Updates In Management Of Urothelial Carcinoma

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MOFFITT CANCER CENTER

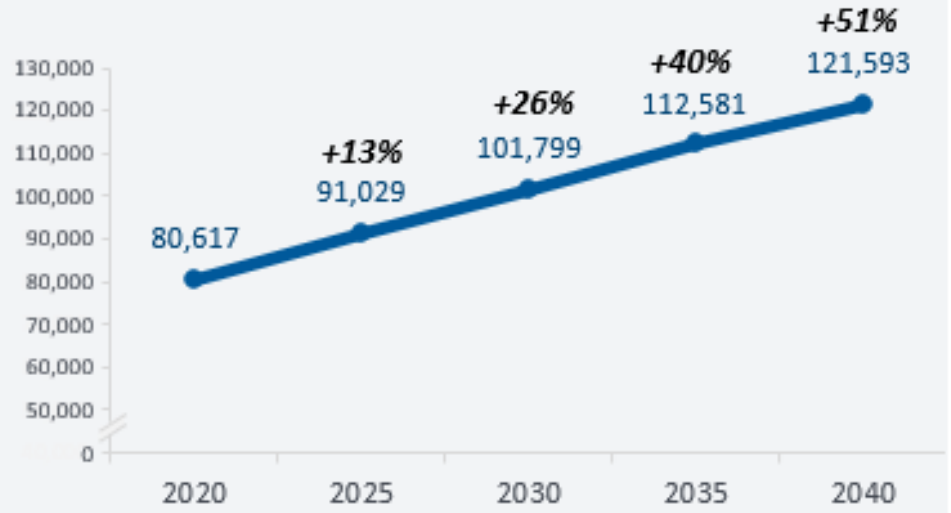
Bladder Cancer Is Projected to Be a Growing Health Problem in the US

Bladder cancer is estimated to be the 6th most common cancer in the United States[1]

		Estimated New Cases 2021	Estimated Deaths 2021
1	Breast cancer (female)	281,550	43,600
2	Prostate cancer	248,530	34,130
3	Lung and bronchus cancer	235,760	131,880
4	Colorectal cancer	149,500	52,980
5	Melanoma of the skin	106,110	7,180
6	**Bladder cancer**	**83,730**	**17,200**
7	Non-Hodgkin lymphoma	81,560	20,720
8	Kidney and renal pelvis cancer	76,080	13,780
9	Uterine cancer	66,570	12,940
10	Leukemia	61,090	23,660

In the United States, the incidence of bladder cancer is projected to increase[2]

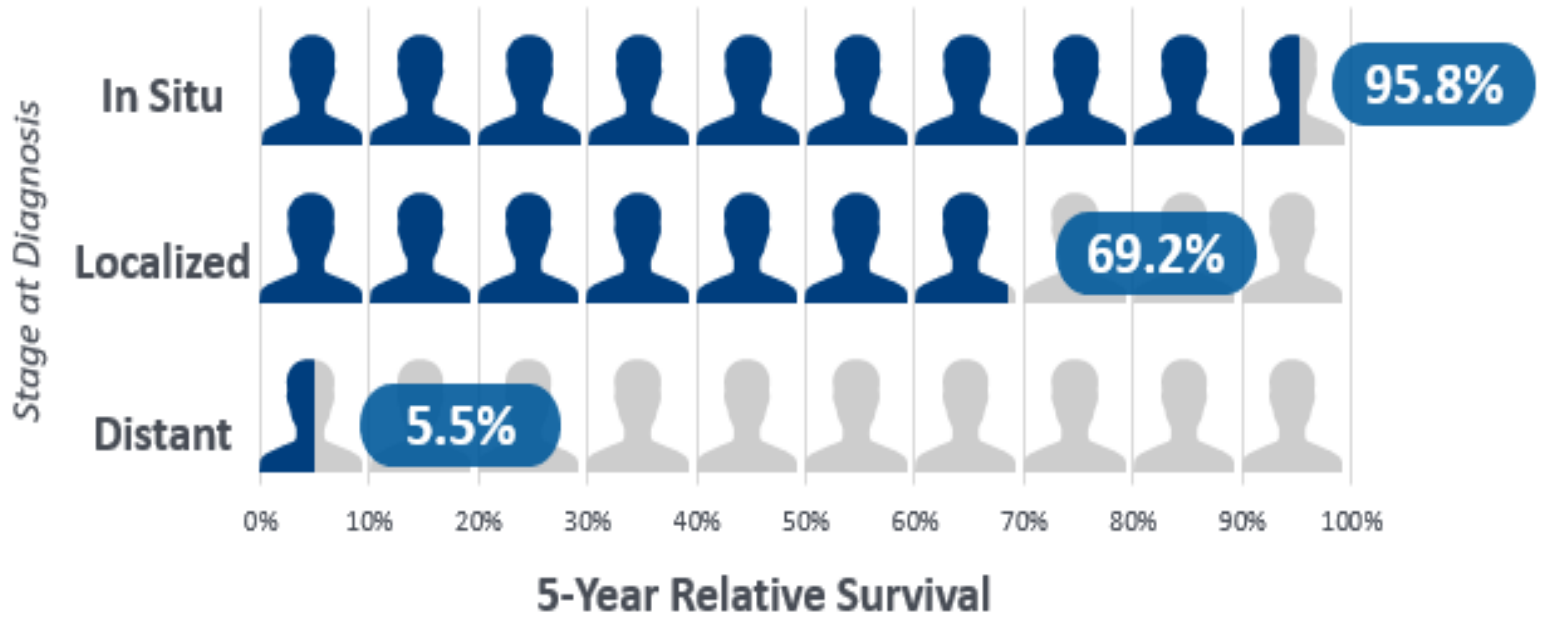
Estimated incidence and increase compared with 2020[2,a]



[a] As with all estimates, cancer predictions for future years should be interpreted with due caution. The key assumptions are that national rates, as estimated in 2020, do not change in the prediction period 2020-2040 and that the national population projections are correct for these years.

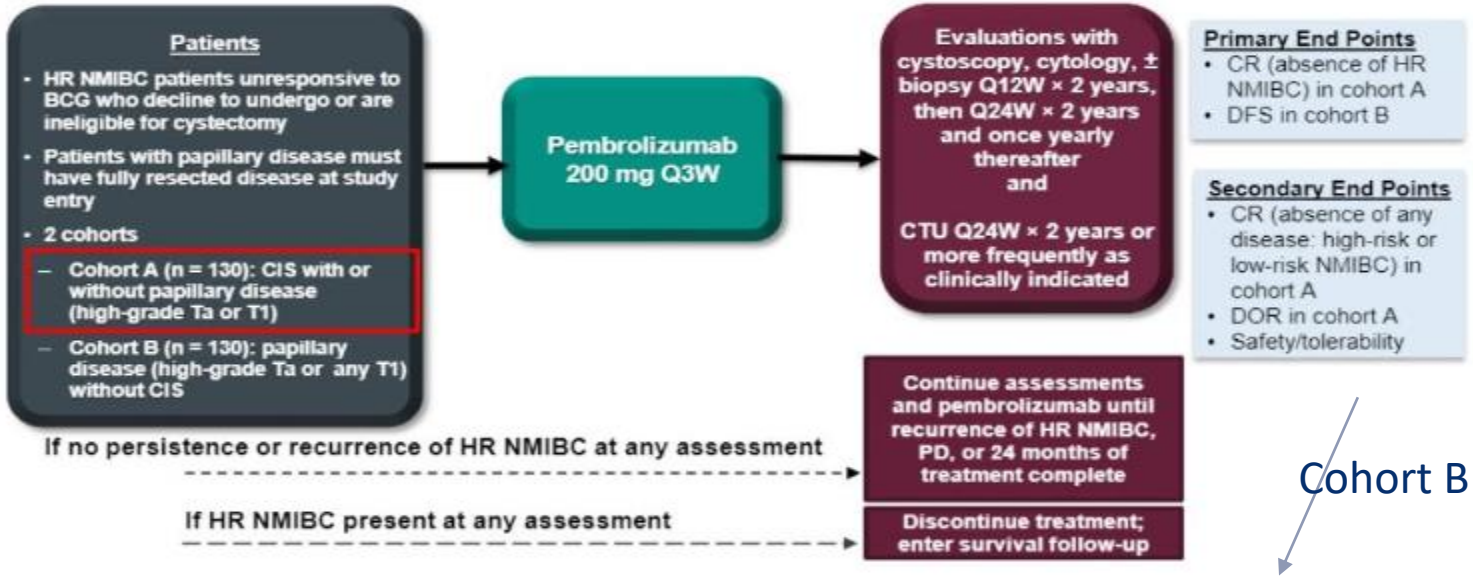
1. National Cancer Institute. Cancer stat facts: bladder cancer. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed 06-08-2021.2. International Agency for Research on Cancer. Cancer tomorrow: bladder. http://gco.iarc.fr/tomorrow. Accessed 02-08-2021.

5-Year Relative Survival Rates of Urinary Bladder Cancer in the US



National Cancer Institute. SEER cancer statistics review (CSR), 1975-2017. Cancer of the urinary bladder (invasive and in situ). https://seer.cancer.gov/csr/1975_2017/. Accessed 02-01-2021.

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)

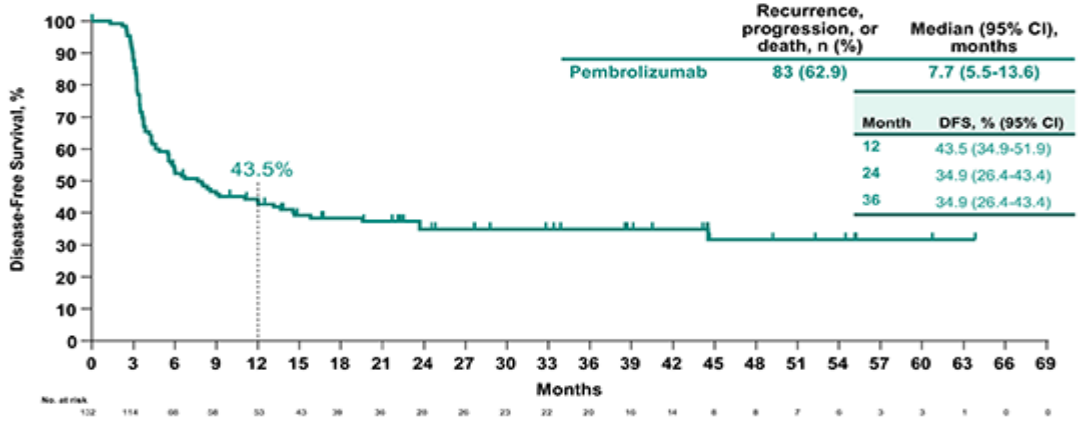


Cohort A

Cohort B

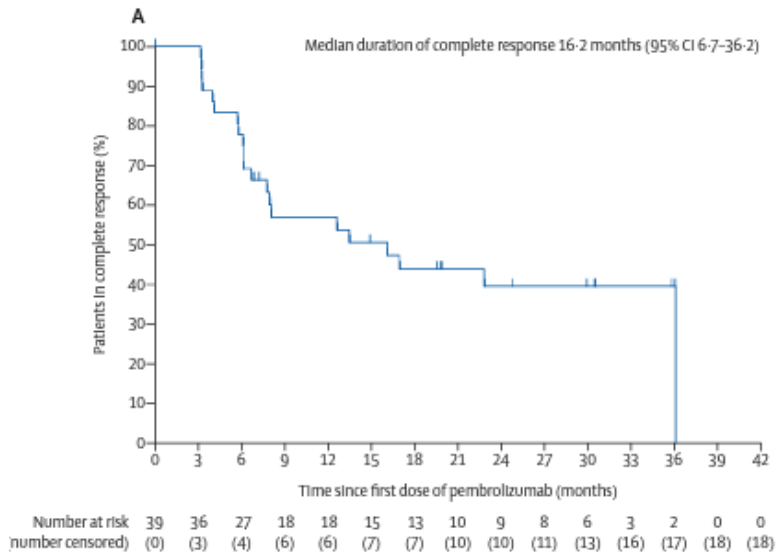
Select Outcomes (N=102)	
Complete Response	41%
DOR	16.2 months (0-30.4)
Progression to MIBC	0%
CR rate at 1 year	19%

Figure 1. Disease-Free Survival for HR NMIBC[a]



[a]Per central pathology/radiology review.
Data cutoff: October 20, 2022.

Summary	Cohort B N = 132
Treatment-related AEs	97 (73.5)
Grade 3 or 4	19 (14.4)
Serious	17 (12.9)
Discontinuations	14 (10.6)
Deaths	0 (0)



Several Studies Have Identified Common Characteristics of a Patient With Metastatic Urothelial Carcinoma

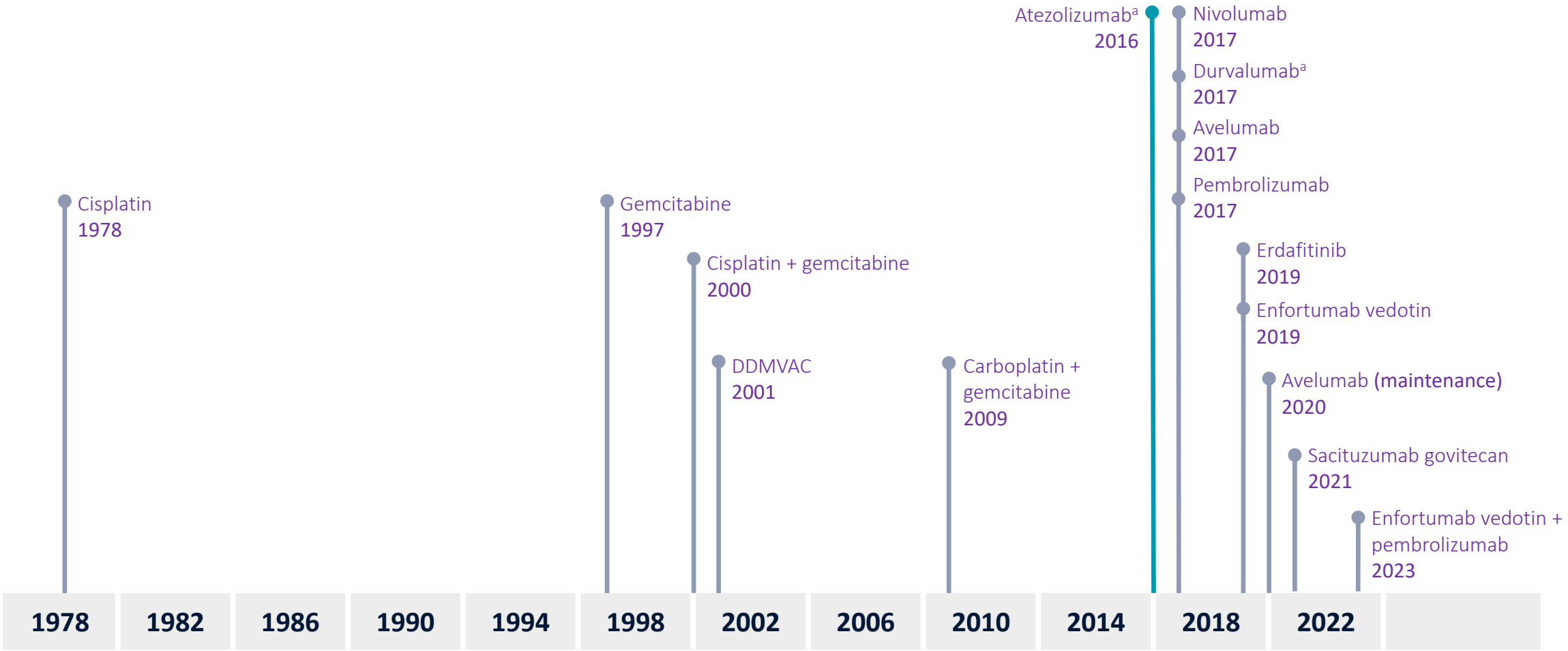
Common Characteristics of a Patient With mUC
Male[1]
White non-Hispanic[1]
6th to 8th decade of life[1]
Smoker[2]
Renal impairment[3]
One or more comorbid conditions[4]

Proposed Working Group Criteria for Cisplatin Ineligibility[3]
At least one of the following
WHO or ECOG PS of 2 or Karnofsky PS of 60%-70%
Creatinine clearance <60 mL/min
Grade ≥2 audiometric hearing loss[a]
Grade ≥2 peripheral neuropathy[a]
NYHA Class III heart failure

CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; mUC, metastatic urothelial carcinoma; NYHA, New York Heart Association; PS, performance status; WHO, World Health Organization.
[a]Per CTCAE v4.

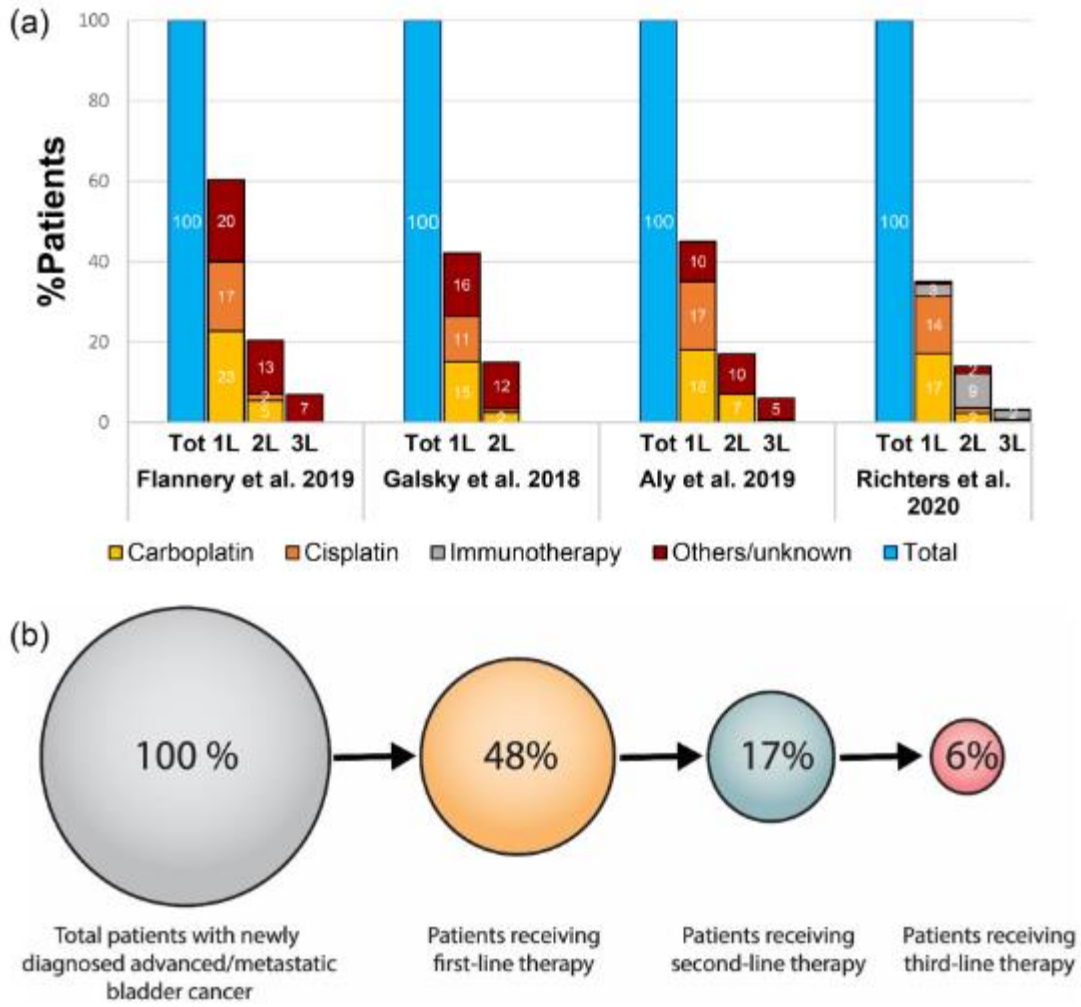
1. National Cancer Institute. SEER cancer statistics review (CSR), 1975-2017. Cancer of the urinary bladder (invasive and in situ). https://seer.cancer.gov/csr/1975_2017/. Accessed 02-01-2021. 2. American Cancer Society. Cancer Facts & Figures 2021. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf. Accessed 01-26-2021. 3. Galsky MD, Hahn NM, Rosenberg J, et al. J Clin Oncol 2011;29(17):2432-8. 4. Megwalu II, Vlahiotis A, Radwan M, Piccirillo JF, Kibel AS. Eur Urol 2008;53(3):581-9.

Treatment Landscape for Ia/mUC



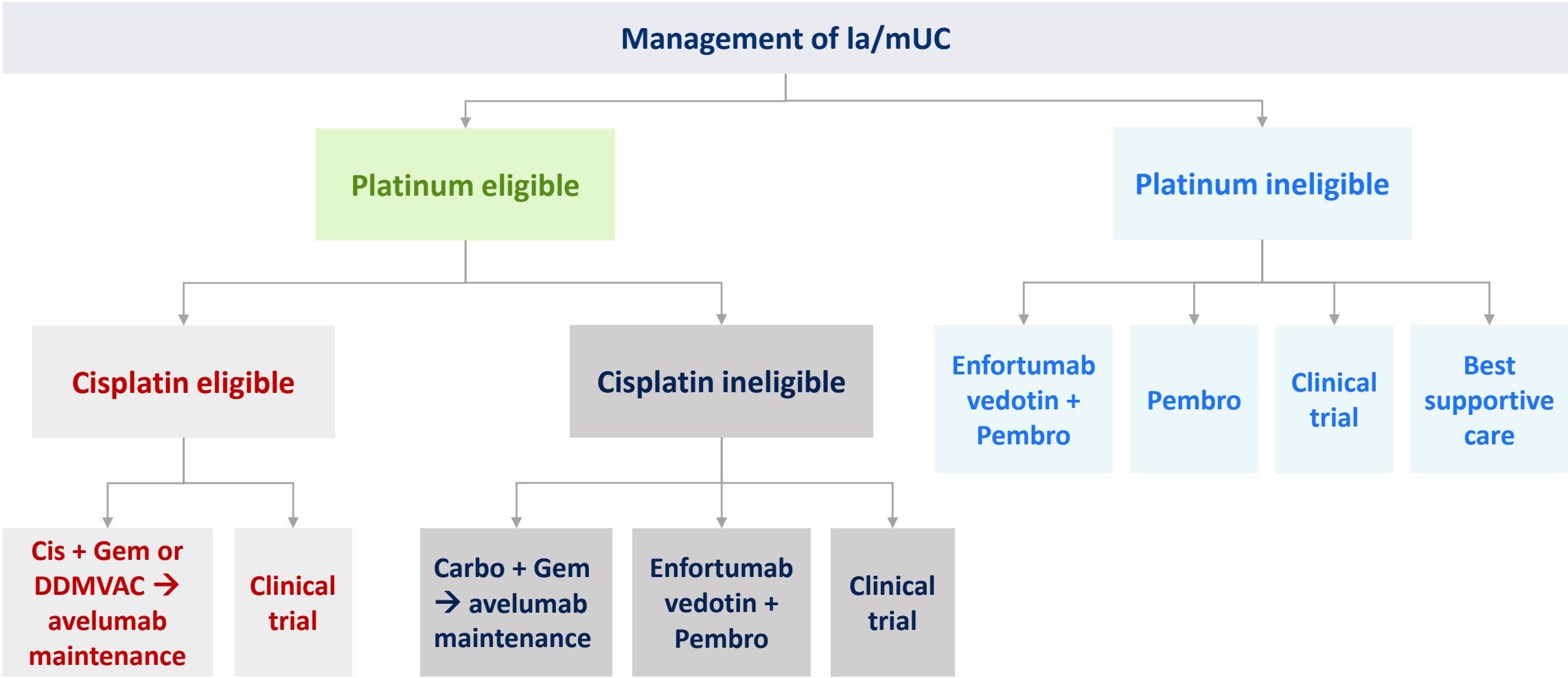
[a] Not FDA approved; indication withdrawn.

Utilization of Systemic Therapies

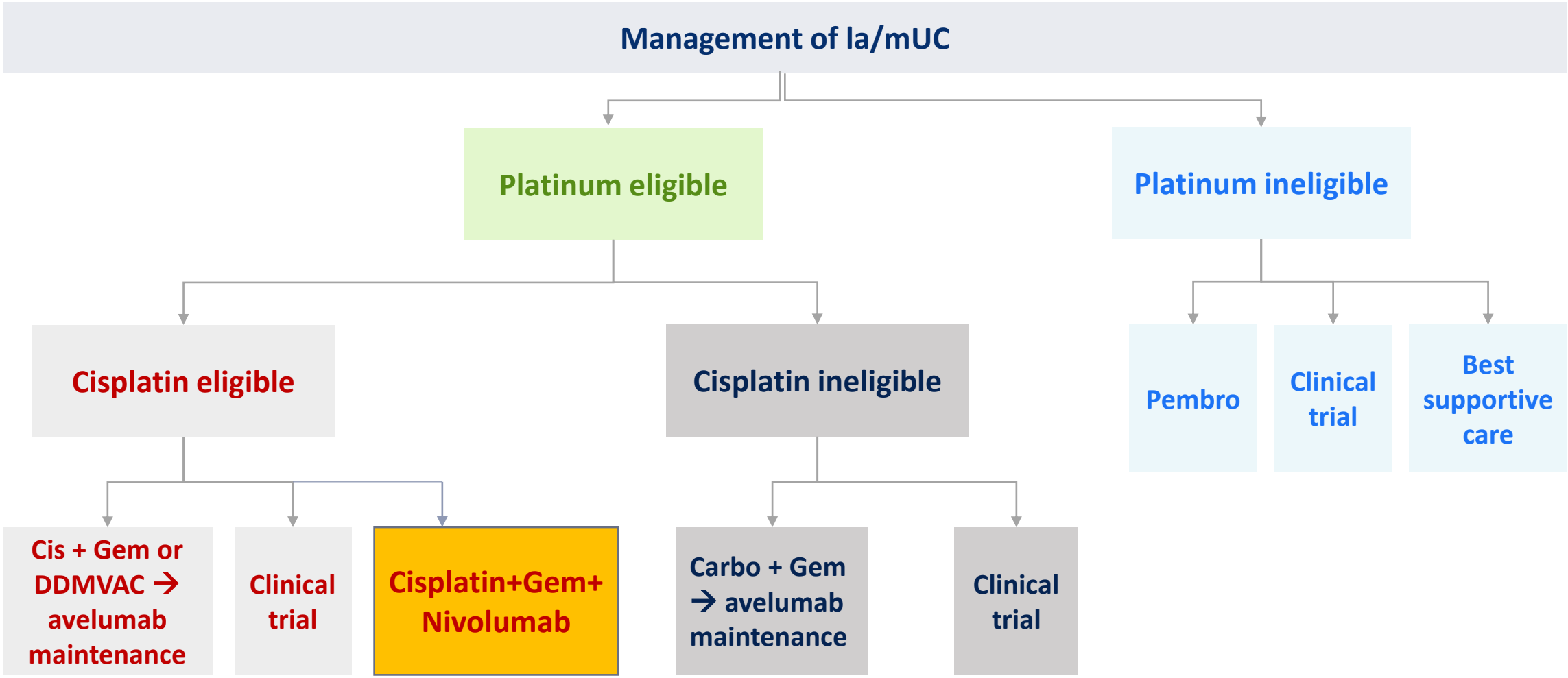


- Swami et al Cancer Treat Research Comm 2021

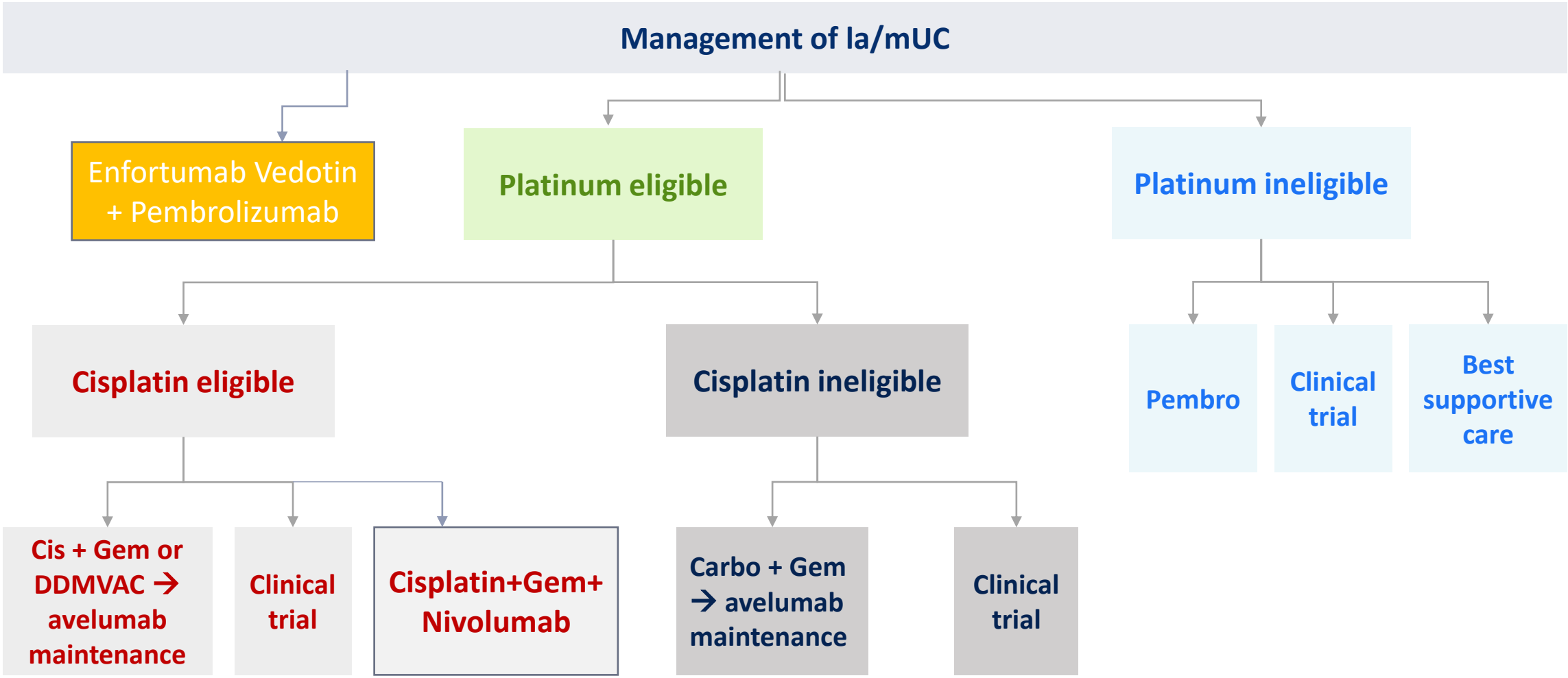
First-Line Management of la/mUC



First-Line Management of la/mUC in 2024

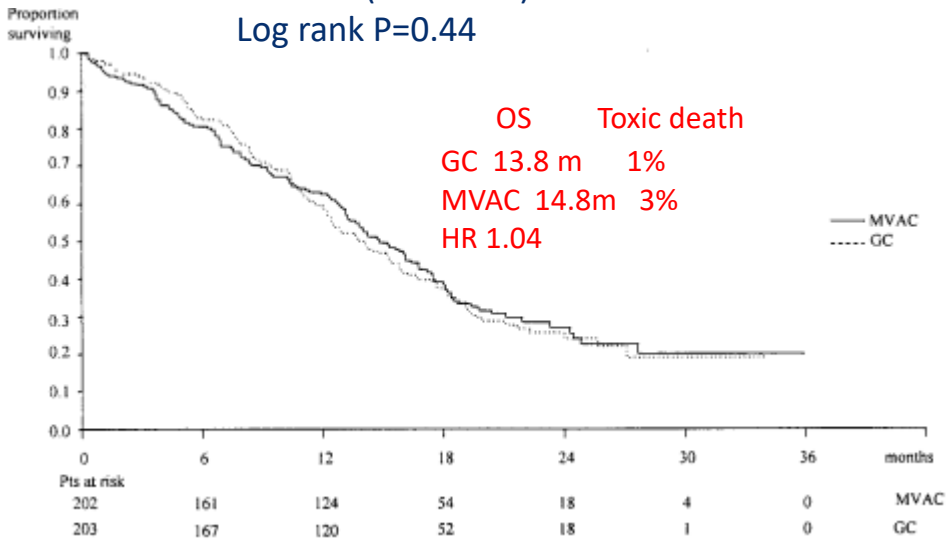


First-Line Management of la/mUC in 2024



First-Line Cisplatin Regimens

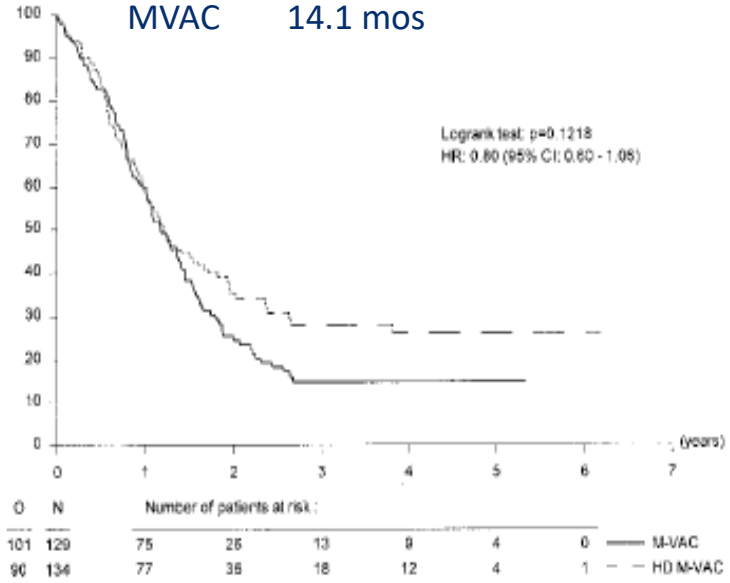
GC median=14 m (12.3-15.5m)
MVAC median=15.2 m (13.2-17.3 m)
HR:1.09 (0.88-1.34)
Log rank P=0.44



OS Toxic death
GC 13.8 m 1%
MVAC 14.8m 3%
HR 1.04

- Von der Maase et al J Clin Oncol.2000; 18:3068
- Von der Maase et al , J Clin Oncol 2005: 21: 4602

EORTC 30924
HD-MVAC 15.5 mos
MVAC 14.1 mos



Sternberg C et al J Clin Oncol,2001; 19:2638

Cisplatin-Ineligible

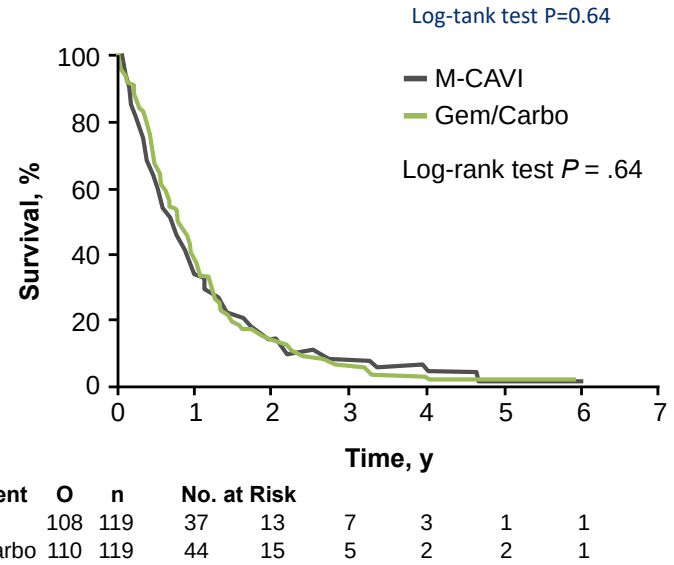
- >40% of patients with age >70 years were ineligible for cisplatin
- Represents 40-60% of patients with advanced urothelial cancer
- Widely-accepted Galsky criteria includes
  - ECOG 2 or worse
  - Creatinine Clearance ≤ 60 ml/min
  - Grade 2 or greater peripheral neuropathy/hearing loss
  - NYHA Class III congestive heart failure

- Galsky M, et al. J Clin Oncol. 2011; 10;29(17):2432-8.

EORTC Study 30986: Carboplatin Combinations for Advanced Bladder Cancer Patients

Randomized phase 2/3 trial in patients with advanced urothelial cancer deemed unfit for cisplatin-based chemotherapy (N=238)

Gemcitabine/carboplatin vs methotrexate/carboplatin/vinblastine



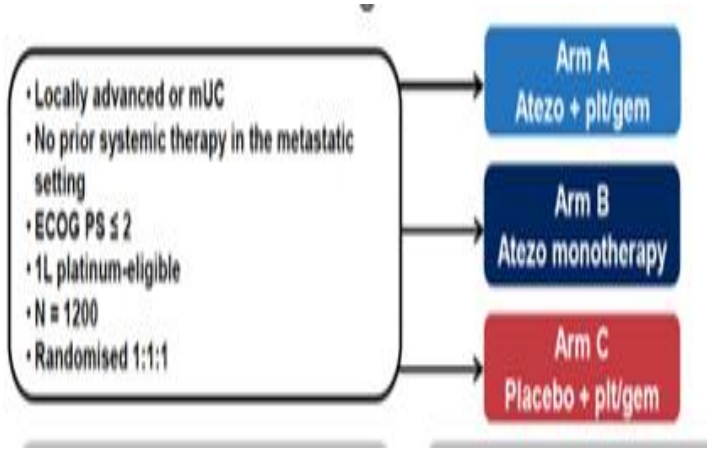
Treatment	O	n	No. at Risk					
M-CAVI	108	119	37	13	7	3	1	1
Gem/Carbo	110	119	44	15	5	2	2	1

Median OS

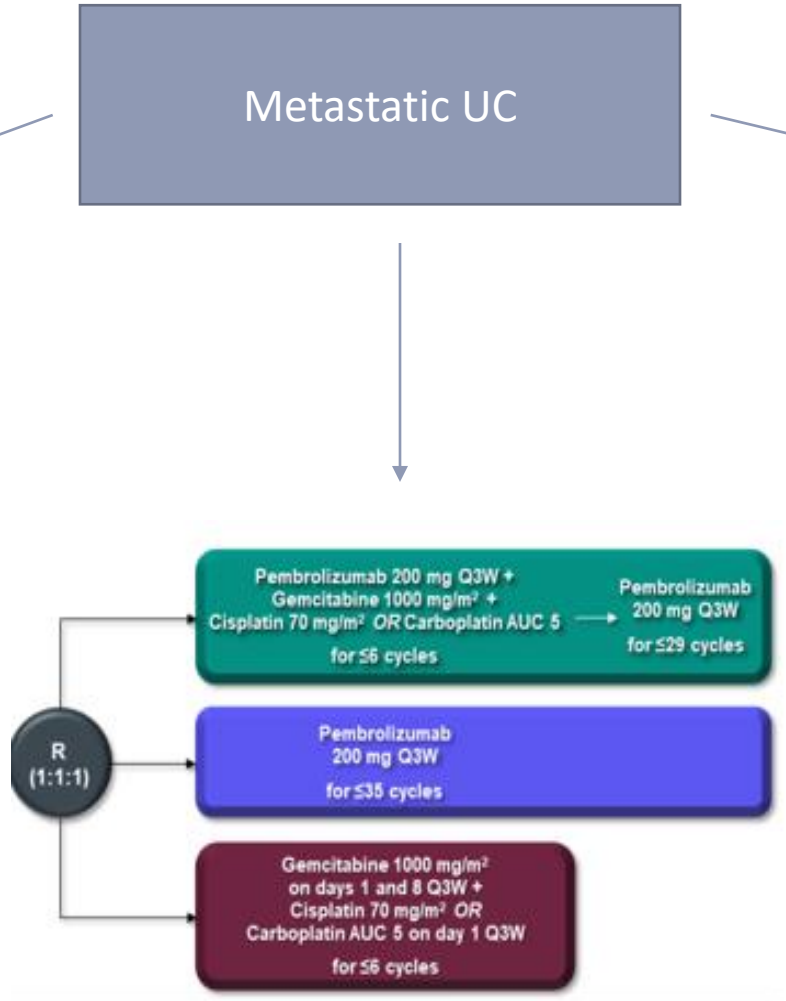
Gem/Carbo	M-CAVI
9.3 months	8.1 months

- De Santis M et al. J Clin Oncol. 2012;30:191-199.

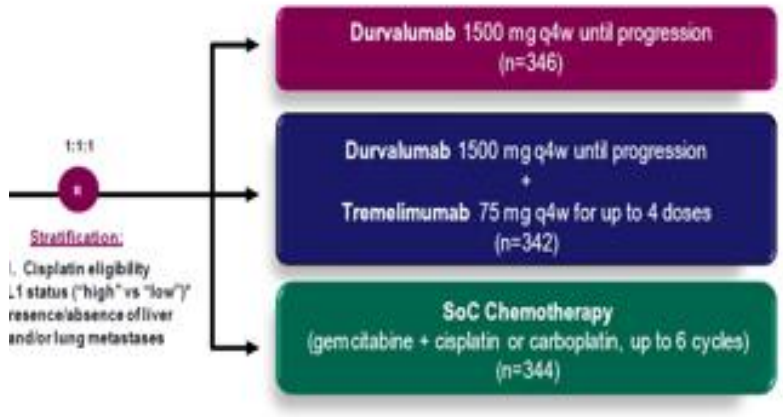
Chemo-Immunotherapy Combinations: Negative Trials



ImVigor 130



KEYNOTE 361



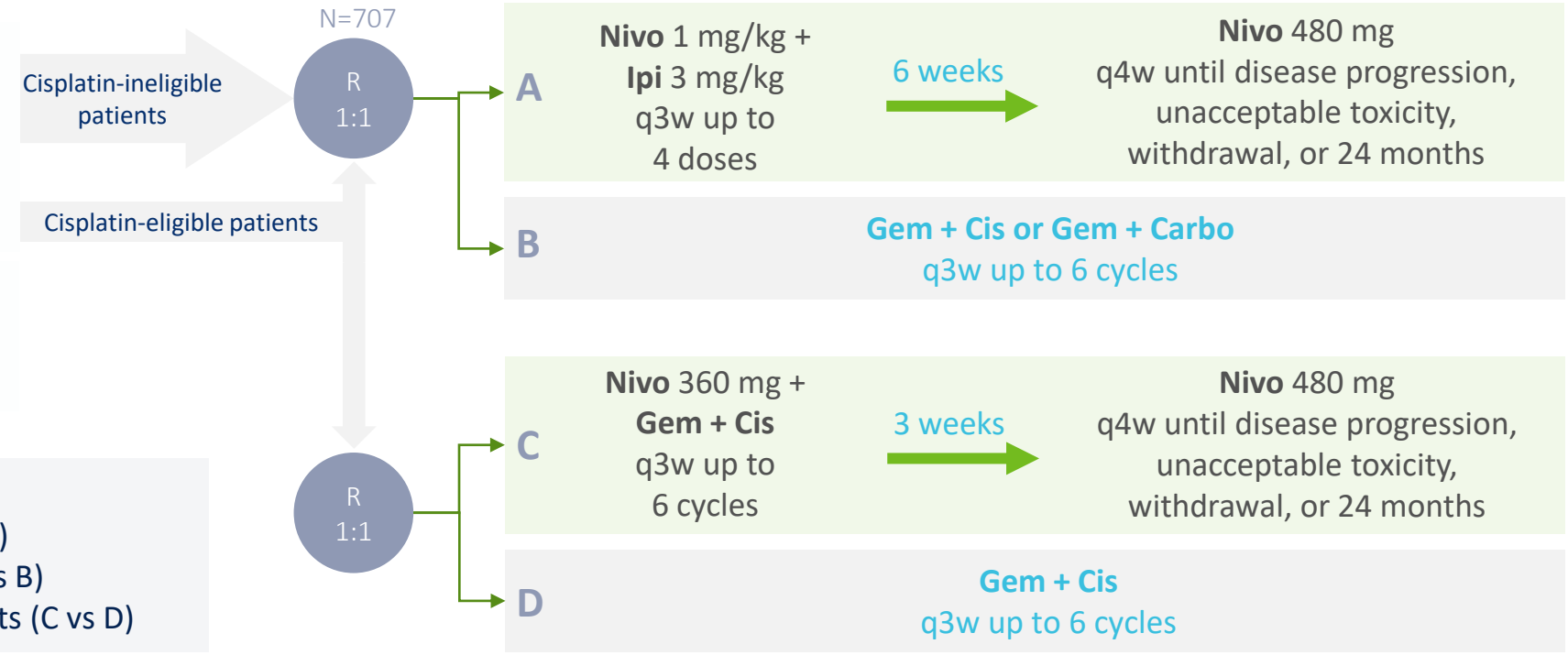
DANUBE

CheckMate 901: Phase 3 Trial of Nivolumab in Combination[1-3]

N=1307
- Previously untreated unresectable or metastatic UC (1L)
- Cisplatin eligible or ineligible
- ECOG PS 0-1

Stratification Factors
- PD-L1 expression <1%
- Cisplatin eligibility
- Presence of liver metastases

Primary endpoints
- OS in patients with PD-L1 ≥1% (A vs B)
- OS in cisplatin-ineligible patients (A vs B)
- OS and PFS in cisplatin-eligible patients (C vs D)



- 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 substudy of Nivo + Cis + Gem vs Cis + Gem reached its primary endpoint of OS and PFS

1. Galsky MD. ASCO 2018. Abstract TPS4588. **2.** ClinicalTrials.gov. Accessed April 5, 2023. https://clinicaltrials.gov/ct2/show/NCT03036098 **3.** Press Release. Bristol Myers Squibb. May 16, 2022.

EV-103 Dose Escalation and Cohort A: Phase 1b/2 Trial of Enfortumab Vedotin + Pembrolizumab

84% of patients had visceral disease and 31% had liver metastasis

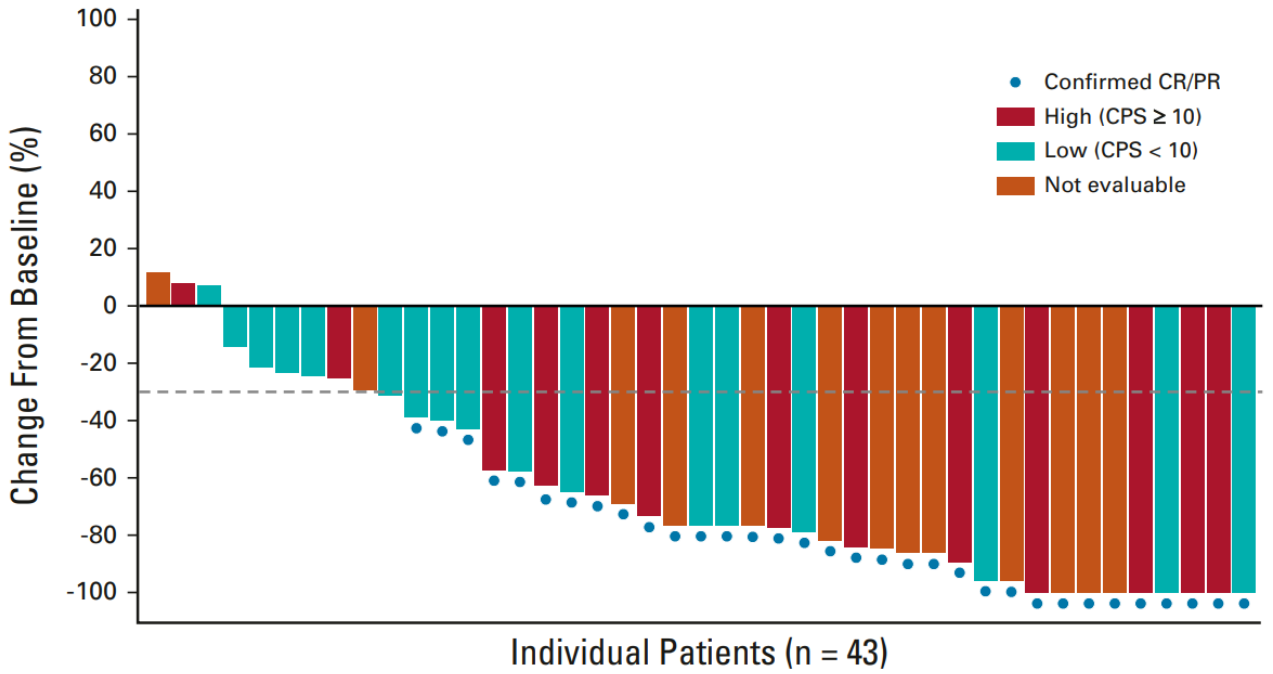
31% of patients had PD-L1 CPS ≥10

Patients With 1L Cisplatin-Ineligible la/mUC (N=45)

Dose escalation phase	**Dose expansion cohort A**
EV + Pembro (n=5)	EV + Pembro (n=40)

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

Change From Baseline in the Sum of Diameters of Target Lesions



Confirmed ORR [95% CI]	**73.3%** (33/45) [58.1-85.4]
Complete response	15.6% (7/45)
Partial response	57.8% (26/45)

- 57.1% ORR in patients with liver metastases

- Hoimes CJ, et al. *J Clin Oncol.* 2023;41(1):22-31.

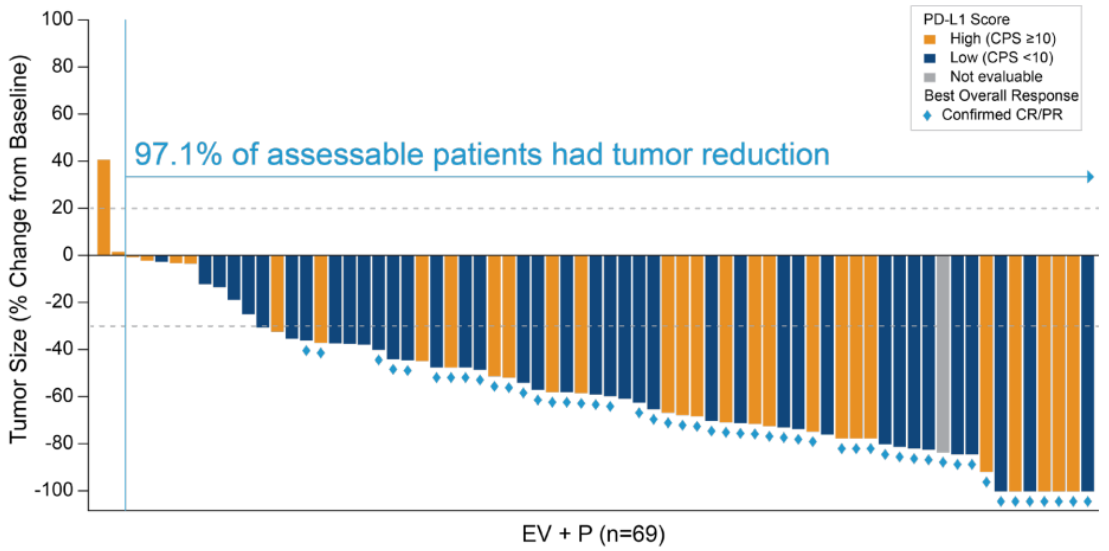
EV-103 Cohort K: Phase 1b/2 Trial of Enfortumab Vedotin + Pembrolizumab

Rosenberg JE, et al. ESMO 2022. Abstract LBA73.

	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 (range)	11.0 (1-29)	8.0 (1-33)

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

EV + Pembro: Maximum Percent Reduction From Baseline of Target Lesion by BICR



	EV + Pembro N=76	EV Mono N=73
Median DOR, mo (95% CI)	NR (10.25-NR)	13.2 (6.14-15.97)
Median PFS, mo (95% CI)	NR (8.31-NR)	8.0 (6.05-10.35)
Median OS, mo (95% CI)	22.3 (19.09-NR)	21.7 (15.21-NR)

Treatment-Related Adverse Events

TRAE rates and types are consistent with those previously reported for EV+P

	Dose Escalation + Cohort A (N = 45)
	Any Grade n (%)
Overall	43 (95.6)
Peripheral sensory neuropathy	25 (55.6)
Fatigue	23 (51.1)
Alopecia	22 (48.9)
Diarrhea	21 (46.7)
Decreased appetite	18 (40.0)
Rash maculo-papular	16 (35.6)
Pruritus	15 (33.3)
Dysgeusia	15 (33.3)

	Dose Escalation + Cohort A (N = 45)
	Grade ≥3[a] n (%)
Overall	29 (64.4)
Lipase increased[b]	8 (17.8)
Rash maculo-papular	5 (11.1)
Fatigue	5 (11.1)
Neutropenia	4 (8.9)
Anemia	4 (8.9)
Hyperglycemia	4 (8.9)
Amylase increased	4 (8.9)
Transaminases increased	3 (6.7)

[a]Events occuring in >5% of patients
[b]Not clinically significant

- One patient died from multiple organ dysfunction syndrome with concurrent bullous dermatitis

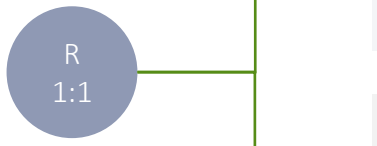
Gupta et al. GU ASCO 2023

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

- Unresectable la/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



A EV (days 1 and 8) + **Pembro** (day 1)
21-day cycle

B[a] **Gemcitabine** (days 1 and 8)
+ cisplatin or carboplatin (day 1)
21-day cycle

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

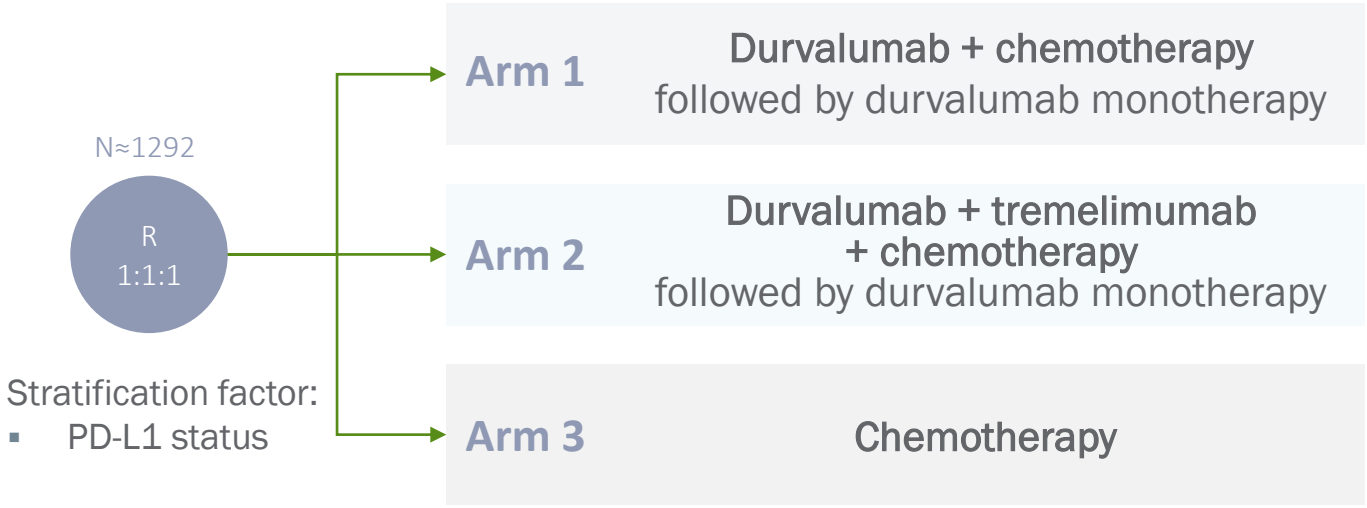
[a] Maintenance therapy (after protocol-specified therapy) may be used following completion and/or discontinuation of platinum-containing therapy, if locally available, and provided the patient is deemed appropriate by the investigator.

9/22/23 MET DUAL PRIMARY ENDPOINTS OF OS AND PFS IN CERTAIN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED OR mUC

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

NILE: Phase 3 Trial of Durvalumab in Combination[1,2]

- Unresectable Ia/mUC
- No prior chemotherapy in the metastatic setting
- ECOG PS 0-1



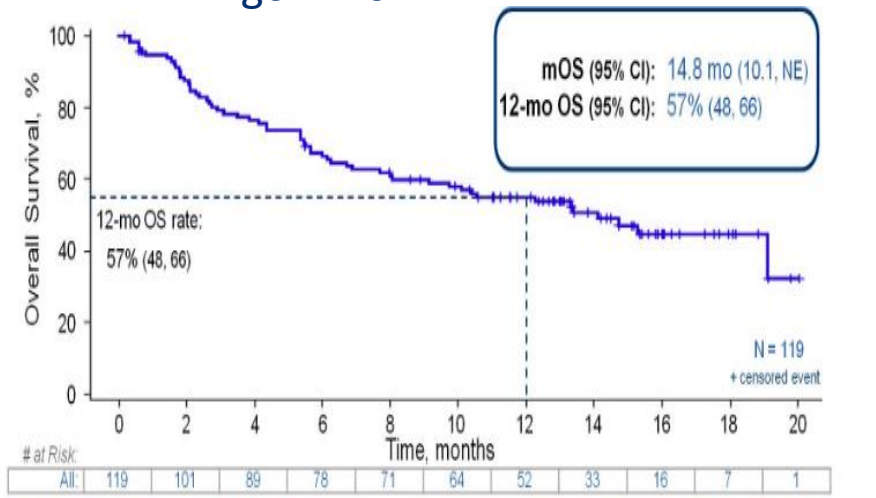
Primary endpoints
- OS (PD-L1 high; arm 1 vs 3)
- OS (PD-L1 high; arm 2 vs 3)

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

1. Galsky MD. ASCO GU 2021. Abstract TPS504. **2.** ClinicalTrials.gov. Accessed April 5, 2023. https://clinicaltrials.gov/ct2/show/NCT03682068

Cisplatin-Ineligible Patients And First-Line Immunotherapy

IMvigor 210



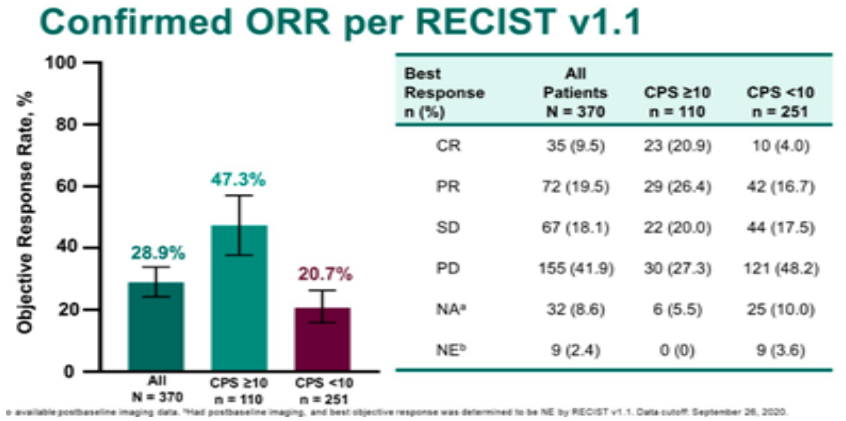
- With a median follow-up of 14.4 months,[a] the event rate is 47%
- Atezolizumab compares favorably with historic data from cisplatin-ineligible patients, both from clinical trials and real-world studies[1,2]

[a] Range, 0.2 to 20.1 mo. Data cutoff: March 14, 2016. 1. De Santis *J Clin Oncol* 2012. 2. Galsky ECC 2015 [poster 115].

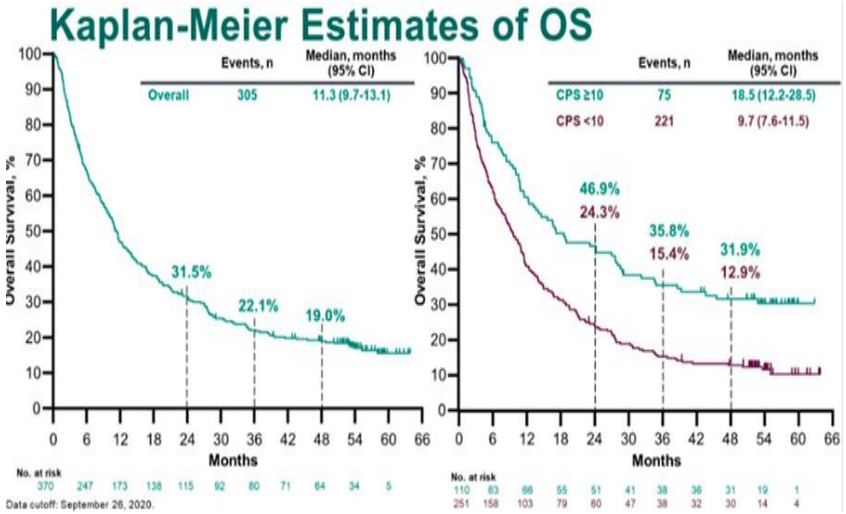
ORR 24%; IC2/3 28%, IC1/2/3 25%

median duration of follow-up 14.4 mo (range, 0.2-20.1 mo)

KEYNOTE 052



Best Response n (%)	All Patients N = 370	CPS ≥10 n = 110	CPS <10 n = 251
CR	35 (9.5)	23 (20.9)	10 (4.0)
PR	72 (19.5)	29 (26.4)	42 (16.7)
SD	67 (18.1)	22 (20.0)	44 (17.5)
PD	155 (41.9)	30 (27.3)	121 (48.2)
NA[a]	32 (8.6)	6 (5.5)	25 (10.0)
NE[b]	9 (2.4)	0 (0)	9 (3.6)



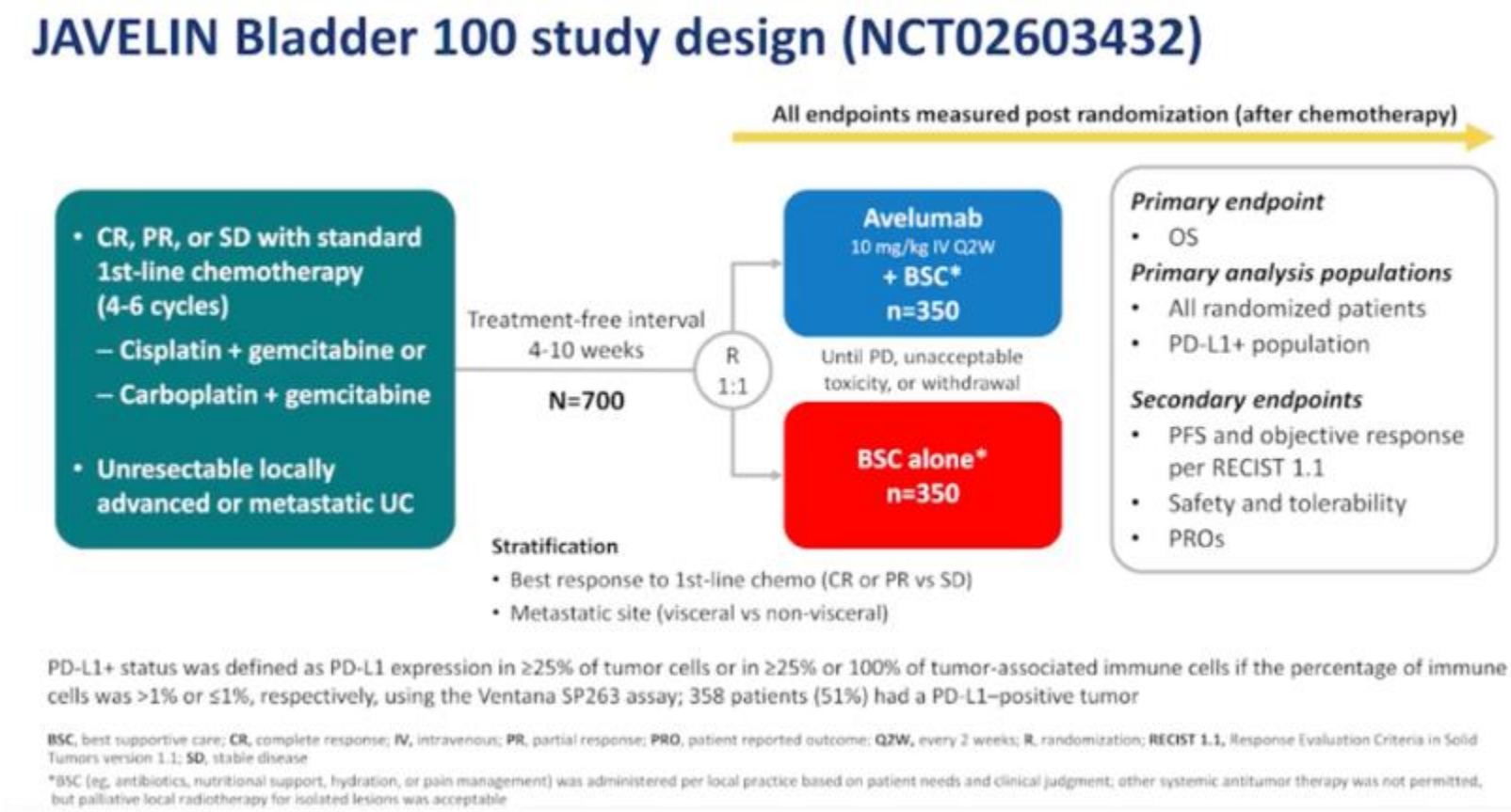
- Balar A et al. Lancet. 2017 O'Donell P. ASCO 2021

Updates

2021: Oncologic Drugs Advisory Committee (ODAC) Meeting

- An accelerated approval for pembrolizumab as therapy for patients with locally advanced or metastatic urothelial cancer who are not eligible to receive platinum-based therapies
- Atezolizumab removed for cisplatin-ineligible high PD-L1 or platinum-in eligible regardless of PD-L1 status.

JAVELIN Bladder 100: Phase 3 Study of First-Line Maintenance with Avelumab

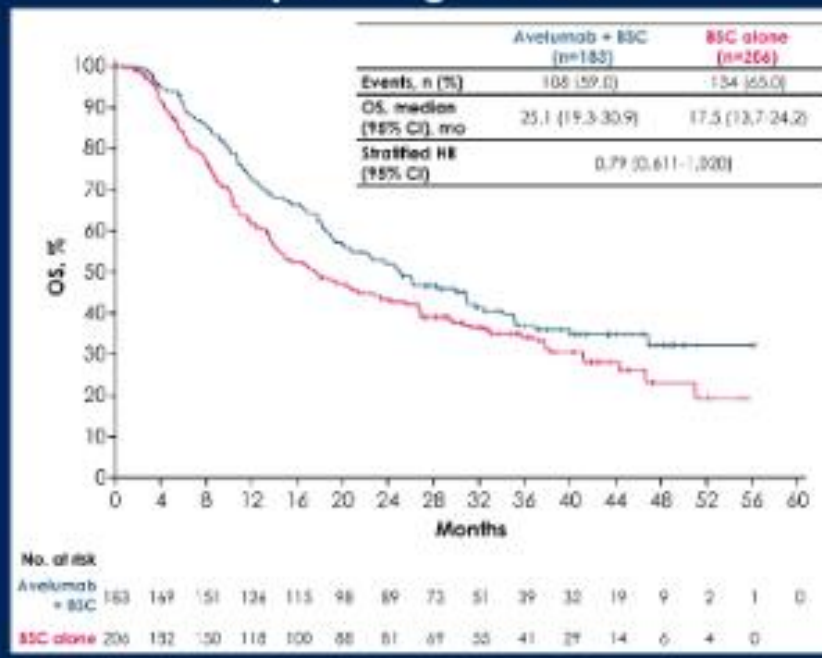


Powles T, et al. J Clin Oncol 38: 2020 (suppl; abstr LBA1

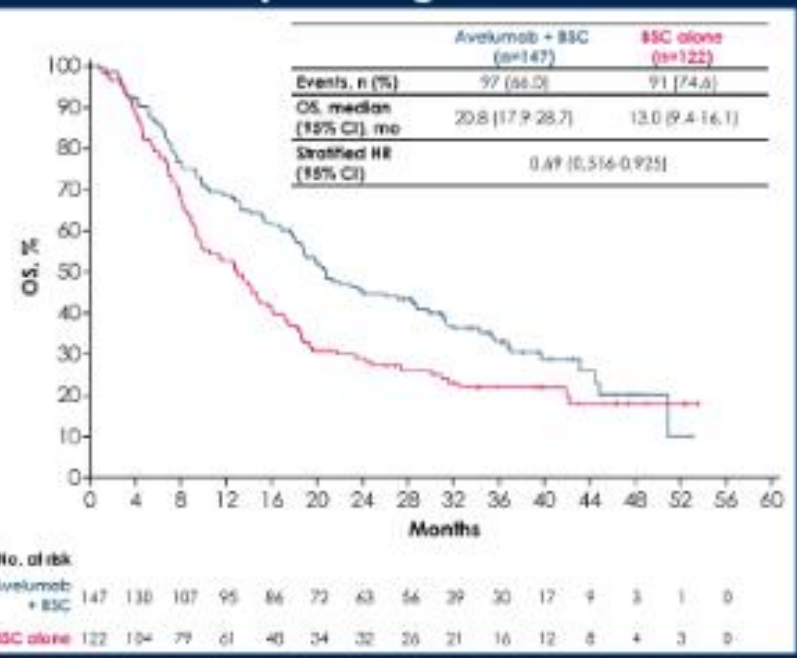
Updated Analysis with >2 years follow up

OS from start of maintenance (randomization)

Cisplatin + gemcitabine



Carboplatin + gemcitabine

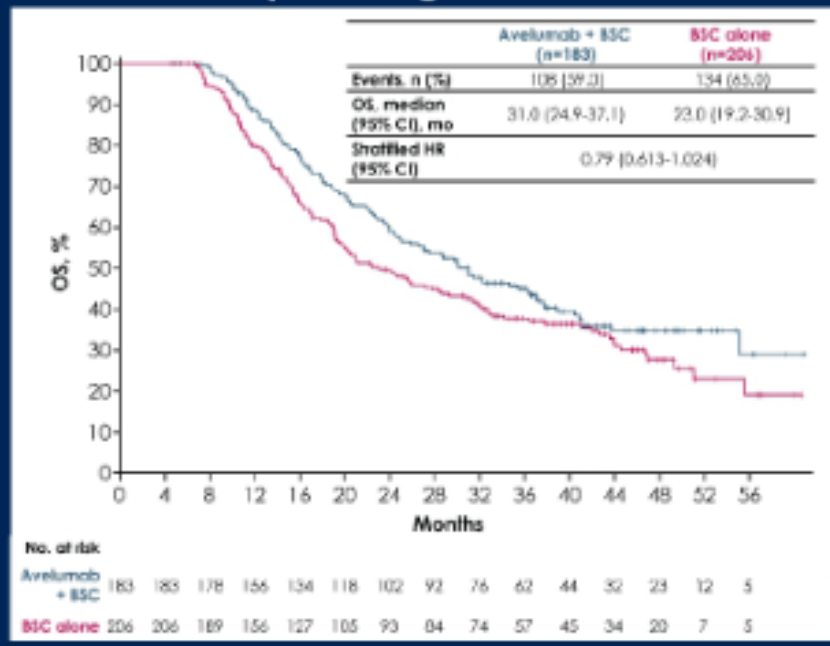


- OS* was longer with avelumab + BSC vs BSC alone in both the cisplatin and carboplatin subgroups
- In both subgroups, investigator-assessed PFS* was also longer with avelumab + BSC vs BSC alone

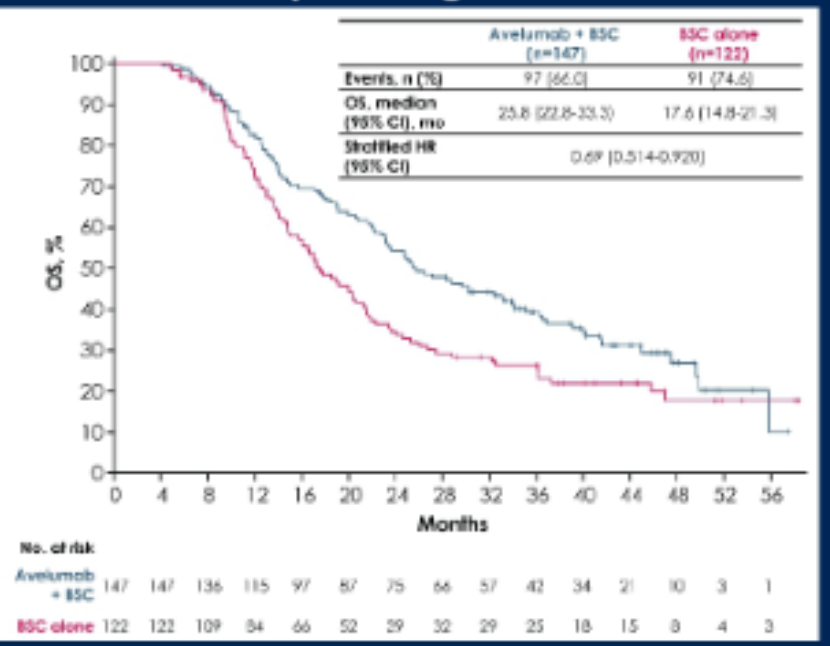
Sridhar et al GUASCO 2023

OS from start of 1L chemotherapy

Cisplatin + gemcitabine



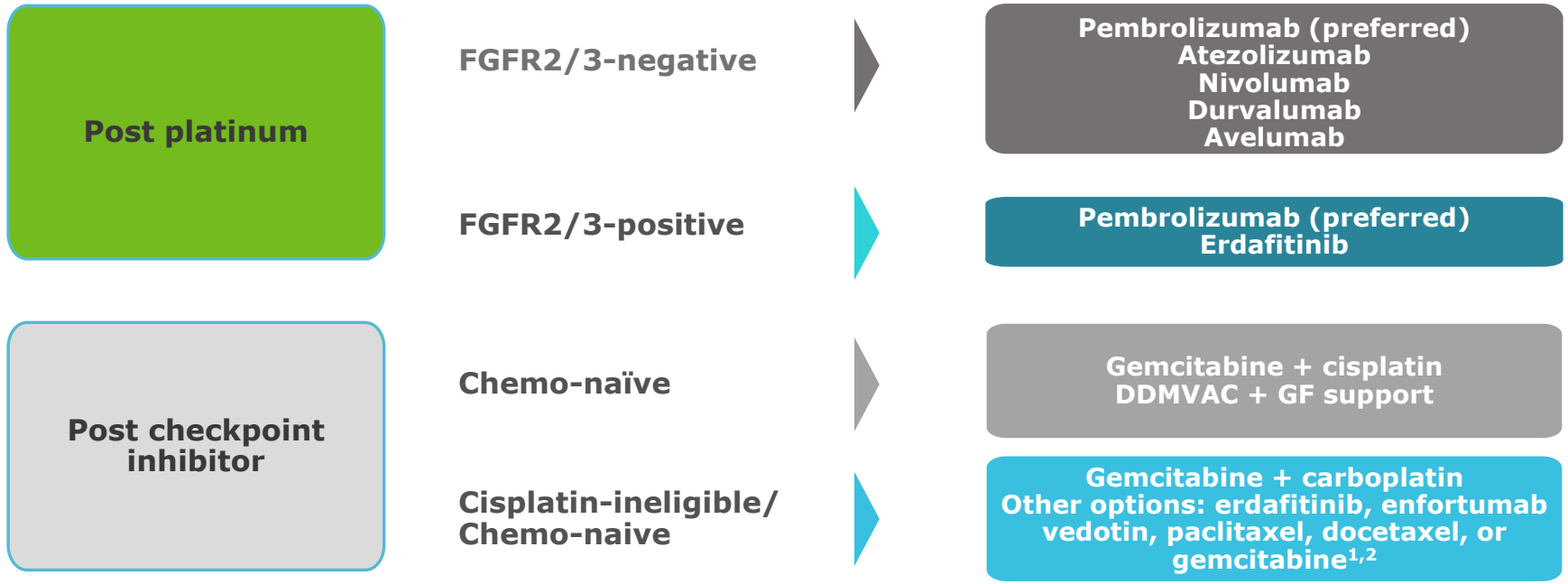
Carboplatin + gemcitabine



- In the overall population, median OS measured from the start of 1L chemotherapy was 29.7 months with avelumab + BSC and 20.5 months with BSC alone
- OS measured from the start of 1L chemotherapy was also longer with avelumab + BSC vs BSC alone irrespective of 1L chemotherapy regimen

Sridhar et al GUASCO 2023

Second-Line Systemic Treatment for Patients With mUC



Second-Line Treatment Options Post-Platinum Treatment*

*No head-to-head studies have been conducted and direct comparisons cannot be made between these studies.

.

	KEYNOTE-045[1] Pembrolizumab Phase 3	IMvigor 210[2] Atezolizumab Phase 2	CheckMate 275[3] Nivolumab Phase 2	Study 1108[4] Durvalumab Phase 1/2	JAVELIN solid tumor [5] Avelumab Phase 1B
Patient number	542	310 (Cohort 2)	270	191	242
Study Arms	**Pembrolizumab** 200 mg (IV) q3w	**Atezolizumab** 1200 mg (IV) q3w	**Nivolumab** 3 mg/kg IV q2w	**Durvalumab** 10 mg/kg IV q2w	**Avelumab** 10 mg/kg q2w
Key Inclusion Criteria	• Metastatic or locally advanced urothelial cancer • Progression after 1 or 2 lines of platinum-based therapy • Measurable disease • ECOG PS 0-2	Cohort 2: • ≥1 Platinum-containing or ≤12 months of neoadjuvant/ adjuvant treatment • Tumor tissue for PD-L1 testing • ECOG PS 0-1	• ≥1 Platinum-containing or ≤12 months of neoadjuvant/ adjuvant treatment • Tumor tissue for PD-L1 testing • ECOG PS 0-1	• Histologically confirmed solid tumors Locally advanced or mUC cohort: • Had progressed, on were ineligible for, or refused any number of prior therapies • ECOG PS 0-1	Solid tumors mUC cohort: • Had progressed post-platinum treatment or cisplatin-ineligible • Unselected for PD-L1 • ECOG PS 0-1
ORR (%)	• 21.1	• 15	• 19.6	• 20.4	• 16.1 (after ≥6 weeks follow-up)
Median PFS (months)	• 2.1	• 2.1	• 2.0	• NA	• NA
Median OS (months)	• 10.3	• 7.9	• 8.7	• NA	• NA

1. Bellmunt et al. N Engl J Med 2017; 376:1015-1026; 2. Loriot Y et al. Poster presentation at ESMO 2016. 783P; 3. Sharma P, et al. Lancet Oncol. 2017; 4. Powles T, et al. Poster presentation at ASCO GU. 286; 5. Patel M et al. Poster presentation at ASCO GU. 330

Second-Line Treatment Options Post-Platinum Treatment*

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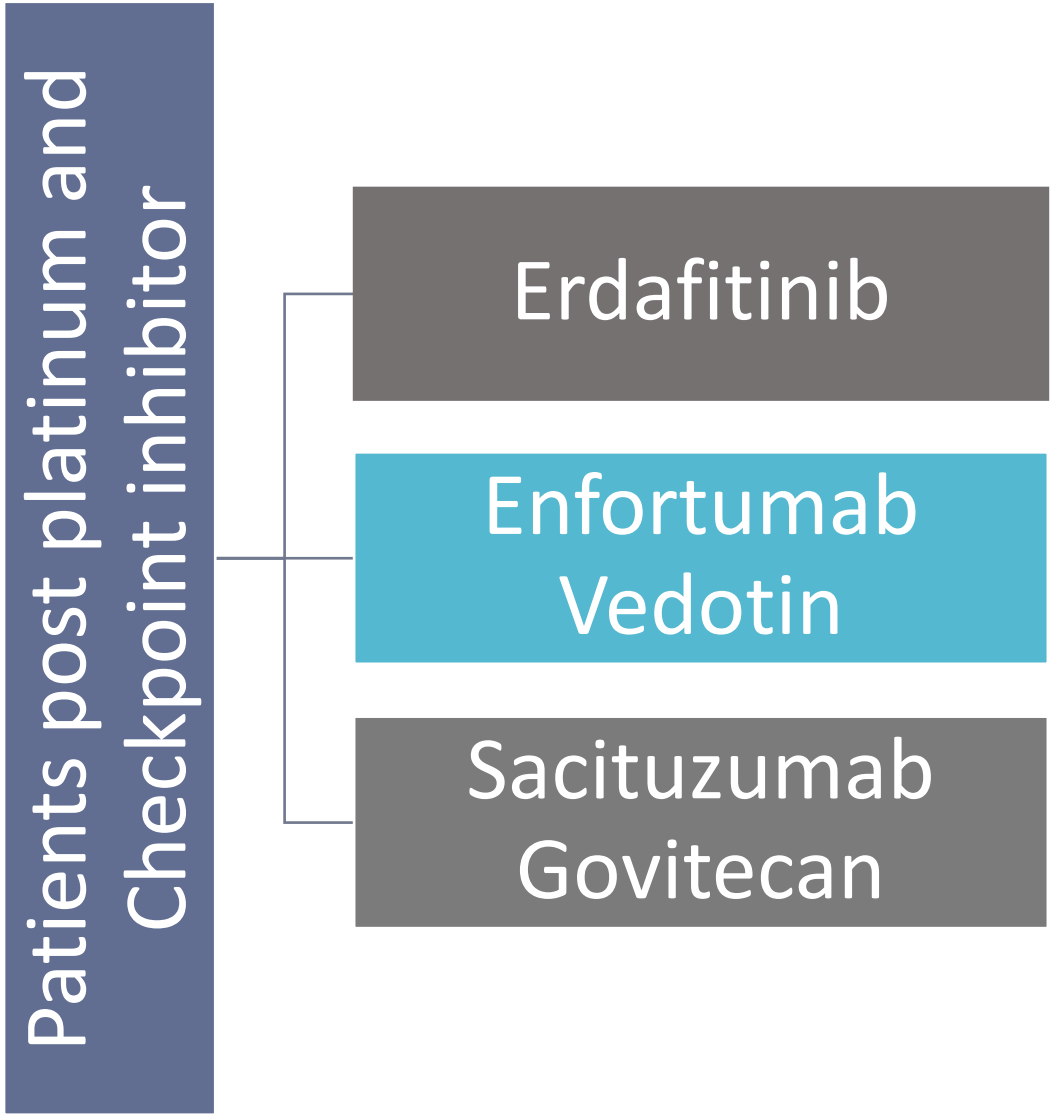
	KEYNOTE-045[1] Pembrolizumab Phase 3	IMvigor 210[2] Atezolizumab Phase 2	CheckMate 275[3] Nivolumab Phase 2	Study 1108[4] Durvalumab Phase 1/2	JAVELIN solid tumor [5] Avelumab Phase 1B
Patient number	542	310 (Cohort 2)	270	191	242
Study Arms	**Pembrolizumab** 200 mg (IV) q3w	**At** 12	**Nivolumab** 3 mg/kg IV q2w	**Du** 10	**Avelumab** 10 mg/kg q2w
Key Inclusion Criteria	• Metastatic or locally advanced urothelial cancer • Progression after 1 or 2 lines of platinum-based therapy • Measurable disease • ECOG PS 0-2	Coh • Withdrawn • ECOG PS 0-1	• ≥1 Platinum-containing or ≤12 months of neoadjuvant/ adjuvant treatment • Tumor tissue for PD-L1 testing • ECOG PS 0-1	• Withdrawn • ECOG 0-1	Solid tumors mUC cohort: • Had progressed post-platinum treatment or cisplatin-ineligible • Unselected for PD-L1 • ECOG PS 0-1
ORR (%)	• 21.1	• 15	• 19.6	• 20.4	• 16.1 (after ≥6 weeks follow-up)
Median PFS (months)	• 2.1	• 2.1	• 2.0	• NA	• NA
Median OS (months)	• 10.3	• 7.9	• 8.7	• NA	• NA

1. Bellmunt et al. N Engl J Med 2017; 376:1015-1026; 2. Loriot Y et al. Poster presentation at ESMO 2016. 783P; 3. Sharma P, et al. Lancet Oncol. 2017; 4. Powles T, et al. Poster presentation at ASCO GU. 286; 5. Patel M et al. Poster presentation at ASCO GU. 330.

Third-Line Systemic Treatment for Patients With mUC



THOR: Phase 3 Trial of Erdafitinib

Erdafitinib is a Pan-FGFR Inhibitor With Activity in Metastatic Urothelial Carcinoma

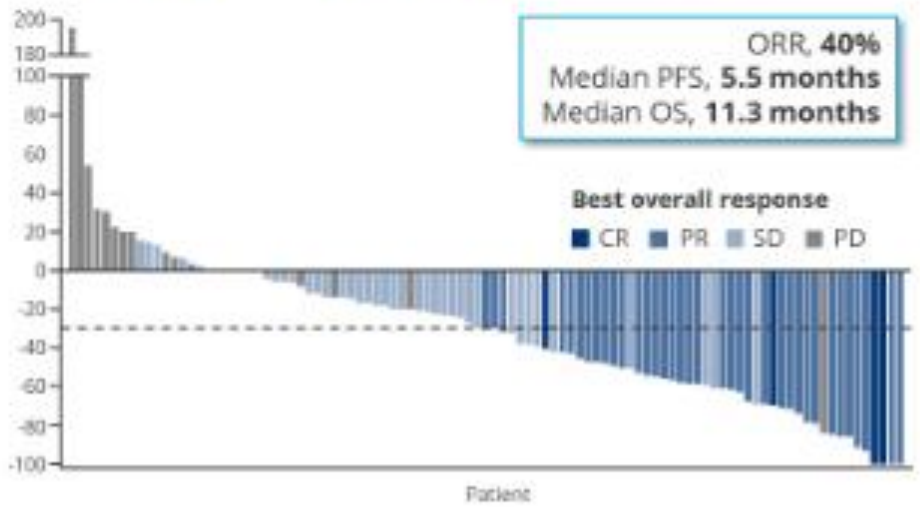
- *FGFRalt* are observed in **~20% of advanced or mUC** and may function as oncogenic drivers[1,2]

Erdafitinib is an oral selective pan-FGFR tyrosine kinase inhibitor[3]

- Erdafitinib was granted accelerated approval in the United States and is approved in 17 other countries to treat locally advanced or mUC in adults with susceptible *FGFR3/2alt* who have progressed after platinum-containing chemotherapy[4-6]

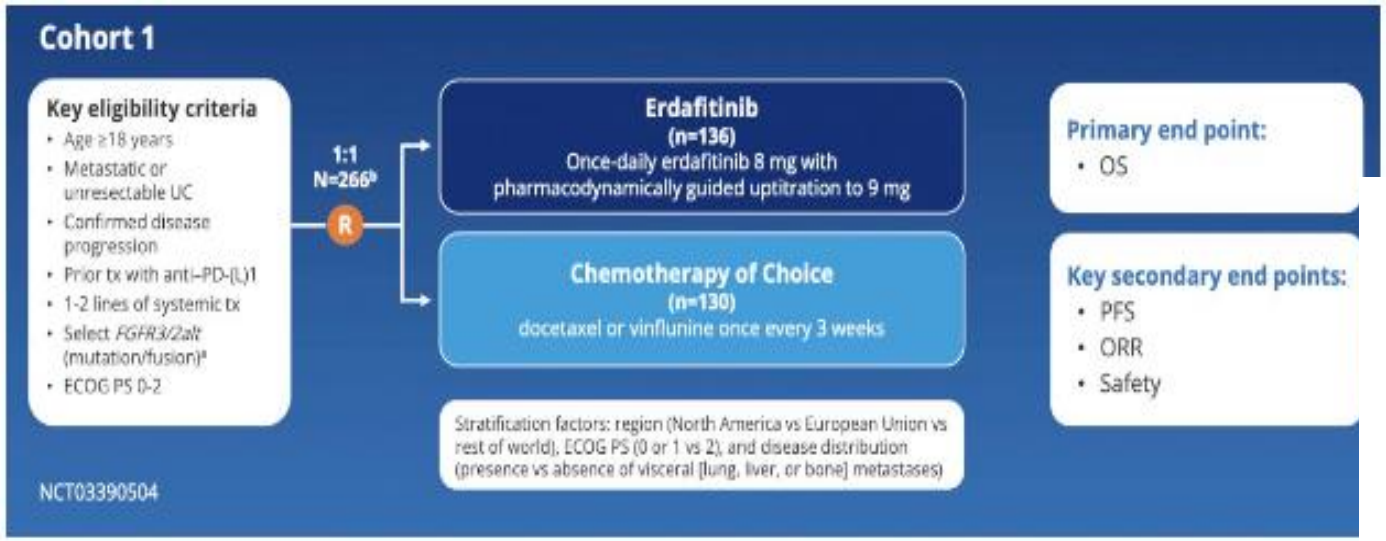
- **THOR** is a confirmatory, randomized phase 3 study:
  - Cohort 1 assessed whether erdafitinib improved survival over chemotherapy in patients with *FGFRalt* mUC who progressed on or after ≥1 prior treatment that included anti–PD-(L)1

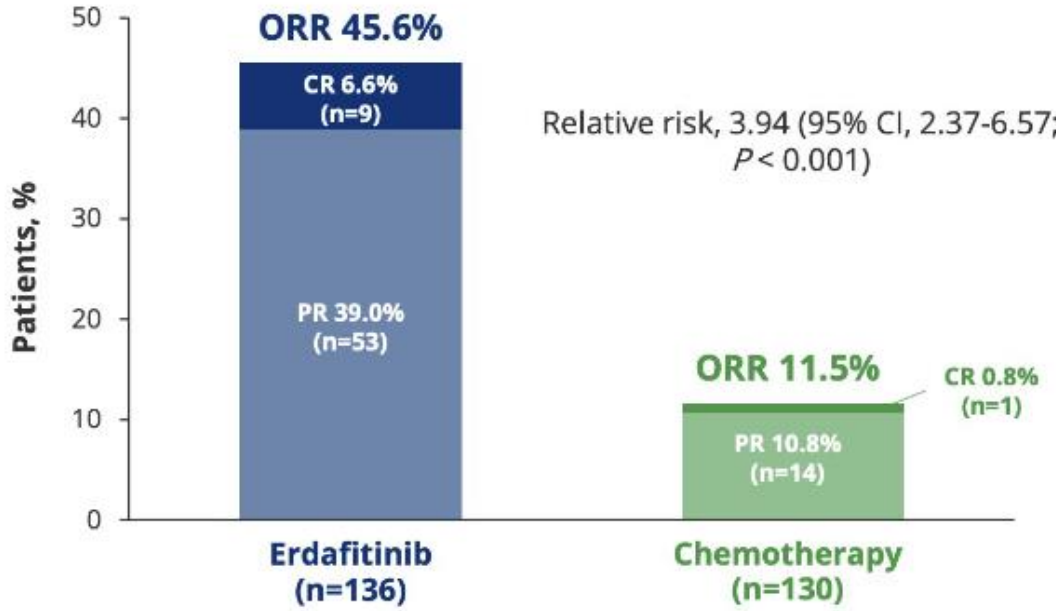
In the single-arm phase 2 BLC2001 trial, erdafitinib showed a benefit in patients with *FGFR-altered* advanced urothelial cancer[4]



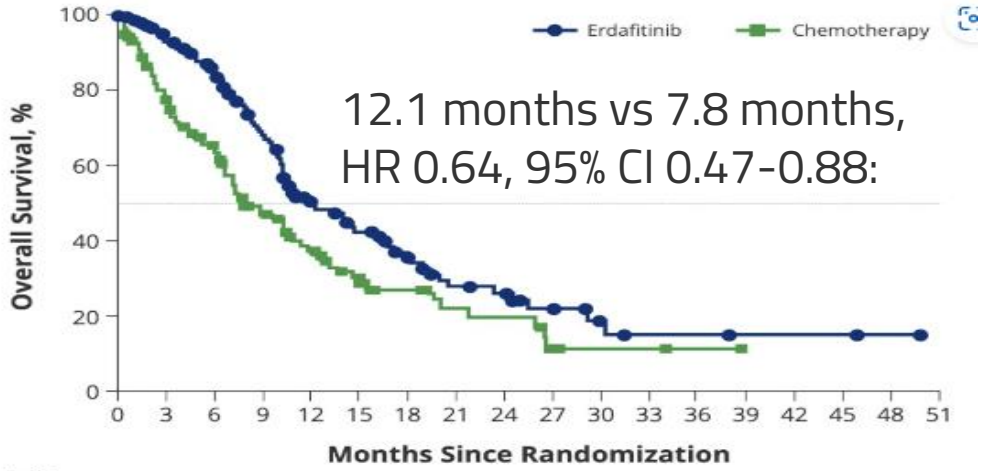
Patients received erdafitinib 8 mg/d with pharmacodynamically guided uptitration to 9 mg/d.

Loriot et al GU ASCO 2023



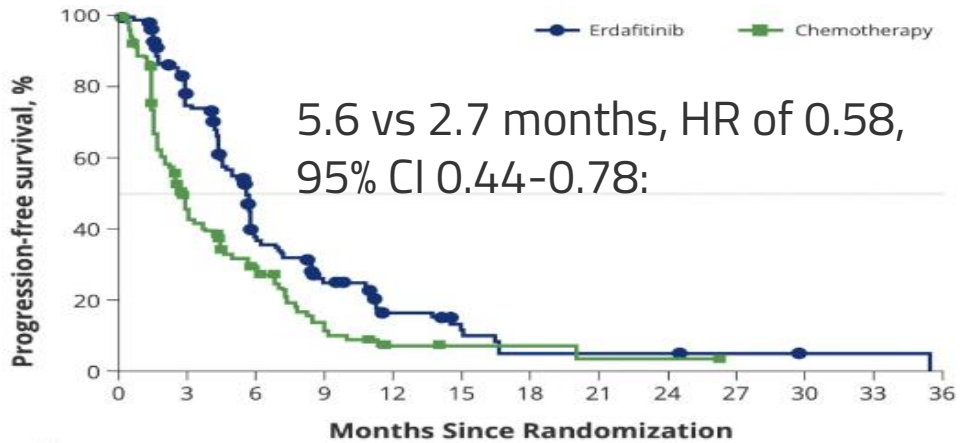


Relative risk, 3.94 (95% CI, 2.37-6.57; $P < 0.001$)



12.1 months vs 7.8 months, HR 0.64, 95% CI 0.47-0.88:

No. at risk																		
Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
motherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0



5.6 vs 2.7 months, HR of 0.58, 95% CI 0.44-0.78:

No. at risk													
rdafitinib	136	90	39	24	12	7	3	3	3	2	1	1	0
iotherapy	130	43	23	9	4	2	2	1	1	0	0	0	0

Loriot Y ASCO 2023

The Safety Profiles Were Consistent With the Known Profiles of Erdafitinib and Chemotherapy (1/2)

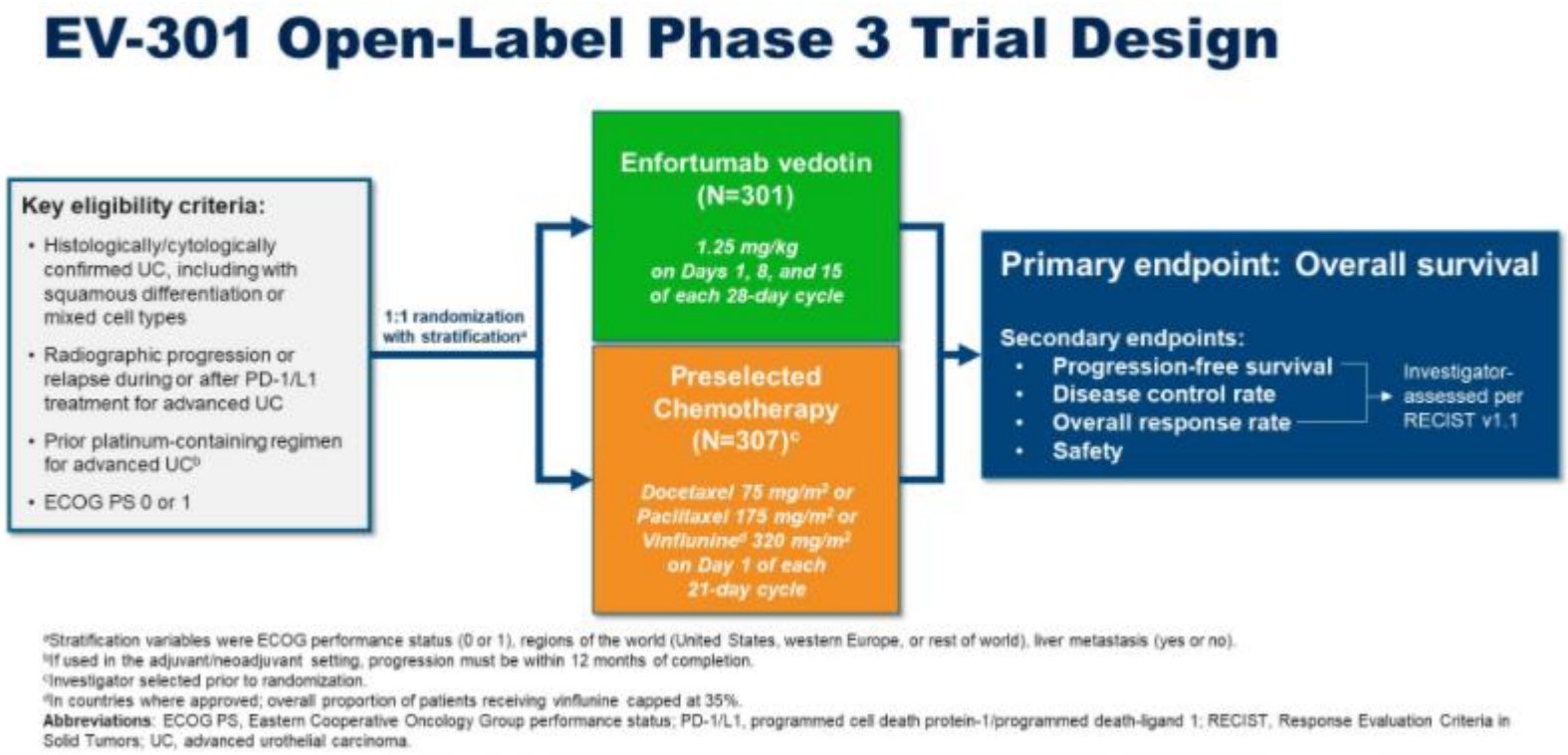
Patients with AEs, n (%)[a]	Erdafitinib (n=135)	
	Any grade	Grade 3-4
≥1 treatment-related AE	131 (97.0)	62 (45.9)
Hyperphosphatemia	106 (78.5)	7 (5.2)
Diarrhea	74 (54.8)	4 (3.0)
Stomatitis	62 (45.9)	11 (8.1)
Dry mouth	52 (38.5)	0
PPE syndrome	41 (30.4)	13 (9.6)
Onycholysis	31 (23.0)	8 (5.9)
Patients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

- **In the erdafitinib group:**
  - 18 patients (13.3%) had treatment-related serious AEs
  - 1 treatment-related death occurred[c]
  - AEs with erdafitinib were mostly manageable with dose modifications and supportive care
- **In the chemotherapy group:**
  - 27 patients (24.1%) had treatment-related serious AEs
  - 6 treatment-related deaths occurred[d]

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

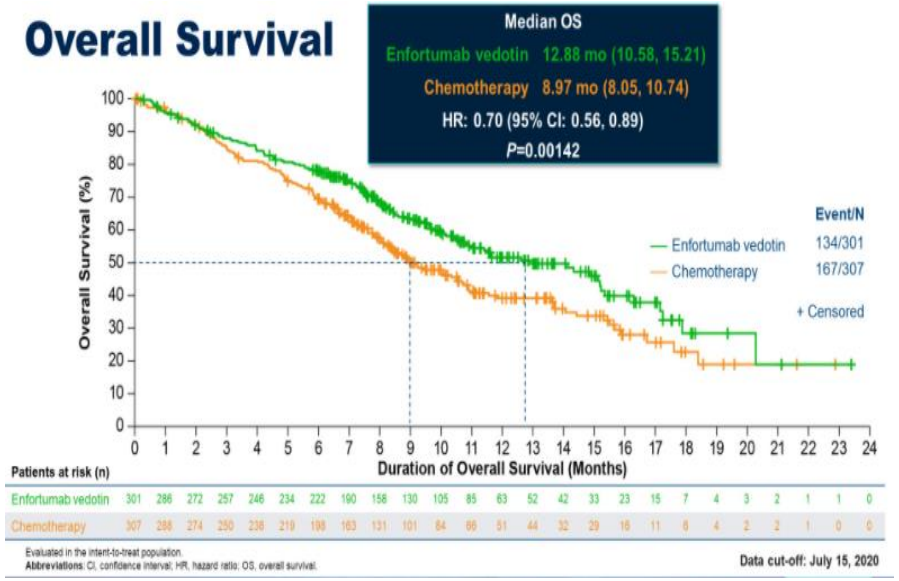
Loriot et al GU ASCO 2023

Phase 3 EV-301



- Poweles et al GU ASCO 2021

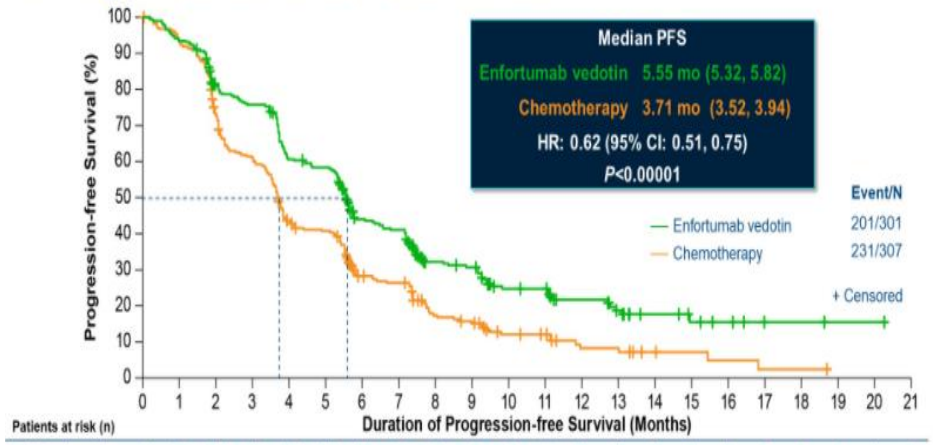
Overall Survival



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

Data cut-off: July 15, 2020

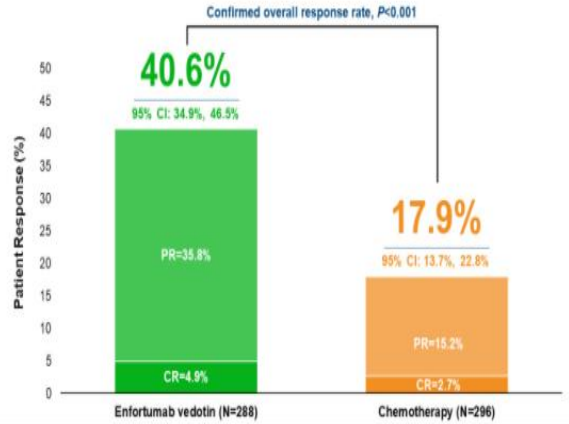
Progression-free Survival



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

Data cut-off: July 15, 2020

Investigator-Assessed Overall Response



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

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

Data cut-off: July 15, 2020

Treatment-Related Adverse Events

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

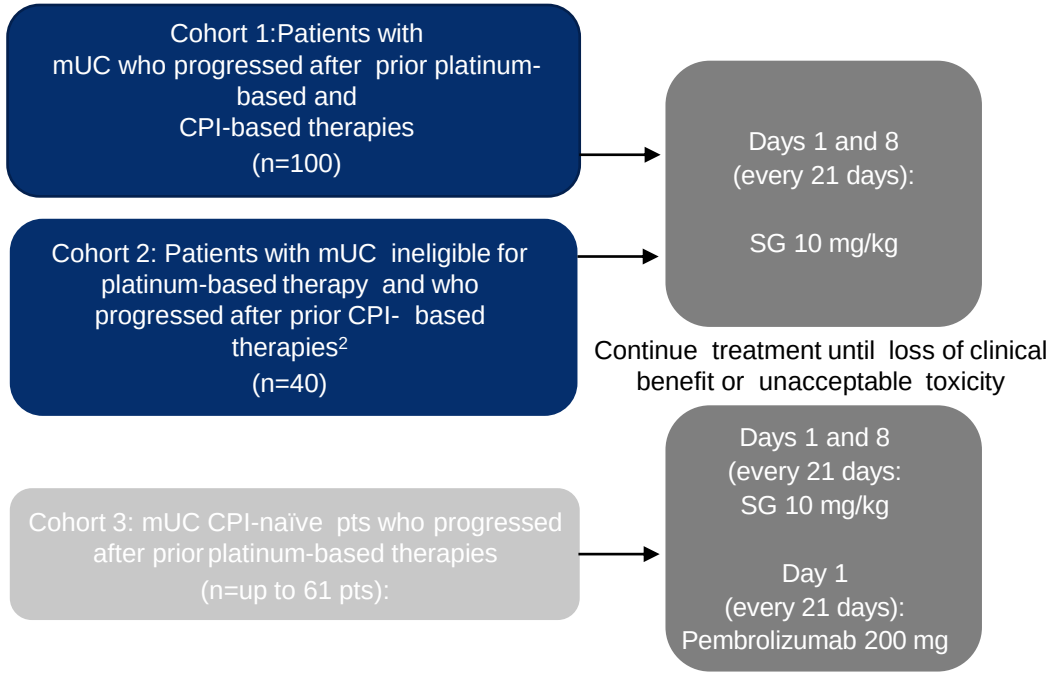
TRAEs leading to death, excluding disease progression, occurred in 7 patients (2.4%) treated with EV and 3 (1.0%) treated with chemotherapy.

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

Data cut-off: July 15, 2020

Rosenberg et al ESMO, Powles NEJM 2021

TROPHY-U-01 Study Design



Primary objective:
- ORR by central review

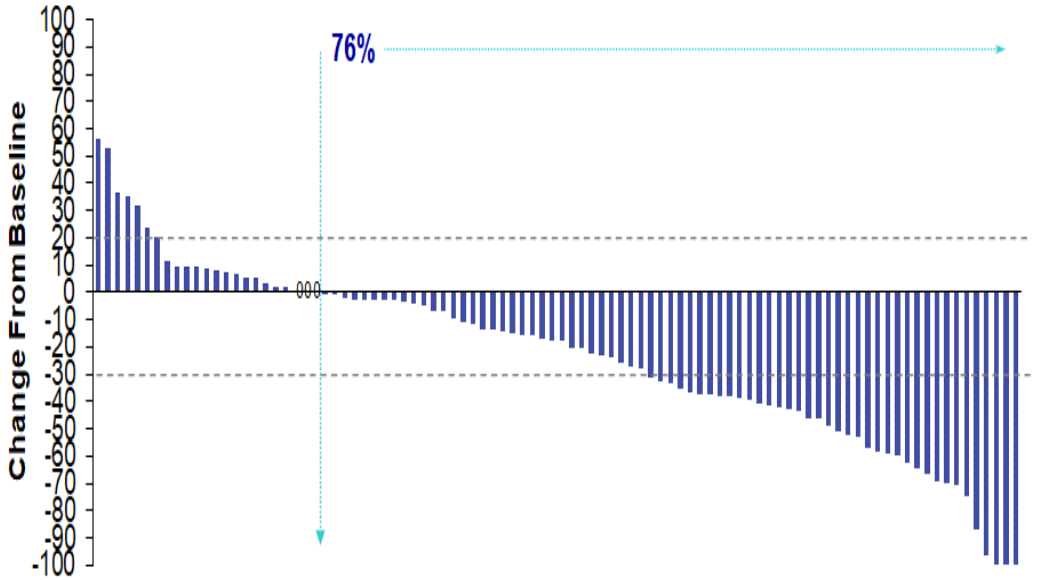
Secondary objectives:
- Safety/tolerability
- DOR
- PFS
- OS

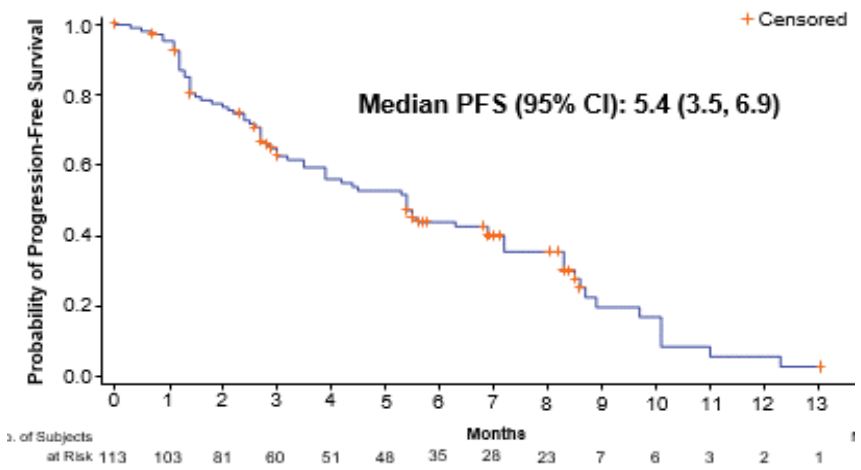
CPI, immune checkpoint inhibitor; DOR, duration of response; mUC, metastatic urothelial cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; pts, patients; SG, sacituzumab govitecan.
EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973; IMMU-132-06 study.
1. Loriot Y, Balar AV, Petrylak DP, et al. Final Results from TROPHY-U-01 Cohort 1: A phase 2 open-label study of sacituzumab govitecan in patients with metastatic urothelial cancer and disease progression after platinum-based regimens and checkpoint inhibitors. Presented at: ESMO Virtual Congress 2020; September 19-21, 2020. 2. Petrylak, DP et al. J Clin Oncol. 2020;38(suppl), abstract 5027.

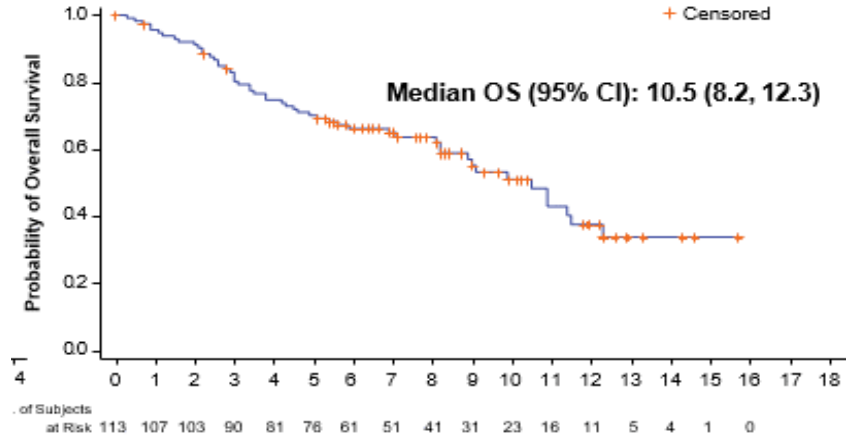
Tagawa et al JCO 2021

TROPHY-U-01 Cohort 1

	Sacituzumab Govitecan (N=113)
ORR, n (%) [95% CI]	31 (27) [19-37]
CR, n (%) PR, n (%)	6 (5) 25 (22)
Median DOR, months [95% CI] (Range)	5.9 [4.70-8.60] (1.4-11.7)
Median time to response, months (Range)	1.6 (1.2-5.5)







Tagawa et al JCO 2021

Treatment-Related Adverse Events ≥20% Any Grade or ≥5% Grade ≥3 (N=113)

7 (6%) pts discontinued due to TRAEs
- 3 discontinued due to neutropenia or its complications

30% GCSF usage

One treatment-related death (sepsis due to febrile neutropenia)

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	Neutropenia	46	22	12
	Leukopenia	26	12	5
	Anemia	34	14	0
	Lymphopenia	12	5	2
	Febrile neutropenia	10	7	3
Gastrointestinal	Diarrhea[b]	65	9	1
	Nausea	58	4	0
	Vomiting	28	1	0
General disorders & administrative site conditions	Fatigue	50	4	0
Skin & subcutaneous tissue	Alopecia	47	0	0
Metabolism & nutrition	Decreased appetite	36	3	0
Infections & infestations	Urinary tract infection	8	6	0

Median treatment cycles: 6 (range: 1–22); worst grade CTCAE reported

[a]"Neutrophil count decreased," "White blood cell count decreased," "Lymphocyte count decreased," and "Hemoglobin decreased" have been re-coded to Neutropenia, Leukopenia, Lymphopenia, and Anemia, correspondingly, for summary purposes. [b]15% of patients treated with SG experienced grade 2 treatment-related diarrhea. CTCAE, Common Terminology Criteria for Adverse Events; GCSF, granulocyte colony-stimulating factor; pt, patient; TRAEs, treatment-related adverse events.

Loriot Y, Balar AV, Petrylak DP, et al. Final Results from TROPHY-U-01 Cohort 1: A phase 2 open-label study of sacituzumab govitecan in patients with metastatic urothelial cancer and disease progression after platinum-based regimens and checkpoint inhibitors. Presented at: ESMO Virtual Congress 2020; September 19-21, 2020.

Tagawa et al JCO 2021

Single agent Chemotherapy

Pts with mUC who progress after platinum-based therapy have limited treatment options[1] and poor outcomes (ORR 5-14%[2-5]); even approved treatments (CPIs) are ineffective for most pts[5]

Drug	Phase	N	Population	ORR (%)	Median PFS (mo)	Median OS (mo)
Single-agent vinflunine[4]	Real-world study	59	Pts receiving vinflunine as 2nd-line therapy	5	3.1	5.9
Single-agent docetaxel[2]	3	267	Progression ≤14 mo after platinum therapy (≤1 previous systemic chemotherapy in relapsed/metastatic setting)[a]	14	2.8	NR
Single-agent chemotherapy[3]	Pooled (44 studies)	1202	2nd-line following platinum therapy (<2 prior lines of systemic chemotherapy)	14	2.7	7.0
Single-agent chemotherapy[5,b]	3	272	Progression after platinum therapy; ≤2 prior lines of systemic chemotherapy	11	3.3	7.3

[a]Included pts with progression post platinum, permitting previous treatment with one CPI regimen post-platinum; [b]Investigator's choice of paclitaxel, docetaxel, or vinflunine.
[c]Cohort 2 continues to enroll patients who were previously treated only with an anti-PD-1/L1 therapy
CPI, immune checkpoint inhibitor; mUC, metastatic urothelial cancer; NR, not reported; ORR, objective response rate; OS, overall survival; pts, patients; PFS, progression-free survival.
1.Bladder Cancer. NCCN Clinical Practice Guidelines in Oncology. Version 03.2019; 2. Petrylak et al. *Lancet.* 2017;390:2266-2277; 3. Raggi et al. *Ann Oncol.* 2016;27:49-61; 4. Niegisch et al. *J Cancer*. 2018;9:1337-1348; 5. Fradet et al. *Ann Oncol*. 2019; 30; 970-976; 6. Rosenberg et al *J Clin Oncol*. 2019; 37:2592-2600; 7. Rosenberg et al. *2020 ASCO GU*, abs 441

Conclusions

- Immunotherapy and ADC's has changed the treatment landscape in GU malignancies
- Combination EV/Pembrolizumab will likely become first-line treatment option
- Subsequent treatment options will need to be optimized
- Biomarkers and appropriate patient selection is required

Thank You

For Your Attention!

Any Questions