Inside the Issue: Optimizing the Management of Metastatic Urothelial Bladder Cancer

A CME/MOC-Accredited Live Webinar

Thursday, June 29, 2023
5:00 PM – 6:00 PM ET

Faculty

Terence Friedlander, MD
Petros Grivas, MD, PhD

Moderator

Neil Love, MD

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Faculty

Terence Friedlander, MD
Professor of Medicine and Robert and Virginia
O'Reilly Family Endowed Chair
Chief, Division of Hematology/Oncology
Zuckerberg San Francisco General Hospital
Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco
San Francisco, California

Petros Grivas, MD, PhD
Professor, Department of Medicine
Division of Oncology
Clinical Director, Genitourinary Cancers Program
University of Washington
Professor, Clinical Research Division
Fred Hutchinson Cancer Center
Seattle, Washington

Moderator
Neil Love, MD
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Dr Love — Disclosures

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Contracted Research	Acrivon Therapeutics Inc, Bavarian Nordic, Bristol Myers Squibb, Clovis Oncology, Debiopharm, G1 Therapeutics Inc, Gilead Sciences Inc, GSK, Merck KGaA, Merck Sharp & Dohme LLC, Mirati Therapeutics Inc, Pfizer Inc, QED Therapeutics
Data and Safety Monitoring Board/Committee	Bristol Myers Squibb

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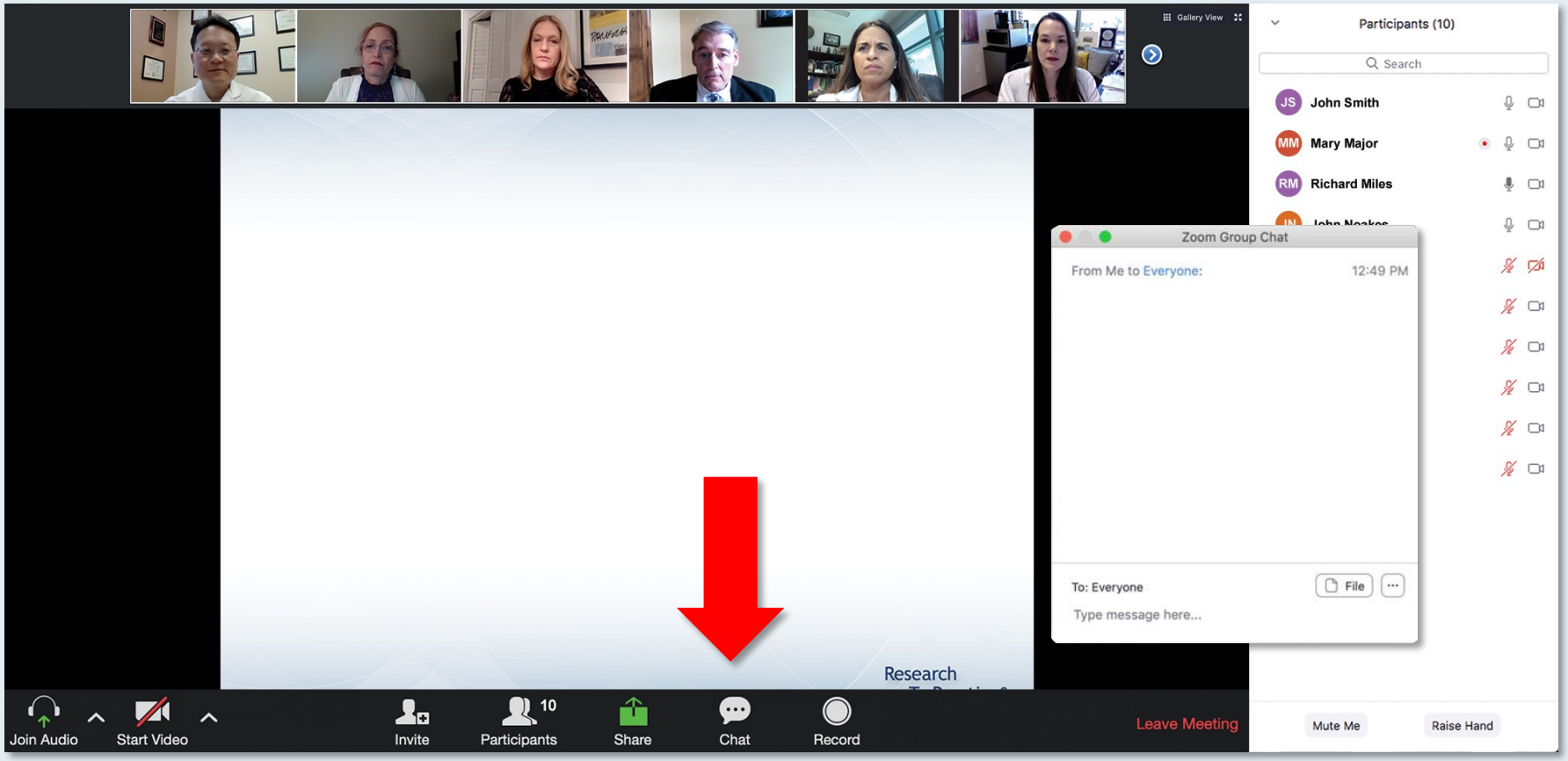

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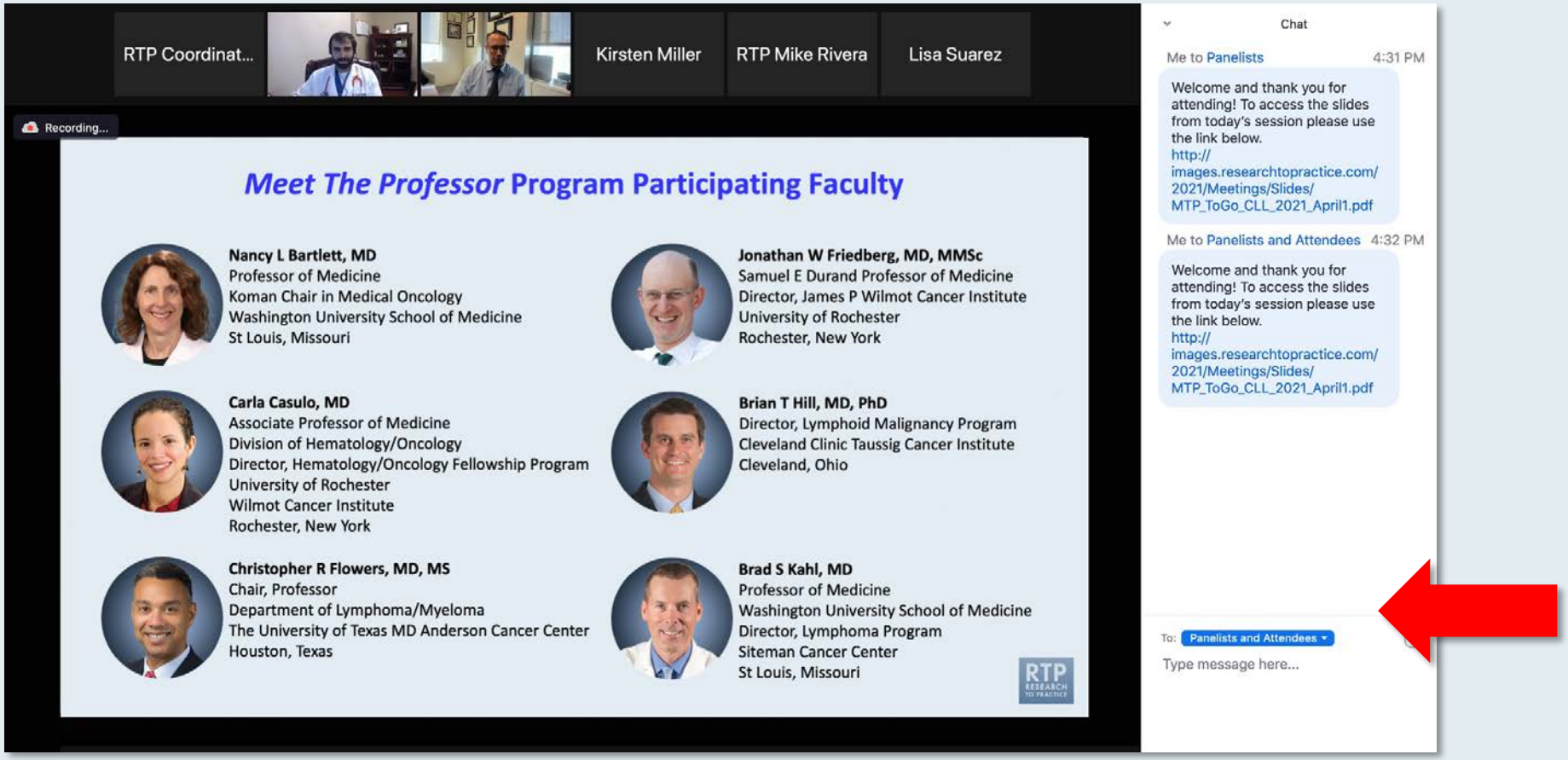

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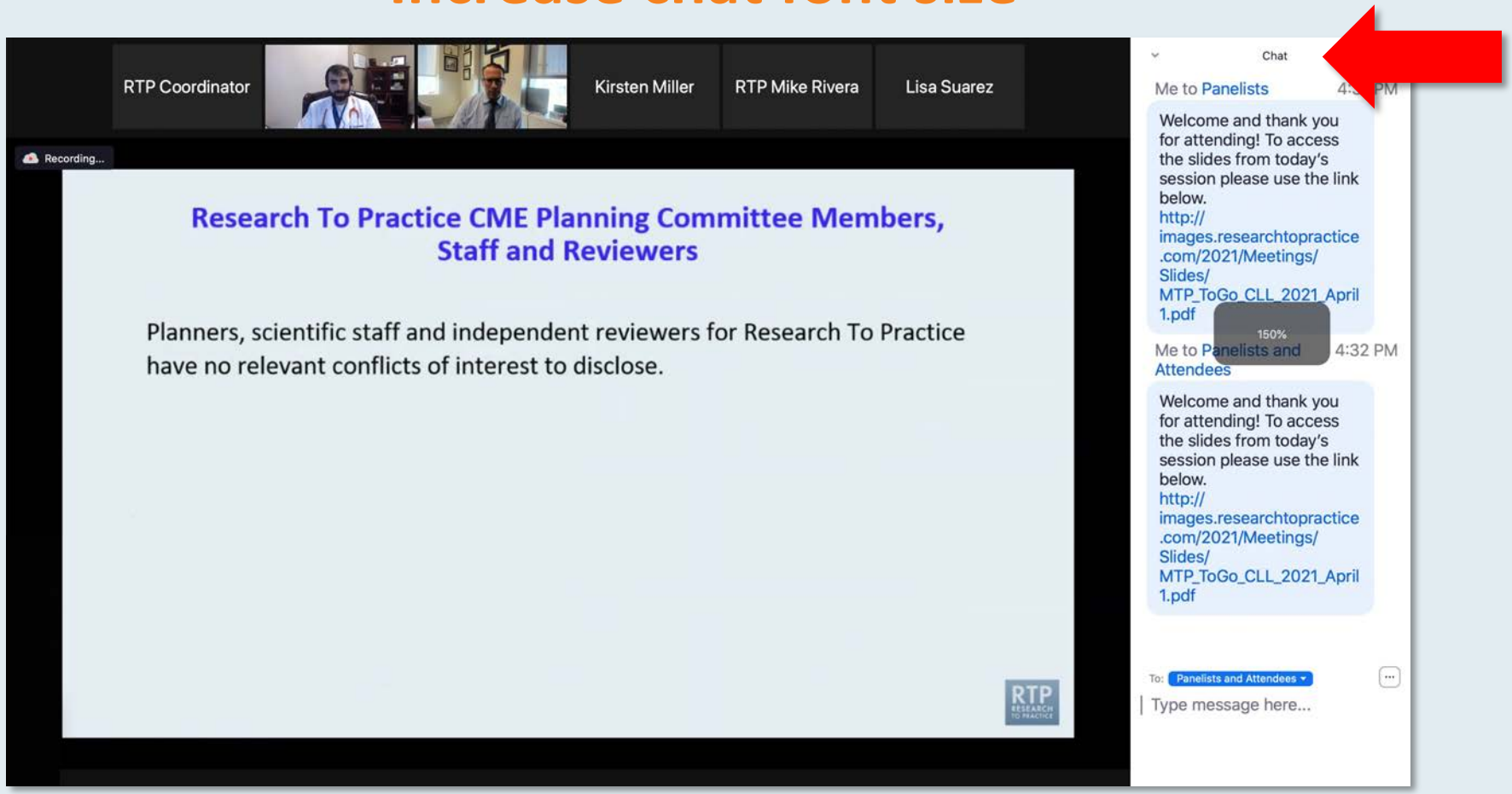

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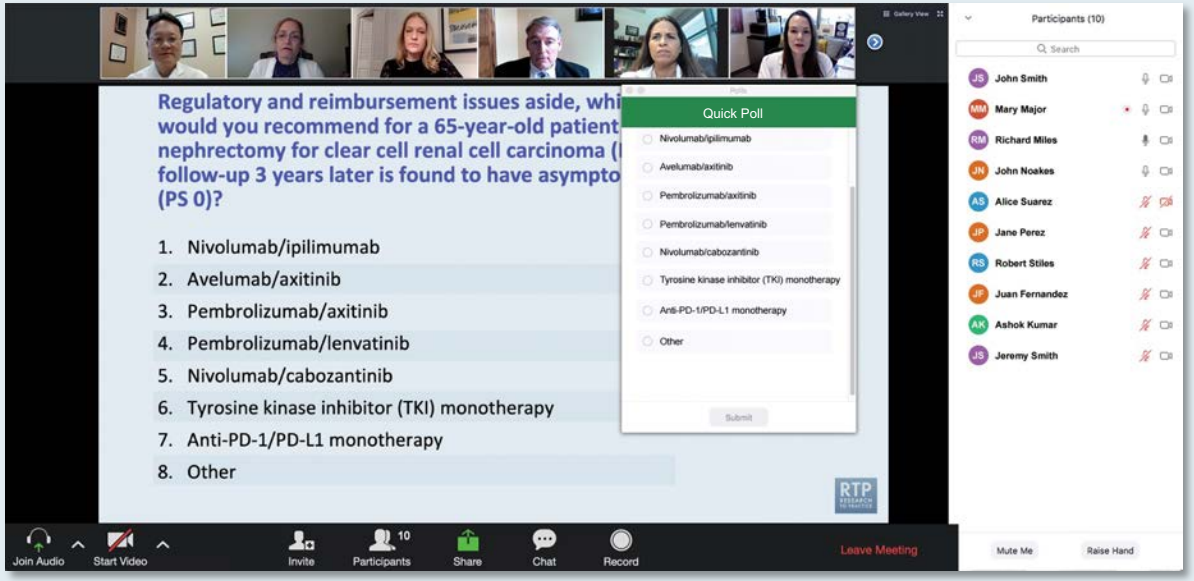

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Managing Metastatic Urothelial Bladder Cancer

DR SCOTT TAGAWA

WEILL CORNELL MEDICINE SANDRA AND EDWARD MEYER CANCER CENTER

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What I Tell My Patients: Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Part 3 of a 3-Part Complimentary NCPD Webinar Series
in Partnership with the 2023 ONS Congress

Chronic Lymphocytic Leukemia

Thursday, July 6, 2023
5:00 PM – 6:00 PM ET

Faculty

Kristen E Battiato, AGNP-C
Jennifer Woyach, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Inside the Issue: Novel Agents, Approaches and Strategies in the Management of Higher-Risk Myelodysplastic Syndromes

A CME/MOC-Accredited Live Webinar

Tuesday, July 11, 2023
5:00 PM – 6:00 PM ET

Faculty

Guillermo Garcia-Manero, MD
David Sallman, MD

Moderator

Neil Love, MD

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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

Melanoma and Nonmelanoma Skin Cancers

Thursday, July 13, 2023
5:00 PM – 6:00 PM ET

Faculty

Omid Hamid, MD

Evan J Lipson, MD

Moderator

Neil Love, MD

RTP Year in Review 2023

Inside the Issue: Integrating Bispecific Antibodies into the Management of Multiple Myeloma — Patient Selection and Toxicity Management

A CME/MOC-Accredited Live Webinar

Tuesday, July 18, 2023
5:00 PM – 6:00 PM ET

Faculty

Hans Lee, MD
Saad Zafar Usmani, MD, MBA

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Inside the Issue: Current and Future Management of ER-Positive Metastatic Breast Cancer After Disease Progression on a CDK4/6 Inhibitor

A CME/MOC-Accredited Live Webinar

Thursday, July 20, 2023
5:00 PM – 6:00 PM ET

Faculty

Aditya Bardia, MD, MPH
Erika Hamilton, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Management of Soft Tissue Sarcoma and Related Connective Tissue Disorders

Tuesday, July 25, 2023
5:00 PM – 6:00 PM ET

Faculty

Richard F Riedel, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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Moderator
Neil Love, MD
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Survey Participants

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Associate Professor
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Elizabeth R Plimack, MD, MS
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Deputy Director, Fox Chase Cancer Center
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Guru P Sonpavde, MD
Director of Genitourinary Medical Oncology and Phase I Clinical Research
Christopher K Glanz Chair for Bladder Cancer Research
AdventHealth Cancer Institute
Professor of Medicine
University of Central Florida
Orlando, Florida

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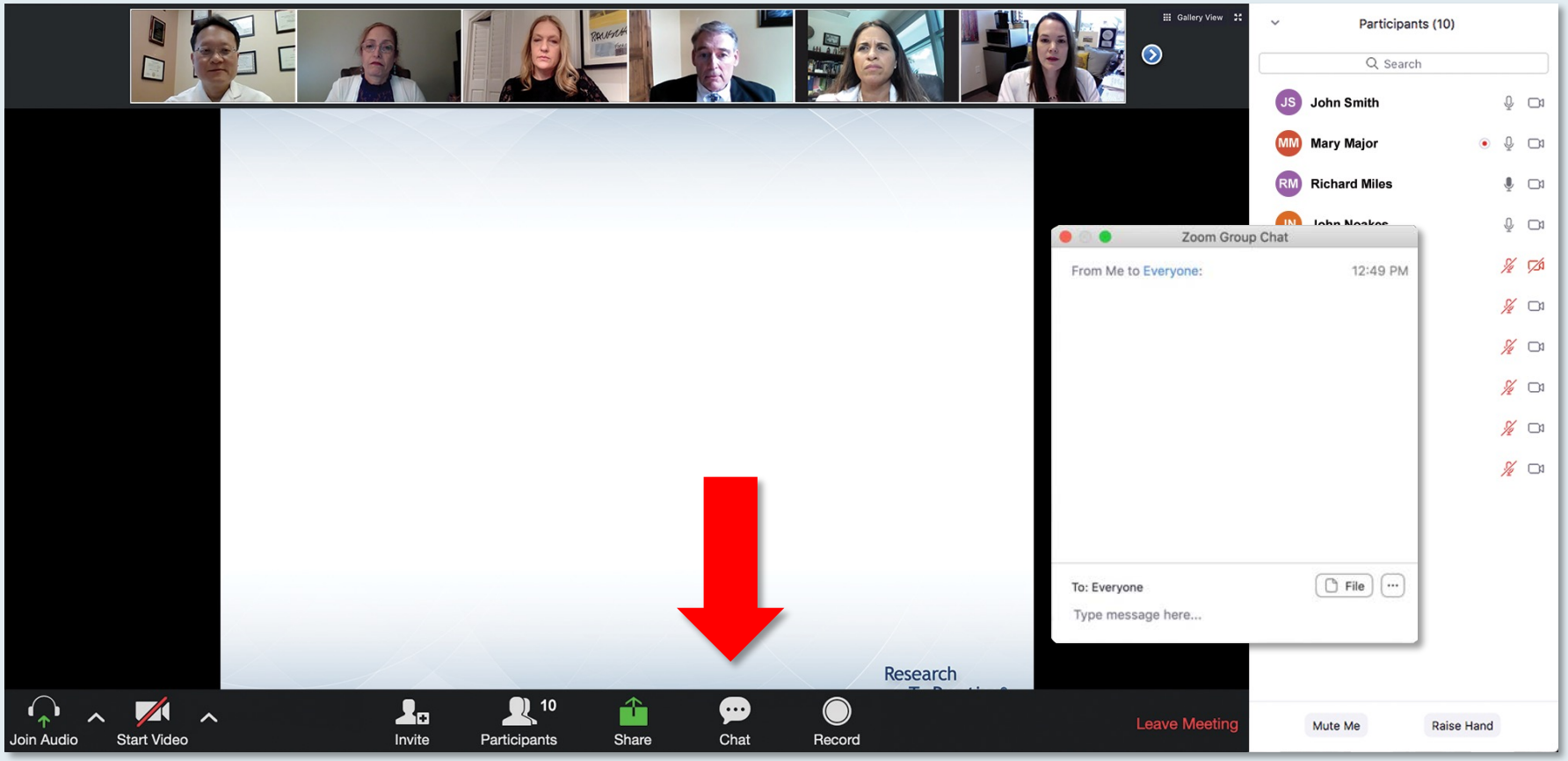

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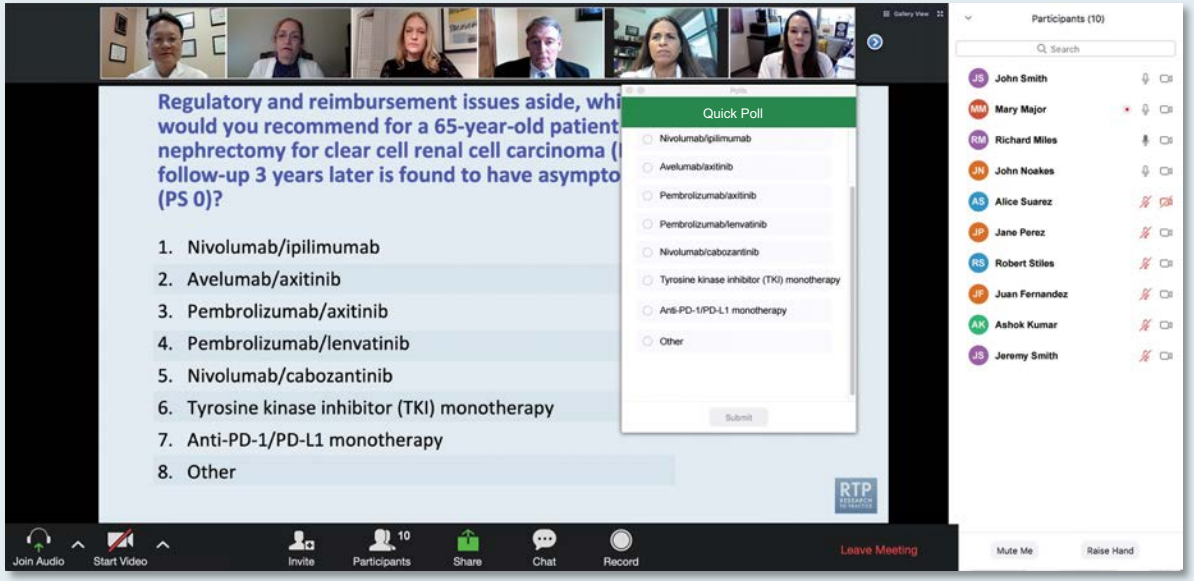

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Data and Safety Monitoring Board/Committee	Bristol Myers Squibb

Immunotherapy-Based Strategies for Metastatic Urothelial Bladder Cancer (mUBC)

Terence Friedlander, MD
Clinical Professor
Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco
Chief of Hematology-Oncology
Zuckerberg San Francisco General Hospital
San Francisco, California

Available data, ongoing investigation and role of novel strategies in metastatic urothelial Ca

Petros Grivas, MD PhD

Professor, Dept. of Medicine, Division of Medical Oncology
Clinical Director, Genitourinary Cancers Program
University of Washington

Professor, Clinical Research Division
Fred Hutchinson Cancer Center

Twitter: @PGrivasMDPhD

BCAN Bladder Cancer Advocacy Network — Leading the way to awareness and a cure

UNIVERSITY of WASHINGTON

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Key Data Sets

Terence Friedlander, MD

- Balar AV et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: Results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up. *Ann Oncol* 2023 March;34(3):289-99.
- Powles T et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): A randomised, open-label, phase 3 trial. *Lancet Oncol* 2021 July;22(7):931-45.
- Swami U et al. Utilization of systemic therapy for treatment of advanced urothelial carcinoma: Lessons from real world experience. *Cancer Treat Res Commun* 2021;27:100325.
- Powles T et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med* 2020 September 24;383(13):1218-30.
- 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 April 18;[Online ahead of print].
- Gupta S et al. Study EV-103 dose escalation/cohort A: Long-term outcome of enfortumab vedotin + pembrolizumab in first-line (1L) cisplatin-ineligible locally advanced or metastatic urothelial carcinoma (la/mUC) with nearly 4 years of follow-up. ASCO 2023;Abstract 4505.

Key Data Sets

Terence Friedlander, MD (continued)

- 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.
- Tagawa ST et al. Updated outcomes in TROPHY-U-01 cohort 1, a phase 2 study of sacituzumab govitecan (SG) in patients (pts) with metastatic urothelial cancer (mUC) that progressed after platinum (PT)-based chemotherapy and a checkpoint inhibitor (CPI). ASCO 2023;Abstract 526.
- Grivas P et al. TROPHY-U-01 Cohort 3: Sacituzumab govitecan (SG) in combination with pembrolizumab (Pembro) in patients (pts) with metastatic urothelial cancer (mUC) who progressed after platinum (PLT)-based regimens. Genitourinary Cancers Symposium 2022;Abstract 434.
- 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.

Key Data Sets

Petros Grivas, MD, PhD

- Necchi A et al. Erdafitinib (ERDA) in patients (pts) with locally advanced or metastatic urothelial carcinoma (mUC): Subgroup analyses of long-term efficacy outcomes of a pivotal phase II trial (BLC2001). ESMO 2020;Abstract 750P.
- Loriot Y et al. Phase 3 THOR study: Results of erdafitinib (erda) versus chemotherapy (chemo) in patients (pts) with advanced or metastatic urothelial cancer (mUC) with select fibroblast growth factor receptor alterations (FGFRalt). ASCO 2023;Abstract LBA4619.
- Yu EY et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): A multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2021;22(6);872-82.
- Rosenberg JE et al. Long-term outcomes in EV-301: 24-month findings from the phase 3 trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma. ASCO 2022;Abstract 4516.
- Tagawa ST et al. Updated outcomes in TROPHY-U-01 cohort 1, a phase 2 study of sacituzumab govitecan in patients with metastatic urothelial cancer that progressed after platinum (PT)-based chemotherapy and a checkpoint inhibitor. Genitourinary Cancers Symposium 2023; Abstract 526.

Key Data Sets

Petros Grivas, MD, PhD (continued)

- 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
- Petrylak DP et al. TROPHY-U-01 cohort 2, a phase 2 study of sacituzumab govitecan in platinum-ineligible patients with metastatic urothelial cancer who progressed after prior checkpoint inhibitor therapy. Genitourinary Cancers Symposium 2023;Abstract 520.
- Grivas P et al. Primary analysis of TROPHY-U-01 cohort 3, a phase 2 study of sacituzumab govitecan (SG) in combination with pembrolizumab (Pembro) in patients (pts) with metastatic urothelial cancer (mUC) that progressed after platinum (PT)-based therapy. Genitourinary Cancers Symposium 2023;Abstract 518.
- Sheng X et al. RC48-ADC for metastatic urothelial carcinoma with HER2-positive: Combined analysis of RC48-C005 and RC48-C009 trials. ASCO 2022;Abstract 4520.
- Xu Y et al. A phase II study of RC48-ADC in HER2-negative patients with locally advanced or metastatic urothelial carcinoma. ASCO 2022;Abstract 4519.

Agenda

INTRODUCTION

MODULE 1: First-Line Treatment of Metastatic Urothelial Bladder Cancer

MODULE 2: Second-Line Therapy and Beyond

- **Enfortumab vedotin**
- **Sacituzumab govitecan**
- **Erdafitinib**
- **HER2-targeted treatment**
- **Other novel strategies**

Agenda

INTRODUCTION

MODULE 1: First-Line Treatment of Metastatic Urothelial Bladder Cancer

MODULE 2: Second-Line Therapy and Beyond

- **Enfortumab vedotin**
- **Sacituzumab govitecan**
- **Erdafitinib**
- **HER2-targeted treatment**
- **Other novel strategies**

2023 ASCO ANNUAL MEETING

Distant Metastasis-Free Survival Results From the Randomized, Phase 2 mRNA-4157-P201/ KEYNOTE-942 Trial

Adnan Khattak,[1,2] Jeffrey S. Weber,[3] Tarek Meniawy,[4] Matthew H. Taylor,[5] George Ansstas,[6] Kevin B. Kim,[7] Meredith McKean,[8] Georgina V. Long,[9] Ryan J. Sullivan,[10] Mark B. Faries,[11] Thuy Tran,[12] C. Lance Cowey,[13] Theresa M. Medina,[14] Jennifer M. Segar,[15] Victoria Atkinson,[16] Geoffrey T. Gibney,[17] Jason J. Luke,[18] Elizabeth I. Buchbinder,[19] Robert S. Meehan,[20] Matteo S. Carlino,[9,21] Moderna Author's Group[20]

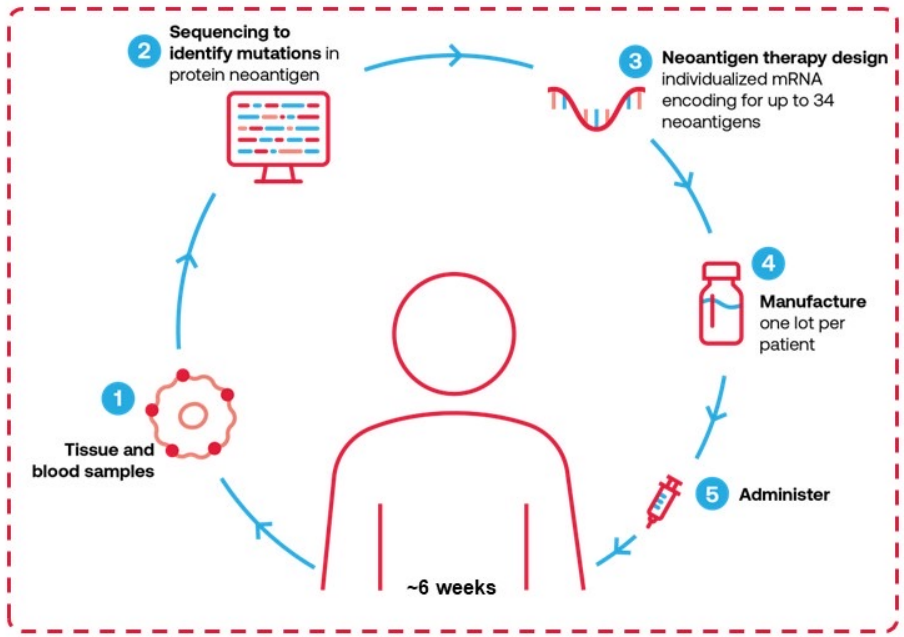
[1]Hollywood Private Hospital, Nedlands, Australia; [2]Edith Cowan University, Perth, Australia; [3]NYU Langone Medical Center, New York, NY; [4]Saint John of God Subiaco Hospital, Subiaco, Australia; [5]Earle A. Chiles Research Institute, Portland, OR, USA; [6]Washington University School of Medicine, St Louis, MO, USA; [7]California Pacific Medical Center Research Institute, Oakland, CA, USA; [8]Sarah Cannon Research Institute, Nashville, TN, USA; [9]Melanoma Institute Australia, Wollstonecraft, Australia; [10]Massachusetts General Hospital, Boston, MA, USA; [11]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [12]Yale-New Haven Hospital, New Haven, CT, USA; [13]Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [14]University of Colorado, Aurora, CO, USA; [15]The University of Arizona Cancer Center, Tucson, AZ, USA; [16]Princess Alexandra Hospital, Woolloongabba, Australia; [17]Lombardi Cancer Center, Washington, DC, USA; [18]UPMC Hillman Cancer Center, Pittsburg, PA, USA; [19]Dana-Farber Cancer Institute, Boston, MA, USA; [20]Moderna Inc., Cambridge, MA, USA; [21]Westmead Hospital, Westmead, Australia.

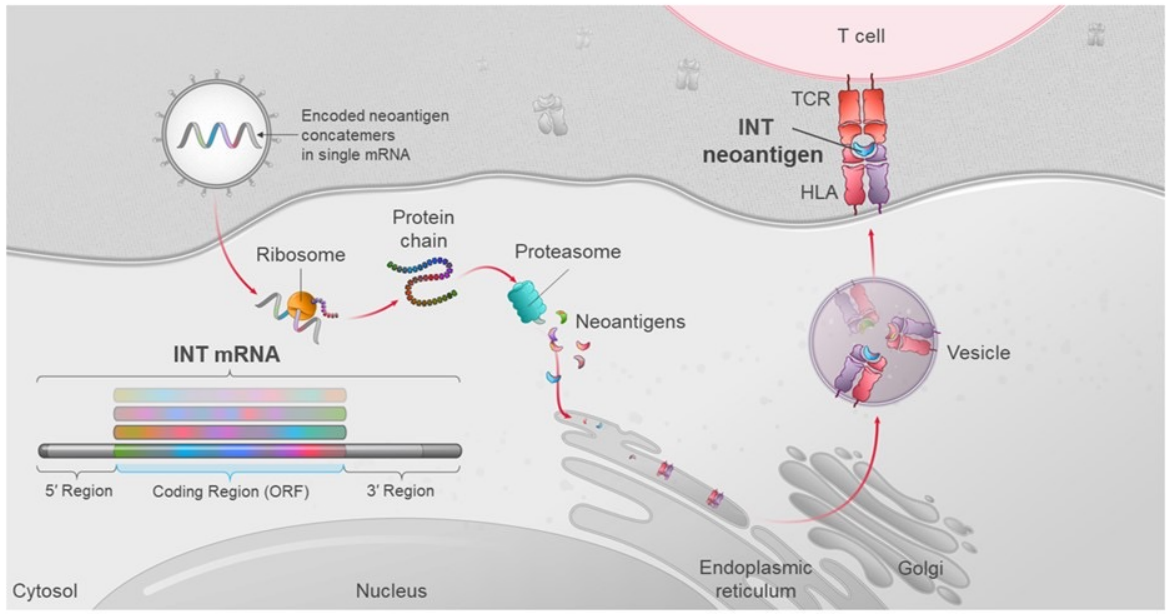
Sponsored by Moderna, Inc., in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Courtesy of Evan J Lipson, MD

mRNA-4157 (V940) Mechanism of Action

- mRNA-4157 (V940) is **an individualized neoantigen therapy** designed to target an individual patient's unique tumor mutations and encodes up to 34 neoantigens[1,2]
- Therapies targeting neoantigens can increase endogenous **neoantigen T-cell responses and induce epitope spreading** to novel antigens with the ability **to drive antitumor responses** and **maintain memory** with cytolytic properties, potentially **producing long-term disease control** for patients[3-7]





HLA, human leukocyte antigen; INT, individualized neoantigen therapy; ORF, open reading frame.

1. Burris HA, et al. *J Clin Oncol*. 2019;37(suppl 15). Abstract 2523. 2. Zhong S, et al. *Cancer Res*. 80(suppl 16). Abstract 6539. 3. Wirth TC, Kühnel F. *Front Immunol*. 2017;8:1848. 4. Ott PA, et al. *Nature*. 2017;547:217-221. 5. Hu Z, et al. *Nat Med*. 2021;27:515-525. 6. Ott PA, et al. *Cell*. 2020;183:347-362. 7. Palmer CD, et al. *Nat Med*. 2022;28:1619-1629.

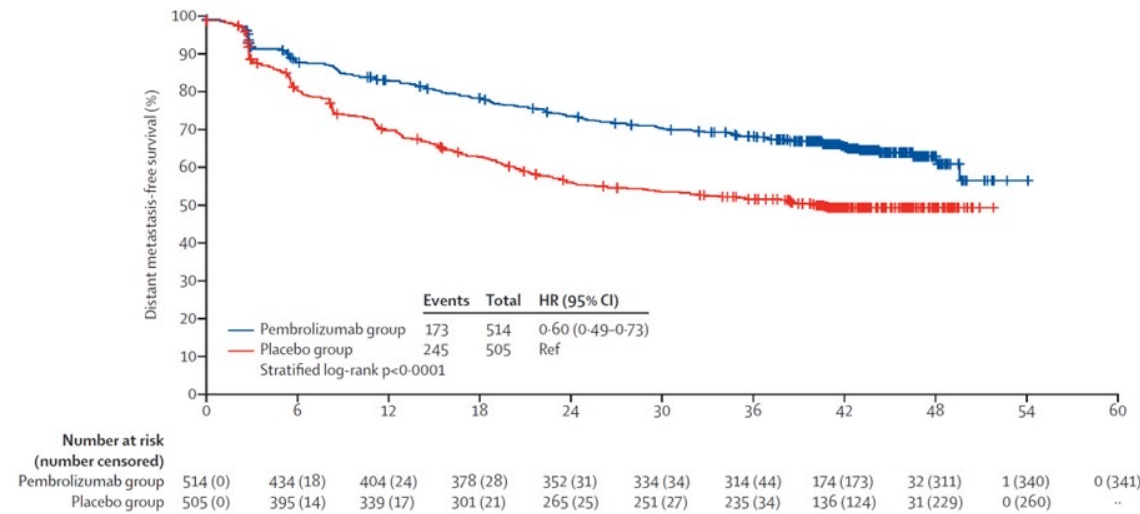
PRESENTED BY: Adnan Khattak, MBBS, FRACP, PhD

Courtesy of Evan J Lipson, MD

Adjuvant ICI Therapy and DMFS in High-risk Melanoma

- **Both RFS and DMFS** have been evaluated as surrogates for overall survival. **DMFS** captures patients whose **relapse is associated with a worse prognosis** and who may need further systemic treatment[1]
- The **KEYNOTE-054** study showed that the **3.5-year DMFS** was **significantly higher for patients receiving pembrolizumab** (65.3%) versus placebo (49.4%) in the ITT population (*P* <0.0001)[2]
- These analyses suggest an **unmet clinical need with high metastasis rates** even with effective adjuvant melanoma therapy
- **mRNA-4157 (V940) + pembrolizumab significantly improved RFS** versus pembrolizumab monotherapy (HR = 0.561 [95% CI, 0.309,1.017; *P* = 0.0266][3]
- Here, we report **the first DMFS results** from the **mRNA-4157-P201/KEYNOTE-942** study

KEYNOTE-054: DMFS



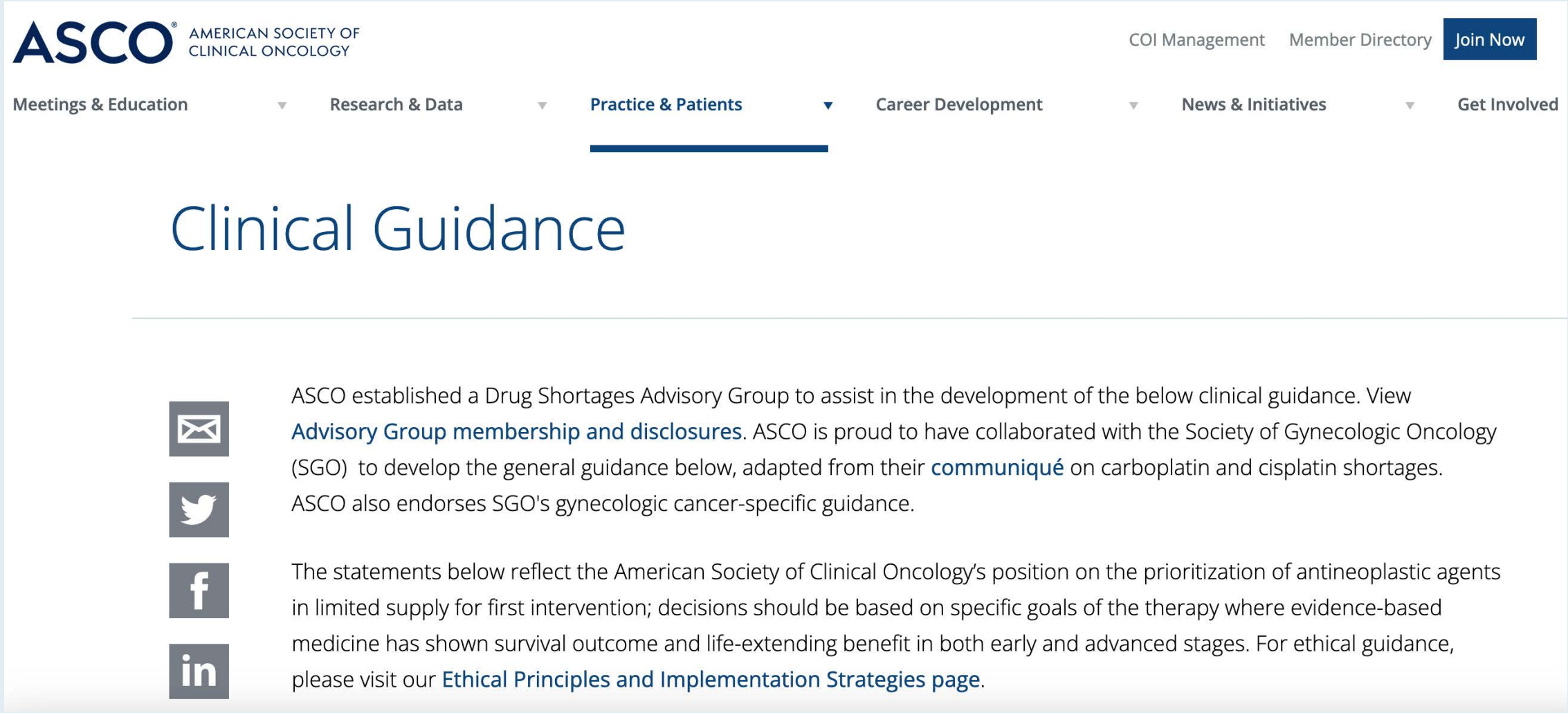
Reprinted from *Lancet Oncology*, Volume No. 22, Eggermont AMM, et al, Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial, Pages No. 643–654, Copyright 2021, with permission from Elsevier.

1. Amabile S, et al. *J Clin Med*. 2021;10:5475. 2. Eggermont AMM, et al. *Lancet Oncol*. 2021.22:643-654. 3. Khattak A, et al. Presented at the American Association for Cancer Research® (AACR) Annual Meeting; April 14-19, 2023; Orlando, FL, USA. Oral presentation CT001.

PRESENTED BY: Adnan Khattak, MBBS, FRACP, PhD

Courtesy of Evan J Lipson, MD

ASCO Clinical Guidance – Drug Shortages



https://old-prod.asco.org/practice-patients/practice-support/drug-shortages/clinical-guidance

RTP RESEARCH TO PRACTICE

ASCO Clinical Guidance – Drug Shortages (Continued)

Effective immediately, ASCO recommends the following:

1. **Re-prioritize non-essential use of antineoplastic agents in limited supply.** If an alternative agent, intervention, or sequence with comparable efficacy and safety is available, then the limited agent should not be ordered.
2. **Increase the interval between cycles and/or reduce the total treatment dose when clinically acceptable.** Where nationally recognized guidelines (e.g., ASCO, NCCN, etc.) state a range for cycle duration, default to the longer end of that range (e.g. if platinum is recommended every 3 to 4 weeks, default to every 4). Where guidelines indicate a range of dosing, default to the lowest therapeutically proper dose.
3. **Minimize** or **omit** the limited agent for recurrent agent-resistant cancers.
4. **Minimize waste by optimizing vial size, dose rounding, and using multi-use vials.**
5. **Institutions should establish a working multidisciplinary utilization committee** to monitor drug shortages, **provide and communicate internal policies on utilization**, and act as an independent arbiter to **promote equitable use of drugs in short supply**.

https://old-prod.asco.org/practice-patients/practice-support/drug-shortages/clinical-guidance

RTP RESEARCH TO PRACTICE

ASCO Clinical Guidance – Drug Shortages (Continued)

Effective immediately, ASCO recommends the following:

6. **Select an evidence-based alternative regimen** if adequate supplies are unavailable and **consider a second opinion consultation** with oncology/hematology colleagues to discuss disease site-specific options.
7. Providers should **offer counseling referrals (if available) to patients affected by shortage-related distress.**
8. **Clinicians should have support services available for shortage-related distress.**

- Institutions should communicate to clinical staff about measures being taken to address drug shortages and resources available to help oncology care teams manage distress.
- Drug shortages impact clinicians, members of oncology care teams and multidisciplinary allocation committees, and the inability of the care teams to provide optimal treatment may cause psychological or moral distress requiring support
- Institutions, practices, clinician societies, and others, should provide or offer referrals for support services such as peer to peer, counseling, discussion forums, or any other services addressing the distress or challenges inherent in providing care in the setting of drug shortages. Of note, ASCO member services also include the ASCO Safe Haven clinician support program, and several national resources focused on moral distress can be found here.

https://old-prod.asco.org/practice-patients/practice-support/drug-shortages/clinical-guidance

RTP RESEARCH TO PRACTICE

ASCO Urothelial Cancer Guidance

"The American Society of Clinical Oncology offers the following clinical guidance on treatment alternatives during shortages of antineoplastic agents. Decisions should be based on specific goals of the therapy where evidence-based medicine has shown survival outcomes and life-extending benefits in both early and advanced stages. For more information on ASCO's general principles during drug shortages, please visit ASCO's Clinical Guidance page. For further consideration of ethical guidance, please visit ASCO's Ethical Principles and Implementation Strategies page.

Disclaimer: Disease site-specific guidance for clinical management during drug shortages is provided by the American Society of Clinical Oncology, Inc. ("ASCO") for voluntary, informational use in the context of limited carboplatin or cisplatin availability. This and other guidance on ASCO's website (together "Guidance") is not a comprehensive or definitive guide to treatment options. New evidence may emerge between the time information is developed and when it is published or read and should only be used in conjunction with independent professional medical judgement. Guidance is based on expert opinion of the Drug Shortages Advisory Group and non-systematic review of relevant literature. It is not medical or pharmacologic advice and is not intended as a statement of the standard of care. ASCO does not endorse third-party drugs, devices, services, or therapies and assumes no responsibility for any harm arising from or related to the use of this information."

https://old-prod.asco.org/sites/new-www.asco.org/files/content-files/practice-patients/documents/2023-final-urothelial-guidance.pdf

RTP RESEARCH TO PRACTICE

ASCO Urothelial Cancer Guidance

3. First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)

A. Cisplatin eligible

Recommended options:

- Gemcitabine and cisplatin followed by avelumab maintenance therapy
- ddMVAC with growth factor support followed by avelumab maintenance therapy

ALTERNATIVES:

- Enfortumab vedotin and pembrolizumab (EV/pembro)
- Pembrolizumab

B. Cisplatin ineligible

Recommended options:

- Gemcitabine and carboplatin followed by avelumab maintenance therapy
- Enfortumab vedotin and pembrolizumab (EV/pembro)

ALTERNATIVES:

- Pembrolizumab
- Gemcitabine
- Gemcitabine + paclitaxel
- Ifosfamide, doxorubicin, and gemcitabine are options for patients with good kidney function and good performance status

https://old-prod.asco.org/sites/new-www.asco.org/files/content-files/practice-patients/documents/2023-final-urothelial-guidance.pdf

Agenda

INTRODUCTION

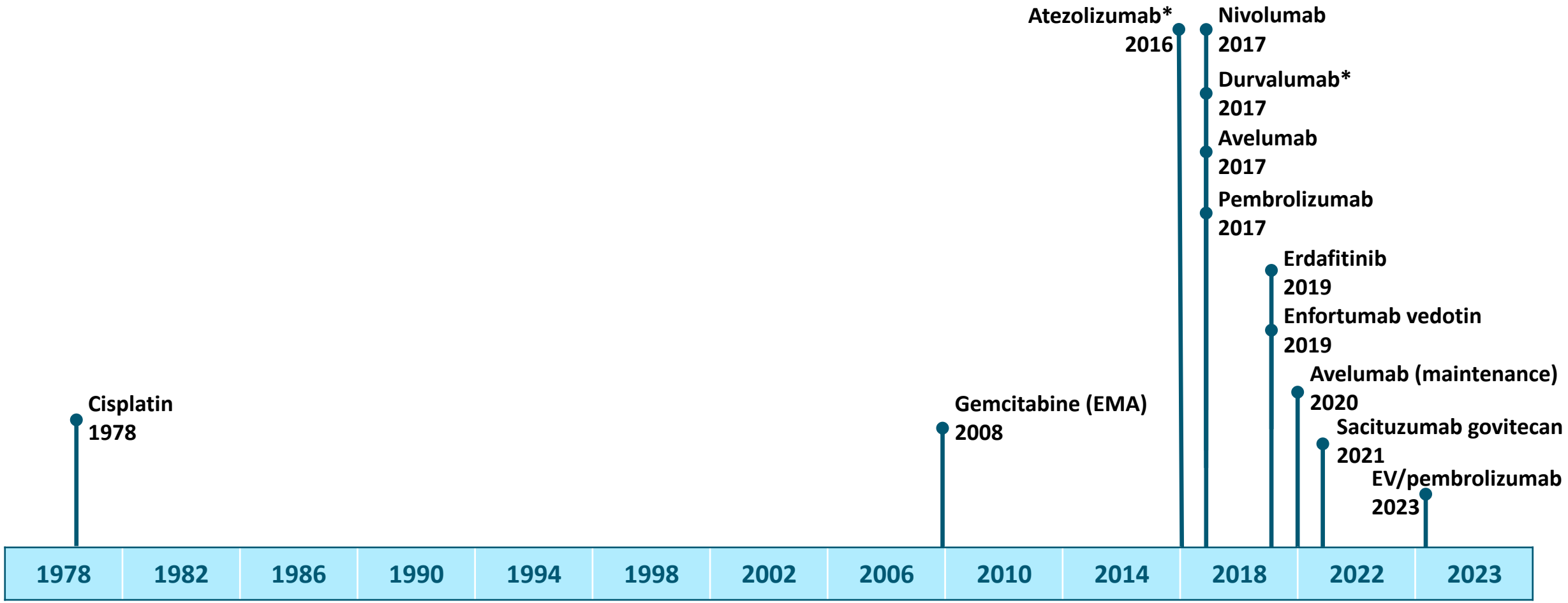
MODULE 1: First-Line Treatment of Metastatic Urothelial Bladder Cancer

MODULE 2: Second-Line Therapy and Beyond

- Enfortumab vedotin
- Sacituzumab govitecan
- Erdafitinib
- HER2-targeted treatment
- Other novel strategies

RTP
RESEARCH
TO PRACTICE

The Treatment Landscape for Locally Advanced/ Metastatic Urothelial Carcinoma Has Evolved Rapidly

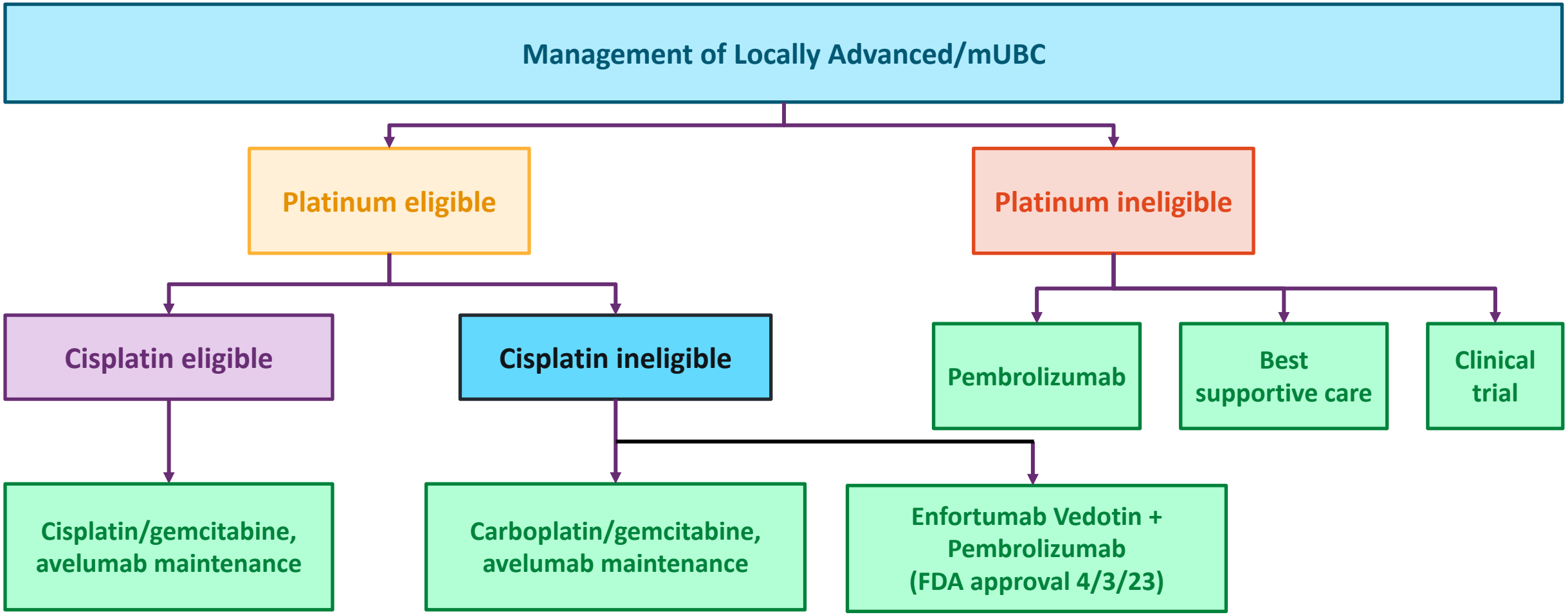


*Not FDA approved; indication withdrawn.

Cisplatin PI. www.ema.europa.eu/en/medicines/human/referrals/gemzar. Rhea. Clin Med Insights Oncol. 2021;15:11795549211044963. Nivolumab PI. Avelumab PI. Pembrolizumab PI. Erdafitinib PI. Enfortumab vedotin PI. Avelumab PI. Sacituzumab govitecan PI.

Courtesy of Terence Friedlander, MD

Frontline Management of Locally Advanced/Metastatic Urothelial Carcinoma



Courtesy of Terence Friedlander, MD

Who is eligible for platinum chemotherapy?

- Approximately **30% to 50%** of patients are ineligible for cisplatin due to impairment in renal function and performance status[1]

- **Working Group cisplatin-unfit criteria include**[2]
  - ECOG PS ≥2
  - Creatinine clearance <60 mL/min
  - Grade ≥2 peripheral neuropathy or hearing loss
  - NYHA Class III/IV heart failure

Courtesy of Terence Friedlander, MD

1. Dash. Cancer. 2006;107:506. 2. Galsky. J Clin Oncol. 2011;29:2432.

Who is ineligible for (even) carboplatin-based chemotherapy?

- Survey of 60 medical oncologists:

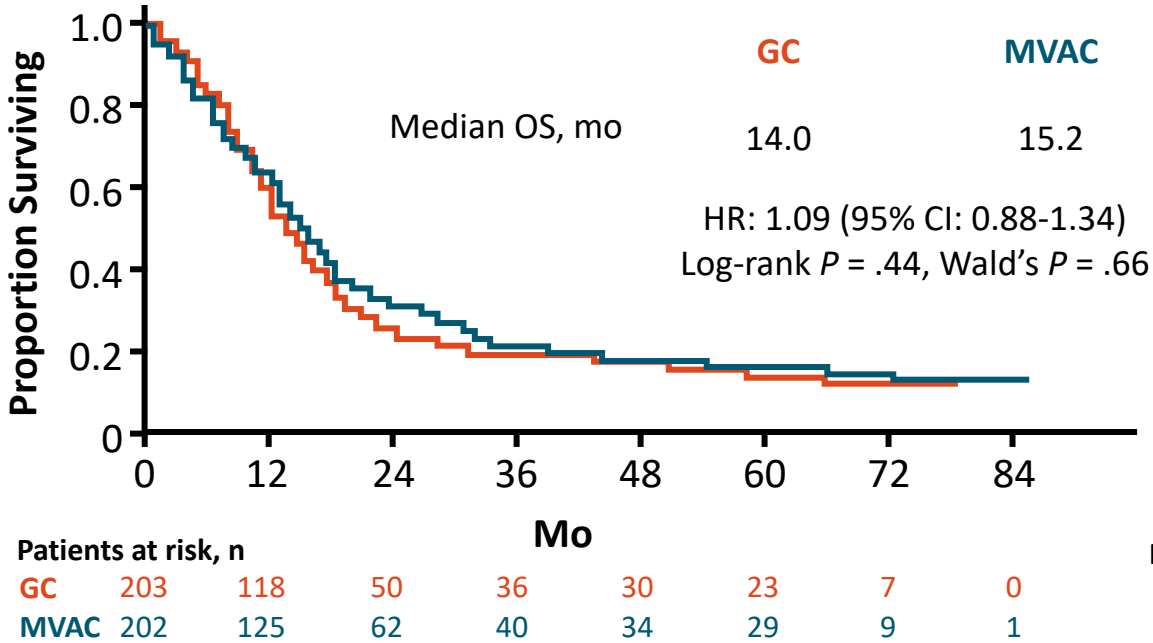
What threshold ECOG PS should be used to define "platinum-ineligibility"?	ECOG PS > / = 3	# Responses 41/60 (68.3%)
What threshold Cr Cl should be used for "platinum-ineligibility"?	< 30 ml/min	# Responses 41/60 (68.3%)
What grade of peripheral neuropathy would you consider for "platinum-ineligibility"?	> / = Grade 2	# Responses 32/60 (53.3%)
What class of Heart Failure do you consider to define "platinum-ineligibility"?	NYHA Class III	# Responses 48/60 (80%)
In a patient with ECOG PS 2, what Cr Cl cut-off would you use to define "platinum-ineligibility" differently of what is used for “cisplatin-ineligibility”?	< 30 ml/min	# Responses 29/60 (48.3%)

Courtesy of Terence Friedlander, MD

Gupta et al, Journal of Clinical Oncology 2022 40:16_suppl, 4577-4577

Frontline Cisplatin Regimens: Gem/Cis or ddMVAC

Median Overall Survival[1]



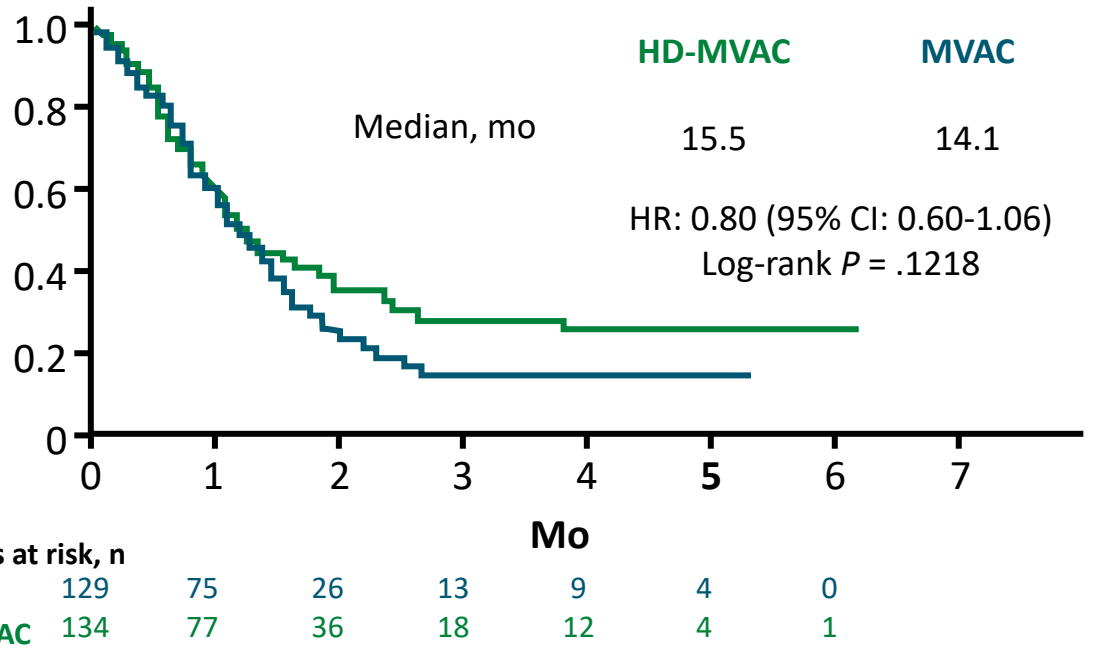
	GC	MVAC
Median OS, mo	14.0	15.2

HR: 1.09 (95% CI: 0.88-1.34)
Log-rank *P* = .44, Wald's *P* = .66

Patients at risk, n								
GC	203	118	50	36	30	23	7	0
MVAC	202	125	62	40	34	29	9	1

ORR[2]		Toxic Death Rate[2]	
GC	49%	GC	1%
MVAC	46%	MVAC	3%

Median Overall Survival[3]



	HD-MVAC	MVAC
Median, mo	15.5	14.1

HR: 0.80 (95% CI: 0.60-1.06)
Log-rank *P* = .1218

Patients at risk, n								
MVAC	129	75	26	13	9	4	0	
HD-MVAC	134	77	36	18	12	4	1	

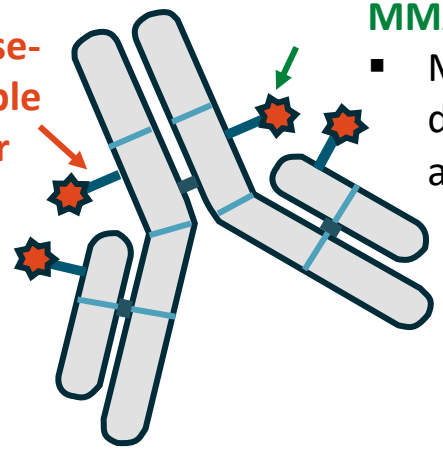
ORR[3]		Toxic Death Rate[3]	
HD-MVAC	62%	HD-MVAC	3%
MVAC	50%	MVAC	4%

1. von der Maase. J Clin Oncol. 2005:23:4602. 2. von der Maase H. J Clin Oncol. 2000;18:3068.
3. Sternberg. J Clin Oncol. 2001;19:2638.

Courtesy of Terence Friedlander, MD

Enfortumab Vedotin: First Approved ADC in mUBC

Enfortumab Vedotin



MMAE Payload

- Microtubule-disrupting agent

Fully Humanized Antibody

- Targets nectin-4, a transmembrane cell adhesion molecule highly expressed in mUBC

- **FDA approval:** for adults with locally advanced or mUBC who have previously received a PD-1 or PD-L1 inhibitor, and a platinum-containing CT or are ineligible for cisplatin-containing chemotherapy and have previously received ≥1 prior lines of therapy. **Accelerated approval:** in combination with pembrolizumab for the treatment of adult patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing chemotherapy

- EV 301- Randomized Phase III trial comparing EV to taxane/vinflunine chemotherapy
- Significant OS benefit
  - Median OS 12.91 vs 8.94 mo (HR: 0.70 (95% CI: 0.58-0.85; *P* = .00015)
- FDA approved in 2nd/3rd line mUBC in 2019

Courtesy of Terence Friedlander, MD

Samanta. Cell Mol Life Sci. 2015;72:645. Rosenberg. JCO. 2019; 37:2592. Enfortumab vedotin PI.

2023 ASCO ANNUAL MEETING

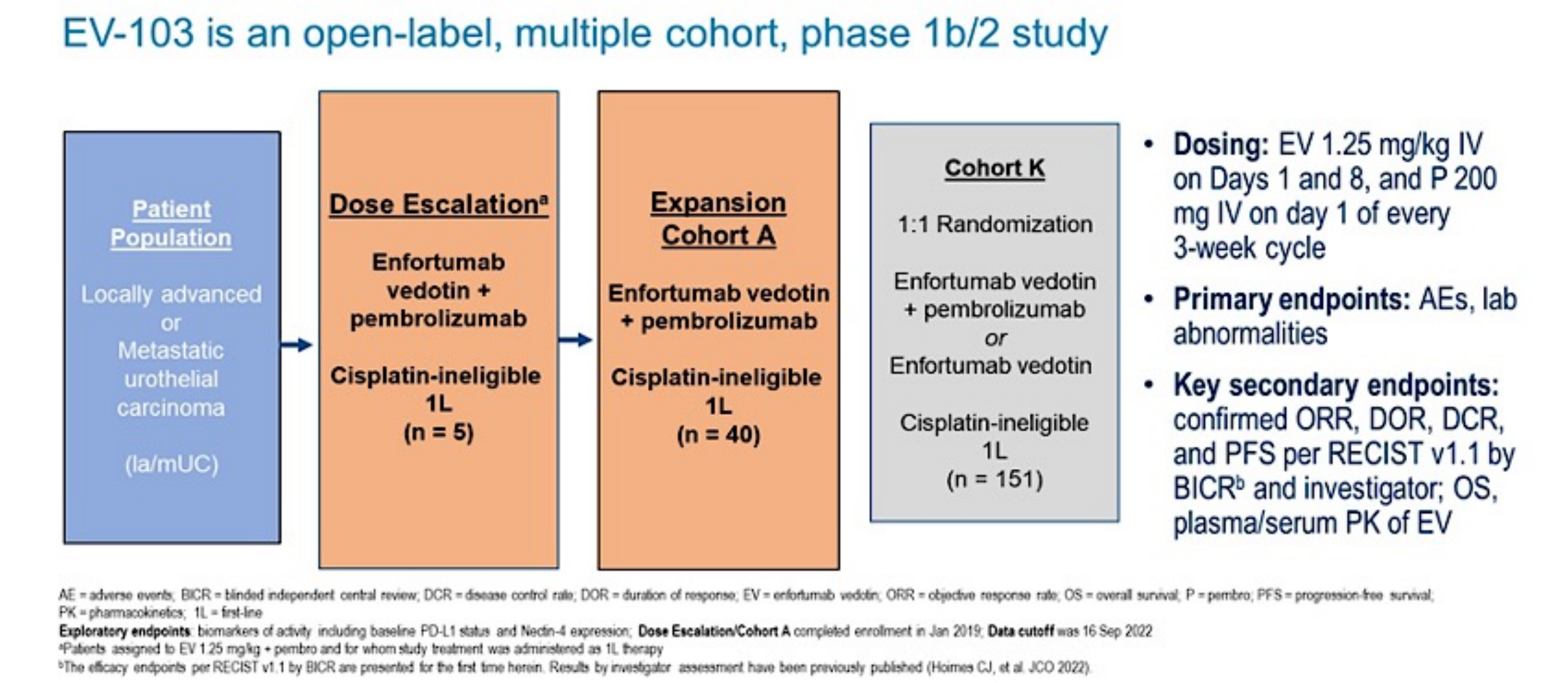
Abstract 4505

Study EV-103 Dose Escalation/Cohort A: Long-term Outcome of Enfortumab Vedotin + Pembrolizumab in First-line (1L) Cisplatin-ineligible Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC) with Nearly 4 Years of Follow-up

Shilpa Gupta, MD[1]; Jonathan E. Rosenberg, MD[2]; Rana R. McKay, MD[3]; Thomas W. Flaig, MD[4]; Daniel Peter Petrylak, MD[5]; Christopher J. Hoimes, DO[6]; Terence W. Friedlander, MD[7]; Mehmet Asim Bilen, MD[8]; Sandy Srinivas, MD[9]; Earle Burgess, MD[10]; Jaime R. Merchan, MD[11]; Scott Tagawa, MD[12]; Jason Brown, MD[13]; Yao Yu, PhD[14]; Anne-Sophie Carret, MD[14]; Heidi S. Wirtz, PharmD, PhD[14]; Maria Guseva, MD, PharmD[15]; Blanca Homet Moreno, MD, PhD[16]; Matthew I. Milowsky, MD[17]

[1]Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH, USA; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [3]University of California San Diego, San Diego, CA, USA; [4]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; [5]Yale Cancer Center, New Haven, CT, USA; [6]Duke Cancer Institute, Duke University, Durham, NC, USA; [7]University of California San Francisco Medical Center, San Francisco, CA, USA; [8]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [9]Stanford University Medical Center, Stanford, CA, USA; [10]Atrium Health Levine Cancer Institute, Charlotte, NC, USA; [11]University of Miami, Miami, FL, USA; [12]Weill Cornell Medical Center, New York, NY, USA; [13]University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [14]Seagen Inc, Bothell, WA, USA; [15]Astellas Pharma, Northbrook, IL, USA; [16]Merck & Co., Inc., Rahway, NJ, USA; [17]University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

EV-103 Study Design: EV/Pembrolizumab Cohorts



Gupta S et al. ASCO 2023;Abstract 4505.

EV-103 Dose Escalation Cohort A: Long-Term Efficacy Outcomes

ORR by BICR	Dose Escalation + Cohort A (N = 45)
Objective Response Rate, n (%)	33 (73.3)
95% CI[a] for ORR	58.1-85.4
Best Overall Response, n (%)	
Complete response	7 (15.6)
Partial response	26 (57.8)
Stable disease	5 (11.1)
Progressive disease	5 (11.1)
No assessment[b]	2 (4.4)
Disease Control Rate, n (%)	38 (84.4)
95% CI[a] for DCR	70.5-93.5
Concordance rate of BOR between BICR and INV[c] assessment	95.3%

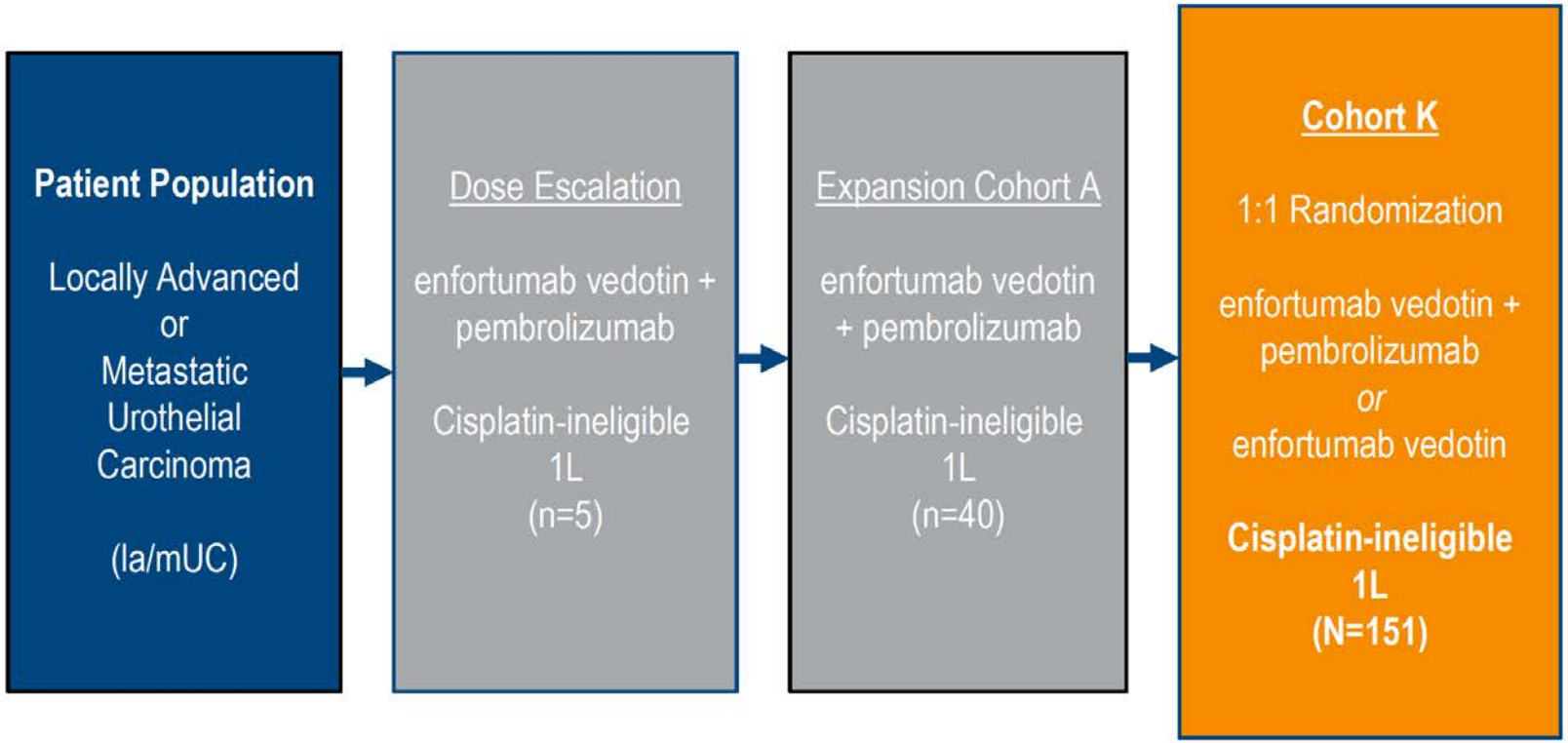
BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; DCR = disease control rate; INV = investigator; ORR = objective response rate
[a]CI was computed using the Clopper-Pearson method (Clopper 1934)
[b]Patients had no response assessment post-baseline
[c]ORR per INV assessment was 33/45 (73.3%)

- Median duration of response was 22.1 months
- Median overall survival was 26.1 months

Gupta S et al. ASCO 2023;Abstract 4505.

EV-103 Cohort K

Part of an open-label, multiple cohort, phase 1b/2 study in patients with urothelial carcinoma



- **Dosing:** EV 1.25 mg/kg IV on days 1 and 8, and P 200 mg IV on day 1 of every 3-week cycle
- **Primary endpoint:** confirmed ORR by RECIST v1.1 per BICR
- **Key secondary endpoints:** confirmed ORR per RECIST v1.1 by investigator, DOR, DCR, PFS, OS, safety/ tolerability, and lab abnormalities

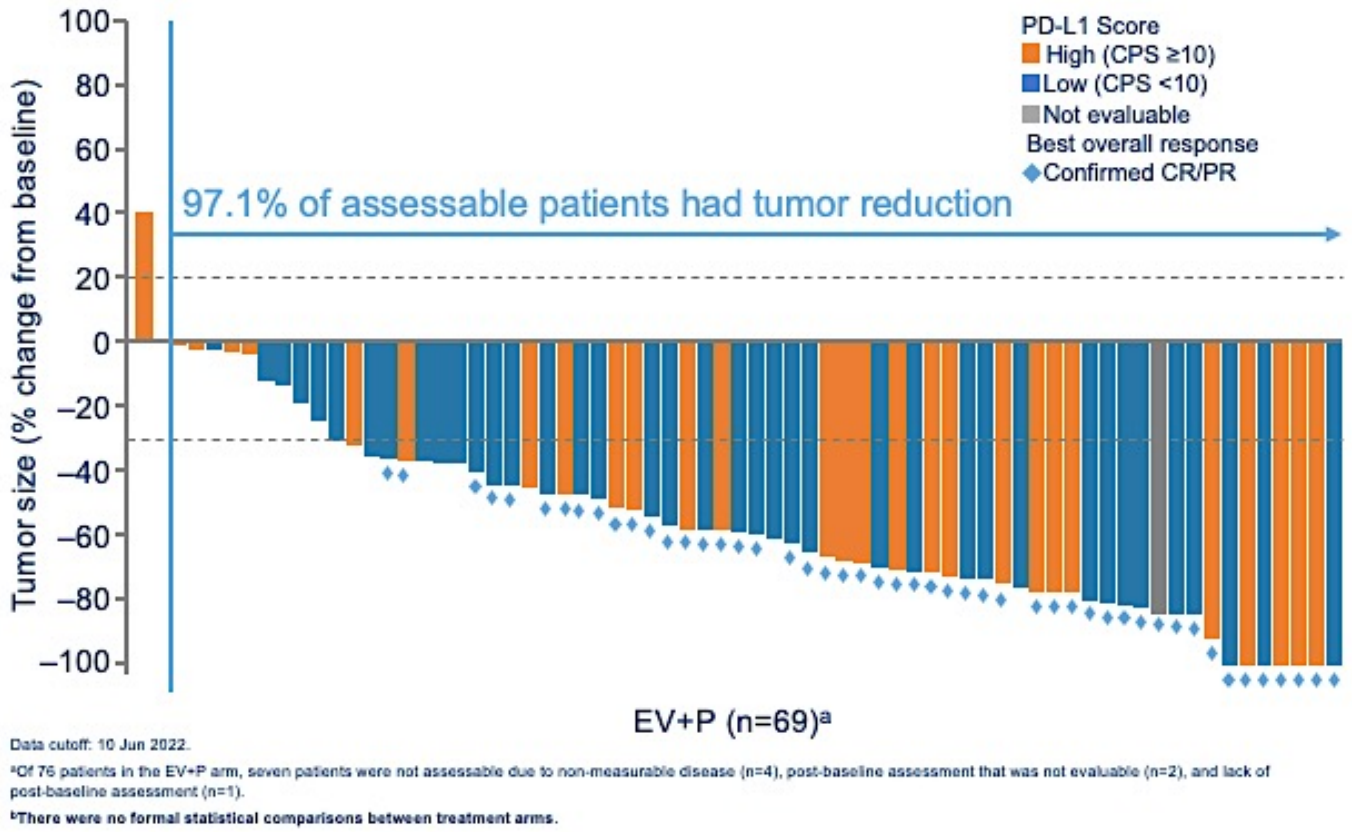
Statistical considerations

- The sample size was based on precision of the estimate for ORR characterized by 95%CIs
- No formal statistical comparisons between the 2 treatment arms

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; **Cohort K** completed enrollment on 11 Oct 2021; **Data cutoff was 10 Jun 2022**

Rosenberg JE et al. ESMO 2022;Abstract LBA73.

EV-103 Cohort K: Efficacy and Safety



Data cutoff: 10 Jun 2022.

[a]Of 76 patients in the EV+P arm, seven patients were not assessable due to non-measurable disease (n=4), post-baseline assessment that was not evaluable (n=2), and lack of post-baseline assessment (n=1).

[b]There were no formal statistical comparisons between treatment arms.

	EV+P[b] (n=76)	EV mono[b] (n=73)
cORR, n (%) (95% CI)	49 (64.5) (52.7-75.1)	33 (45.2) (33.5-57.3)
Median time to objective response (range), mo	2.07 (1.1-6.6)	2.07 (1.9-15.4)
Median number of treatment cycles (range)	11.0 (1-29)	8.0 (1-33)

EV+P

- 42/49 (85.7%) of responses observed at first assessment (week 9±1 week)
- Most common AEs were fatigue, peripheral sensory neuropathy, alopecia, and maculopapular rash

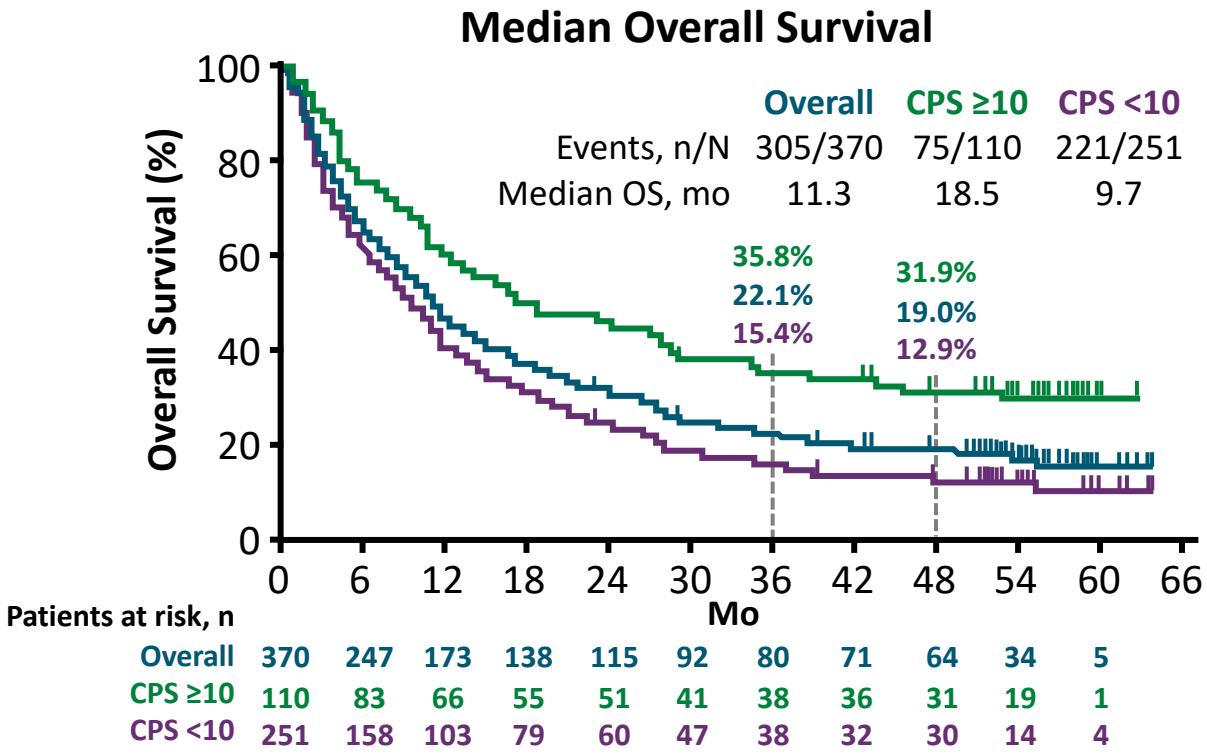
EV mono

- Activity is consistent with prior results in 2L+ la/mUC
- Safety profile consistent with previous studies

Rosenberg JE et al. ESMO 2022;Abstract LBA73.

KEYNOTE-052: Single-Agent Pembrolizumab in Locally Advanced mUBC

- Multisite, single-arm, open-label phase II trial
- Patients with locally advanced/metastatic urothelial cancer with measurable disease; no prior systemic chemotherapy and cisplatin-ineligible; ECOG PS 0-2 (N = 370)
- **Primary endpoint:** confirmed ORR per RECIST v1.1 by IRR
- **Secondary endpoints:** PFS, DoR per RECIST v1.1 by IRR, OS, safety
- Endpoints analyzed in full population and subgroups with PD-L1 CPS* ≥10 and CPS* <10



Response, n (%)	Pembrolizumab		
	All (N = 370)	CPS ≥10 (n = 110)	CPS <10 (n = 251)
ORR	107 (28.9)	52 (47.3)	52 (20.7)
▪ CR	35 (9.5)	23 (20.9)	10 (4.0)

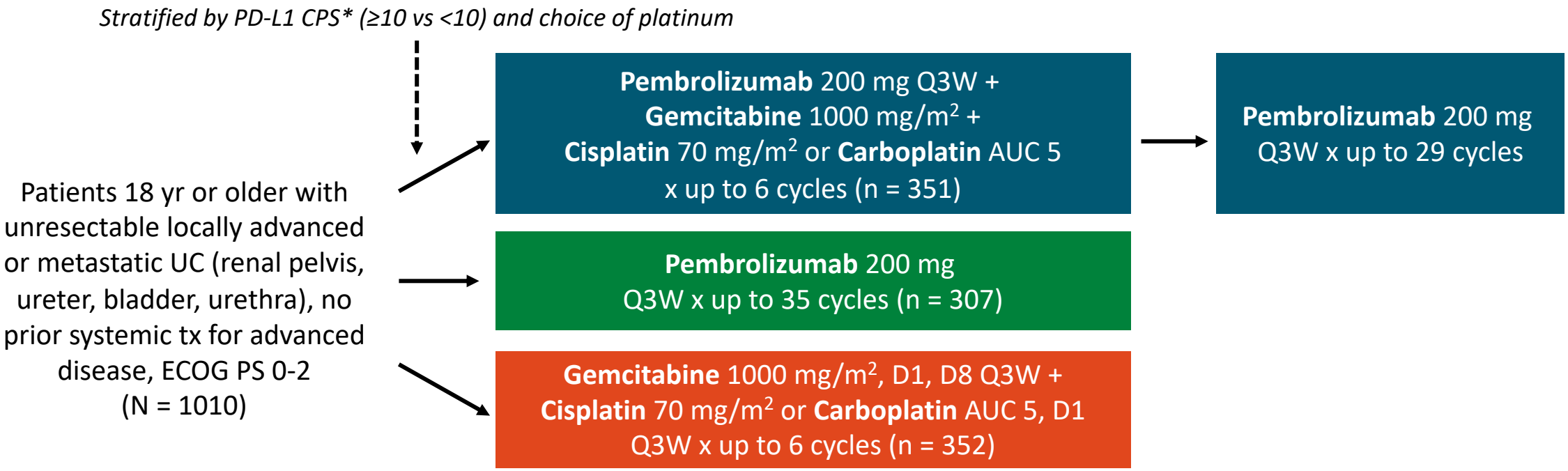
* Defined as number of PD-L1–staining cells divided by total number of viable tumor cells x100.

Balar. Ann Oncol. 2023;34:289.

Courtesy of Terence Friedlander, MD

KEYNOTE-361: First-Line Pembrolizumab, Chemotherapy, or Both in Advanced Urothelial Carcinoma

- Randomized, open-label, phase III trial



- **Primary endpoints:** PFS (BICR), OS
- **Secondary endpoints:** ORR, DCR, DoR (BICR); safety

Median follow-up: 31.7 mo

* Per PD-L1 pharmDx IHC assay. CPS = no. of PD-L1–staining tumor cells, lymphocytes, and macrophages divided by total no. viable tumor cells, multiplied by 100.

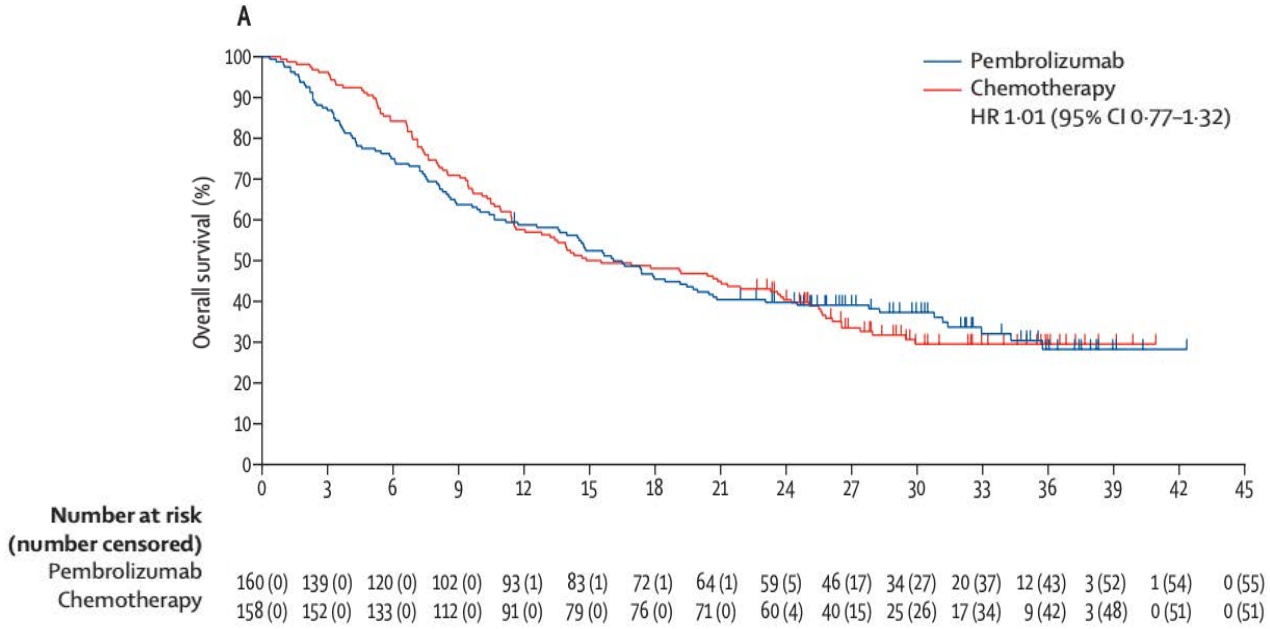
Alva. ESMO 2020. Abstr LBA23. Powles. Lancet Oncol. 2021;22:931.

Courtesy of Terence Friedlander, MD

KEYNOTE-361: Comparing Pembrolizumab to Chemotherapy in Advanced Urothelial Carcinoma

	Pembrolizumab group (n=307)	Chemotherapy group (n=352)
Proportion of patients with a complete or partial response	93 (30·3%, 25·2–35·8)	158 (44·9%, 39·6–50·2)
Chosen to receive cisplatin	46/137 (33·6%, 25·7–42·1)	76/156 (48·7%, 40·6–56·8)
Chosen to receive carboplatin	47/170 (27·6%, 21·1–35·0)	82/196 (41·8%, 34·8–49·1)
Best overall response		
Complete response	34 (11%)	43 (12%)
Partial response	59 (19%)	115 (33%)
Stable disease	52 (17%)	109 (31%)
Progressive disease	118 (38%)	39 (11%)
Non-complete response or non-progressive disease	8 (3%)	16 (5%)
Not evaluable or assessed*	36 (12%)	30 (9%)
Median duration of complete or partial response, months	28·2 (13·5–not evaluable)	6·2 (5·8–6·5)
Estimated ongoing responses at 12 months	65% (54–74)	24% (17–31)
Estimated ongoing responses at 18 months	54% (43–64)	19% (13–26)

Overall Survival (Pembrolizumab vs Chemotherapy)



Courtesy of Terence Friedlander, MD

In general, what is your preferred first-line treatment regimen for a 65-year-old patient with metastatic urothelial bladder cancer (UBC) and a PS of 0 who has received no prior systemic therapy?
Does PD-L1 level affect your treatment decision?
How long would you continue treatment?

	Preferred treatment	Affected by PD-L1?	Duration
 Dr Friedlander	Cisplatin/gemcitabine → avelumab	No	2 years
 Dr Grivas	Cisplatin/gemcitabine → avelumab	No	4-6 cycles, avelumab until PD/toxicity
 Dr Gupta	Cisplatin/gemcitabine → avelumab	No	2 years
 Dr Petrylak	Cisplatin/gemcitabine → avelumab	No	4-6 cycles
 Dr Plimack	Dose-dense MVAC → pembrolizumab	No	Chemo x 4, pembro x 2 years
 Dr Sonpavde	Cisplatin/gemcitabine → avelumab	No	Until PD/toxicity*

* Stop after 1 year if complete remission; PD = progressive disease; MVAC = methotrexate/vinblastine/doxorubicin/cisplatin

In general, what is your preferred first-line treatment regimen for an 80-year-old patient with metastatic UBC who has received no prior systemic therapy and is not a candidate for cisplatin?
Does PD-L1 level affect your treatment decision?
How long would you continue treatment?

	Preferred treatment	Affected by PD-L1?	Duration
 Dr Friedlander	Pembrolizumab/EV	No	EV until toxicity, pembrolizumab 2 years
 Dr Grivas	Pembrolizumab/EV	No	EV until toxicity, pembrolizumab 2 years
 Dr Gupta	Carboplatin/gemcitabine → avelumab	No	2 years
 Dr Petrylak	Carboplatin/gemcitabine → avelumab	No	4-6 cycles
 Dr Plimack	Pembrolizumab/EV	No	Until toxicity or PD
 Dr Sonpavde	Pembrolizumab/EV	No	Until PD/toxicity

EV = enfortumab vedotin; PD = progressive disease

In general, what is your preferred first-line treatment regimen for an 80-year-old patient with de novo metastatic UBC who has received no prior systemic therapy and is not a candidate for cisplatin or carboplatin?
Does PD-L1 level affect your treatment decision?
How long would you continue treatment?

	Preferred treatment	Affected by PD-L1?	Duration
 Dr Friedlander	Pembrolizumab	No	2 years
 Dr Grivas	Pembrolizumab	No	2 years
 Dr Gupta	Pembrolizumab	No	2 years
 Dr Petrylak	Enfortumab vedotin/ pembrolizumab	No	10 cycles
 Dr Plimack	Enfortumab vedotin/ pembrolizumab	No	Until toxicity or PD
 Dr Sonpavde	Pembrolizumab	Yes	Until PD/toxicity*

* Stop after 1 year if complete remission; PD = progressive disease

Agenda

INTRODUCTION

MODULE 1: First-Line Treatment of Metastatic Urothelial Bladder Cancer

MODULE 2: Second-Line Therapy and Beyond

- **Enfortumab vedotin**
- **Sacituzumab govitecan**
- **Erdafitinib**
- **HER2-targeted treatment**
- **Other novel strategies**

RTP
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Advanced Urothelial Ca Treatment Algorithm

Disease State	Setting	Preferred Option	Other Options
Metastatic, no prior chemotherapy	**Cisplatin-eligible**	**Cisplatin/gemcitabine f/b avelumab maintenance**	***aMVAC f/b avelumab maintenance***
Metastatic, no prior chemotherapy	**Cisplatin-ineligible**	**Gemcitabine/Carboplatin (in fit patients) f/b avelumab maintenance *OR* Pembrolizumab/Enfortumab-vedotin**	***Pembrolizumab*** ***Single agent chemotherapy***
Metastatic, prior platinum chemotherapy or relapse within 1 year of perioperative cisplatin-based therapy		**Pembrolizumab *OR* Erdafitinib (tumors with FGFR2/3 activating mutation or fusion) *OR* Enfortumab-vedotin (cisplatin-unfit pts)**	***Avelumab*** ***Nivolumab***
Metastatic, prior chemotherapy & immunotherapy		**Enfortumab-vedotin *OR* Sacituzumab-govitecan *OR* Erdafitinib (tumors with FGFR2/3 activating mutation or fusion)**	***Taxane (US)*** ***Vinflunine (EU)***

Clinical trials are critical throughout disease spectrum & treatment settings!

Petros Grivas

Courtesy of Petros Grivas, MD, PhD

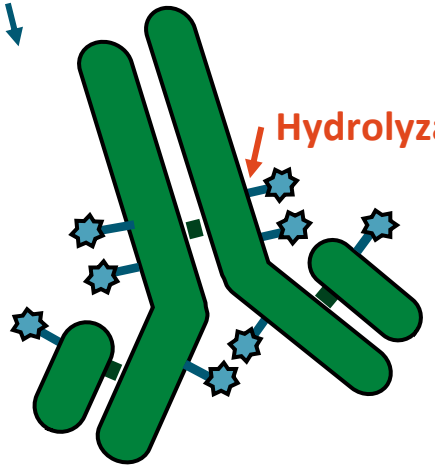
What is on the horizon?

- Sacituzumab Govitecan
  - Accelerated approval as monotherapy in later line mUBC
  - TROPHY-U-01 cohort A
    - N=113
    - 28% ORR, DOR 6.1 mo, mPFS 5.4 mo, mOS 10.9 mo
  - Is there synergy with PD-1 immunotherapy?

Sacituzumab Govitecan

SN-38 Payload

- Active metabolite of irinotecan



Humanized RS7 Antibody

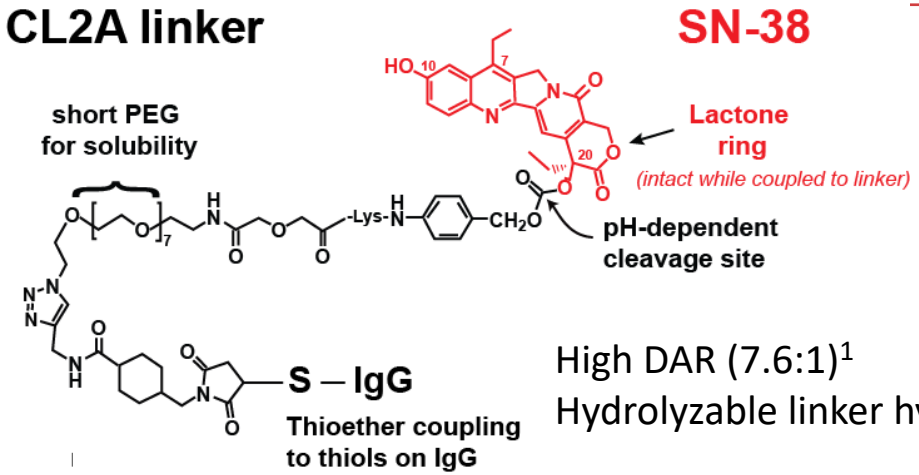
- Targets Trop-2, an epithelial cell surface antigen highly expressed in UC

- **Accelerated FDA approval:** for adults with locally advanced or metastatic UC who previously received a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor

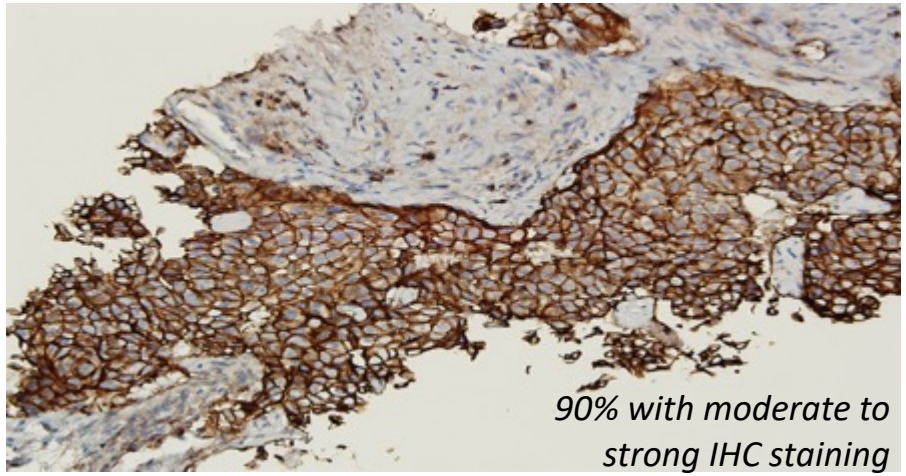
Courtesy of Terence Friedlander, MD

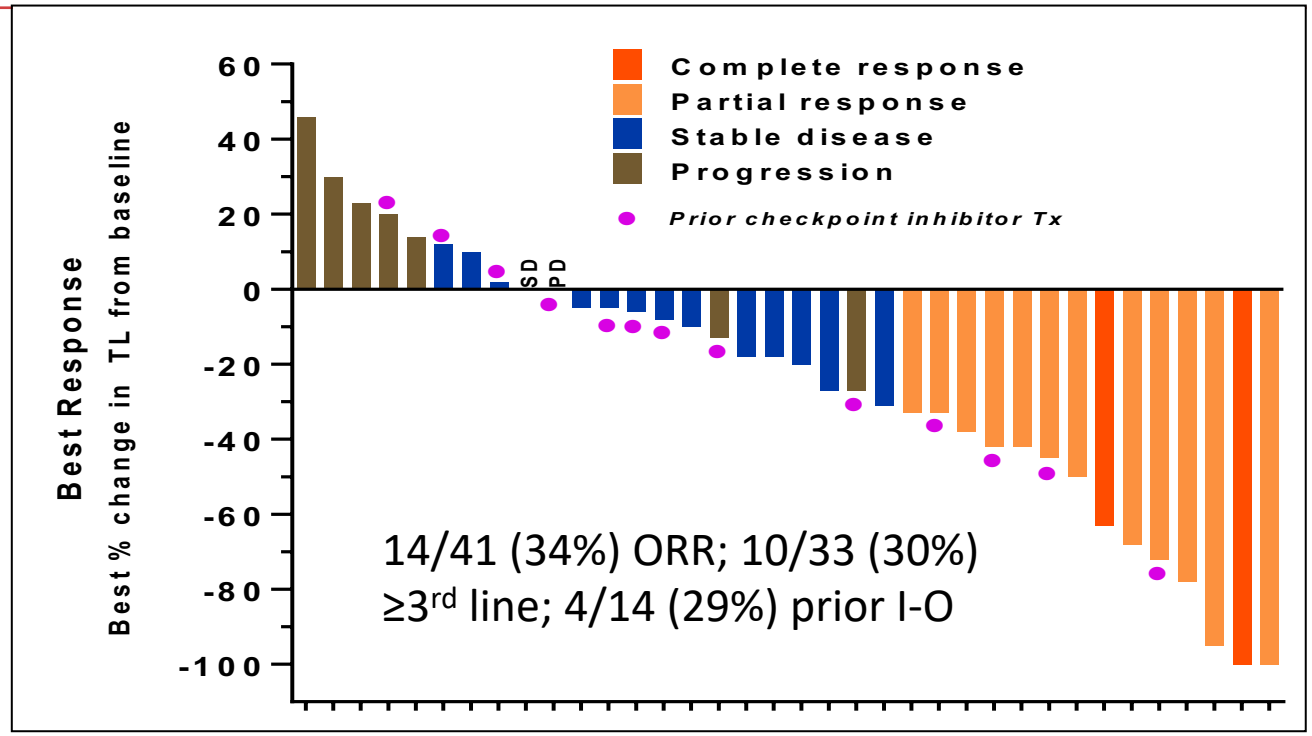
Sacituzumab govitecan PI. Avellini. Oncotarget. 2017;8:58642. Starodub. Clin Cancer Res. 2015;21:3870. Cardillo. Bioconjugate Chem. 2015;26:919. Tagawa et al Journal of Clinical Oncology 2023 41:6_suppl, 526-526

Sacituzumab govitecan



High DAR (7.6:1)[1]
Hydrolyzable linker hydrolysis[2]





- Final 14/45 (31%) ORR
- Median PFS 7.3 months
- Median OS 18.9 months

1. Cardillo TM, et al. Bioconjug Chem 2015; 26:919-31
2. Govindan SV, et al. Mol Cancer Ther 2013; 12:968-78

Courtesy of Petros Grivas, MD, PhD

Tagawa S, et al. Ann Oncol (2017) 28 (suppl_5):v295-v329
Tagawa S, et al. J Clin Oncol 37, no. 7_suppl (March 1, 2019) 354-354

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

TROPHY U-01

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

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

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

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

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

Continue treatment in the absence of unacceptable toxicity or disease progression

Continue until a maximum of 6 cycles has been completed,[d] disease progression, lack of clinical benefit, toxicity, or withdrawal of consent → **Maintenance avelumab (800 mg every 2 weeks) with SG (Days 1 and 8 every 21 days) for those without disease progression**

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

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

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

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

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

1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

Abstract # 434.

ASCO Genitourinary Cancers Symposium

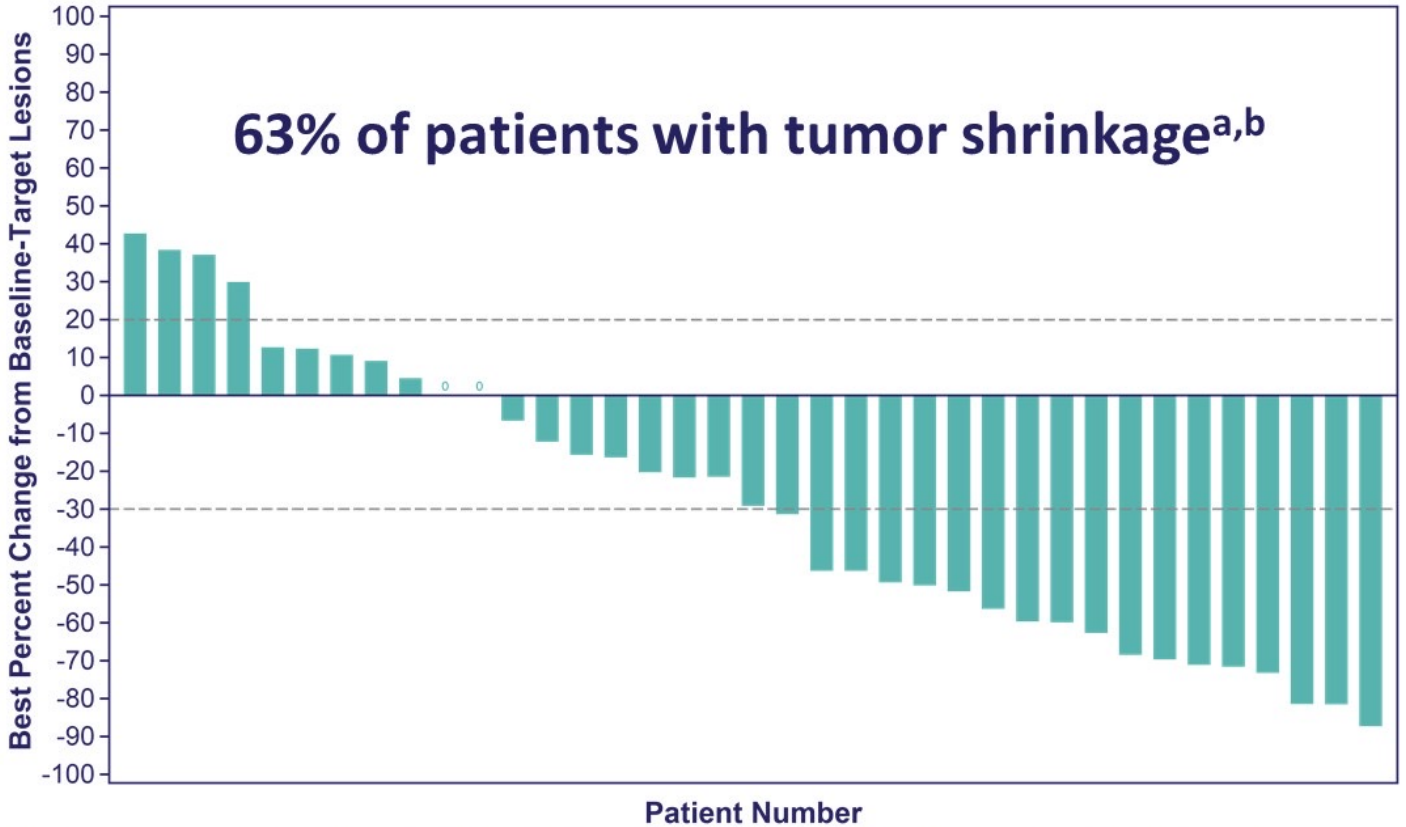
Courtesy of Terence Friedlander, MD

Grivas et al Journal of Clinical Oncology 2022 40:6_suppl, 434-434

Overall Response and Best % Change From Baseline in Tumor Size

TROPHY U-01

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



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

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

Abstract # 434

Courtesy of Terence Friedlander, MD

How would you generally sequence the following agents for a patient with metastatic UBC who is eligible to receive both?

 Dr Friedlander	Enfortumab vedotin → sacituzumab govitecan
 Dr Grivas	Enfortumab vedotin → sacituzumab govitecan
 Dr Gupta	Enfortumab vedotin → sacituzumab govitecan
 Dr Petrylak	Enfortumab vedotin → sacituzumab govitecan
 Dr Plimack	Enfortumab vedotin → sacituzumab govitecan
 Dr Sonpavde	Enfortumab vedotin → sacituzumab govitecan

RTP RESEARCH TO PRACTICE

What would be your next line of therapy for a 65-year-old patient with metastatic UBC and a PS of 0 who experiences disease progression on your preferred first-line treatment?

 Dr Friedlander	Enfortumab vedotin +/- pembrolizumab
 Dr Grivas	Enfortumab vedotin
 Dr Gupta	Enfortumab vedotin
 Dr Petrylak	Enfortumab vedotin/pembrolizumab
 Dr Plimack	Enfortumab vedotin
 Dr Sonpavde	Enfortumab vedotin/pembrolizumab

RTP RESEARCH TO PRACTICE

What would be your most likely next line of therapy for an 80-year-old patient with metastatic UBC who has received no prior systemic therapy, is not a candidate for cisplatin or carboplatin and experienced disease progression on your preferred first-line treatment?

 Dr Friedlander	Enfortumab vedotin
 Dr Grivas	Enfortumab vedotin
 Dr Gupta	Enfortumab vedotin
 Dr Petrylak	Carboplatin/gemcitabine
 Dr Plimack	Gemcitabine
 Dr Sonpavde	Enfortumab vedotin

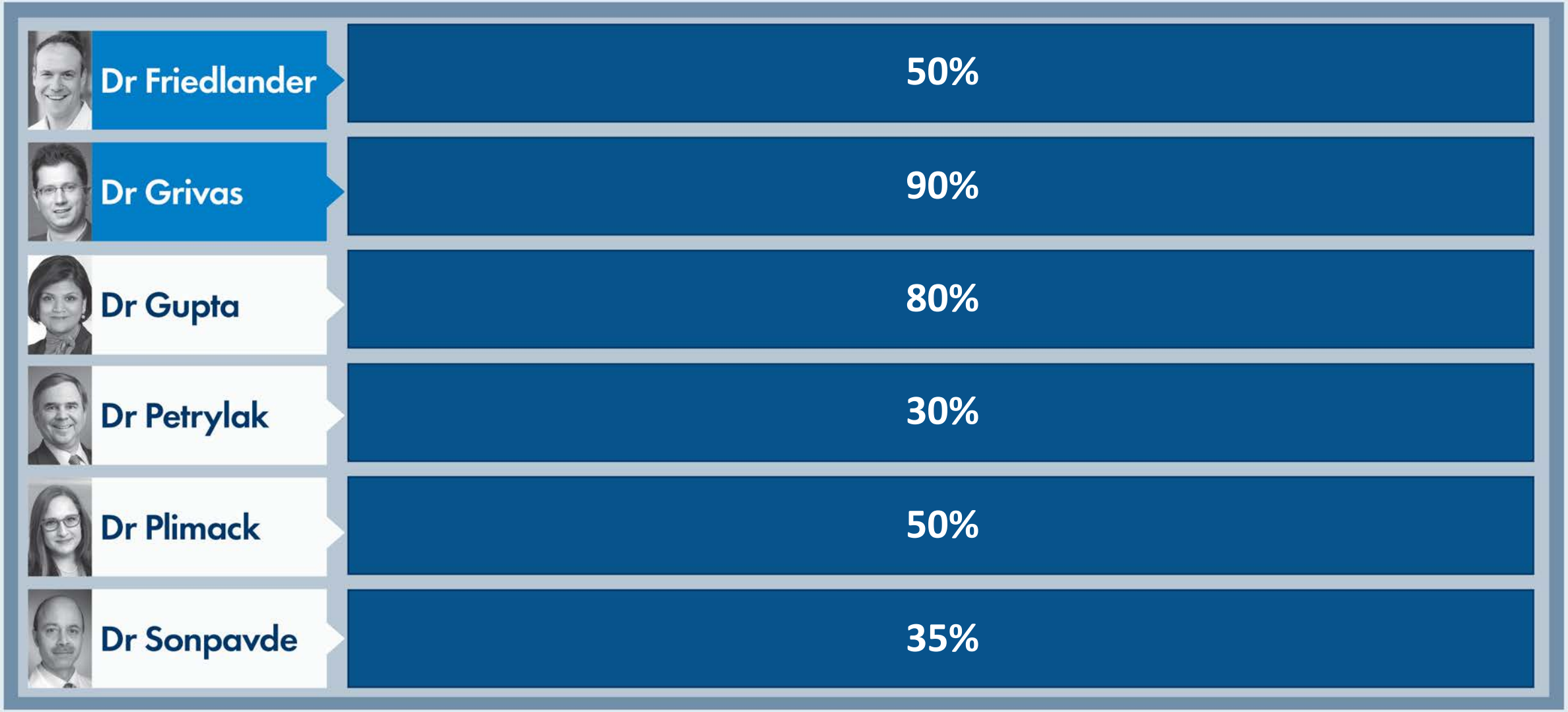
RTP RESEARCH TO PRACTICE

A 65-year-old patient receives neoadjuvant cisplatin/gemcitabine followed by cystectomy and then adjuvant nivolumab for FGFR wild-type UBC but develops disease recurrence in the liver 9 months after starting nivolumab. Regulatory and reimbursement issues aside, what would you likely recommend?

 Dr Friedlander	Pembrolizumab +/- enfortumab vedotin
 Dr Grivas	Enfortumab vedotin
 Dr Gupta	Enfortumab vedotin
 Dr Petrylak	Enfortumab vedotin
 Dr Plimack	Enfortumab vedotin
 Dr Sonpavde	Pembrolizumab/enfortumab vedotin

RTP RESEARCH TO PRACTICE

Based on available data and your clinical experience, approximately what proportion of patients who are receiving enfortumab vedotin for metastatic UBC will require a dose reduction due to toxicity?

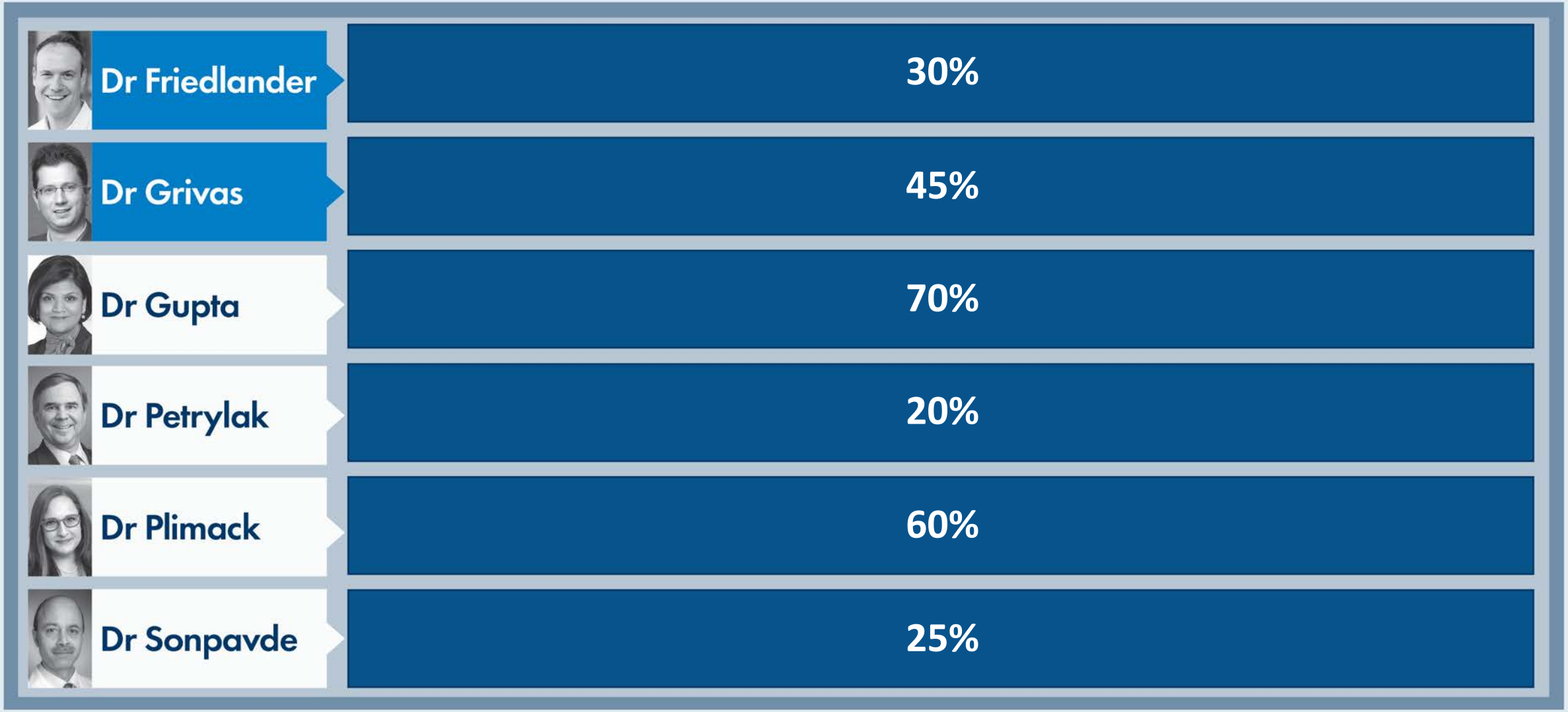


What would be your next line of therapy for an 80-year-old patient with metastatic UBC who is not a candidate for cisplatin and experienced disease progression on your preferred first-line treatment?

 Dr Friedlander	Sacituzumab govitecan
 Dr Grivas	Carboplatin/gemcitabine
 Dr Gupta	Enfortumab vedotin
 Dr Petrylak	Enfortumab vedotin/pembrolizumab
 Dr Plimack	Gemcitabine
 Dr Sonpavde	Carboplatin/gemcitabine

RTP RESEARCH TO PRACTICE

Based on available data and your clinical experience, approximately what proportion of patients who are receiving sacituzumab govitecan for metastatic UBC will require a dose reduction due to toxicity?



RTP
RESEARCH
TO PRACTICE

In general, when you administer sacituzumab govitecan for metastatic UBC, do you preemptively prescribe growth factors for the prevention of treatment-related neutropenia?

 Dr Friedlander	Yes
 Dr Grivas	Yes
 Dr Gupta	Yes
 Dr Petrylak	Yes
 Dr Plimack	No
 Dr Sonpavde	Yes

RTP RESEARCH TO PRACTICE

A patient who is experiencing a good response to sacituzumab govitecan for metastatic UBC is found to have an absolute neutrophil count of 900/mm^3 without fever. What would be your treatment approach?

 Dr Friedlander	Hold sacituzumab govitecan (SG) until counts return to normal, and restart at the same dose
 Dr Grivas	Hold SG until counts return to normal and start G-CSF if not already started; if already on G-CSF, SG at reduced dose
 Dr Gupta	Hold SG until counts return to normal, and restart at a reduced dose
 Dr Petrylak	Continue SG at a reduced dose
 Dr Plimack	Hold SG until counts return to normal, and restart at a reduced dose
 Dr Sonpavde	Hold SG until counts return to normal, and restart at the same dose

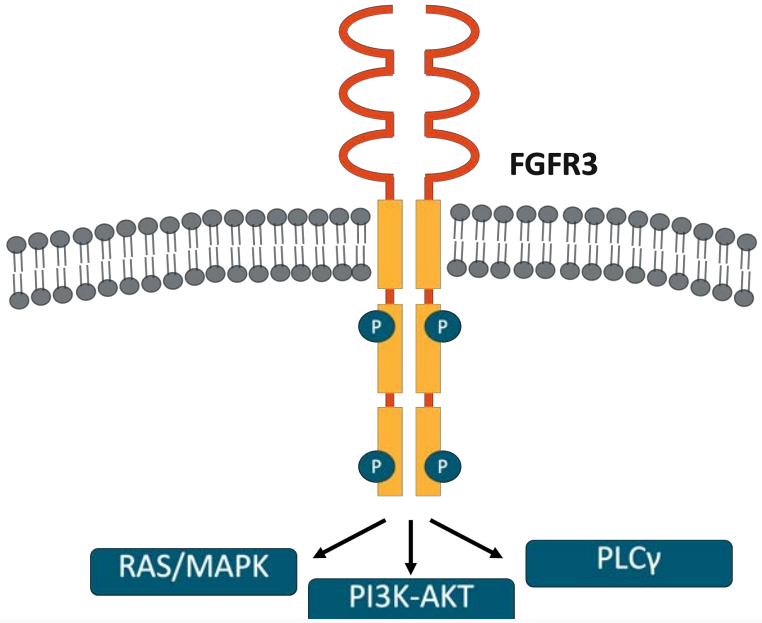
RTP RESEARCH TO PRACTICE

In general, when you administer sacituzumab govitecan for metastatic UBC, do you preemptively initiate medication for …?

	Nausea and vomiting	Diarrhea
 Dr Friedlander	Yes	Yes
 Dr Grivas	Yes	No
 Dr Gupta	Yes	Yes
 Dr Petrylak	Yes	Yes
 Dr Plimack	Yes	No
 Dr Sonpavde	Yes	No

What else is on the horizon?

- FGFR3 mutations present in ~20% of mUBC
- Erdafitinib is an approved pan-FGFR inhibitor: Phase III THOR study
- Is there synergy with PD-1 immunotherapy?



	Erda n=136	Chemo n=130
OS, median (95% CI), mo	12.1	7.8
Hazard ratio (95% CI)	0.64 (0.47-0.88), p=0.0050	
PFS, median (95% CI), mo	5.6	2.7
Hazard ratio (95% CI)	0.58 (0.44-0.78), p=0.0002	
ORR, %	46	12
Relative risk (95% CI)	3.94 (2.37-6.57), p<0.001	

1. The Cancer Genome Atlas. Nature. 2014:507:315. 2. Helsten. CCR. 2016;22:259.
3. Li. Curr Urol Rep. 2016;17:12. 4. Pandith. Urol Oncol. 2013;31:398.

Courtesy of Terence Friedlander, MD

How would you generally sequence the following agents for a patient with metastatic UBC who is eligible to receive all 3?

 Dr Friedlander	Enfortumab vedotin → erdafitinib → sacituzumab govitecan
 Dr Grivas	Erdafitinib → enfortumab vedotin → sacituzumab govitecan
 Dr Gupta	Enfortumab vedotin → erdafitinib → sacituzumab govitecan
 Dr Petrylak	Enfortumab vedotin → sacituzumab govitecan → erdafitinib
 Dr Plimack	Enfortumab vedotin → erdafitinib → sacituzumab govitecan
 Dr Sonpavde	Erdafitinib → enfortumab vedotin → sacituzumab govitecan

RTP RESEARCH TO PRACTICE

A 65-year-old patient receives neoadjuvant chemotherapy followed by cystectomy and then adjuvant nivolumab for UBC with an FGFR mutation but develops disease recurrence in the liver 9 months after starting nivolumab. Regulatory and reimbursement issues aside, what would you likely recommend?

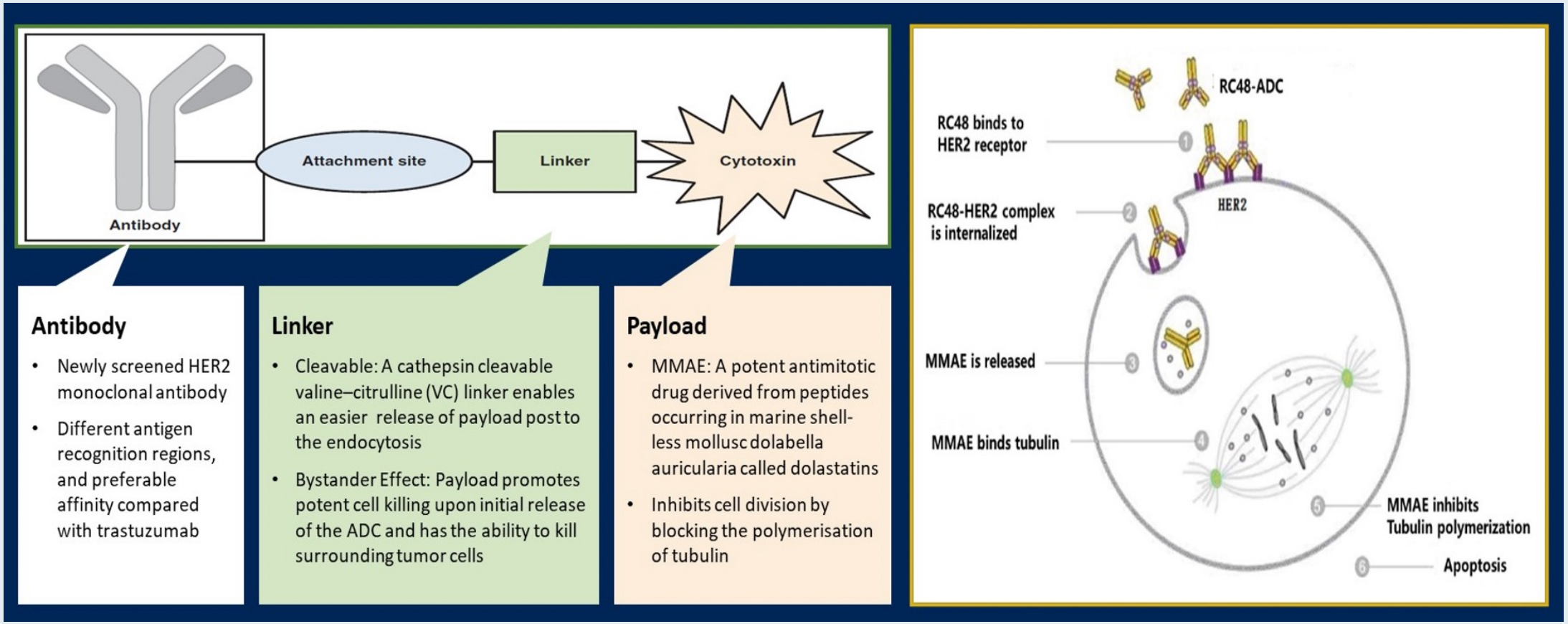
 Dr Friedlander	Erdafitinib
 Dr Grivas	Erdafitinib
 Dr Gupta	Enfortumab vedotin
 Dr Petrylak	Enfortumab vedotin
 Dr Plimack	Enfortumab vedotin
 Dr Sonpavde	Erdafitinib

Based on available data and your clinical experience, approximately what proportion of patients who are receiving erdafitinib for metastatic UBC will require a dose reduction due to toxicity?

 Dr Friedlander	75%
 Dr Grivas	90%
 Dr Gupta	75% to 80%
 Dr Petrylak	60%
 Dr Plimack	80%
 Dr Sonpavde	50%

RTP RESEARCH TO PRACTICE

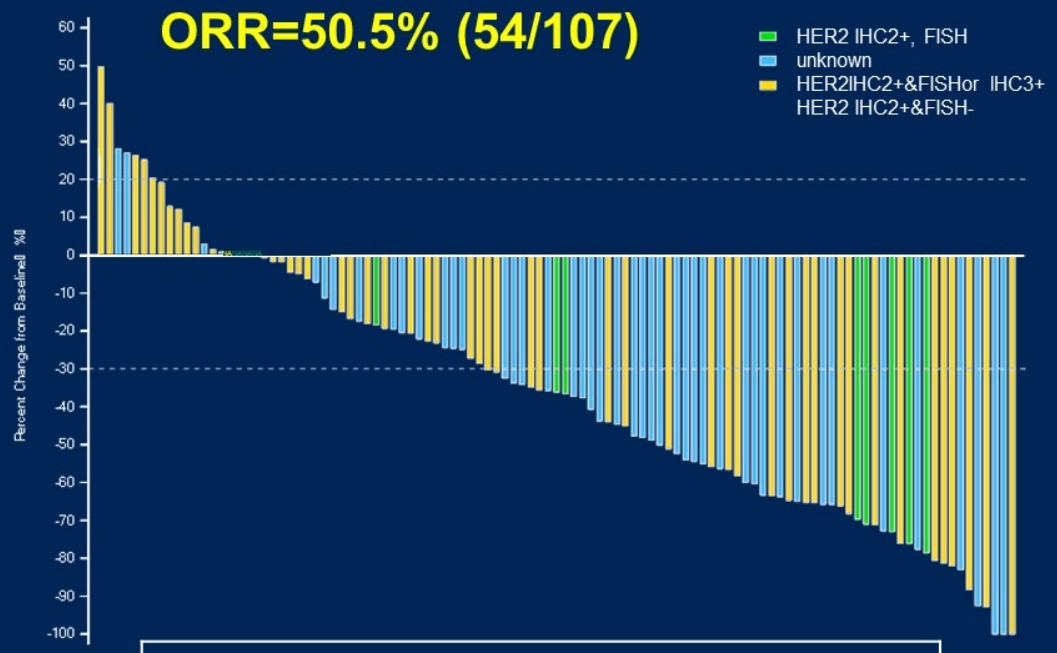
Disitamab Vedotin (RC48-ADC) Structure and Mechanisms of Action



Sheng X et al. ASCO 2022;Abstract 4520.

RC48 active in HER2 2-3+ mUC (#4520 – Sheng et al)

Target Lesion Change from Baseline



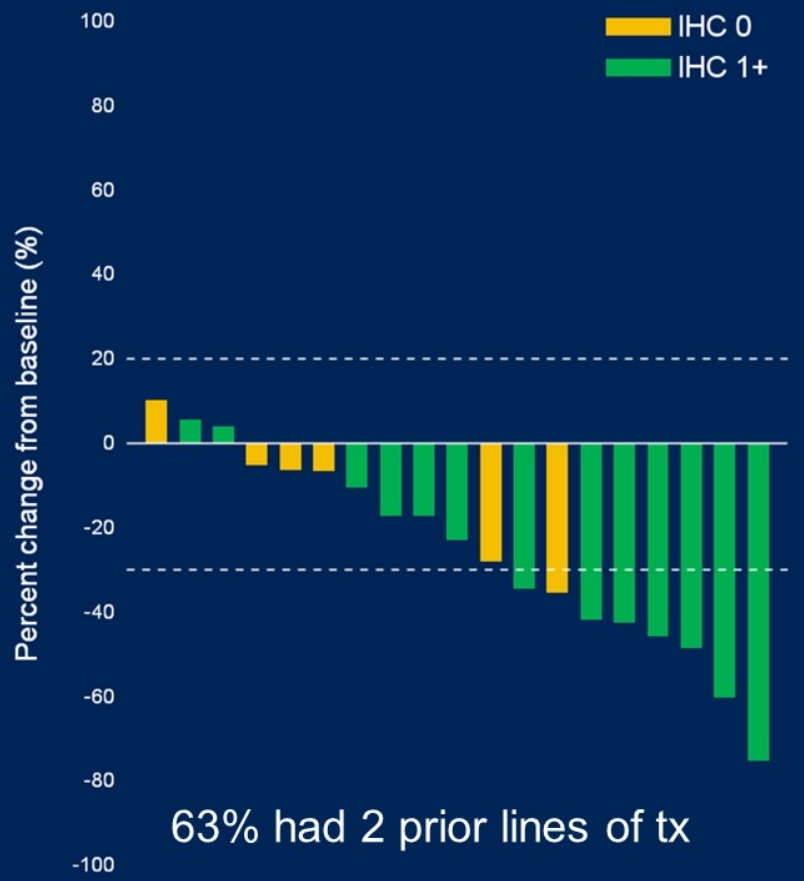
Number of prior systemic therapies (n, %)	
Only one line	38 (35.5%)
≥two lines	69 (64.5%)

Subgroup Analysis for cORR

Subgroups	cORR (%, 95% CI)
HER2 status	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
Metastasis site	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
Prior therapies	
Post PD1/PDL1 Treatments (n=27)	55.6% (35.3%, 74.5%)
Post 1 line of Chemotherapy (n=38)	50.0% (33.4%, 66.6%)
Post ≥2 Lines of Chemotherapy (n=69)	50.7% (38.4%, 63.0%)

Courtesy of Petros Grivas, MD, PhD

RC48 active in HER2 1+ mUC (#4519 – Xu et al)



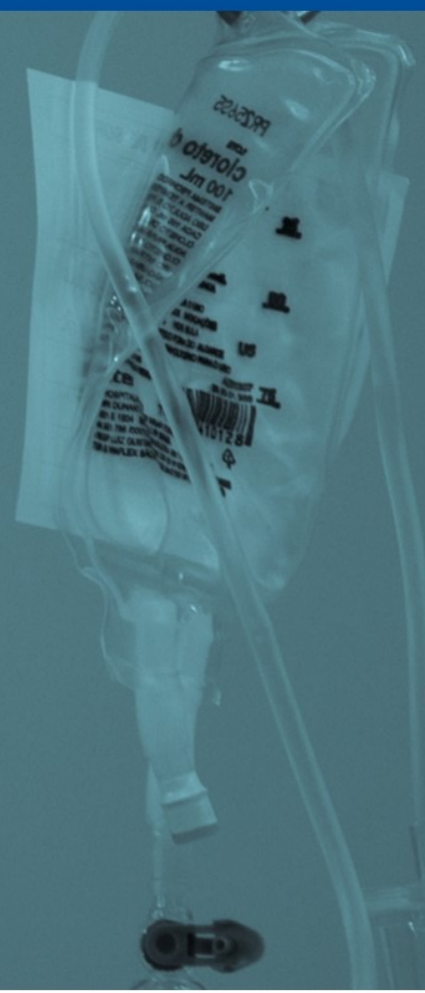
Confirmed ORR	
n (%)	5 (26.3%)
95%CI	9.1%, 51.2%

Subgroups	cORR (%, 95% CI)
IHC 0 (n=6)	0
IHC 1+ (n=13)	38.5 (13.9, 68.4)

Courtesy of Petros Grivas, MD, PhD

RC48 AEs somewhat distinct from other ADCs

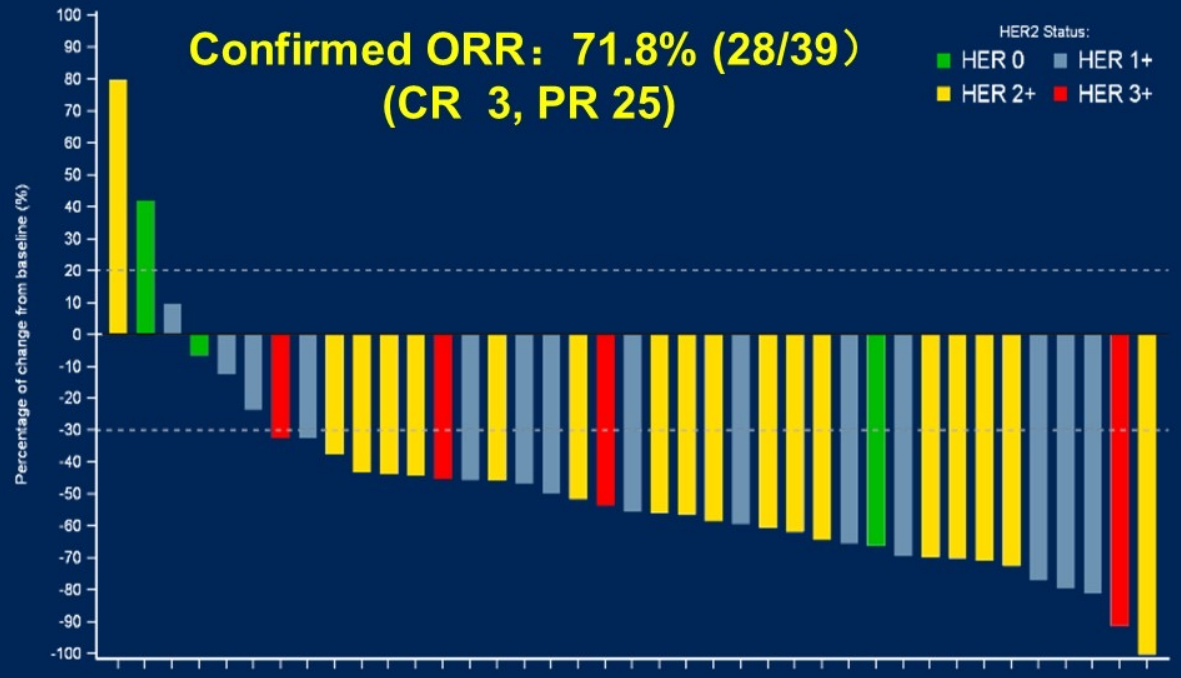
Adverse Event	RC48	Enfortumab Vedotin	Trastuzumab Deruxtecan
Neuropathy	+	+	-
↑ AST	+	-/+	-
↓ neutrophils	+	-/+	+
Rash	-/+	+	-
↑ glucose	+	+	-
Diarrhea	-	-	+
Pneumonitis	-	-	+

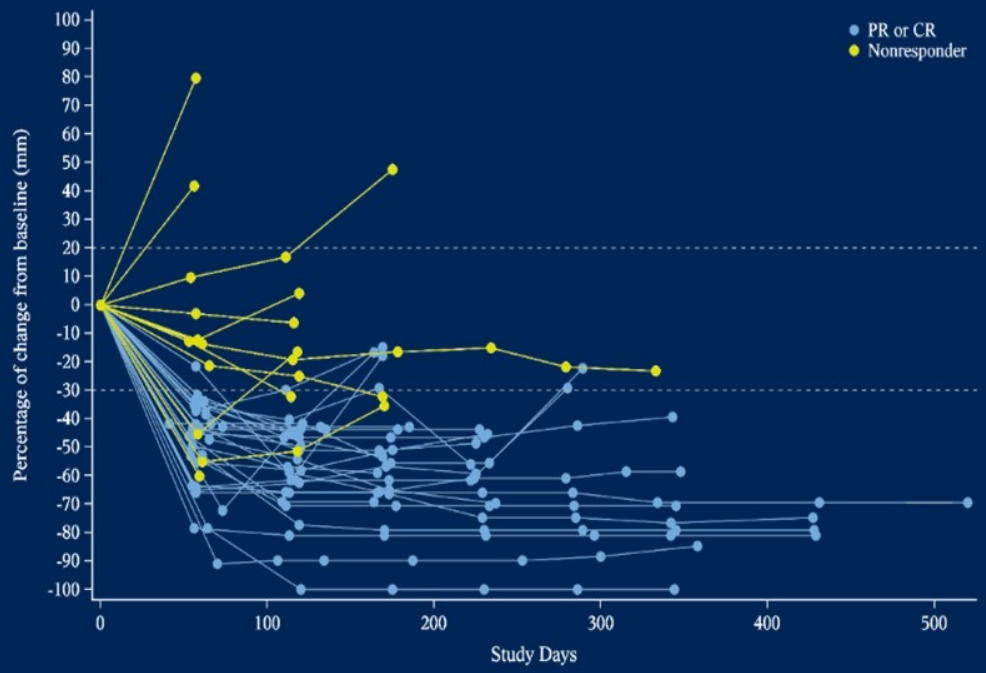


Courtesy of Petros Grivas, MD, PhD

RC48 + Toripalimab (#4520 – Sheng et al)

Confirmed ORR：71.8% (28/39）
(CR 3, PR 25)





Prior systemic treatment (n,%)	
0 Line	25 (60.98%)
≥1 Lines	16 (39.02%)

Courtesy of Petros Grivas, MD, PhD

Is there something special about MMAE?

Regimen	Payload	N	Population	HER2	ORR
Enfortumab vedotin + Pembrolizumab	MMAE (tubulin)	43	Cis-ineligible, tx naive	All	73%
Disitamab vedotin + Toripalimab	MMAE (tubulin)	39	60% tx naive	All	72%
Trastuzumab deruxtecan + Nivolumab	Dxd (Topo I)	26	Progressed despite prior platinum	2+ or 3+	36%
Sacitizumab govitecan + Pembrolizumab	SN38 (Topo I)	41	Progressed despite prior platinum	All	34%

Friedlander, ASCO 2021; Sheng, ASCO 2022; Galsky GU ASCO 2022; Grivas GU ASCO 2022

Courtesy of Petros Grivas, MD, PhD

Regulatory and reimbursement issues aside, which agent or regimen would you be most likely to use for a patient with HER2-positive metastatic UBC?

 Dr Friedlander	Trastuzumab/chemotherapy, disitamab vedotin, trastuzumab deruxtecan
 Dr Grivas	Disitamab vedotin
 Dr Gupta	Trastuzumab deruxtecan or disitamab vedotin
 Dr Petrylak	Trastuzumab
 Dr Plimack	Disitamab vedotin
 Dr Sonpavde	Disitamab vedotin

RTP RESEARCH TO PRACTICE

Have you offered or would you offer HER2-targeted therapy to your patients with HER2-positive metastatic UBC outside of a protocol setting?

 Dr Friedlander	I have – trastuzumab deruxtecan
 Dr Grivas	I have not but would for the right patient
 Dr Gupta	I have not and would not
 Dr Petrylak	I have – trastuzumab
 Dr Plimack	I have not and would not
 Dr Sonpavde	I have not and would not

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer targeted treatment to a patient with HER2-positive metastatic UBC?

 Dr Friedlander	Third line
 Dr Grivas	Beyond third line
 Dr Gupta	Beyond third line
 Dr Petrylak	Third line
 Dr Plimack	Beyond third line
 Dr Sonpavde	Second line

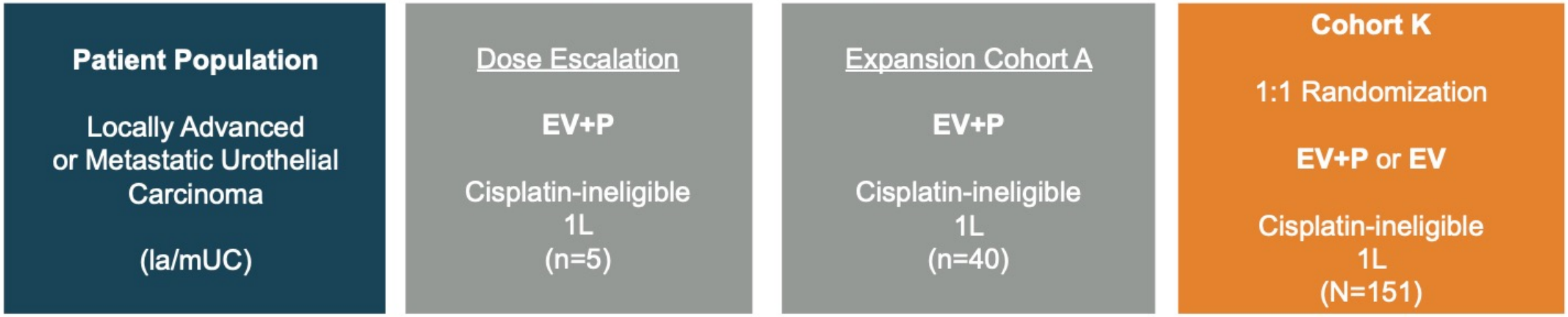
RTP RESEARCH TO PRACTICE

APPENDIX

EV-103 Cohort K: First-Line Enfortumab Vedotin + Pembrolizumab in Cisplatin-Ineligible mUC

EV-103 Cohort K

Part of an open-label, multiple cohort, phase 1b/2 study in patients with urothelial carcinoma



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

Courtesy of Terence Friedlander, MD

Friedlander et al. ASCO 2023. Journal of Clinical Oncology 2023 41:16_suppl, 4568-4568

EV-103 Cohort K: First-Line Enfortumab Vedotin + Pembrolizumab in Cisplatin-Ineligible mUC

Overall Response Rate by BICR

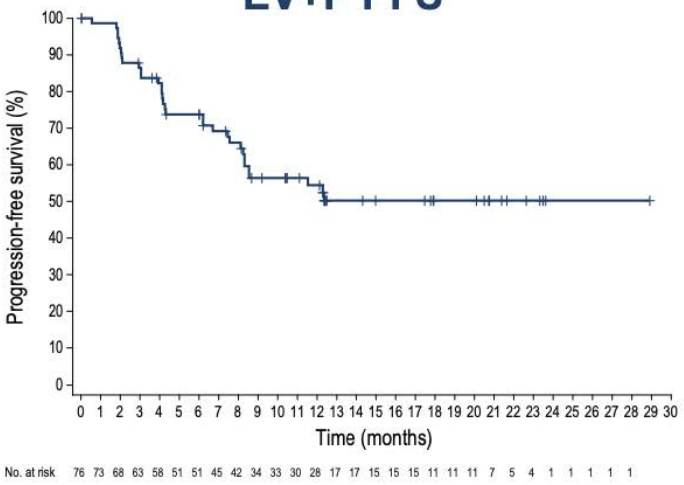
EV+P: 64.5% confirmed ORR with rapid response

	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)

Progression-Free Survival per BICR and Overall Survival

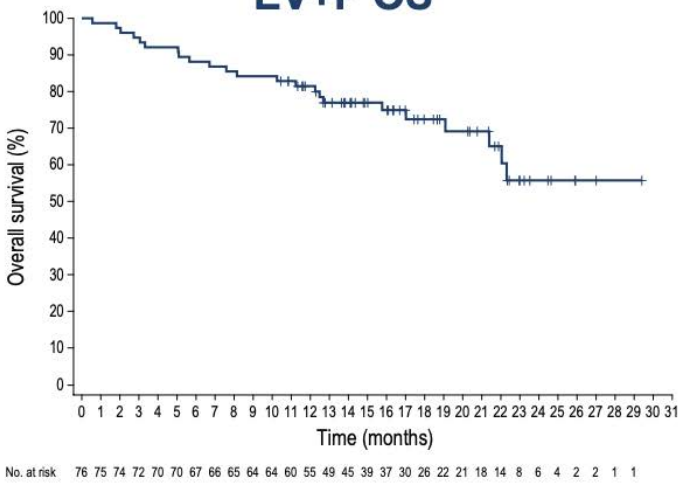
Median PFS and OS for EV+P were not reached

EV+P PFS



	EV+P (N=76)	EV Mono (N=73)
PFS events, n	33	37
mPFS (95% CI), mos	– (8.31, –)	8.2 (6.05, 15.28)
PFS at 12 mos, %	54.5	40.3

EV+P OS



	EV+P (N=76)	EV Mono (N=73)
OS events, n	23	30
mOS (95% CI), mos	– (21.39, –)	21.7 (15.47, –)
OS at 12 mos, %	81.5	69.7
Median follow-up time, mos	17.6	18.2

No new safety signals

Courtesy of Terence Friedlander, MD

Friedlander et al. ASCO 2023. Journal of Clinical Oncology 2023 41:16_suppl, 4568-4568

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

TROPHY U-01

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

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

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

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

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

Continue treatment in the absence of unacceptable toxicity or disease progression

Continue until a maximum of 6 cycles has been completed,[d] disease progression, lack of clinical benefit, toxicity, or withdrawal of consent → **Maintenance avelumab (800 mg every 2 weeks) with SG (Days 1 and 8 every 21 days) for those without disease progression**

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

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

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

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

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

1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

Abstract # 434.

ASCO Genitourinary Cancers Symposium

Courtesy of Terence Friedlander, MD

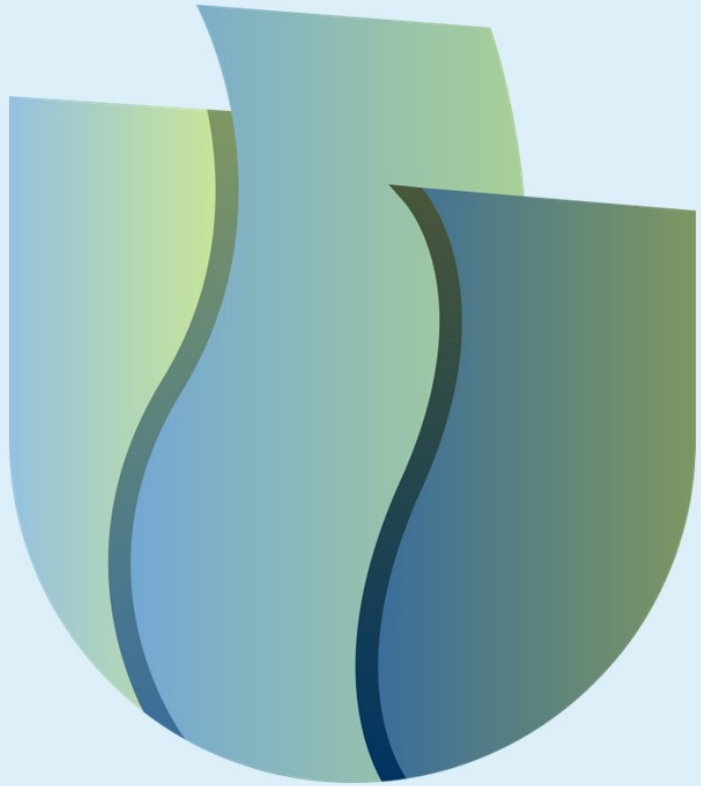
Grivas et al Journal of Clinical Oncology 2022 40:6_suppl, 434-434

TROPHY U-01 Cohort 3

- Modest increase in ORR with addition of pembrolizumab
- Some long-term responders
  - Would this be seen with pembrolizumab monotherapy?
- More data needed to better understand interaction of SG and immunotherapy
- TROPiCS 04 Phase III monotherapy study of SG vs chemotherapy underway

Courtesy of Terence Friedlander, MD

TROPHY-U-01 Cohort 2, a Phase 2 Study of Sacituzumab Govitecan in Platinum-Ineligible Patients With Metastatic Urothelial Cancer who Progressed After Prior Checkpoint Inhibitor Therapy

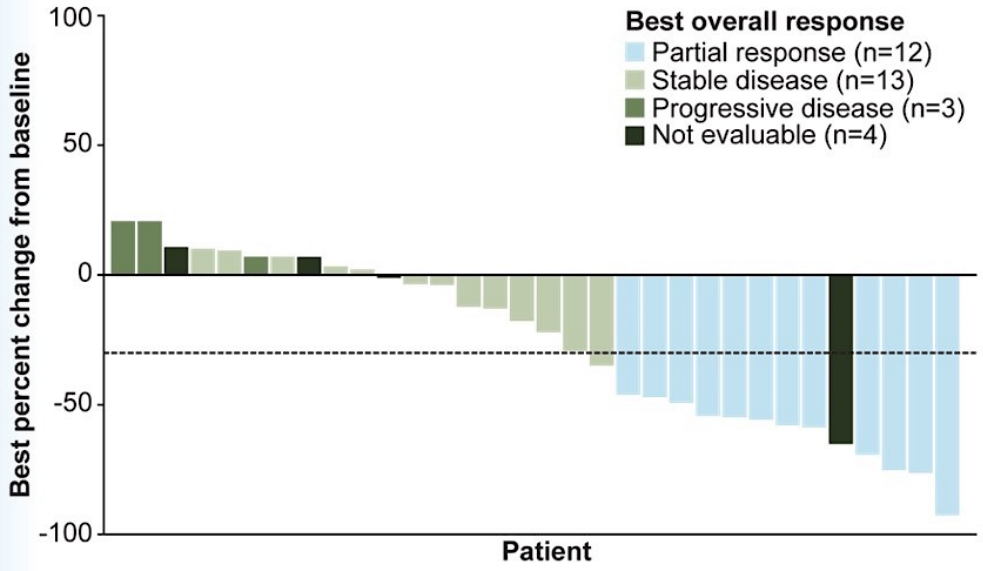


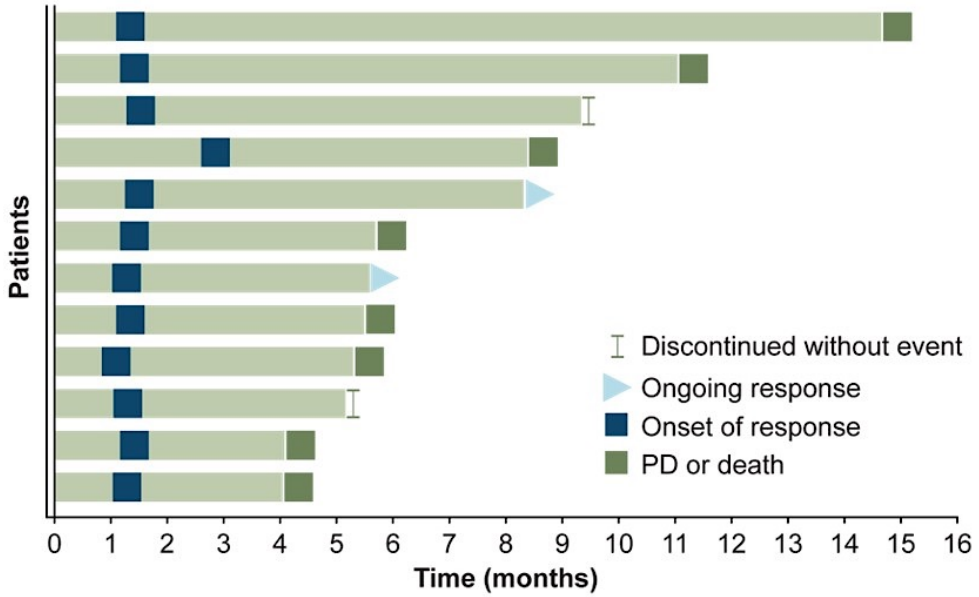
Daniel P. Petrylak,[1] Scott T. Tagawa,[2] Rohit K. Jain,[3] Manojkumar Bupathi,[4] Arjun Balar,[5] Arash Rezazadeh Kalebasty,[6] Saby George,[7] Phillip Palmbos,[8] Luke Nordquist,[9] Nancy Davis,[10] Chethan Ramamurthy,[11] Cora N. Sternberg,[2] Yohann Loriot,[12] Neeraj Agarwal,[13] Chandler Park,[6] Julia Tonelli,[14] Morganna Vance,[14] Huafeng Zhou,[14] and Petros Grivas[15]

[1]Yale School of Medicine, New Haven, CT, USA; [2]Weill Cornell Medical College of Cornell University, New York, NY, USA; [3]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [4]Rocky Mountain Cancer Centers, Littleton, CO, USA; [5]New York University Langone Medical Center, New York, NY, USA; [6]Norton Cancer Institute, Louisville, KY, USA; [7]Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA; [8]University of Michigan, Ann Arbor, MI, USA; [9]Urology Cancer Center, Omaha, NE, USA; [10]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [11]University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; [12]Institut de Cancérologie Gustave Roussy, Université Paris-Saclay, Villejuif, France; [13]Huntsman Cancer Institute, Salt Lake City, UT, USA; [14]Gilead Sciences, Inc, Foster City, CA, USA; and [15]University of Washington, Fred Hutchinson Cancer Center, Seattle, WA, USA

Poster # 520
ClinicalTrials.gov registration number: NCT03547973.

TROPHY U-01 Cohort 2: Best Change in Target Lesions and Response Assessment from Start of Treatment to Disease Progression



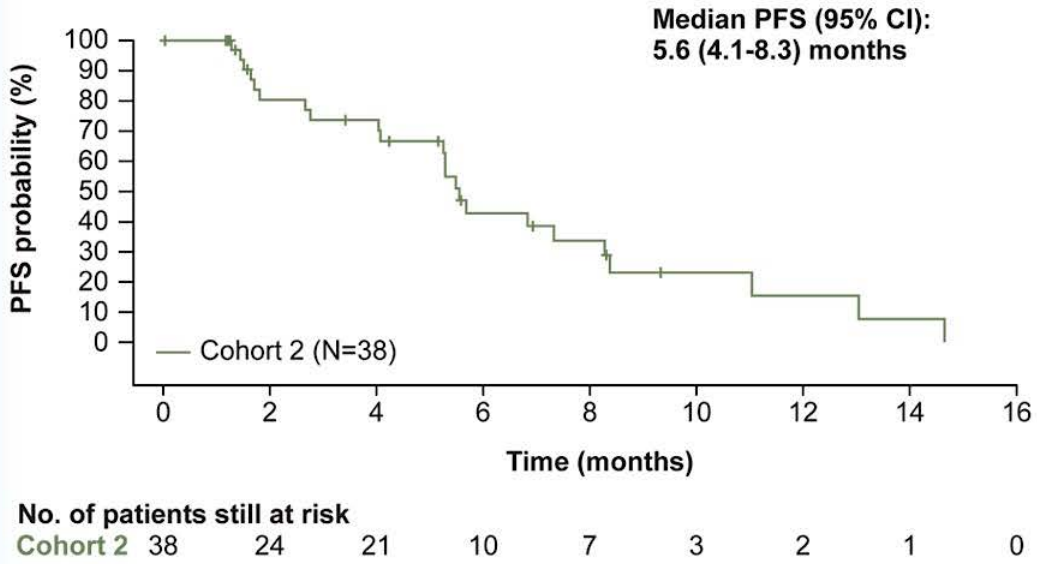


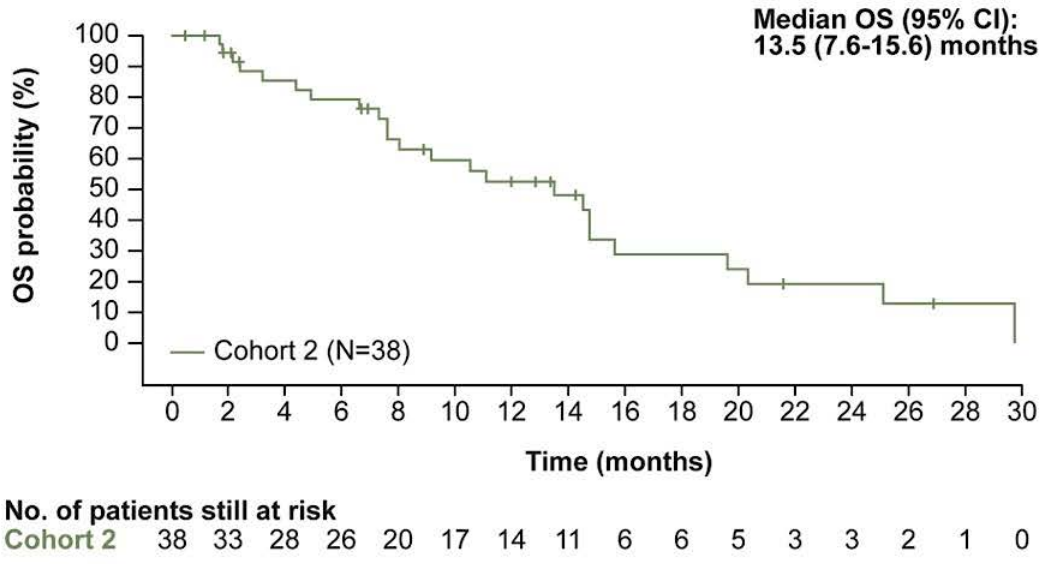
- 69% of assessed patients (22/32) experienced target lesion reduction
- 2 patients had an ongoing response at data cutoff

[a]Patients with missing percent change from baseline are not reported.
PD, progressive disease.

Petrylak D et al. Genitourinary Cancers Symposium 2023;Abstract 520.

TROPHY U-01 Cohort 2: Progression-Free Survival and Overall Survival





- Median follow-up was 9.3 months
- Median PFS was 5.6 months (95% CI, 4.1-8.3)
- Median OS was13.5 months (95% CI, 7.6-15.6)

OS, overall survival; PFS, progression-free survival.

Petrylak D et al. Genitourinary Cancers Symposium 2023;Abstract 520.

TROPHY U-01 Cohort 2: Updated Safety Outcomes

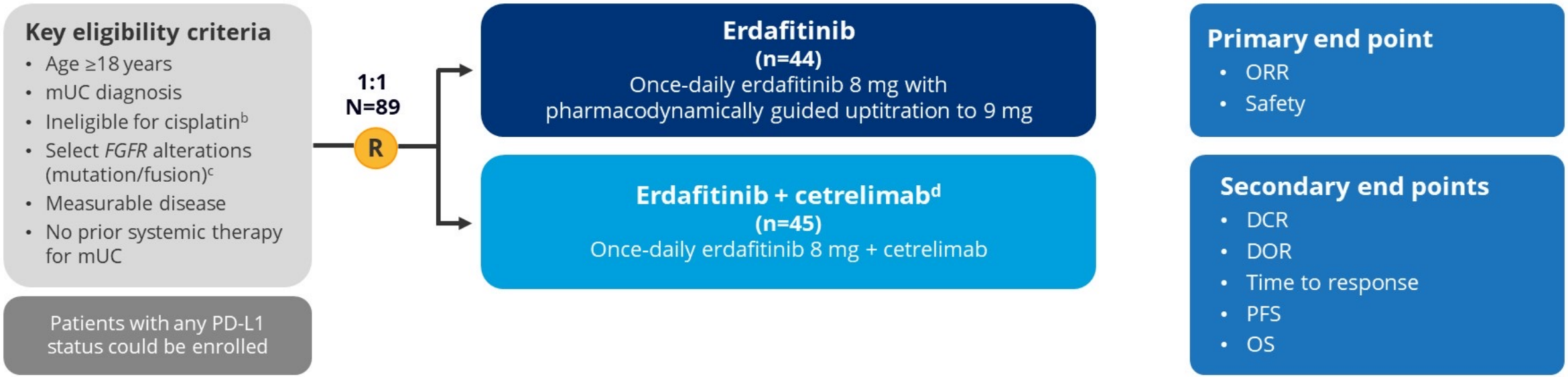
TRAEs Occurring in >20% of Patients, n (%)	Cohort 2 (N=38)	
	All Grade	Grade ≥3
Diarrhea	24 (63)	6 (16)
Alopecia	19 (50)	0
Nausea	18 (47)	0
Neutropenia	17 (45)	13 (34)
Fatigue	16 (42)	7 (18)
Anemia	14 (37)	8 (21)
Leukopenia	13 (34)	7 (18)
Decreased appetite	10 (26)	0

- 26 (68%) patients had grade ≥3 TRAEs
  - The most common were neutropenia (34%), anemia (21%), leukopenia (18%), fatigue (18%), diarrhea (16%)
- 3 (8%) patients had treatment-related febrile neutropenia (2 with grade 3; 1 with grade 4)
- 14 (37%) patients had SG dose reduction due to TRAEs
- 7 (18%) patients discontinued treatment due to TRAEs
- No treatment-related death occurred
- G-CSF was received by 7 (18%) patients for primary prophylaxis and 10 (26%) patients for secondary prophylaxis

G-CSF, granulocyte colony-stimulating factor; SG, sacituzumab govitecan; TRAE, treatment-related adverse event.

Petrylak D et al. Genitourinary Cancers Symposium 2023;Abstract 520.

NORSE Phase 2 Study Design[a]

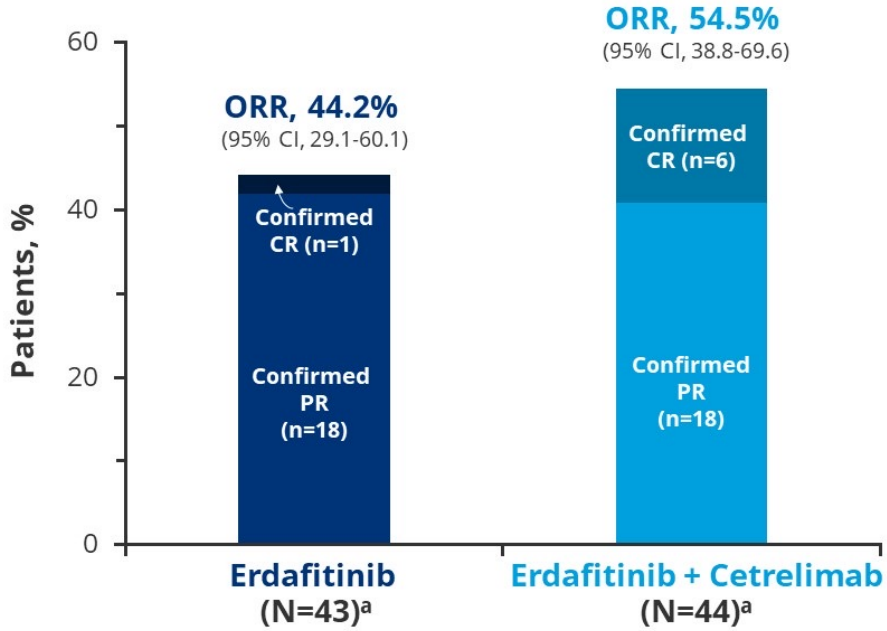


- Molecular eligibility was determined by central or local testing; a total of 1430 patients underwent central molecular screening[c]
- **No formal statistical comparisons** between arms were prespecified

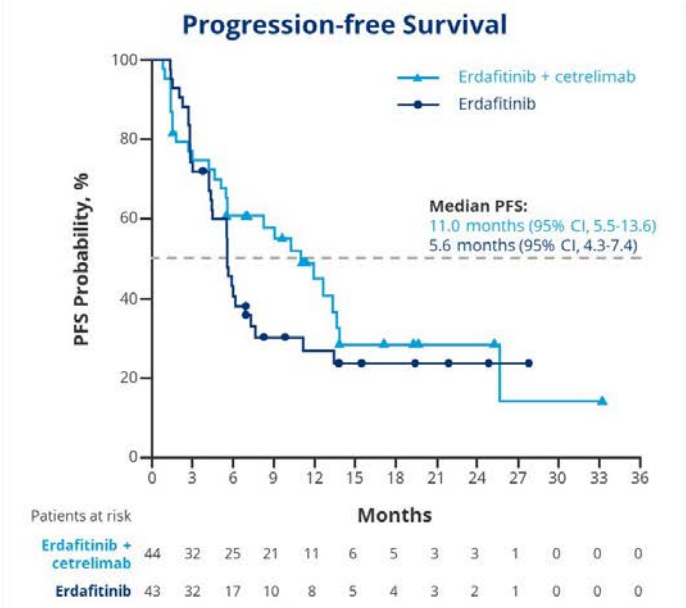
Courtesy of Terence Friedlander, MD

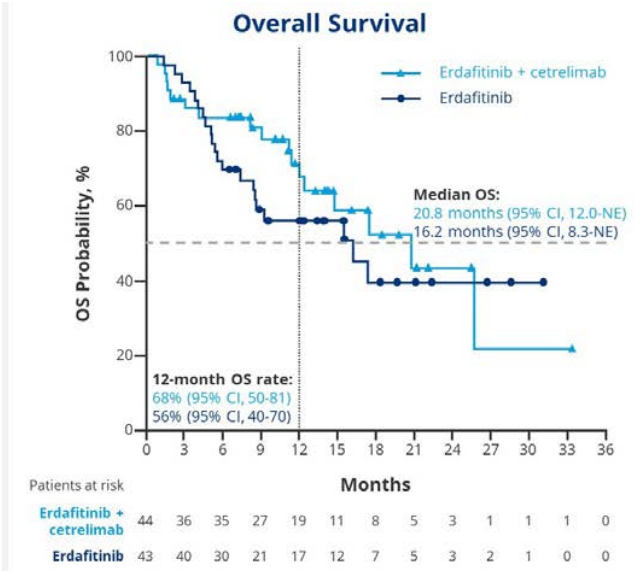
NORSE Trial: Erdafitinib +/- Pembrolizumab

- Increase in ORR
- Better PFS/OS
- Is this additive or synergistic?
- No new safety signals



Responses are investigator assessed.





Courtesy of Terence Friedlander, MD

Siefker-Radke et al 2023 ASCO Annual Meeting J Clin Oncol 41, 2023 (suppl 16; abstr 4504)

Phase 3 THOR: Results of Erdafitinib vs Chemo in Advanced or Metastatic Urothelial Cancer With Fibroblast Growth Factor Receptor Alterations

THOR is a phase 3, randomized, open-label ongoing study of erdafitinib vs chemotherapy (vinflunine or docetaxel) or pembrolizumab in patients with metastatic or unresectable UC and selected FGFR alterations who have progressed on or after 1 prior line of therapy

- Locally advanced or metastatic UC
- Prior systemic therapy (tx) that included anti-PD-(L)1 agent, and ≤ 2 prior lines of tx
- Prespecified *FGFR2/3* alterations (mutations and fusions)
- ECOG PS 0-2

Prior anti-PD-(L)1 therapy
(N = 266)

R
1:1

Erdafitinib
8 mg/day

Chemotherapy
Docetaxel 75 mg/m^2 Q3W, or vinflunine 320 mg/m^2 Q3W

Primary Endpoint:

- OS

Secondary Endpoints:

- PFS
- ORR and DOR
- QOL
- Safety and pharmacokinetics

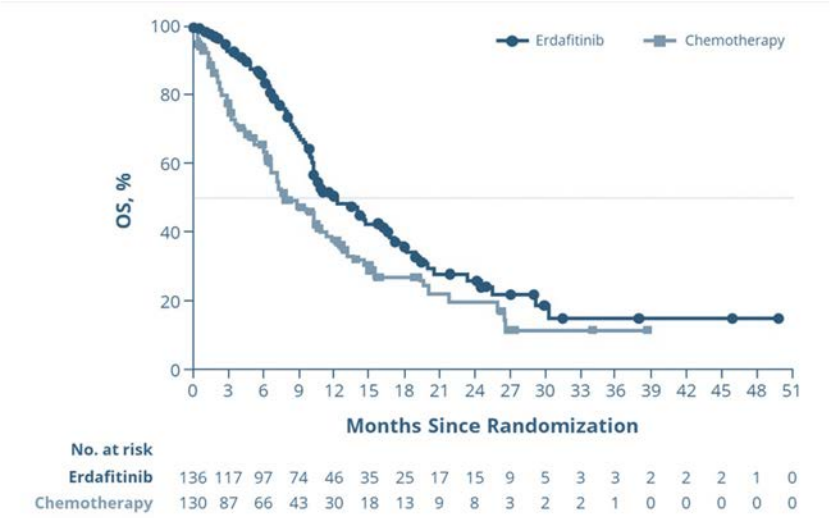
DOR, duration of response; IV, intravenous; Q3W, every 3 weeks.
Loriot Y, et al. J Clin Oncol 41, 2023 (suppl 17; abstr LBA4619)

Courtesy of Petros Grivas, MD, PhD

Phase 3 THOR: Results of Erdafitinib vs Chemo in Advanced or Metastatic Urothelial Cancer With Fibroblast Growth Factor Receptor Alterations

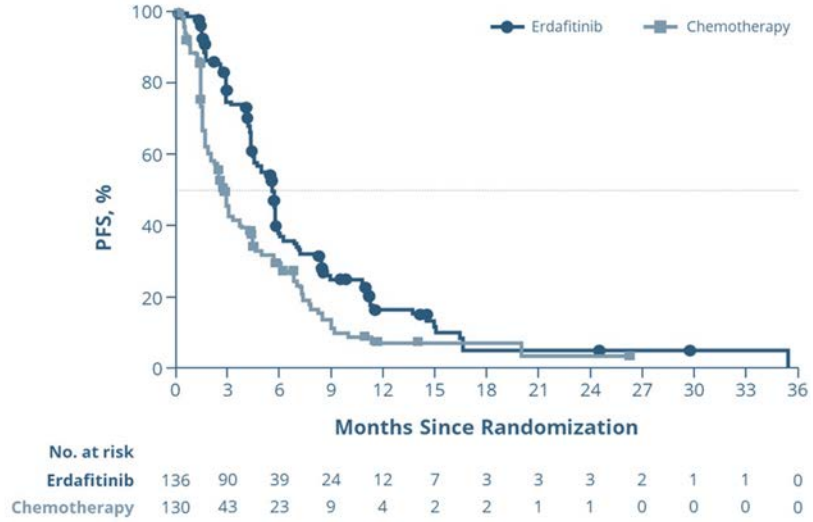
Prior treatment with PD-(L)1, Erdafitinib significantly improved OS, PFS, and ORR vs investigator's choice of chemo.

OS



Erdafitinib reduced the risk of death by 36% vs chemotherapy
HR: 0.64 (95% CI: 0.47, 0.88; *P* = .005)

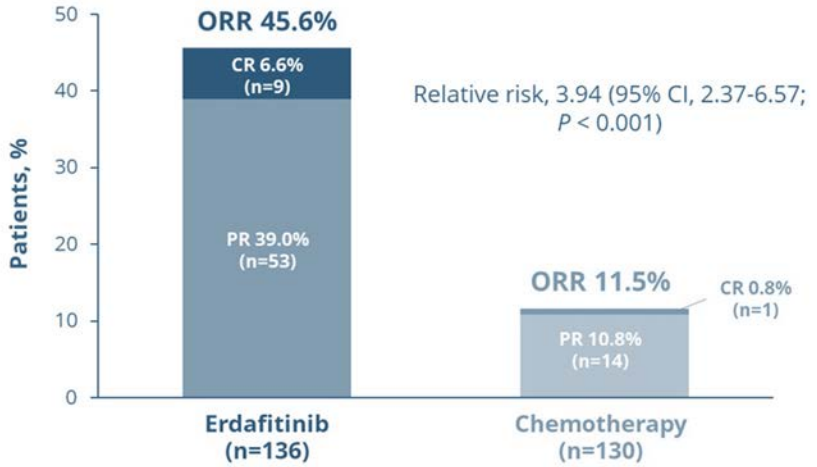
PFS



Median PFS was 5.6 versus 2.7

Erdafitinib reduced the risk of progression or death by 42% versus chemotherapy
HR: 0.58 (95% CI: 0.44, 0.78; *P* = .0002)

ORR



Overall survival (OS), Progression-free survival (PFS), Objective Response Rate (ORR)
Loriot Y, et al. J Clin Oncol. 2023;41(suppl 17); abstr LBA4619.

Courtesy of Petros Grivas, MD, PhD

Phase 3 THOR: Results of Erdafitinib vs Chemo in Advanced or Metastatic Urothelial Cancer With Fibroblast Growth Factor Receptor Alterations

Erdafitinib toxicity was consistent with known safety profile

Patients with AEs, n (%)	Erdafitinib (n=135)	
	Any grade	Grade 3-4
≥1 treatment-related AE	131 (97.0)	62 (45.9)
Hyperphosphatemia	106 (78.5)	7 (5.2)
Diarrhea	74 (54.8)	4 (3.0)
Stomatitis	62 (45.9)	11 (8.1)
Dry mouth	52 (38.5)	0
PPE syndrome	41 (30.4)	13 (9.6)
Onycholysis	31 (23.0)	8 (5.9)
Patients who discontinued study treatment, n (%)		
Discontinuation due to treatment-related AEs	11 (8.1%)	

Patients with AEs, n (%)	Chemotherapy (n=112)	
	Any grade	Grade 3-4
≥1 treatment-related AE	97 (86.6)	52 (46.4)
Anemia	31 (27.7)	7 (6.3)
Alopecia	24 (21.4)	0
Nausea	22 (19.6)	2 (1.8)
Neutropenia	21 (18.8)	15 (13.4)
Leukopenia	13 (11.6)	9 (8.0)
Febrile neutropenia	9 (8.0)	10 (8.9)
Patients who discontinued study treatment, n (%)		
Discontinuation due to treatment-related AEs	15 (13.4)	

- 18 patients (13.3%) treatment-related serious AEs
- 1 treatment-related death occurred

- 27 patients (24.1%) treatment-related serious AEs
- 6 treatment-related deaths occurred

Loriot Y, et al. J Clin Oncol. 2023;41(suppl 17); abstr LBA4619.

Courtesy of Petros Grivas, MD, PhD

What I Tell My Patients: Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Part 3 of a 3-Part Complimentary NCPD Webinar Series
in Partnership with the 2023 ONS Congress

Chronic Lymphocytic Leukemia

Thursday, July 6, 2023
5:00 PM – 6:00 PM ET

Faculty

Kristen E Battiato, AGNP-C
Jennifer Woyach, MD

Moderator

Neil Love, MD

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Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

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

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