Management of Advance Bladder Cancer

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MPMMCC & HBCH,

TMH VARANASI

Case

65 years gentleman, HTN

TCC Bladder, also involving ureter cT3N1 disease

Post NACT with Gem Cis 3 cycles -> Robotic Nephroureterectomy + Bladder cuff excision and in 12.4.17

Nodal and Liver Recurrence in 2021

Questions for Discussion

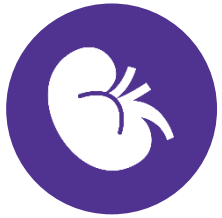
- **Which criteria's do we consider for platinum ineligibility? What percentage of patient getting systemic therapy will be platinum eligible (cisplatin or carboplatin)?**
- **What % of above population will be cisplatin eligible & cisplatin ineligible but carboplatin eligible?**

PBCT eligibility

There are no defined criteria to determine platinum ineligibility, but PS and renal impairment may determine the treatment decision

Patients meeting one of the following five criteria are deemed platinum-ineligible:*[1]

ECOG PS >3



Cr Cl <30 mL/min

Peripheral neuropathy >3

NYHA Heart Failure Class >III

ECOG PS 2 and Cr Cl <30 mL/min

Carboplatin can be used in patients where Cr Cl <60 mL/min[2]

- However, **lower response rates and increased toxicity** have been observed in patients that were both unfit and had renal impairment[3]

*Based on a survey of 56 genitourinary medical oncologists. Cr Cl, creatinine clearance; ECOG, European Cooperative Oncology Group; NYHA, New York Heart Association; PBCT, platinum-based chemotherapy; PS, performance score.

1. Gupta, S et al. J Clin Oncol 2019;37(7_suppl):451; 2. NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer. V3. 2020;
3. De Santis M et al. J Clin Oncol 2009;27:5634–9.

The Current Standard Has Not Changed in about a Decade – Chemotherapy combinations still dominant

Regimen	Response Rate (%)	Median Survival (months)
Gemcitabine, Cisplatin	49%	13.8 mos
MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)	39–65%	12.5–14.8 mos
CMV (cisplatin, methotrexate, vinblastine)	36%	7 mos
Carboplatin, Paclitaxel	21–65%	8.5–9.5 mos
Cisplatin, Paclitaxel	50%	10.6 mos
Cisplatin, Docetaxel	50–60%	8.0–13.6 mos
Cisplatin, Gemcitabine, Paclitaxel	78%	15.8 mos
Gemcitabine, Paclitaxel	54–60%	14.4 mos

Treatment outcomes with CT for metastatic disease have limited durability and high levels of toxicity

Cisplatin-eligible[1–4]

1st-line therapy	HD-MVAC[1]	Gemcitabine + cisplatin
Median PFS, months	9.5	7.7[2]
Median OS, months	15.1	14.0[2]
ORR, %	64	49.4[3]

2nd-line therapy[4]*	Single-agent CT	Doublet CT
Median PFS, months	2.69	4.05
Median OS, months	6.98	8.50
ORR, %	14.2	31.9

Hematologic toxicity is observed with both gemcitabine + cisplatin and HD-MVAC[1,3]

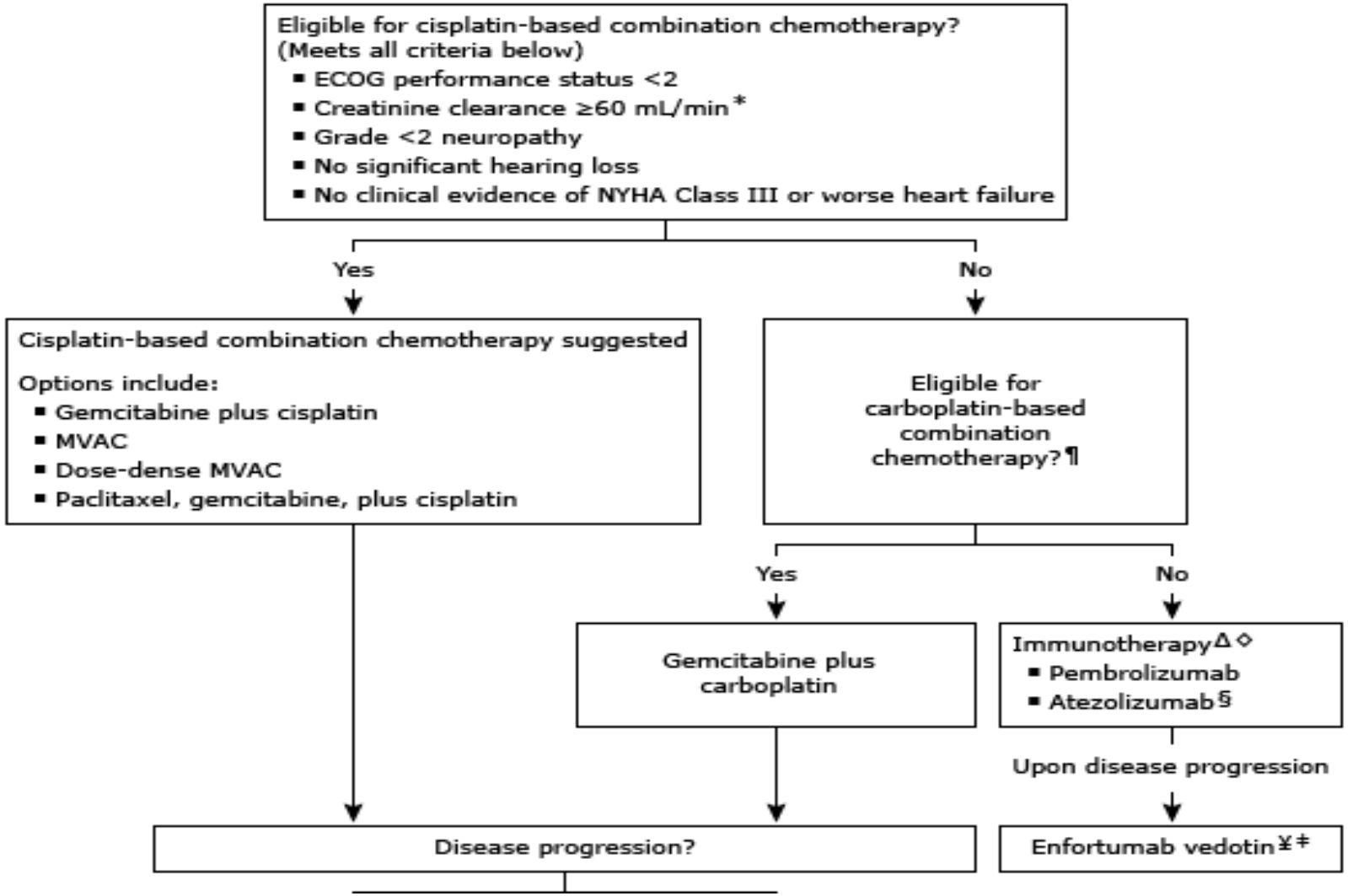
Cisplatin-ineligible[5–7]

1st-line therapy	M-CAVI	Gem + carbo	IO monotherapy	
			Atezo	Pembro
Median PFS, months	4	6	2.7[6]	2[7]
Median OS, months	8	9	15.9	NR
ORR, %	30	41	23	29

Note: The typical duration of treatment is 4–6 cycles of PBCT ranging from 3–6 months followed by BSC. *Single agents.
Atezo, atezolizumab, carbo, carboplatin; CT, chemotherapy; gem, gemcitabine; HD-MVAC, high-dose intensity methotrexate, vinblastine, doxorubicin, cisplatin; IO, immunotherapy; M-CAVI, methotrexate, carboplatin, and vinblastine; NR, not reported;
ORR, objective response rate; OS, overall survival; PBCT, platinum-based chemotherapy; pembro, pembrolizumab; PFS, progression-free survival.

1. Sternberg CN et al. Eur J Cancer 2006;42:50–4; 2. von der Maase H et al. J Clin Oncol 2005;23:4602–8; 3. von der Maase H et al. J Clin Oncol 2000;17:3068–77; 4. Raggi D et al. Ann Oncol 2016;27:49–61; 5. Dietrich B, Srinivas S. Res Rep Urol 2015;10:7–16;
6. Balar AV et al. Lancet 2017;389:67–76; 7. Balar AV et al. Lancet Oncol 2017;18:1483–92.

Treatment of metastatic urothelial carcinoma



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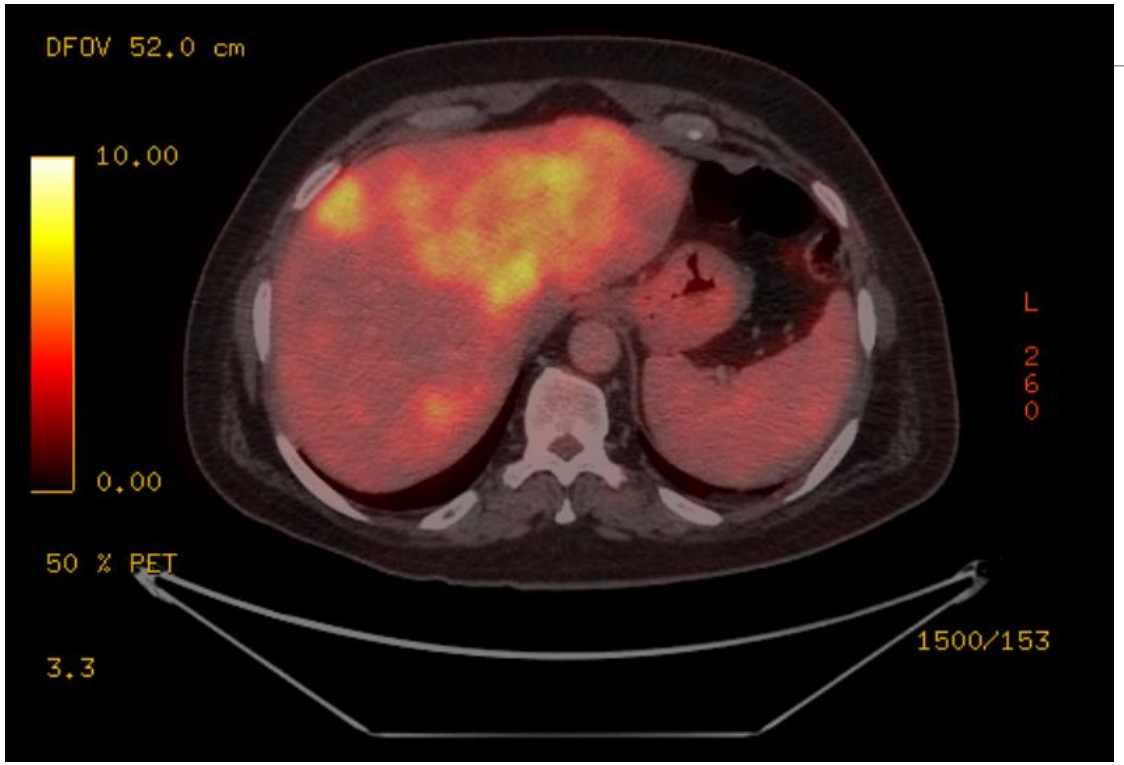

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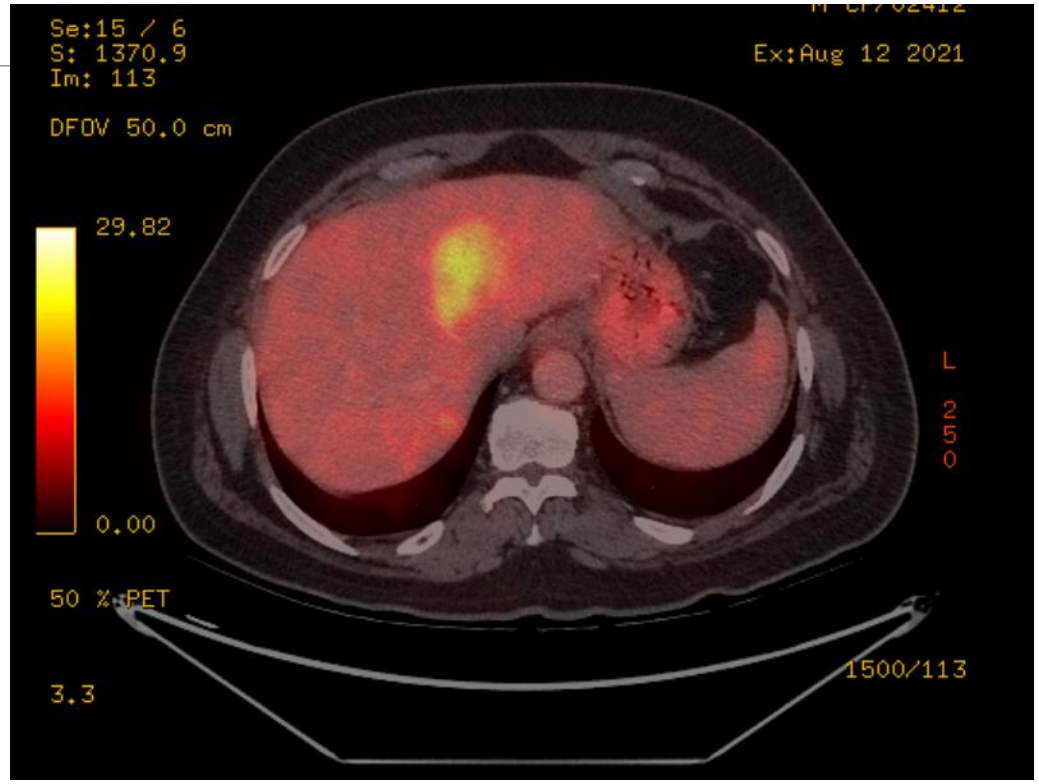

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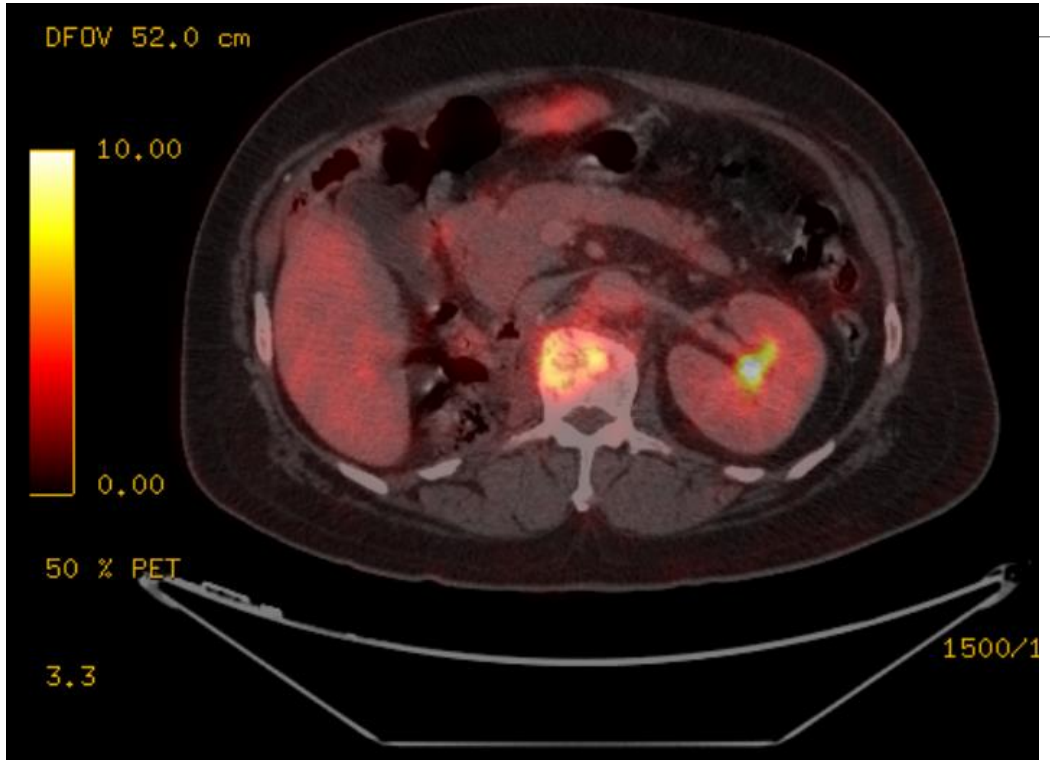

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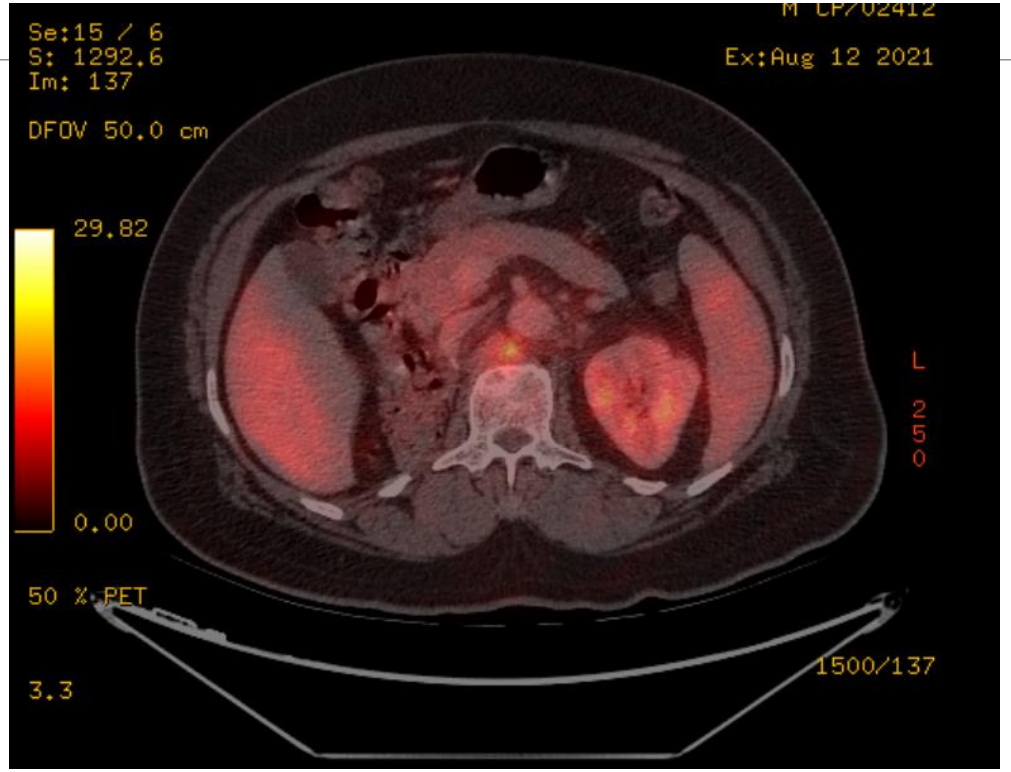
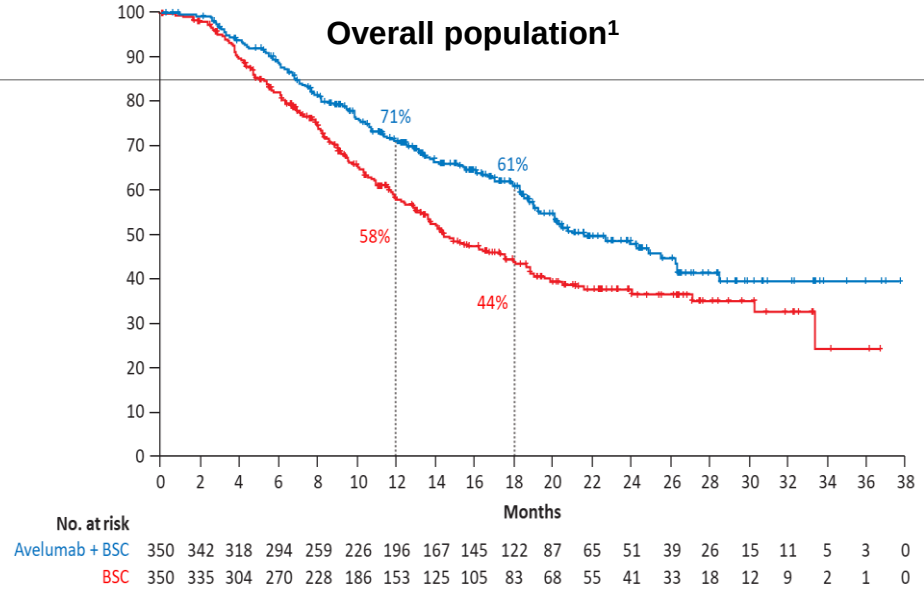
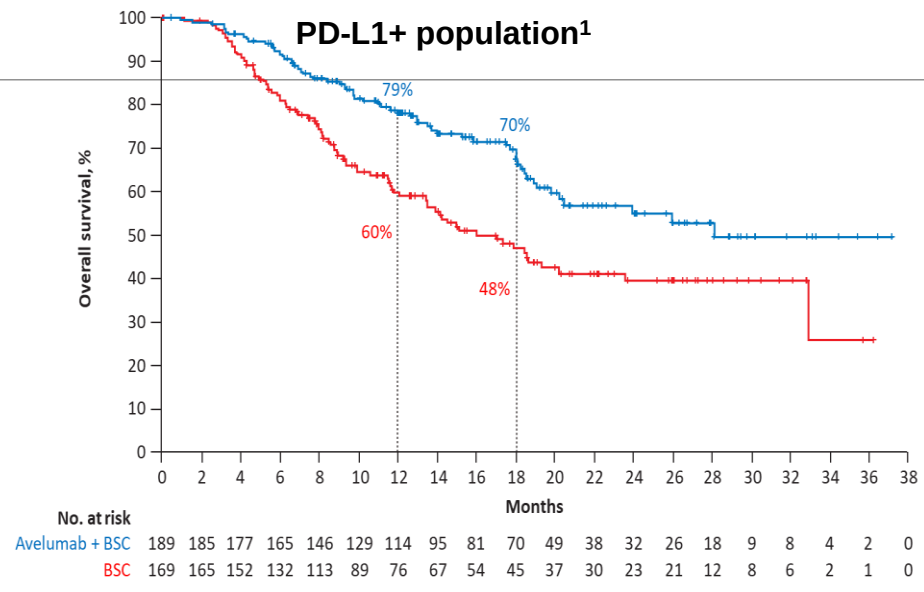


- Post how many cycles of chemotherapy we evaluate for response? And how many achieve CR, PR or SD?
- How long the disease control usually last with 4-6 cycles of CT?
- Are we doing PD-L1 testing in 1st/ post progression of CT/2nd line?

JAVELIN Bladder 100: Avelumab Improves OS in the Overall Study & PD-L1 Population

Primary endpoints: OS in the overall and PD-L1+ populations





Median OS (overall population), months (95% CI)[1]	
Avelumab + BSC	21.4 (18.9–26.1)
BSC alone	14.3 (12.9–17.9)
Stratified hazard ratio for death, 0.69 (95% CI, 0.56–0.86) p<0.001	

Median OS (PD-L1+ population), months (95% CI)[2]	
Avelumab + BSC	NE (20.3–NE)
BSC alone	17.1 (13.5–23.7)
Stratified hazard ratio for death, 0.56 (95% CI, 0.40–0.79) p<0.001	

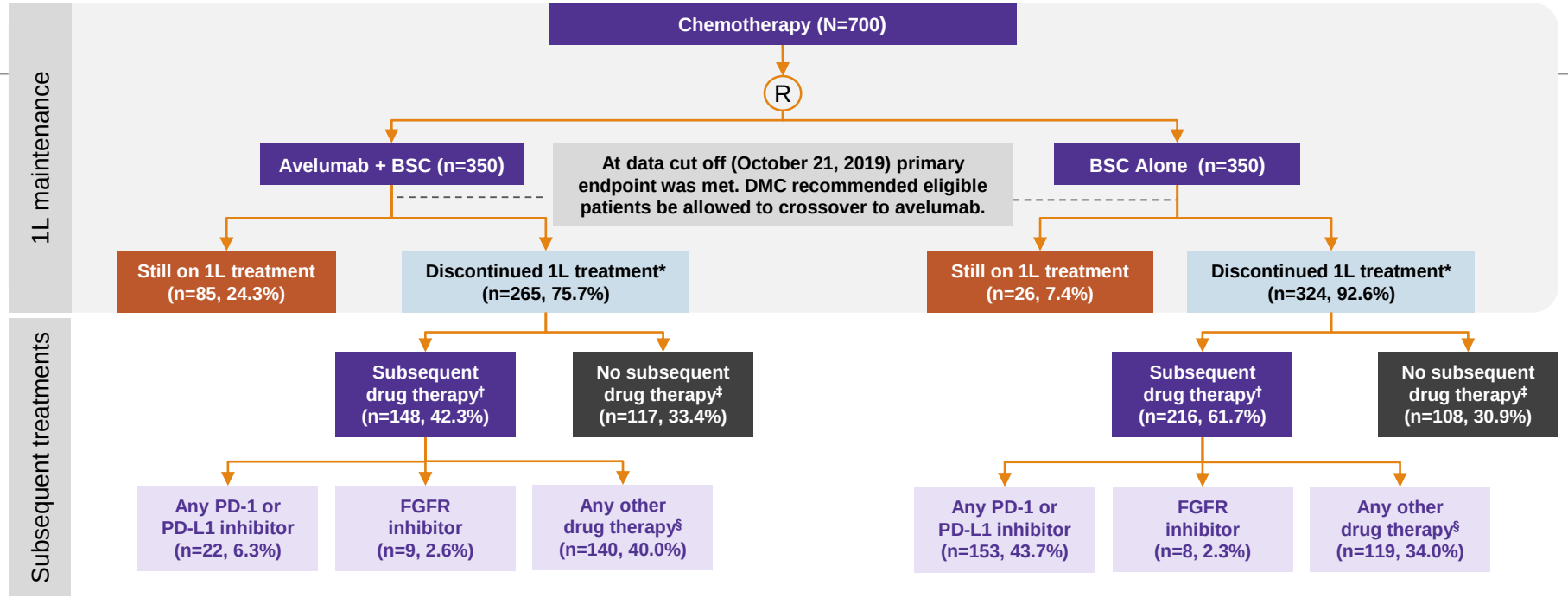
Median duration of treatment:[1]

- Avelumab + BSC: 24.9 weeks (range, 2.0–159.9)
- BSC: 13.1 weeks (0.1–155.6)

1. Powles T et al. Presentation at ASCO 2020. Abstract LBA1.

Avelumab trials: JAVELIN Bladder 100

Subsequent anticancer therapies in all randomized patients[1,2]

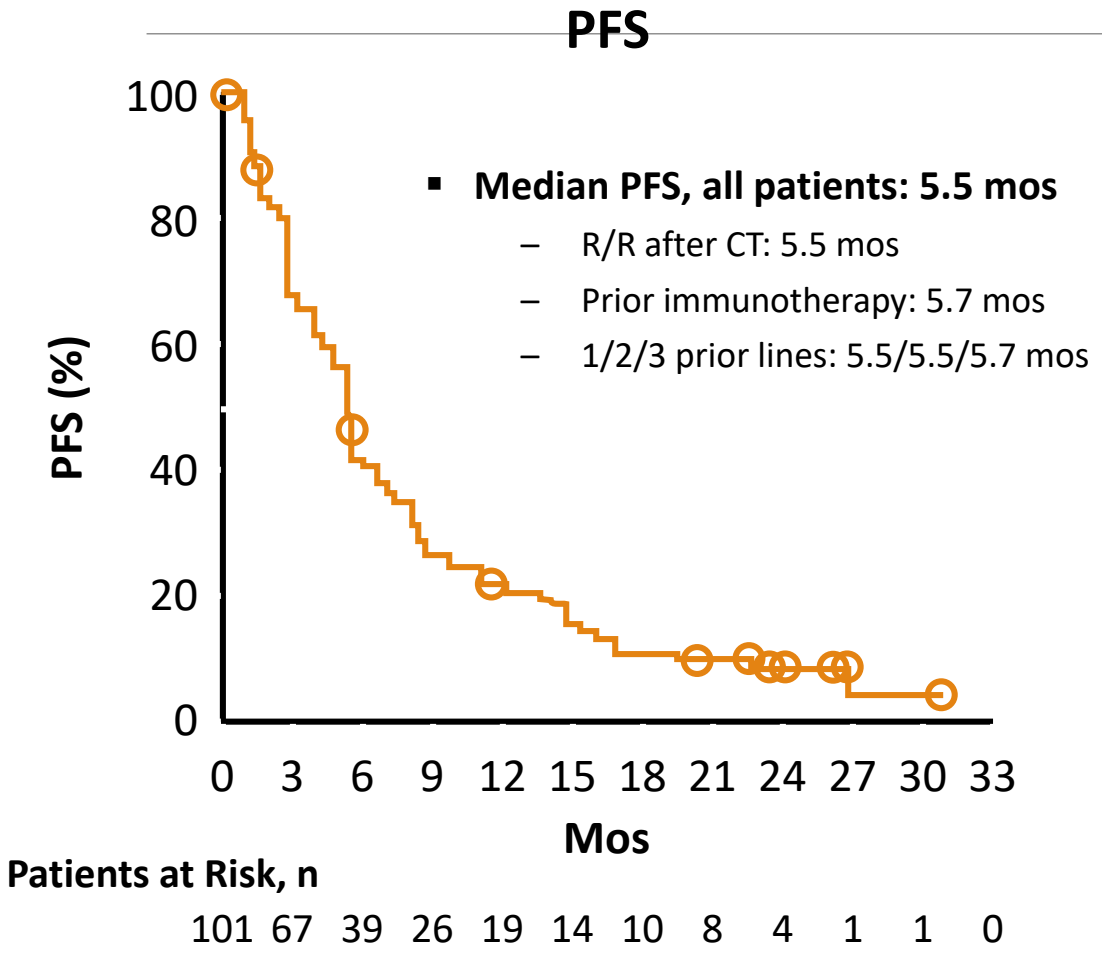


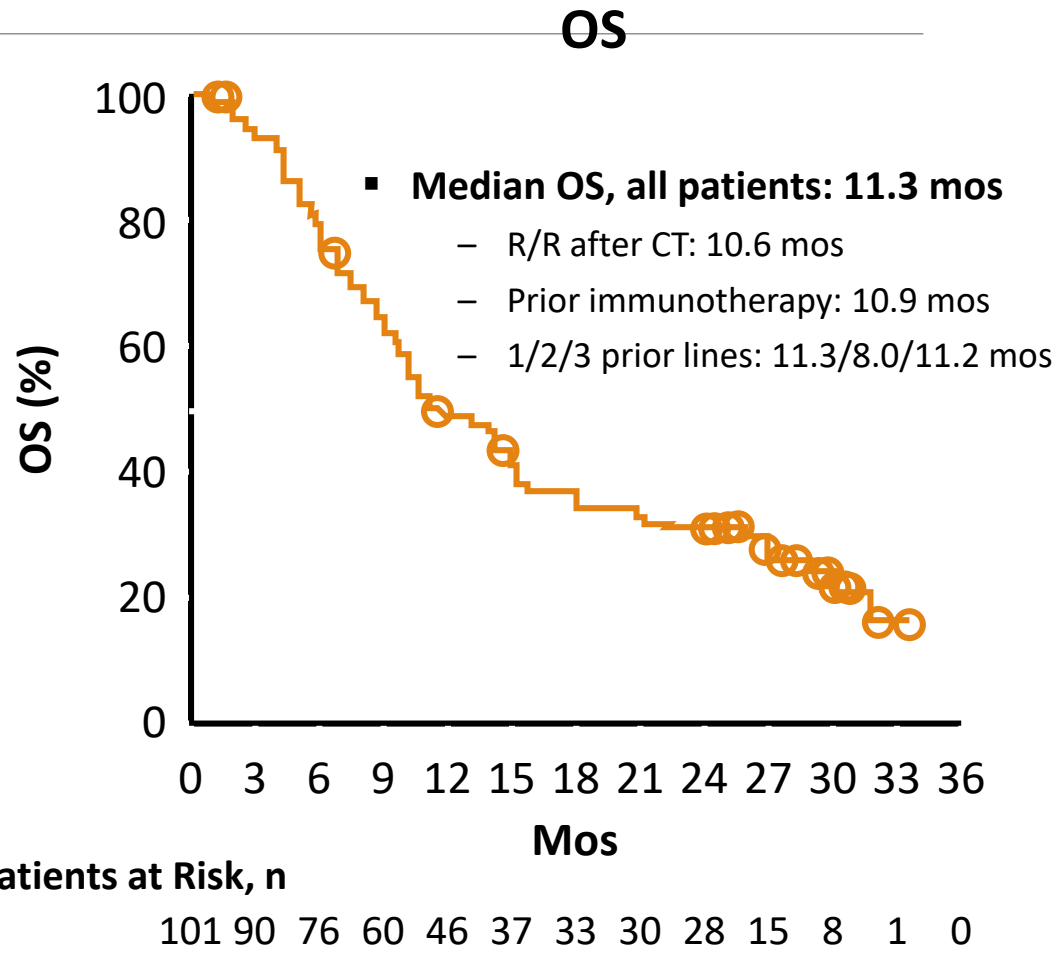
These data highlight the benefit of starting avelumab immediately after 1L CT instead of waiting for disease progression[2]

*Patients discontinued treatment due to progressive disease (54%, avelumab arm; 75%, BSC), adverse events (11%, avelumab; 1%, BSC), consent withdrawal (5%, avelumab; 8%, BSC), death (1%, avelumab; 4%, BSC), physician decision (1%, avelumab; 2%, BSC), global health deterioration (1%, avelumab; 2%, BSC), or other reasons (2%, avelumab; 1%, BSC). Other reasons included no longer meeting eligibility criteria (1%, avelumab), lost to follow-up (0.6%, avelumab; 0.6%, BSC), non-compliance with study drug (0.3%, avelumab) and other (0.3%, avelumab; 0.3%, BSC); †Some patients received >1 category of subsequent therapy. All percentages were calculated using the denominator of all patients in the treatment arm within each population; ‡Some patients who did not receive subsequent drug therapy received anticancer radiotherapy and/or anticancer surgery (n=19, avelumab; n=12, BSC); §Other drug therapies included single agent or combination chemotherapies, TKI, antibody-drug conjugates, IDO1 inhibitors, PARP inhibitors, mTOR inhibitors, monoclonal antibodies, immune-stimulating vaccines or investigational agents.

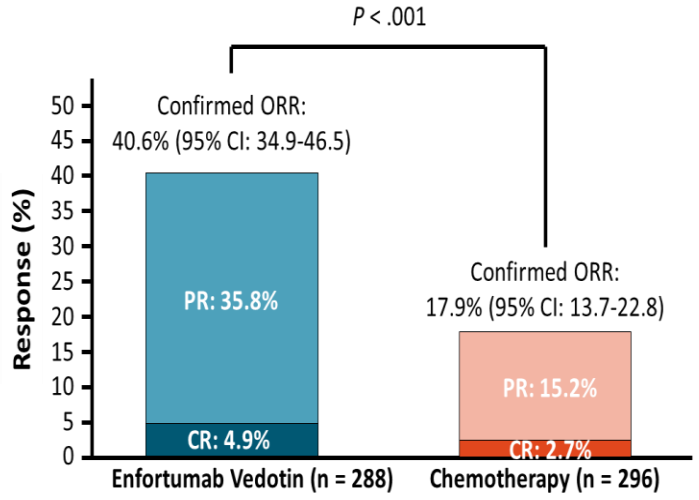
1. Powles T et al. N Engl J Med 2020; 383:1218–30 suppl; 2. Powles T et al. N Engl J Med 2020; 383:1218–30.

Pivotal Phase II Erdafitinib Study: Updated PFS and OS

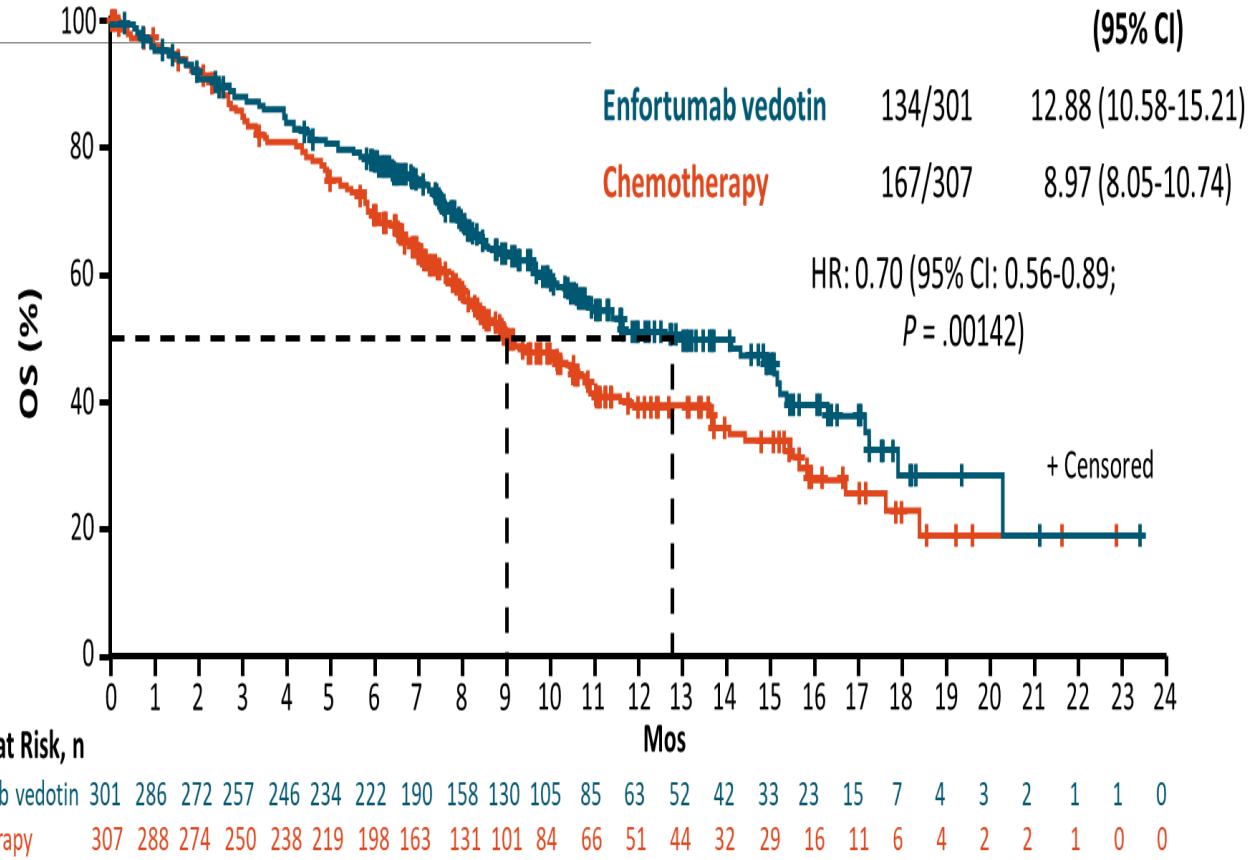




EV-301: Enfortumab Vedotin vs Chemotherapy in LA or Metastatic UC After Platinum and Anti–PD-(L)1 Therapy



Disease control rate, % (95% CI)	71.9 (66.3-77.0)	53.4 (47.5-59.2)	P < .001

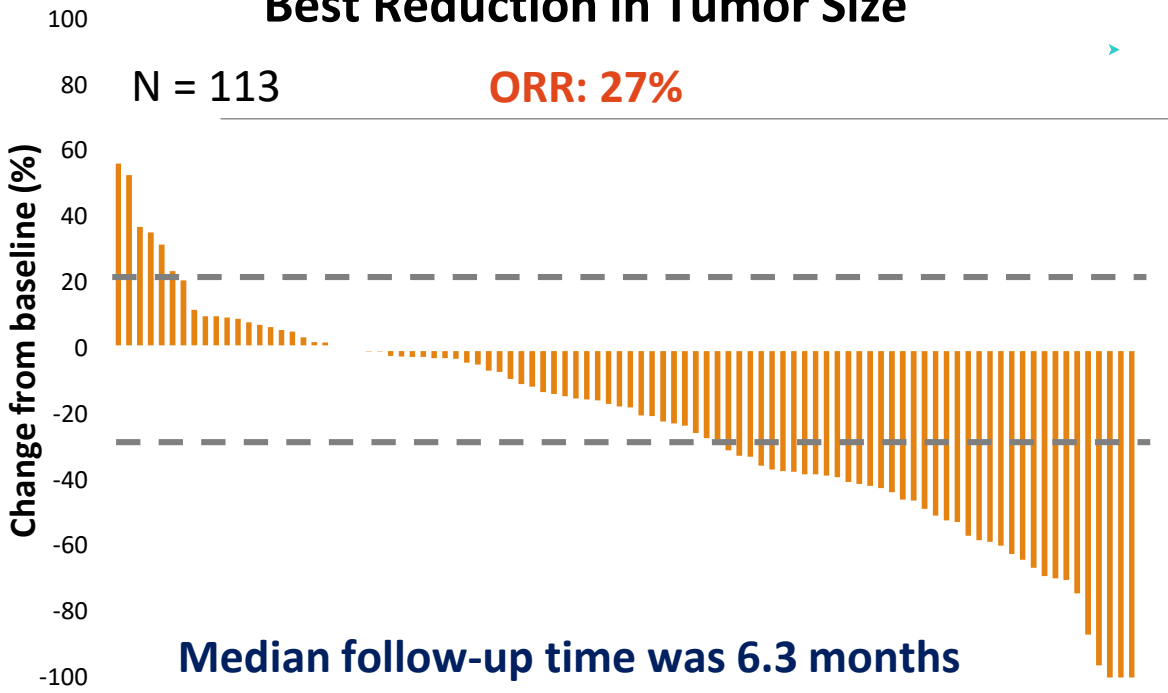


- Interim analysis met primary endpoint: significantly improved OS with EV vs CT (*P* = .00142)
- OS favored EV across all subgroups except women (HR: 1.17; 95% CI: 0.72-1.89)

Powles. ASCO GU 2021. Abstr 393.

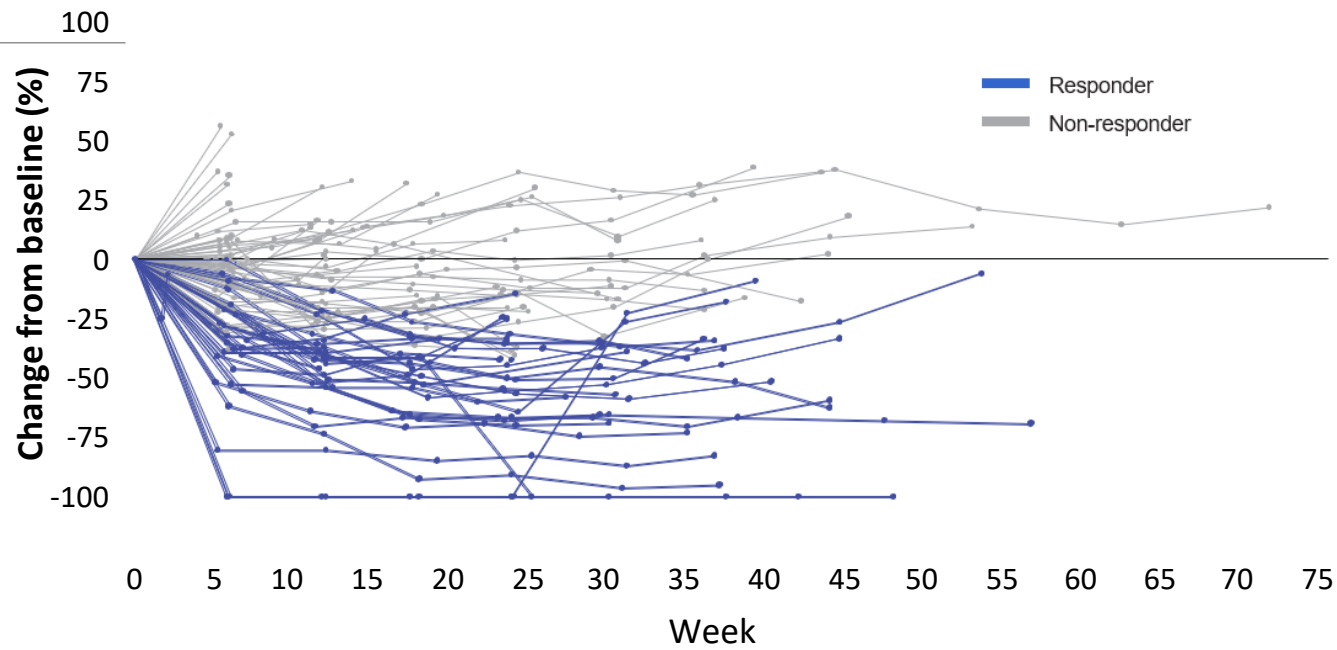
TROPHY-U-01 Cohort 1: Final Results With Sacituzumab Govitecan for mUC After Platinum-Based CT and IO

Best Reduction in Tumor Size



mPFS: 5.4 mos (95% CI: 3.5-6.9)

Reduction in Tumor Size



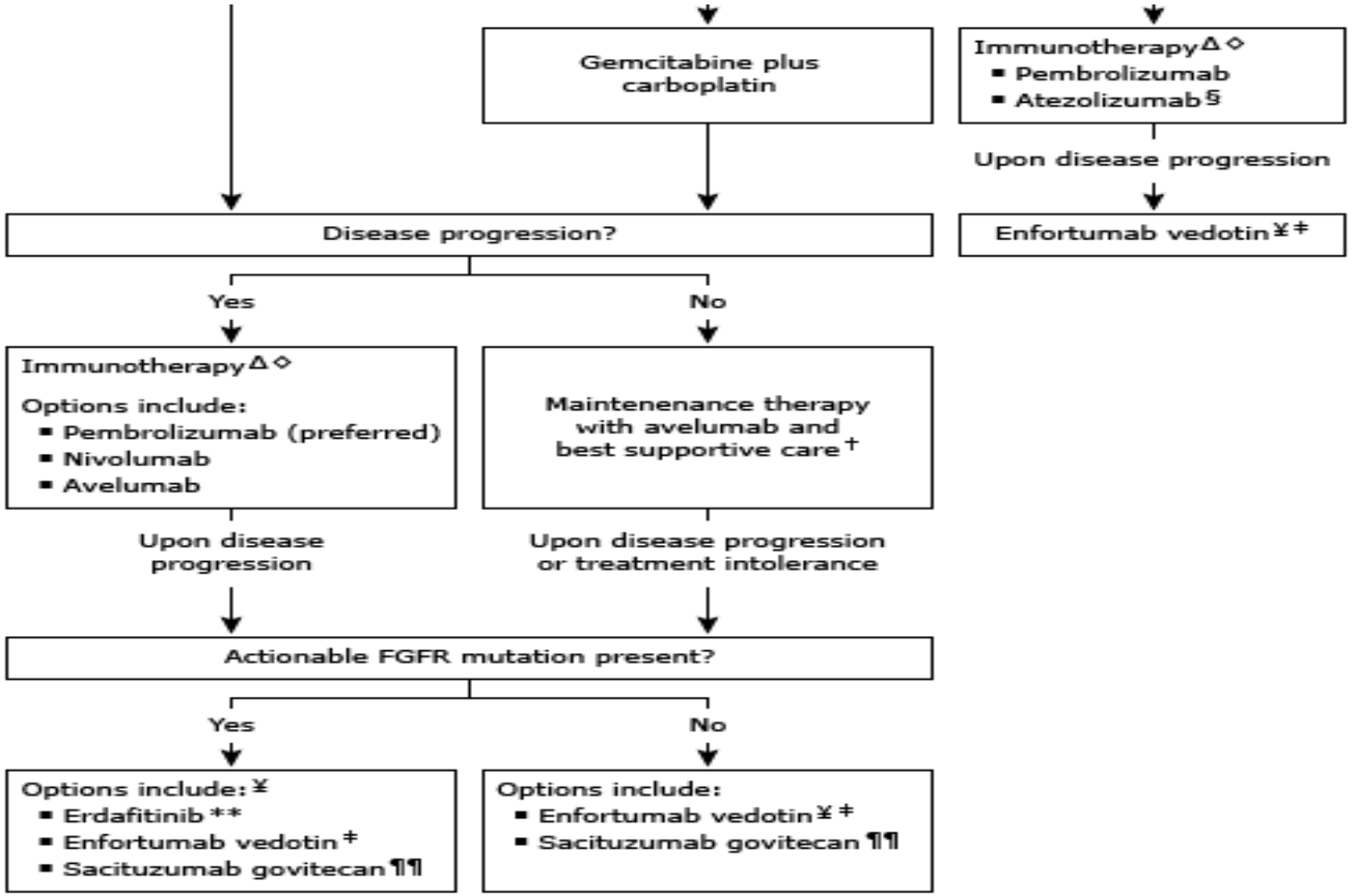
mOS: 10.5 mos (95% CI: 8.2-12.3)

In April 2020, sacituzumab govitecan received fast track designation by the FDA for this indication

A phase III confirmatory trial in mUC, TROPiCS-04 is underway

Loriot. ESMO 2020. Abst LBA24.

Subsequent Line Therapies



Greetings from TMH Varanasi