Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Urothelial Bladder Cancer

Part 3 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Genitourinary Cancers Symposium

Friday, February 17, 2023
6:30 PM – 8:00 PM PT

Faculty

Matthew D Galsky, MD
Arlene Siefker-Radtke, MD
Jonathan E Rosenberg, MD

Moderator

Elisabeth I Heath, MD

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Faculty

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Moderator
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Translational Sciences
Chair, Genitourinary Oncology
Multidisciplinary Team
Professor of Oncology and Medicine
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Director, Prostate Cancer Research
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Commercial Support

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Matthew D Galsky, MD — Disclosures
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Jonathan E Rosenberg, MD — Disclosures
Faculty

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Elisabeth I Heath, MD — Disclosures
Moderator

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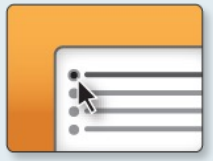
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the pre- and postmeeting surveys.

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

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

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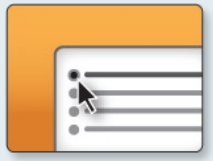
Clinicians Attending via Zoom

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



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

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
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Agenda

Module 1: Integrating Novel Treatment Strategies into the Management of Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Galsky

Module 2: Current and Future Front-Line Treatment for Metastatic UBC (mUBC) — Dr Rosenberg

Module 3: Selection and Sequencing of Therapy for Relapsed/Refractory mUBC — Dr Siefker-Radtke

Module 4: Novel Investigational Agents and Strategies in the Treatment of mUBC — Dr Heath

Georges Azzi, MD
Holy Cross Health
Fort Lauderdale, Florida

Sunil Gandhi, MD
Florida Cancer Specialists
Lecanto, Florida

Spencer H Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Victoria Giffi, MD
Meritus Hematology and Oncology Specialists
Hagerstown, Maryland

Gigi Chen, MD
John Muir Health
Pleasant Hill, California

Ranju Gupta, MD
Lehigh Valley Topper Cancer Institute
Bethlehem, Pennsylvania

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Yanjun Ma, MD
Tennessee Oncology
Murfreesboro, Tennessee

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Athens, Georgia

Paul Markowski, MD
Atlantic Health System
Summit, New Jersey

Swati Vishwanathan, MD
WVU Medicine
Bridgeport, West Virginia

Laurie Matt-Amaral, MD, MPH
Northeast Ohio Medical University
College of Medicine
Akron, Ohio

Neil Love, MD
Research To Practice
Miami, Florida

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Module 1: Integrating Novel Treatment Strategies into the Management of Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Galsky

Case Presentation: 79-year-old man with superficial transitional cell carcinoma of the bladder, s/p BCG with positive ureteral washing

Dr Sunil Gandhi (Lecanto, Florida)

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QUESTIONS FOR THE FACULTY

Sunil Gandhi, MD, FACP

What is the role of IOs and other treatment modalities in NMIBC?

How often is bilateral ureteral involvement observed with non-muscle-invasive disease? Does this affect the treatment strategy?

How long should pembrolizumab be continued in a patient with BCG-resistant disease who is responding to treatment?

Does immunotherapy increase the risk or severity of COVID infection?

Case Presentation: 73-year-old man with high-grade papillary MIBC, s/p neoadjuvant gemcitabine/cisplatin and cystectomy, with residual disease

Dr Ranju Gupta (Bethlehem, Pennsylvania)

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Case Presentation: 80-year-old man with pT3N0 high-grade urothelial carcinoma, s/p nephrouretrectomy (GFR: 40)

Dr Swati Vishwanathan (Bridgeport, West Virginia)

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QUESTIONS FOR THE FACULTY

Ranju Gupta, MD

In what situations do you recommend adjuvant nivolumab for patients who initially undergo surgery? What about patients who receive neoadjuvant chemotherapy?

Swati Vishwanathan, MD

How do you determine whether to use neoadjuvant chemotherapy in high-grade urothelial cancer of the upper GU tract? What about adjuvant chemotherapy or immunotherapy?

How does a prior history of psoriasis affect the potential use of IOs?

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Integrating Novel Treatment Strategies into the Management of Nonmetastatic Urothelial Bladder Cancer

Matthew D. Galsky, MD FASCO

Professor of Medicine

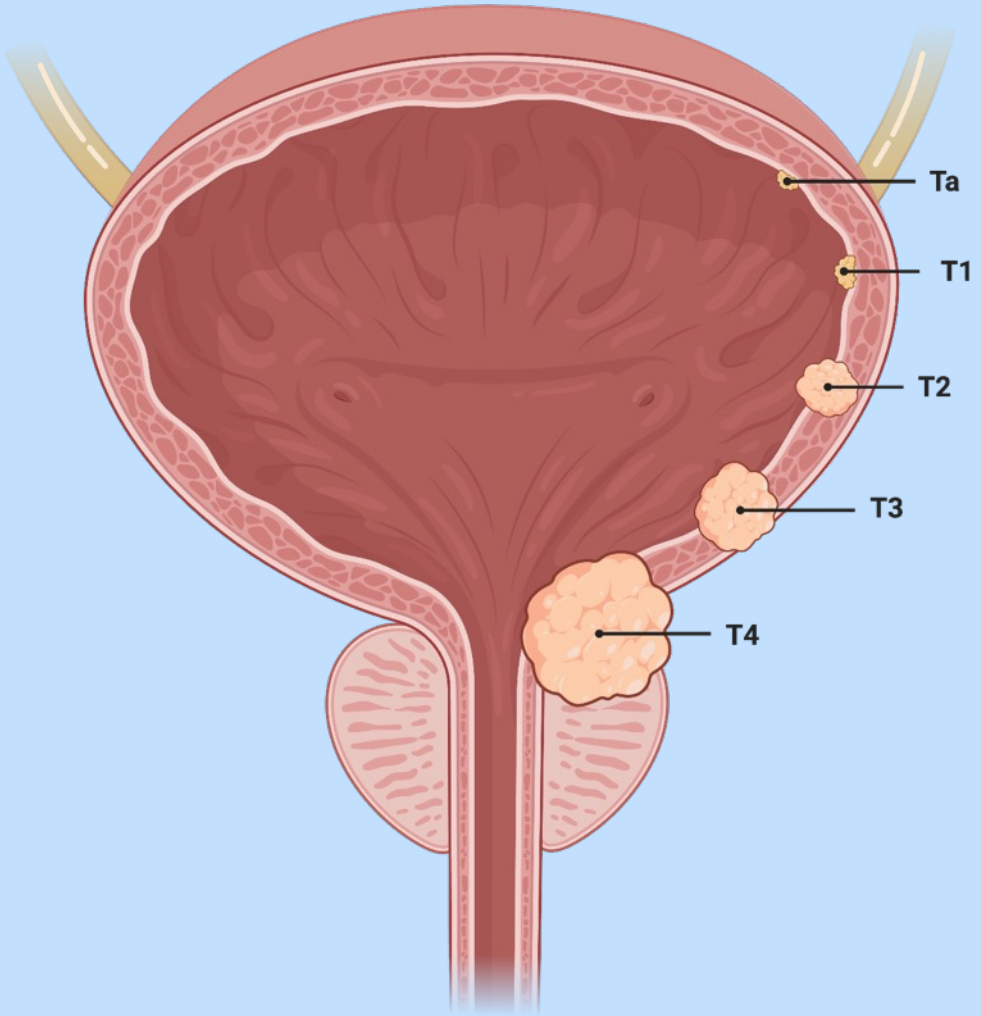
Icahn School of Medicine at Mount Sinai

Director, Genitourinary Medical Oncology

Associate Director, Translational Research

Tisch Cancer Institute

Bladder Cancer



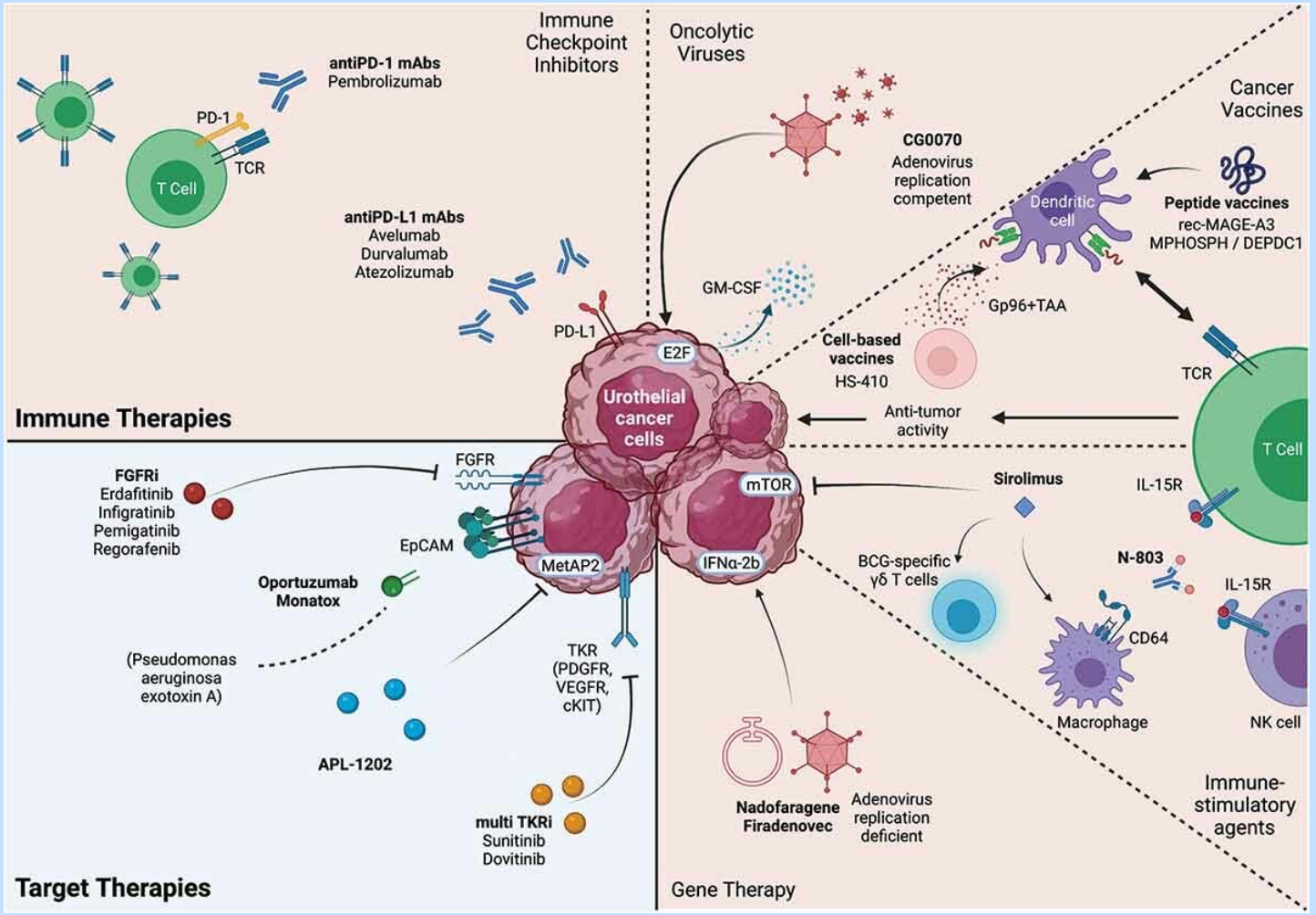
- Non-muscle-invasive: Ta, Tis, T1
  - Endoscopic resection
  - Intravesical therapies
- Muscle-invasive: T2, T3, T4
  - Cystectomy
  - Radiation
- Metastatic (including UTUC)

BCG unresponsive NMIBC

- Persistent or new **T1 HG** disease
  - at first evaluation (3 months) following induction BCG
- Persistent or recurrent **CIS**
  - within **12 months** of completion of **adequate** BCG therapy
- Recurrent **HG Ta/T1** disease
  - within **6 months** of completion of **adequate** BCG therapy

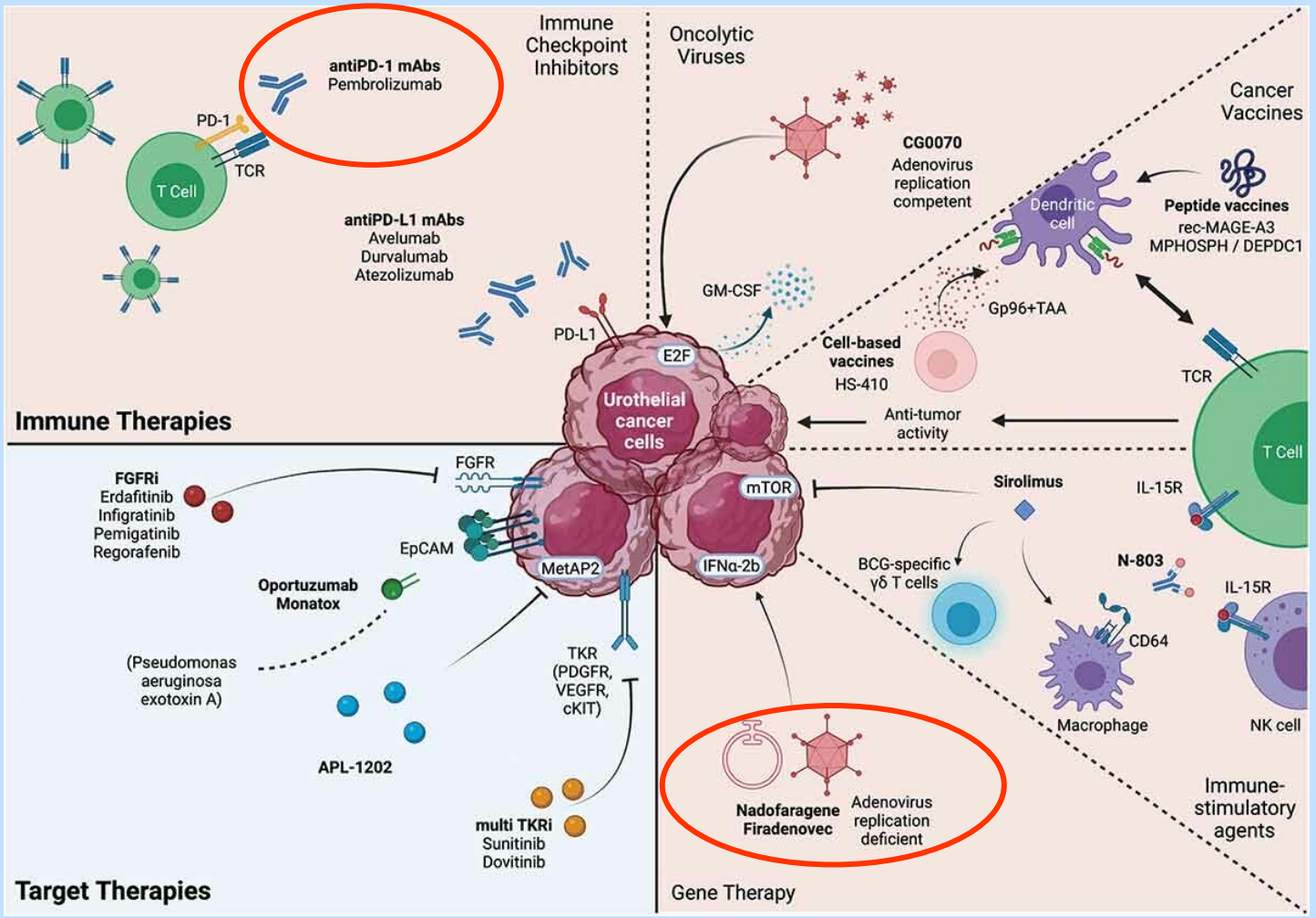
1. Kamat A et al. *J Clin Oncol*. 2016;34:1935-1944. 2. Lerner SP et al. *Bl Cancer*. 2016; 2:165-201. 3. https://www.fda.gov/media/101468/download.

Multiple new agents with distinct mechanisms in development for treatment of BCG unresponsive NMIBC



Valenza et al, Emerging treatment landscape of non muscle invasive bladder cancer, Expert Opinion on Biological Therapy, 2022.

Multiple new agents with distinct mechanisms in development for treatment of BCG unresponsive NMIBC



Valenza et al, Emerging treatment landscape of non muscle invasive bladder cancer, Expert Opinion on Biological Therapy, 2022.

KEYNOTE-057: Pembrolizumab for BCG-Unresponsive NMIBC

Patients

- HR NMIBC patients unresponsive to BCG who refuse or are ineligible for cystectomy
- Patients with papillary disease must have fully resected disease at study entry
- Two cohorts
  - Cohort A (n = 130): CIS with or without papillary disease (high-grade Ta or T1)
  - Cohort B (n = 130): papillary disease (high-grade Ta or any T1) without CIS

Pembrolizumab
200 mg Q3W

Evaluations with cystoscopy, cytology, ± biopsy Q12W × 2 y, then Q24W × 2 y and once yearly thereafter
and
CT urogram Q24W × 2 y or more frequently as clinically indicated

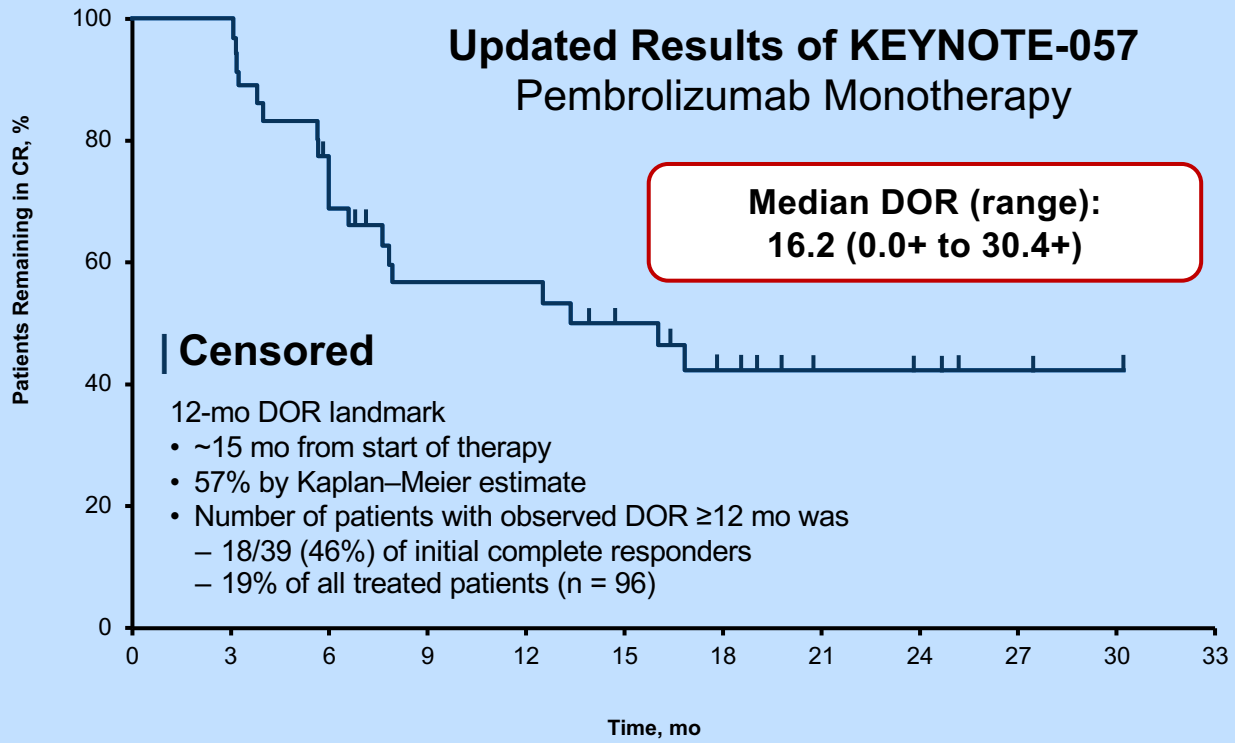
- **Primary endpoints:** CR (absence of HR NMIBC) in cohort A and DFS in cohort B
- **Secondary endpoints:** CR (absence of any disease—high-risk or low-risk NMIBC) in cohort A, DOR in cohort A, and safety/tolerability

If no persistence or recurrence of HR NMIBC at any assessment → Continue assessments and pembrolizumab until recurrence of high-risk NMIBC, PD, or 24 months of treatment complete

If HR NMIBC present at any assessment → Discontinue treatment; enter survival follow-up

1. Balar AV et al. *Lancet Oncol*. 2021;22:919-930.

KEYNOTE-057: Pembrolizumab for BCG-unresponsive CIS



- Of 96 patients, 39 achieved CR at 3 months (41%; 95% CI 30.7–51.1)
- Extended minimum follow-up of 26.3 mo
  - Of 39 responders, 13 (33.3%) remained in CR ≥18 mo and 9 (23.1%) remained in CR ≥24 mo as of the data cutoff date
  - No new safety risks were identified

1. Balar AV et al. ASCO GU 2019. Abstract 350. 2. Balar AV et al. ASCO 2020. Abstract 5041. 3. Balar AV et al. ASCO GU 2021. Abstract 451.
4. Balar AV et al. *Lancet Oncol*. 2021;22:919-930. 5. Black PC et al. ASCO 2020. Abstract 5022.

Phase 3 trial of nadofaragene firadenovec for BCG-unresponsive NMIBC

Patients

- HR NMIBC patients unresponsive to BCG
- CIS with or without papillary disease (high-grade Ta or T1)
- Papillary disease (high-grade Ta or any T1) without CIS

Nadofaragene firadenovec

Intravesical every 3 months

All patients with an absence of HG disease recurrence at month 12 were offered continued treatment every 3 months

Boorjan SA, Lancet Oncology, 2021 Jan; 22(1):107-117.

Phase 3 trial of nadofaragene firadenovec for BCG-unresponsive NMIBC

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

Boorjan SA, Lancet Oncology, 2021 Jan; 22(1):107-117.

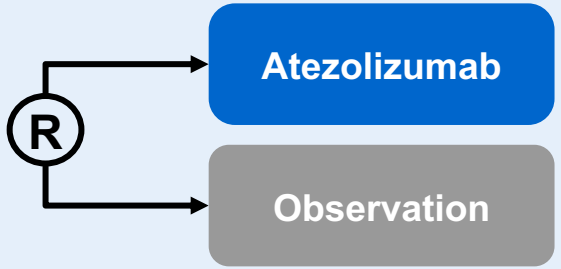
Phase 3 trial of nadofaragene firadenovec for BCG-unresponsive NMIBC

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

Boorjan SA, Lancet Oncology, 2021 Jan; 22(1):107-117.

Adjuvant PD-1/PD-L1 blockade

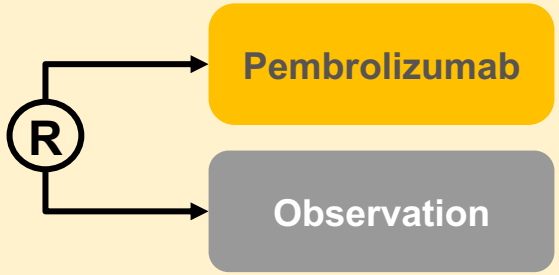
IMvigor010
NCT02450331



Primary endpoint
DFS

Secondary endpoints
OS, DSS, distant metastasis-free survival, AEs and ATAs

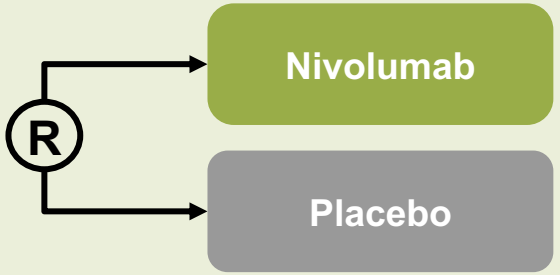
AMBASSADOR
NCT03244384



Co-primary endpoints
DFS and OS

Secondary endpoints
OS and DFS in PD-L1+ and PD-L1− patients

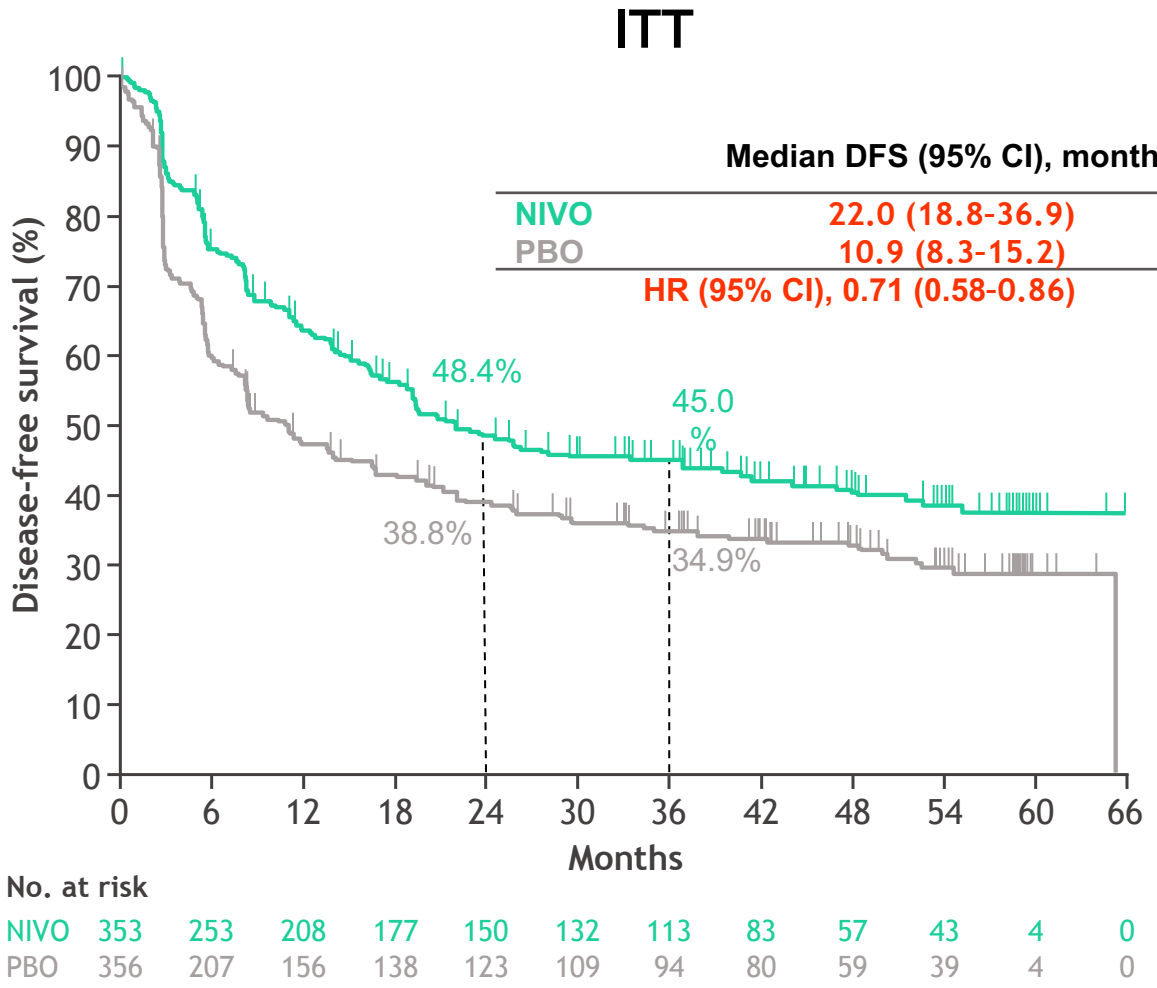
CheckMate 274
NCT02632409

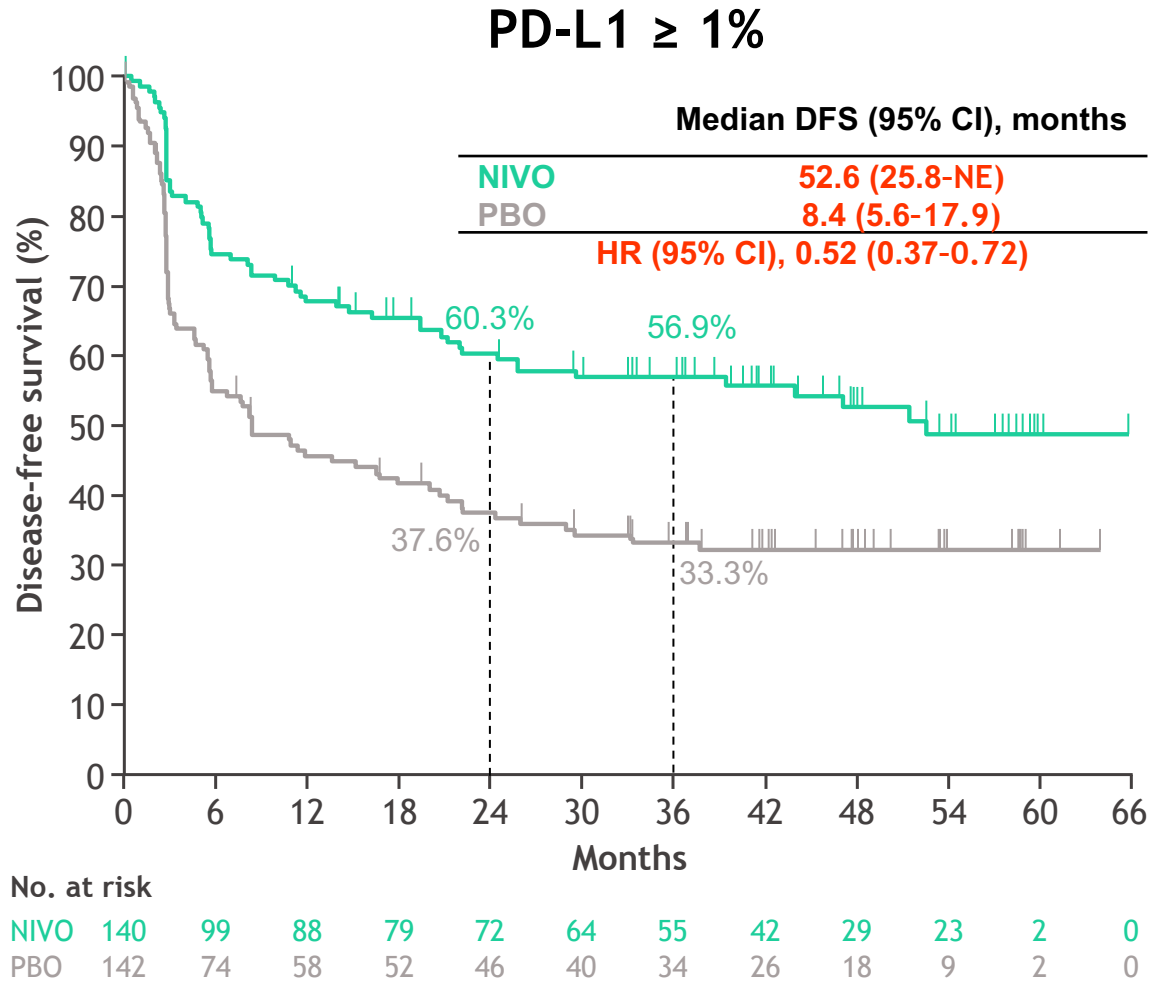


Primary endpoint
DFS in ITT and PD-L1 ≥1%

Secondary endpoints
OS,
non-urothelial tract RFS,
disease-specific survival

Disease-free survival (primary endpoint)





Galsky et al, ASCO GU, 2023; Abstract LBA443.

Summary of efficacy outcomes over time

ITT

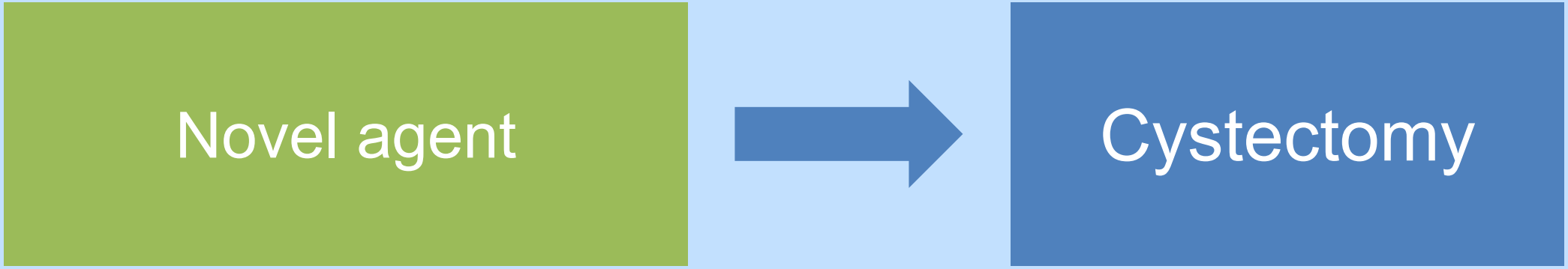
	NIVO (N = 353)	PBO (N = 356)	NIVO (N = 353)	PBO (N = 356)	NIVO (N = 353)	PBO (N = 356)
Minimum follow-up, months	**31.6**		**11.0[1]**		**5.9[2]**	
Median DFS, months	22.0	10.9	22.0	10.9	20.8	10.8
DFS HR (95% CI)	0.71 (0.58–0.86)		0.70 (0.57–0.85)		0.70 (0.55–0.90)[a]	
Median NUTRFS, months	25.9	13.7	26.0	13.7	22.9	13.7
NUTRFS HR (95% CI)	0.72 (0.59–0.88)		0.71 (0.58–0.88)		0.72 (0.59–0.89)	
Median DMFS, months	47.1	28.7	41.1	29.2	40.5	29.5
DMFS HR (95% CI)	0.74 (0.60–0.92)		0.73 (0.58–0.92)		0.75 (0.59–0.94)	

PD-L1 ≥ 1%

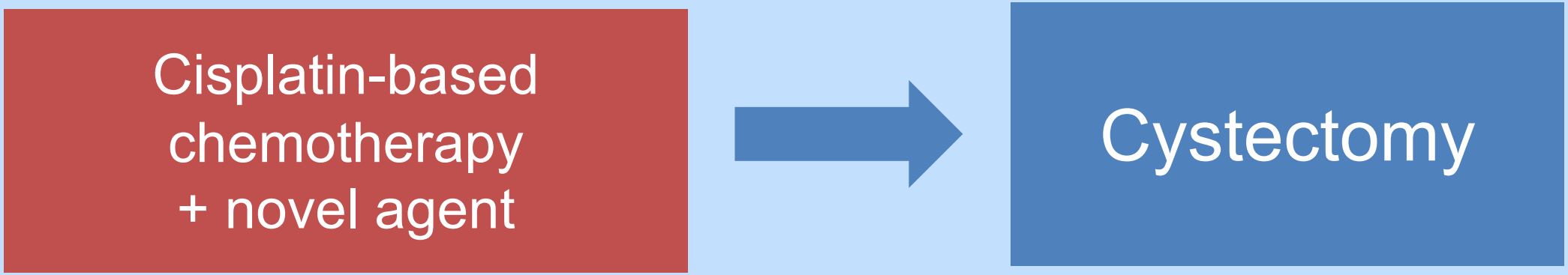
	NIVO (N = 140)	PBO (N = 142)	NIVO (N = 140)	PBO (N = 142)	NIVO (N = 140)	PBO (N = 142)
Minimum follow-up, months	**31.6**		**11.0[1]**		**5.9[2]**	
Median DFS, months	52.6	8.4	NR	8.4	NR	8.4
DFS HR (95% CI)	0.52 (0.37–0.72)		0.53 (0.38–0.75)		0.55 (0.35–0.85)[b]	
Median NUTRFS, months	52.6	8.4	NR	10.8	NR	10.8
NUTRFS HR (95% CI)	0.53 (0.38–0.74)		0.54 (0.39–0.77)		0.55 (0.39–0.79)	
Median DMFS, months	NR	20.7	NR	20.7	NR	21.2
DMFS HR (95% CI)	0.58 (0.40–0.84)		0.60 (0.41–0.88)		0.61 (0.42–0.90)	

Galsky et al, ASCO GU, 2023; Abstract LBA443.

Cisplatin-ineligible patients



Cisplatin-eligible patients

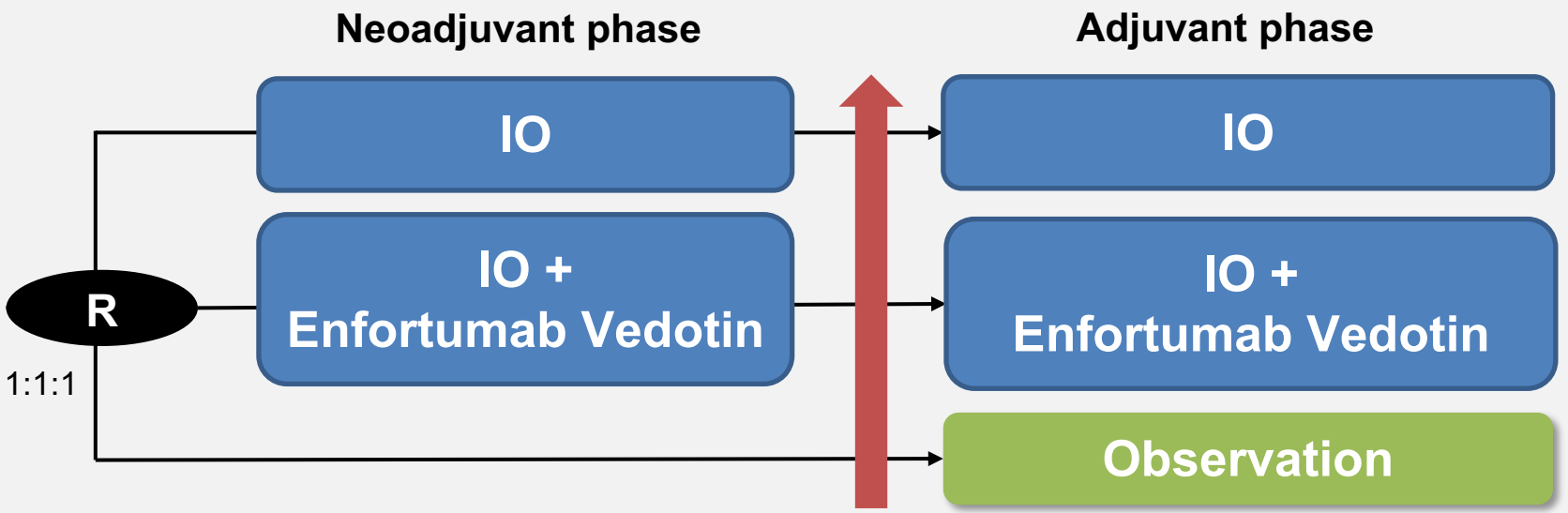


Phase 2 studies exploring neoadjuvant IO in bladder cancer

	PURE-01	ABACUS	NABUCCO			DUTRE NEO	MDACC	PrE0807	MSKCC	
	Pembro	Atezo	Ipi > Ipi/Nivo > Nivo	Ipi^{3} + Nivo^{1}	Ipi^{1} + Nivo^{3}	Durva + Treme	Durva + Treme	Nivo+ Liri	Nivo^{3}	Ipi^{3} + Nivo^{1}
N	143	88	24	15	15	23	28	30	15	15
cT2	49%	73%	0	0	0	78%	43%	87%	54%	46%
cN1-3	0	0	42%	47%	53%	9%	0	3%	0	0
pCR	39%	31%	46%	43%	7%	35%	38%	18%	13%	7%

Bandini et al, Ann Oncol, 2020; Powles, Nat Med, 2019; van Dijk, Nat Med, 2019; Van Dorp, Ann Oncol, 2021; Grande, ASCO, 2020; Gao, Nat Med, 2020; Grivas, ASCO, 2021; Guercio, ASCO GU 2022

Phase 3 studies exploring neoadjuvant IO in cisplatin-ineligible patients with muscle-invasive bladder cancer



- **KEYNOTE-905/EV-303[1]:** pembrolizumab + enfortumab vedotin
- **VOLGA[2,3]:** durvalumab + tremelimumab + enfortumab vedotin

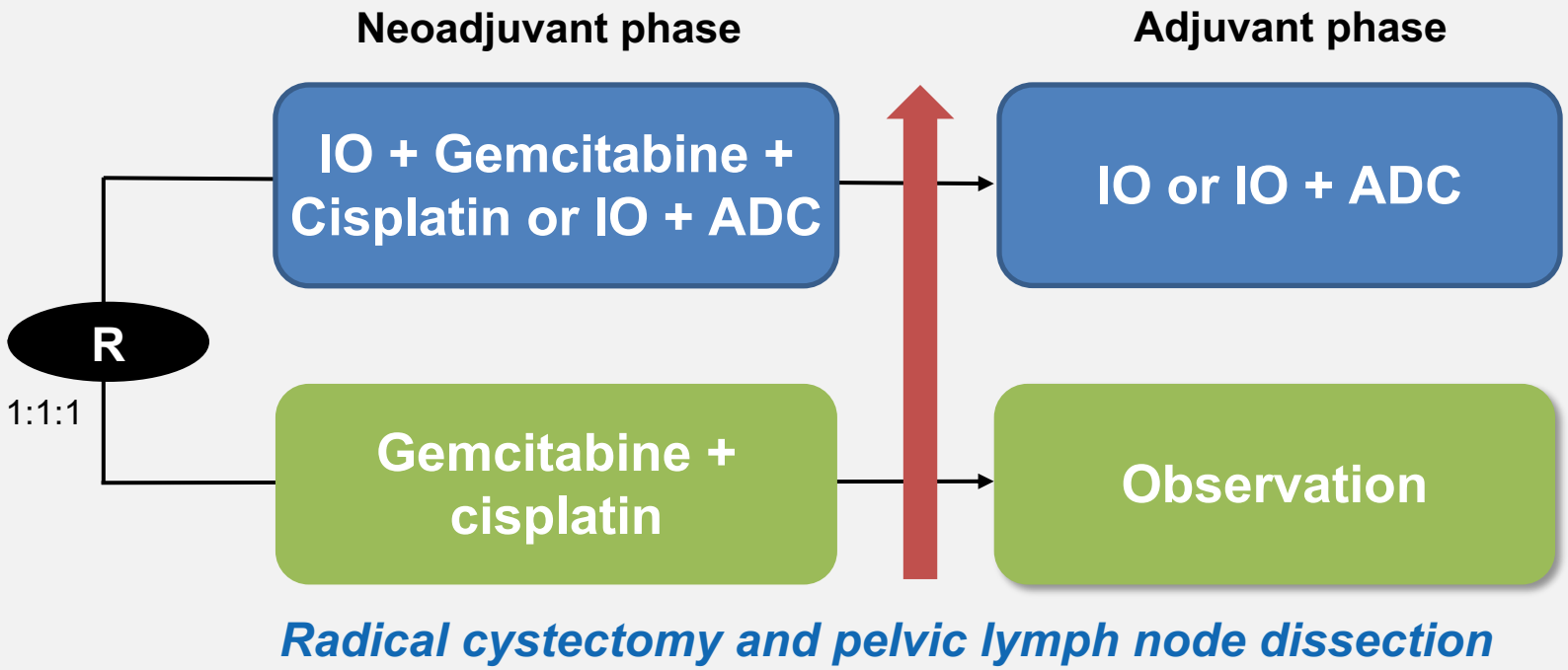
1. https://www.clinicaltrials.gov/ct2/show/NCT03924895. 2. https://clinicaltrials.gov/ct2/show/NCT04960709.
3. Powles T et al. ASGO GU 2022. TPS579.

Phase 2 studies exploring neoadjuvant chemo-IO

	HCRN GU14-188		BLASST	SAKK06/17	MSKCC	LCCC1520	SMC	ONCOSITINCT-004	
	Pembro + GC	Pembro + G	Nivo + GC	Durva + GC	Atezo + GC	Pembro + GC (split)	Nivo + GC	Ave + ddMVAC	Ave + GC
N	43	37	41	58	39	39	51	28	28
cT2	47%	43%	90%	69%	79%	72%	NA	61%	64%
cN1-3	0	0	3%	17%	0	0	NA	11%	18%
pCR	44%	45%	34%	34%	44%	36%	24%	43%	32%

Hoimes ASCO 2020; Kaimakliotis, ASCO, 2020; Gupta, GU ASCO, 2020; Cathomas, ASCO, 2021; Funt, ASCO, 2021; Martinez, ESMO 2021; Kim, GU ASCO, 2022

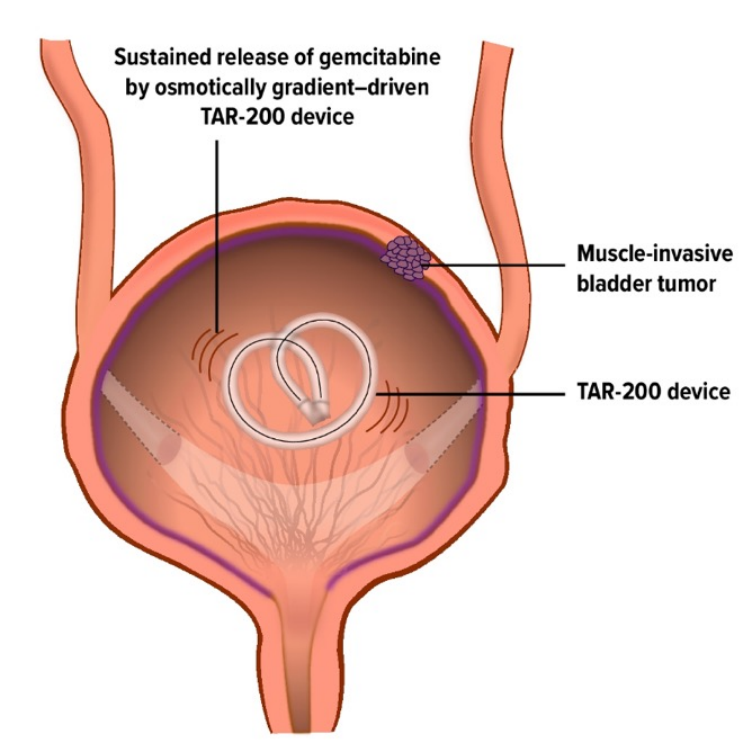
Phase 3 studies exploring neoadjuvant IO in cisplatin-eligible patients with muscle-invasive bladder cancer

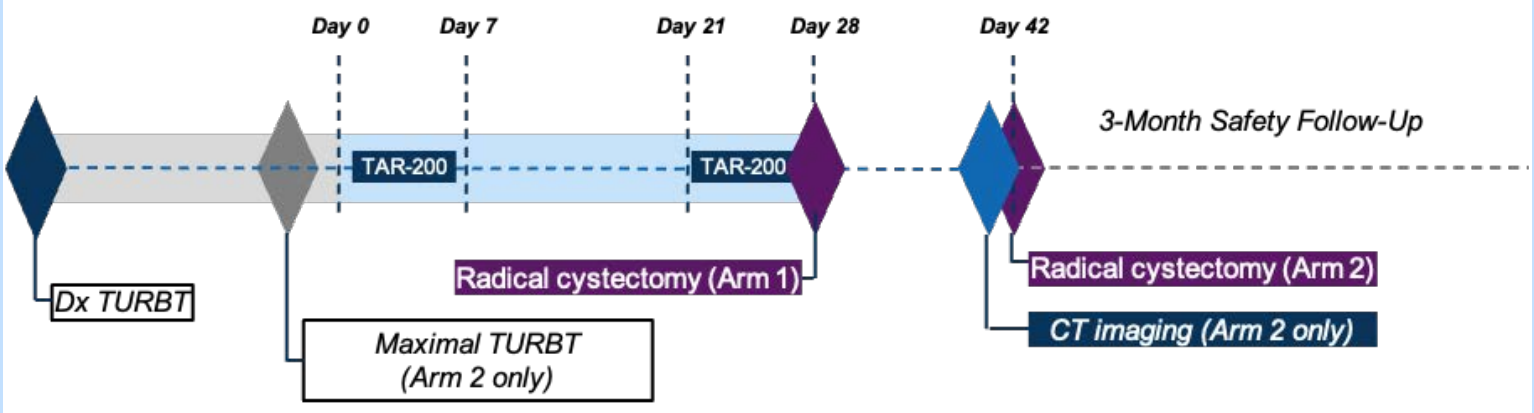


- **ENERGIZE[1]:** gem/cis ± nivolumab ± IDO1i
- **NIAGARA[2]:** gem/cis ± durvalumab
- **KEYNOTE-866[3]:** gem/cis + pembrolizumab
- **KEYNOTE-B15/EV-304[4]:** pembrolizumab + EV

1. https://clinicaltrials.gov/ct2/show/NCT03661320. 2. https://clinicaltrials.gov/ct2/show/NCT03732677.
3. https://clinicaltrials.gov/ct2/show/NCT03924856. 4. https://clinicaltrials.gov/ct2/show/NCT04700124

Phase 1 study of a neoadjuvant gemcitabine intravesical drug delivery system (TAR-200)

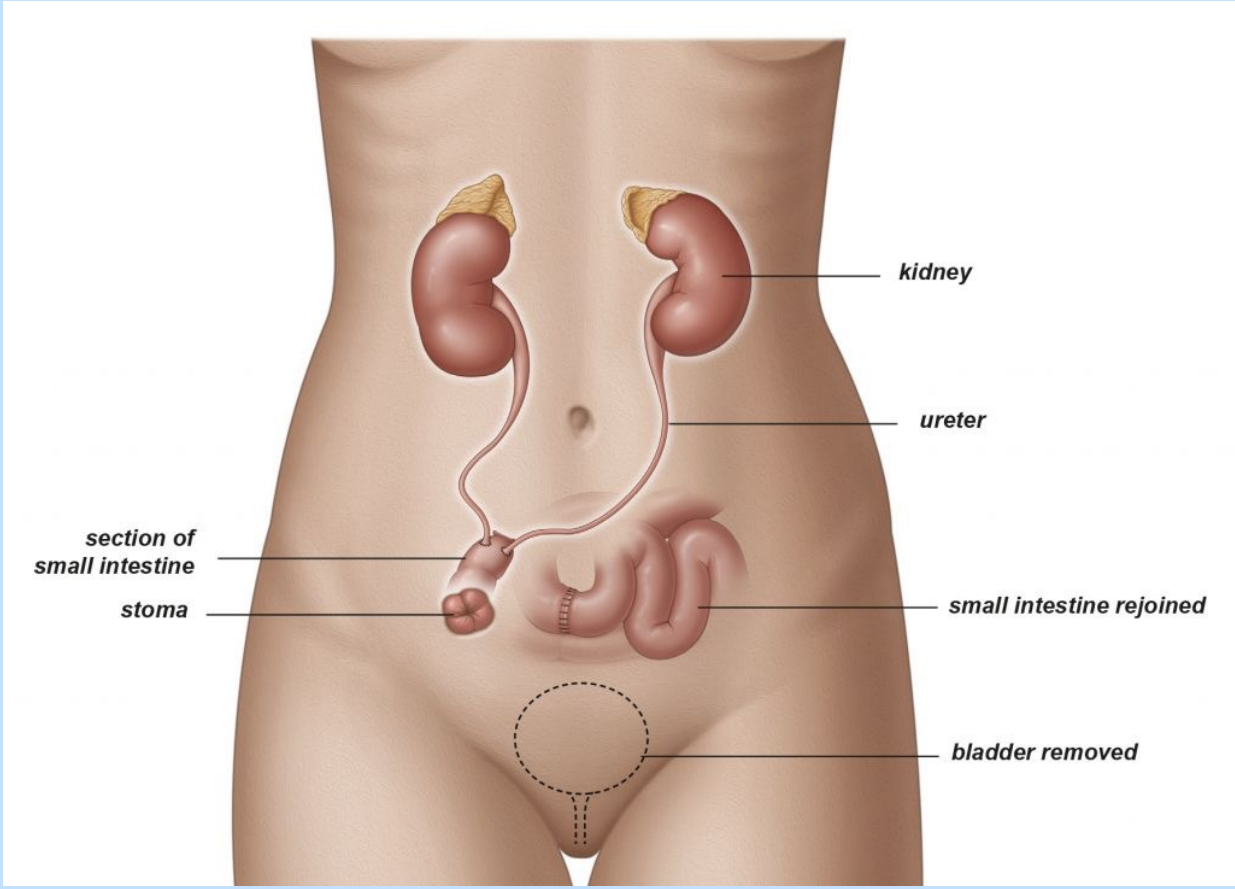




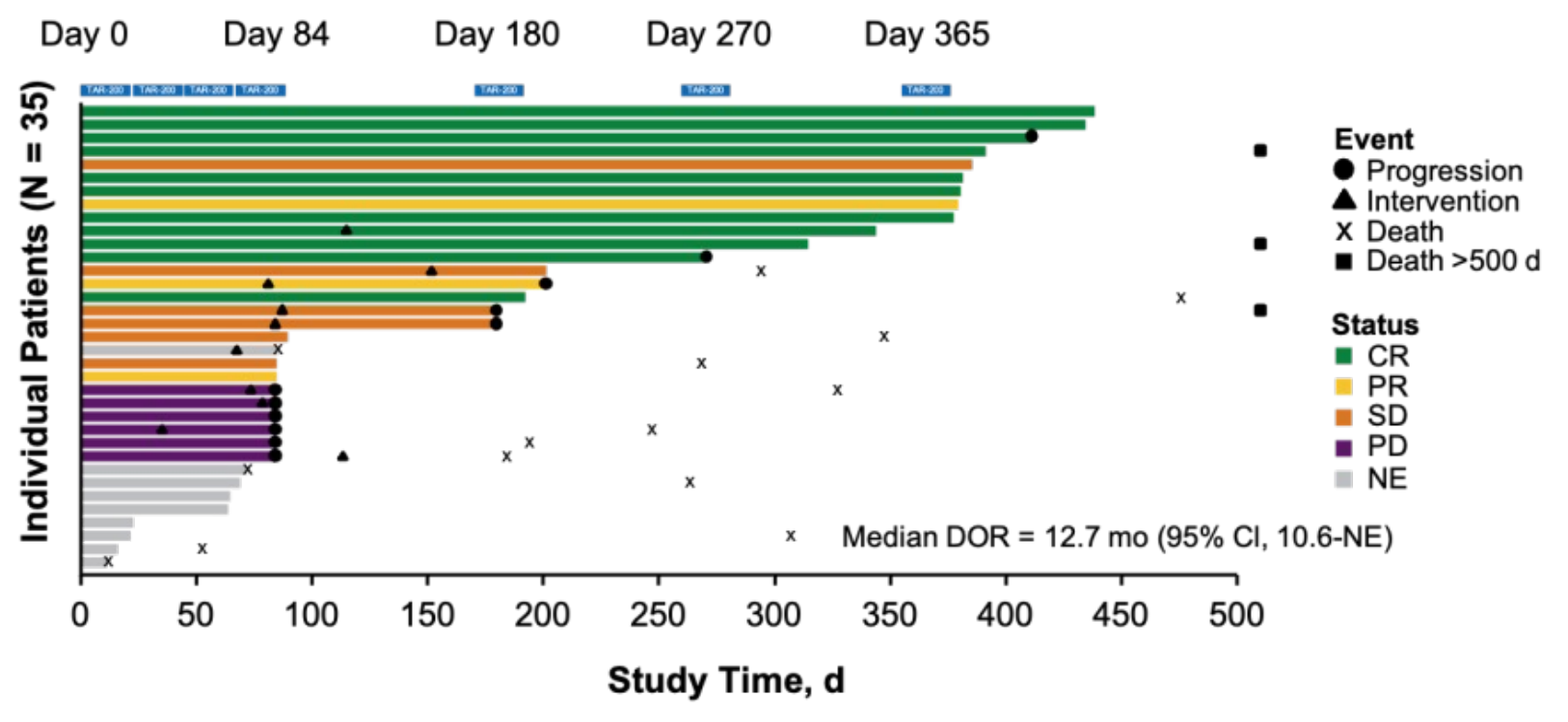
- In Arm 1, those with residual tumor, 4 of 10 patients exhibited pathologic downstaging; 1 experienced a complete response (CR) and 3 a partial response (PR)
- In Arm 2, those undergoing maximal TURBT, 6 of 10 patients exhibited downstaging; 3 experienced a CR and 3 a PR.

Daneshmand S et al. *Urol Oncol: Semin Orig.* 2022;1-9.

Paradoxically, a *pathological* CR can only be determined after the bladder has already been removed.



Phase 1 study of TAR-200 in patients with MIBC who were unfit/refused curative intent therapy



- Preliminary efficacy
  - ORR of 40% at 3 mo
  - mOS of 20.1 mo
  - 12 mo progression-free rate 67.7%
  - Median DOR of 12.7 mo

Tyson MD et al. Society of Urologic Oncology 2021. Abstract 172.

Select Ongoing Trials of TAR-200 in Bladder Cancer

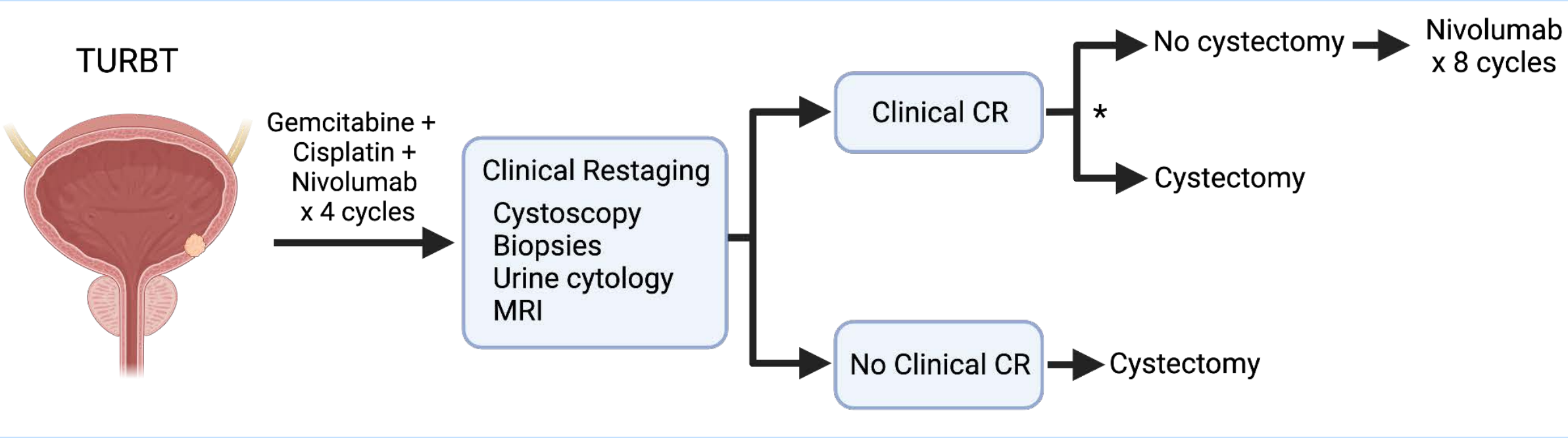
Study	N	Setting	Treatment arms	Primary est completion date
SunRISe-4	160	• MIBC • Scheduled for radical cystectomy • Ineligible/refusing platinum-based neoadjuvant chemotherapy	• TAR-200 + cetrelimab • Cetrelimab	April 2023
SunRISe-2	550	• MIBC • Not receiving radical cystectomy	• TAR-200 + cetrelimab • Cisplatin or gemcitabine + RT	December 2026
SunRISe-3	1,050	• BCG-naïve • High-risk NMIBC	• TAR-200 + cetrelimab • BCG • TAR-200	May 2030

MIBC = muscle-invasive bladder cancer; RT = radiation therapy; NMIBC = non-muscle-invasive bladder cancer

www.clinicaltrials.gov. Accessed February 15, 2023

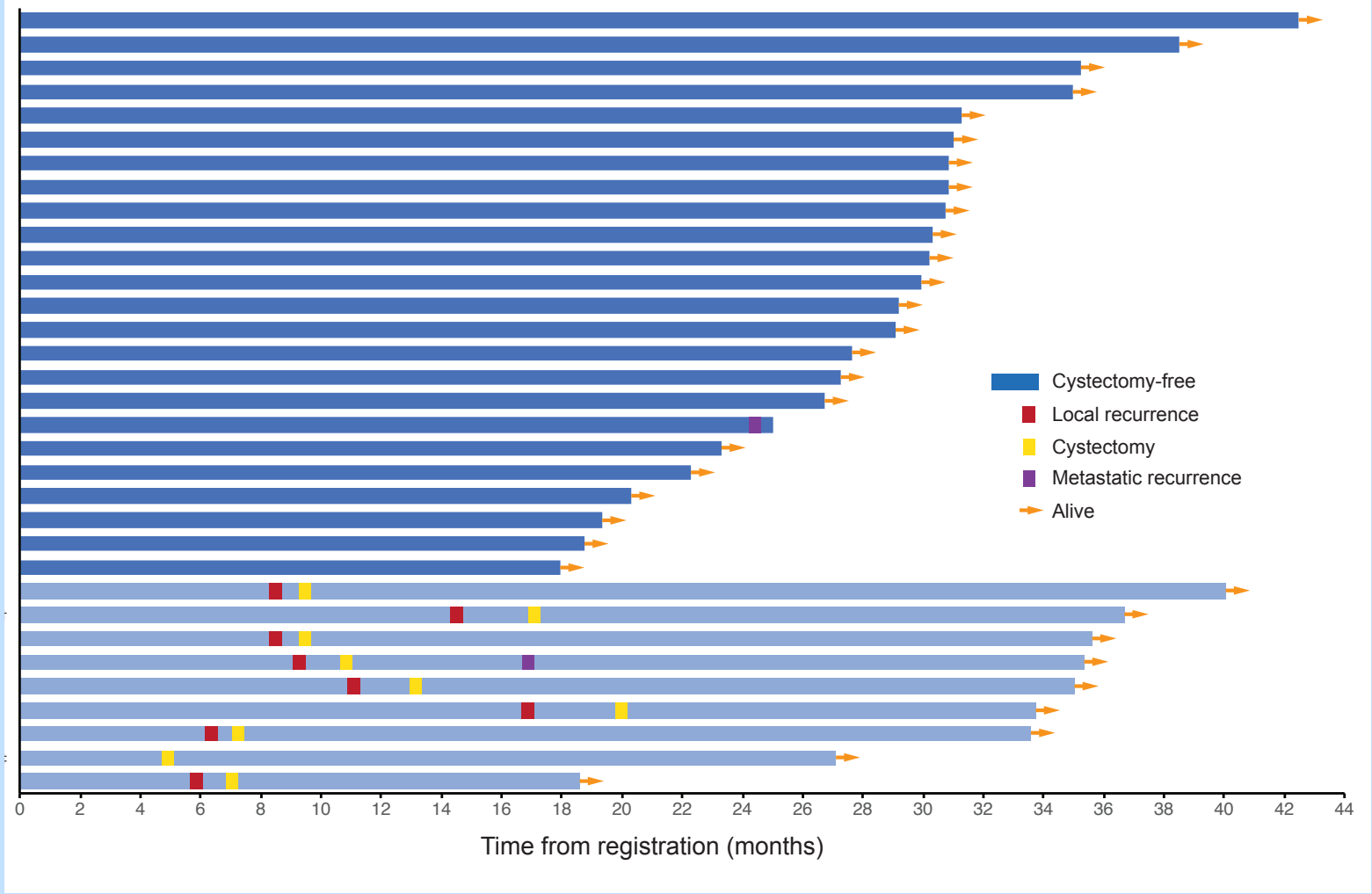
RTP RESEARCH TO PRACTICE

HCRN GU16-257: Phase 2 trial of gemcitabine, cisplatin, plus nivolumab with selective bladder sparing for MIBC



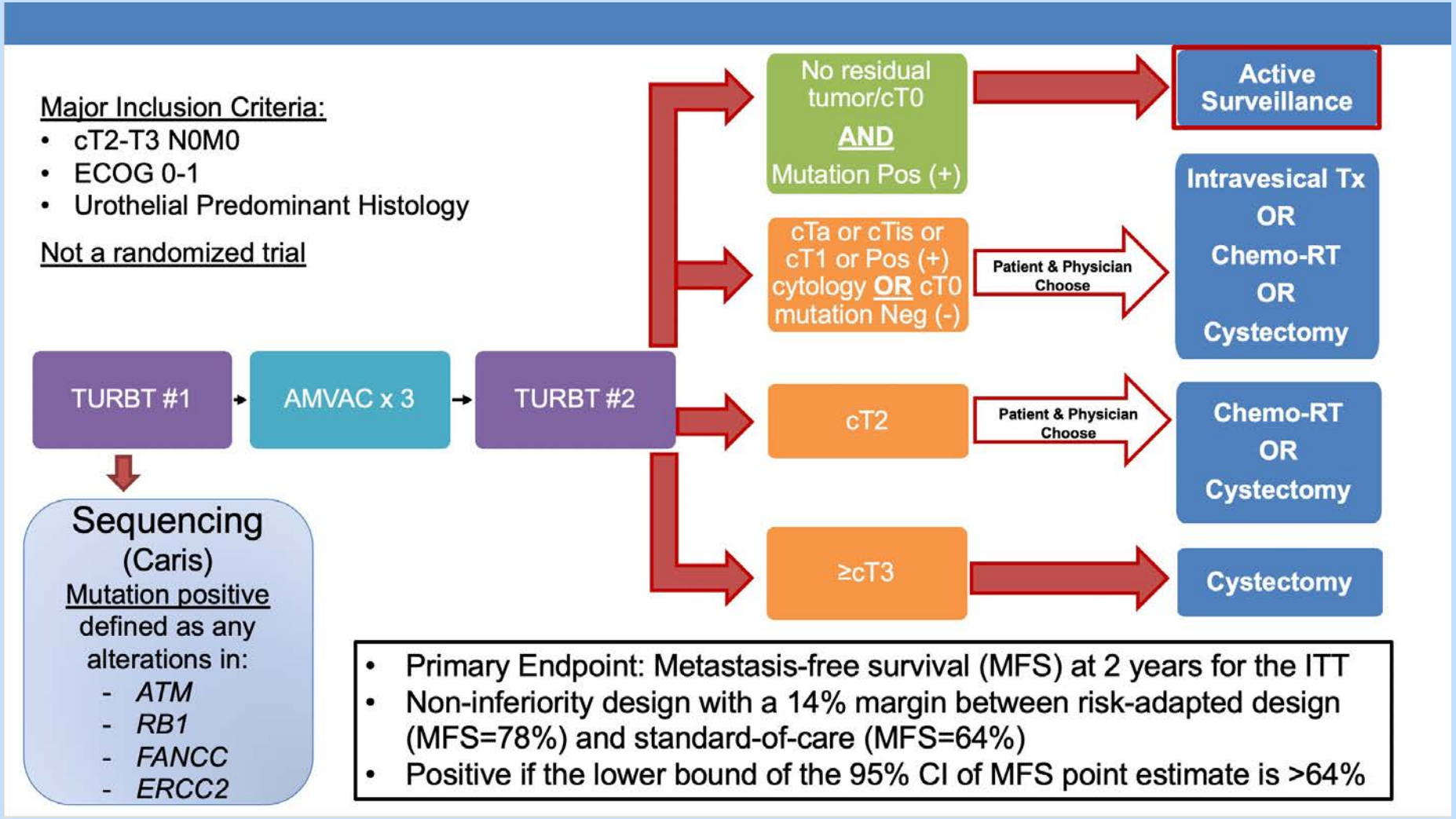
Galsky et al, ASCO GU, 2023; Abstract 447.

HCRN GU16-257: Phase 2 trial of gemcitabine, cisplatin, plus nivolumab with selective bladder sparing for MIBC



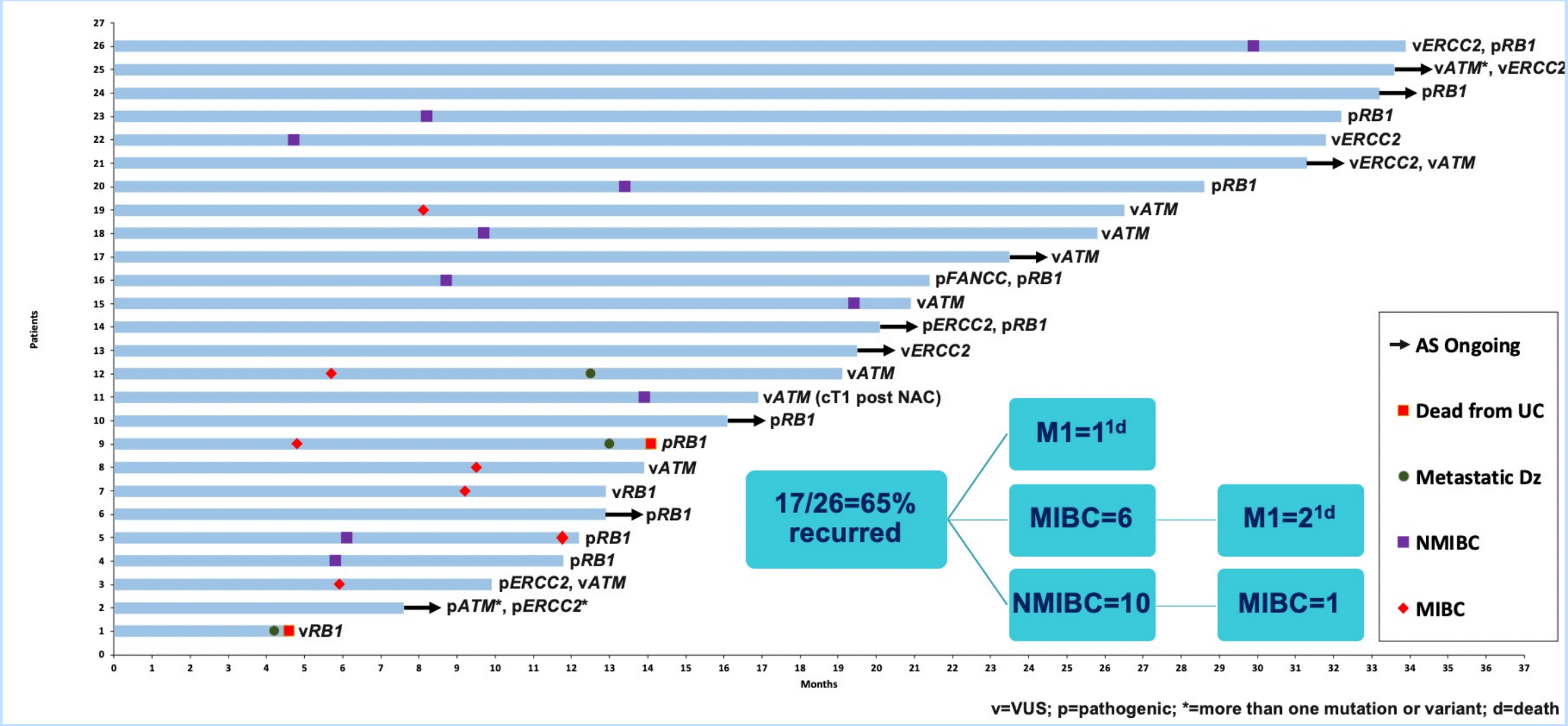
Galsky et al, ASCO GU, 2023

RETAIN BLADDER



Geynisman et al, GU ASCO 2021

RETAIN BLADDER



Geynisman et al, GU ASCO 2021

Module 2: Current and Future Front-Line Treatment for Metastatic UBC (mUBC) — Dr Rosenberg

RTP
RESEARCH
TO PRACTICE

Case Presentation: 75-year-old man with metastatic urothelial carcinoma, s/p gemcitabine/cisplatin, now on maintenance avelumab

Dr Paul Markowski (Summit, New Jersey)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 52-year-old man with a history of ulcerative colitis is diagnosed with metastatic urothelial carcinoma, including brain involvement

Dr Gigi Chen (Pleasant Hill, California)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Paul Markowski, MD

How long should maintenance avelumab be continued?

Gigi Chen, MD

What is the optimal first-line systemic treatment for a patient presenting with brain metastases?

In what situations can a checkpoint inhibitor be administered to a patient with a history of ulcerative colitis?

Case Presentation: 82-year-old woman with unresectable localized urothelial carcinoma – PD-L1 CPS: 5, TMB-low

Dr Spencer Henick Bachow (Boca Raton, Florida)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Spencer Henick Bachow, MD

What would you recommend for a patient who achieves a CR on dose-dense MVAC for unresectable UBC followed by disease relapse?

Have you observed arthralgias on avelumab? What about infusion reactions? How are these issues managed?

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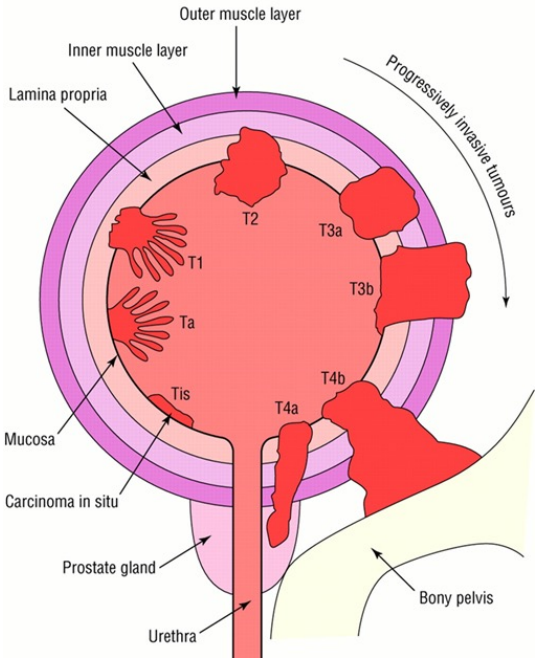
Current and Future Front-Line Treatment for Metastatic Urothelial Cancer

Jonathan Rosenberg, MD
Chief, Genitourinary Oncology Service
Enno Ercklentz Chair
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, NY



Treatment of locally advanced or metastatic UC

- Dramatic changes in the last few years
- Reduced role of ICB as first-line therapy
- Emergence of maintenance avelumab as a new standard
- Negative phase III trials combining ICB and chemotherapy
- Combinations of ICB and targeted therapies and ADCs show significant promise

KEYNOTE-052: First-line pembrolizumab in cisplatin ineligible patients (N=370)

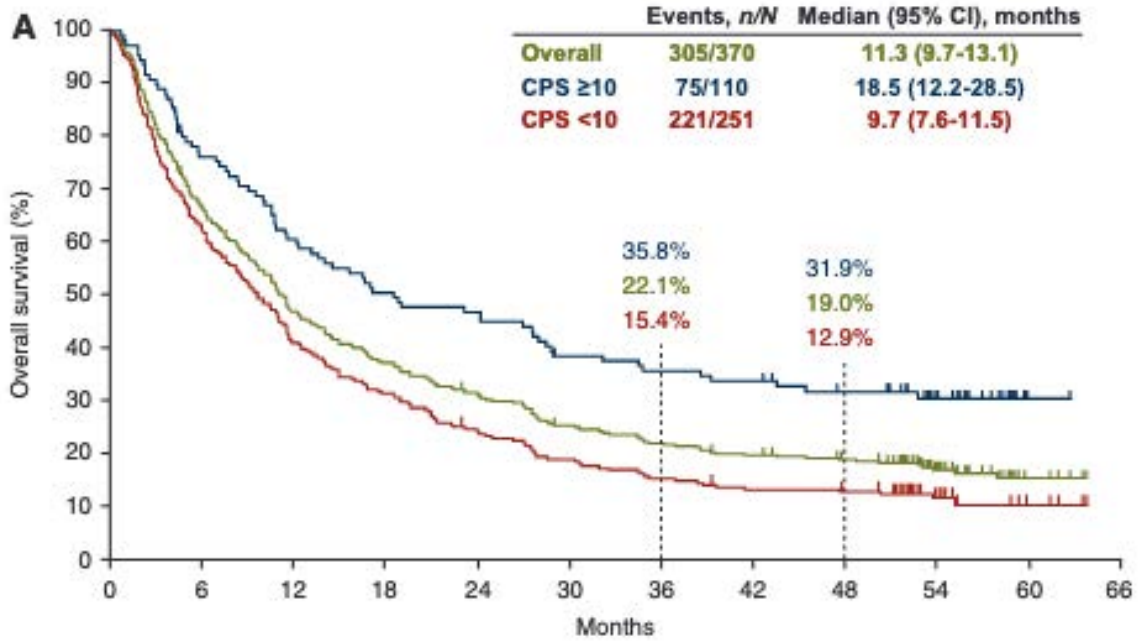
(RECIST 1.1)	All Treated Patients % (95% CI) N=370	CPS ≥10 % (95% CI) N=110
Objective response	28.6 (24.3-33.8)	47.3 (37.7-57.0)
Complete response	9.5	20.9
Partial response	19.5	26.4

Median OS 11.3 months

CPS ≥10% OS 18.5 months

Inclusion Criteria

- Advanced urothelial cancer
- No prior chemotherapy for metastatic disease
- ECOG PS 0-2
- Ineligible for cisplatin based on ≥ 1 of the following:
- CrCl <60 mL/min
- ECOG PS 2
- ≥ grade 2 neuropathy or hearing loss
- NYHA class III CHF



Balar, et al. Ann Oncol 2022

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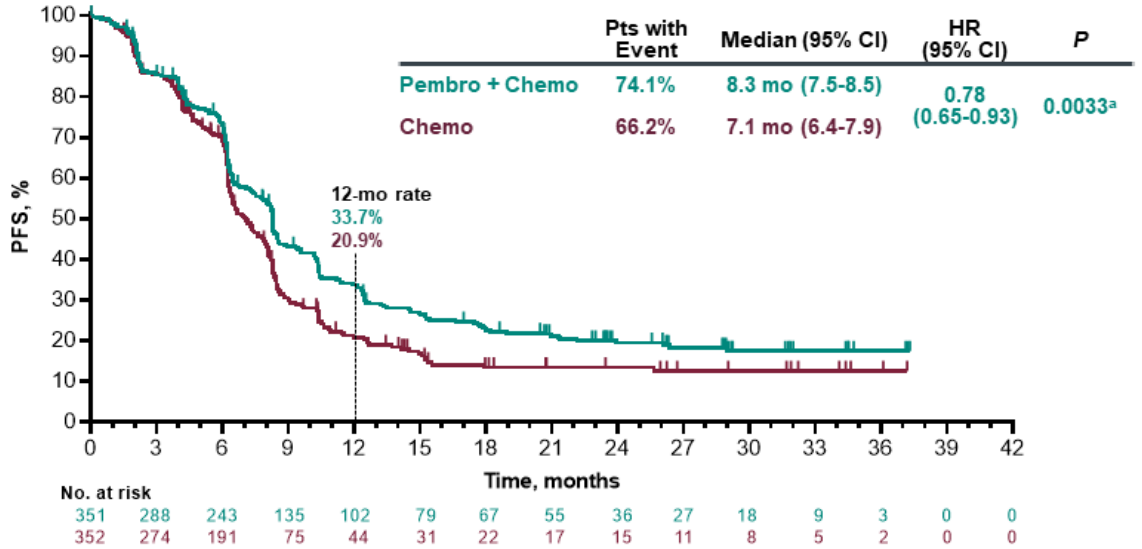
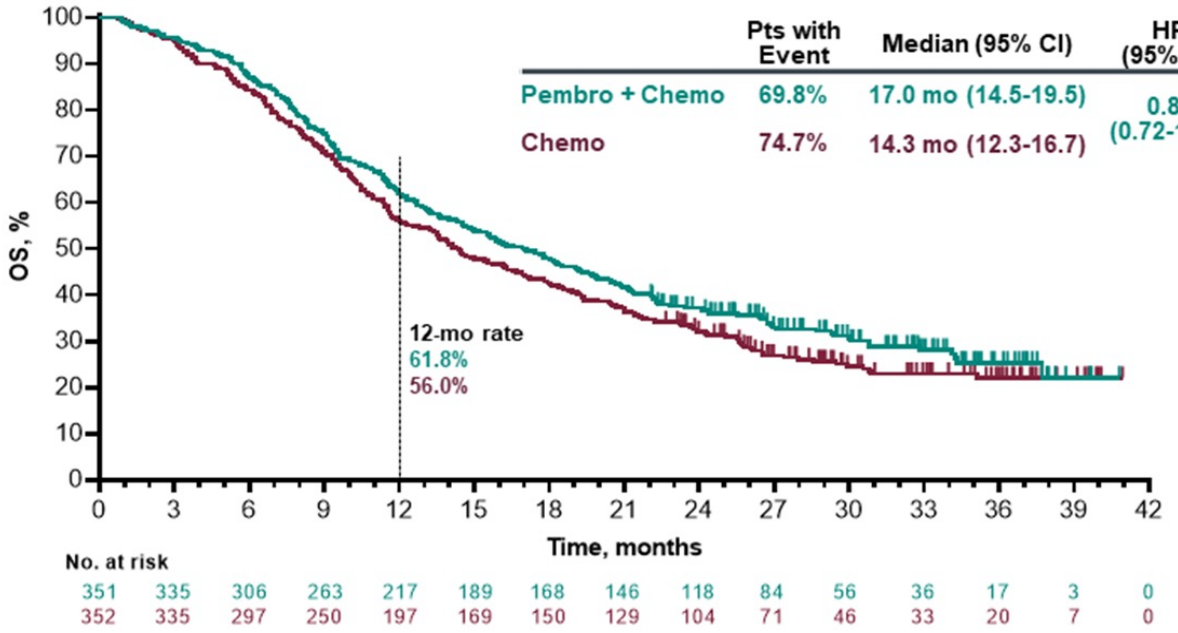
KEYNOTE-361: 1st-line chemotherapy with or without pembrolizumab



	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	74.1%	8.3 mo (7.5-8.5)	0.78 (0.65-0.93)	0.0033[a]
Chemo	66.2%	7.1 mo (6.4-7.9)		

PFS

PFS (primary endpoint) and OS negative (p=NS per analysis plan)



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

OS

- Gemcitabine
- Platinum
- Pembrolizumab

- Pembrolizumab

- Gemcitabine
- Platinum

- Locally advanced or metastatic UC
- No prior chemotherapy for advanced disease

Adapted from Aijai Alva, ESMO 2020; Powles Lancet Oncol 2021

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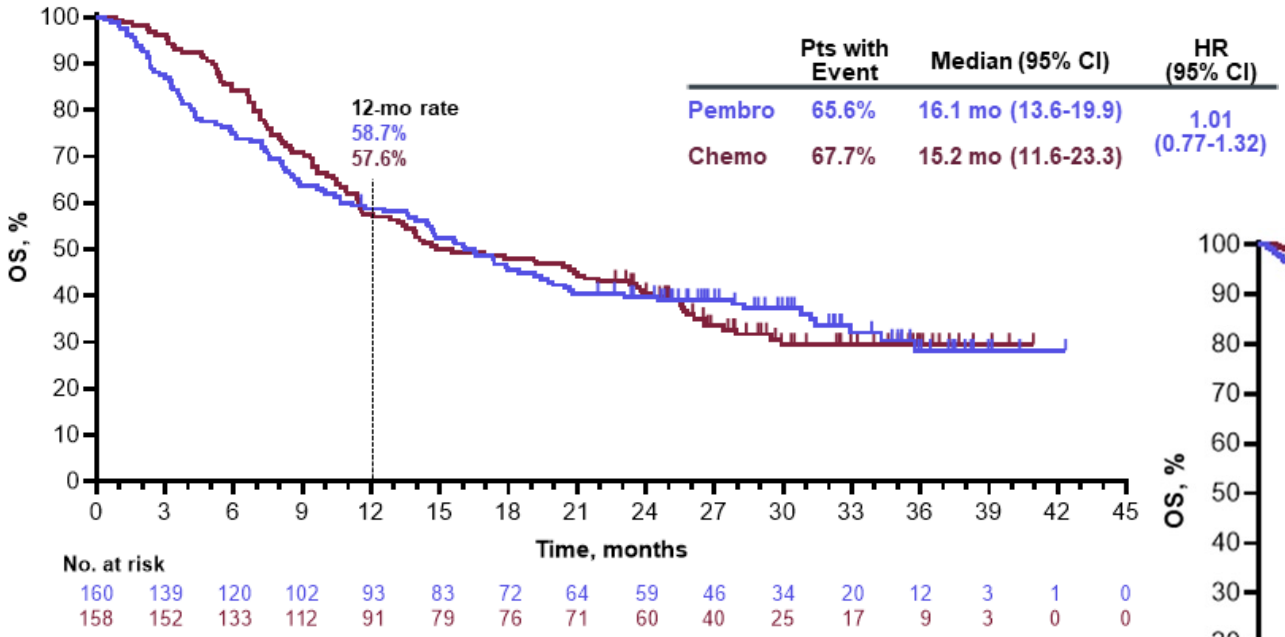
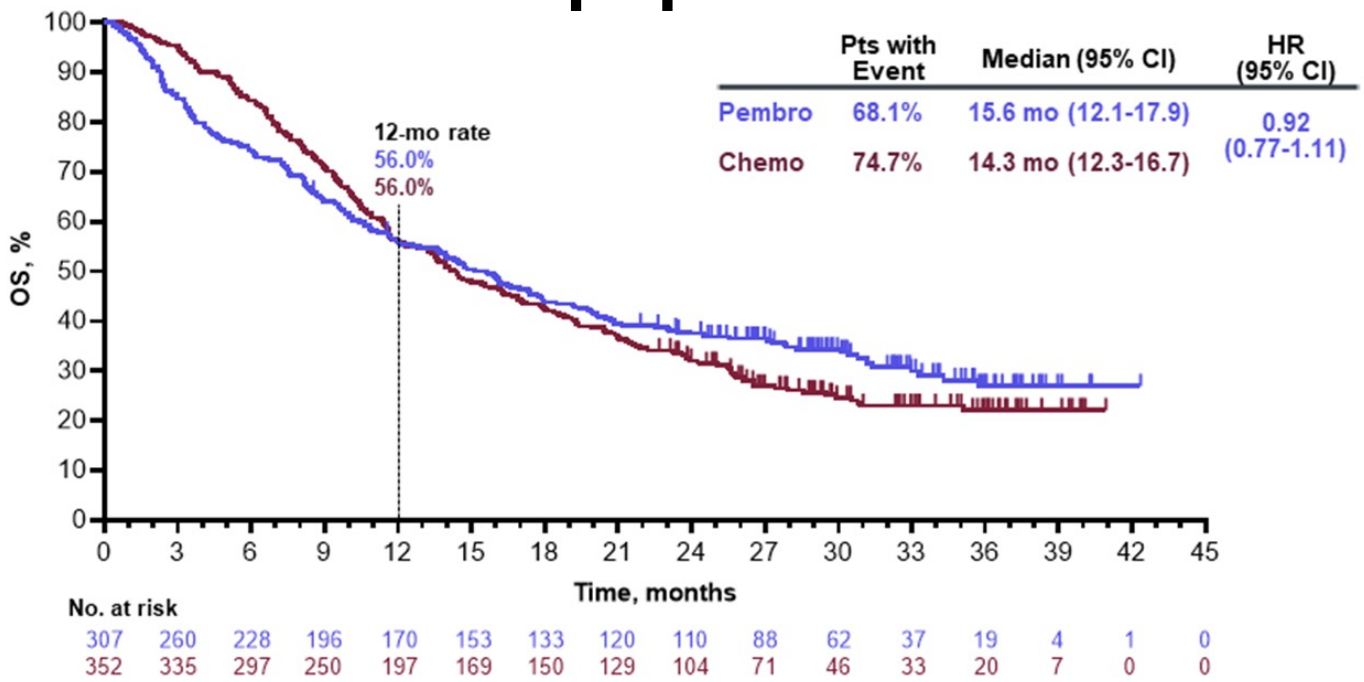
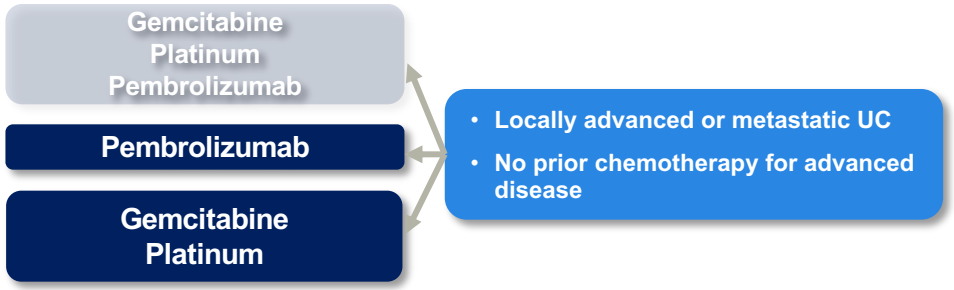
KEYNOTE-361: Pembrolizumab vs 1st-line chemotherapy



CPS ≥10





No improvement in OS either with CPS>10 or ITT population; curves cross at ~1 year timepoint
Biomarker failure!

Adapted from Aijai Alva, ESMO 2020; Powles Lancet Oncol 2021

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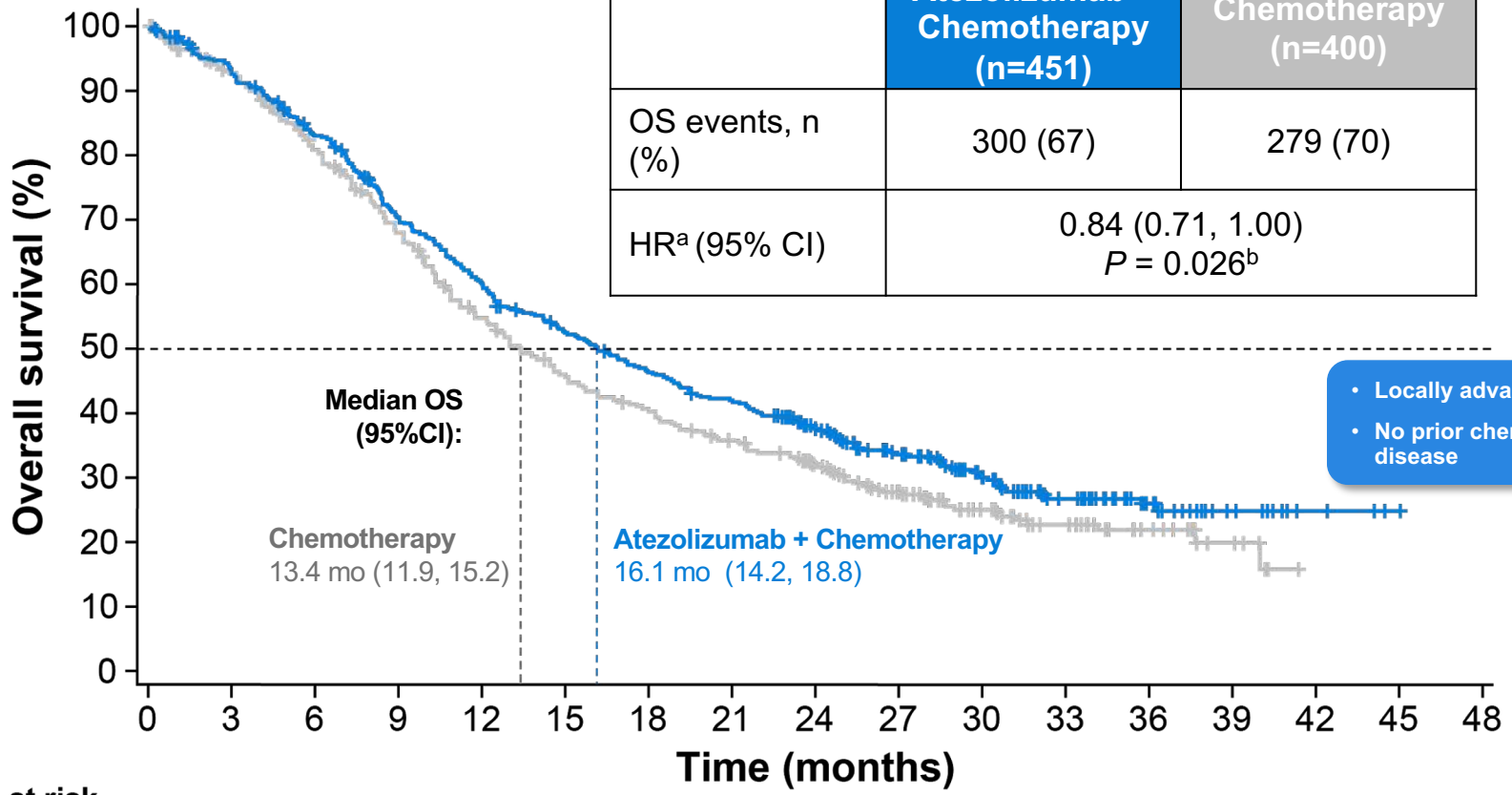
The only 1st-line CPI monotherapy that remains FDA-approved is pembrolizumab for “platinum-ineligible” patients

- Poorly defined population
- Various definitions but no consensus
- Only published prospective study was with durvalumab (control arm of BAYOU study)
  - PFS 3.5 mos (95% CI 1.9-5.4)
  - OS 10.7 mos (95% CI 7.2-17.3)
  - ORR 18.4%

Rosenberg et al. JCO 2023; 41(1):43-53

IMvigor130: 2nd OS Interim Analysis in ITT Atezolizumab + Chemotherapy vs. Chemotherapy

	Atezolizumab + Chemotherapy (n=451)	Chemotherapy (n=400)
OS events, n (%)	300 (67)	279 (70)
HR[a] (95% CI)	0.84 (0.71, 1.00) *P* = 0.026[b]	



- Locally advanced or metastatic UC
- No prior chemotherapy for advanced disease

→ Gemcitabine Platinum Atezolizumab

→ Atezolizumab

→ Gemcitabine Platinum Placebo

Patients at risk

Atezo + plt/gem	451	409	362	302	257	222	195	175	142	107	76	45	27	11	4	1	NE
Placebo + plt/gem	400	359	308	255	201	166	146	127	103	72	49	32	19	8	NE	NE	NE

NE, not estimable.
Clinical cut-off: June 14, 2020. Median follow-up: 13.3 mo. [a] Stratified HR.
[b] Did not cross interim OS boundary for statistical significance 0.014.

Data presented at ODAC, April 28, 2021

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IMvigor130: 2nd OS Interim Analysis in ITT
Atezolizumab + Chemotherapy vs. Chemotherapy

Press release November 28, 2022:

Final analysis did not meet the co-primary endpoint of overall survival (OS) for atezolizumab plus chemotherapy compared with chemotherapy alone.

The indication as frontline treatment for urothelial cancer was voluntarily withdrawn

Time (months)

Patients at risk																	
Atezo + plt/gem	451	409	362	302	257	222	195	175	142	107	76	45	27	11	4	1	NE
Placebo + plt/gem	400	359	308	255	201	166	146	127	103	72	49	32	19	8	NE	NE	NE

NE, not estimable.
Clinical cut-off: June 14, 2020. Median follow-up: 13.3 mo. [a] Stratified HR.
[b] Did not cross interim OS boundary for statistical significance 0.014.

Data presented at ODAC, April 28, 2021

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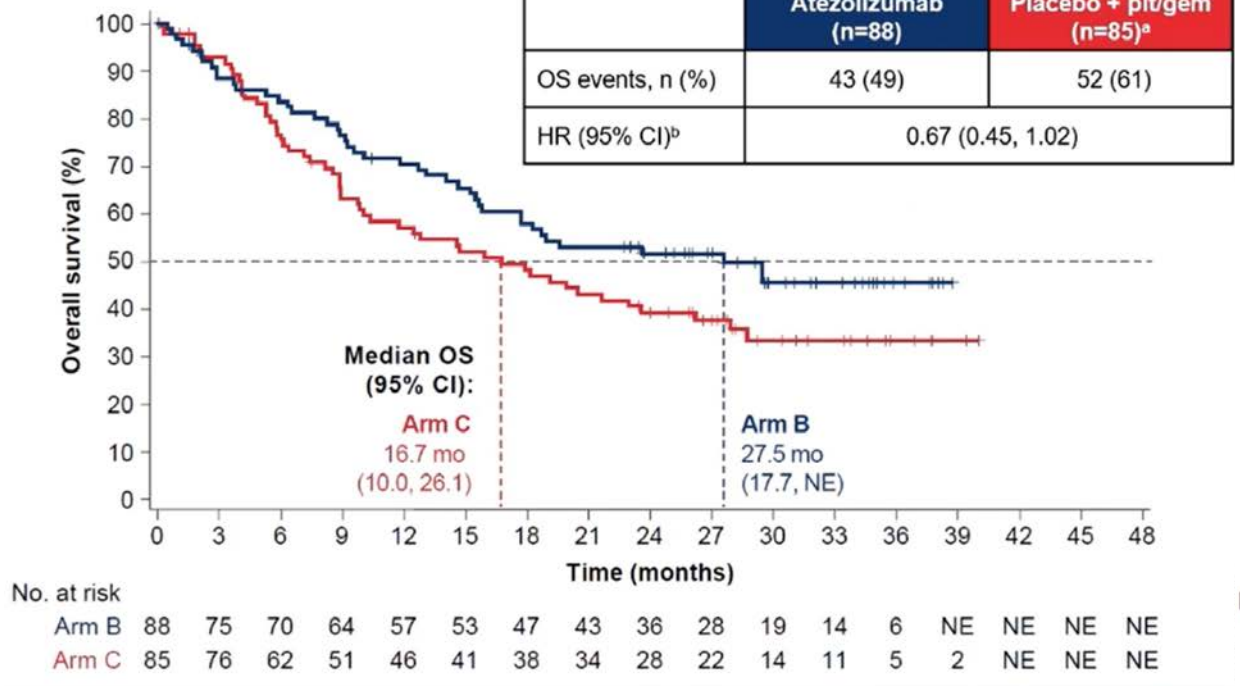
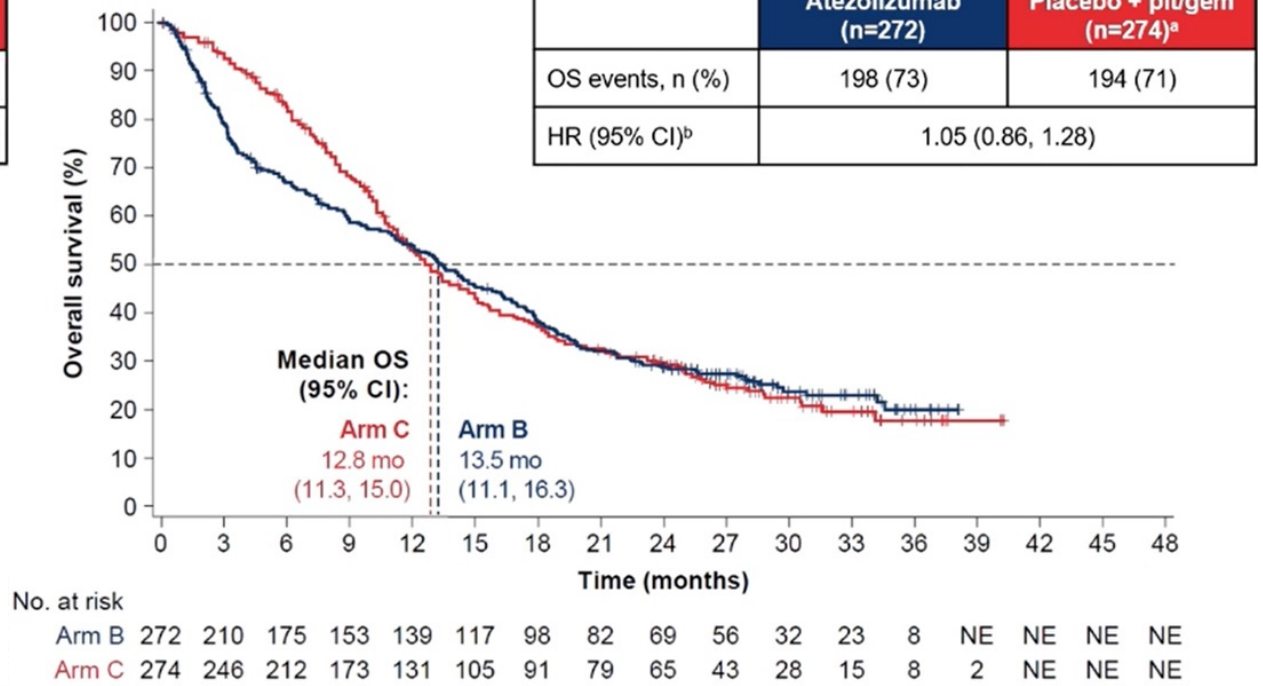
IMvigor130: 2nd Interim OS for atezolizumab vs. chemotherapy: PD-L1 status (Arm B vs Arm C)

	Arm B Atezolizumab (n=88)	Arm C Placebo + plt/gem (n=85)[a]
OS events, n (%)	43 (49)	52 (61)
HR (95% CI)[b]	0.67 (0.45, 1.02)	



PD-L1 IC2/3

	Arm B Atezolizumab (n=272)	Arm C Placebo + plt/gem (n=274)[a]
OS events, n (%)	198 (73)	194 (71)
HR (95% CI)[b]	1.05 (0.86, 1.28)	



PD-L1 IC0/1

- Locally advanced or metastatic UC
- No prior chemotherapy for advanced disease

→ Gemcitabine Platinum Atezolizumab

→ Atezolizumab

→ Gemcitabine Platinum Placebo

Adapted from Davis et al. AACR Annual Meeting 2021

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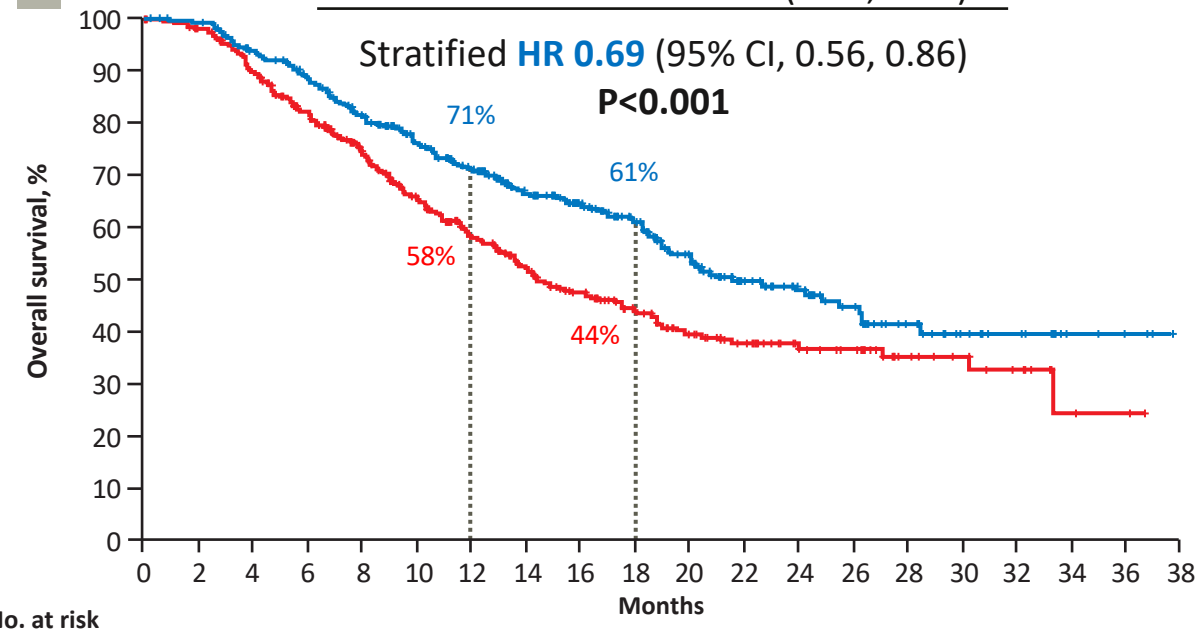
Avelumab improves OS in the overall study population and PDL1+ population

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

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

P<0.001



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

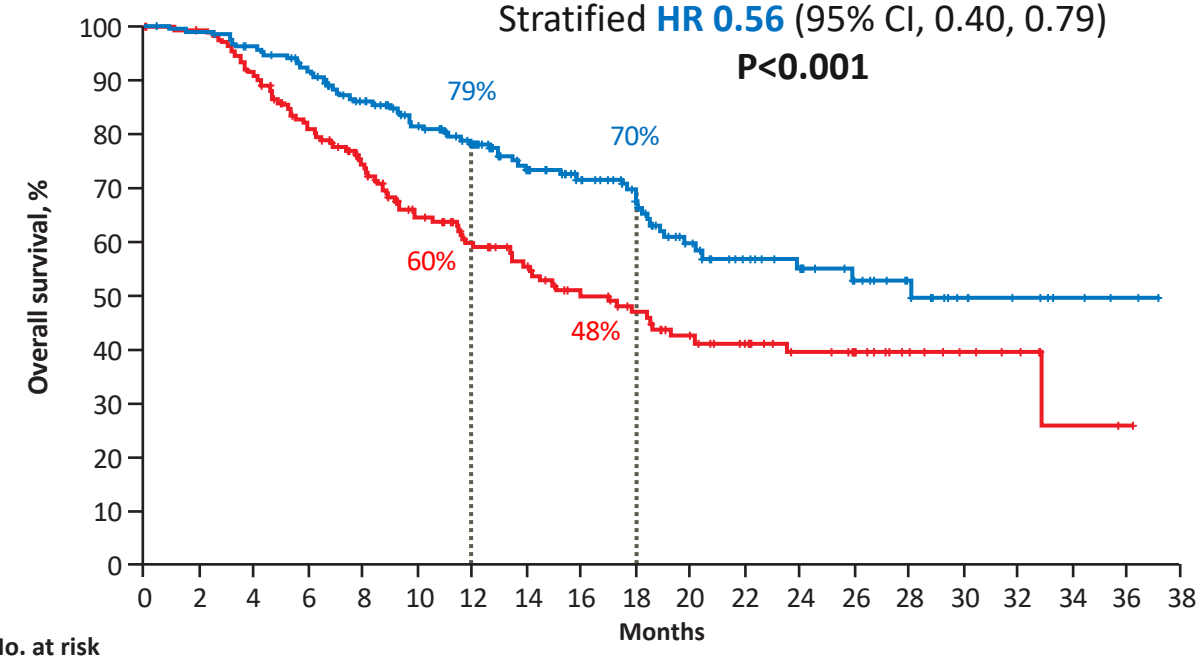
BSC

ITT

Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.3, NE)
BSC alone	**17.1** (13.5, 23.7)

Stratified **HR 0.56** (95% CI, 0.40, 0.79)

P<0.001



No. at risk																				
Avelumab +	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
BSC	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

BSC

PDL1+

Adapted from Powles et al. ASCO 2020

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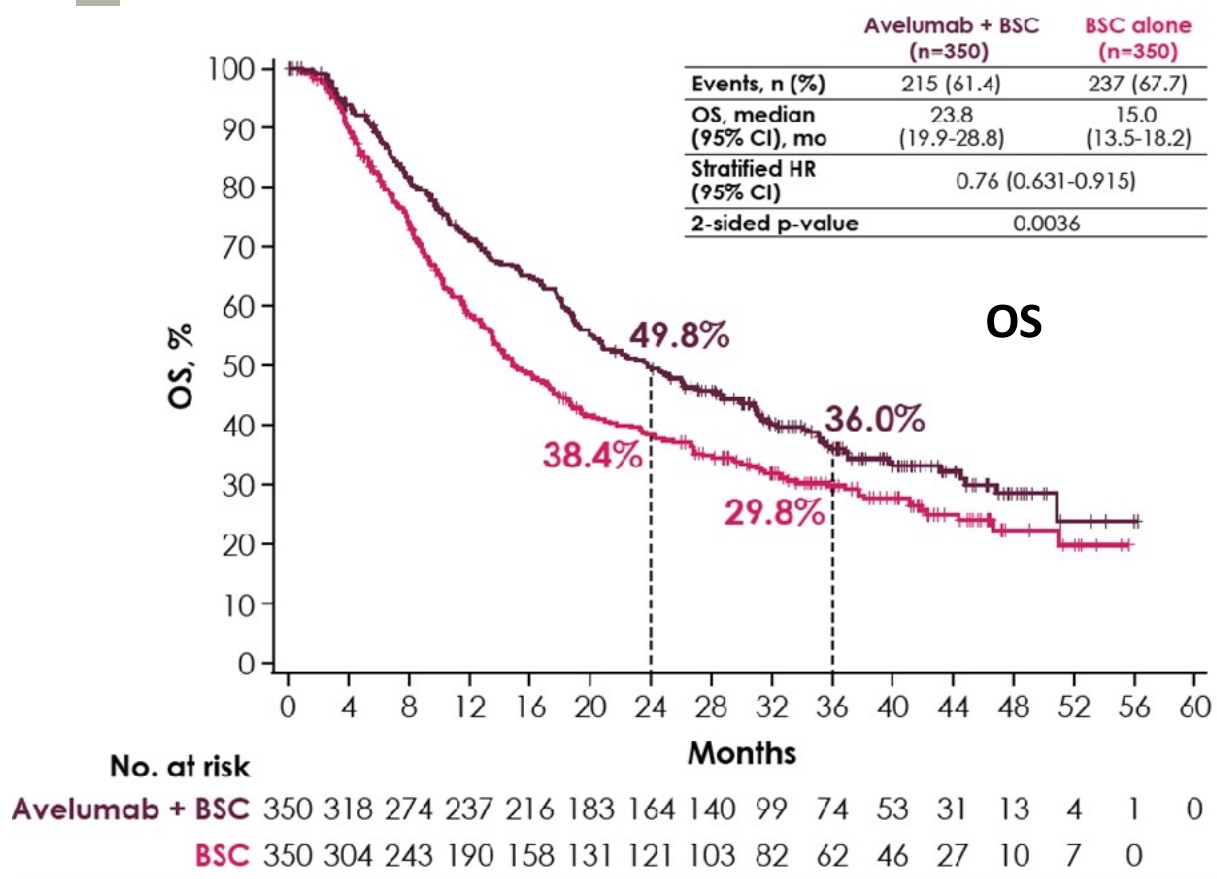
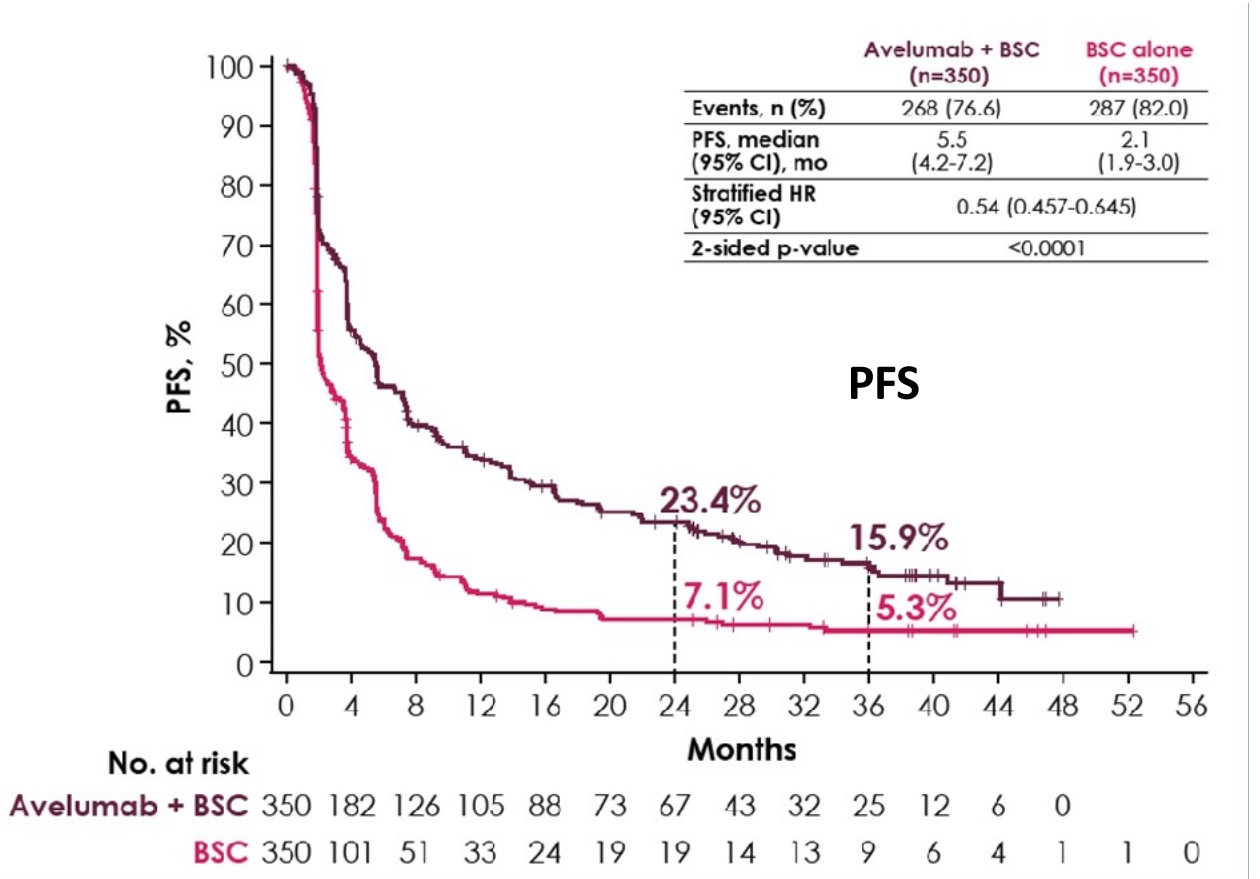
Longer term follow-up (≥ 2 years) confirms initial data





Powles, et al. J Clin Oncol 40, 2022 (suppl 6; abstr 487)

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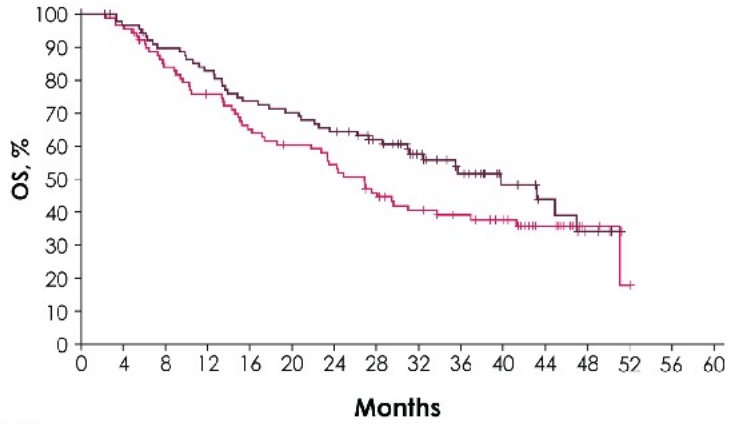
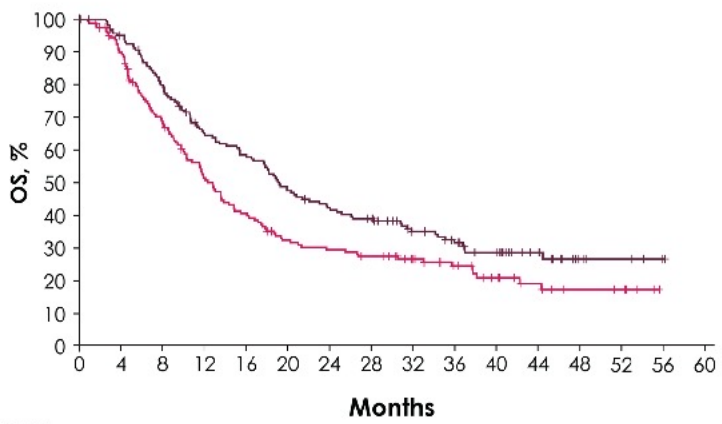
Overall, outcomes favor avelumab no matter prior chemo response

Complete response



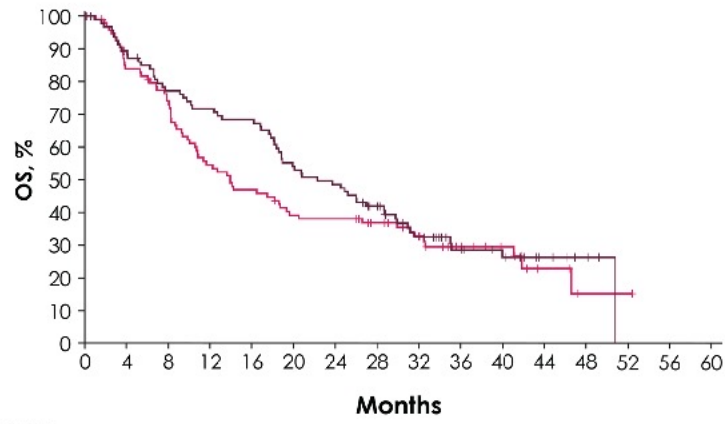
No. at risk														
Avelumab + BSC	90	85	78	72	64	61	56	47	34	24	14	9	4	0
BSC	89	86	72	64	55	50	45	37	30	26	21	13	3	1	0

Partial response



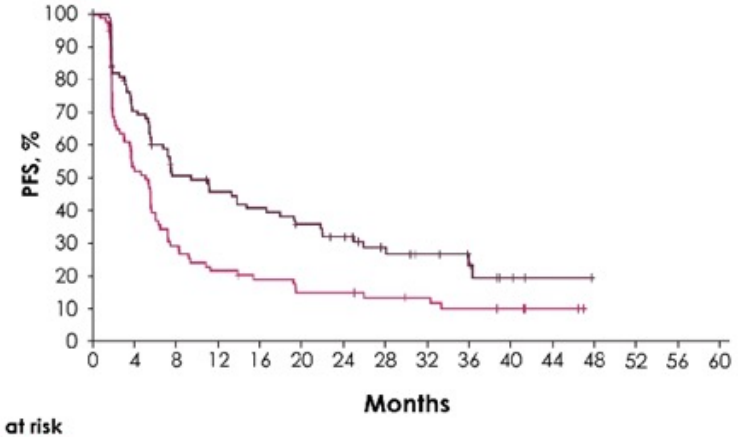
No. at risk															
Avelumab + BSC	163	151	126	100	90	73	64	58	42	35	27	16	6	4	1	0
BSC	163	140	103	76	60	46	42	37	29	22	15	10	6	5	0

Stable disease



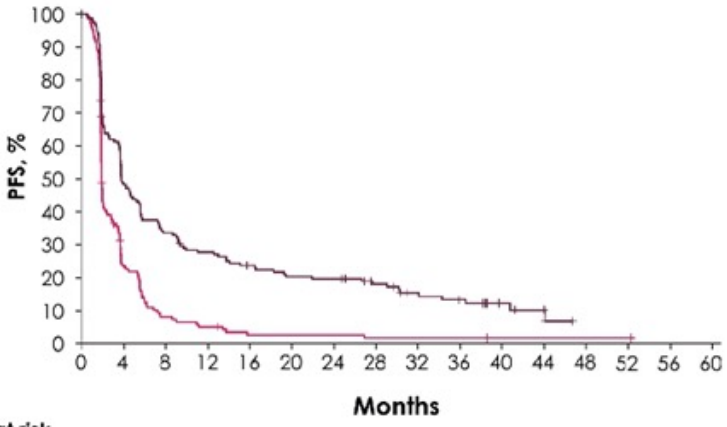
No. at risk														
Avelumab + BSC	97	82	70	65	62	49	44	35	23	15	12	6	3	0
BSC	98	78	68	50	43	35	34	29	23	14	10	4	1	1	0

Complete response



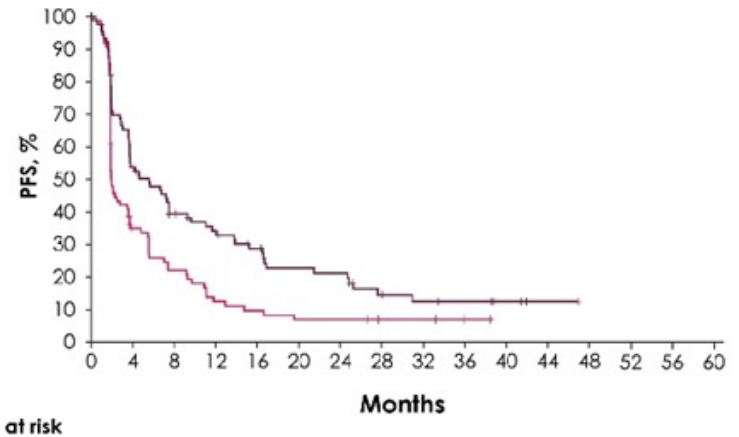
No. at risk													
Avelumab + BSC	90	61	42	37	33	28	24	14	11	7	3	1	0
BSC	89	42	23	17	14	11	11	9	8	6	5	3	0

Partial response



No. at risk														
Avelumab + BSC	163	75	52	42	35	30	29	21	15	13	6	4	0	
BSC	163	32	11	7	3	3	3	2	2	2	1	1	1	1	0

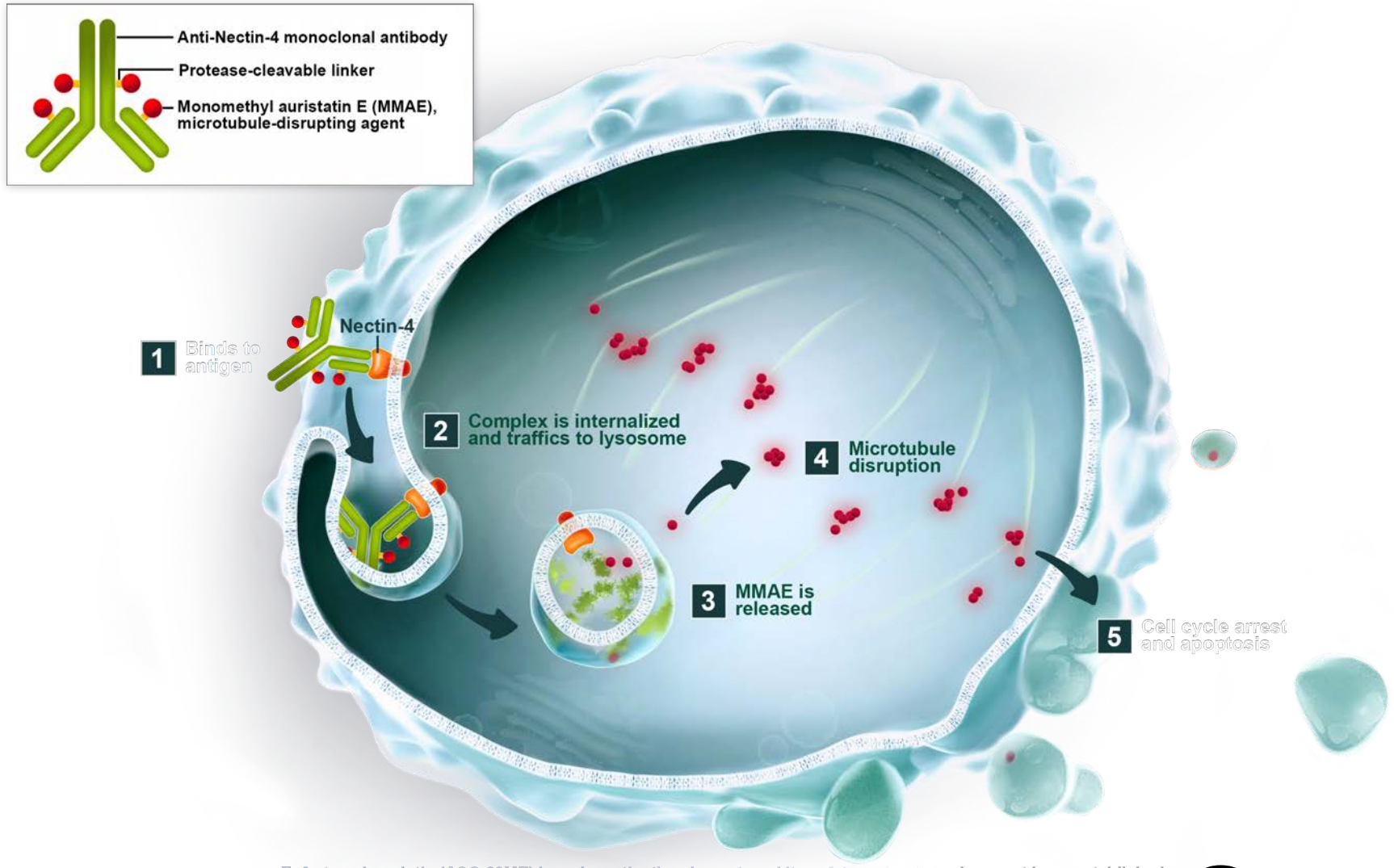
Stable disease



No. at risk													
Avelumab + BSC	97	46	32	26	20	15	14	8	6	5	3	1	0
BSC	98	27	17	9	7	5	5	3	3	1	0

Sridhar et al. ASCO 2022

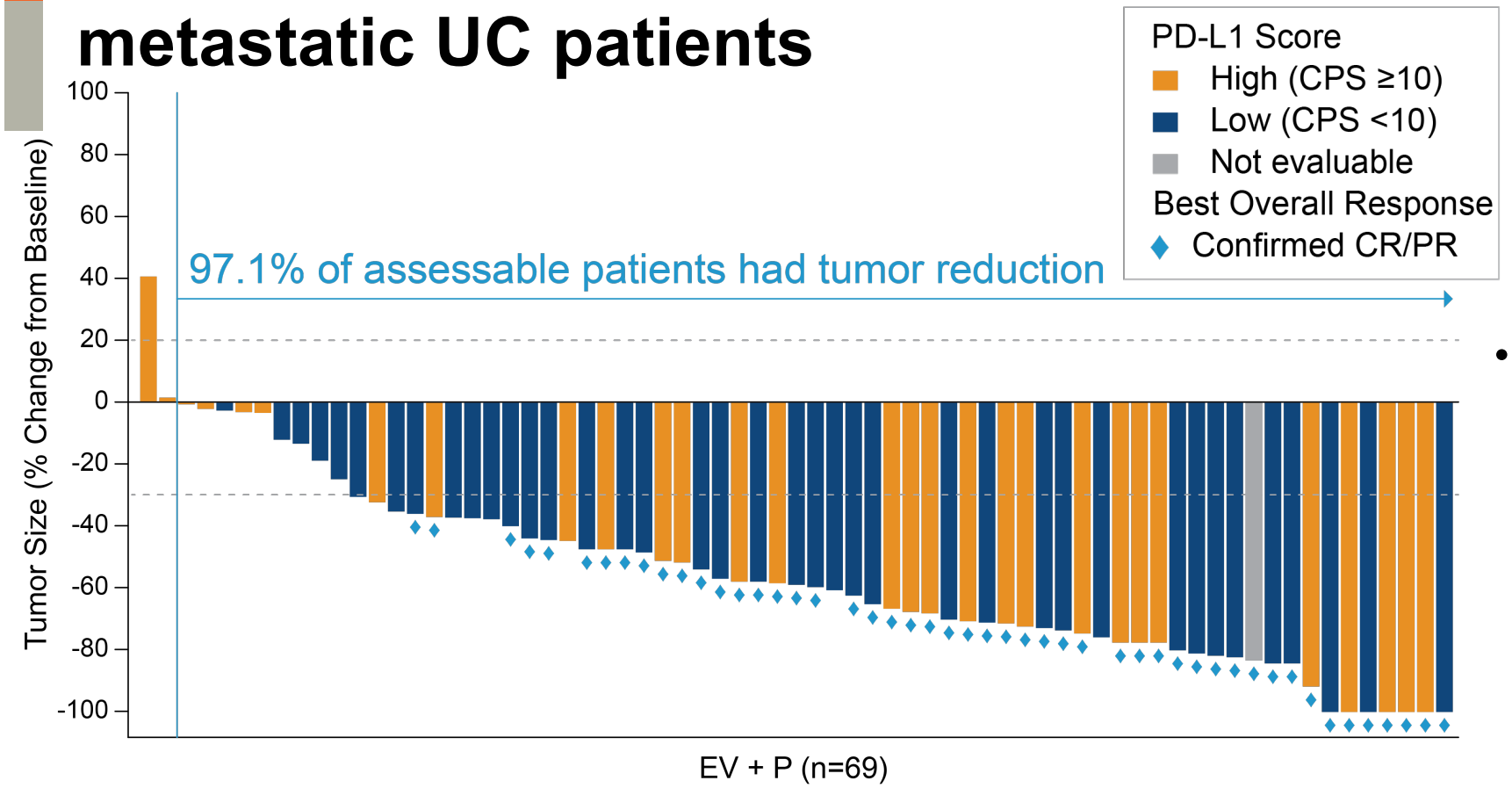
Enfortumab Vedotin: Nectin-4 Targeted Therapy



Enfortumab vedotin (ASG-22ME) is an investigational agent, and its safety and efficacy have not been established.
Enfortumab vedotin is being developed in collaboration with Astellas.

Memorial Sloan Kettering Cancer Center

EV 103 Cohort K:
EV + pembrolizumab tested in randomized noncomparative phase II cohort of cisplatin-ineligible locally advanced or metastatic UC patients



- Activity seen regardless of PD-L1 status
  - 27/44 (61.4%) cORR in CPS<10
  - 21/31 (67.7%) cORR in CPS≥10

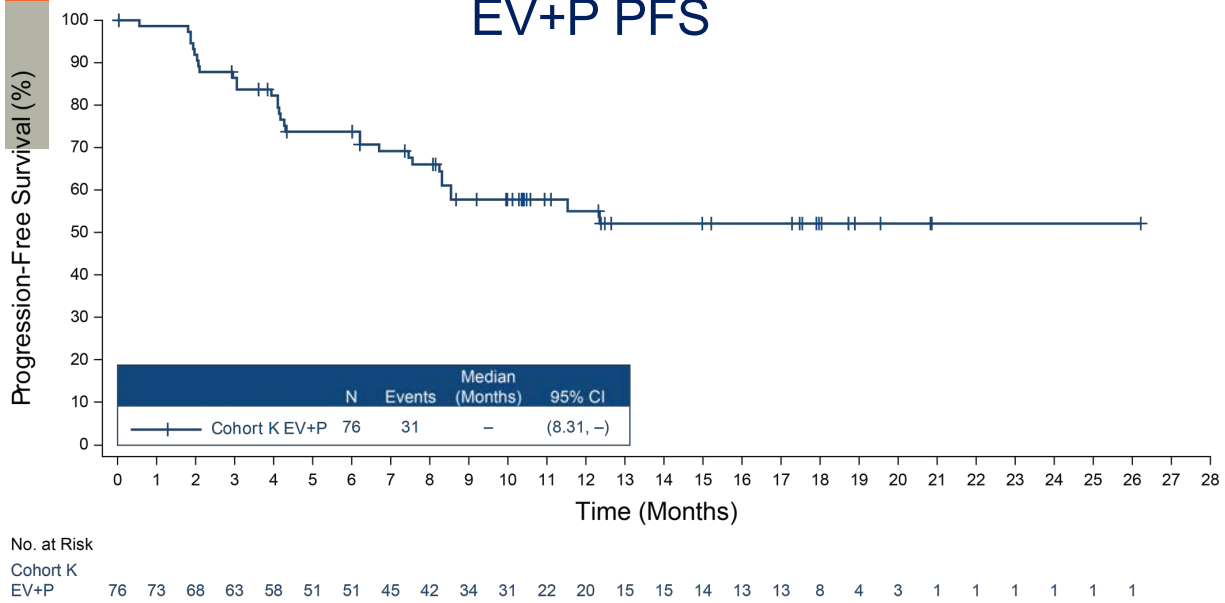
BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

Rosenberg et al. ESMO 2022

Memorial Sloan Kettering Cancer Center

Progression-Free Survival per BICR and Overall Survival

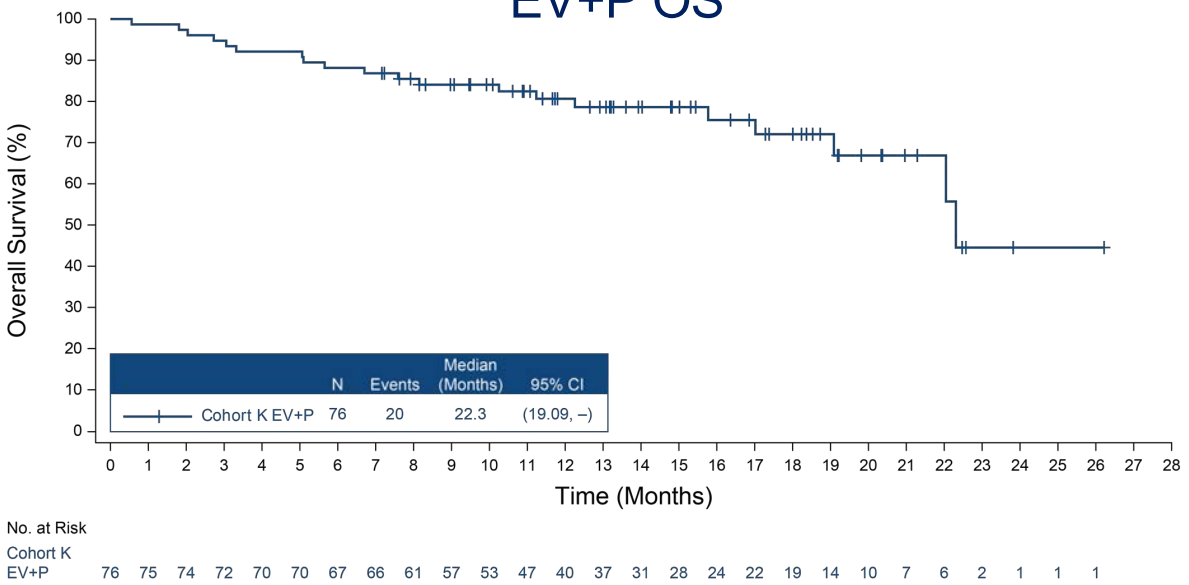
EV+P PFS



No. at Risk

Cohort K EV+P	76	73	68	63	58	51	51	45	42	34	31	22	20	15	15	14	13	13	8	4	3	1	1	1	1	1	1

EV+P OS



No. at Risk

Cohort K EV+P	76	75	74	72	70	70	67	66	61	57	53	47	40	37	31	28	24	22	19	14	10	7	6	2	1	1	1

	EV+P (N=76)	EV Mono (N=73)
PFS events, n	31	38
mPFS (95% CI), mos	- (8.31, -)	8.0 (6.05, 10.35)
PFS at 12 mos, %	55.1%	35.8%

	EV+P (N=76)	EV Mono (N=73)
OS Events, n	20	26
mOS (95% CI), mos	22.3 (19.09, -)	21.7 (15.21, -)
OS at 12 mos, %	80.7%	70.7%
Median follow-up time, mos	14.8	15.0

Data continue to evolve

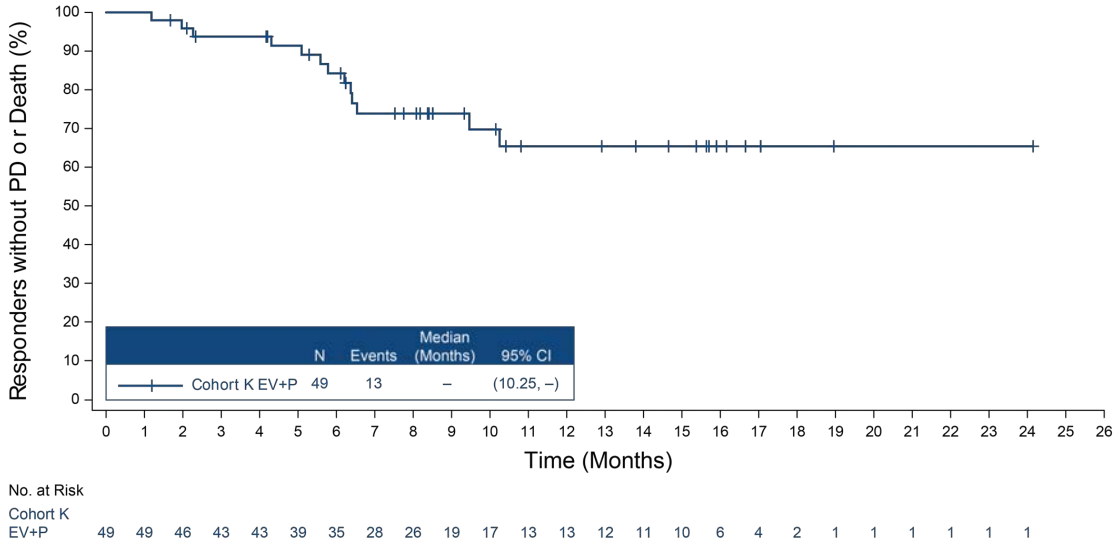
Rosenberg et al. ESMO 2022

Memorial Sloan Kettering Cancer Center

EV+Pembro: Duration of Response

- Median DOR for EV+P was not reached
- 65.4% of responders were still responding at 12 months

EV+P DOR



	EV+P (N=76)	EV Mono (N=73)
Responders, n	49	33
Progression events, n	13	14
mDOR (95% CI), mos	- (10.25, -)	13.2 (6.14, 15.97)
DOR ≥12 mos, %	65.4%	56.3%

Rosenberg et al. ESMO 2022

Memorial Sloan Kettering Cancer Center

EV-103 Cohort K: Treatment-Related Adverse Events (TRAEs)

Most common AEs with EV+P were fatigue, peripheral sensory neuropathy, alopecia, and maculo-papular rash

TRAEs **Any Grades** by Preferred Term **≥20% of Patients**	EV+P (N=76) n (%)		EV Mono (N=73) n (%)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Overall	76 (100.0)	48 (63.2)	68 (93.2)	35 (47.9)
Fatigue	43 (56.6)	7 (9.2)	29 (39.7)	6 (8.2)
Peripheral sensory neuropathy	39 (51.3)	1 (1.3)	32 (43.8)	2 (2.7)
Alopecia	35 (46.1)	0	26 (35.6)	0
Rash maculo-papular	35 (46.1)	13 (17.1)	21 (28.8)	1 (1.4)
Pruritus	30 (39.5)	3 (3.9)	19 (26.0)	1 (1.4)
Dysgeusia	23 (30.3)	0	25 (34.2)	0
Weight decreased	23 (30.3)	3 (3.9)	21 (28.8)	1 (1.4)
Diarrhea	22 (28.9)	5 (6.6)	20 (27.4)	4 (5.5)
Decreased appetite	20 (26.3)	0	28 (38.4)	0
Nausea	19 (25.0)	0	25 (34.2)	1 (1.4)
Dry eye	15 (19.7)	0	8 (11.0)	0

Serious TRAEs
- 18 (23.7%) EV+P
- 11 (15.1%) EV Mono

TRAEs leading to death (per investigator)
- 3 (3.9%) EV+P (Pneumonitis, Respiratory failure, Sepsis)
- 2 (2.7%) EV Mono (Multiple organ dysfunction, Respiratory failure)

Rosenberg et al. ESMO 2022

EV-103 Cohort K EV Treatment-Related Adverse Events of Special Interest (AESI)

	EV+P (N=76)		EV Mono (N=73)	
	Any Grade n (%)	**Grade ≥3 n (%)**	**Any Grade n (%)**	**Grade ≥3 n (%)**
Skin reactions	51 (67.1)	16 (21.1)	33 (45.2)	6 (8.2)
Peripheral neuropathy	46 (60.5)	2 (2.6)	40 (54.8)	2 (2.7)
Ocular disorders	20 (26.3)	0	21 (28.8)	0
Dry eye	18 (23.7)	0	9 (12.3)	0
Blurred vision	9 (11.8)	0	10 (13.7)	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
  - No serious skin reactions occurred with EV+P
- Peripheral neuropathy remains the most common reason for treatment-related discontinuations

The majority of treatment-related AESIs were grade ≤2

Rosenberg et al. ESMO 2022

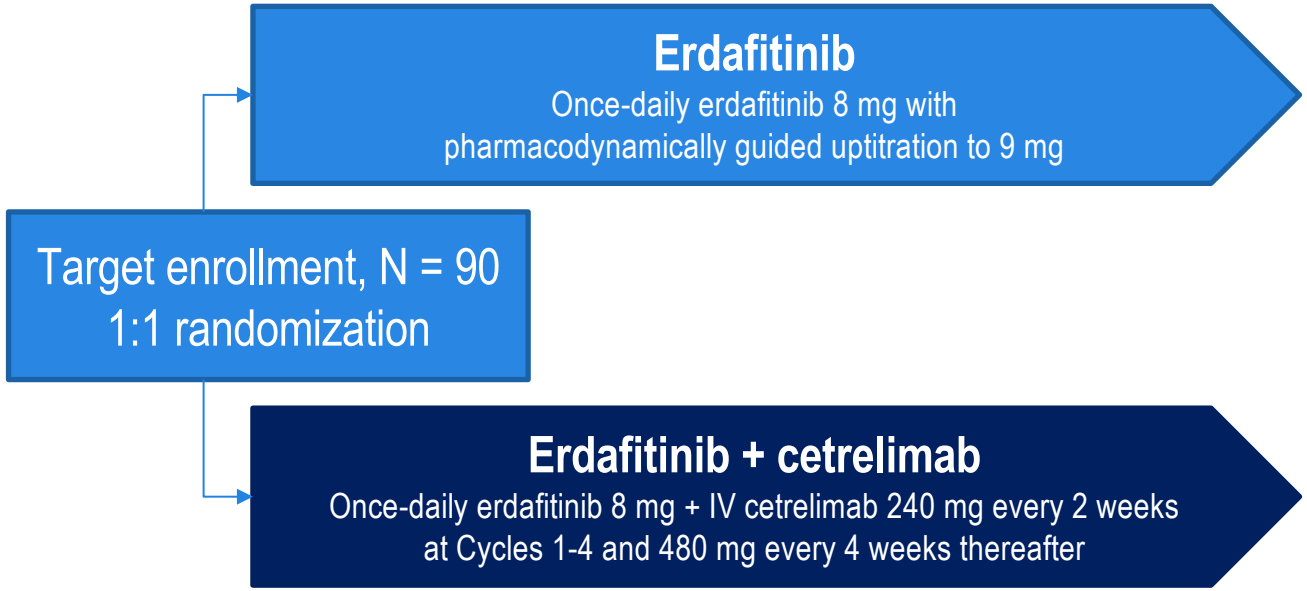
Memorial Sloan Kettering Cancer Center

FGFR3+CPI: NORSE Phase 2 Study Design

Key eligibility criteria

- Age ≥ 18 years
- mUC diagnosis
- Ineligible for cisplatin
- Select *FGFRa* (mutation/fusion)
- Measurable disease
- No prior systemic therapy for mUC

Patients with any PD-L1 status could be enrolled



Primary end points

- ORR
- Safety

Key secondary end points

- DCR
- DOR
- Time to response

No formal statistical comparisons between arms are prespecified

Point estimates along with 95% CI will be presented for each arm.

Powles et al. ESMO 2021

NCT03473743

Memorial Sloan Kettering Cancer Center

Interim analysis: NORSE Trial of erdafitinib and cetrelimab

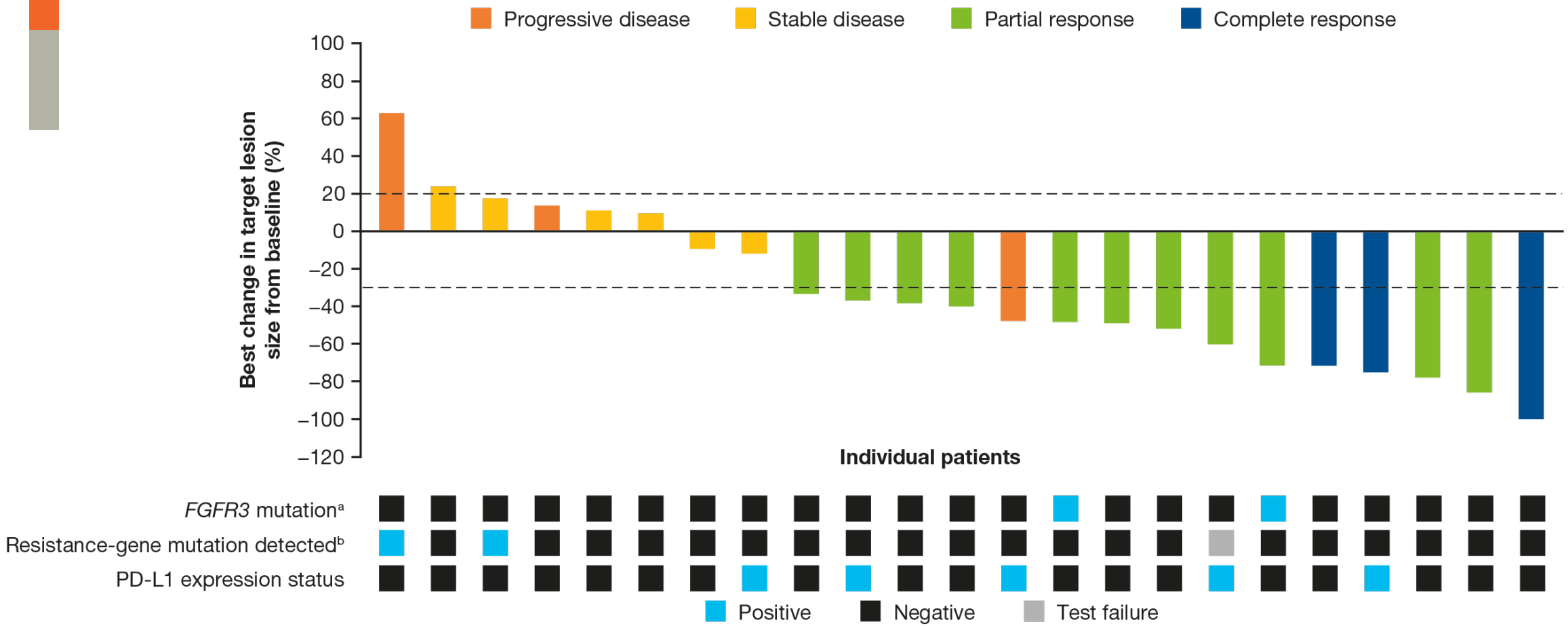
	Erdafitinib (n = 18)	Erdafitinib + Cetrelimab (n = 19)
ORR[a], n (%) [95% CI]	6 (33%) [13%-59%]	13 (68%) [43%-87%]
Complete response, n (%)	1 (6%)	4 (21%)
Partial response, n (%)	5 (28%)	9 (47%)
DOR, median, months [95% CI]	NE [4.4-NE]	6.9 [1.6-NE]
Responses ongoing, n (%)	5 (28%)	10 (53%)
Time to response, median (range), months	2.3 (1-6)	1.8 (1-4)
DCR, n (%) [95% CI]	18 (100%) [82%-100%]	17 (90%) [67%-99%]

- High ORR, small number of patients
- Study has completed accrual, further data awaited

Powles et al. ESMO 2021

Memorial Sloan Kettering Cancer Center

Similar results seen in FORT-2: mUC (n=26) treated with rogaratinib and atezolizumab



ORR 58%, 13% CR

Of the **14** responders, **11** (**79%**) had low or negative PD-L1 expression

Rosenberg et al. ASCO 2021

Memorial Sloan Kettering Cancer Center

Metastatic urothelial cancer treatment is rapidly evolving

- First line platinum-based chemotherapy is standard
- EV + pembrolizumab is showing significant promise
- Maintenance avelumab after response is standard
- EV monotherapy as 2nd/3rd line therapy currently
- FGFR inhibition + CPI remains a promising area of further investigation

Module 3: Selection and Sequencing of Therapy for Relapsed/Refractory mUBC — Dr Siefker-Radtke

Case Presentation: 65-year-old man with metastatic bladder cancer and PD on cisplatin/gemcitabine, now receiving sacituzumab govitecan

Dr Priya Rudolph (Athens, Georgia)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Priya Rudolph, MD, PhD

What is your experience with the efficacy and tolerability of the 2 antibody-drug conjugates approved for use in patients with UBC (enfortumab vedotin, sacituzumab govitecan)?

What do you believe is the optimal sequence of these agents?

Case Presentation: 65-year-old man with de novo metastatic urothelial bladder cancer, s/p gemcitabine/carboplatin (rapid PD), now receiving pembrolizumab — FGFR3 mutation

Dr Yanjun Ma (Murfreesboro, Tennessee)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Yanjun Ma, MD

In general, what would be your third-line systemic treatment after combination chemotherapy followed by immunotherapy for a patient with mUBC and an FGFR3 mutation?

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

Selection and Sequencing: Targeted Therapy in Metastatic Urothelial Cancer

Arlene Siefker-Radtke, MD
Professor
Department of Genitourinary Medical Oncology

CHOOSING A GOOD TARGET

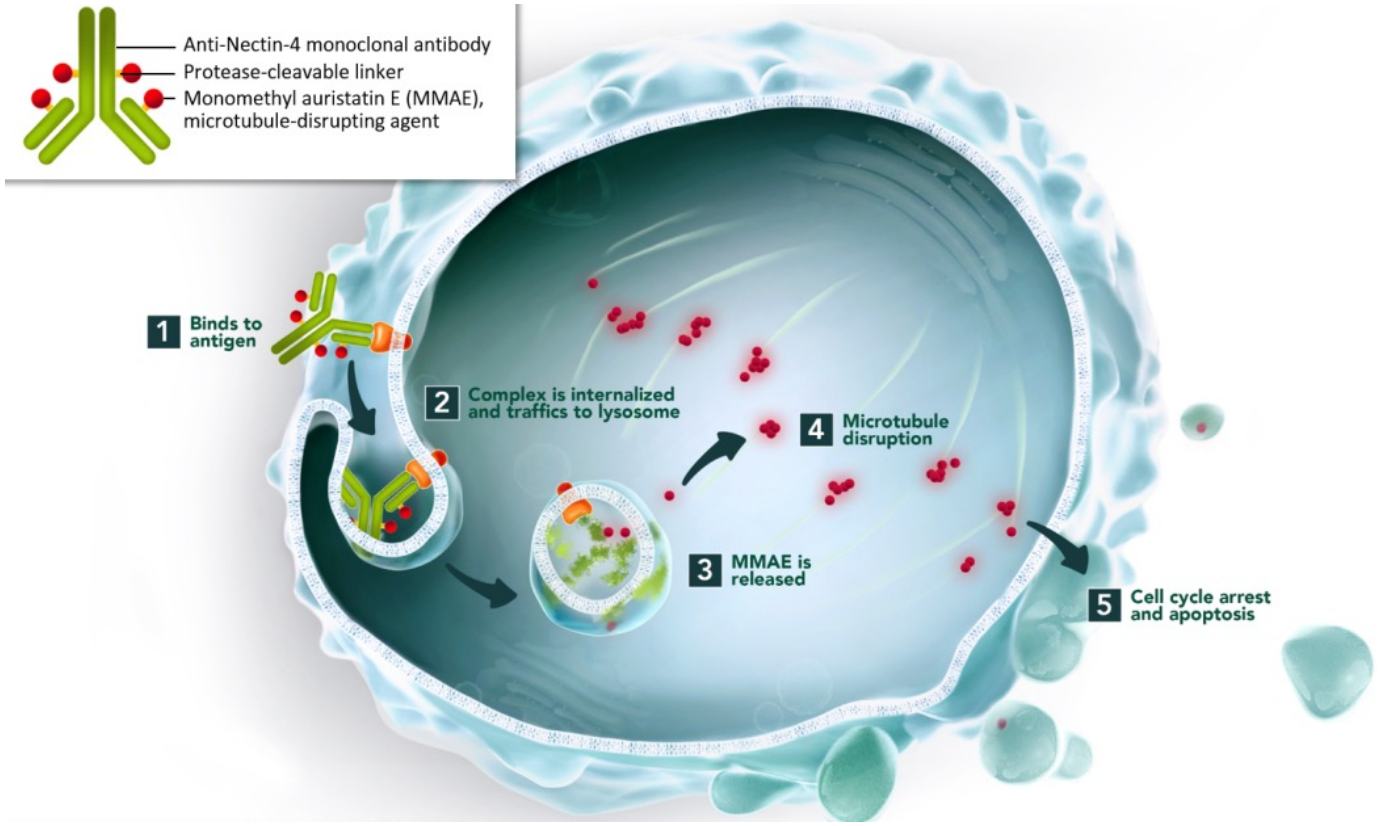
Easily reproducible

- Anyone can do it
- CLIA certification
- Not open to interpretation/everyone agrees
- Does not fluctuate or change

Predicts response or benefit!


Enfortumab Vedotin:
The First Antibody Drug Conjugate in mUC

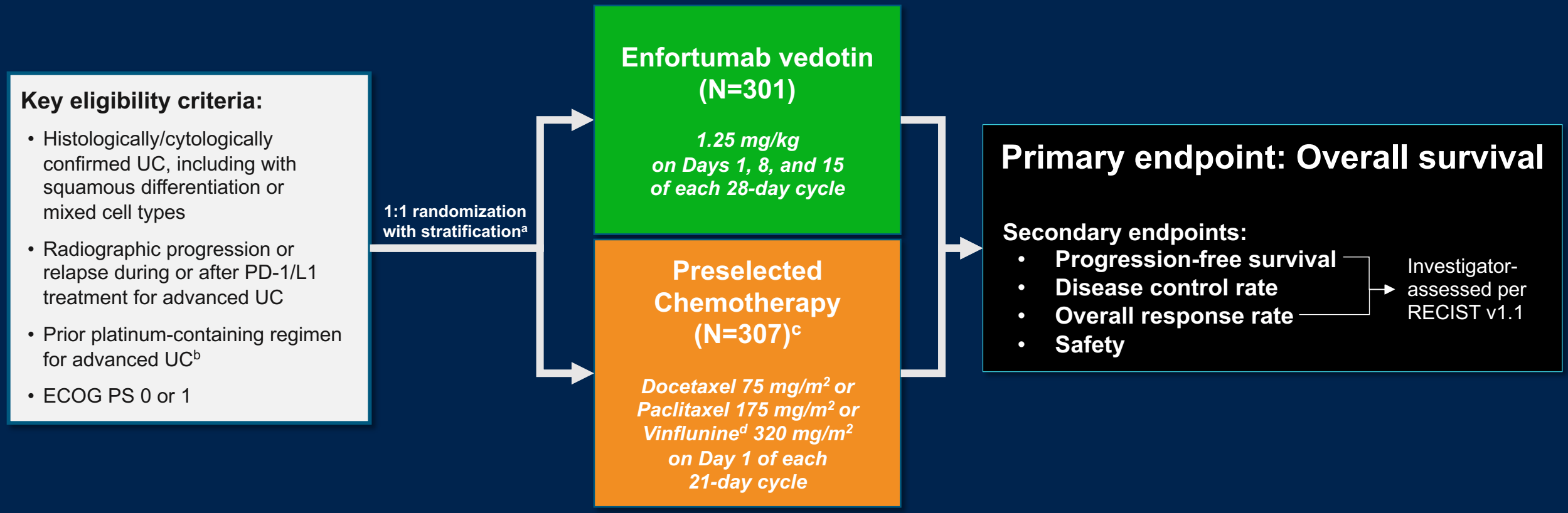
Enfortumab Vedotin



- Fully humanized monoclonoclonal antibody targeting Nectin-4
- Nectin-4
  - A transmembrane cell adhesion molecule
  - Expressed in 93% of mUC patient samples
- “Payload” is auristatin-E, a microtubule disrupting agent
- Antibody is conjugated by a protease cleavable linker

Abstract 393

EV-301 Open-Label Phase 3 Trial Design



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

PRESENTED AT: Genitourinary Cancers Symposium

PRESENTED BY: Thomas Powles

Overall Survival

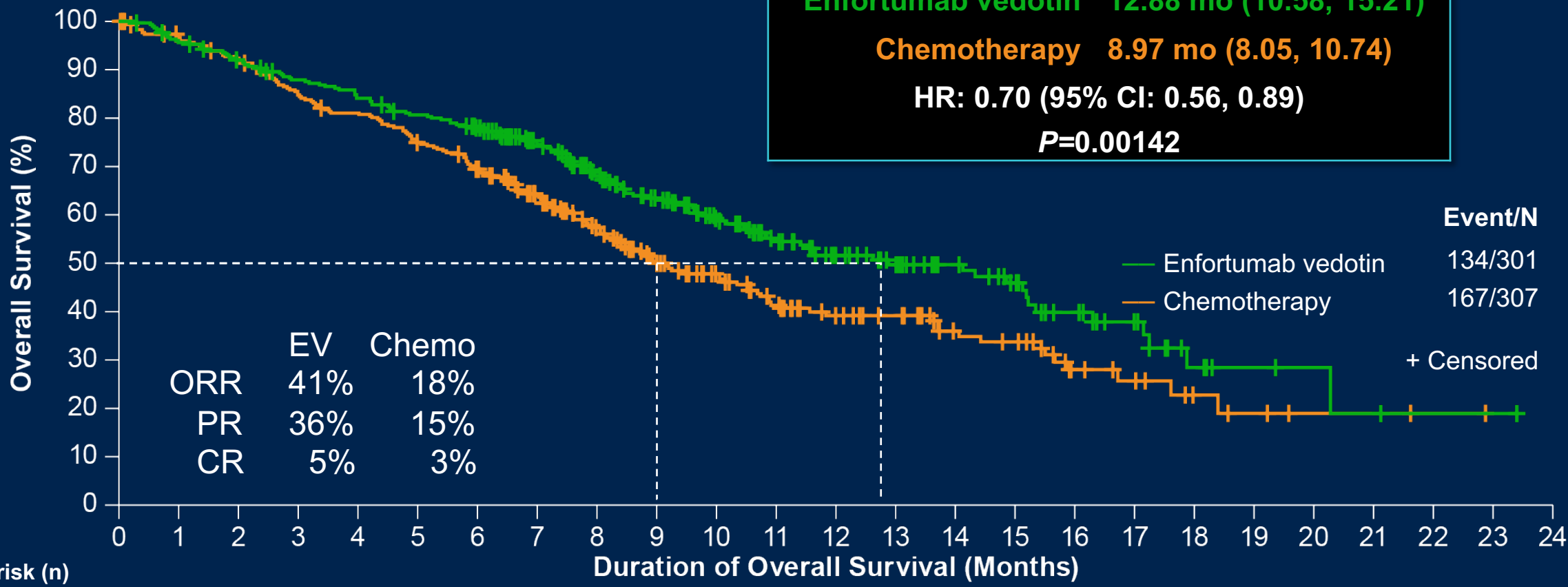
Median OS

Enfortumab vedotin 12.88 mo (10.58, 15.21)

Chemotherapy 8.97 mo (8.05, 10.74)

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

***P*=0.00142**



Patients at risk (n)

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

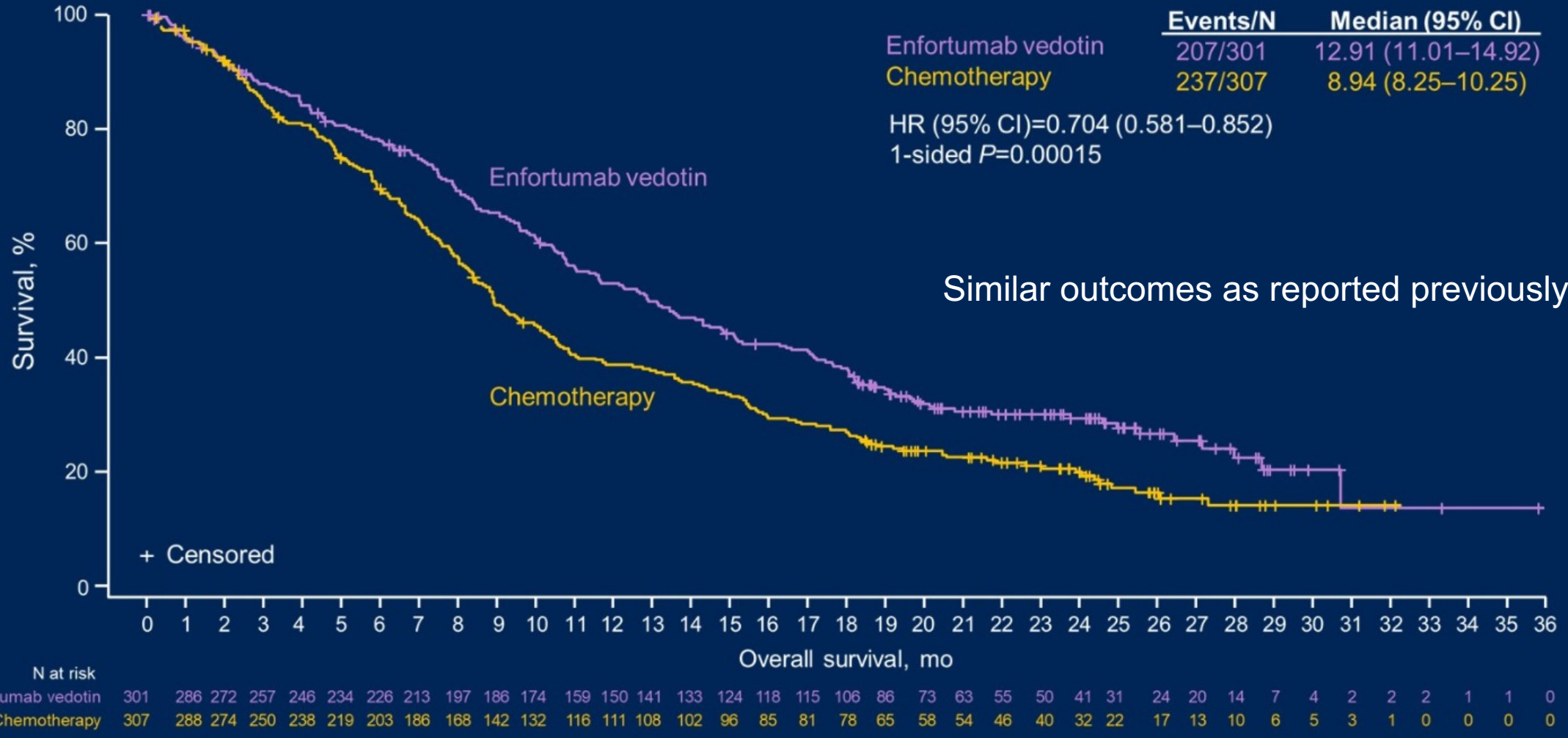
Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off: July 15, 2020

PRESENTED AT: Genitourinary Cancers Symposium

PRESENTED BY: Thomas Powles

Overall Survival



	Events/N	Median (95% CI)
Enfortumab vedotin	207/301	12.91 (11.01–14.92)
Chemotherapy	237/307	8.94 (8.25–10.25)

HR (95% CI)=0.704 (0.581–0.852)
1-sided *P*=0.00015

Similar outcomes as reported previously!

Data shown for intention-to-treat population.
HR, hazard ratio.

Data cutoff date: July 30, 2021

Adverse Events of Special Interest[a] (Safety Population)

Treatment-related adverse event, n (%)	Enfortumab vedotin (N=296)						Chemotherapy (N=291)					
		Grade						Grade				
	Any	1	2	3	4	5	Any	1	2	3	4	5
Rash	133 (44.9)	41 (13.9)	48 (16.2)	43 (14.5)	1 (0.3)	NR	28 (9.6)	21 (7.2)	6 (2.1)	1 (0.3)	0	NR
Severe cutaneous adverse reaction	60 (20.3)	20 (6.8)	25 (8.4)	14 (4.7)	1 (0.3)	NR	22 (7.6)	12 (4.1)	8 (2.7)	2 (0.7)	0	NR
Peripheral neuropathy	142 (48.0)	36 (12.2)	84 (28.4)	22 (7.4)	NR	NR	92 (31.6)	43 (14.8)	41 (14.1)	8 (2.7)	NR	NR
Peripheral neuropathy sensory events	135 (45.6)	35 (11.8)	82 (27.7)	18 (6.1)	NR	NR	89 (30.6)	42 (14.4)	39 (13.4)	8 (2.7)	NR	NR
Peripheral neuropathy motor events	23 (7.8)	6 (2.0)	11 (3.7)	6 (2.0)	NR	NR	7 (2.4)	5 (1.7)	2 (0.7)	0	NR	NR
Dry eye	48 (16.2)	34 (11.5)	12 (4.1)	2 (0.7)	NR	NR	9 (3.1)	6 (2.1)	2 (0.7)	1 (0.3)	NR	NR
Blurred vision	13 (4.4)	11 (3.7)	2 (0.7)	0	NR	NR	6 (2.1)	5 (1.7)	0	1 (0.3)	NR	NR
Corneal disorders	2 (0.7)	2 (0.7)	NR	NR	NR	NR	0	0	NR	NR	NR	NR
Infusion-related reaction	27 (9.1)	12 (4.1)	11 (3.7)	4 (1.4)	NR	NR	14 (4.8)	7 (2.4)	7(2.4)	0	NR	NR
Systemic infusion-related reaction event	24 (8.1)	11 (3.7)	9 (3.0)	4 (1.4)	NR	NR	9 (3.1)	4 (1.4)	5 (1.7)	0	NR	NR
Local infusion-related reaction event	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR	7 (2.4)	5 (1.7)	2 (0.7)	0	NR	NR
Infusion-site reaction	2 (0.7)	0	2 (0.7)	0	NR	NR	5 (1.7)	4 (1.4)	1 (0.3)	0	NR	NR
Extravasation-site reaction	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR
Hyperglycemia	20 (6.8)	3 (1.0)	4 (1.4)	12 (4.1)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	0

MedDRA, Medical Dictionary for Regulatory Activities; NR, not reported.

[a]Adverse events of special interest to enfortumab vedotin. Events represent listings by preferred term and are sponsor-specific query/customized medical queries or standard MedDRA queries. Order of adverse events is as it appears in the Supplementary Appendix to the EV-301 primary publication (Powles, et al. *N Engl J Med.* 2021;384:1125-1135).

Data cutoff date: July 30, 2021

Adverse Events of Special Interest[a] (Safety Population)

Treatment-related adverse event, n (%)	Enfortumab vedotin (N=296)						Chemotherapy (N=291)					
	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash	133 (44.9)	41 (13.9)	48 (16.2)	43 (14.5)	1 (0.3)	NR	28 (9.6)	21 (7.2)	6 (2.1)	1 (0.3)	0	NR
Severe cutaneous adverse reaction										2 (0.7)	0	NR
Peripheral neuropathy										8 (2.7)	NR	NR
Peripheral neuropathy sensory events										8 (2.7)	NR	NR
Peripheral neuropathy motor events										0	NR	NR
Dry eye										1 (0.3)	NR	NR
Blurred vision										1 (0.3)	NR	NR
Corneal disorders										NR	NR	NR
Infusion-related reaction										0	NR	NR
Systemic infusion-related reaction event										0	NR	NR
Local infusion-related reaction event										0	NR	NR
Infusion-site reaction	2 (0.7)	0	2 (0.7)	0	NR	NR	5 (1.7)	4 (1.4)	1 (0.3)	0	NR	NR
Extravasation-site reaction	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR
Hyperglycemia	20 (6.8)	3 (1.0)	4 (1.4)	12 (4.1)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	0

WARNING: SERIOUS SKIN REACTIONS

See full prescribing information for complete boxed warning.

- **Enfortumab vedotin can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).**
- **Immediately withhold enfortumab vedotin and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue enfortumab vedotin in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions. (2.2), (5.1) (6.1)**

MedDRA, Medical Dictionary for Regulatory Activities; NR, not reported.

[a]Adverse events of special interest to enfortumab vedotin. Events represent listings by preferred term and are sponsor-specific query/customized medical queries or standard MedDRA queries. Order of adverse events is as it appears in the Supplementary Appendix to the EV-301 primary publication (Powles, et al. *N Engl J Med.* 2021;384:1125-1135).

Data cutoff date: July 30, 2021

Metabolism of Enfortumab Vedotin

- Metabolite MMAE
  - 17% recovered in feces over 1 week period
  - 6% recovered in urine over 1 week period
- Dose reduction
  - Renal impairment: No differences in AUC for mild-mod-severe
    - no significant dose reductions
    - Effect on end-stage renal disease/dialysis is unknown
  - Liver impairment: Mild hepatic impairment 48% AUC increase in MMAE
    - Mild hepatic impairment: bilirubin 1-1.5 x ULN with NL AST and ALT or bilirubin ≤ ULN and AST > ULN
    - Frequency of ≥ Grade 3 adverse reactions and deaths in moderate (Child-Pugh B) or severe (Child-Pugh C)
- AVOID use in moderate-severe hepatic impairment

FDA Package insert 12/2019

Monitoring Caveats

- Grade-3-4 hyperglycemia increase in greater BMI and higher HgbA1C
  - HgbA1C ≥ 8 excluded
- HOLD for:
  - Glucose > 250 mg/dL
    - Could be a sign of impaired clearance of MMAE
    - Mechanism unknown
    - ~~Personal hypothesis: impaired glycogen storage as a sign of saturation of liver metabolism~~
    - New Hypothesis: potent tubule stabilization resulting in decreased glucose transport and muscle weakness resulting in decreased glucose utilization and even rhabdomyolysis
  - Peeling skin or bullous skin lesions
    - May have more diffuse rash preceding this
  - Grade 3 diarrhea


Erdafitinib:
The First Biomarker Targeted Therapy in mUC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Y. Loriot, A. Necchi, S.H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran, S.T. Tagawa, Y. Zakharia, B. Zhong, K. Stuyckens, A. Santiago-Walker, P. De Porre, A. O'Hagan, A. Avadhani, and A.O. Siefker-Radtke, for the BLC2001 Study Group*

ABSTRACT

NEJM July 25, 2019.

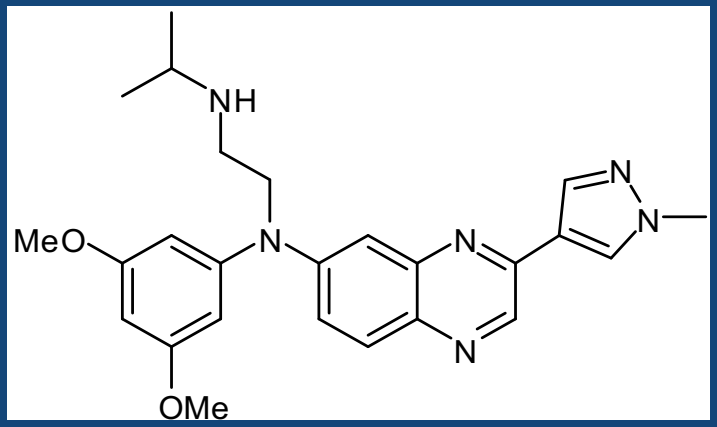
Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of a phase 2 study

*Arlene O Siefker-Radtke, Andrea Necchi, Se Hoon Park, Jesús García-Donas, Robert A Huddart, Earle F Burgess, Mark T Fleming, Arash Rezazadeh Kalebasty, Begoña Mellado, Sergei Varlamov, Monika Joshi, Ignacio Duran, Scott T Tagawa, Yousef Zakharia, Sydney Akapame, Ademi E Santiago-Walker, Manish Monga, Anne O'Hagan, Yohann Loriot, on behalf of the BLC2001 Study Group**

The Lancet Oncology, February, 2022.

Erdafitinib Is a Potent FGFR Inhibitor

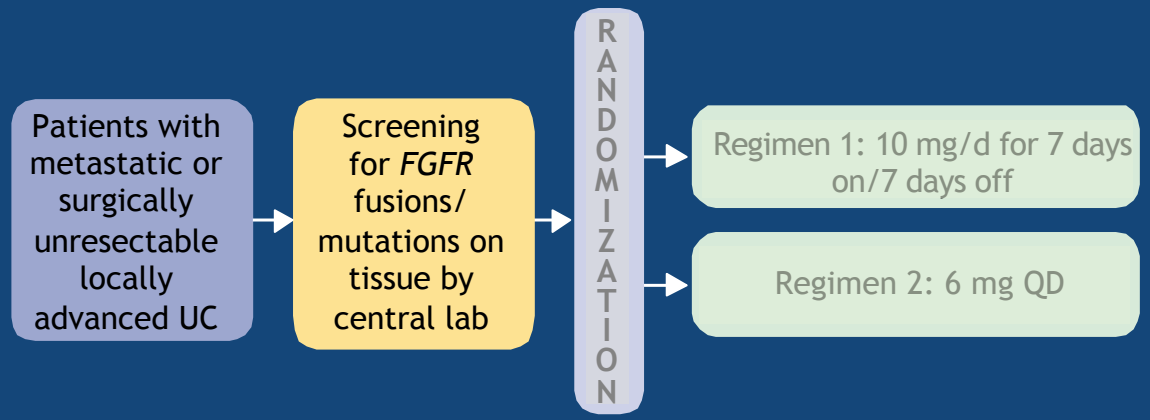
- Erdafitinib* is an oral pan-FGFR (1-4) inhibitor with IC_{50} in the single-digit nanomolar range[1]
- Erdafitinib is taken up by lysosomes, resulting in sustained intracellular release, which may contribute to its long-lasting activity[1]
- Erdafitinib has demonstrated promising activity in patients with metastatic or unresectable UC and other histologies (eg, cholangiocarcinoma) with *FGFR* alterations[2-5]



Abbreviation: IC_{50}, drug concentration at which 50% of target enzyme activity is inhibited.

1. Perera TPS, et al. *Mol Cancer Ther*. 2017;16:1010-1020.
2. Tabernero J, et al. *J Clin Oncol*. 2015;33:3401-3408.
3. Soria J-C, et al. ESMO 2016. Abstract 781PD.
4. Loriot Y, et al. ASCO GU 2018. Abstract 411.
5. Siefker-Radtke A, et al. ASCO GU 2018. Abstract 450.

Phase 2 BLC2001 Study Design



Regimen 3[a]:
8 mg QD with PD Uptitration to 9 mg QD
n = 99

Primary end point
ORR
Secondary end points
PFS, DoR, OS, safety, predictive biomarker evaluation, and PK

Patients
• Progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo OR • Chemo-naïve: cisplatin ineligible per protocol criteria[b]
• Prior immunotherapy was allowed

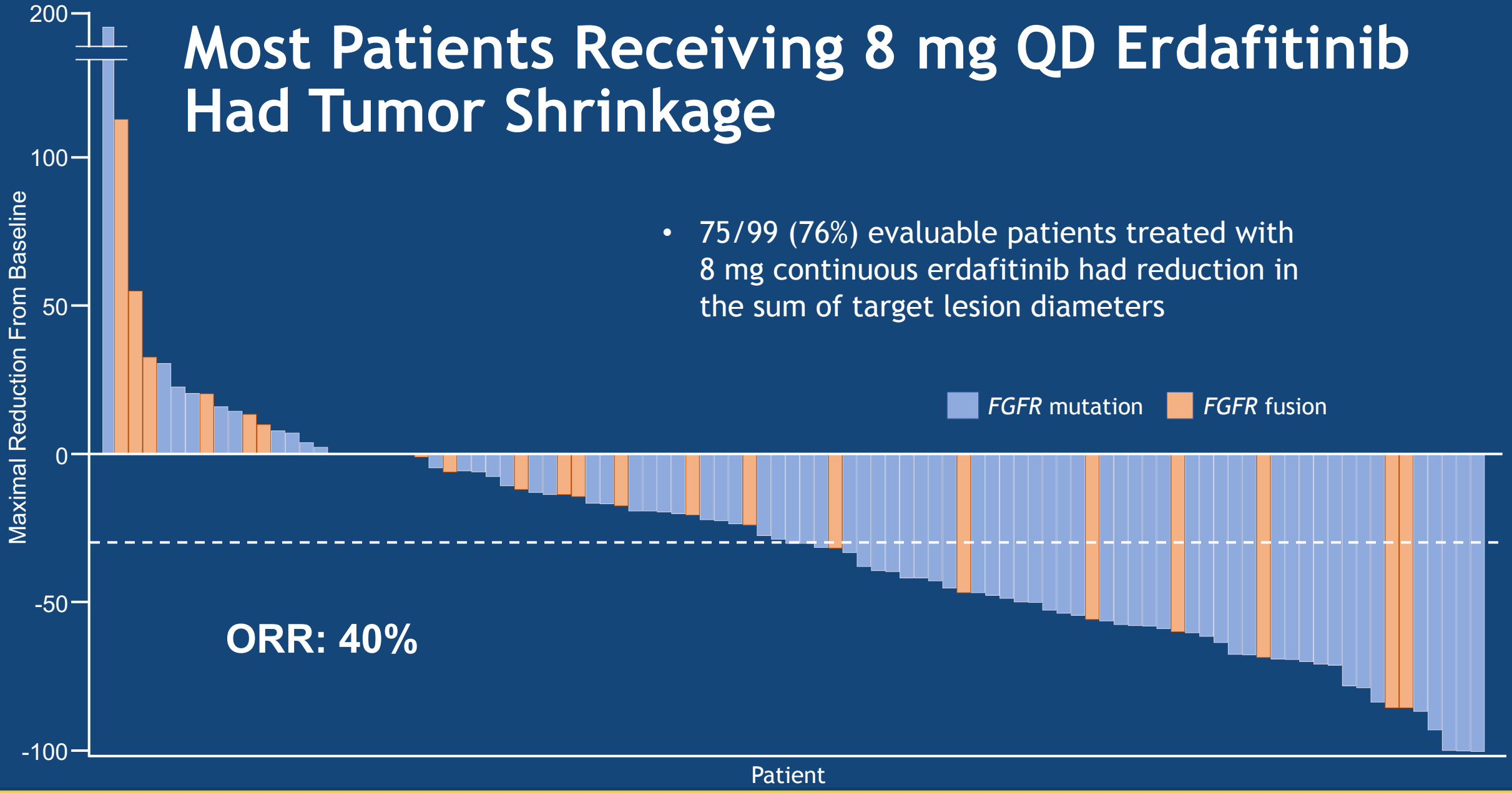
Primary hypothesis:
- ORR in Regimen 3 is > 25%
- One-sided α = 0.025
- 85% power

[a]Dose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.
[b]Ineligibility for cisplatin: impaired renal function or peripheral neuropathy.

Abbreviations: DoR, duration of response; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; QD, daily; TRAEs, treatment-related adverse events.

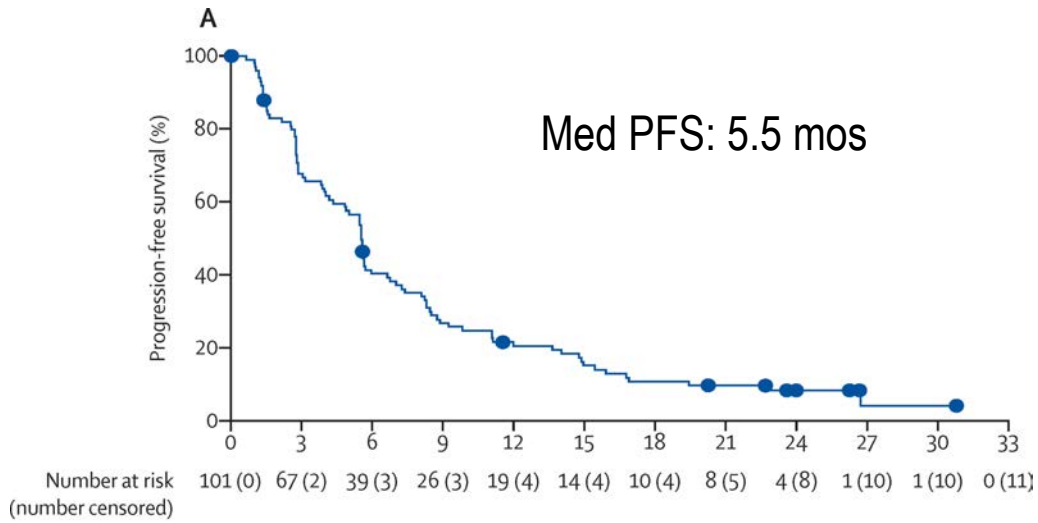
Most Patients Receiving 8 mg QD Erdafitinib Had Tumor Shrinkage

- 75/99 (76%) evaluable patients treated with 8 mg continuous erdafitinib had reduction in the sum of target lesion diameters

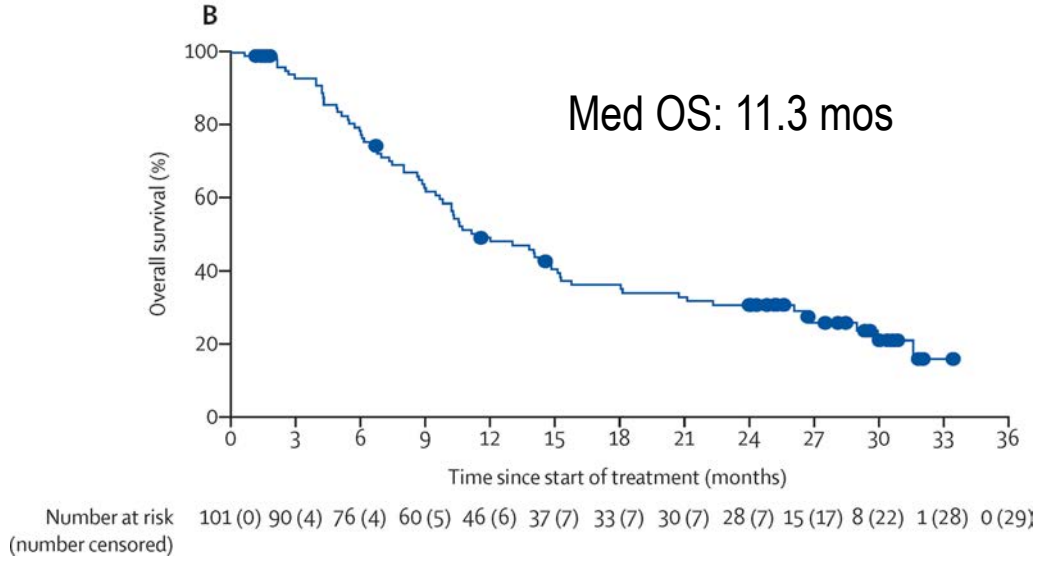


Erdafitinib – Long-term Outcomes

	Participants (n=101)*
Age, years	67 (61–73)
ECOG performance status	
0	51 (50%)
1	43 (43%)
2	7 (7%)
Pretreatment†	
Progressed or relapsed after chemotherapy	89 (88%)
Chemotherapy-naive	12 (12%)
Previous immunotherapy	24 (24%)
Number of lines of previous treatment‡	
0	10 (10%)
1	48 (48%)
2	28 (28%)
≥3	15 (15%)
Visceral metastases§	
Present	78 (77%)
Absent	23 (23%)
Liver	20 (20%)
Lung	57 (56%)
Bone	23 (23%)
Lymph node metastases only	9 (9%)
Other metastases¶	14 (14%)
Haemoglobin concentration, g/dL	
≥10	86 (85%)
<10	15 (15%)
Primary tumour location	
Upper tract	25 (25%)
Lower tract	76 (75%)
Creatinine clearance rate	
<60 mL/min	53 (52%)
≥60 mL/min	48 (48%)
FGFR alteration	
FGFR mutation present and fusion absent	70 (69%)
FGFR mutation absent and fusion present	25 (25%)
FGFR mutation and fusion present	6 (6%)



Med PFS: 5.5 mos



Med OS: 11.3 mos

Siefker-Radtke et al. Lancet Onc, 2022

Erdafitinib – Most Common Treatment-Related AEs

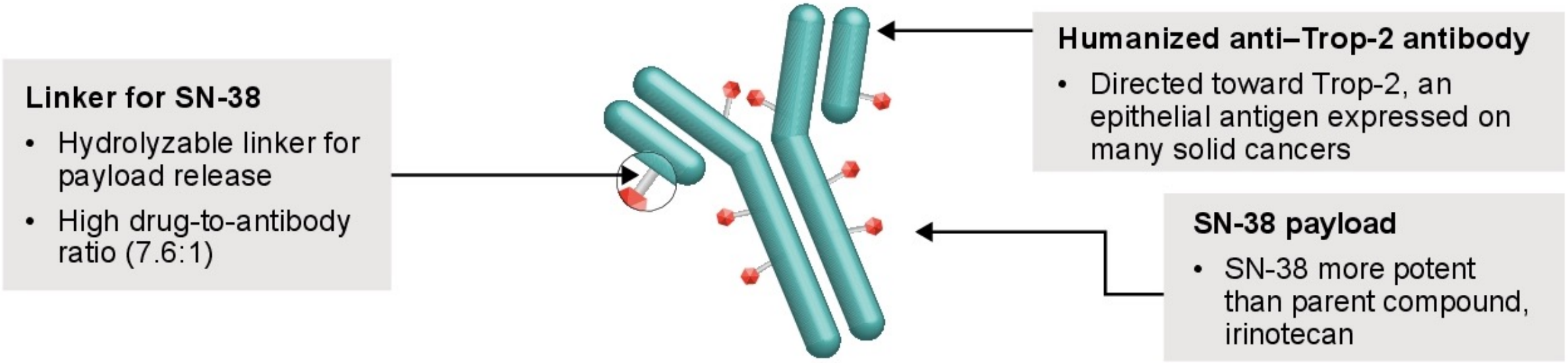
	Grade 1–2	Grade 3	Grade 4	Grade 5*
All treatment-emergent adverse events	29 (29%)	58 (57%)	6 (6%)	8 (8%)
Hyperphosphataemia†	77 (76%)	2 (2%)	0	0
Stomatitis	46 (21%)	14 (14%)	0	0
Diarrhoea	51 (50%)	4 (4%)	0	0
Dry mouth	45 (45%)	1 (1%)	0	0
Decreased appetite	40 (40%)	1 (1%)	0	0
Dysgeusia	39 (39%)	2 (2%)	0	0
Alopecia	34 (34%)	0	0	0
Dry skin	34 (34%)	0	0	0
Fatigue	31 (31%)	2 (2%)	0	0
Constipation	28 (28%)	1 (1%)	0	0
Dry eye	27 (27%)	1 (1%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	20 (20%)	5 (5%)	0	0
Asthaenia	15 (15%)	6 (6%)	0	2 (2%)
Anaemia	17 (17%)	5 (5%)	0	0
Nausea	21 (21%)	1 (1%)	0	0
Alanine aminotransferase increased	17 (17%)	2 (2%)	0	0
Onycholysis	17 (17%)	2 (2%)	0	0
Paronychia	16 (16%)	3 (3%)	0	0
Urinary tract infection	13 (13%)	5 (5%)	0	0
Vision blurred	18 (18%)	0	0	0
Weight decreased	17 (17%)	1 (1%)	0	0
Nail dystrophy	11 (11%)	6 (6%)	0	0

- Majority of events were grade 1-2
- All grade 4 and 5 events were deemed unrelated to erdafitinib by the investigator
- Few patients (N=16) discontinued due to TRAEs
- Most events were treated by dose holds/modification
- More hyperphosphatemia in the non-uptitrated group
- CSR is a known class effect of inhibitors of the MEK and MAPk pathways
  - 27 patients developed CSR
  - Most events occurred within first 3 mo

Siefker-Radtke et al. Lancet Onc, 2022

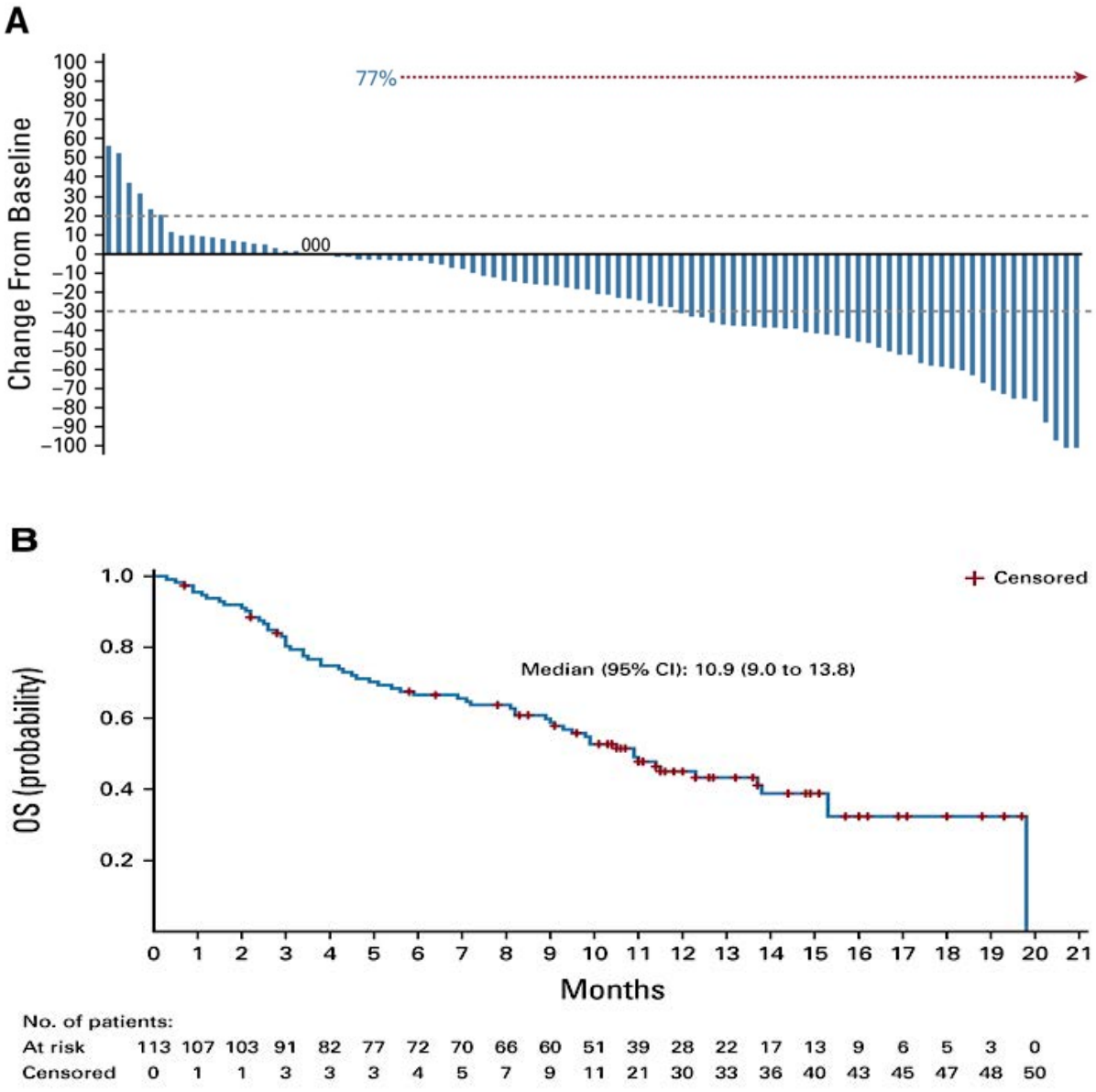

Sacituzumab Govitecan:
The Second Antibody Drug Conjugate in mUC

Sacituzumab Govitecan



- Humanized monoclonal antibody targeting Trop-2 expression
- Trop-2
  - Epithelial antigen expressed on many solid cancers
  - Expressed in ~ 83% of mUC patient samples; testing for expression not necessary
- “Payload” is SN-38, the active metabolite of irinotecan, inhibiting topoisomerase 1
- Payload is conjugated by a hydrolyzable linker

Sacituzumab Govitecan



- N=113, post-platinum and post-IO
- SG 10 mg/kg d1, d8 q 3-wk
- GCSF as clinically indicated
- ORR 27%
- Med PFS: 5.4 mo
- Med OS: 10.9 mo
- Toxicity
  - Neutropenia ≥G3: 34%
  - Diarrhea ≥G3: 10%
- UGT1A homozygous/heterozygous
  - Potential increased risk neutropenia, pre-screening not required

Tagawa, et al. JCO 2021

Sacituzumab Govitecan

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

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

Abbreviation: TRAEs, treatment-related adverse events.

[a]Neutrophil count decreased, WBC count decreased, lymphocyte count decreased, and hemoglobin decreased have been recoded to neutropenia, leukopenia, lymphopenia, and anemia, respectively, for summary purposes.

Tagawa, et al. JCO 2021


Combinations!

Combine targeted therapy with immunotherapy:

- Two great standards go great together!

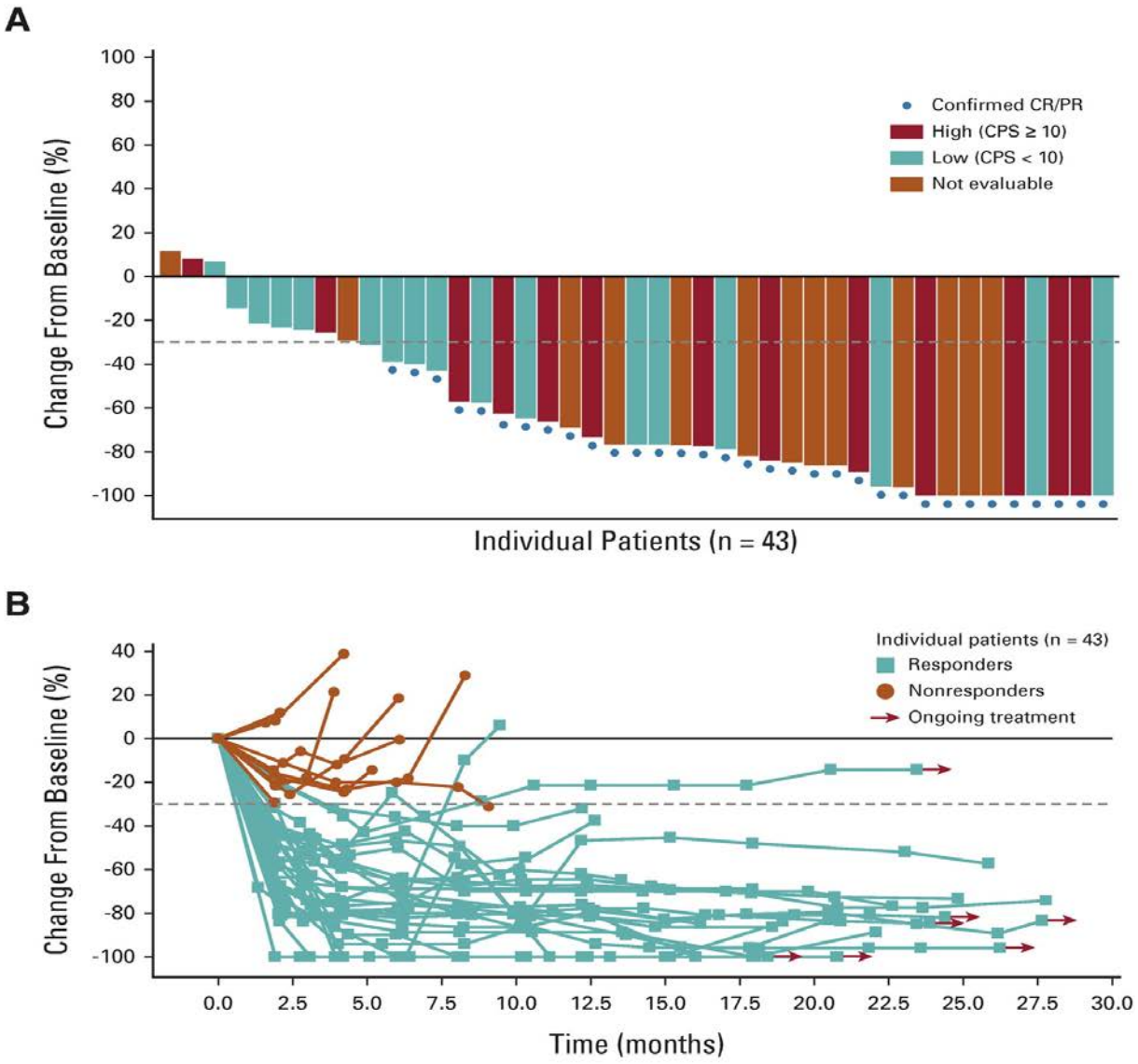
+

=

US/FDA Approval

EU/EMA Approval

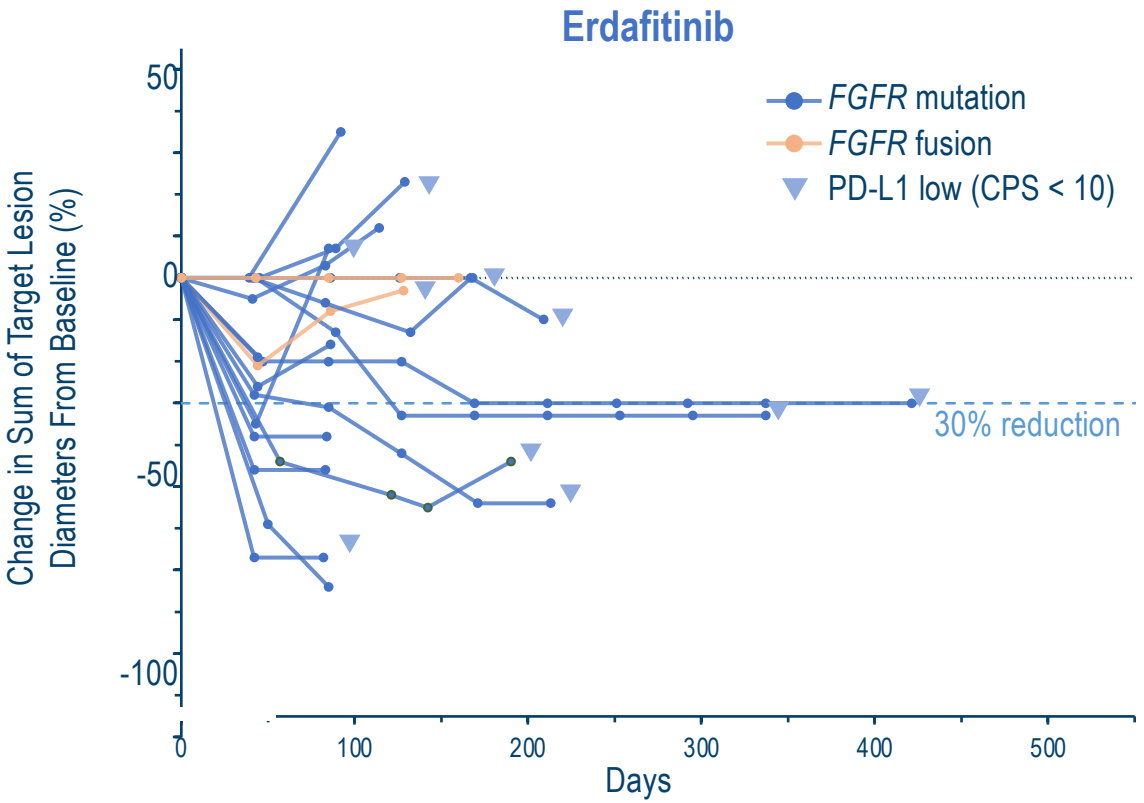
Enfortumab Vedotin + Pembrolizumab

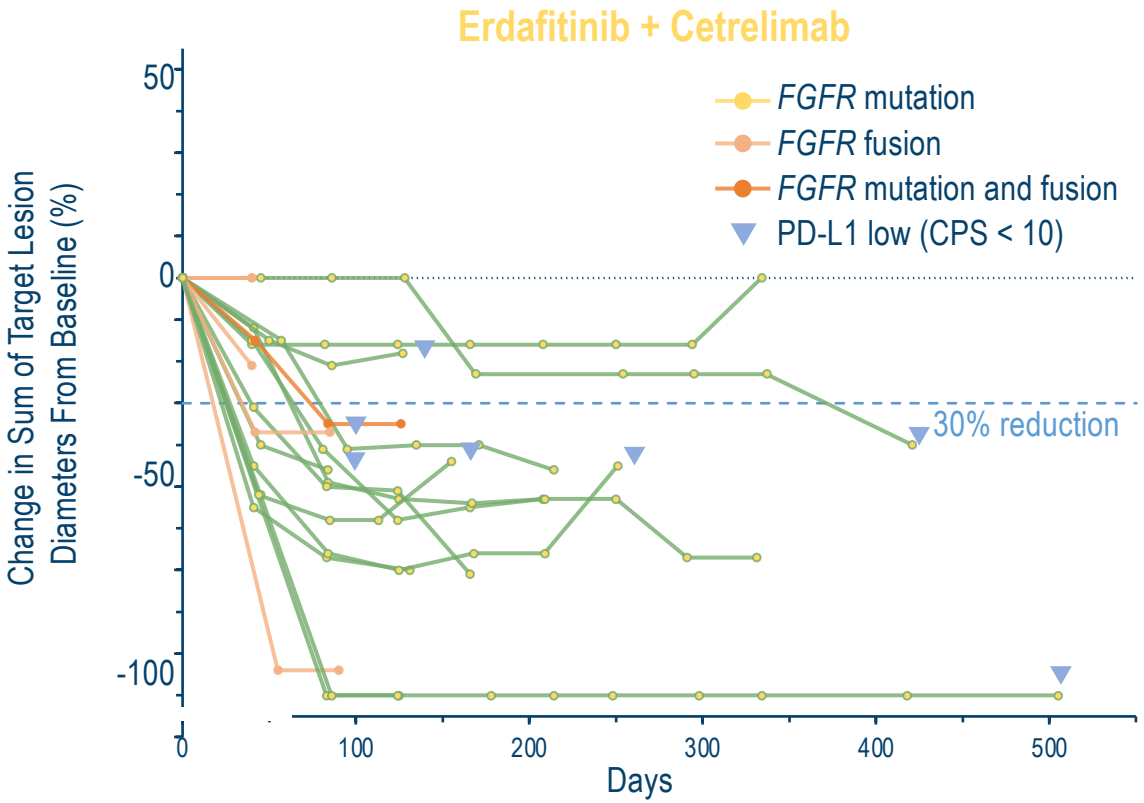


- N=45 cisplatin-ineligible, no prior treatment
- EV 1.25 mg/kg d1, d8 q 3-wk
- Pembrolizumab 200 mg IV q 3-wk
- ORR 73.3%
  - CR 15.6%
- Med DOE: 25.6 Mo
- Med OS: 26.1 Mo
- Most common TRAE:
  - Neuropathy 55.6%
  - Fatigue 51.1%
  - Alopecia 48.9%

Hoimes, et al. JCO 2023

NORSE: Antitumor Activity Over Time, by *FGFRa* type and PD-L1 status



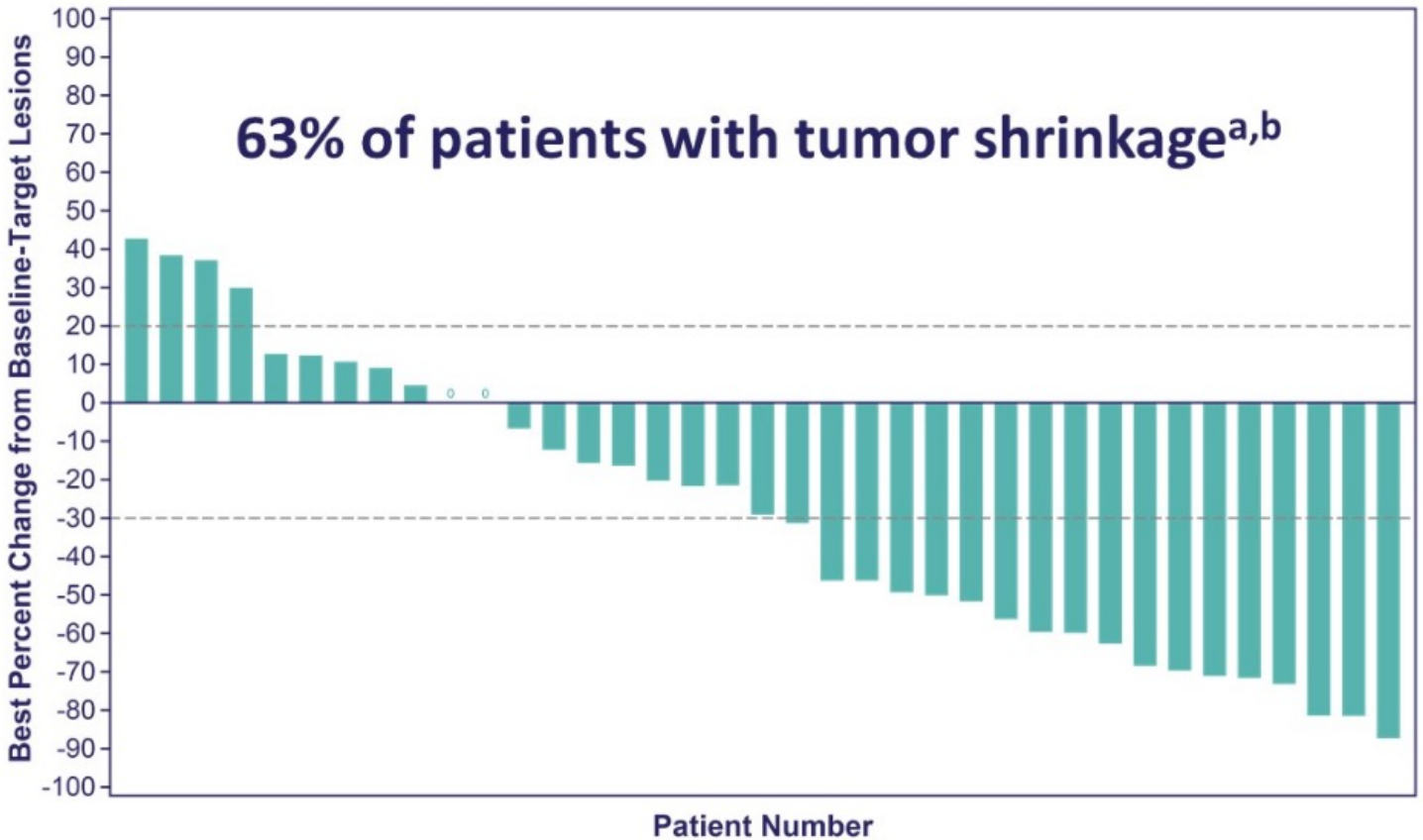


- Responses were observed in patients with both *FGFR* mutations and fusions
- In patients with PD-L1 low status, responses were observed in 50% in the erdafitinib arm (5 of 10) and in 71% patients in the erdafitinib + cetrelimab arm (5 of 7); few patients with PD-L1 positive status had available data at the time of this analysis

Overall Response and Best % Change From Baseline in Tumor Size

TROPHY U-01

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



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

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

ASCO Genitourinary Cancers Symposium

Abstract # 434.

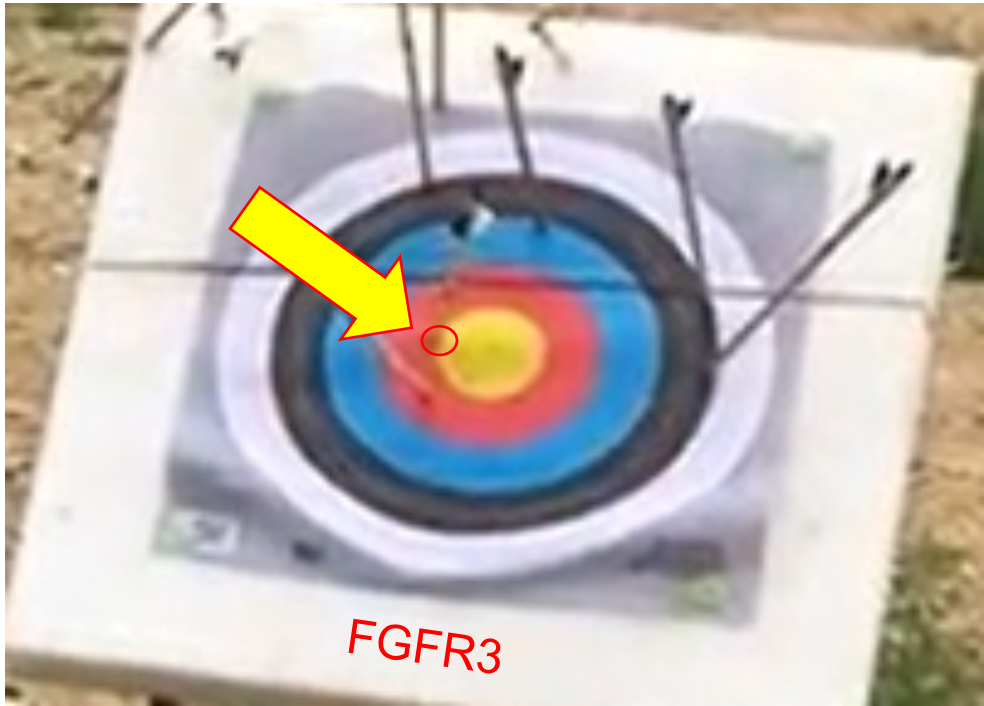
Conclusions:

- Multiple new agents
  - ADC
  - TKI
- Clinical activity
  - Enfortumab Vedotin and Erdafitinib (~40% ORR) > Sacituzumab Govitecan (~27% ORR)
    - Or is this an effect of more prior treatment in SG?
- Each have their specific toxicities
  - Enfortumab Vedotin: watch closely in cirrhosis/fatty liver
  - Erdafitinib: Watch for CSR
  - Sacituzumab Govitecan: Neutropenia and diarrhea
    - Advocate for routine use of GCSF

Future: Combinations!

- Improved ORR ~70%
  - Enfortumab Vedotin + IO
  - Erdafitinib + IO
- Sacituzumab + IO had no significant benefit by ORR
  - Perhaps due to myelosuppression and lymphopenia impacting the immune response?

We are getting closer…



Module 4: Novel Investigational Agents and Strategies in the Treatment of mUBC — Dr Heath

RTP
RESEARCH
TO PRACTICE

Case Presentation: 67-year-old man with metastatic urothelial carcinoma, PS of 2

Dr Georges Azzi (Fort Lauderdale, Florida)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Georges Azzi, MD

Reimbursement aside, in what situations, if any, would you administer enfortumab vedotin/pembrolizumab as first-line treatment for a patient with mUBC who is not eligible for platinum chemotherapy?

Case Presentation: 75-year-old man with metastatic mixed-histology (urothelial, small cell) bladder cancer receives pembrolizumab and remains in remission 5 years later

Dr Victoria Giffi (Hagerstown, Maryland)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 50-year-old man with metastatic small cell carcinoma of the bladder receives cisplatin, etoposide, and durvalumab → maintenance durvalumab, now NED

Dr Laurie Matt-Amaral (Akron, Ohio)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Victoria Giffi, MD

When should an IO be discontinued in a patient with metastatic disease?

What explains extraordinary responses to IOs?

Laurie Matt-Amaral, MD, MPH

How do you treat patients with small cell cancer of the bladder?

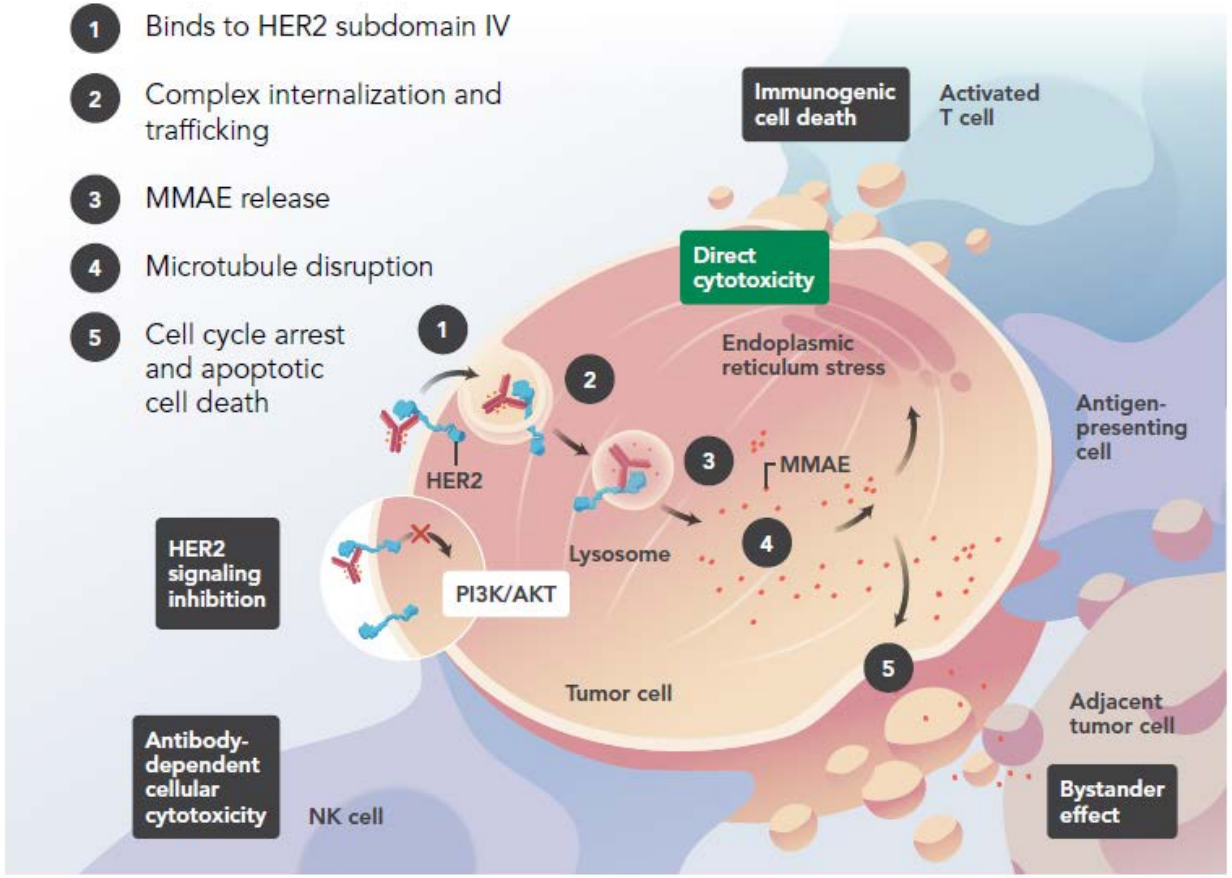
NOVEL INVESTIGATIONAL AGENTS AND STRATEGIES IN THE TREATMENT OF METASTATIC UROTHELIAL BLADDER CANCER

Elisabeth Heath, MD, FACP
Associate Center Director, Translational Sciences
Hartmann Endowed Chair for Prostate Cancer Research
Chair, Genitourinary Multidisciplinary Team
Professor of Oncology and Medicine

Disitamab Vedotin (RC48)

Proposed Mechanism of Action[1-6]

1. Binds to HER2 subdomain IV
2. Complex internalization and trafficking
3. MMAE release
4. Microtubule disruption
5. Cell cycle arrest and apoptotic cell death



AKT: protein kinase; **HER2**: human epidermal growth factor receptor 2; **MMAE**: monomethyl auristatin E; **NK**: natural killer; **PI3K**: phosphoinositide 3-kinase

1. Yao X, et al. *Breast Cancer Res Treat.* 2015:153(1):123-133. **2**. Li H, et al. *Cancer Biol Ther.* 2016;17(4):346-354. **3**. Jiang J, et al. *Eur J Pharm Sci.* 2016;93:274-286. **4**. Li L et al. *Eur Rev Med Pharmacol Sci.* 2020;24(24):12929-12937. **5**. Klussman K, et al. Poster presented at: SITC; Nov 2020 Virtual. Poster 618. **6**. Cao AT, et al. Abstract presented at: AACR; Apr 2017; Washington, DC. Abstract 5588.

DISITAMAB VEDOTIN

An investigational antibody–drug conjugate directed to HER2

Anti-HER2 antibody

Recombinant, humanized, high-affinity IgG1 monoclonal antibody that binds to HER2[4]

Key Attributes

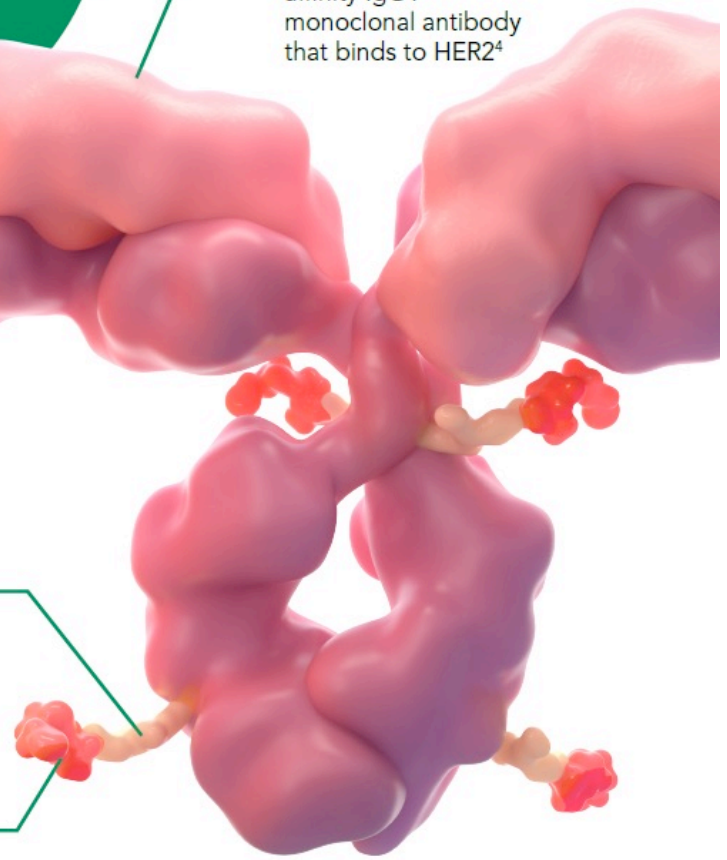
- Binds to a distinct epitope on subdomain IV of the HER2 extracellular domain[1,4]
- Optimized for enhanced internalization and delivery of cytotoxic MMAE to target cells

Protease-cleavable mc-vc linker

Covalently attaches MMAE to the antibody and releases agent within the target cell

MMAE

Microtubule-disrupting agent



Disitamab Vedotin

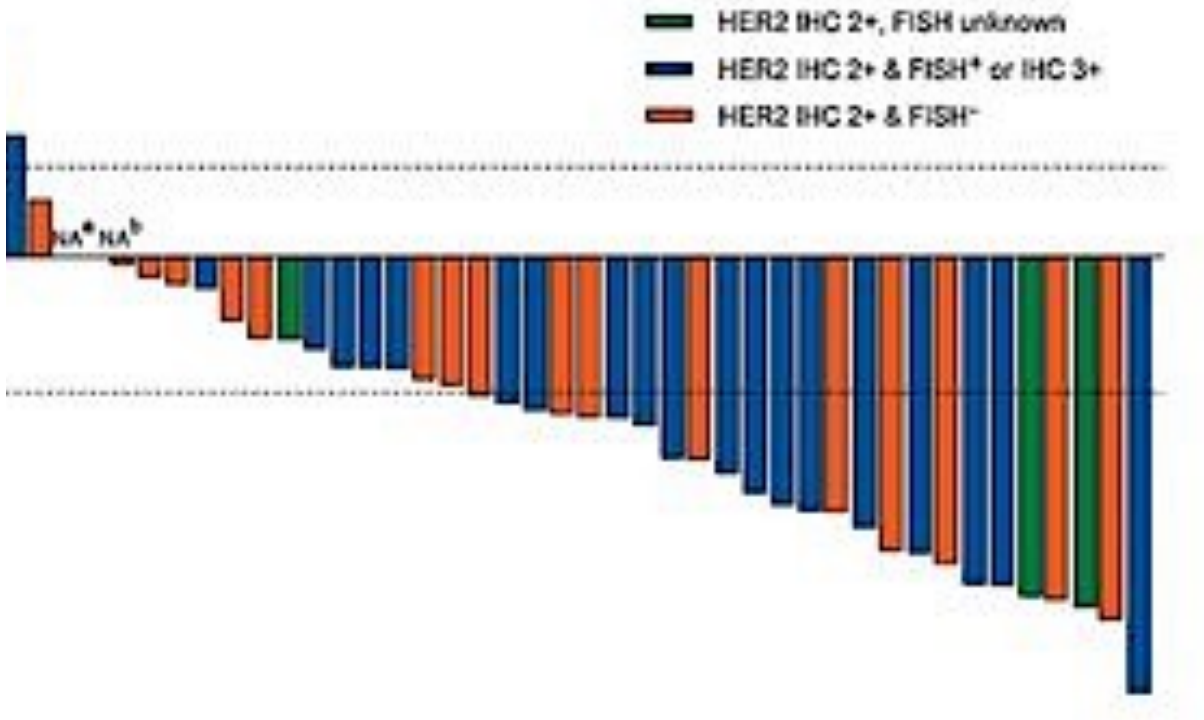
- HER-2-directed antibody drug conjugate
- Recombinant humanized anti-HER2 monoclonal antibody-MMAE Conjugate
- Phase II:
  - 43 patients
  - HER2 IHC 2+ or 3+
  - Received at least one systemic chemotherapy
  - 86% had visceral metastasis
  - 33% had two prior lines of treatment

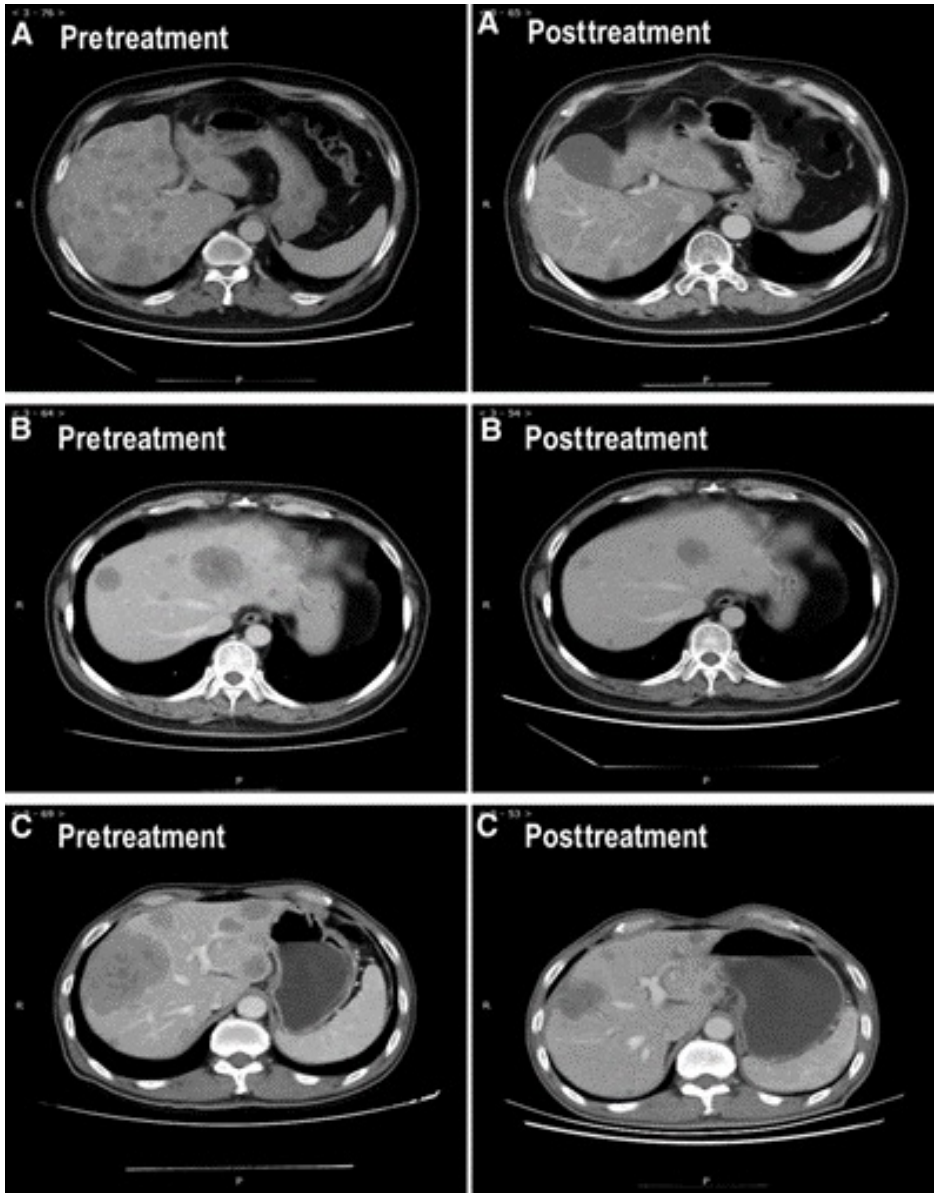
- ORR: 51.2%
- Median PFS: 6.9 months
- Median OS: 13.9 months
- Treatment related AEs (Grade 3)
  - Hypoesthesia (23%)
  - Neutropenia (14%)

Sheng X et al. Clin Cancer Res 2021 Jan 1;27(1):43-51.

NCT03507166

Disitamab Vedotin





FDA Fast Track Designation on September 25, 2020

Sheng X et al. Clin Cancer Res 2021 Jan 1;27(1):43-51.

2022 ASCO ANNUAL MEETING

Abstract 4520

RC48-ADC for Metastatic Urothelial Carcinoma with HER2-positive: combined analysis of RC48-C005 and RC48-C009 trials

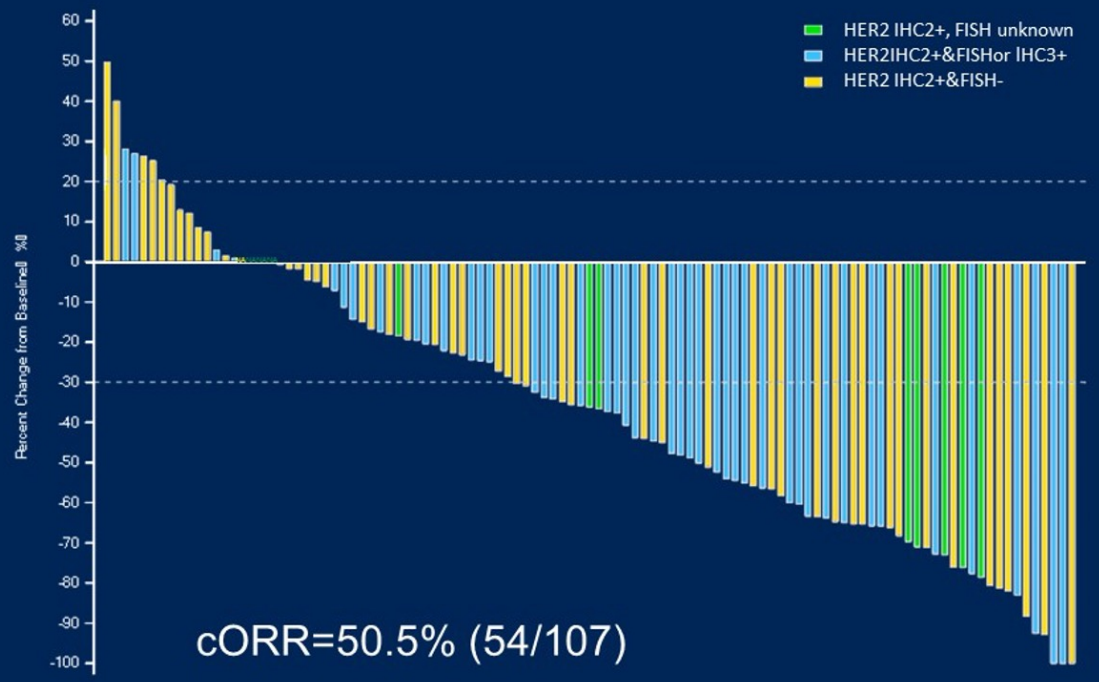
Xinan Sheng[1*], Zhisong He[3], Yan-Xia Shi[4], Hong Luo[5],Weiqing Han[6], Xin Yao[7], Benkang Shi[8], Jiyan Liu[9], Changlu Hu[10] Ziling Liu[11], Hongqian Guo[12], Guohua Yu[13], Zhigang Ji[14] , Shi Ying Yu[15], Yi Hu[16], Jianming Guo[17], Jianmin Fang[18] , Ai-Ping Zhou[2] **, Jun Guo[1]**

1.Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; 2.Peking University Cancer Hospital and Institute, Beijing, China Department of Medical Oncology, Cancer Hospital, CAMS, Beijing, China; 3.Department of Urology, Peking university First Hospital, Institute of Urology, Peking University, Beijing, China; 4.Department of Medical Oncology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China; 5.Chongqing Cancer Hospital, Chongqing, China; 6.Hunan Cancer Hospital, Changsha, China; 7.Tianjin Cancer Hospital, Tianjin, China; 8.Qilu Hospital of Shandong University, Jinan, China; 9.West China Hospital, Sichuan University, Chengdu,China;10. Anhui Provincial Cancer Hospital, Hefei, China; 11. Department of Cancer Centre, First Hospital of Jilin University, Changchun, China; 12. Nanjing Drum Tower Hospital, Nanjing, China; 13.Weifang People's Hospital, Weifang, China; 14. Peking Union Medical College Hospital, Beijing, China; 15. Tongji Hospital, Wuhan, China; 16. Chinese PLA General Hospital, Beijing, China; 17. Zhongshan Hospital, Fudan University, Shanghai, China; 18. Remegen, Ltd

*Presenting author * * Corresponding author

RC48-C005 and RC48-C009 Combined Analysis of Disitamab Vedotin for HER2-Positive mUC After ≥1 Line of Chemotherapy

Target Lesion Change from Baseline



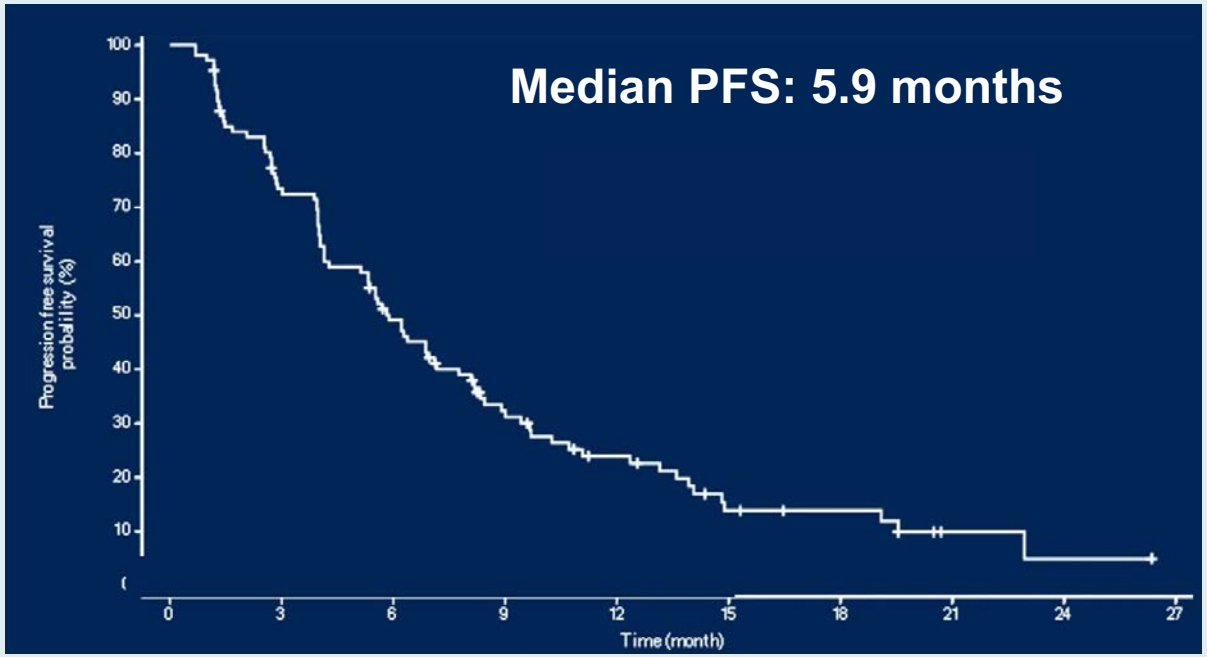
Subgroup Analysis for cORR

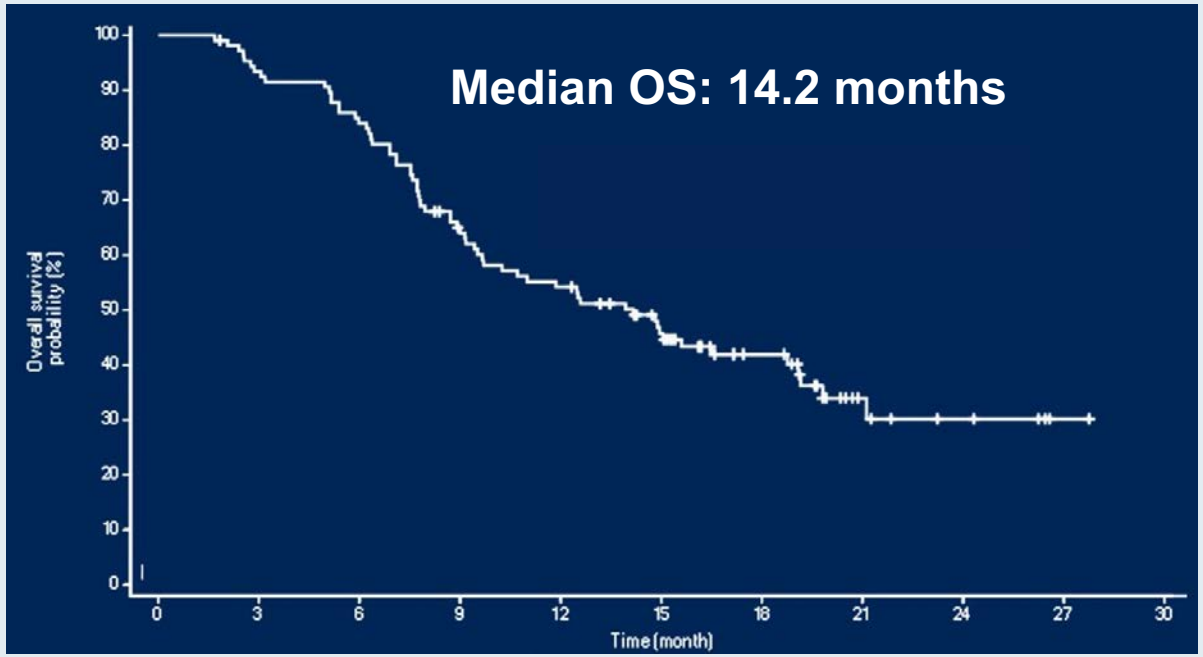
Subgroups	cORR (%, 95% CI)
HER2 status	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
metastasis site	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
Prior therapies	
Post PD1/PDL1 Treatments (n=27)	55.6% (35.3%, 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%)

mUC = metastatic urothelial carcinoma; cORR = confirmed objective response rate

Sheng X et al. ASCO 2022;Abstract 4520.

RC48-C005 and RC48-C009 Combined Analysis of Disitamab Vedotin for HER2-Positive mUC After ≥1 Line of Chemotherapy (continued)





Sheng X et al. ASCO 2022;Abstract 4520.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

Abstract 4519

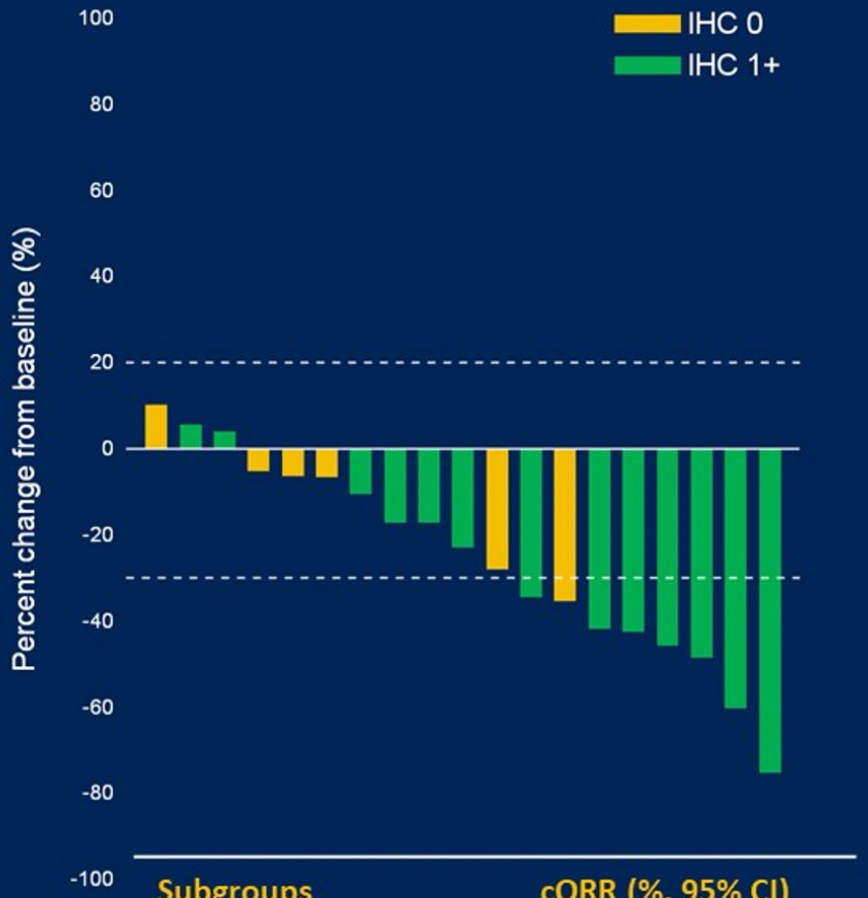
A phase II study of RC48-ADC in HER2-negative patients with locally advanced or metastatic urothelial carcinoma.

Huayan Xu*, Xinan Sheng, Li Zhou, Xieqiao Yan, Siming Li, Zhihong Chi, Chuanliang Cui, Lu Si, Bixia Tang, Lili Mao, Bin Lian, Xuan Wang, Xue Bai, Juan Li, Jun Guo**

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education, Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute

*Presenting author ** Corresponding author

Disitamab Vedotin for HER2 IHC 0 or 1+ Locally Advanced or Metastatic Urothelial Carcinoma After ≥1 Line of Chemotherapy



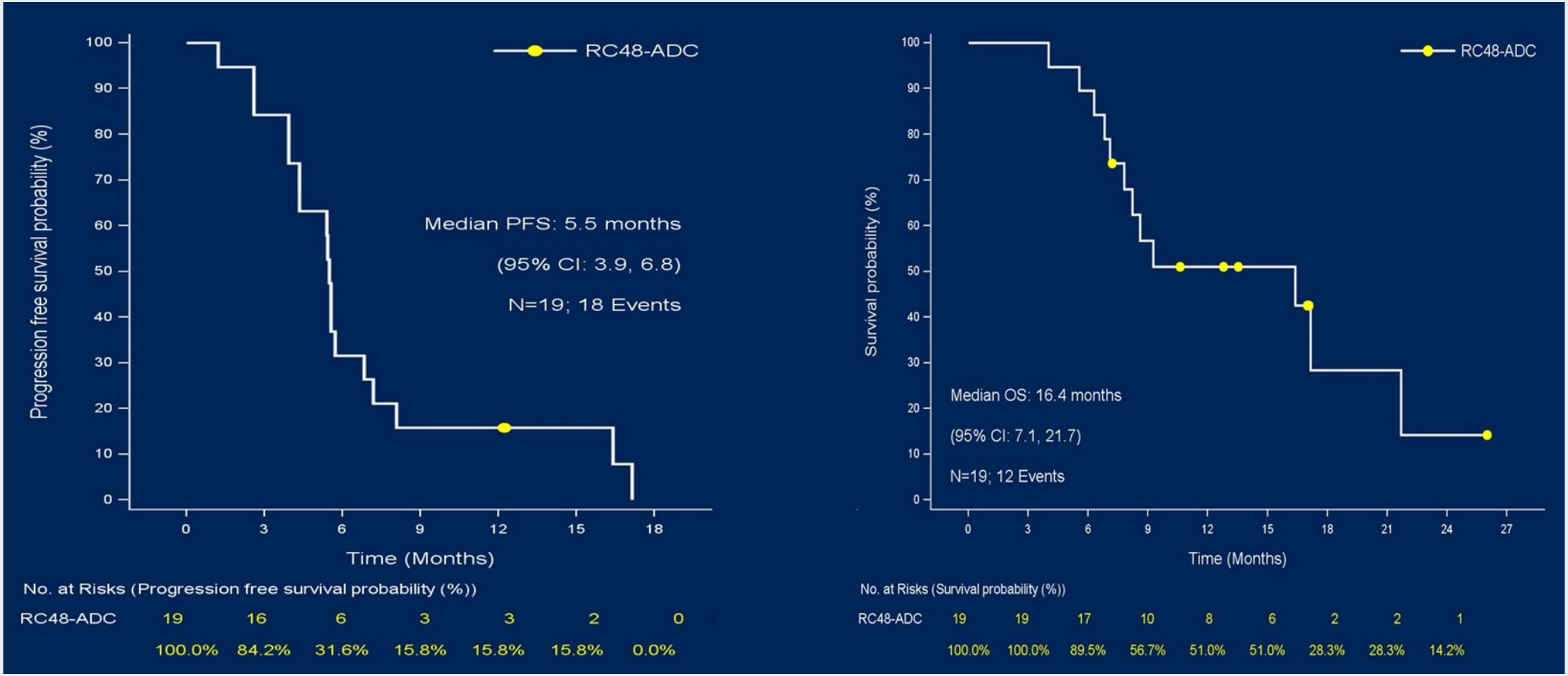
Subgroups	cORR (%, 95% CI)
IHC 0 (n=6)	0
IHC 1+ (n=13)	38.5 (13.9, 68.4)

Confirmed ORR	
n (%)	5 (26.3%)
95%CI	9.1%, 51.2%
Best overall response, n (%)	
CR	0
PR	5 (26.3%)
SD	13 (68.4%)
PD	1 (5.3%)
DCR	
n (%)	18 (94.7%)
95%CI	74.0%, 99.9%

ORR = overall response rate; DCR = disease control rate

Xu H et al. ASCO 2022;Abstract 4519.

Disitamab Vedotin for HER2 IHC 0 or 1+ Locally Advanced or Metastatic Urothelial Carcinoma After ≥1 Line of Chemotherapy (continued)

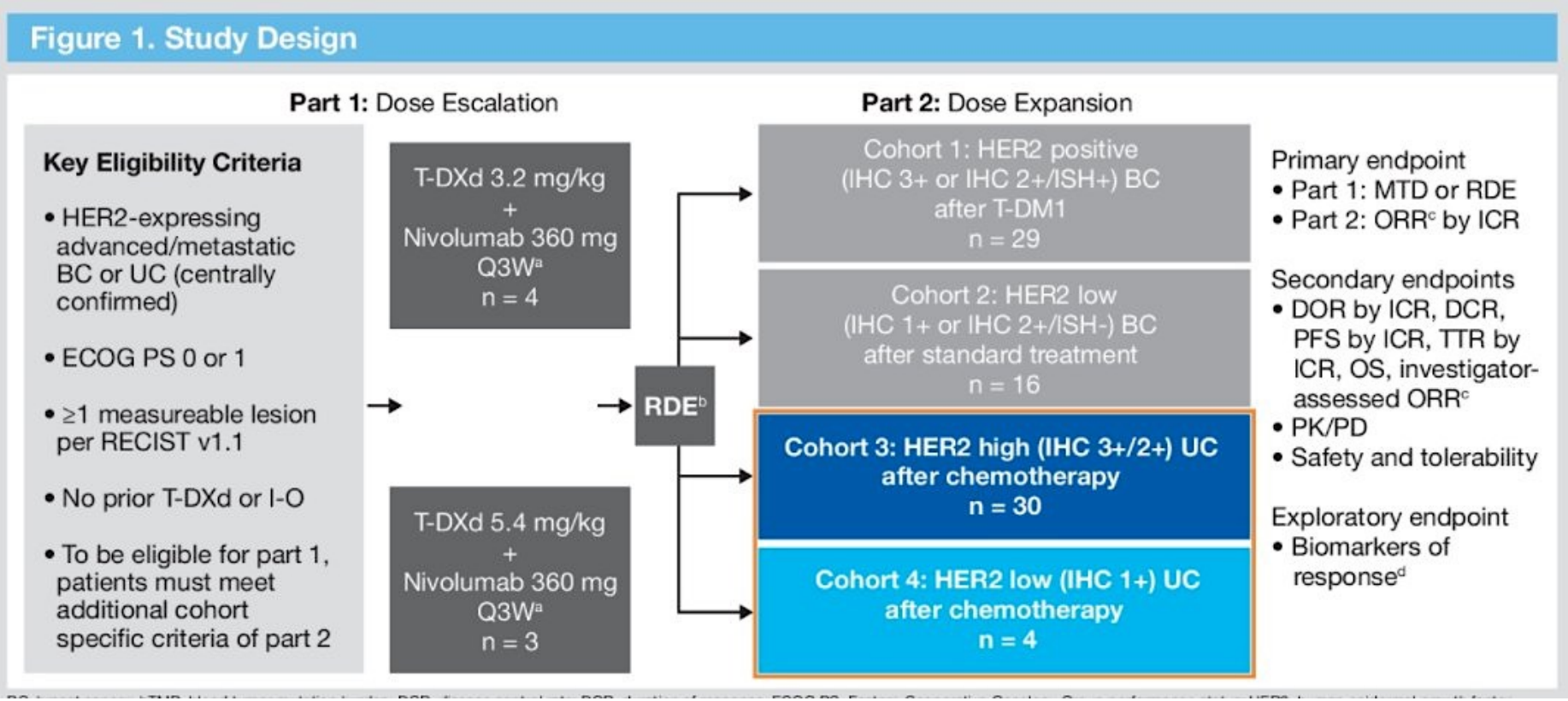


Xu H et al. ASCO 2022;Abstract 4519.

RTP RESEARCH TO PRACTICE

Trastuzumab Deruxtecan and Nivolumab in HER2-expressing mUBC

- DS8201-A-U105 Trial of T-Dxd with nivolumab
- T-Dxd: antibody drug conjugate of anti-HER2 antibody, a cleavable linker, and topoisomerase I inhibitor payload



NCT03523572

Galsky M et al. Journal of Clinical Oncology 2022 40:6_suppl, 438-438.

Trastuzumab Deruxtecan and Nivolumab in HER2-expressing mUBC

Table 2. Summary of Efficacy in HER2 IHC 3+/2+ Cohort

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

Table 3. Overall Safety Summary

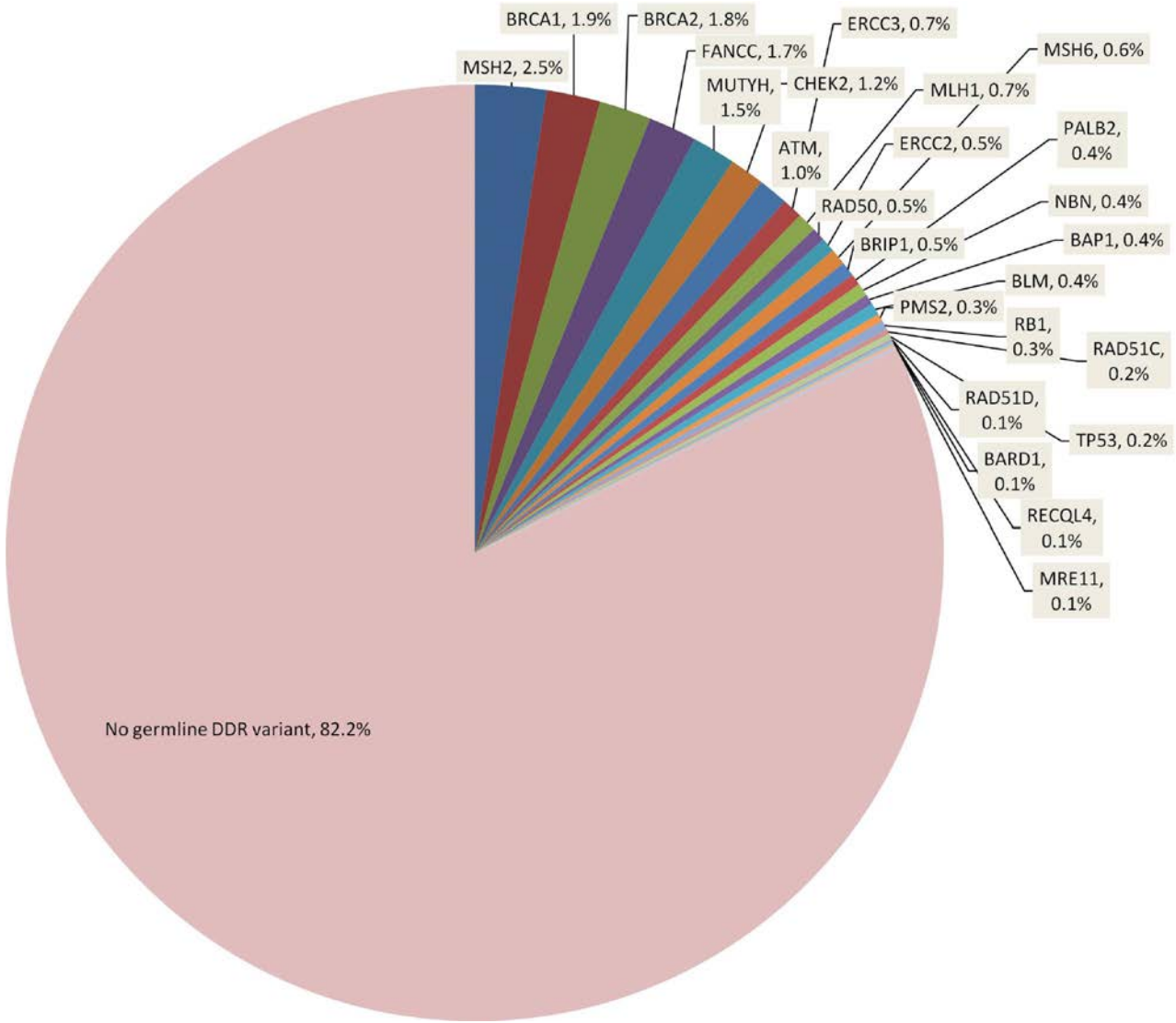
n (%)	Cohort 3 HER2 IHC 3+/2+ n = 30	Cohort 4 HER2 IHC 1+ n = 4	Overall N = 34
TEAEs	**30 (100)**	**4 (100)**	**34 (100)**
Related to T-DXd	30 (100)	4 (100)	34 (100)
Related to nivolumab	26 (86.7)	4 (100)	30 (88.2)
Grade ≥3 TEAEs	**21 (70.0)**	**4 (100)**	**25 (73.5)[a]**
Related to T-DXd	12 (40.0)	3 (75.0)	15 (44.1)
Related to nivolumab	9 (30.0)	0	9 (26.5)
Serious TEAEs	**17 (56.7)**	**3 (75.0)**	**20 (58.8)**
Related to T-DXd	5 (16.7)	2 (50.0)	7 (20.6)
Related to nivolumab	5 (16.7)	0	5 (14.7)
TEAEs leading to any study drug discontinuation[b]	**9 (30.0)**	**2 (50.0)**	**11 (32.4)**
Related to T-DXd	6 (20.0)	2 (50.0)	8 (23.5)
Related to nivolumab	9 (30.0)	0	9 (26.5)
TEAEs leading to T-DXd discontinuation[b]	**5 (16.7)**	**2 (50.0)**	**7 (20.6)**
Related to and leading to T-DXd discontinuation	4 (13.3)[c]	2 (50.0)[d]	6 (17.6)
TEAEs leading to nivolumab discontinuation[b]	**8 (26.7)**	**1 (25.0)**	**9 (26.5)**
Related to and leading to nivolumab discontinuation	8 (26.7)[e]	0	8 (23.5)
TEAEs leading to T-DXd dose reduction and related to T-DXd	**4 (13.3)**	**1 (25.0)**	**5 (14.7)**
TEAEs leading to any study drug interruption	**18 (60.0)**	**2 (50.0)**	**20 (58.8)**
Related to T-DXd	10 (33.3)	2 (50.0)	12 (35.3)
Related to nivolumab	7 (23.3)	0	7 (20.6)
TEAEs associated with death	**7 (23.3)**	**0**	**7 (20.6)**
Drug-related[f]	1 (3.3)	0	1 (2.9)

NCT03523572

Galsky M et al. Journal of Clinical Oncology 2022 40:6_suppl, 438-438.

PARP Inhibitors

- Average frequency of shared pathogenic/likely pathogenic germline DDR variants across two large UC cohorts
- 82% no germline DDR variant
- 19% pathogenic or likely pathogenic DDR mutation



Carlo MI et al. J Clin Oncol 35 (15suppl), 2017. Alaiwi SA et al. J Clin Oncol 37 (15suppl), 2019.

PARP Inhibitors Clinical Trials

- ATLAS (rucaparib) (NCT03397394)
- BISCAY (olaparib plus durvalumab) (NCT02546661)
- BAYOU (olaparib plus durvalumab, cis-inelig) (NCT03459846)
- ATLANTIS (rucaparib) (ISRCTN25859465)
- NEODURVARIB (olaparib plus durvalumab neo) (NCT03534492)
- NCI (olaparib) (NCT03375307)

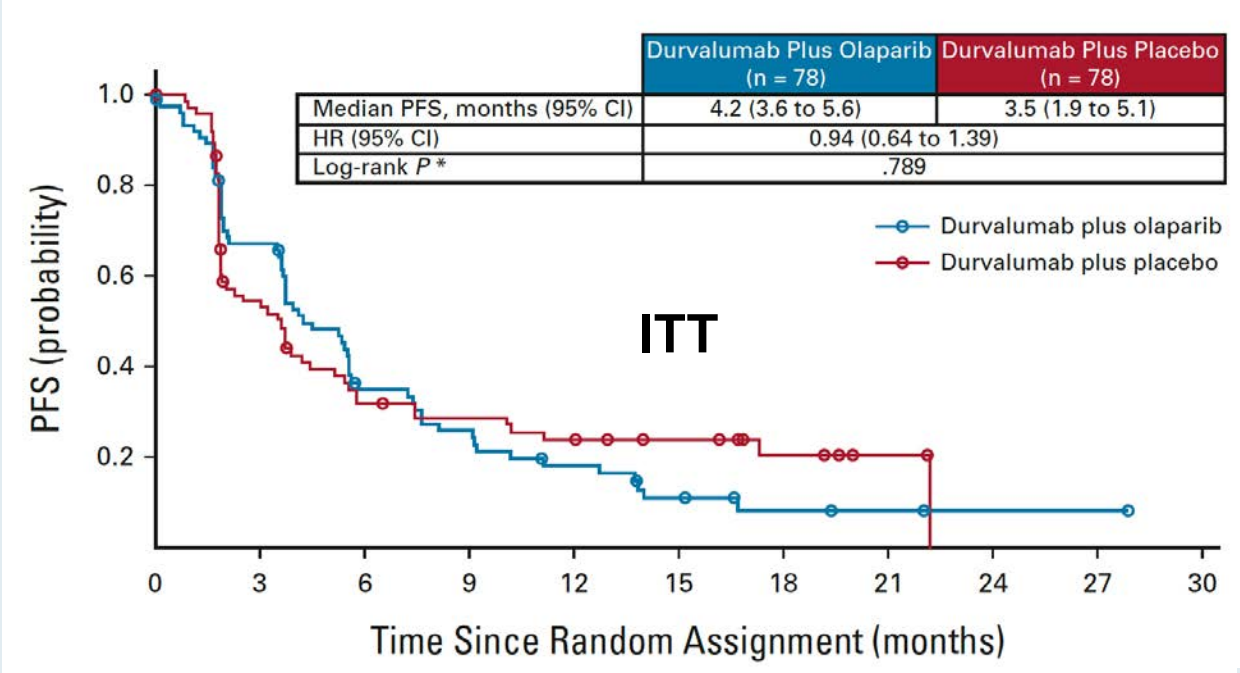
original reports

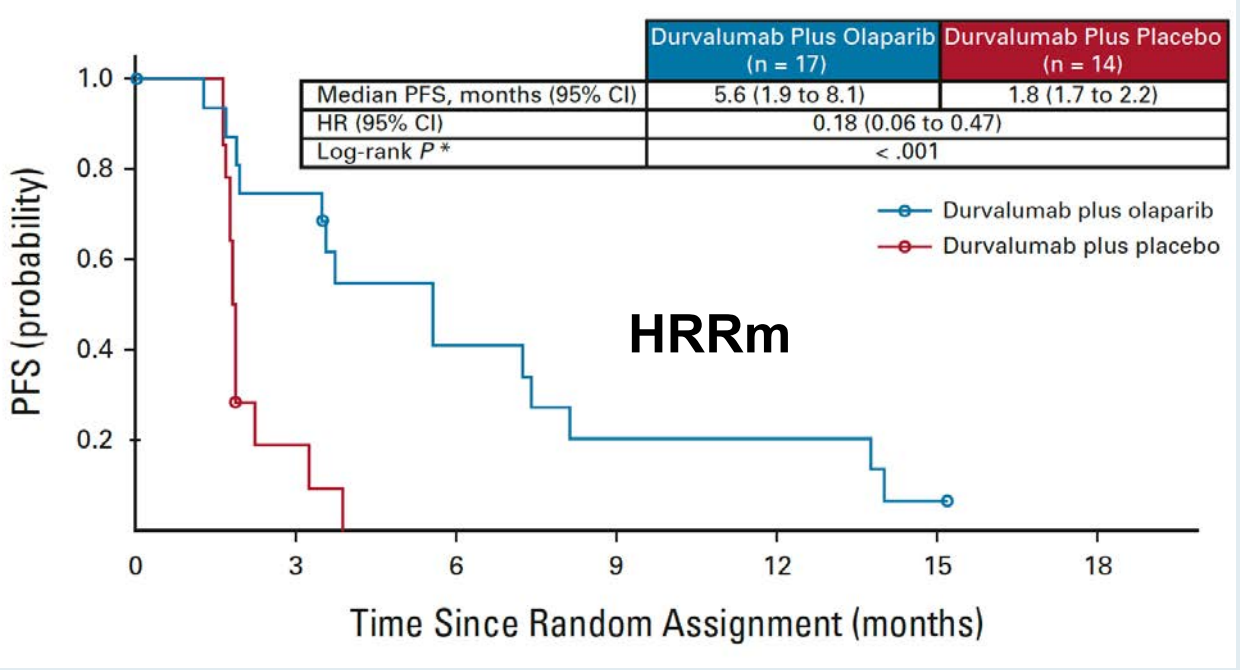
Durvalumab Plus Olaparib in Previously Untreated, Platinum-Ineligible Patients With Metastatic Urothelial Carcinoma: A Multicenter, Randomized, Phase II Trial (BAYOU)

Jonathan E. Rosenberg, MD[1]; Se Hoon Park, MD, PhD[2]; Vadim Kozlov, MD[3]; Tu V. Dao, MD, PhD[4]; Daniel Castellano, MD[5]; Jian-Ri Li, MD, PhD[6]; Som D. Mukherjee, MD[7]; Kathryn Howells, MSc[8]; Hannah Dry, BSc[9]; Mark C. Lanasa, MD, PhD[9]; Ross Stewart, PhD[8]; and Dean F. Bajorin, MD[1]

J Clin Oncol 2023 Jan 1;41(1):43-53.

BAYOU: PFS in the Intent-to-Treat (ITT) and Homologous Recombination Repair Gene Mutation (HRRm) Populations

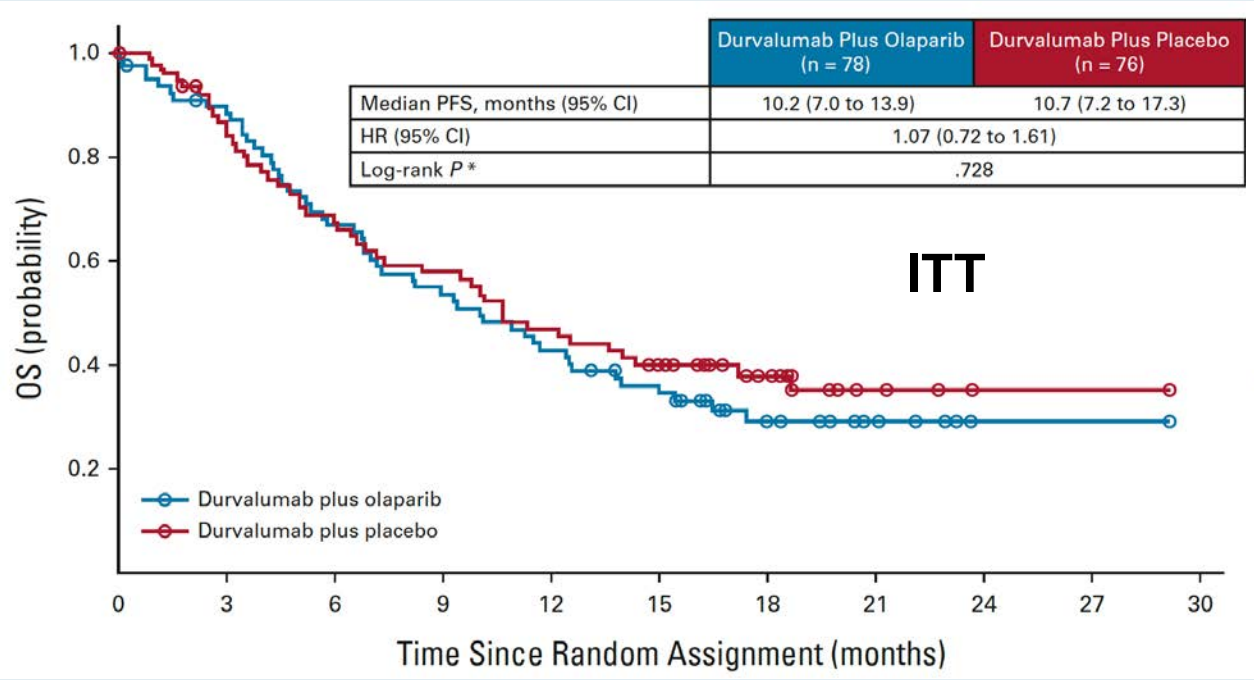


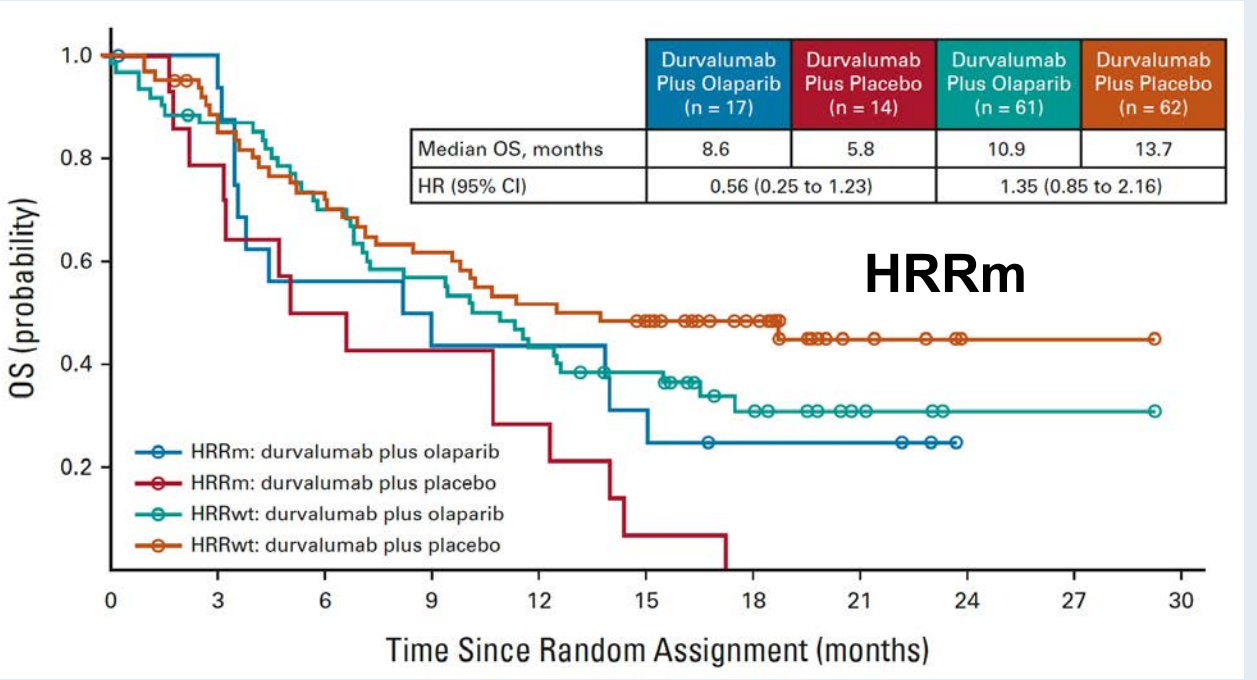


Rosenberg JE et al. *J Clin Oncol* 2023 Jan 1;41(1):43-53.

RTP RESEARCH TO PRACTICE

BAYOU: OS in the Intent-to-Treat (ITT) and Homologous Recombination Repair Gene Mutation (HRRm) Populations





Rosenberg JE et al. *J Clin Oncol* 2023 Jan 1;41(1):43-53.

RTP RESEARCH TO PRACTICE

FGFR Inhibitors

- **Rogaratinib** (pan-FGFR1-4 inhibitor)
- Phase II/III (FORT-1): rogaratinib versus chemotherapy (docetaxel/paclitaxel/vinflunine)
  - Progression after at least one platinum-containing regimen
  - Selection based on FGFR1-3 mRNA overexpression and/or FGFR3-activating mutations/translocations
  - 175 patients
  - ORR=20.7% (vs 19.3%)
  - Median OS= 8.3 months (vs 9.8 months)
  - Patients with FGFR3 DNA alterations had ORR 52.4%
- Phase Ib/II (FORT-2): rogaratinib and atezolizumab
  - Must be cisplatin-ineligible
  - Selection based on FGFR1 or FGFR3 mRNA defined as RANscope score of 3+ or 4+
  - 31 patients
  - ORR=44%
  - CR=13%
  - AEs: hyperphosphatemia (45% and retinal pigment detachment (3%))

Sternberg CN et al. J Clin Oncol 2023 Jan 20;41(3):629-639. Rosenberg J et al. J Clin Oncology 2021 39:15_suppl, 4521-4521.

FGFR Inhibitors

- **Infigratinib** (FGFR1-3 inhibitor)
- Phase I trial: platinum-refractory, FGFR3 alterations
- 67 patients
  - ORR: 33% with hyperphosphatemia vs 5.3%
  - Different genomic alterations between upper tract and bladder
    - Upper tract: FGFR3-TACC3 fusions, FGFR3-R248C mutations

- PROOF 302: Infigratinib as adjuvant treatment
  - Undergo nephroureterectomy, distal ureterectomy, or cystectomy
  - Ineligible to receive cisplatin-based adjuvant chemotherapy (if not received neoadjuvant)
  - FGFR3 alteration

Pal SK et al. Cancer Discovery 2018 July 1;8(7):912-21. Lyou Y et al. European Urology, 78, 6, December 2020: 916-924. Dizman N et al. 2019 ASCO Annual Meeting.

FGFR Inhibitors

- **Pemigatinib** (FGFR1-3 inhibitor)
- FIGHT-201: progressed on > 1 line of treatment or platinum ineligible
- ORR=25%
- Adverse events: diarrhea, alopecia, fatigue, hyperphosphatemic
- FIGHT-205: pemigatinib and pembrolizumab in cisplatin ineligible patient (NCT04003610)

- **Futibatinib** (irreversible FGFR1-4 inhibitor)
- Multicohort phase I/II study
- 21 patient cohort
- ORR=10%
- Adverse events: hyperphosphatemia

Necchi A et al. Ann Oncol 2018;29(suppl 8) 900P. Meric-Bernstam F et al. Cancer Discov 2022 12(2) 402-415.

CheckMate 032

- CheckMate 032: nivolumab with or without ipilimumab followed by nivolumab
- Nivolumab 1 mg/kg plus Ipilimumab 3 mg/kg
  - ORR = 38%
  - OS = 15.3 months
  - PFS = 4.9 months

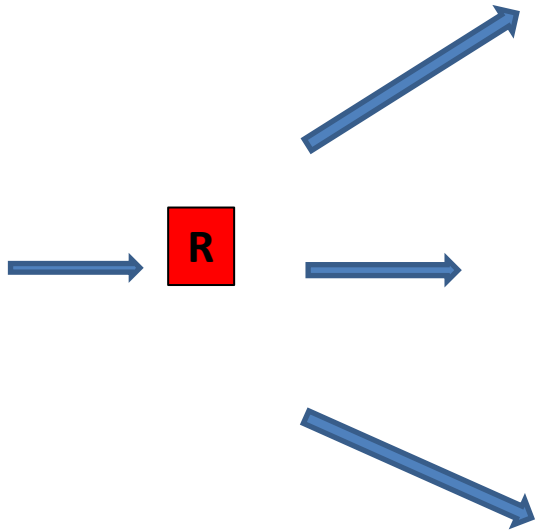
- PD-1 involved in inhibition of effector T-cell and NK cell activation in peripheral tissues and in induction of Treg cell differentiation
- CTLA-4 involved in regulation of T-cell activation in lymph nodes/tissues and in suppression of dendritic cell activity by Treg cells
- Combination inhibitors should increase synergistic action to result in greater response rates

Sharma P et al. J Clin Oncol 37:1608-1616, 2019. Cheng W et al. Oncogenesis (2018)7:2.

NCT01928394

CheckMate 901

- First line unresectable or metastatic UC
- ECOG PS ≤ 1
- Co-Primary Endpoints: PFS and OS
- 897 patients



Nivolumab + Ipilimumab

Nivolumab + Gemcitabine/Cisplatin

Gemcitabine/Cisplatin OR
Gemcitabine/Carboplatin

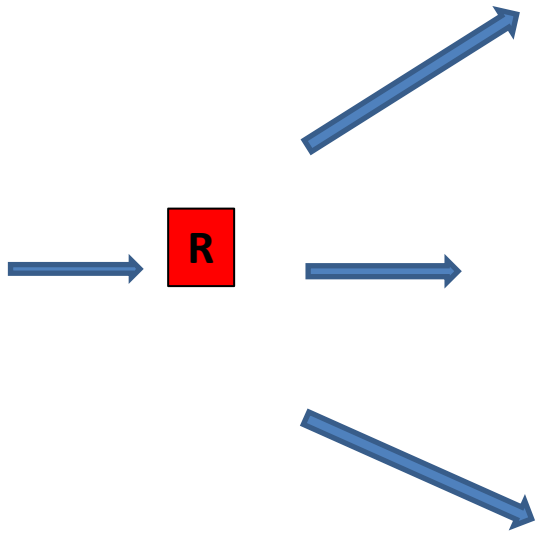
Press Release on May 16, 2022:

The Phase III CheckMate 901 trial comparing nivolumab with ipilimumab to standard-of-care chemotherapy as a first-line treatment for untreated unresectable or metastatic urothelial carcinoma did not meet the primary endpoint of overall survival (OS) in patients whose tumor cells express PD-L1 ≥1% at final analysis. The company remains blinded to the data, and an independent Data Monitoring Committee recommended that the trial continue to assess other primary and secondary endpoints. No new safety signals were observed at the time of the analysis.

www.clinicaltrials.gov, NCT03036098

NILE

- First line unresectable or metastatic UC
- ECOG PS ≤ 1
- Co-Primary Endpoints: PFS and OS
- 885 patients



Durvalumab + Gemcitabine/Cisplatin OR
Durvalumab + Gemcitabine/Carboplatin

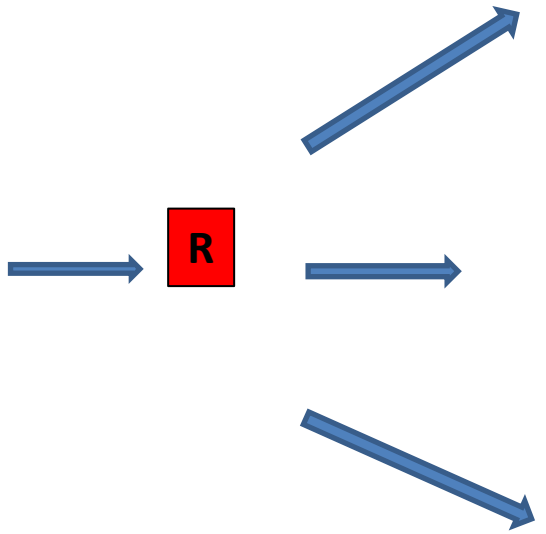
Durvalumab + Tremelimumab + Gemcitabine/Cisplatin OR
Durvalumab + Tremelimumab + Gemcitabine/Carboplatin

Gemcitabine/Cisplatin OR
Gemcitabine/Carboplatin

www.clinicaltrials.gov, NCT03682068.

DANUBE

- First line unresectable or metastatic UC
- Co-Primary Endpoints: PFS and OS
- 1005 patients



Durvalumab

Durvalumab + Tremelimumab

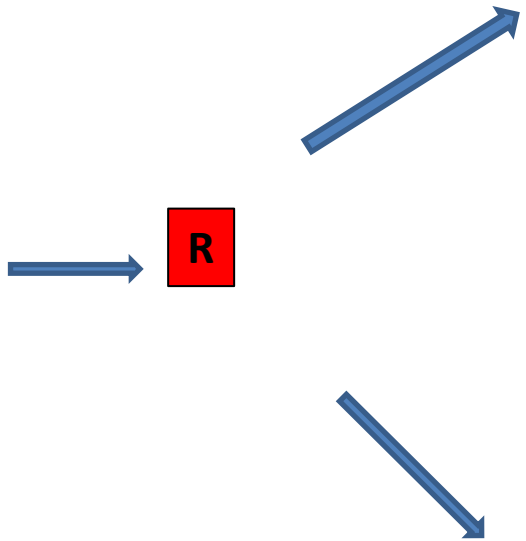
Gemcitabine/Cisplatin OR
Gemcitabine/Carboplatin

Press Release: March 6, 2020. DANUBE did not meet the primary endpoints of improving OS versus standard of care.

www.clinicaltrials.gov, NCT02516241. Powles TB et al. Ann Oncol 2020;31(suppl 4):S1142-S1215.

LEAP-001

- First line cisplatin ineligible with PD-L1 or platinum ineligible
- Co-Primary Endpoints: PFS and OS
- 700 patients



Placebo + Pembrolizumab

Lenvatinib + Pembrolizumab

Lenvatinib did not add any additional antitumor activity

Loriot Y et al. J Clin Oncol 2022;40(suppl6):432.

NCT03898180

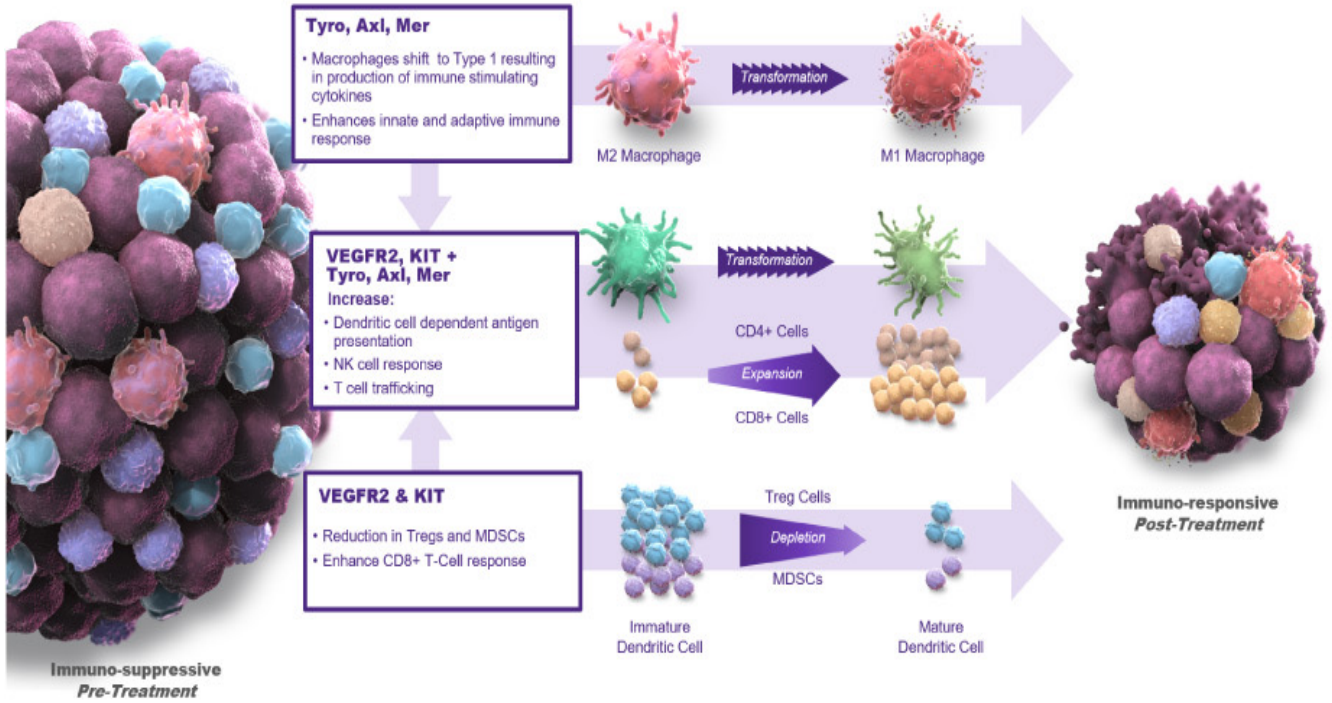
Cabozantinib Combinations

- Cabozantinib plus nivolumab and/or ipilimumab (NCT02496208)
- Cabozantinib plus durvalumab (ARCADIA) (NCT03824961)
- Cabozantinib plus atezolizumab (COSMIC-021) (NCT03170960)
  - UC expansion cohort 2
  - 30 patients with prior platinum-containing chemotherapy
  - Median follow-up 19.7 months
  - ORR= 27%, 2 CR
  - Median PFS = 5.4 months
  - AEs: asthenia (37%), diarrhea (27%), mucosal inflammation (20%)
- Cabozantinib plus niraparib (NCT03425201)
- Cabozantinib maintenance (ATLANTIS) (ISRCTN25859465)

Pal SK et al J Clin Oncol 38: 2020 (suppl; abstr 5013).

Sitravatinib

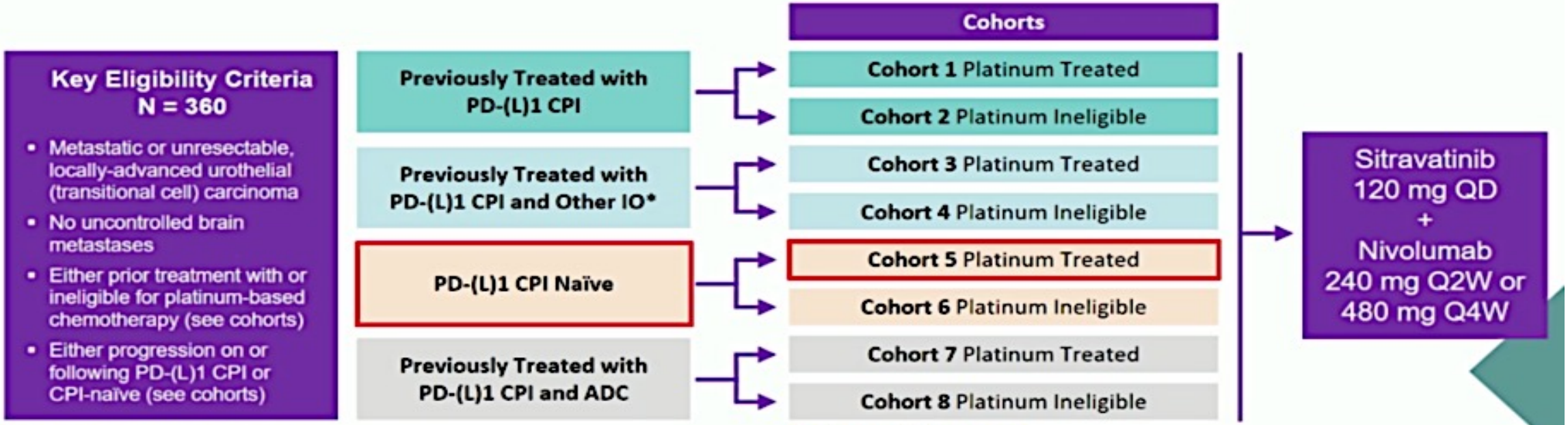
- Receptor tyrosine kinase
- Involved in creating immunosuppressive tumor microenvironment
- Sitravatinib targets TAM family (TYRO3, AXL, and MER), VEGFR2, and KIT



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

VIRTUAL 2020 ESMO congress

Study 516-003: Open-Label Phase 2 Trial of Sitravatinib and PD-(L)1 CPIs in Urothelial Carcinoma



Start Date: September 11, 2018
Status: Enrolling
Sponsor: Mirati Therapeutics

Outcome Measures
Primary: ORR
Secondary: AEs, CBR, DOR, PFS, OS, PK
Exploratory: Circulating and tissue biomarkers

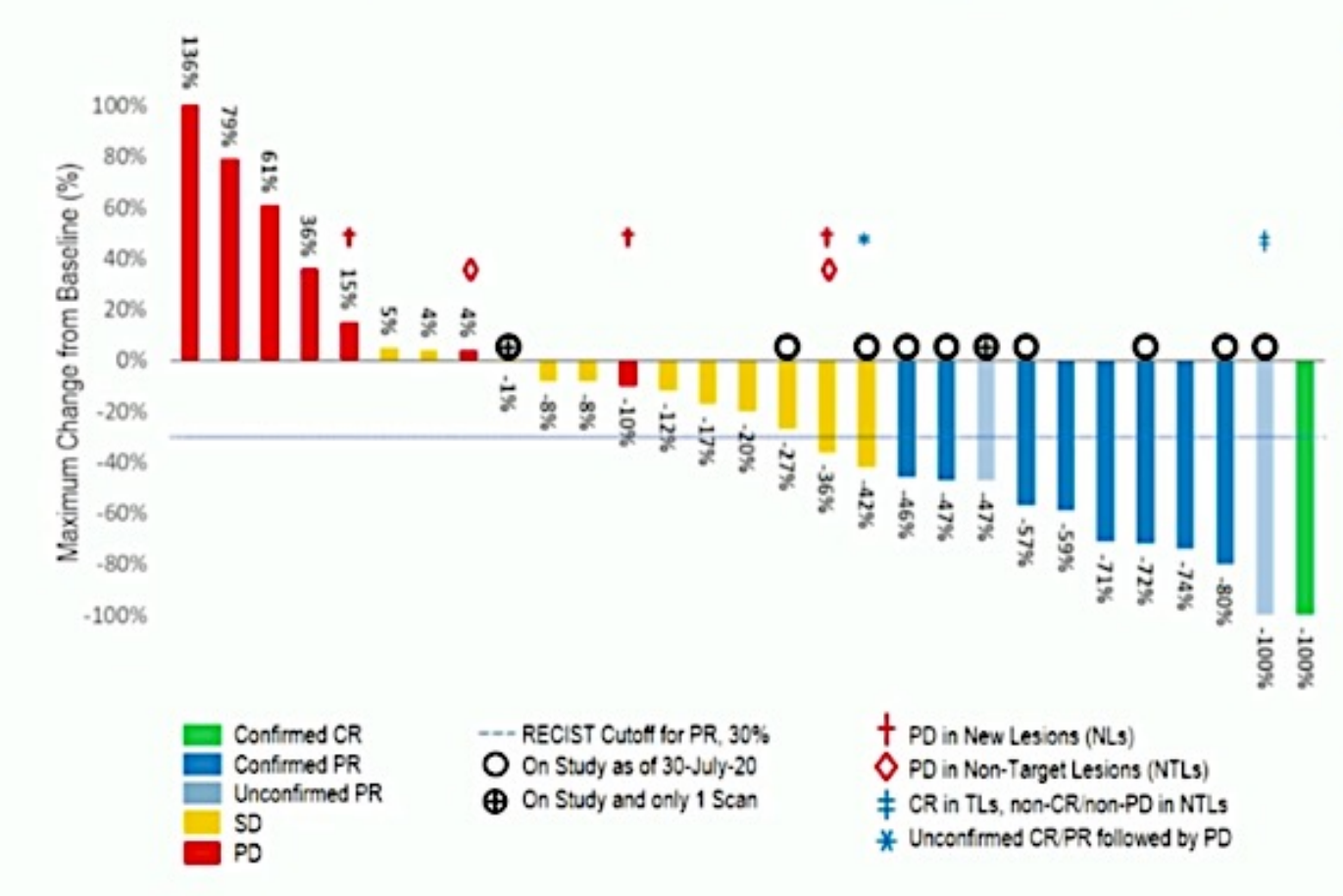
* Other IOs including but not limited to DNA vaccines, anti-CTLA-4, anti-OX40, anti-CD137 therapy or anti-IDO1 therapies, or recombinant IL-2 (CD-122) or IL-7 therapies
Abbreviations: ADC, antibody drug conjugate; AEs, adverse events; CBR, clinical benefit rate; CPI, checkpoint inhibitor; DOR, duration of response; IO, immune-based therapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q2/4W, every 2/4 weeks; QD, once daily
ClinicalTrials.gov. NCT03606174. Accessed August 17, 2020.

Doshi GK et al. J Clin Oncol 37, 2019 (suppl 7S; abstr TPS498). Msaouel P et al. Annals of Oncology (2020) 31 (suppl_4): S550-S550. 10.1016/annonc/annonc274.

NCT03606174

Sitravatinib

- Phase II (cohort 5)
  - 30 patients with prior platinum-based chemotherapy
  - ORR=37%
  - CR=3%
  - PR=34%
  - SD=37%
  - PD=23%
- AEs (Grades 3/4)
  - Hypertension (13%)
  - Diarrhea (8%)
  - Fatigue (5%)
  - Dysphonia (3%)



Msaouel P et al. Annals of Oncology (2020) 31 (suppl_4): S550-S550. 10.1016/annonc/annonc274.

Next Steps

- Evaluation of targets (HER2, DDR, FGFR) remain appealing for advancing drug development
- Approaches using IHC, DNA or RNA evaluation contributes to a diverse strategy
- Sequencing and combination therapies in clinical trials are underway

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Urothelial Bladder Cancer

Part 3 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Genitourinary Cancers Symposium

Friday, February 17, 2023
6:30 PM – 8:00 PM PT

Faculty

Matthew D Galsky, MD
Arlene Siefker-Radtke, MD
Jonathan E Rosenberg, MD

Moderator

Elisabeth I Heath, MD

RTP RESEARCH TO PRACTICE

Georges Azzi, MD
Holy Cross Health
Fort Lauderdale, Florida

Sunil Gandhi, MD
Florida Cancer Specialists
Lecanto, Florida

Spencer H Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Victoria Giffi, MD
Meritus Hematology and Oncology Specialists
Hagerstown, Maryland

Gigi Chen, MD
John Muir Health
Pleasant Hill, California

Ranju Gupta, MD
Lehigh Valley Topper Cancer Institute
Bethlehem, Pennsylvania

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Yanjun Ma, MD
Tennessee Oncology
Murfreesboro, Tennessee

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Athens, Georgia

Paul Markowski, MD
Atlantic Health System
Summit, New Jersey

Swati Vishwanathan, MD
WVU Medicine
Bridgeport, West Virginia

Laurie Matt-Amaral, MD, MPH
Northeast Ohio Medical University
College of Medicine
Akron, Ohio

Neil Love, MD
Research To Practice
Miami, Florida

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RESEARCH
TO PRACTICE

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