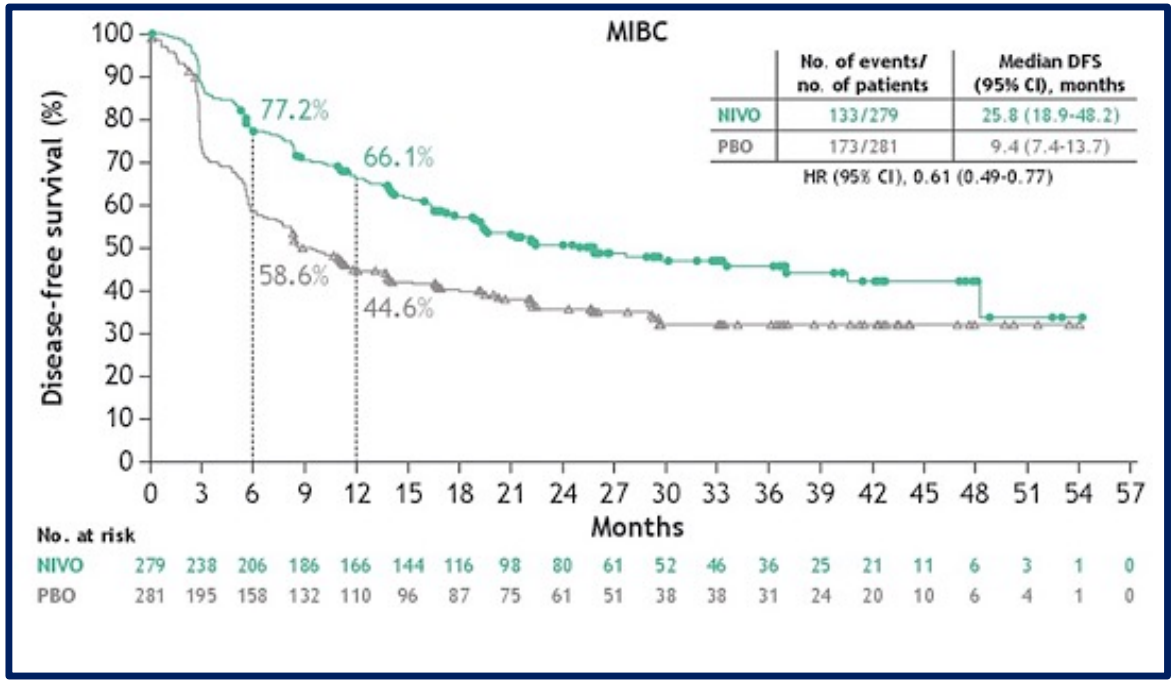


PD-L1 ≥1%







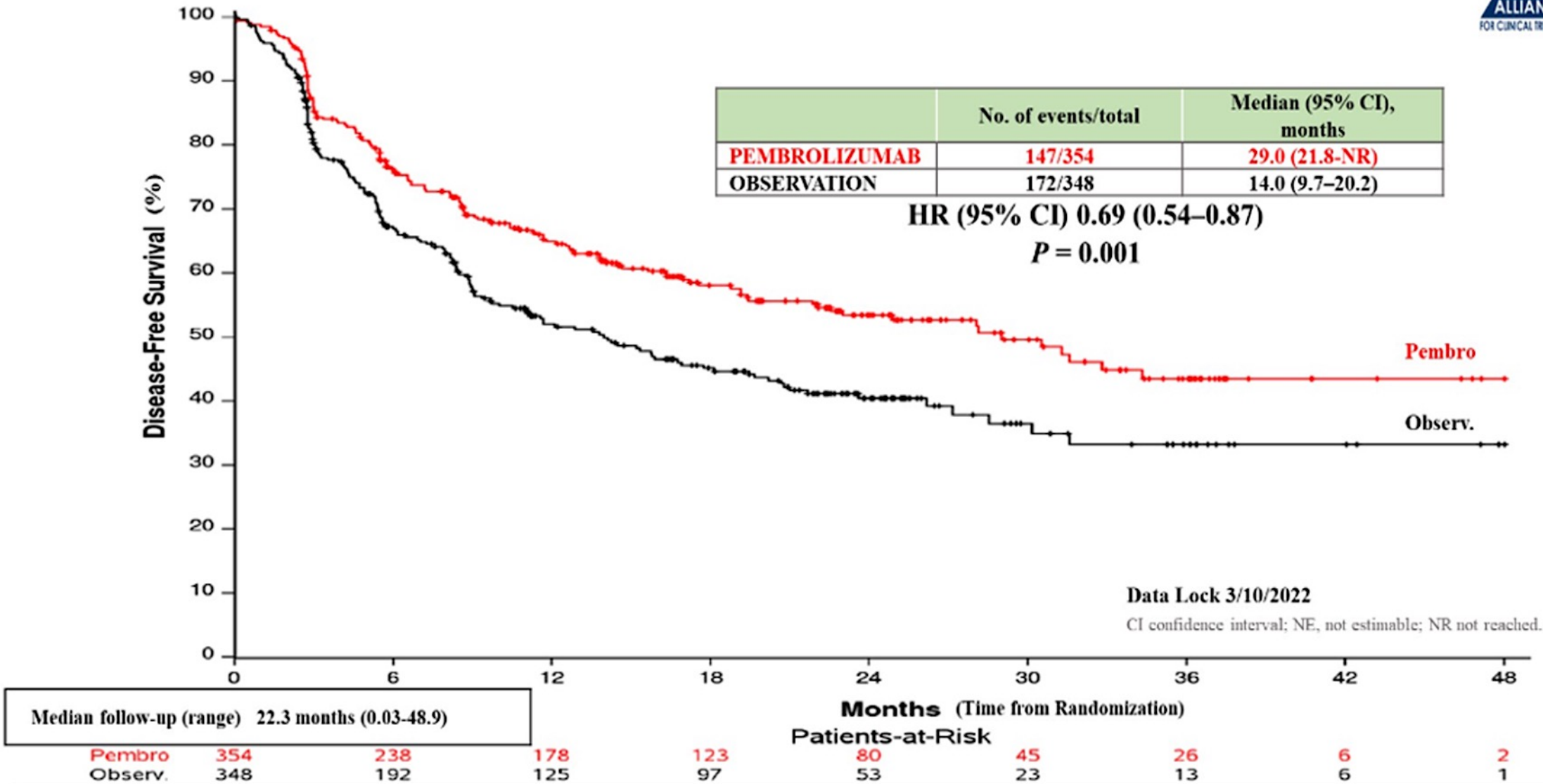


MIBC only

Bajorin DF et al. NEJM 021, Galsky MD et al. ASCO 2023, Milowsky M et al. AUA 2023

Courtesy of Shilpa Gupta, MD

A031501 AMBASSADOR: Disease-Free Survival (ITT)



	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	147/354	29.0 (21.8-NR)
OBSERVATION	172/348	14.0 (9.7–20.2)

HR (95% CI) 0.69 (0.54–0.87)

***P* = 0.001**

Data Lock 3/10/2022

CI confidence interval; NE, not estimable; NR not reached.

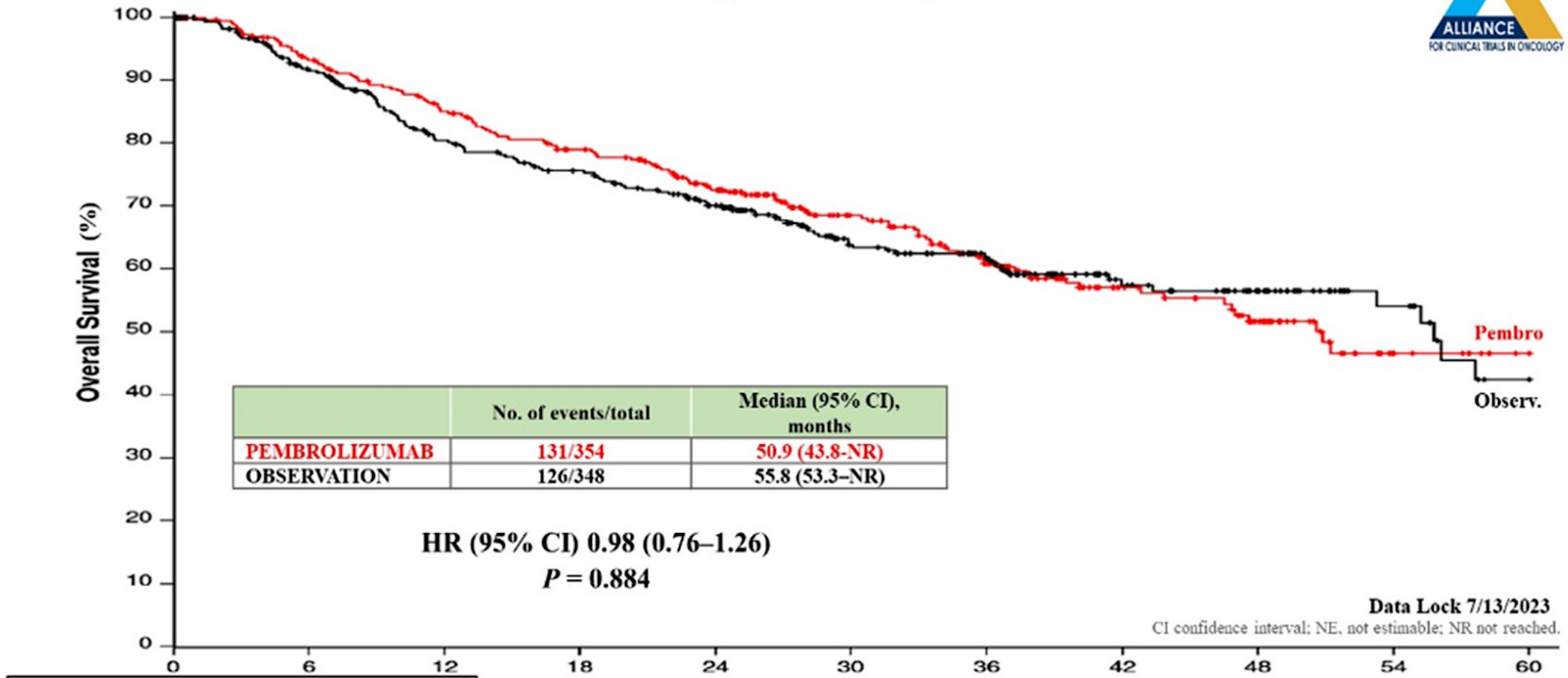
Median follow-up (range) 22.3 months (0.03-48.9)

Patients-at-Risk

Pembro	354	238	178	123	80	45	26	6	2
Observ.	348	192	125	97	53	23	13	6	1

Courtesy of Shilpa Gupta, MD

A031501 AMBASSADOR: (interim) Overall Survival



	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	131/354	50.9 (43.8-NR)
OBSERVATION	126/348	55.8 (53.3–NR)

HR (95% CI) 0.98 (0.76–1.26)
***P* = 0.884**

Data Lock 7/13/2023

CI confidence interval; NE, not estimable; NR not reached.

Median follow-up (range) 36.9 months (0-63.9)

Patients-at-Risk

Pembro	354	313	280	253	218	152	115	69	50	17	10
Observ.	348	296	249	227	195	139	117	65	45	23	12

ASCO Genitourinary Cancers Symposium #GU24

PRESENTED BY: Andrea B. Apolo, MD

@apolo_andrea

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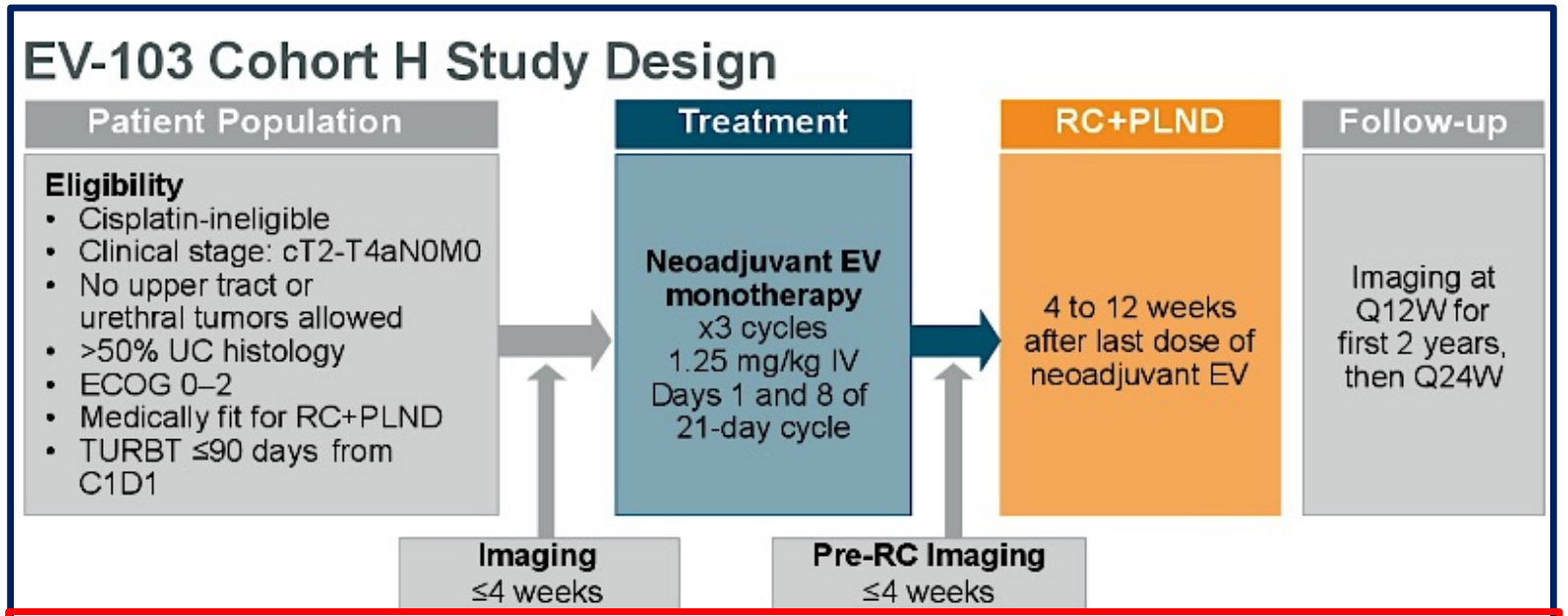
Courtesy of Shilpa Gupta, MD

Muscle-Invasive Bladder Cancer – Enfortumab Vedotin

- Flaig TW et al. **Study EV-103**: **Neoadjuvant** treatment with **enfortumab vedotin** monotherapy in **cisplatin-ineligible** patients (pts) with **muscle invasive** bladder cancer (MIBC): Updated results for **Cohort H**. ASCO 2023;Abstract 4595.
- Sridhar S et al. **Study EV-103 cohort L**: **Perioperative** treatment w/ **enfortumab vedotin (EV)** monotherapy in cisplatin **(cis)-ineligible** patients (pts) w/ **muscle invasive** bladder cancer (MIBC). ESMO 2023;Abstract 2365MO.

Neoadjuvant treatment with EV monotherapy in cisplatin-ineligible patients with MIBC: EV-103 Cohort H



CrCl ≥30 to <60 mL/min was the most common reason for cisplatin-ineligibility (n=11; 50.0%), followed by grade ≥2 hearing loss (n=9, 40.9%), CrCl ≥30 to <60 mL/min and grade ≥2 hearing loss (n=1; 4.5%), and ECOG PS of 2 (n=1; 4.5%)

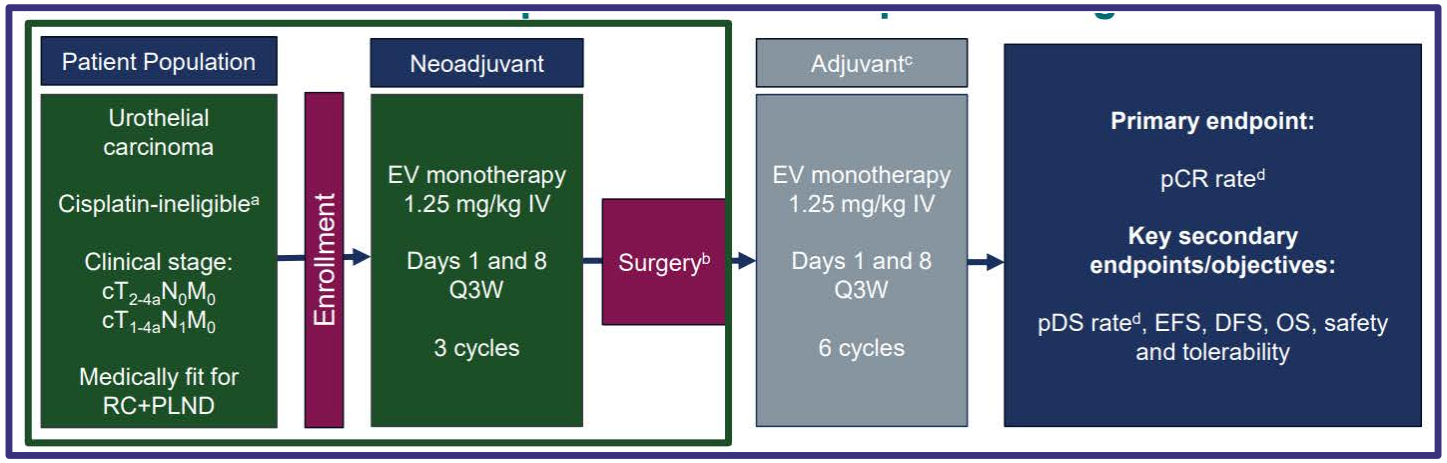
Pathological Response	Central Pathology Results (N=22) n (%) [95% Confidence Interval]
pCR rate (defined as absence of any viable tumor tissue; ypT0 and N0)	8 (36.4) [17.2-59.3]
pDS rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	11 (50.0) [28.2-71.8]

- 19/22 pts completed all 3 cycles prior to RC
- No delays to surgery
- **1 death from AKI**

Flaig, T et al. ASCO 2023

Courtesy of Shilpa Gupta, MD

Perioperative treatment with EV monotherapy in cisplatin-ineligible patients with MIBC: EV-103 Cohort L

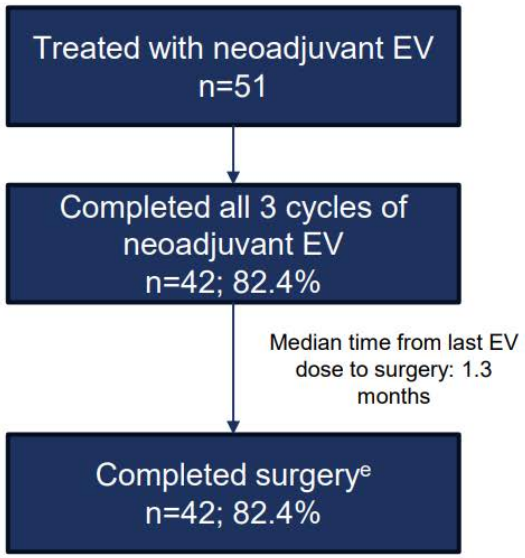


pCR: 17/51 (34%
pDS: 21/51 (42%)

Over 80% of patients completed 3 cycles of neoadjuvant EV and surgery

Characteristics	Cohort L (n=51[a])
Male, n (%)	39 (76.5)
Median age (range), years	74.0 (54, 85)
ECOG PS 0-1, n (%)	49 (96.1)
Baseline stage[b], n (%)	
cT2N0	29 (56.9)
cT3N0	13 (25.5)
cT4N0	4 (7.8)
cT2-3N1[c]	5 (9.8)
Creatinine clearance (CrCl) <60 and ≥30 mL/min[d]	23 (45.1)

ECOG PS: Eastern Cooperative Oncology Group Performance Status



Adverse Events:

- 29/51 (56.9%) of pts. had skin reactions; **1 death from Stevens-Johnson syndrome**
- 17/ 51 (33.3%) of pts. had peripheral neuropathy
- No delays to surgery

Sridhar S et al. ESMO 2023
Courtesy of Shilpa Gupta, MD

Muscle-Invasive Bladder Cancer – TAR-200

- Tyson MD et al. Safety, tolerability, and preliminary efficacy of **TAR-200** in patients with **muscle-invasive** bladder cancer who refused or were unfit for curative-intent therapy: A phase 1 study. *J Urol* 2023;209(5):890-900.

Safety, Tolerability, and Preliminary Efficacy of TAR-200 in Patients with Muscle-Invasive Bladder Cancer Who Refused or Were Unfit for Curative-Intent Therapy: A Phase 1 Study

TAR-200-103 (NCT03404791): A global, phase 1, single-arm, open-label study

- Eligible patients with cT2-cT3bN0M0 urothelial bladder cancer received 4 consecutive 21-day cycles of **TAR-200** over 84 days

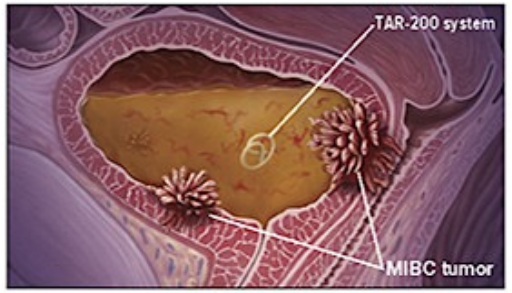
- **Primary endpoints:** Safety and tolerability at 84 days
- **Secondary endpoints:** Rates of clinical complete response (CR), partial response (PR), duration of response (DOR) and overall survival (OS)

TAR-200: A novel, intravesical drug delivery system

A. TAR-200 consists of a small, flexible silicone delivery system that contains gemcitabine
B. TAR-200 continuously releases drug directly into the bladder over the indwelling period

A

B



Safety and tolerability profile of TAR-200 in muscle-invasive bladder cancer

- Of the 35 enrolled patients, 15 experienced TAR-200-related treatment-emergent adverse events (TEAEs)
  - Dysuria (n=7) and urinary frequency (n=5) were the most common

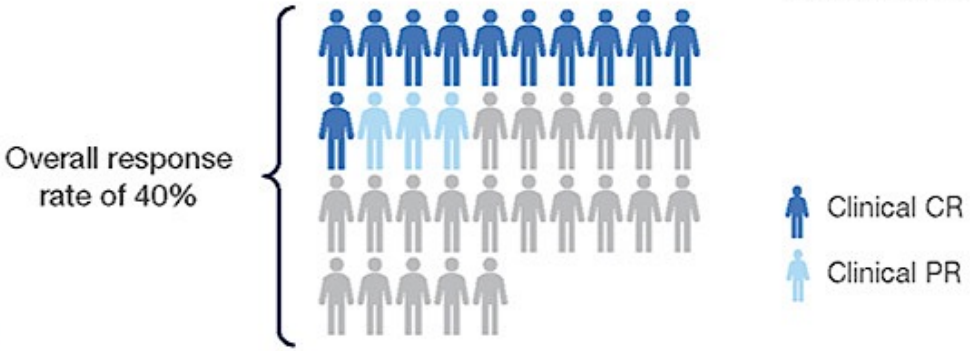
Patients with TEAEs classified as TAR-200-related

Patients with TEAEs classified as procedure-related

- TAR-200 was generally well tolerated, with only 2 unscheduled TAR-200 removals

Efficacy

- Overall, 11 patients had CR and 3 had PR
- Median OS was 27.3 months
- Median DOR was 14.0 months

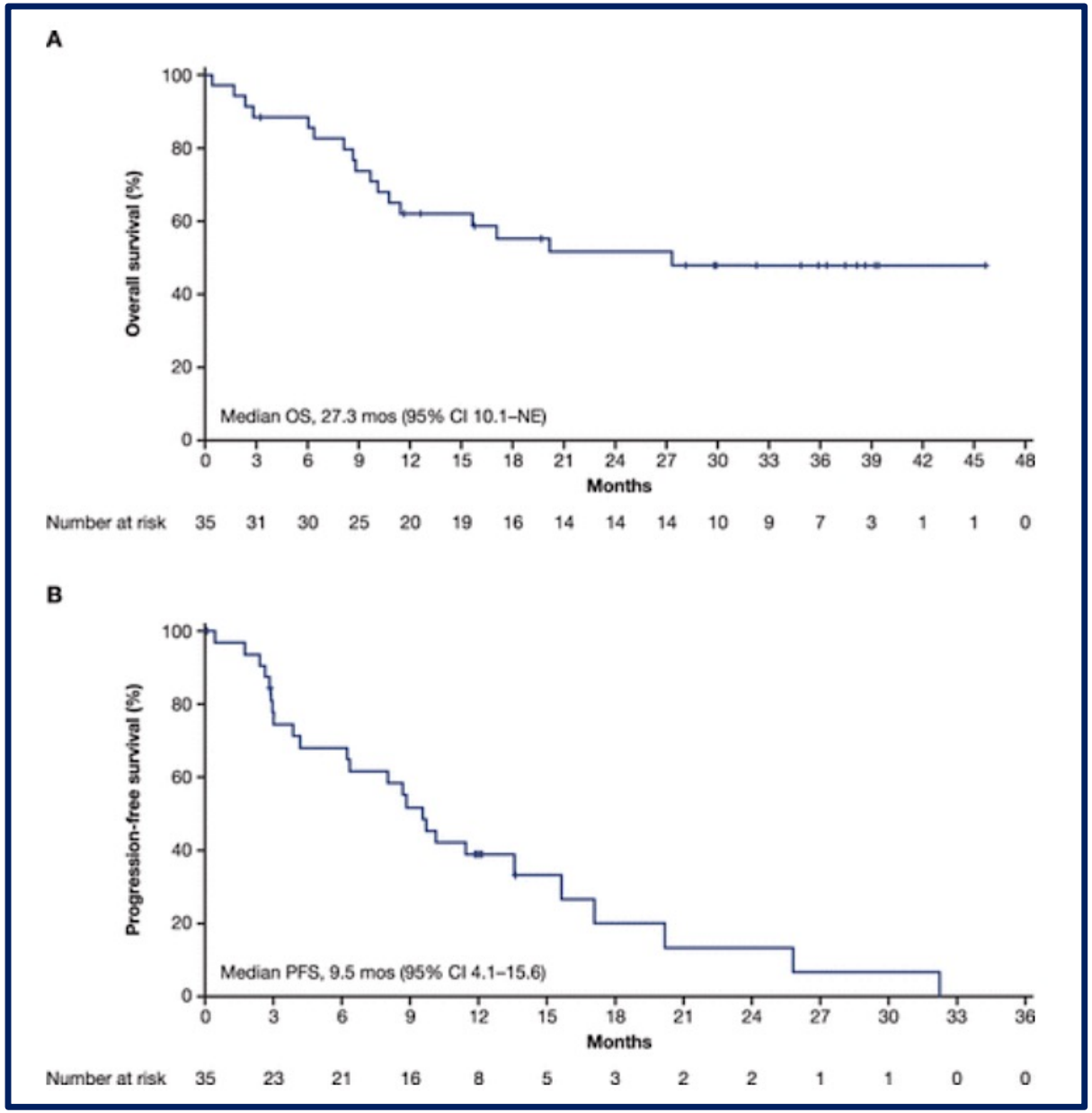


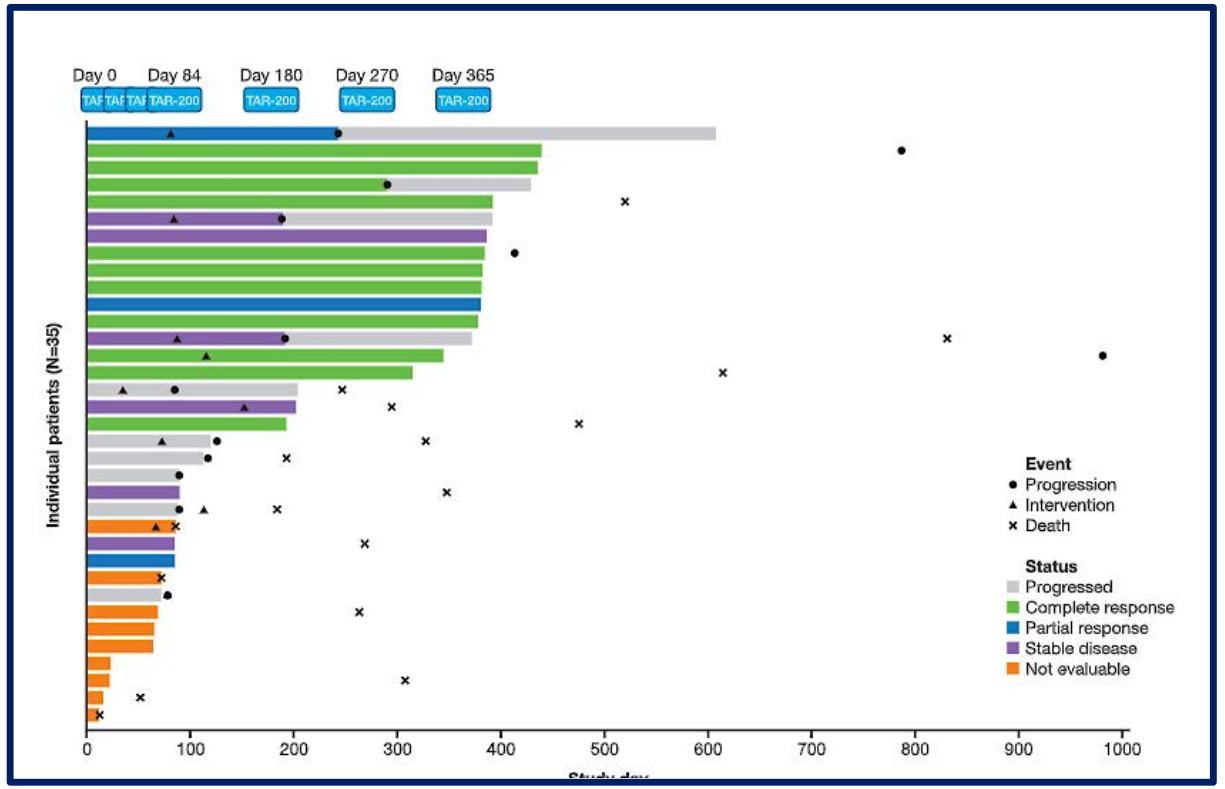
Conclusions

- TAR-200 was safe and well tolerated in elderly patients with muscle-invasive bladder cancer who refused or were unfit for curative-intent therapy
- Intravesical TAR-200 monotherapy had beneficial preliminary efficacy on patient outcomes, warranting further study as a therapeutic option

Tyson MD et al. J Urol 2023

Courtesy of Shilpa Gupta, MD





Cleveland Clinic

Tyson MD et al. J Urol 2023

Courtesy of Shilpa Gupta, MD

Other Strategies for Localized Urothelial Bladder Cancer

- Galsky MD et al. **Gemcitabine and cisplatin** plus **nivolumab** as **organ-sparing** treatment for **muscle-invasive** bladder cancer: A phase 2 trial. *Nat Med* 2023;29(11):2825-34.
- Cathomas R et al. Perioperative chemoimmunotherapy with **durvalumab** for **muscle-invasive** urothelial carcinoma: Primary analysis of the single-arm phase II trial **SAKK 06/17**. *J Clin Oncol* 2023;41(33):5131-9.
- Joshi M et al. Concurrent **durvalumab and radiation therapy** (DUART) followed by **adjuvant durvalumab** in patients with localized urothelial cancer of bladder: Results from phase II study, **BTCRC-GU15-023**. *J Immunother Cancer* 2023;11(2):e006551.

Agenda

INTRODUCTION: The Cancer-Immunity Cycle

MODULE 1: Nonmetastatic Urothelial Bladder Cancer — Dr Gupta

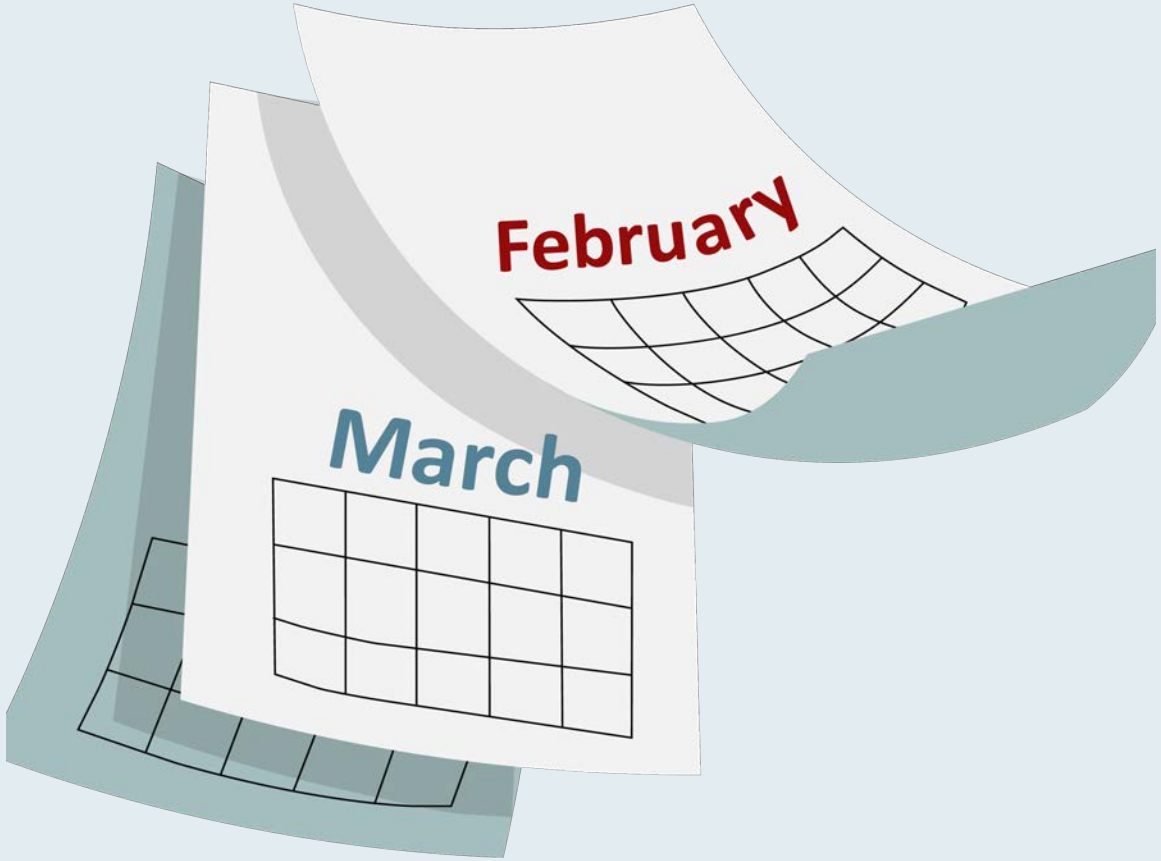
- Non-Muscle-Invasive Bladder Cancer – Checkpoint Inhibitors
- Non-Muscle-Invasive Bladder Cancer – Intravesical Therapies
- Muscle-Invasive Bladder Cancer – Adjuvant Checkpoint Inhibition
- Muscle-Invasive Bladder Cancer – Enfortumab Vedotin
- Muscle-Invasive Bladder Cancer – TAR-200
- Other Strategies for Localized Urothelial Bladder Cancer

MODULE 2: Metastatic Urothelial Bladder Cancer (mUBC) — Prof Powles

- Checkpoint Inhibition for Previously Untreated mUBC
- Enfortumab Vedotin/Pembrolizumab for Previously Untreated mUBC
- Erdafitinib-Based Therapy for Previously Treated mUBC
- Sacituzumab Govitecan for Previously Treated mUBC
- HER2-Directed Therapies

Where we were February 22, 2023

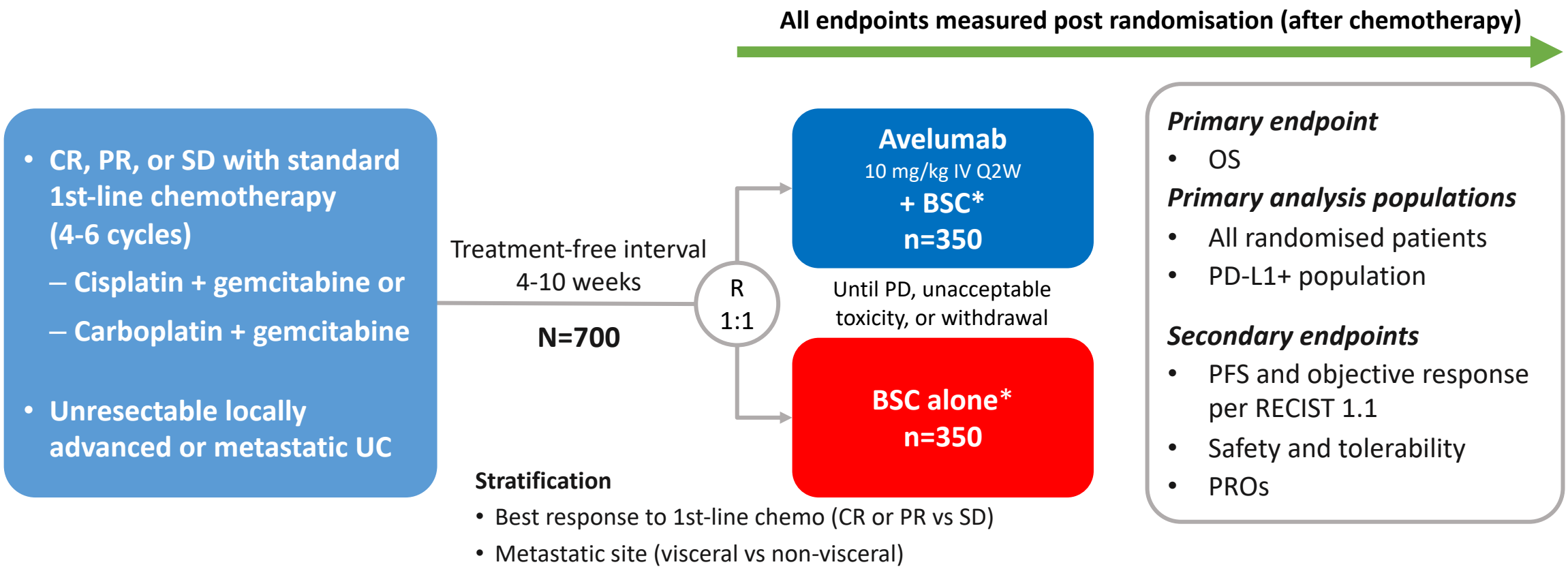
Nonmetastatic Urothelial Bladder Cancer



Checkpoint Inhibition for Previously Untreated mUBC

- Powles T et al. **Avelumab first-line maintenance** for advanced urothelial carcinoma: Results from the **JAVELIN Bladder 100** trial after ≥2 years of follow-up. *J Clin Oncol* 2023;41(19):3486-92
- Grivas P et al. **Avelumab first-line** maintenance (1LM) for advanced urothelial carcinoma (aUC): Long-term **patient-reported outcomes** (PROs) in the **phase 3 JAVELIN Bladder 100** trial. Genitourinary Cancers Symposium 2024;Abstract 581.
- van der Heijden MS et al. **Nivolumab** plus **gemcitabine-cisplatin** in advanced urothelial carcinoma. *N Engl J Med* 2023;389(19):1778-89.
- Ozyilkan O et al. Outcomes by complete response to **first-line pembrolizumab** or platinum-based chemotherapy in advanced urothelial carcinoma (UC) in **KEYNOTE-361**. ASCO 2023;Abstract 4513.

JAVELIN Bladder 100 study design (NCT02603432)[1,2]



PD-L1+ status was defined as PD-L1 expression in ≥25% of tumour cells or in ≥25% or 100% of tumour-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumour

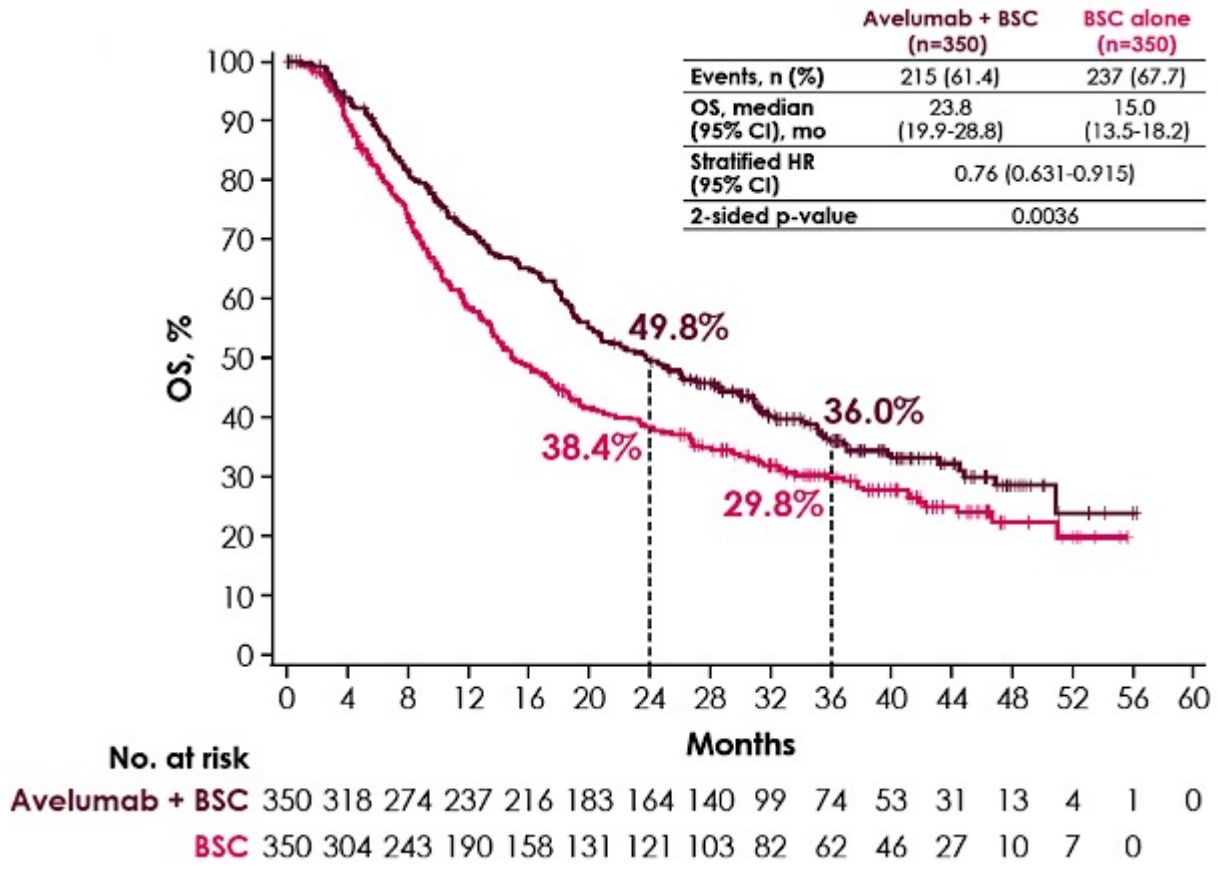
BSC, best supportive care; **CR,** complete response; **IV,** intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W,** every 2 weeks; **R**, randomization; **RECIST 1.1,** Response Evaluation Criteria in Solid Tumours version 1.1; **SD**, stable disease

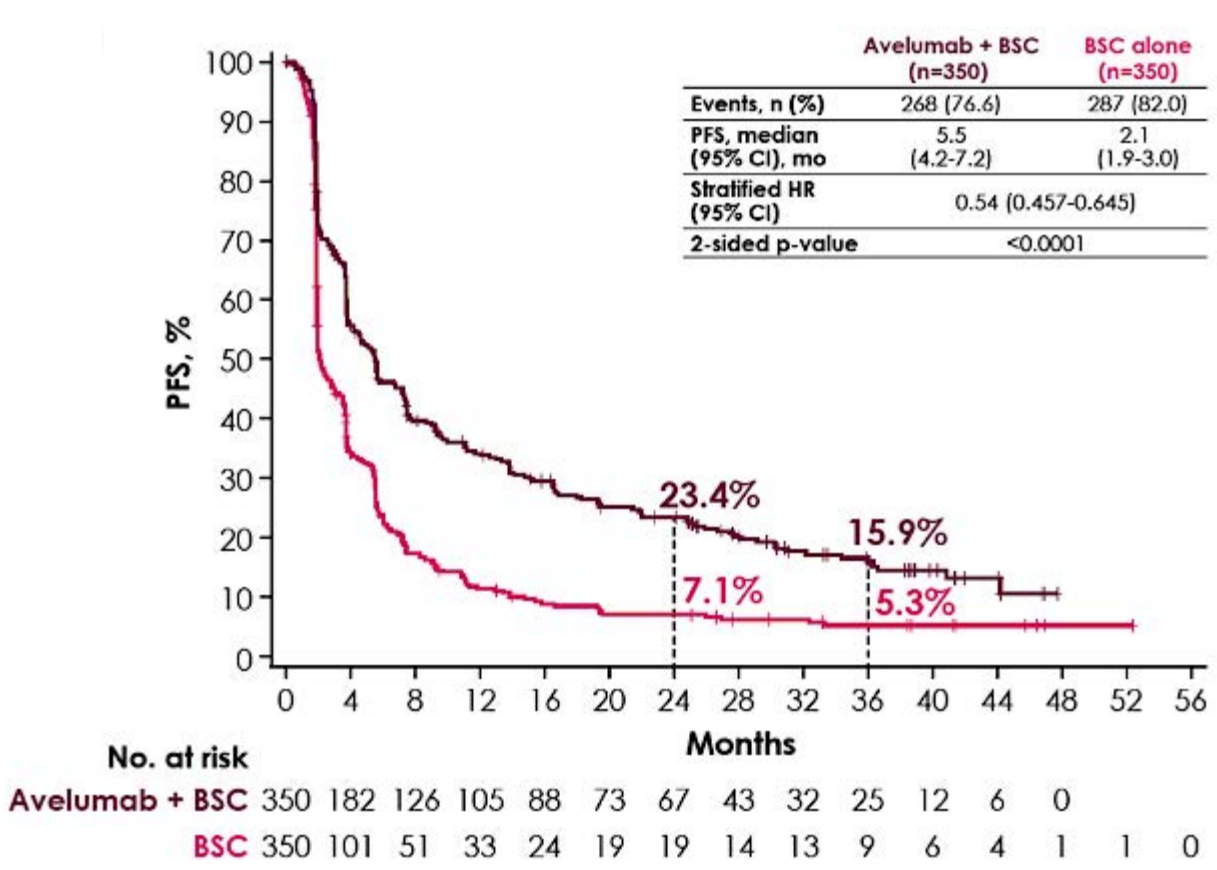
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumour therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable.

1. Powles T, et al. N Engl J Med 2020;383:1218–30; 2. Powles T, et al. Oral presentation at ASCO 2020 (Abstract LBA1).

Courtesy of Thomas Powles, MBBS, MRCP, MD

JAVELIN Bladder 100: Long-term follow-up continues to show prolonged OS and PFS with avelumab + BSC vs BSC alone



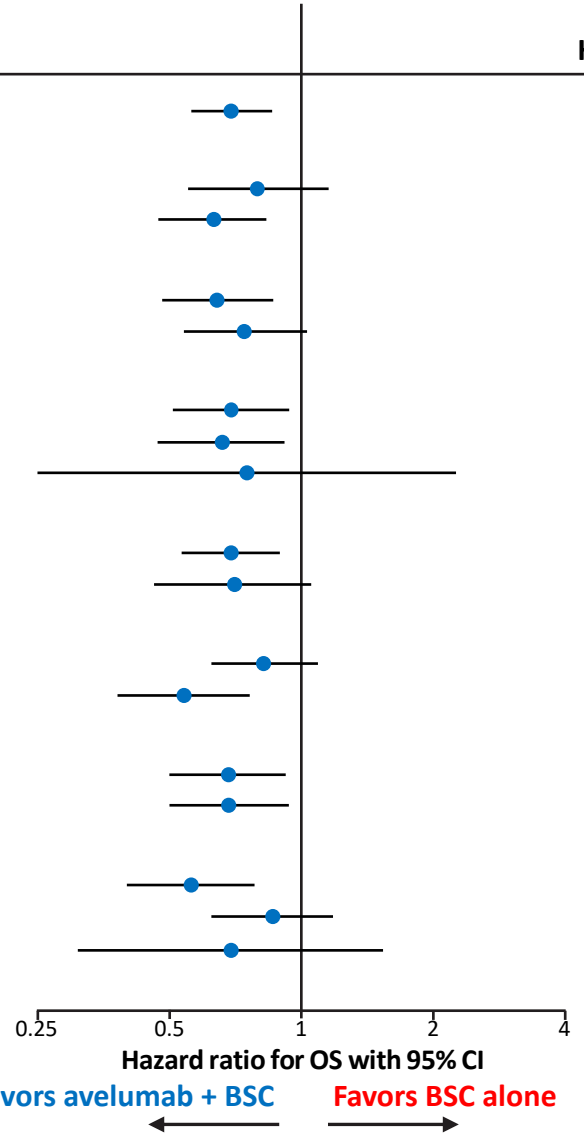


Powles T et al. *J Clin Oncol* 2023;41(19):3486-92.

Courtesy of Thomas Powles, MBBS, MRCP, MD

JAVELIN Bladder 100: Subgroup analysis of OS in the overall population

Subgroup		Events/patients, n: Avelumab + BSC	Events/patients, n: BSC alone	Hazard ratio (95% CI)
All patients		145/350	179/350	**0.69** (0.56, 0.86)*
Age	<65 years	61/129	53/107	**0.79** (0.55, 1.15)
	≥65 years	84/221	126/243	**0.63** (0.47, 0.83)
ECOG PS score	0	77/213	101/211	**0.64** (0.48, 0.86)
	≥1	68/137	78/139	**0.74** (0.54, 1.03)
1st-line chemotherapy regimen	Gemcitabine + cisplatin	71/183	98/206	**0.69** (0.51, 0.94)
	Gemcitabine + carboplatin	68/147	73/122	**0.66** (0.47, 0.91)
	Gemcitabine + cisplatin/carboplatin	6/20	7/20	**0.75** (0.25, 2.25)
Best response to 1st-line chemotherapy	CR or PR	104/253	127/252	**0.69** (0.53, 0.89)
	SD	41/97	52/98	**0.70** (0.46, 1.05)
Site of baseline metastasis	Visceral	93/191	101/191	**0.82** (0.62, 1.09)
	Nonvisceral	52/159	78/159	**0.54** (0.38, 0.76)
Creatinine clearance	≥60 mL/min	74/181	97/196	**0.68** (0.50, 0.92)
	<60 mL/min	71/168	81/148	**0.68** (0.50, 0.94)
PD-L1 status	Positive	61/189	82/169	**0.56** (0.40, 0.78)
	Negative	76/139	72/132	**0.86** (0.62, 1.18)
	Unknown	8/22	25/49	**0.69** (0.31, 1.53)



Error bars show 95% CI

*Stratified (all other analyses are unstratified)

Thomas Powles, MD

Courtesy of Thomas Powles, MBBS, MRCP, MD

Avelumab first-line maintenance for advanced urothelial carcinoma: long-term patient-reported outcomes in the phase 3 JAVELIN Bladder 100 trial

P. Grivas,[1] J.B. Aragon-Ching,[2] J. Bellmunt,[3] Y. Loriot,[4] S. S. Sridhar,[5] P.-J. Su,[6] S. H. Park,[7] Y. Yamamoto,[8] N. Jacob,[9] J. Hoffman,[10] M. Kearney,[3] M. Schlichting,[3] T. Powles[11]

[1]University of Washington; Fred Hutchinson Cancer Center, Seattle, WA, USA; [2]Inova Schar Cancer Institute, Fairfax, VA, USA; [3]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [4]Gustave Roussy, INSERM U981, Université Paris-Saclay, Villejuif, France; [5]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [6]Chang Gung Memorial Hospital, Linkou, Taiwan; [7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [8]Yamaguchi University Hospital, Ube, Yamaguchi, Japan; [9]the healthcare business of Merck KGaA, Darmstadt, Germany; [10]EMD Serono, Billerica, MA, USA; [11]Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, UK

JAVELIN Bladder 100

CONCLUSIONS

- Long-term and exploratory analyses of patient-reported outcomes (PROs) in patients with advanced urothelial carcinoma (aUC) who received avelumab first-line (1L) switch maintenance + best supportive care (BSC) in the JAVELIN Bladder 100 trial showed that prolonged avelumab treatment, including in patients treated for ≥12 months, was associated with stable PROs, indicating preservation of health-related quality of life
  - These results complement previously reported results that compared PROs between study arms[1] and post hoc analyses showing the acceptable long-term safety profile of avelumab 1L maintenance, including in patients treated for ≥12 months[2]
  - These results are also consistent with a previous analysis showing that patients treated with avelumab 1L maintenance + BSC had a consistently longer quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) than patients who received BSC alone, reflecting the safety profile of avelumab 1L maintenance in the context of an overall survival (OS) benefit[3]
  - Overall, these data suggest that patients receiving long-term avelumab treatment may have preserved health-related quality of life and control of cancer-related symptoms with manageable treatment-related toxicity
- PRO results from this trial further support the use of avelumab 1L maintenance until progression or unacceptable toxicity as standard of care in patients with aUC who are progression free after platinum-based chemotherapy

PLAIN LANGUAGE SUMMARY

- In the JAVELIN Bladder 100 study, avelumab switch maintenance treatment given after chemotherapy helped people with advanced urothelial cancer live longer
  - "Switch" maintenance treatment means giving a different treatment to people whose cancer disappeared, shrank, or stopped growing with chemotherapy
- In this new analysis, researchers looked at the long-term effects of avelumab treatment on people's quality of life
  - Quality of life is a measure of well-being. It includes how a person feels about their physical health, emotional well-being, ability to be active, and several other factors affecting everyday life
- Overall, avelumab treatment was found to maintain people's quality of life, and this was seen in both people treated with avelumab for any length of time and in people treated for at least 1 year
- Overall, these results support using avelumab switch maintenance (after chemotherapy) as a standard treatment for people with advanced urothelial cancer

BACKGROUND

- In the JAVELIN Bladder 100 phase 3 trial, avelumab 1L maintenance + BSC significantly prolonged OS and progression-free survival compared with BSC alone in patients with aUC that had not progressed with 1L platinum-based induction chemotherapy[4]
  - After ≥2 years of follow-up (data cutoff: June 4, 2021), median OS (from randomization) was 23.8 vs 15.0 months, respectively (hazard ratio [HR], 0.76 [95% CI, 0.63-0.91]; p=0.0036)[4]
  - In a post hoc exploratory analysis, median OS with avelumab 1L maintenance, measured from start of 1L platinum-based chemotherapy in this selected population without cancer progression was 29.7 months[5]
  - The long-term safety of avelumab 1L maintenance was also demonstrated[2,4]
- Based on results from JAVELIN Bladder 100, avelumab 1L maintenance has been approved in multiple countries worldwide[7,8] and is recommended as a standard of care in international guidelines[9-11]
- In a post hoc analysis, treatment with avelumab 1L maintenance + BSC resulted in a consistently longer Q-TWiST than BSC alone, indicating a net benefit in quality survival or well-being with avelumab[3]
- Initial analyses of PROs in JAVELIN Bladder 100 showed that avelumab 1L maintenance treatment resulted in stable health-related quality of life[1]
- Here, we report PRO data with long-term follow-up in the overall avelumab + BSC arm (any treatment duration) and in a subgroup with ≥12 months of avelumab treatment

METHODS

- JAVELIN Bladder 100 (NCT02603432) enrolled 700 patients with unresectable locally advanced or metastatic UC that had not progressed with 1L platinum-based chemotherapy
- Patients were randomized 1:1 to receive avelumab 1L maintenance + BSC or BSC alone
- The primary endpoint was OS
- PROs were a secondary endpoint and were assessed at baseline, on day 1 of each 4-week cycle, at end of treatment or withdrawal from the study, and up to 90 days post treatment
- PRO instruments used were the NCCN/FACT Bladder Symptom Index-18 (NFBlSI-18) and EuroQol EQ-5D-5L
  - NFBlSI-18 measures symptoms and quality of life in the past 7 days; score ranges are: NFBlSI-18 total score, 0-72; disease-related symptoms – physical (DRS-P), 0-36; disease-related symptoms – emotional (DRS-E), 0-8; treatment side effects (TSE), 0-20; and function/well-being (F/WB), 0-8
  - EQ-5D-5L measures general health status based on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; EQ-5D-5L index score is calculated based on UK weights, and scores range from −0.594 to 1; EQ-5D-5L visual analog scale scores range from 0 to 100
- Descriptive and mixed-effect model analyses were conducted
- PROs were examined in all patients who received treatment in the avelumab + BSC arm for any duration and in a subgroup who had received ≥12 months of avelumab treatment
  - In this analysis, data were not evaluated in the BSC alone arm because few patients remained on study treatment at later time points, and comparative assessment was deemed not appropriate due to this attrition bias

RESULTS

- At data cutoff (June 4, 2021), median follow-up in the avelumab + BSC arm (n=350) was 38.0 months (≥2 years in all patients), and median duration of treatment was 5.8 months
- In patients treated for ≥12 months (n=118 [33.7%]), baseline characteristics were similar to those of patients in the overall avelumab + BSC arm, except for a higher proportion with ECOG performance status 0 (70.3% vs 60.9%) and PD-L1+ tumors (61.0% vs 54.0%) and a lower proportion with visceral metastases (47.5% vs 54.6%) (**Table 1**)
- In both populations, completion rates for both PRO instruments among evaluable patients were ≥80% at all time points during treatment (**Table 2**)

Table 1. Patient baseline characteristics

	Overall avelumab + BSC arm (n=350)	Patients treated with avelumab for ≥12 months (n=118)
Age, median (range), years	68 (37-90)	69 (43-86)
Sex, n (%)		
Male	266 (76.0)	91 (77.1)
Female	84 (24.0)	27 (22.9)
Pooled geographic region, n (%)		
Europe	214 (61.1)	61 (51.7)
North America	12 (3.4)	6 (5.1)
Asia	73 (20.9)	32 (27.1)
Australasia	34 (9.7)	15 (12.7)
Rest of the world	17 (4.9)	4 (3.4)
ECOG performance status, n (%)		
0	213 (60.9)	83 (70.3)
1	136 (38.9)	35 (29.7)
2	1 (0.3)	0
PD-L1 status, n (%)		
Positive	189 (54.0)	72 (61.0)
Negative	139 (39.7)	39 (33.1)
Unknown	22 (6.3)	7 (5.9)
1L chemotherapy regimen, n (%)		
Gemcitabine + cisplatin	183 (52.3)	67 (56.8)
Gemcitabine + carboplatin	147 (42.0)	43 (36.4)
Gemcitabine + cisplatin or carboplatin[a]	20 (5.7)	8 (6.8)
Best response to 1L chemotherapy, n (%)		
CR	90 (25.7)	36 (30.5)
PR	183 (52.3)	51 (43.2)
SD	77 (22.0)	31 (26.3)
Site of metastasis at start of 1L chemotherapy, n (%)		
Visceral	191 (54.6)	56 (47.5)
Nonvisceral	159 (45.4)	62 (52.5)
Site of primary tumor, n (%)		
Upper tract	106 (30.3)	34 (28.8)
Lower tract	244 (69.7)	84 (71.2)

1L, first line; BSC, best supportive care; CR, complete response; PR, partial response; SD, stable disease.
[a]Patients who switched platinum regimens while receiving 1L chemotherapy.

Table 2. Completion rates for the NFBlSI-18 and EQ-5D-5L instruments

	NFBlSI-18, n completed/N eligible (%)		EQ-5D-5L, n completed/N eligible (%)	
	Overall avelumab + BSC arm (n=350)	Patients treated with avelumab for ≥12 months (n=118)	Overall avelumab + BSC arm (n=350)	Patients treated with avelumab for ≥12 months (n=118)
Baseline	[illegible]	114/118 (97)	[illegible]	117/118 (99)
Cycle 2/day 1	317/334 (95)	116/118 (98)	316/334 (95)	116/118 (98)
Cycle 5/day 1	211/227 (93)	111/118 (94)	214/227 (94)	111/118 (94)
Cycle 10/day 1	135/141 (96)	114/118 (97)	136/141 (96)	115/118 (97)
Cycle 15/day 1	[illegible]	109/114 (96)	109/114 (96)	[illegible]
Cycle 20/day 1	76/83 (92)	76/83 (92)	76/83 (92)	76/83 (92)
Cycle 25/day 1	69/72 (96)	69/72 (96)	69/72 (96)	69/72 (96)
Cycle 30/day 1	51/58 (88)	51/58 (88)	51/58 (88)	51/58 (88)
Cycle 35/day 1	33/36 (92)	33/36 (92)	33/36 (92)	33/36 (92)
Cycle 40/day 1	25/25 (100)	25/25 (100)	25/25 (100)	25/25 (100)
Cycle 45/day 1	6/10 (60)	10/19 [illegible]	10/19 [illegible]	6/10 (60)
End of treatment	227/291 (78)	54/70 (77)	227/291 (78)	54/70 (77)
Follow-up day 30	81/128 (63)	26/40 (65)	80/128 (63)	25/40 (63)
Follow-up day 60	70/99 (71)	23/30 (77)	70/99 (71)	23/30 (77)
Follow-up day 90	52/76 (68)	19/25 (76)	52/76 (68)	19/25 (76)

[illegible]
BSC, best supportive care; NFBlSI-18, NCCN/FACT Bladder Symptom Index-18.

- On average, PRO scores remained stable throughout treatment, and no clinically important changes from baseline were reported (**Table 3; Figures 1 and 2**)
  - Mixed-model analyses, including data after treatment discontinuation, had similar results (data not shown)
- In the overall avelumab + BSC arm and in patients treated with avelumab for ≥12 months, approximately 75% of evaluable patients reported no change or a decrease in how much they were bothered by treatment side effects throughout 24 months of treatment (**Figure 3**)

Table 3. Mixed-effect model analysis of NFBlSI-18 and EQ-5D-5L scores over all cycles prior to end of treatment

	Least-squares mean change from baseline (95% CI)	
	Overall avelumab + BSC arm (n=350)	Patients treated with avelumab for ≥12 months (n=118)
NFBlSI-18 total score	−2.15 (−3.28, −1.01)	1.28 (0.08, 2.49)
DRS-P	−1.29 (−1.88, −0.69)	−0.05 (−0.63, 0.52)
DRS-E	0.27 (0.11, 0.44)	0.68 (0.46, 0.91)
Treatment side effects	−0.42 (−0.73, −0.11)	0.22 (−0.16, 0.59)
Function/well-being	−0.15 (−0.34, 0.04)	0.36 (0.09, 0.62)
EQ-5D-5L index score	−0.02 (−0.04, −0.01)	−0.02 (−0.04, 0.00)
Visual analog scale	−1.14 (−2.95, 0.67)	4.16 (2.09, 6.23)

[illegible]
BSC, best supportive care; DRS-E, disease-related symptoms – emotional; DRS-P, disease-related symptoms – physical; NFBlSI-18, NCCN/FACT Bladder Symptom Index-18.

Figure 1. NFBlSI-18 total scores over time

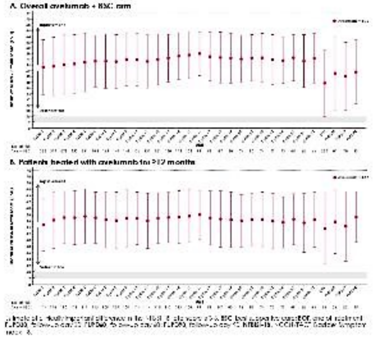


Figure 2. EQ-5D-5L index scores over time

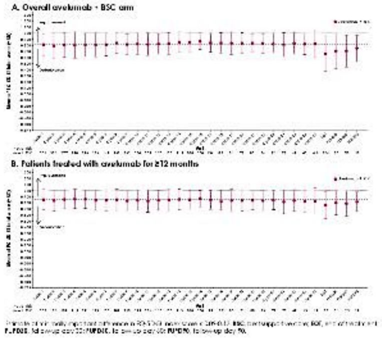
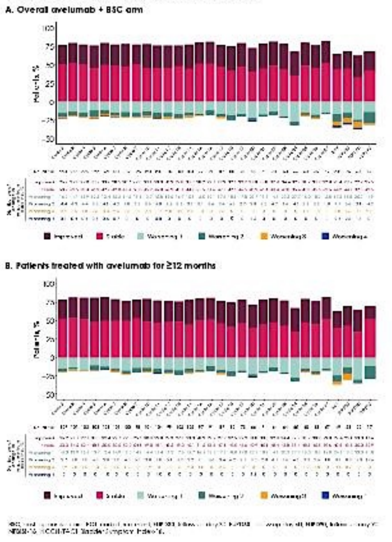


Figure 3. Distribution of patients over time who reported being bothered by treatment side effects in NFBlSI-18 instrument



BSC, best supportive care; NFBlSI-18, NCCN/FACT Bladder Symptom Index-18.

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Correspondence: Petros Grivas, pgrivas@uw.edu

REFERENCES [illegible]

Abstract No. 581. Presented at the ASCO Genitourinary Cancers Symposium, January 25-27, 2024; San Francisco, CA.

Grivas P et al. Genitourinary Cancers Symposium 2024;Abstract 581.

Courtesy of Thomas Powles, MBBS, MRCP, MD

Avelumab first-line maintenance for advanced urothelial carcinoma: long-term patient-reported outcomes in the phase 3 JAVELIN Bladder 100 trial

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BACKGROUND

- In the JAVELIN Bladder 100 phase 3 trial, avelumab 1L maintenance + BSC significantly prolonged OS and progression-free survival compared with BSC alone in patients with aUC that had not progressed with 1L platinum-based induction chemotherapy[1,2]
  - After ≥2 years of follow-up (data cutoff: June 4, 2021), median OS (from randomization) was 20.8 vs 15.0 months, respectively (hazard ratio [HR], 0.76 [95% CI, 0.63–0.91]; p=0.0036)[1]
  - In a post hoc exploratory analysis, median OS with avelumab 1L maintenance, measured from start of 1L platinum-based chemotherapy in the selected population without disease progression was 29.7 months[2]
  - The long-term safety of avelumab 1L maintenance was also demonstrated[1,2]
- Based on results from JAVELIN Bladder 100, avelumab 1L maintenance has been approved in multiple countries worldwide[3,4] and is recommended as a standard of care in international guidelines[5,6]
- In a post hoc analysis, treatment with avelumab 1L maintenance + BSC resulted in a consistently longer Q-TWiST than BSC alone, indicating a net benefit in quality-adjusted survival with avelumab[2]
- Initial analyses of PROs in JAVELIN Bladder 100 showed that avelumab 1L maintenance treatment resulted in stable health-related quality of life[1]
- Here, we report PRO data with long-term follow-up in the overall avelumab + BSC arm (any treatment duration) and in a subgroup with ≥12 months

METHODS

- JAVELIN Bladder 100 (NCT02603432) enrolled 700 patients with unresectable locally advanced or metastatic UC that had not progressed with 1L platinum-based chemotherapy
- Patients were randomized 1:1 to receive avelumab 1L maintenance + BSC or BSC alone
- The primary endpoint was OS
- PROs were a secondary endpoint and were assessed at baseline, on day 1 of each 4-week cycle, at end of treatment or withdrawal from the study, and up to 90 days post treatment
- PRO instruments used were the NCCN/FACT Bladder Symptom Index-18 (NFBSI-18) and EuroQol EQ-5D-5L
  - NFBSI-18 measures symptoms and quality of life in the past 7 days; score ranges are: NFBSI-18 total score, 0–72 (lower levels = less symptoms – physical [0–45], bladder/kidney related symptoms, emotional [0–15], 0–8; treatment side effects [0–3], 0–3; and function/well-being [0–9], 0–6
  - EQ-5D-5L measures general health status based on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; EQ-5D-5L index score is calculated based on UK weights, and scores range from −0.594 to 1; EQ-5D-5L visual analog scale scores range from 0 to 100
- Descriptive and mixed-effect models analyses were conducted
- PROs were examined in all patients who received treatment in the avelumab + BSC arm for any duration and in a subgroup who had received ≥12 months of avelumab treatment

SSC alone arm, because few patients remained on study treatment at later time points, and comparisons to risk attrition bias

CONCLUSIONS

- Long-term and exploratory analyses of patient-reported outcomes (PROs) in patients with advanced urothelial carcinoma (aUC) who received avelumab first-line (1L) switch maintenance + best supportive care (BSC) in the JAVELIN Bladder 100 trial showed that prolonged avelumab treatment, including in patients treated for ≥12 months, was associated with stable PROs, indicating preservation of health-related quality of life
  - These results complement previously reported results that compared PROs between study arms[1] and post hoc analyses showing the acceptable long-term safety profile of avelumab 1L maintenance, including in patients treated for ≥12 months[2]
  - These results are also consistent with a previous analysis showing that patients treated with avelumab 1L maintenance + BSC had a consistently longer quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) than patients who received BSC alone, reflecting the safety profile of avelumab 1L maintenance in the context of an overall survival (OS) benefit[3]
  - Overall, these data suggest that patients receiving long-term avelumab treatment may have preserved health-related quality of life and control of cancer-related symptoms with manageable treatment-related toxicity
- PRO results from this trial further support the use of avelumab 1L maintenance until progression or unacceptable toxicity as standard of care in patients with aUC who are progression free after platinum-based chemotherapy

PLAIN LANGUAGE SUMMARY

- In the JAVELIN Bladder 100 study, avelumab switch maintenance
  - "Switch" maintenance treatment means giving a different
- In this new analysis, researchers looked at the long-term effects of avelumab treatment on people's quality of life
  - Quality of life is a measure of well-being. It includes how a person feels about their physical health, emotional well-being, ability to be active, and several other factors affecting everyday life
- Overall, avelumab treatment was found to maintain people's quality of life, and this was seen in both people treated with avelumab for any length of time and in people treated for at least 1 year
- Overall, these results support using avelumab switch maintenance (after chemotherapy) as a standard treatment for people with advanced urothelial cancer

Figure 3. Distribution of patients over time who reported being bothered by treatment side effects in NFBSI-18 instrument

A. Overall avelumab + BSC arm

B. Patients treated with avelumab for ≥12 months

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Abstract No. 581. Presented at the ASCO Genitourinary Cancers Symposium, January 25-27, 2024; San Francisco, CA.

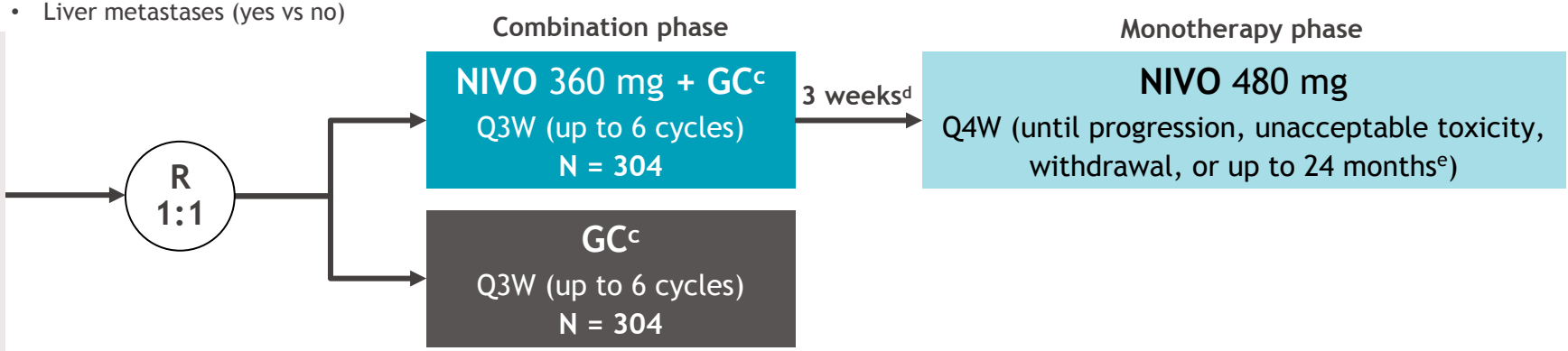
Grivas P et al. Genitourinary Cancers Symposium 2024;Abstract 581.

Courtesy of Thomas Powles, MBBS, MRCP, MD

CheckMate 901: Study design (NIVO+GC vs GC in cisplatin-eligible patients)[a]

Key inclusion criteria
- Age ≥ 18 years
- Previously untreated unresectable or mUC involving the renal pelvis, ureter, bladder, or urethra
- Cisplatin eligible[b]
- ECOG PS of 0-1

Stratification factors:
- Tumor PD-L1 expression (≥ 1% vs < 1%)
- Liver metastases (yes vs no)



Median (range) study follow-up, 33.6 (7.4–62.4) months

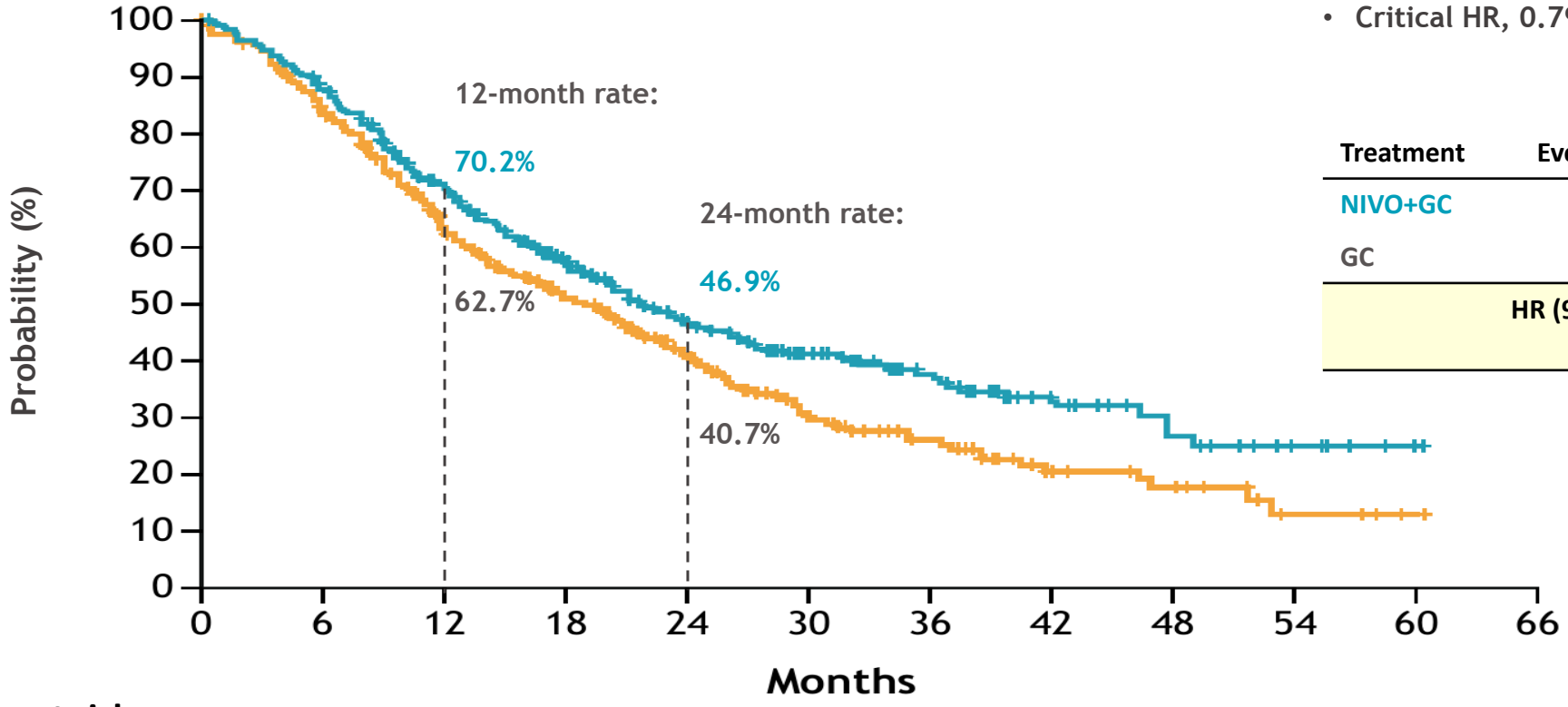
Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%, HRQoL
Key exploratory endpoints: ORR per BICR, safety

[a]Further CheckMate 901 study design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Cisplatin eligibility was determined in the study population by a GFR ≥ 60 mL/min (assessed by direct measurement, ie, creatinine clearance, or, if not available, using the Cockcroft-Gault formula), and absence of CTCAE v.4 grade ≥ 2 hearing loss and grade ≥ 2 peripheral neuropathy. [c]Patients who discontinued cisplatin alone could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to six cycles in total). [d]NIVO monotherapy should begin 3 weeks after the last dose of NIVO+GC combination. [e]Represents a maximum of 24 months from the first dose of NIVO administered as part of the NIVO+GC combination.
BICR, blinded independent central review; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; HRQoL, health-related quality of life; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q×W, every × weeks; R, randomization.

Courtesy of Thomas Powles, MBBS, MRCP, MD

CheckMate 901: OS (primary endpoint)

OS final analysis statistical boundaries:
- *P* value boundary, 0.0311
- Critical HR, 0.7980



Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7–22.4)
HR (95% CI), 0.78 (0.63–0.96) *P* = 0.0171		

No. at risk

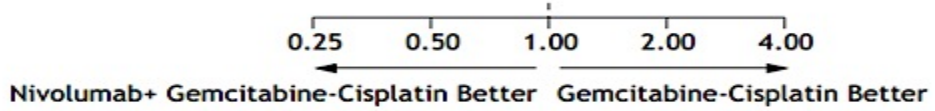
NIVO+GC	304	264	196	142	97	69	48	25	15	7	2	0
GC	304	242	166	122	82	49	33	17	13	4	1	0

Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as the time from date of randomization to date of death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with no follow-up, OS was censored at the date of randomization.

Courtesy of Thomas Powles, MBBS, MRCP, MD

CheckMate 901: OS in subgroups

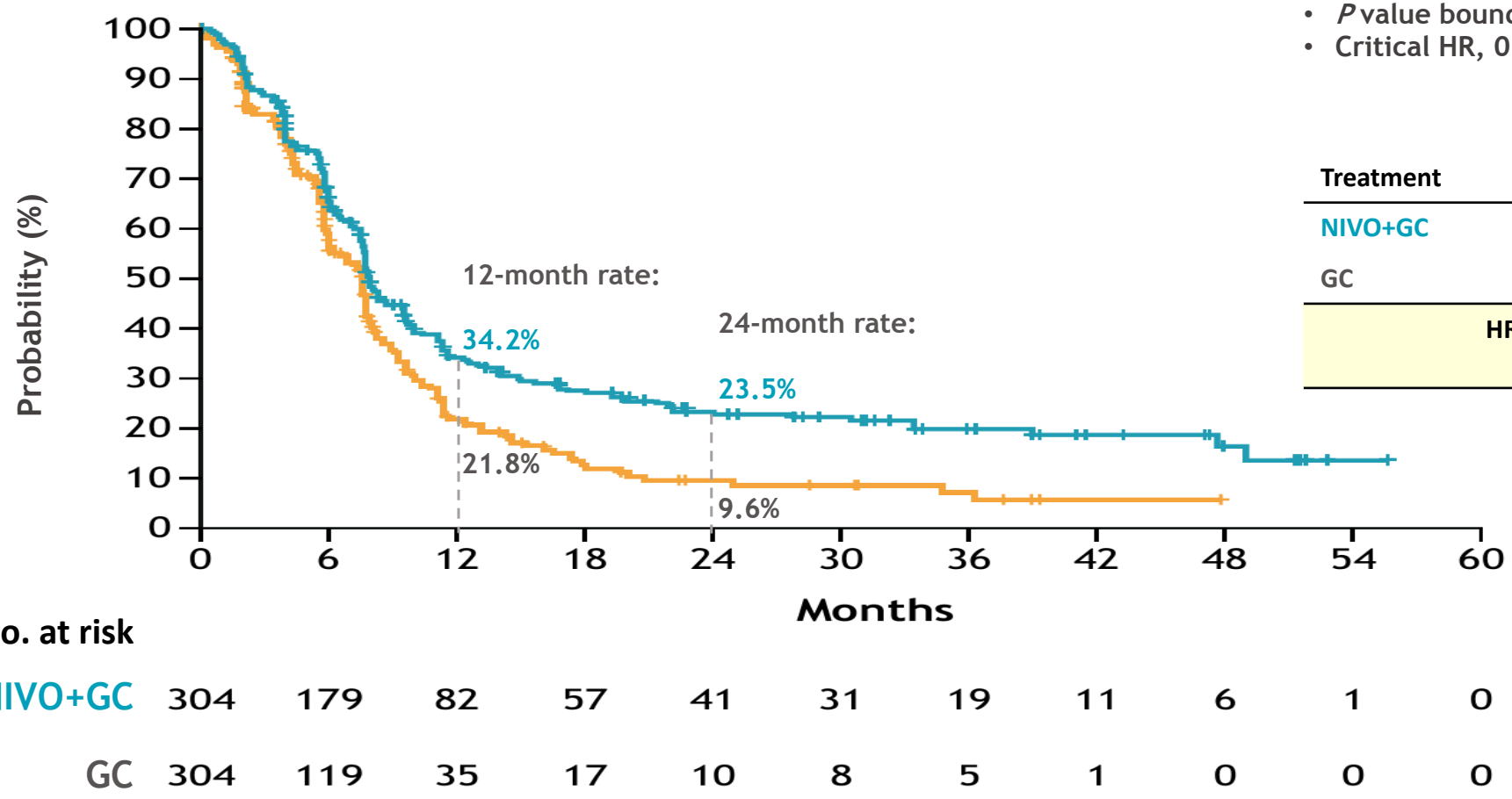
Subgroup	No. of Patients	Nivolumab+ Gemcitabine-Cisplatin	Gemcitabine-Cisplatin	Unstratified Hazard Ratio for Death (95% CI)
		No. of events/no. of patients		
Overall (N=608)		172/304	193/304	0.78 (0.63-0.95)
Age				
<65 yr	298	85/150	100/148	0.69 (0.51-0.92)
≥65 and <75 yr	236	65/120	66/116	0.89 (0.63-1.26)
≥65 yr	74	22/34	27/40	0.86 (0.49-1.52)
Sex				
Male	470	133/236	147/234	0.76 (0.60-0.97)
Female	138	39/68	46/70	0.82 (0.54-1.26)
Race				
White	436	123/211	145/225	0.80 (0.63-1.02)
Asian	138	38/75	36/63	0.71 (0.45-1.12)
Other	32	11/18	10/14	0.84 (0.35-1.97)
Region				
US	40	18/19	15/21	1.92 (0.95-3.88)
Asia	133	36/72	34/61	0.73 (0.46-1.17)
Europe	276	72/134	90/142	0.73 (0.53-0.99)
Rest of the world	159	46/79	54/80	0.73 (0.49-1.08)
ECOG PS				
0	324	74/162	87/162	0.70 (0.51-0.95)
1	282	96/140	106/142	0.85 (0.64-1.11)
PD-L1 expression (IRT)				
≥1%	221	64/111	67/110	0.75 (0.53-1.06)
<1% or indeterminate	387	108/193	126/194	0.80 (0.62-1.04)
Liver metastases (IRT)				
Yes	128	45/64	48/64	0.77 (0.51-1.16)
No	480	127/240	145/240	0.77 (0.61-0.98)
Previous systemic cancer therapy*				
Yes	156	44/88	41/68	0.90 (0.59-1.38)
No	452	128/216	152/236	0.76 (0.60-0.96)



Courtesy of Thomas Powles, MBBS, MRCP, MD

CheckMate 901: PFS per BICR (primary endpoint)

PFS final analysis statistical boundaries:
- *P* value boundary, 0.01
- Critical HR, 0.7734

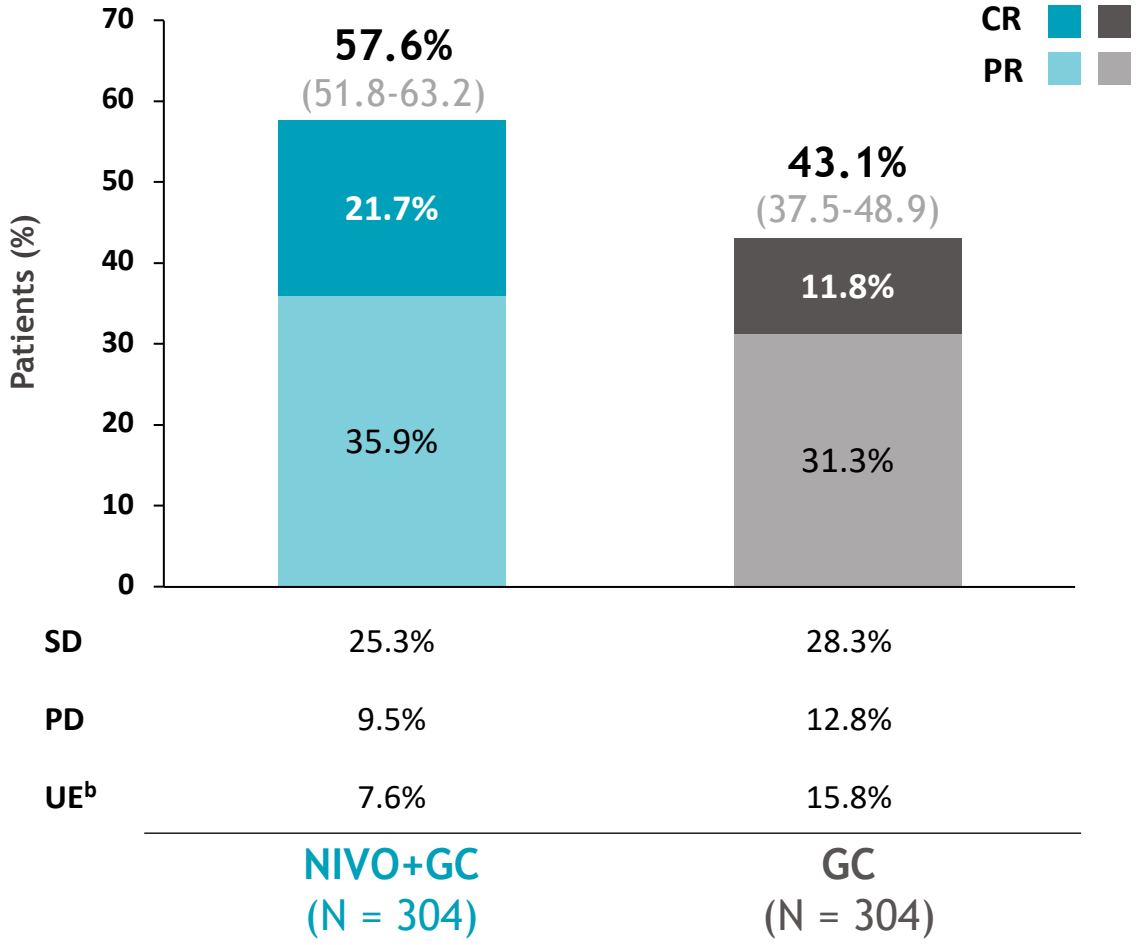


Treatment	Events/patients	Median PFS (95% CI), months
NIVO+GC	211/304	7.9 (7.6-9.5)
GC	191/304	7.6 (6.1–7.8)
HR (95% CI), 0.72 (0.59–0.88) *P* = 0.0012		

Median (range) study follow-up was 33.6 (7.4-62.4) months. PFS was estimated in all randomized patients and defined as the time from date of randomization to date of first documented disease progression (per BICR assessments using RECIST v1.1) or death due to any cause, whichever occurred first. Patients who died without reported progression were considered to have progressed on the date of death. Patients who did not progress or die were censored on the last evaluable tumor assessment date. Patients without on-study tumor assessments who did not die were censored on the date of randomization. **Patients who started any subsequent anticancer therapy without prior reported progression were censored at the last evaluable tumor assessment before initiation of subsequent anticancer therapy.**
RECIST, Response Evaluation Criteria in Solid Tumors.

Courtesy of Thomas Powles, MBBS, MRCP, MD

CheckMate 901: Objective response outcomes



Time to and duration of responses

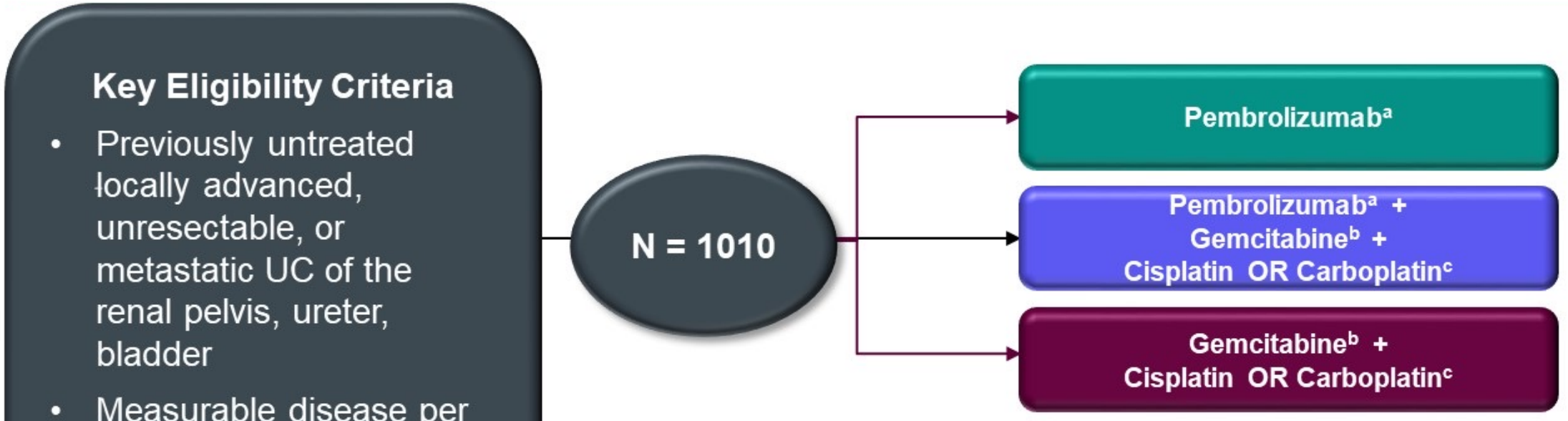
Any objective response[c]	NIVO+GC (n = 175)	GC (n = 131)
Median TTR (Q1-Q3), months	2.1 (2.0–2.3)	2.1 (2.0–2.2)
Median DoR (95% CI), months	9.5 (7.6–15.1)	7.3 (5.7–8.9)
Complete response[d]	**NIVO+GC (n= 66)**	**GC (n = 36)**
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

ORR (95% CI) and BOR per BICR[a]

[a]In all randomized patients. [b]The most common reasons for UE response included death before first tumor assessment, withdrawal of consent, treatment stopped due to toxicity, patient never treated, and receipt of subsequent anticancer therapy before first tumor assessment. [c]Based on patients with an objective response per BICR (PR or CR as BOR). [d]Based on patients with a CR per BICR.
BOR, best overall response; CR, complete response; DoCR, duration of complete response; DoR, duration of objective response; NE, not estimable; PD, progressive disease; PR, partial response; Q, quartile; SD, stable disease; TTCR, time to complete response; TTR, time to objective response; UE, unevaluable.

Courtesy of Thomas Powles, MBBS, MRCP, MD

KEYNOTE-361 Study Design

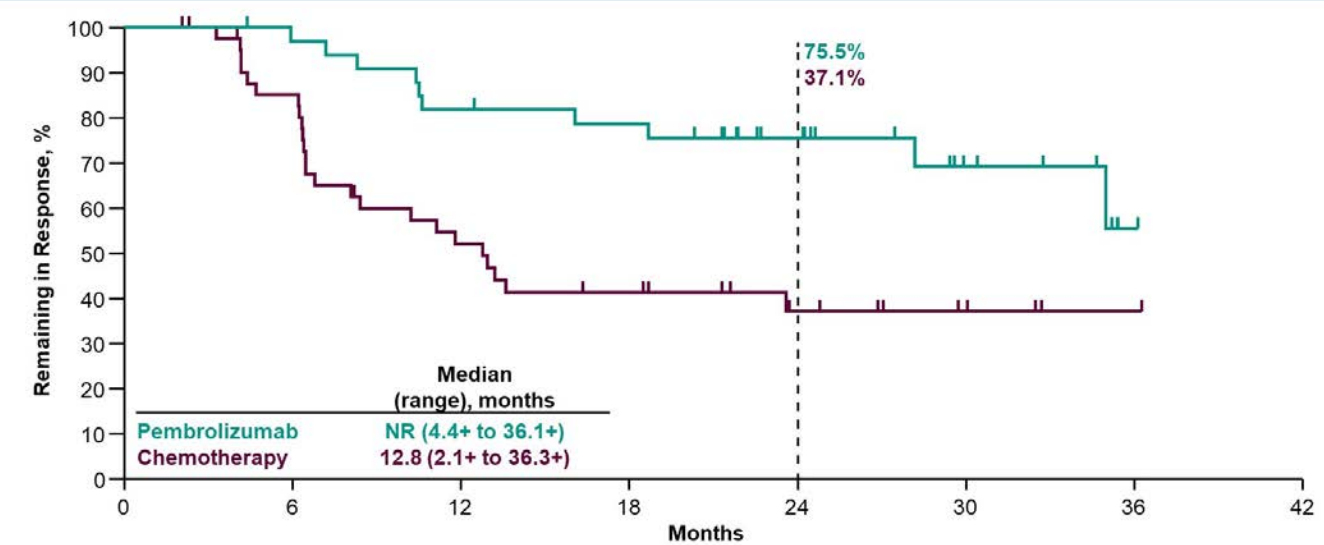


Post Hoc Analysis End Points in Patients With CR in Pembrolizumab Monotherapy or Chemotherapy Arms

- DOR and PFS per RECIST v1.1 by BICR
- OS

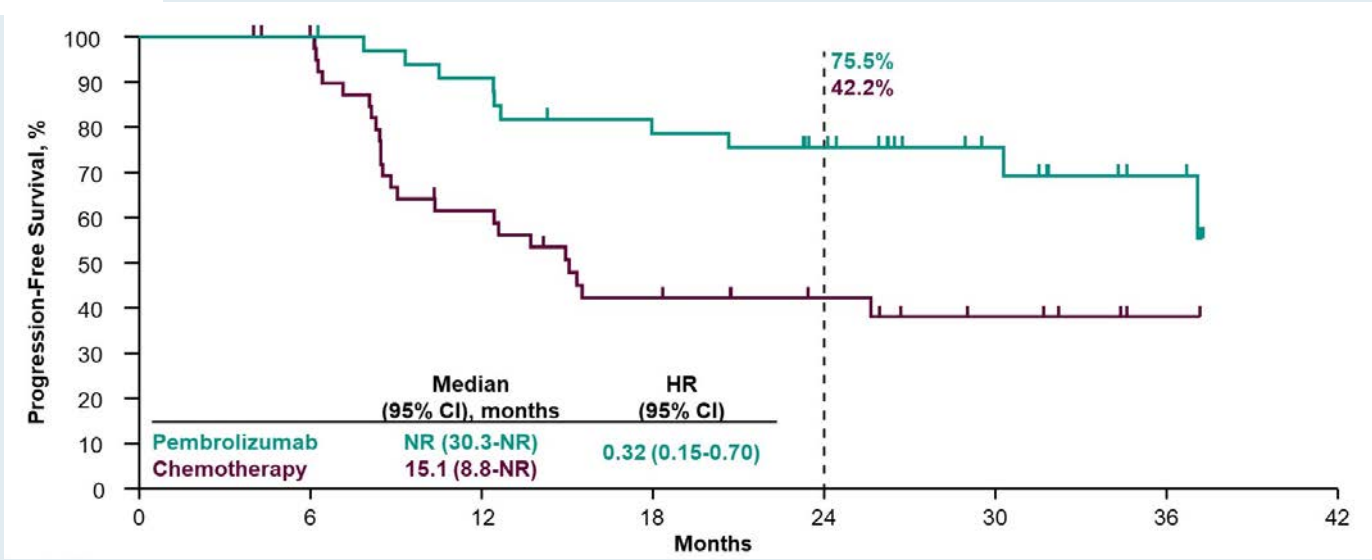
Ozyilkan O et al. ASCO 2023;Abstract 4513.

KEYNOTE-361: Efficacy



- **PFS**
- **HR (95% CI): 0.32 (0.16-0.70)**

- **OS**
- **HR (95% CI): 0.20 (0.06-0.70)**



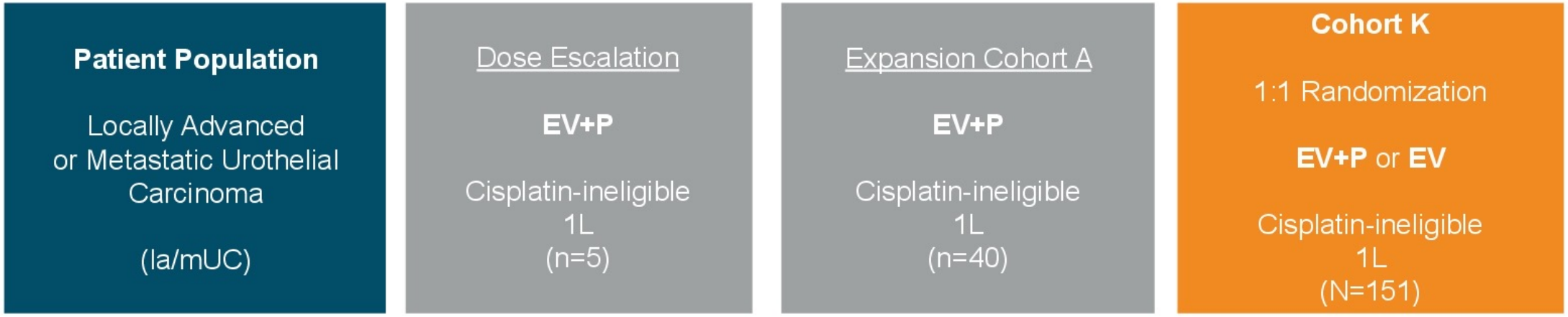
Ozyilkan O et al. ASCO 2023;Abstract 4513.

RTP RESEARCH TO PRACTICE

Enfortumab Vedotin/Pembrolizumab for Previously Untreated mUBC

- Friedlander TW et al. **Enfortumab vedotin (EV)** with or without **pembrolizumab (P)** in patients (pts) who are **cisplatin-ineligible** with **previously untreated** locally advanced or metastatic urothelial cancer (la/mUC): Additional 3-month follow-up on **cohort K** data. ASCO 2023;Abstract 4568.
- Powles TB et al. **EV-302/KEYNOTE-A39**: Open-label, randomized phase III study of **enfortumab vedotin** in combination with **pembrolizumab** (EV + P) vs chemotherapy (chemo) in **previously untreated** locally advanced metastatic urothelial carcinoma (la/mUC). ESMO 2023;Abstract LBA6.
- Van der Heijden MS et al. **Enfortumab vedotin (EV)** in combination with **pembrolizumab (P)** versus chemotherapy in **previously untreated** locally advanced metastatic urothelial carcinoma (la/mUC): **Subgroup** analyses results from **EV-302**, a **phase 3** global study. Genitourinary Cancers Symposium 2024;Abstract LBA530.

Phase Ib/II EV-103 Cohort K Study Design



Stratification factors: Liver metastases (present/absent) and ECOG PS (0 or 1/2);
Exploratory endpoints: pharmacokinetics, antitherapeutic antibody, biomarkers of activity including baseline PD-L1 status and Nectin-4 expression, progression-free survival on subsequent therapy by investigator, patient reported outcomes
Data cutoff was 16SEP2022 except for time to objective response analysis and subgroup analysis of objective response, both of which had a data cutoff of 10JUN2022.

- **Primary endpoint:** confirmed ORR by RECIST v1.1 per BICR
- **Key secondary endpoints:** confirmed ORR per RECIST v1.1 by investigator, DOR, DCR, PFS by BICR and by investigator, OS, safety/tolerability, and laboratory abnormalities

Friedlander TW et al. ASCO 2023;Abstract 4568.

Phase Ib/II EV-103 Cohort K: Overall Response Rate (ORR)

EV+P: 64.5% confirmed ORR with rapid response

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	**49 (64.5) (52.7, 75.1)**	**33 (45.2) (33.5, 57.3)**
Best overall response, n (%)		
Complete response	8 (10.5)	4 (5.5)
Partial response	41 (53.9)	29 (39.7)
Stable disease	17 (22.4)	25 (34.2)
Progressive disease	6 (7.9)	7 (9.6)
Not evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response, mos (range)	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	12.0 (1, 34)	8.0 (1, 33)

Friedlander TW et al. ASCO 2023;Abstract 4568.

Phase Ib/II EV-103 Cohort K: Adverse Events of Special Interest (AESIs)

Treatment-Related Adverse Events of Special Interest for EV

The majority of treatment-related AESIs were low grade

	EV+P (N=76) n (%)		EV Mono (N=73) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin reactions	51 (67.1)	16 (21.1)	33 (45.2)	5 (6.8)
Peripheral neuropathy	48 (63.2)	2 (2.6)	40 (54.8)	2 (2.7)
Ocular disorders	20 (26.3)	0	21 (28.8)	0
Dry eye	20 (26.3)	0	21 (28.8)	0
Blurred vision	2 (2.6)	0	5 (6.8)	0
Corneal disorders	0	0	4 (5.5)	0
Hyperglycemia	11 (14.5)	5 (6.6)	8 (11.0)	7 (9.6)
Infusion-related reactions	3 (3.9)	0	4 (5.5)	0

- Skin reactions were observed more frequently with EV+P
- Peripheral neuropathy remains the most common reason for study treatment discontinuation

Treatment-Emergent Adverse Events of Special Interest for Pembrolizumab

	EV+P (N=76) n (%)	
	Any grade	Grade ≥3
Severe skin reactions[a]	21 (27.6)	15 (19.7)
Hypothyroidism	10 (13.2)	0
Pneumonitis	7 (9.2)	4 (5.3)
Adrenal insufficiency	3 (3.9)	0
Colitis	3 (3.9)	1 (1.3)
Hyperthyroidism	3 (3.9)	0
Infusion reactions	3 (3.9)	0
Hepatitis	2 (2.6)	2 (2.6)
Myasthenic syndrome	2 (2.6)	2 (2.6)
Myositis	2 (2.6)	0
Pancreatitis	2 (2.6)	1 (1.3)
Hypophysitis	1 (1.3)	0
Myocarditis	1 (1.3)	0
Nephritis	1 (1.3)	1 (1.3)
Thyroiditis	1 (1.3)	0

- Pembrolizumab TEAEs were consistent with previously observed results with pembrolizumab monotherapy, except for severe skin reactions, which were reported with a higher incidence in this study.

[a]There are differences in the rates of skin reactions reported for EV treatment-related AESIs and pembrolizumab TEAEs of special interest because the analyses for reporting these events were conducted using different methods developed for EV and pembrolizumab monotherapies

EV = enfortumab vedotin; P = pembrolizumab; TEAEs = treatment-emergent adverse events

Friedlander TW et al. ASCO 2023;Abstract 4568.

EV-302/KEYNOTE-A39 (NCT04223856)

Patient population

- Previously untreated la/mUC
- Eligible for platinum, EV, and P
- PD-(L)1 inhibitor naive
- GFR ≥30 mL/min[a]
- ECOG PS ≤2[b]

N=886

R 1:1

EV + Pembrolizumab
No maximum treatment cycles for EV, maximum 35 cycles for P

Treatment until disease progression per BICR, clinical progression, unacceptable toxicity, or completion of maximum cycles

Chemotherapy[c]
(Cisplatin or carboplatin + gemcitabine)
Maximum 6 cycles

Dual primary endpoints:

- **PFS by BICR**
- **OS**

Select secondary endpoints:

- ORR per RECIST v1.1 by BICR and investigator assessment
- Safety

Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors
[a]Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine
[b]Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure
[c]Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy

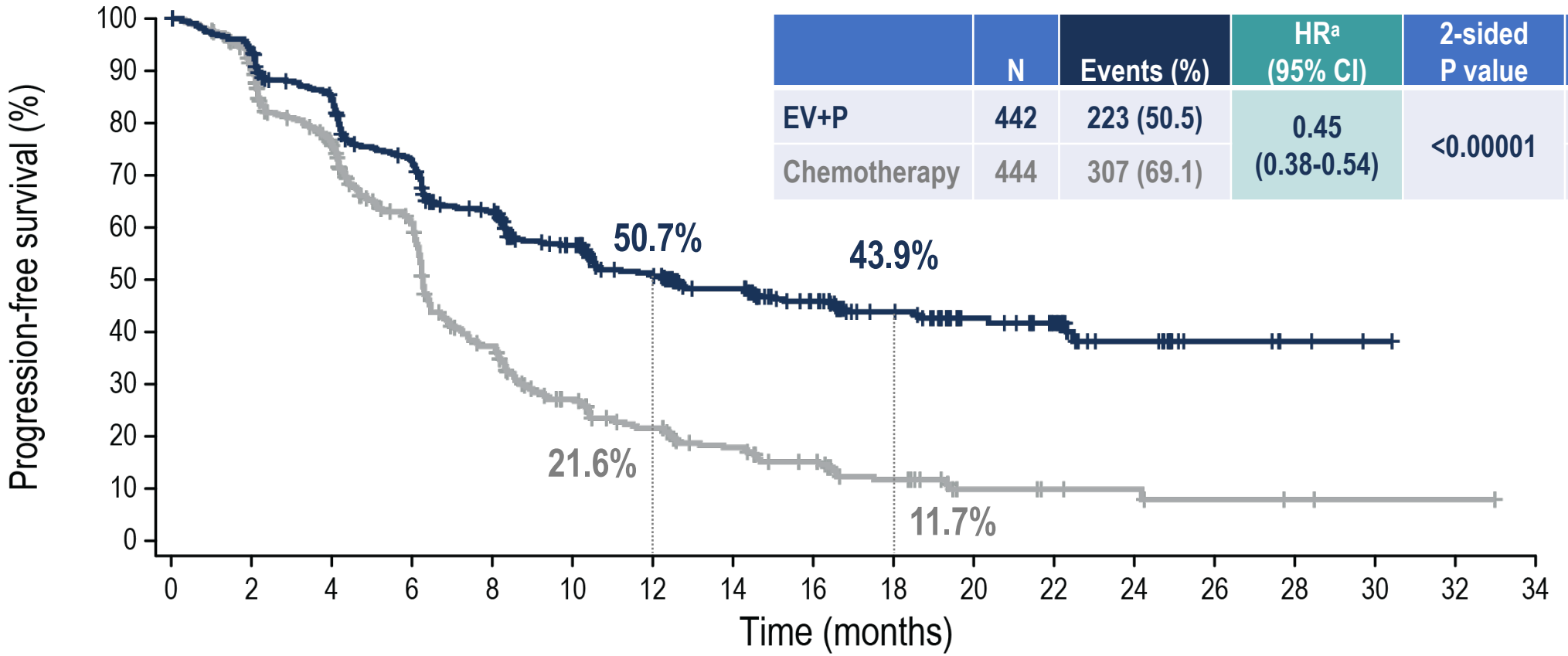
Data cutoff: 08 Aug 2023; FPI: 7 Apr 2020, LPI: 09 Nov 2022

Courtesy of Thomas Powles, MBBS, MRCP, MD

EV-302/KEYNOTE-A39: Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



N at risk

EV+P	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

Data cutoff: 08 Aug 2023

PFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

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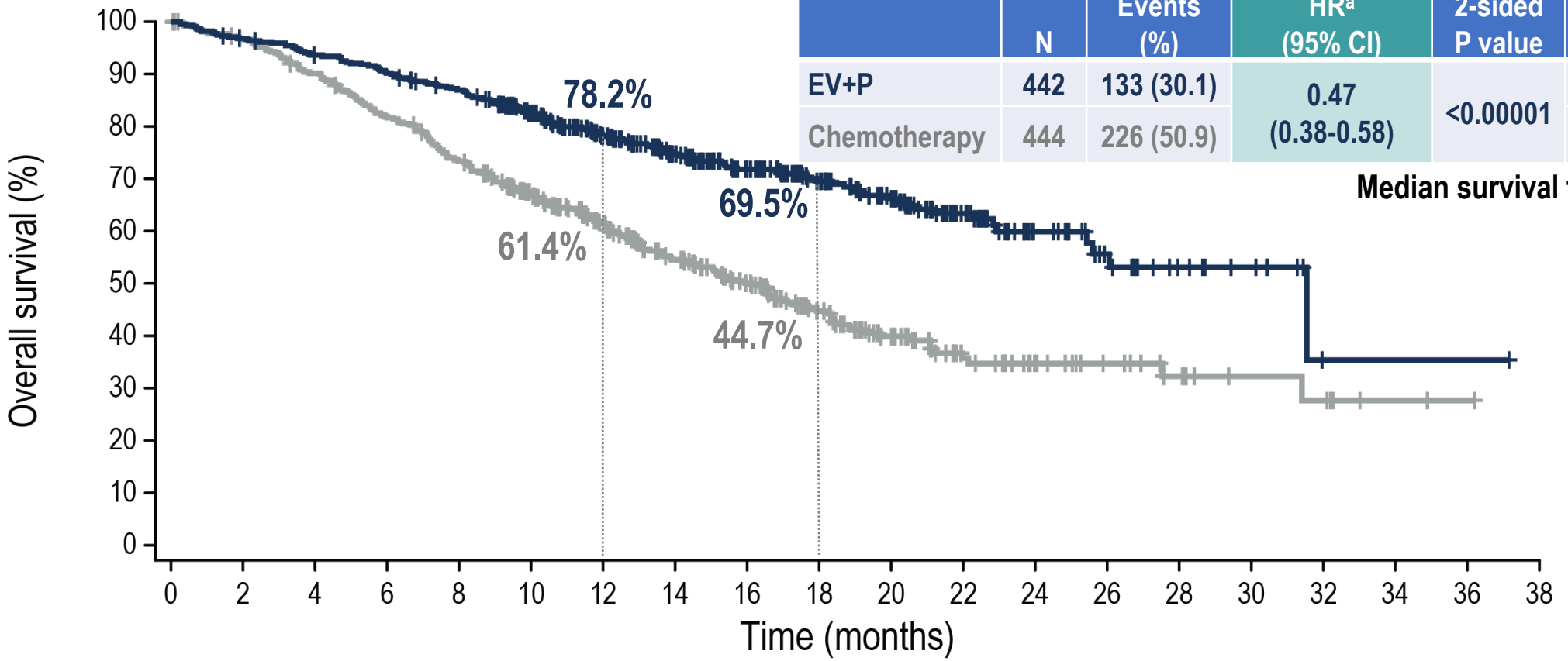
Courtesy of Thomas Powles, MBBS, MRCP, MD

EV-302/KEYNOTE-A39: Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months



N at risk

EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

Data cutoff: 08 Aug 2023

OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

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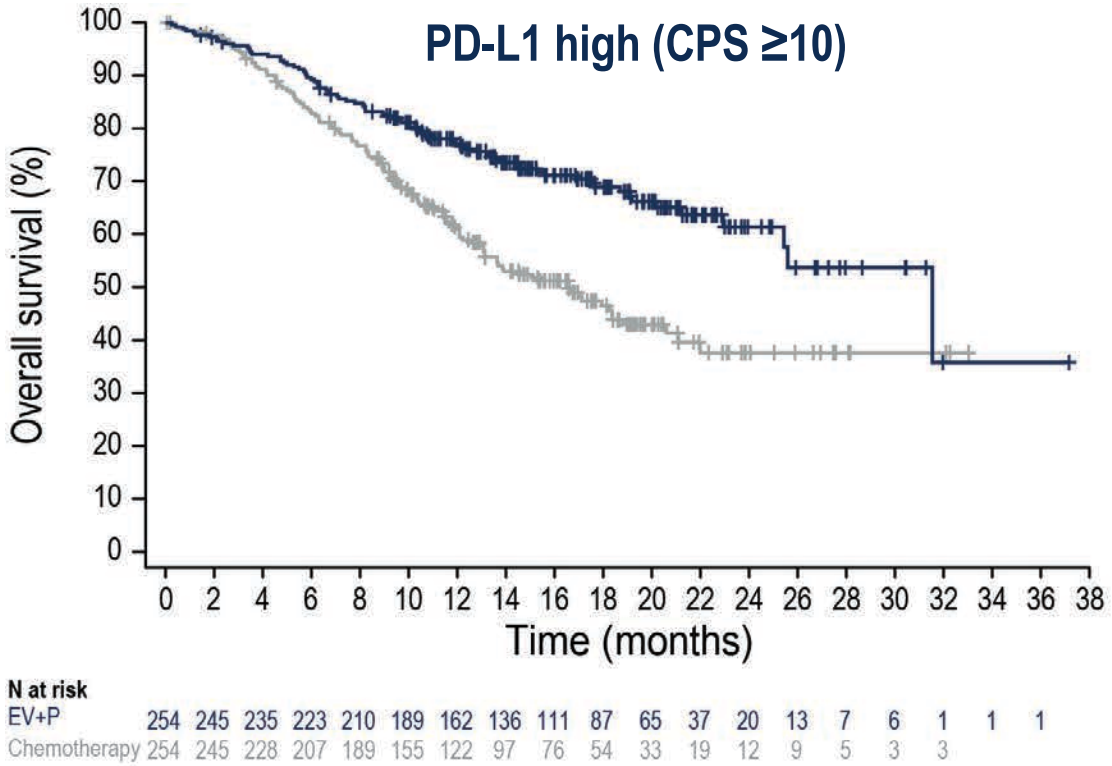
Courtesy of Thomas Powles, MBBS, MRCP, MD

EV-302/KEYNOTE-A39: OS Subgroup Analysis – PD-L1 Expression

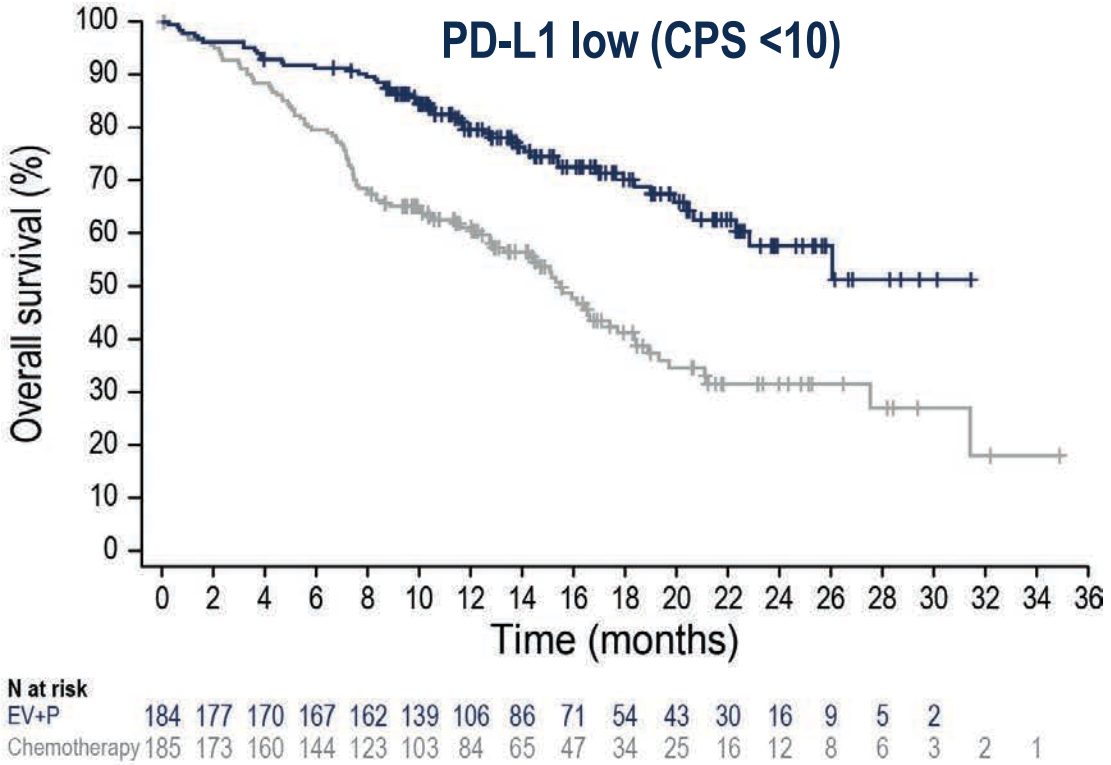
OS benefit was consistent with overall population regardless of PD-L1 expression status

PD-L1 high (CPS ≥10)



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	79	0.49 (0.37-0.66)	31.5 (25.4-NR)
Chemotherapy	125		16.6 (13.1-20.6)

PD-L1 low (CPS <10)



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	53	0.44 (0.31-0.61)	NR (22.3-NR)
Chemotherapy	99		15.5 (12.9-17.7)

Data cutoff: 08 Aug 2023

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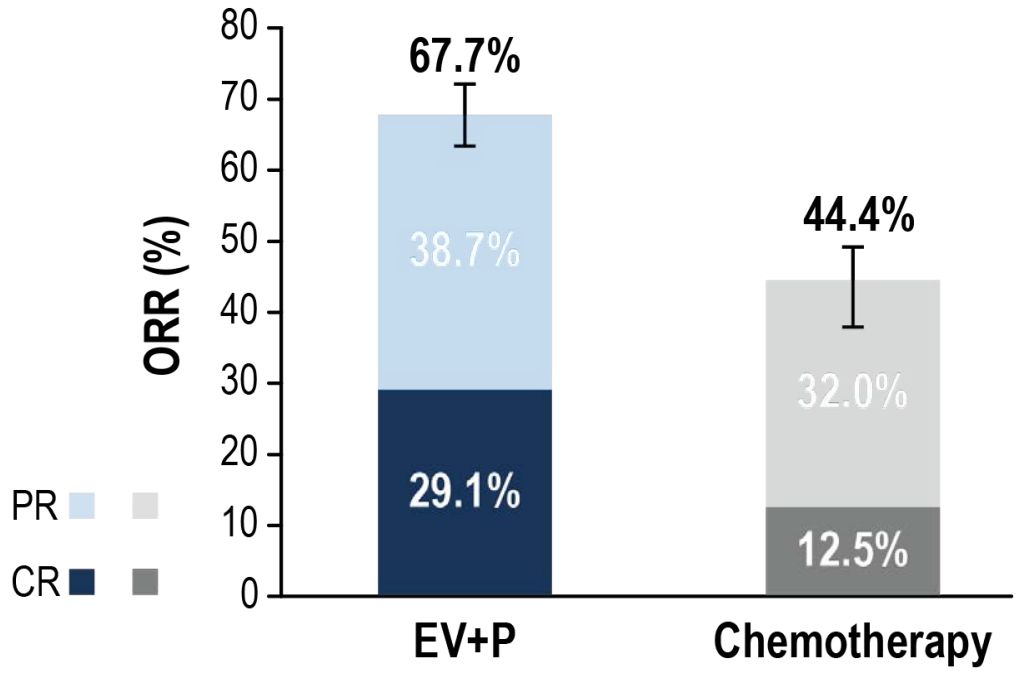
Courtesy of Thomas Powles, MBBS, MRCP, MD

EV-302/KEYNOTE-A39: Confirmed Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P



	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)
Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

CR, complete response; DOR, duration of response; PR, partial response

[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response

[b]Patients had either post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1 or no response assessment post-baseline

Data cutoff: 08 Aug 2023

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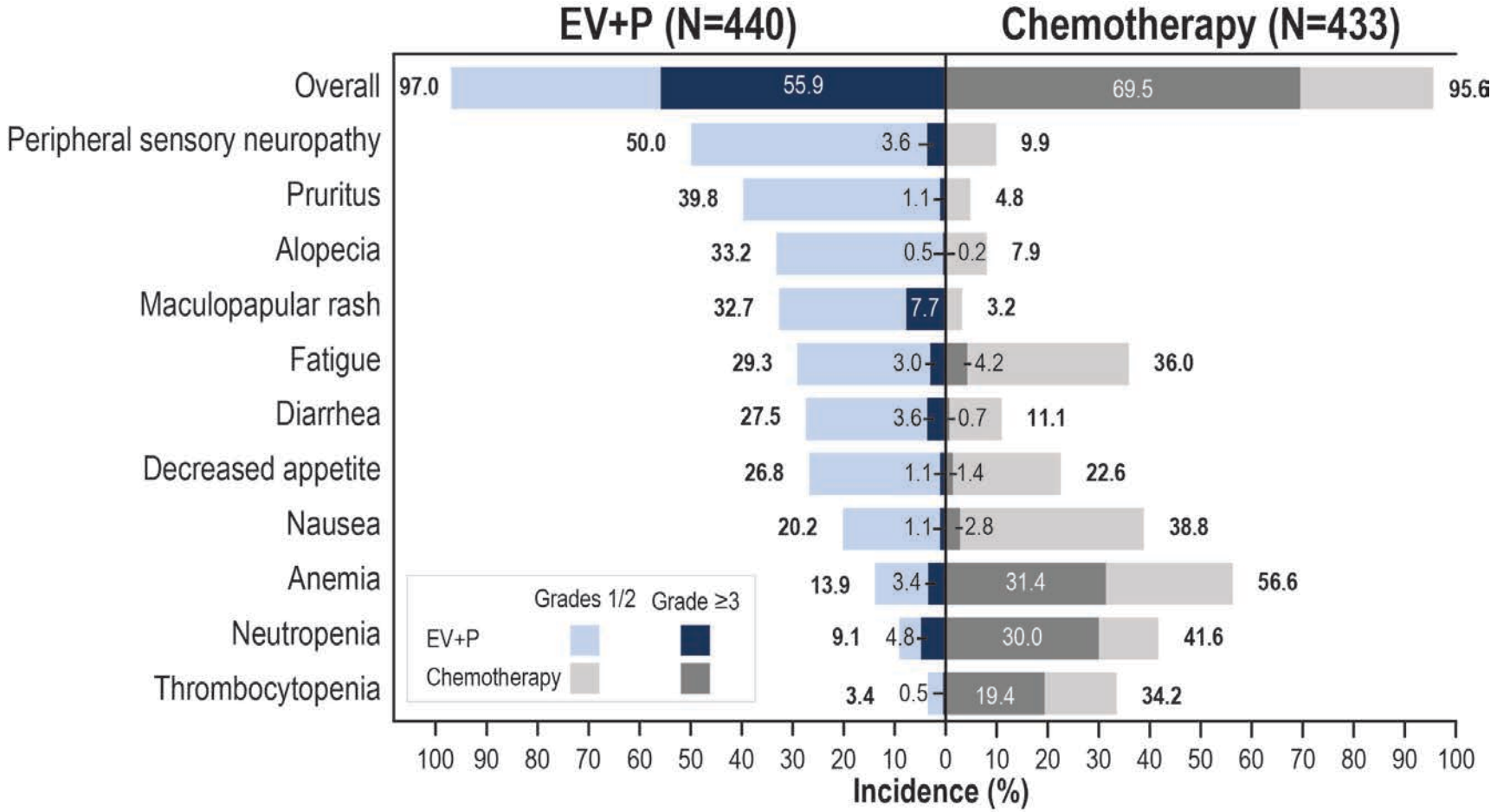
Courtesy of Thomas Powles, MBBS, MRCP, MD

EV-302/KEYNOTE-A39: Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:
- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):
EV+P: 4 (0.9%)
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)
- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

Data cutoff: 08 Aug 2023

MADRID 2023 ESMO congress

Powles et al.

TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm
TRAEs, treatment-related adverse events

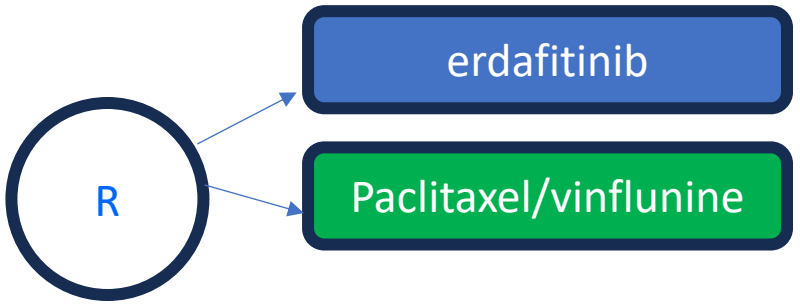
Courtesy of Thomas Powles, MBBS, MRCP, MD

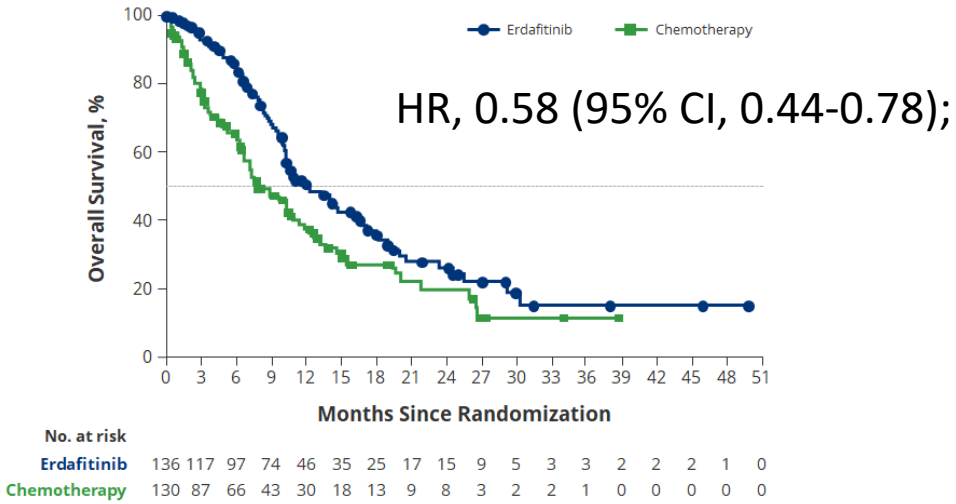
Erdafitinib-Based Therapy for Previously Treated mUBC

- Siefker-Radtke AO et al. **Erdafitinib (ERDA)** vs **ERDA plus cetrelimab** (ERDA + CET) for patients (pts) with metastatic urothelial carcinoma (mUC) and fibroblast growth factor receptor alterations (**FGFRa**): **Final results** from the phase 2 **Norse study**. ASCO 2023;Abstract 4504.
- Loriot Y et al. **Erdafitinib** or chemotherapy in advanced or metastatic urothelial carcinoma. *N Engl J Med* 2023;389(21):1961-71.
- Siefker-Radtke AO et al. **Erdafitinib** versus **pembrolizumab** in pretreated patients with advanced or metastatic urothelial cancer with **select FGFR alterations**: Cohort 2 of the randomized **phase III THOR** trial. *Ann Oncol* 2024;35(1):107-17.

OS results in the THOR Trial of Erdafitinib in pretreated FGFR+ve UC raise many questions.

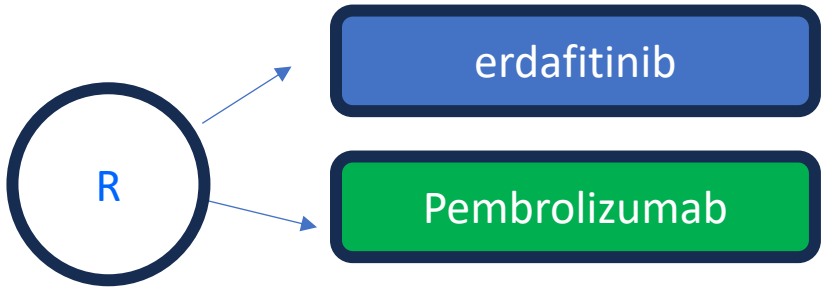
Advanced disease
Prior PD-(L)1 therapy
1-2 lines of prior therapy
FGFR alterations

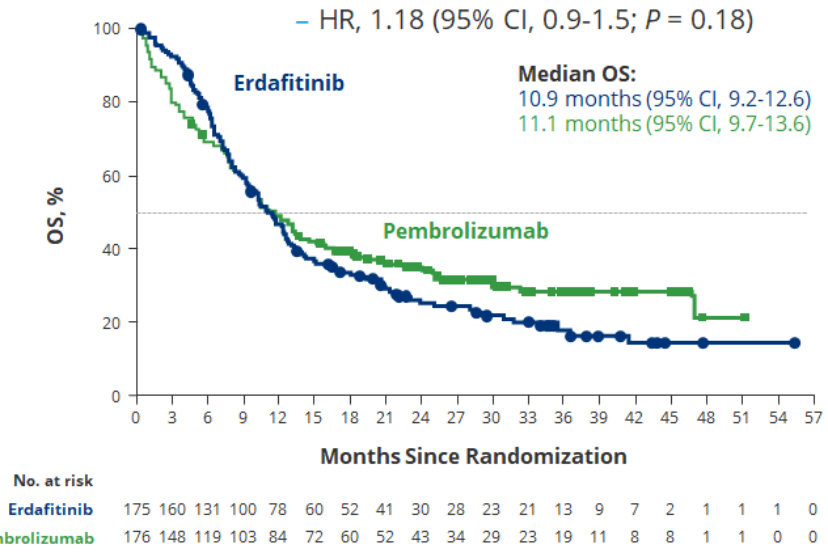




HR, 0.58 (95% CI, 0.44-0.78);

Advanced disease
1 prior therapy
No prior PD-(L)1 therapy
FGFR alterations





Lotiott NEJM23; Arlene Siefker-Radtke Ann Oncol24

Courtesy of Thomas Powles, MBBS, MRCP, MD

NORSE trial of erdafitinib + PD-1 in FGFR+ve 1st line advanced UC

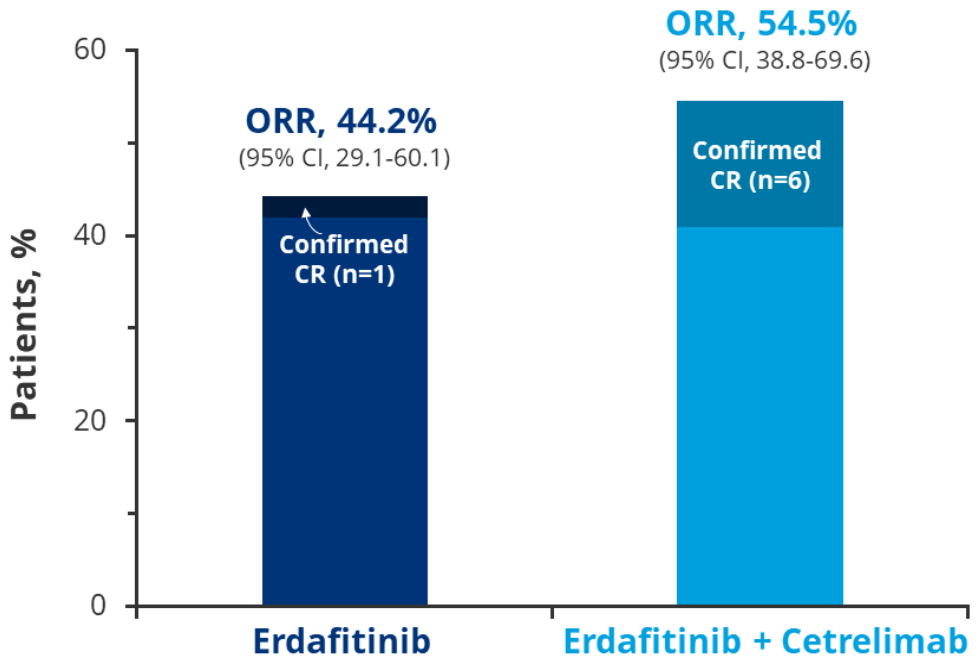
Key eligibility criteria
- Ineligible for cisplatin[b]
- Select *FGFR* alterations (mutation/fusion)[c]
- Measurable disease
- No prior systemic therapy for mUC

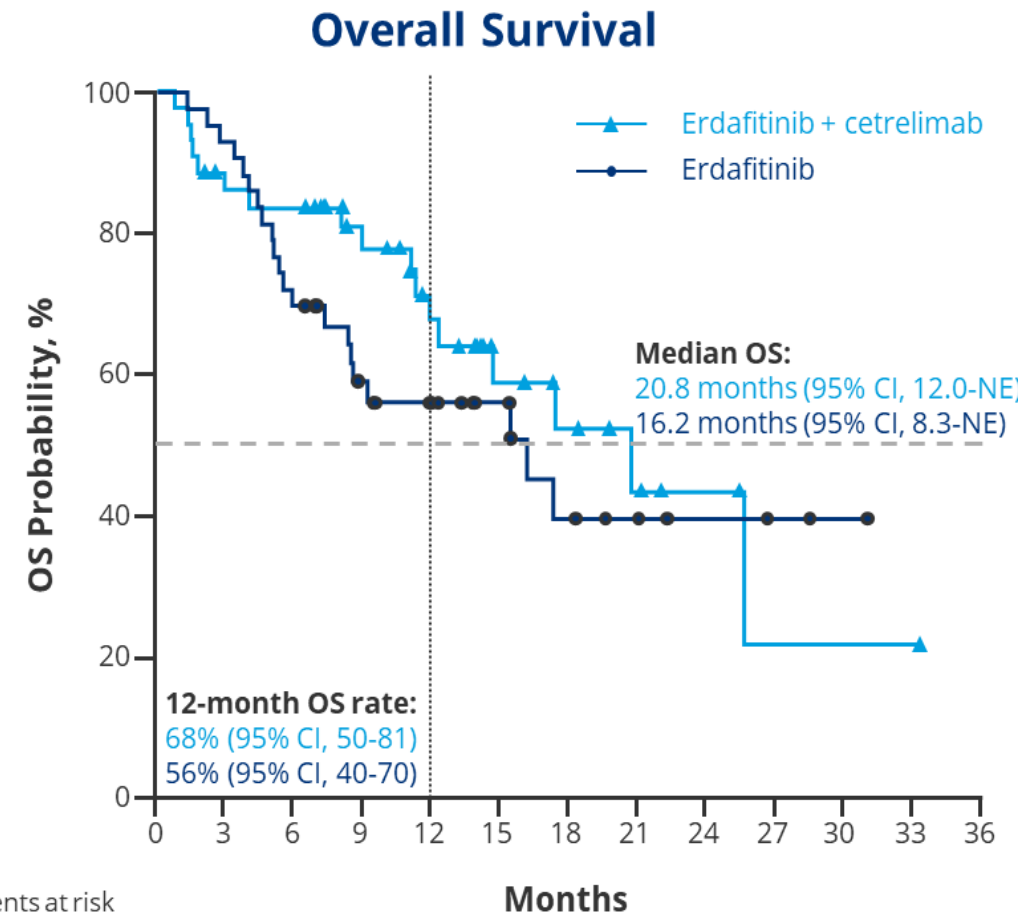
1:1
N=89
R

Erdafitinib (n=44)

Erdafitinib + cetrelimab[d] (n=45)

Primary end point
- ORR
- Safety





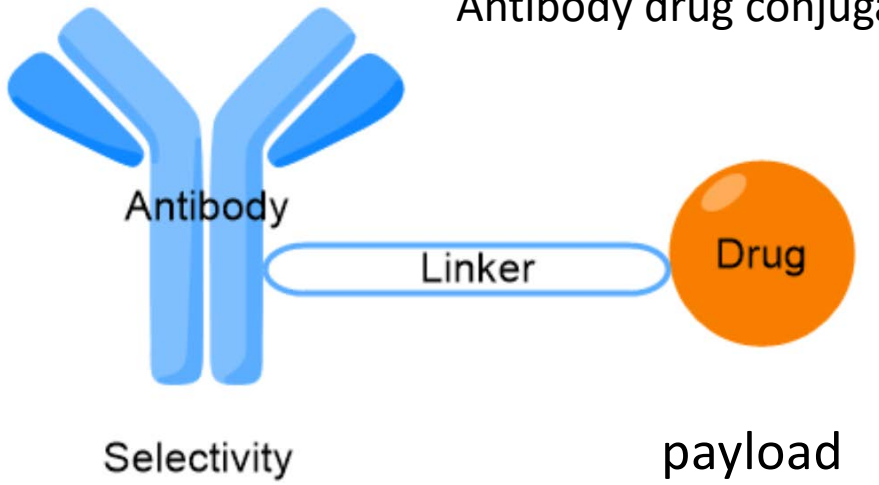
Arlene Siefker-Radtke ASCO23

Courtesy of Thomas Powles, MBBS, MRCP, MD

Sacituzumab Govitecan for Previously Treated mUBC

- McGregor BA et al. The **Double Antibody Drug** Conjugate (**DAD**) phase I trial: **Sacituzumab govitecan plus enfortumab vedotin** for metastatic urothelial carcinoma. *Ann Oncol* 2024 January;35(1):91-7.
- Loriot Y et al. Safety analysis by **UGT1A1 status** of **TROPHY-U-01 cohort 1**, a phase 2 study of **sacituzumab govitecan (SG)** in patients (pts) with metastatic urothelial cancer (mUC) who progressed after platinum (PT)-based chemotherapy and a checkpoint inhibitor (CPI). ASCO 2023;Abstract 4514.

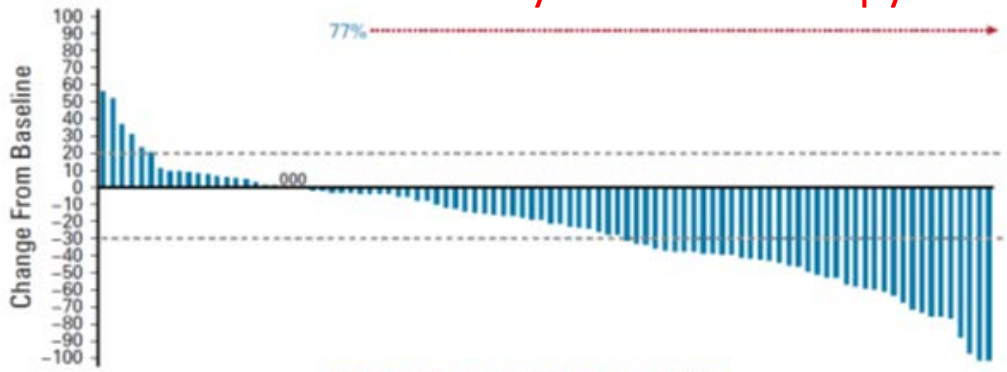
ADC strategies in advanced UC: Sacituzumab Govitecan



	Sacituzumab Govitecan
Target	TROP2
Payload	SN-38
Biomarker data	X

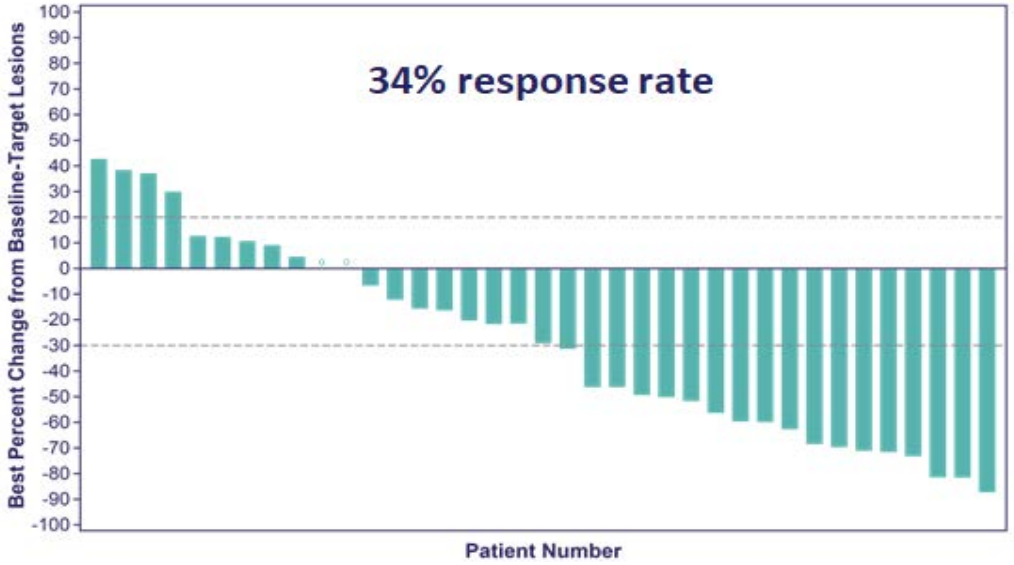
Grivas et al ASCO 2021

Platinum refractory UC monotherapy



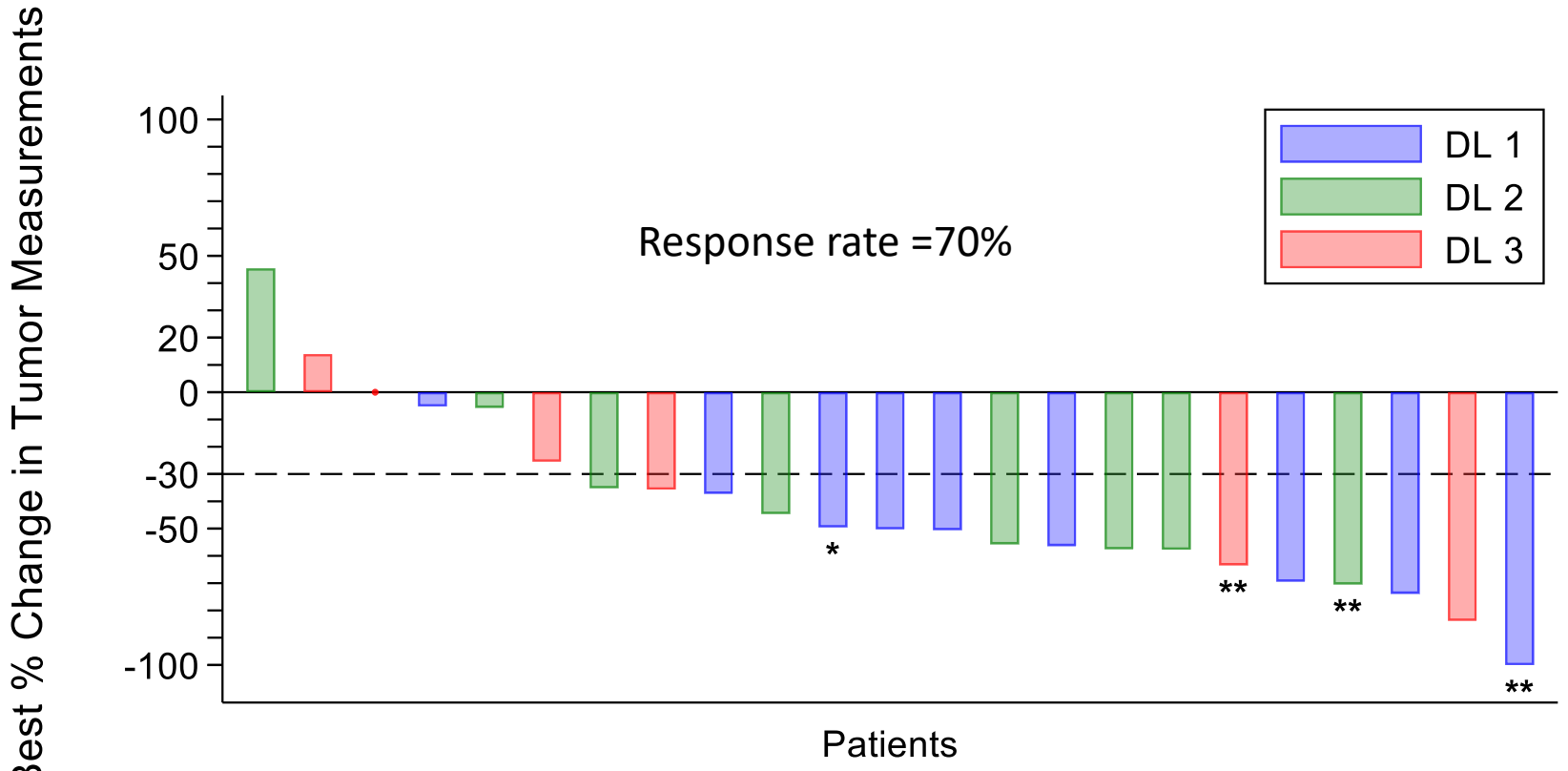
Response rate =27%

Platinum refractory UC combination with PD1 inhibitor



Courtesy of Thomas Powles, MBBS, MRCP, MD

Enfortumab vedotin with Sacituzumab govitecan in pretreated advanced urothelial cancer



One patient who did not undergo any post-baseline scans was marked as having 0 percentage change.

* One patient experienced progressive disease due to the emergence of a new non-target lesion, despite the reduction in a target lesion.
** Among three patients with complete response, two had lymph node lesions and the sum of lesions was not zero for those achieving a complete response.

McGregor B
ESMO 23

Courtesy of Thomas Powles, MBBS, MRCP, MD

HER2-Directed Therapies

- Sheng X et al. Efficacy and safety of **disitamab vedotin** in patients with human epidermal growth factor receptor 2-positive locally advanced or metastatic urothelial carcinoma: A **combined analysis** of two phase II clinical trials. *J Clin Oncol* 2023;[Online ahead of print].
- Sheng X et al. **Disitamab vedotin**, a novel humanized anti-HER2 antibody-drug conjugate (ADC), combined **with toripalimab** in patients with locally advanced or metastatic urothelial carcinoma: An open-label phase 1b/2 study. ASCO 2023;Abstract 4566.
- Meric-Bernstam F et al. Efficacy and safety of **trastuzumab deruxtecan** in patients with HER2-expressing solid tumors: Primary results from the **DESTINY-PanTumor02** phase II trial. *J Clin Oncol* 2024;42(1):47-58.

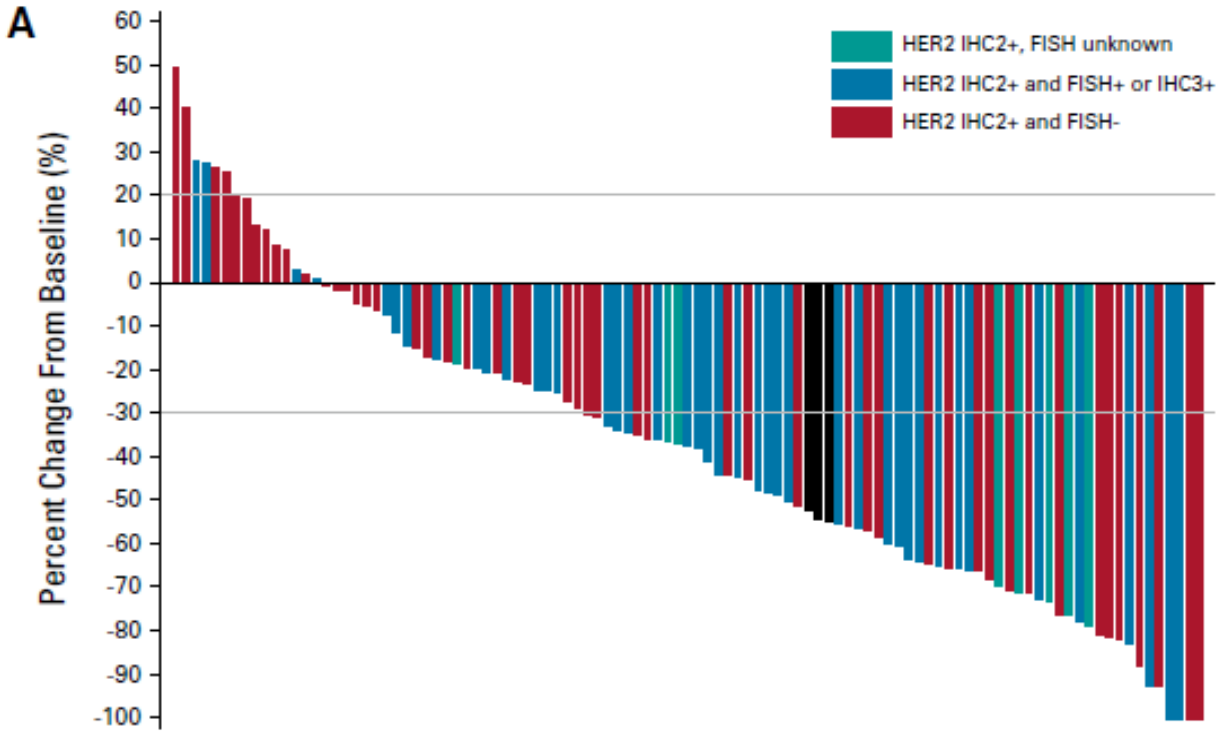
Original Reports | Genitourinary Cancer

Efficacy and Safety of Disitamab Vedotin in Patients With Human Epidermal Growth Factor Receptor 2–Positive Locally Advanced or Metastatic Urothelial Carcinoma: A Combined Analysis of Two Phase II Clinical Trials

Xinan Sheng, MD[1]; Lin Wang, MD[2]; Zhisong He, MD[3]; Yanxia Shi, MD[4]; Hong Luo, MD[5]; Weiqing Han, MD[6]; Xin Yao, MD[7]; Benkang Shi, MD[8]; Jiyan Liu, MD[9]; Changlu Hu, MD[10]; Ziling Liu, MD[11]; Hongqian Guo, MD[12]; Guohua Yu, MD[13]; Zhigang Ji, MD[14]; Jianming Ying, MD[15]; Yun Ling, MD[15]; Shiying Yu, MD[16]; Yi Hu, MD[17]; Jianming Guo, MD[18]; Jianmin Fang, PhD[19,20]; Aiping Zhou, MD[2]; and Jun Guo, MD[1]

DOI https://doi.org/10.1200/JCO.22.02912

	C005 (N=43)	C009 (N=64)	Pooled (N=107)
HER2-Positive IHC3+ or 2+/FISH+	**60%**	**64%**	**62.2%**
HER2 Low IHC2+/FISH-	**40%**	**39.4%**	**39.6%**
IHC2+/FISH Unknown	66%	50%	55.6%



Most frequent TRAEs All grades (≥30%)	
Any event	100%
Peripheral sensory neuropathy	68%
Leukopenia	51%
AST increase	42%
Neutropenia	42%
Alopecia	40%
Asthenia	39%
ALT increase	36%
Decreased appetite	32%

Sheng X et al. *J Clin Oncol*. Published online November 21, 2023. doi:10.1200/JCO.22.02912

Courtesy of Thomas Powles, MBBS, MRCP, MD

Disitamab vedotin in HER2-low or in combination with PD-1 therapy

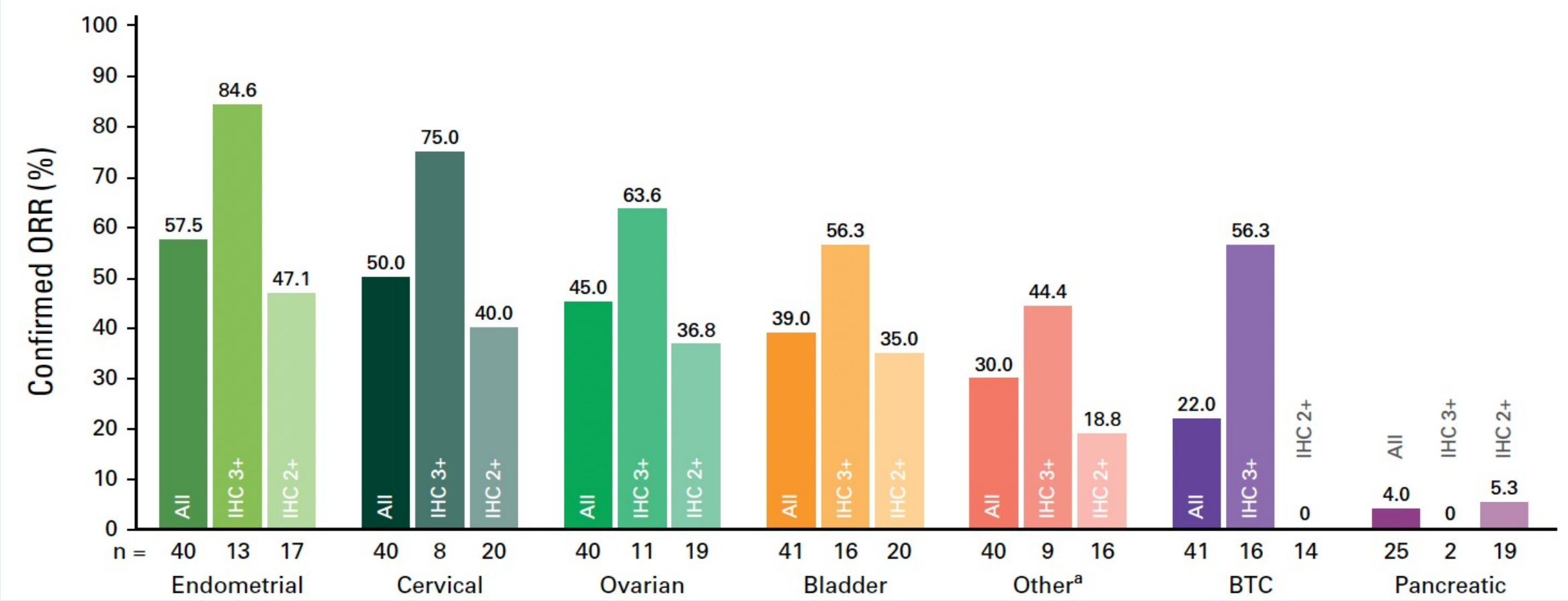
	C011 DV monotherapy in HER2-low	C014 DV + toripalimab in all comers
Drug	DV monotherapy	DV + toripalimab (anti-PD-1)
n	19	41
HER2 status	IHC 0 and 1+	All-comers
Dose	2.0 mg/kg Q2W	2.0 mg/kg Q2W
Prior therapy	2L+ Post platinum and/or anti-PD(L)1 68% had prior anti-PD(L)1	1L Treatment naive or previously treated, cis-ineligible or refused cis
Efficacy outcomes	**ORR = 26.3%** DCR = 94.7% (0 CR, 5 PR) mOS = 16.4 mos mPFS = 5.5 mos	**ORR = 73.2%** DCR = 90.2% (4 CR, 26 PR) 2-year OS = 63.2% mPFS = 9.2 mos
Status	Completed	Follow-up ongoing

Xu H, et al. American Society of Clinical Oncology; June 3-7, 2022; Chicago, IL. Abstract 4519

2. Sheng X, et al. American Society of Clinical Oncology; May 31, 2023; Chicago, IL. Abstract 4566

Courtesy of Thomas Powles, MBBS, MRCP, MD

Phase II DESTINY-PanTumor02: Objective Response Rate (ORR)



Meric-Bernstam F et al. *J Clin Oncol* 2024;42(1):47-58.

RTP RESEARCH TO PRACTICE

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Prostate Cancer

Wednesday, February 28, 2024
5:00 PM – 6:00 PM ET

Faculty

Andrew J Armstrong, MD, ScM

Maha Hussain, MD, FACP, FASCO

Moderator

Neil Love, MD

RTP Year in Review 2024

Thank you for joining us!

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