Metastatic Bladder Cancer Updates

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Master Lecture Series Denver, CO
Oct 14th , 2023

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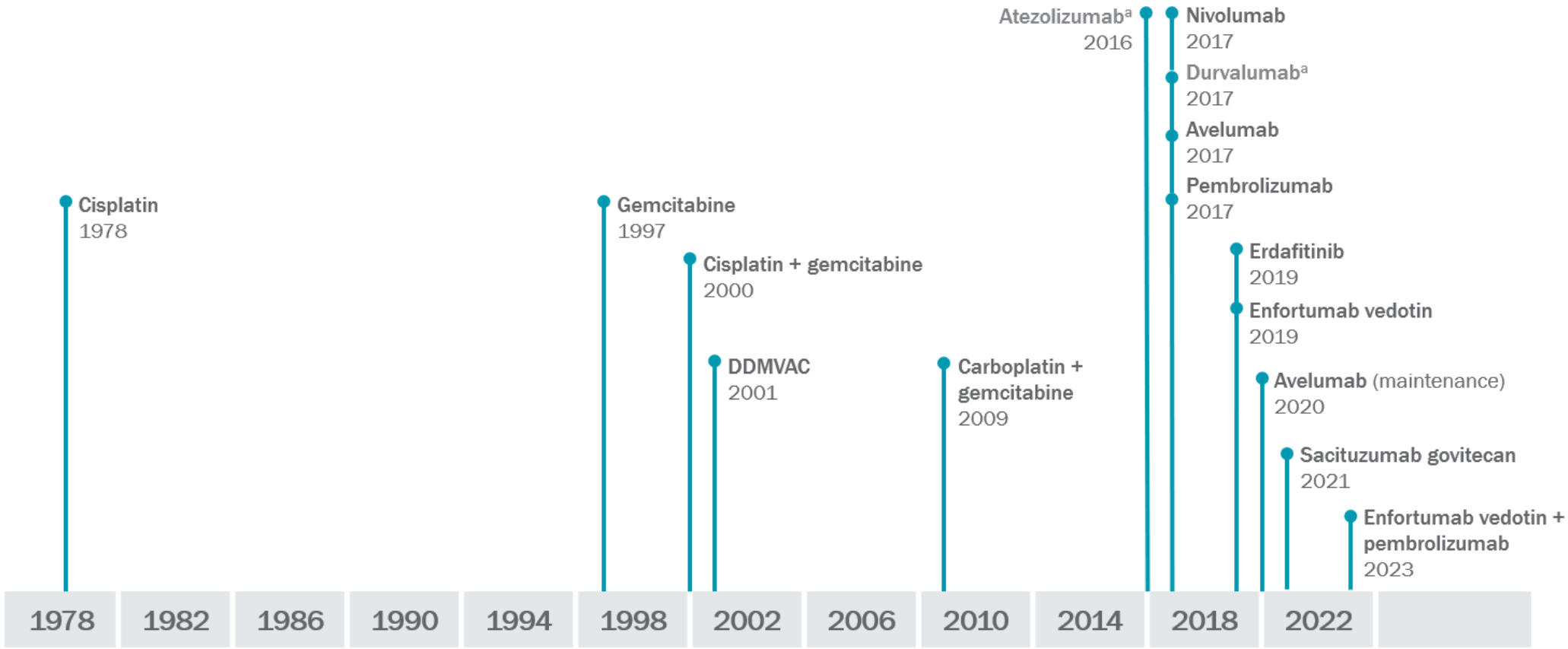
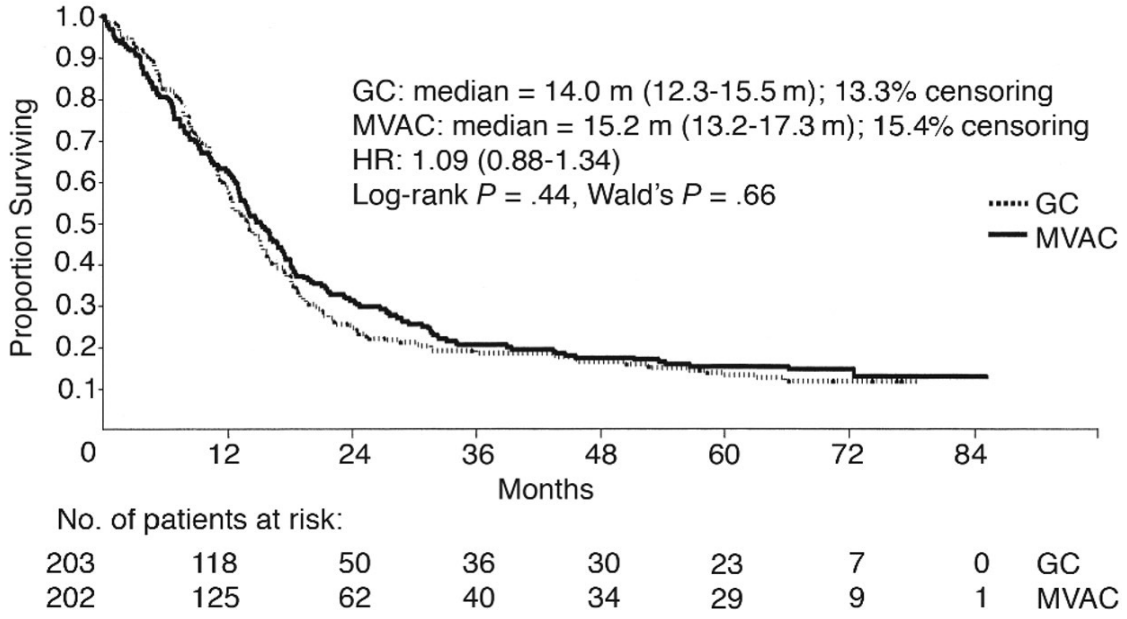
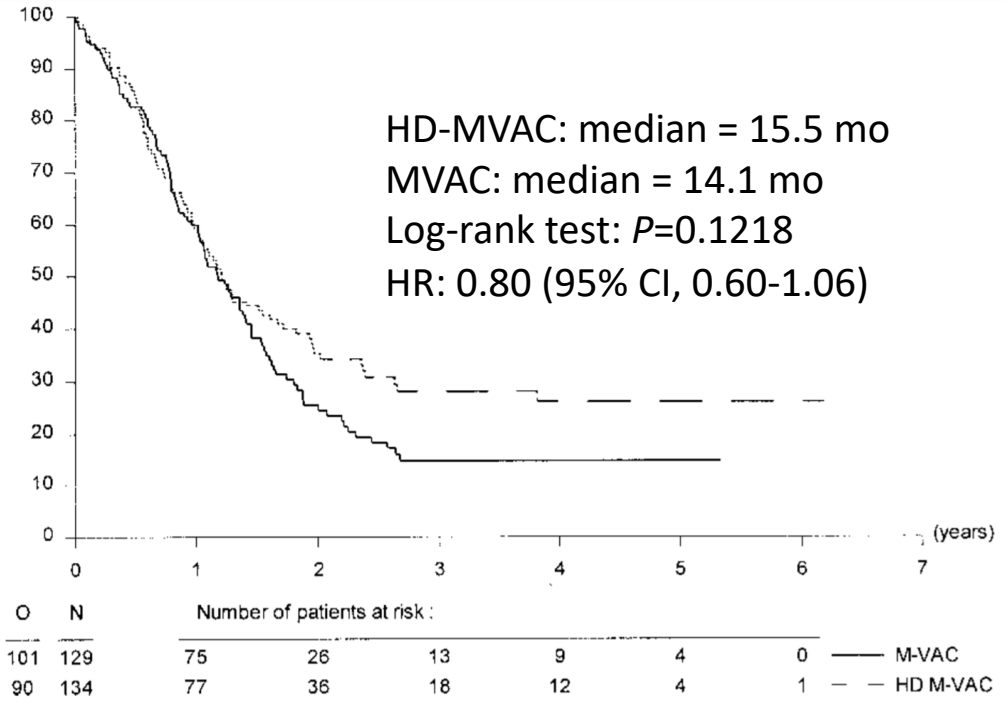
Treatment Landscape for Ia/mUC



First-Line Cisplatin Regimens[1]





ORR[2]	
GC	49%
MVAC	46%

Toxic Death Rate[2]	
GC	1%
MVAC	3%

ORR[3]	
HD-MVAC	62%
MVAC	50%

Toxic Death Rate[3]	
HD-MVAC	3%
MVAC	4%

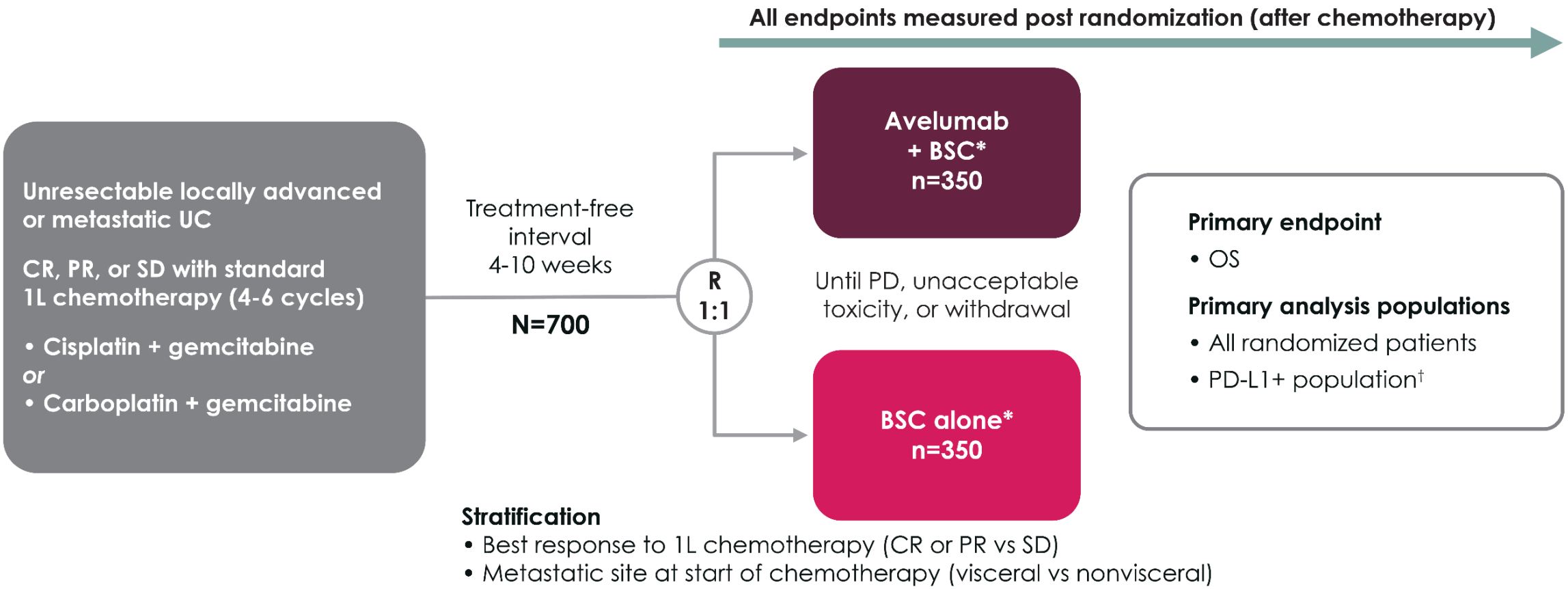
1. von der Maase H, et al. *J Clin Oncol.* 2005:23(21):4602-4608. **2.** von der Maase H, et al. *J Clin Oncol*. 2000;18(17):3068-3077. **3.** Sternberg CN, et al. *J Clin Oncol.* 2001;19(10):2638-2646.

Cisplatin-Ineligible Patients

- 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 heart failure

1. Dash A, et al. *Cancer.* 2006;107(3):506-513. **2.** Galsky MD, et al. *J Clin Oncol.* 2011;29(17):2432-2438.

JAVELIN Bladder 100 Phase III Study Design



Data cutoff date: June 2021

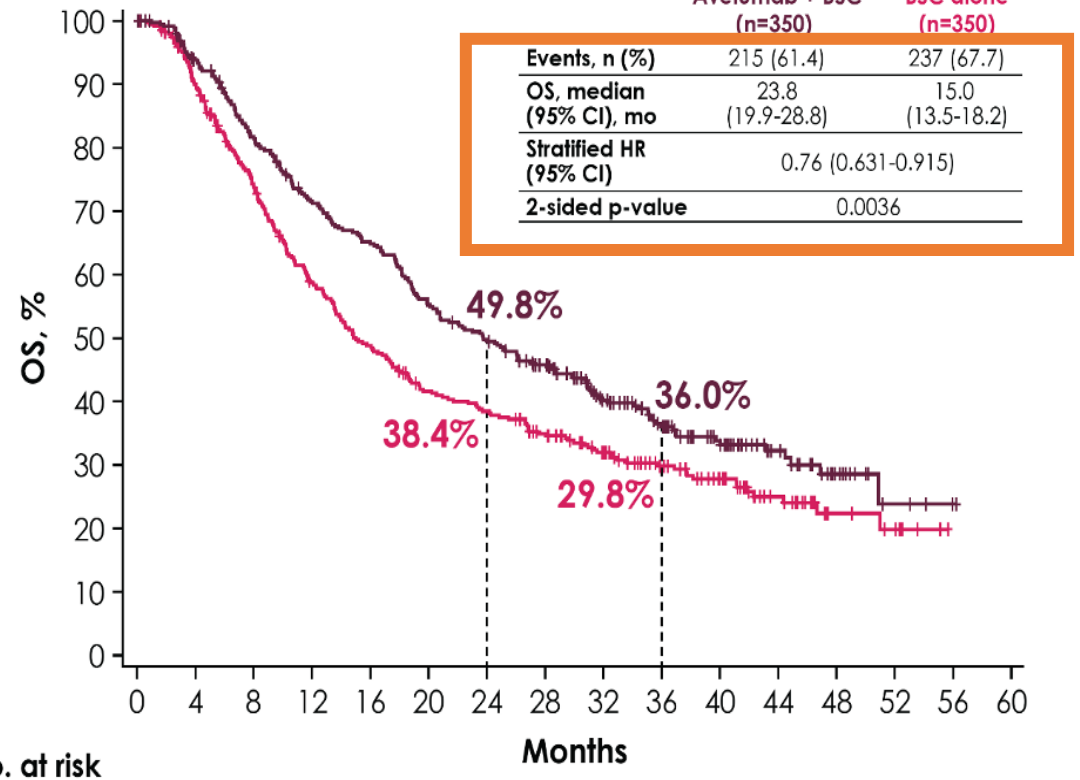
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable. †Assessed using the Ventana SP263 assay.

1L, first line; BSC, best supportive care; CR, complete response; PR, partial response; OS, overall survival; PD, progressive disease; R, randomization; SD, stable disease; UC, urothelial carcinoma.

Presented by Srikala Sridhar at ASCO 2021 Annual Meeting June 4-8, 2021. Abstract 4527.

OS and PFS in the Overall Population: 38m Follow-up

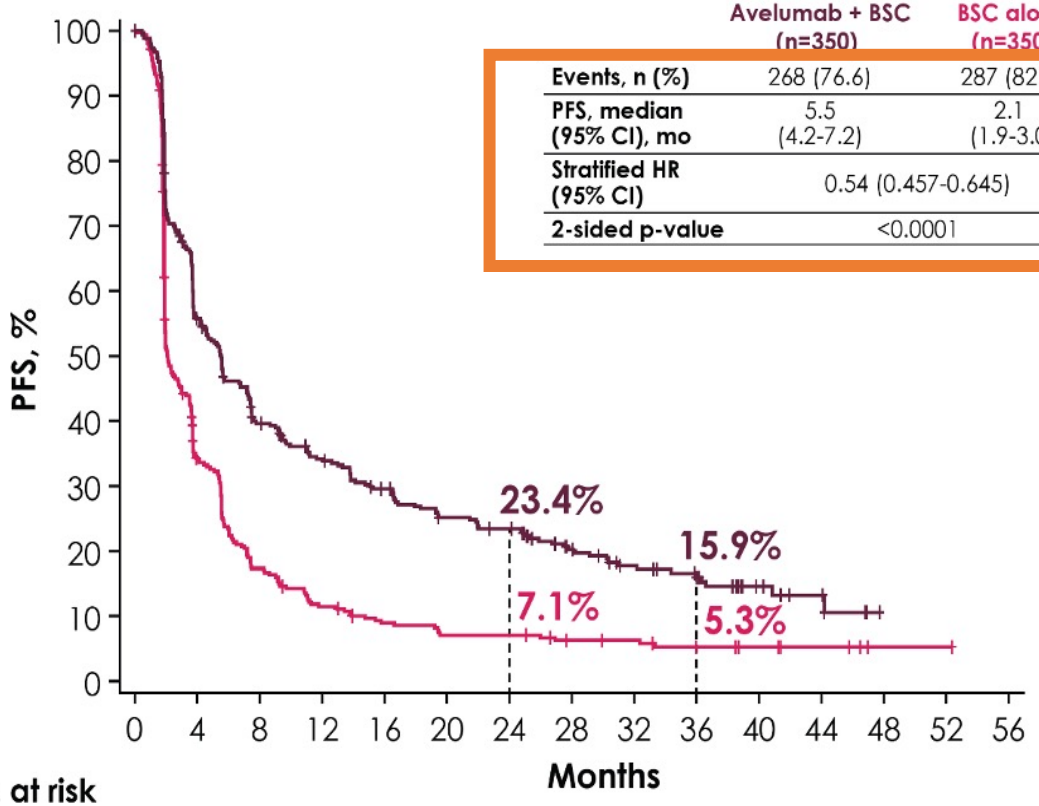
OS in the overall population



	Avelumab + BSC (n=350)	BSC alone (n=350)
Events, n (%)	215 (61.4)	237 (67.7)
OS, median (95% CI), mo	23.8 (19.9-28.8)	15.0 (13.5-18.2)
Stratified HR (95% CI)	0.76 (0.631-0.915)	
2-sided p-value	0.0036	

No. at risk																
Avelumab + BSC	350	318	274	237	216	183	164	140	99	74	53	31	13	4	1	0
BSC	350	304	243	190	158	131	121	103	82	62	46	27	10	7	0	

PFS in the overall population



	Avelumab + BSC (n=350)	BSC alone (n=350)
Events, n (%)	268 (76.6)	287 (82.0)
PFS, median (95% CI), mo	5.5 (4.2-7.2)	2.1 (1.9-3.0)
Stratified HR (95% CI)	0.54 (0.457-0.645)	
2-sided p-value	<0.0001	

No. at risk															
Avelumab + BSC	350	182	126	105	88	73	67	43	32	25	12	6	0		
BSC	350	101	51	33	24	19	19	14	13	9	6	4	1	1	0

Presented by Srikala Sridhar at ASCO 2021 Annual Meeting June 4-8, 2021. Abstract 4527.

First-line mUC – cisplatin ineligible

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First-line mUC – cisplatin ineligible

Carboplatin + Gemcitabine followed by maintenance Avelumab remains valid option at the time of this presentation.

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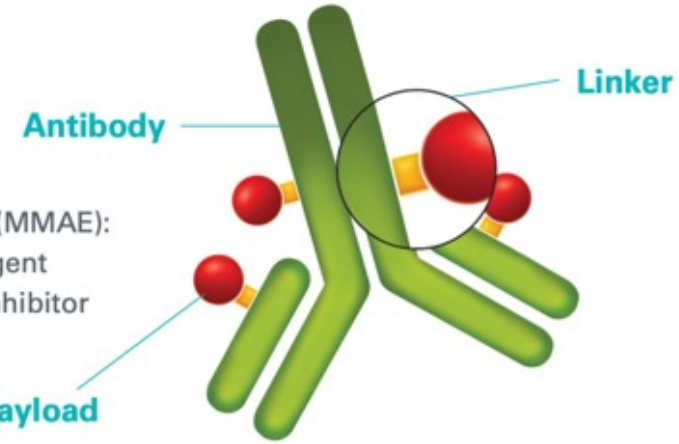
ADC targets expression rates:

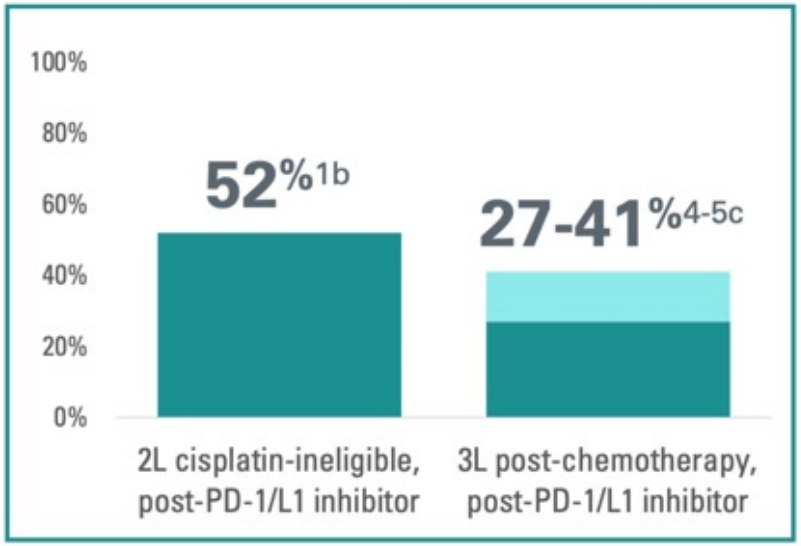
- Nectin-4: **99%-100%** in la/mUC[1,2a]
- Trop-2: **≤83%** in UC[3]

ADC targets in la/mUC[2,3]
- Nectin-4
- Trop-2

ADC payloads in la/mUC[2,5]
- Monomethyl auristatin E (MMAE): microtubule-disrupting agent
- SN-38: topoisomerase I inhibitor



Objective Response Rates With 2L or 3L ADCs in la/mUC



[a] Based on 2 studies: a phase 2 clinical trial with 80 evaluable patients with la/mUC;[1] and a phase 2 clinical trial with 120 evaluable patients with la/mUC.[2]
[b] Based on a phase 2 clinical trial of 89 cisplatin-ineligible patients with la/mUC post-PD-1/L1 inhibitor who received an ADC.[1]
[c] Based on 2 studies: a phase 2 clinical trial of 113 patients with la/mUC and progressed after platinum chemotherapy and a PD-1/L1 inhibitor who received an ADC;[5] and a phase 3 trial of 608 patients with la/mUC who progressed after platinum chemotherapy and a PD-1/L1 inhibitor and were randomized to an ADC (n=301) or chemotherapy (n=307).[4]

2L, second line; 3L, third line; ADC, antibody-drug conjugate; IO, immuno-oncology; la/mUC, locally advanced/metastatic urothelial carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Trop-2, trophoblast cell surface antigen 2.

References: 1. Yu EY, Petrylak DP, O'Donnell PH, et al. Lancet Oncol 2021;22(6):872-82. Erratum in: Lancet Oncol 2021;22(6):e239. **2.** Rosenberg JE, O'Donnell PH, Balar AV, et al. J Clin Oncol 2019;37(29):2592-600. **3.** Faltas B, Goldenberg DM, Ocean AJ, et al. SClin Genitourin Cancer 2016;14(1):e75-9. **4.** Powles T, Rosenberg JE, Sonpavde GP, et al. N Engl J Med 2021;384(12):1125-35. **5.** Tagawa ST, Balar AV, Petrylak DP, et al. J Clin Oncol 2021;39(22):2474-85.

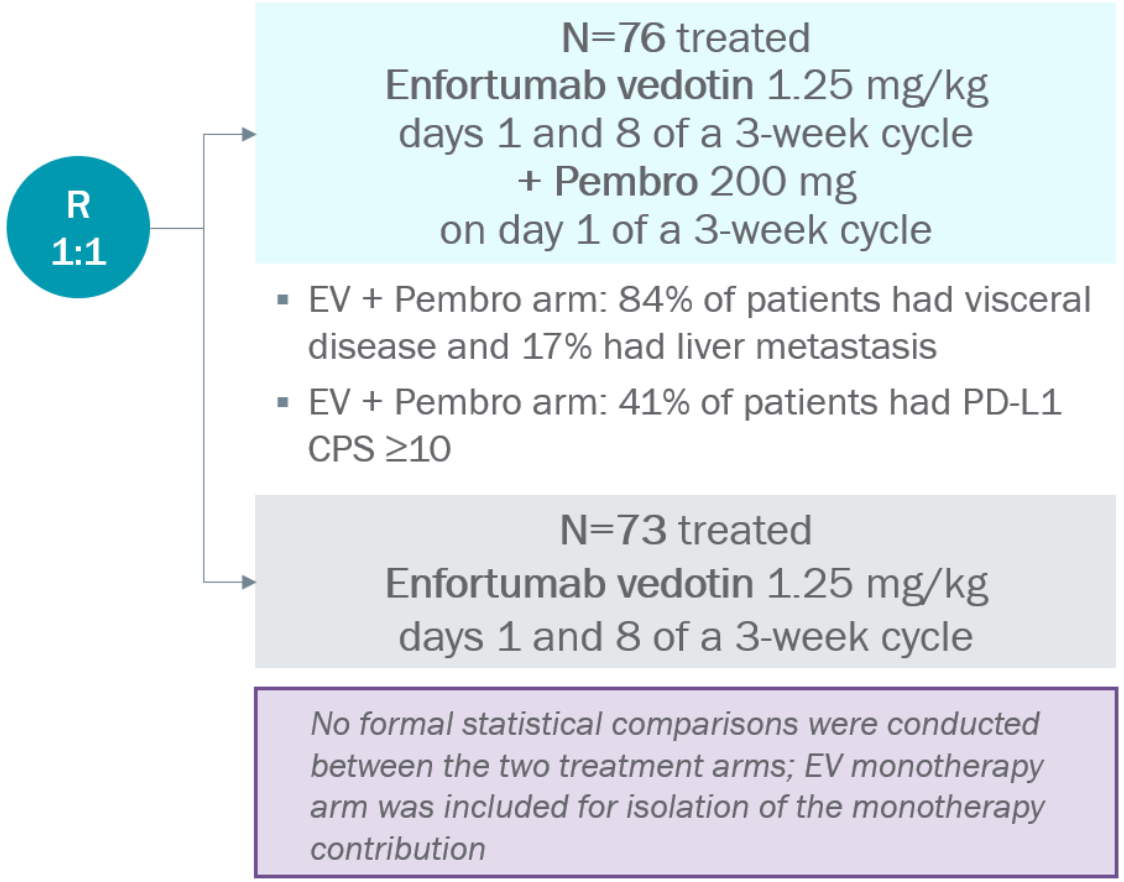
EV-103 Cohort K: Phase 1b/2 Trial of EV + Pembrolizumab

Cohort K

- la/mUC
- Cisplatin ineligible
- No prior treatment for la/mUC

Primary endpoint: ORR per BICR

Key secondary endpoints: ORR per investigator assessment, DOR, disease control rate, PFS, OS, safety/tolerability



- O'Donnell PH, et al. *J Clin Oncol*. 2023. doi: 10.1200/JCO.22.02887. Online ahead of print.

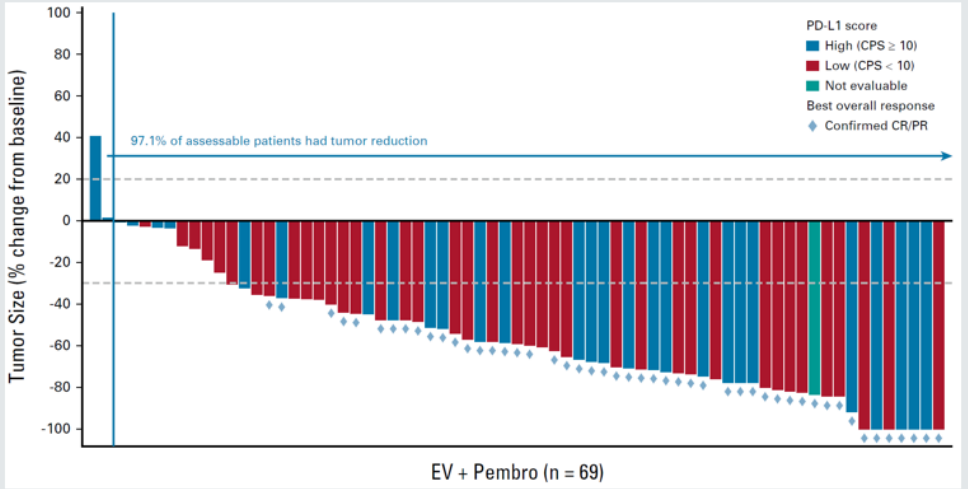
EV-103 Cohort K: Efficacy

	EV + Pembro N=76	EV Mono N=73
Confirmed ORR (95% CI)	49 (**64.5%**) (52.7-75.1)	33 (45.2%) (33.5-57.3)
Best overall response		
CR	8 (10.5%)	3 (4.1%)
PR	41 (53.9%)	30 (41.1%)
SD	17 (22.4%)	25 (34.2%)
PD	6 (7.9%)	7 (9.6%)
NE	3 (3.9%)	5 (6.8%)
No assessment	1 (1.3%)	3 (4.1%)
Median time to objective response, mo (range)	2.07 (1.1-6.6)	2.07 (1.9-15.4)
Median number of treatment cycles, mo (range)	11.0 (1-29)	8.0 (1-33)

- EV + Pembro arm: 7/13 (53.8%) confirmed ORR observed in patients with liver metastases

No formal statistical comparisons were conducted between the two treatment arms

EV + Pembro: Percentage Reduction of Tumor Size From Baseline of Target Lesion by BICR



	EV + Pembro N=76	EV Mono N=73
mDOR, mo (95% CI)	**NR** (10.25-NR)	13.2 (6.14-15.97)
mPFS, mo (95% CI)	**NR** (8.31-NR)	8.0 (6.05-10.35)
mOS, mo (95% CI)	**22.3** (19.09-NR)	21.7 (15.21-NR)
Median follow-up, mo	14.8	15.0

- O'Donnell PH, et al. *J Clin Oncol*. 2023. doi: 10.1200/JCO.22.02887. Online ahead of print.

Enfortumab Vedotin + Pembrolizumab Indication

FDA approved – April 3, 2023

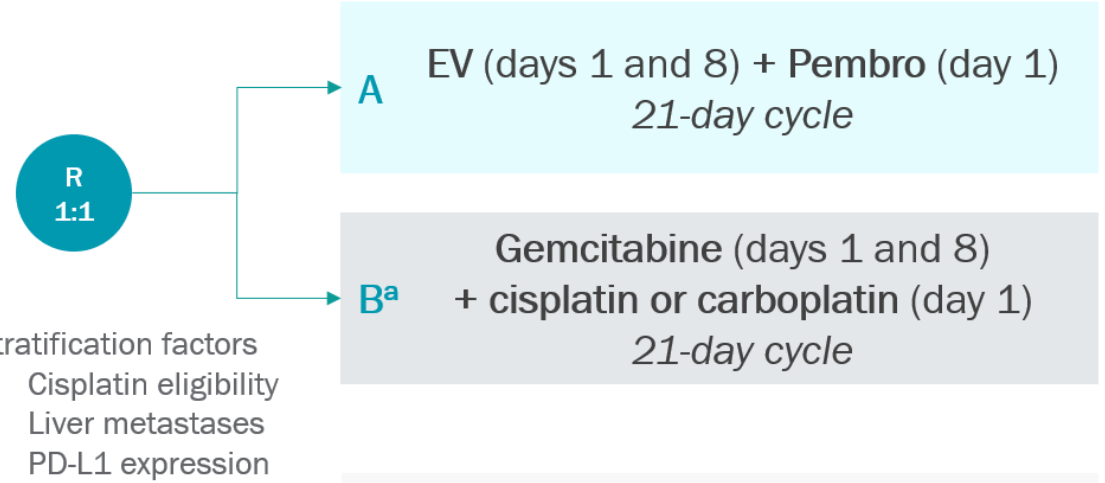
- Enfortumab vedotin, in combination with pembrolizumab, is indicated for the **treatment of adult patients with la/mUC who are not eligible for cisplatin-containing chemotherapy**
- This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials

EV-302: Phase 3 Trial of Enfortumab Vedotin + Pembrolizumab[1,2]

- Unresectable Ia/mUC
- No prior systemic therapy except for neoadjuvant or adjuvant (with cystectomy) chemotherapy with recurrence >12 months after therapy completion
- Eligible for cisplatin- or carboplatin-based chemotherapy and pembrolizumab
- ECOG PS 0-2

Primary endpoints
- PFS per BICR
- OS

Secondary endpoints
- ORR, DOR, DCR, safety, and PROs

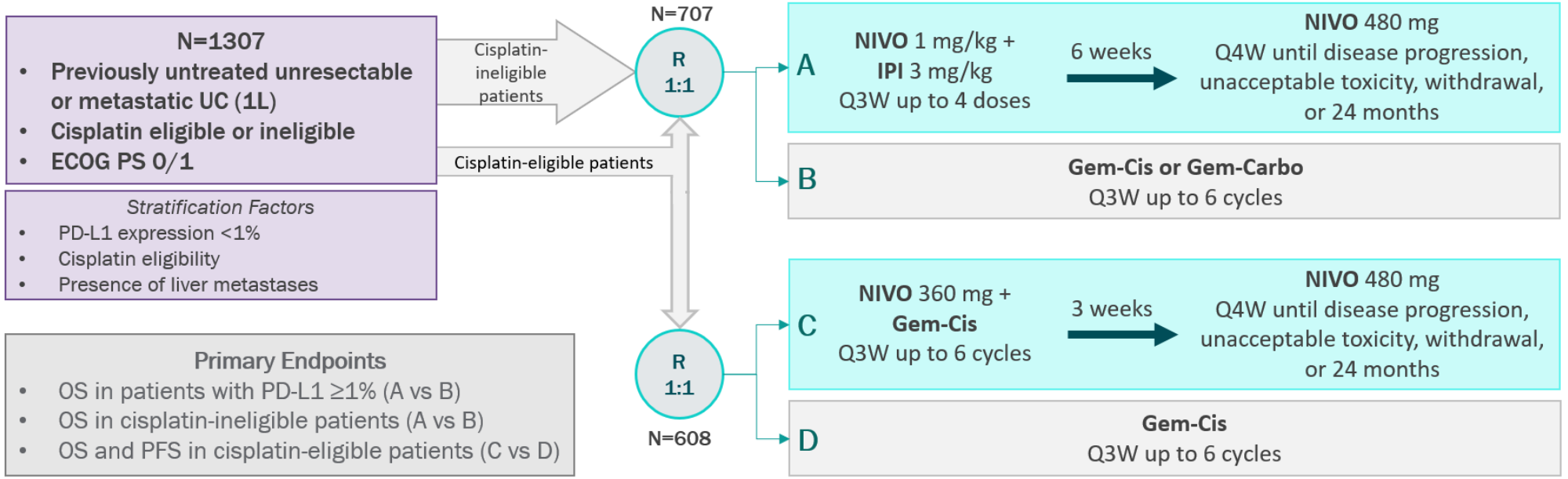


Stratification factors
- Cisplatin eligibility
- Liver metastases
- PD-L1 expression

[a] Maintenance therapy (after protocol-specified therapy) may be used following completion and/or discontinuation of platinum-containing therapy, if locally available, and provided the patient is deemed appropriate by the investigator.

1. van der Heijden MS, et al. ASCO GU 2022. Abstract TPS589. **2.** ClinicalTrials.gov. Accessed April 5, 2023. https://clinicaltrials.gov/ct2/show/NCT04223856

CheckMate-901: Phase 3 Trial



May 16, 2022

- **Nivo + Ipi vs Chemo did not meet the primary endpoint of OS in patients with PD-L1 ≥1%**
- **Ongoing assessment of Nivo + Ipi vs Carbo/Gem in cisplatin-ineligible patients**
- **Ongoing sub-study of Nivo + Cis/Gem vs Cis/Gem**

July 12, 2023

- **Sub-study of Nivo + Cis/Gem vs Cis/Gem met dual primary endpoints of OS and PFS at final analysis**

- Galsky MD. ASCO 2018. Abstract TPS4588. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03036098.
- Press Release. Bristol Myers Squibb. May 16, 2022.
- Press Release. Bristol Myers Squibb. July 11, 2023.

Second-line and Beyond mUC

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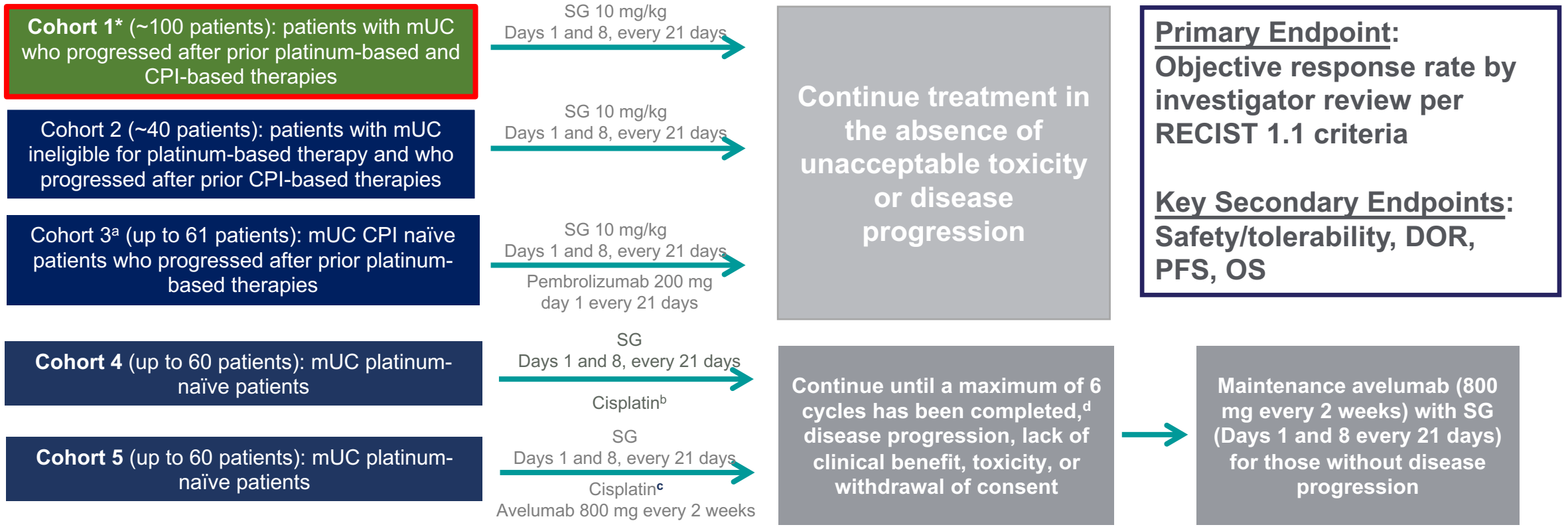
Postplatinum Treatment: Immunotherapy

Level 1 Evidence

Study[a]	**Pembrolizumab** KEYNOTE-045[1] Phase 3	**Nivolumab** CheckMate 275[2] Phase 2	**Avelumab** JAVELIN Solid Tumor[3,4] Phase 1b (mUC cohort)
N	542	270	249
Treatment arm(s)	**Pembrolizumab** (n=270) 200 mg IV q3w vs Chemo (n=272)	**Nivolumab** 3 mg/kg IV q2w	**Avelumab** 10 mg/kg IV q2w
Patient population	▪ la/mUC ▪ Progression after 1-2 lines of platinum-based therapy ▪ ECOG PS 0-2	▪ la/mUC ▪ ≥1 platinum-containing therapy or ≤12 months of neoadjuvant/adjuvant treatment ▪ ECOG PS 0-1	▪ la/mUC ▪ Progressed on platinum-based Chemo or platinum ineligible ▪ ECOG PS 0-1
ORR	21.1%	19.6%	16.5%
mPFS, mo	2.1	2.0	1.6
mOS, mo	10.1	8.7	7.0

1. Fradet Y, et al. *Ann Oncol.* 2019;30(6):970-976
2. Sharma P, et al. Lancet Oncol. 2017 Mar
3. Appolo A, et al: JITC. 2020

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



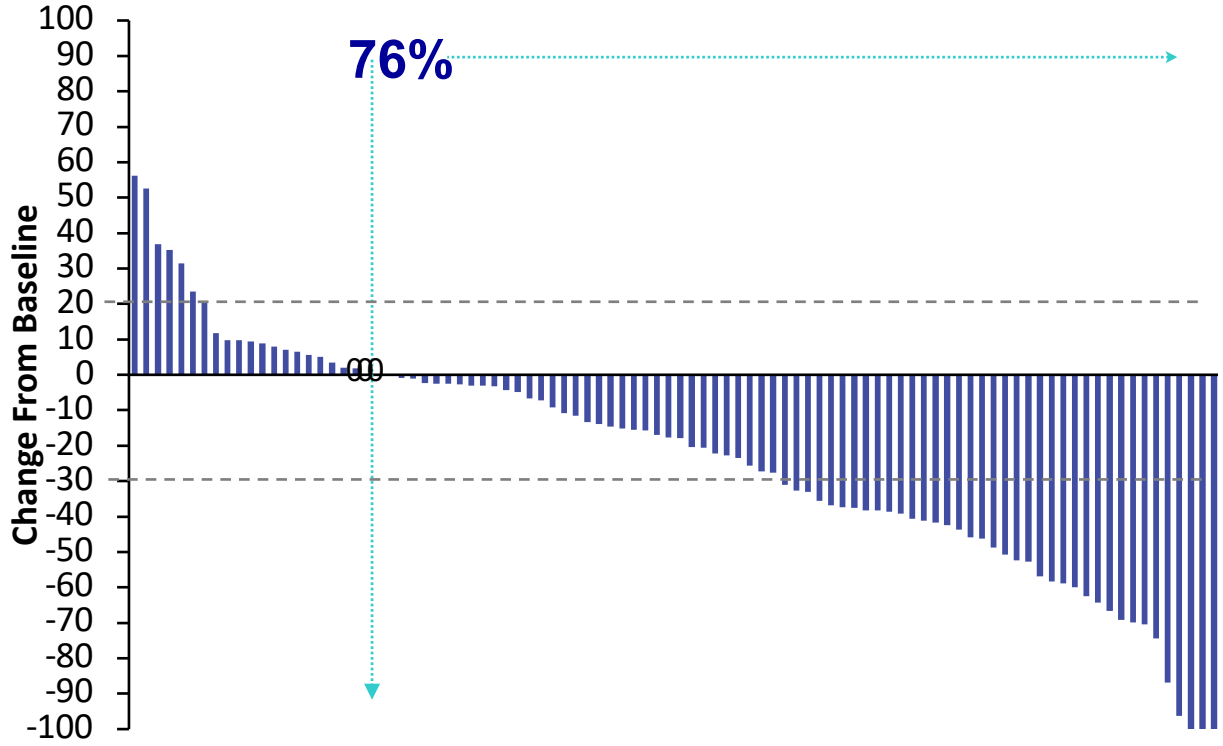
Key Inclusion Criteria: Age ≥18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥30 mL/min,[b,c] adequate hepatic function
Key Exclusion Criteria: Immunodeficiency, active Hepatitis B or C, active secondary malignancy, or active brain metastases

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

ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.
Grivas, P. Abstract 434. Presented at ASCO GU 2022; February 17 – 19; San Francisco, CA.

TROPHY-U-01 Cohort 1: Response and Reduction in Tumor Size

Endpoint	Cohort 1 (N=113)
ORR, No. (%) [95% CI]	31 (27) [19, 37]
CR, No. (%)	6 (5)
PR, No. (%)	25 (22)
Median duration of response, mo [95% CI] (range)	5.9 [4.70, 8.60] (1.4–11.7)
Median time to onset of response, mo (range)	1.6 (1.2–5.5)

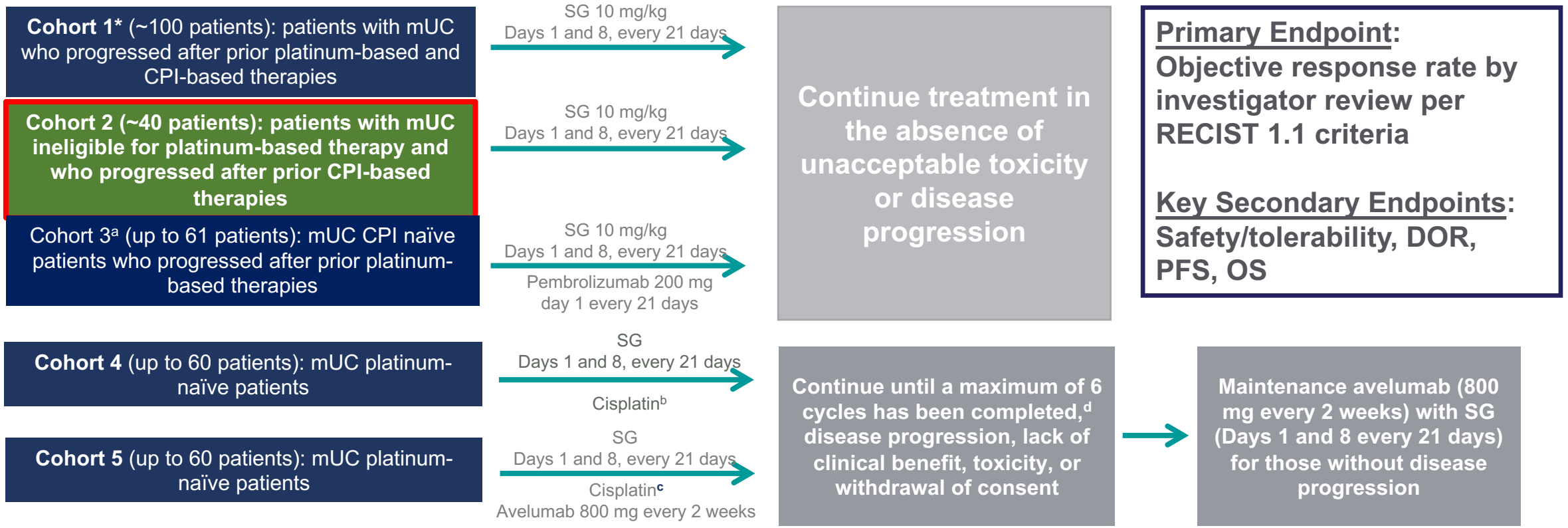


Assessments were per Blinded Independent Review Assessment, RECIST v1.1.

71/94 patients with at least one post-baseline target lesion measurement and accepted for central review. Fourteen patients had no post-treatment imaging, 1 patient lacked measurable lesions by central review, and 4 patients had poor image quality.

Loriot Y, et al. *Annal Oncol*. 2020;31(suppl 4):S1142-S1215 (LBA24).

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



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

NCI Designated Comprehensive Cancer Center

Grivas, P. Abstract 434. Presented at ASCO GU 2022; February 17 – 19; San Francisco, CA.

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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. GU Cancers Symposium 2023;Abstract 520.

TROPHY-U-01 Cohort 2: Duration of Response in Platinum-Ineligible Patients With Prior Anti–PD-1/PD-L1

Response, n (%)	N = 38
ORR 95% CI	12 (32) 17.5-48.7
Best overall response	
▪ CR	0
▪ PR	12 (32)
▪ SD	13 (34)
▪ SD ≥6 mo	4 (11)
▪ PD	4 (11)
▪ Not evaluable	4 (11)
▪ Not assessed	5 (13)
CBR (CR + PR + SD ≥6 mo) 95% CI	16 (42) 26.3-59.2

Outcome	N = 38
Median time to response, mo	1.4
Median duration of response, mo (95% CI)	(n = 12) 5.6 (2.8-13.3)
Median PFS, mo (95% CI)	5.6 (4.1-8.3)
Median OS, mo (95% CI)	13.5 (7.6-15.6)

- ORR in patients without prior platinum or EV: 53.8% (n = 13)

Petrylak. ASCO GU 2023. Abstr 520.

TROPHY-U-01 Cohort 1: Response and Reduction in Tumor Size

Endpoint
ORR, No. (%) [95
CR, No. (%)
PR, No. (%)
Median duratio [95% CI] (range)
Median time to (range)

FDA grants accelerated approval to sacituzumab govitecan for advanced urothelial cancer

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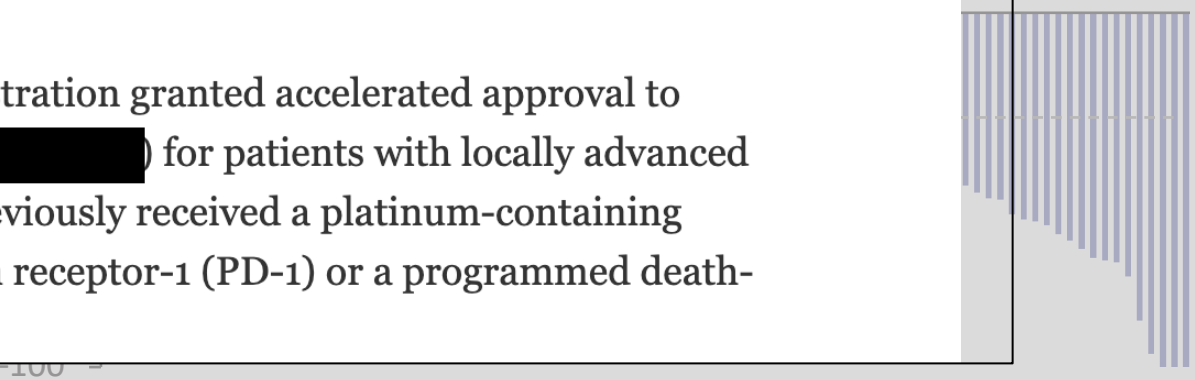
On April 13, 2021, the Food and Drug Administration granted accelerated approval to sacituzumab govitecan ([redacted]) for patients with locally advanced or metastatic urothelial cancer (mUC) who previously received a platinum-containing chemotherapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor.



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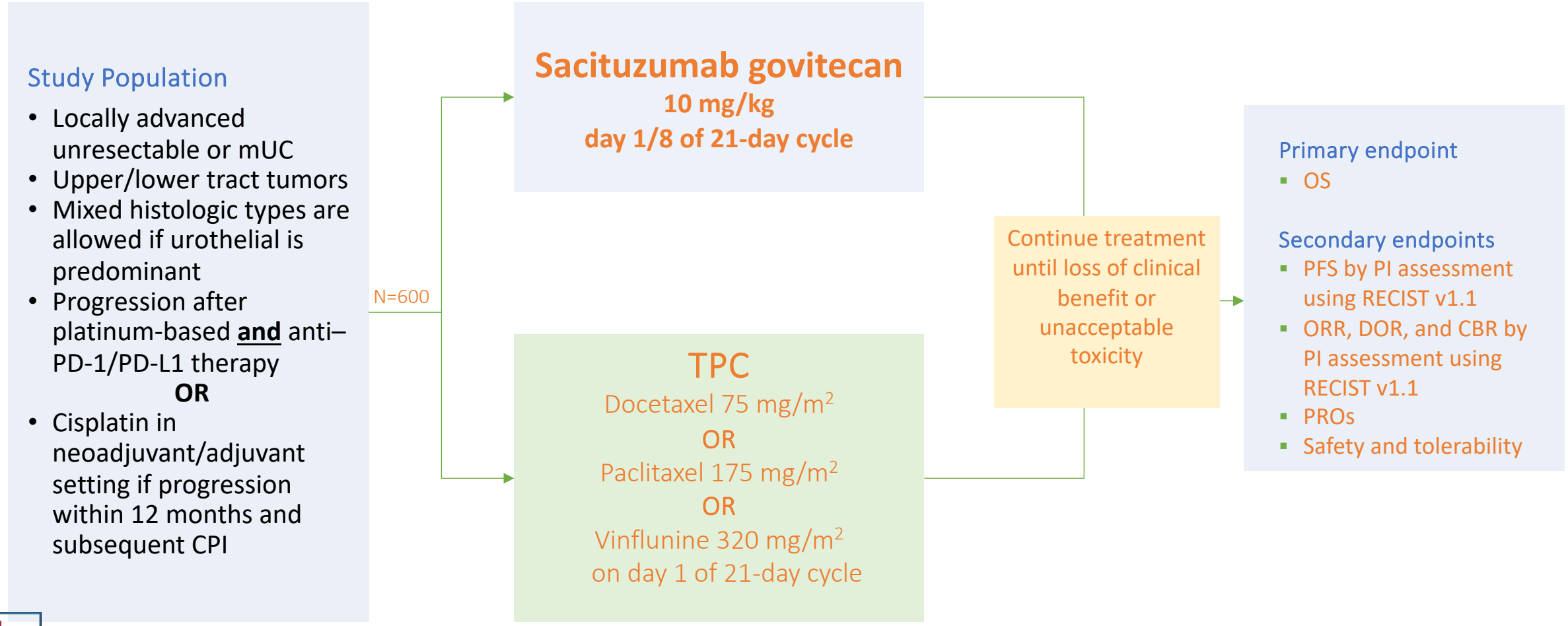
Loriot Y, et al. *Annal Oncol*. 2020;31(suppl 4):S1142-S1215 (LBA24).

TROPiCS-04: Phase 3 Trial of Sacituzumab Govitecan



Grivas, et al. ASCO GU 2021. Abstract TPS498.

THOR: Phase 3 Study of Erdafitinib vs Chemotherapy

- ~20% of patients with advanced UC have *FGFR* alterations
- Erdafitinib is an oral selective pan-FGFR tyrosine kinase inhibitor

Key eligibility criteria

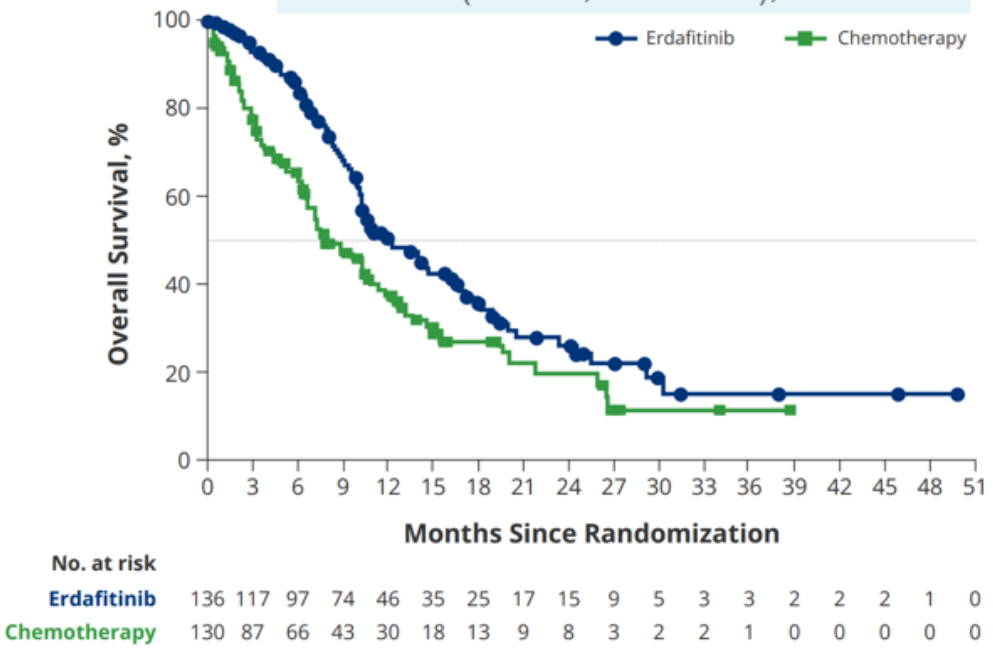
- Unresectable or metastatic UC
- Progressed on or after ≥1 prior treatment that included an anti–PD-(L)1
- Select *FGFR3/2alt* (mutation/fusion)
- ECOG PS 0-2

Erdafitinib (n=136)	Chemo (n=130)
8 mg PO once daily; uptitration to 9 mg	Docetaxel or vinflunine every 3 weeks

- **Primary endpoint: OS**
- Key secondary endpoints: PFS, ORR, safety

	Median OS
Erdafitinib	12.1 mo
Chemotherapy	7.8 mo

HR 0.64 (95% CI, 0.47-0.88), *P*=0.005



Loriot Y, et al. ASCO 2023. Abstract LBA4619.

THOR: Safety

AEs occurring in ≥30% (any grade) or ≥5% (grade 3-4) of patients	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%)

- 1 treatment-related death in the erdafitinib group (sudden death)
- 11 patients (8.1%) discontinued study treatment with erdafitinib due to treatment-related AEs

AEs of interest	Erdafitinib (n=135)		Chemotherapy (N=112)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Nail disorders	90 (66.7%)	15 (11.1%)	6 (5.4%)	0
Skin disorders	74 (54.8%)	16 (11.9%)	14 (12.5%)	0
Eye disorders (excluding central serous retinopathy)	57 (42.2%)	3 (2.2%)	6 (5.4%)	0
Central serous retinopathy	23 (17.0%)	3 (2.2%)	0	0

Loriot Y, et al. ASCO 2023. Abstract LBA4619.

Conclusion:

- Exciting time for UC, but still a lot of unanswered questions.
- Optimal sequencing remains unclear.
- ADC-IO combinations are promising, particularly enfortumab vedotin plus pembrolizumab, awaiting official presentation.

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