Sequencing Therapy Throughout the Urothelial Treatment Continuum

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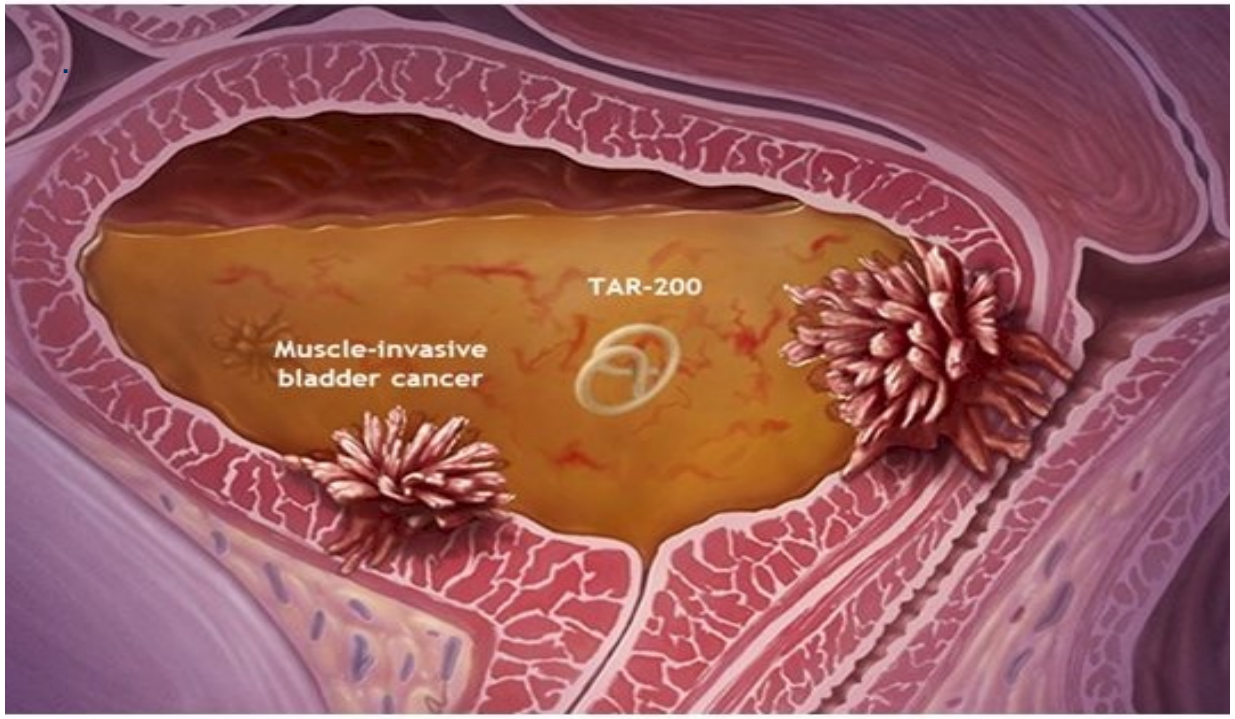
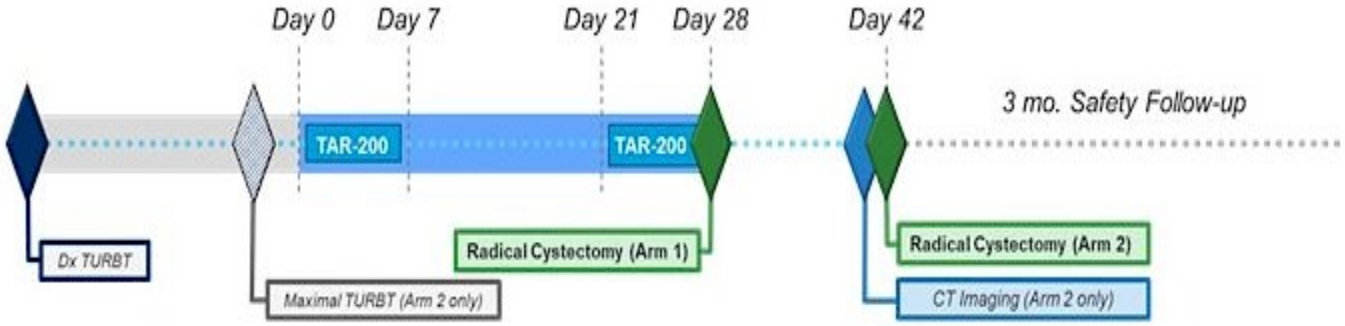
QUESTION 1

What role, if any, do you believe TAR-200 will eventually play in the management of urothelial bladder cancer (UBC)? If this strategy were available today, in which patients with UBC would you prioritize its use?

TAR-200: Intravesical Administration of Gemcitabine in Muscle Invasive Disease: Phase I study





TAR-200 Efficacy

- In Arm 1, patients had, at minimum, residual tumor >3 cm after transurethral resection of bladder tumor (TURBT) while, in arm 2, patients had had maximal TURBT with any residual tumor <3 cm.
- For Arm 1 patients at radical cystectomy, 4 out of 10 patients exhibited pathologic downstaging with 1 demonstrating a pCR and 3 a pPR. In Arm 2, 6 out of 10 patients exhibited downstaging with 3 experiencing a pCR and 3 a pPR.
- No systemic absorption of gemcitabine

TAR-200

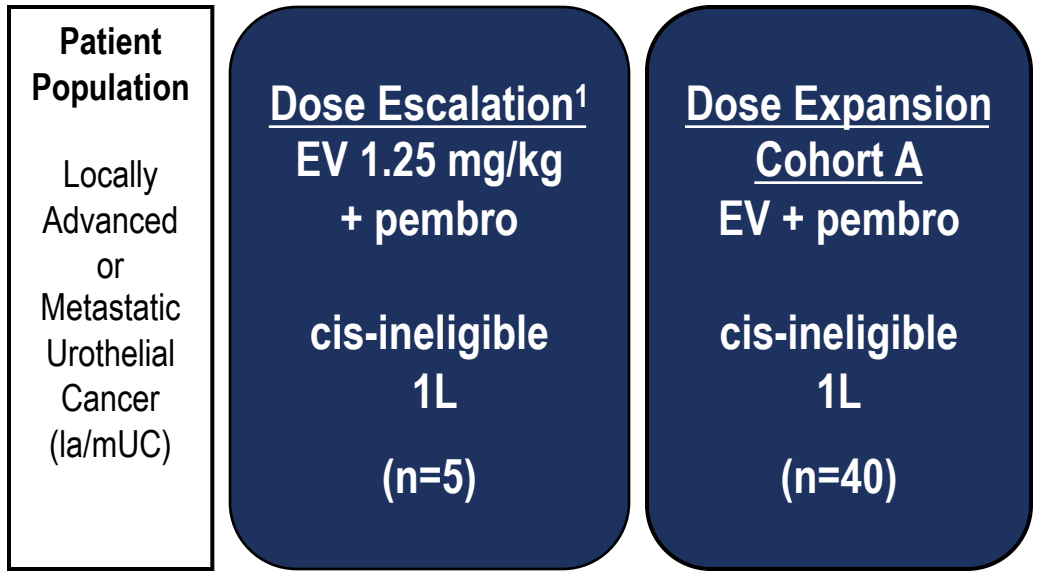
- No systemic absorption: micrometastatic disease untreated.
- In combination with checkpoints for patients ineligible for cystectomy
- SunRISe-1: TAR-200 in Combination With Cetrelimab, TAR-200 Alone, or Cetrelimab Alone in Participants With High Risk NMIBC Unresponsive to Intravesical BCG Who Are Ineligible for or Elected Not To Undergo Radical Cystectomy
- SunRISe-2: Phase 3, Multicenter, Randomized Study Evaluating the Efficacy of TAR-200 in Combination with Cetrelimab versus Concurrent Chemoradiotherapy in Participants with Muscle-Invasive Urothelial Carcinoma of the Bladder

QUESTION 2

What are your thoughts about clinical trials combining antibody-drug conjugates and immune checkpoint inhibitors (eg, enfortumab vedotin and pembrolizumab) in metastatic UBC (mUBC)? Which patients do you feel are best suited for this strategy?

ENFORTUMAB VEDOTIN + PEMBROLIZUMAB COHORTS

EV 1.25 mg/kg + pembrolizumab (200 mg) in 1L la/mUC patients



Dosing: EV days 1 and 8 of 3-wk cycle to align with pembro (day 1 of 3-wk cycle)

EV exposure: Similar to EV monotherapy on 4-wk schedule (EV Days 1, 8, and 15)[2]

Primary endpoints: AEs, lab abnormalities

Key secondary endpoints: DLTs, ORR, DCR, DOR, OS

[1] Not included in the current analysis: three 1L patients treated with EV 1 mg/kg + pembro 200 mg and two 2L patients treated with EV 1.25 mg/kg + pembro 200 mg

[2] Rosenberg et al. *J Clin Oncol. Epub July* 2019

Efficacy

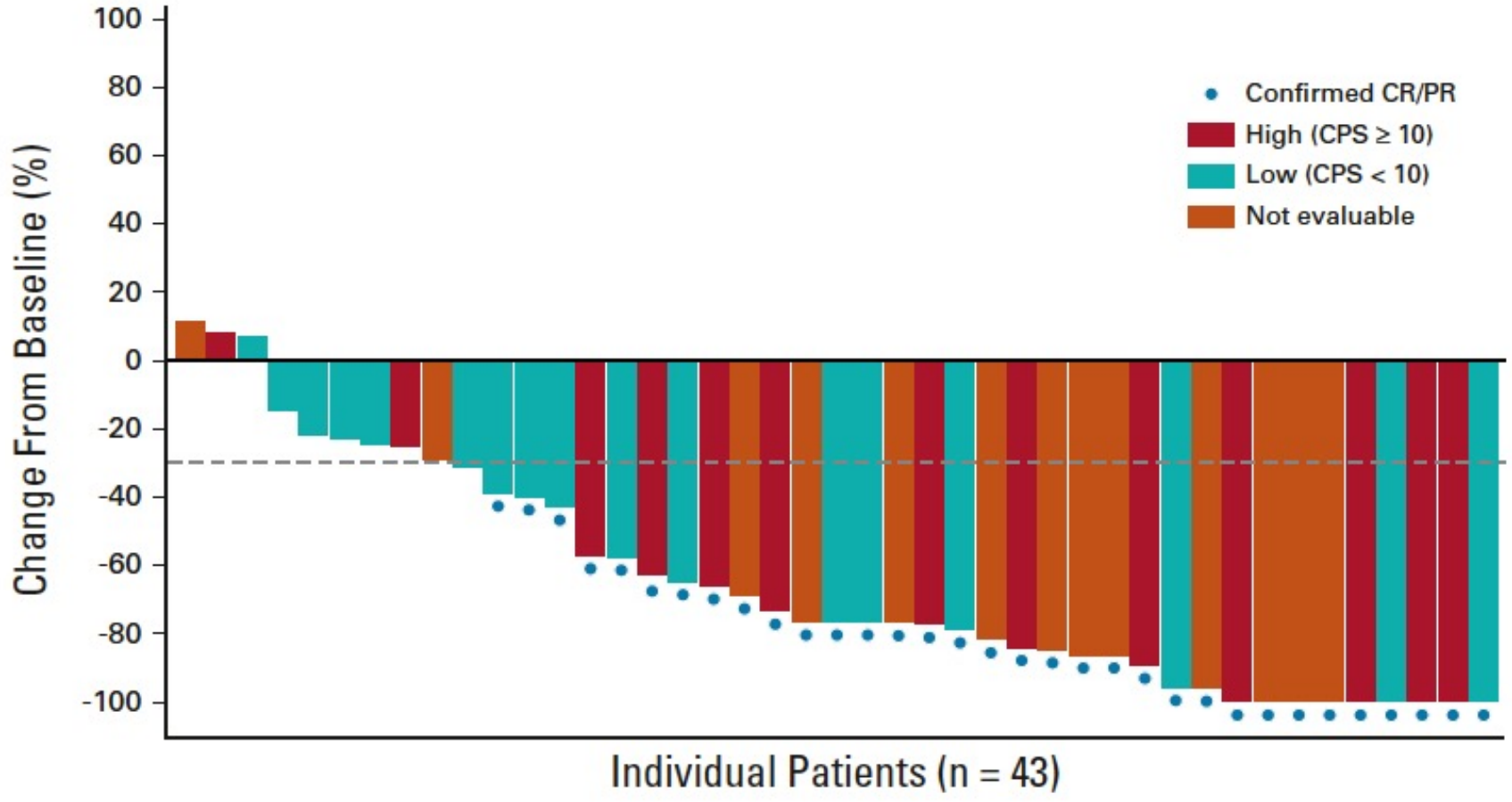
Best Overall Response Per RECIST v 1.1 by investigator (N=45)

Confirmed ORR	73.3% (33)
95% CI	(58.1, 85.4)
Complete response	15.6% (7)
Partial response	57.8% (26)
Stable disease	20.0% (9)
Progressive disease	2.2% (1)
Not evaluable	4.4% (2)
ORR in patients with liver metastasis	53.3% (8/15)
ORR by PD-L1 Expression	
High expression:	78.6% (11/14)
Low expression:	63.2% (12/19)

- Enfortumab vedotin + pembrolizumab demonstrated an ORR of of 73.3% in 1L cisplatin-ineligible la/mUC patients, per investigator
- Responses observed regardless of PD-L1 expression level

Rosenberg et al. Genitourinary Cancers Symposium 2020;Abstract 441.

EV-103: Percent Reduction from Baseline in the Sum of the Diameters of Target Lesions per Investigator by PD-L1 Status

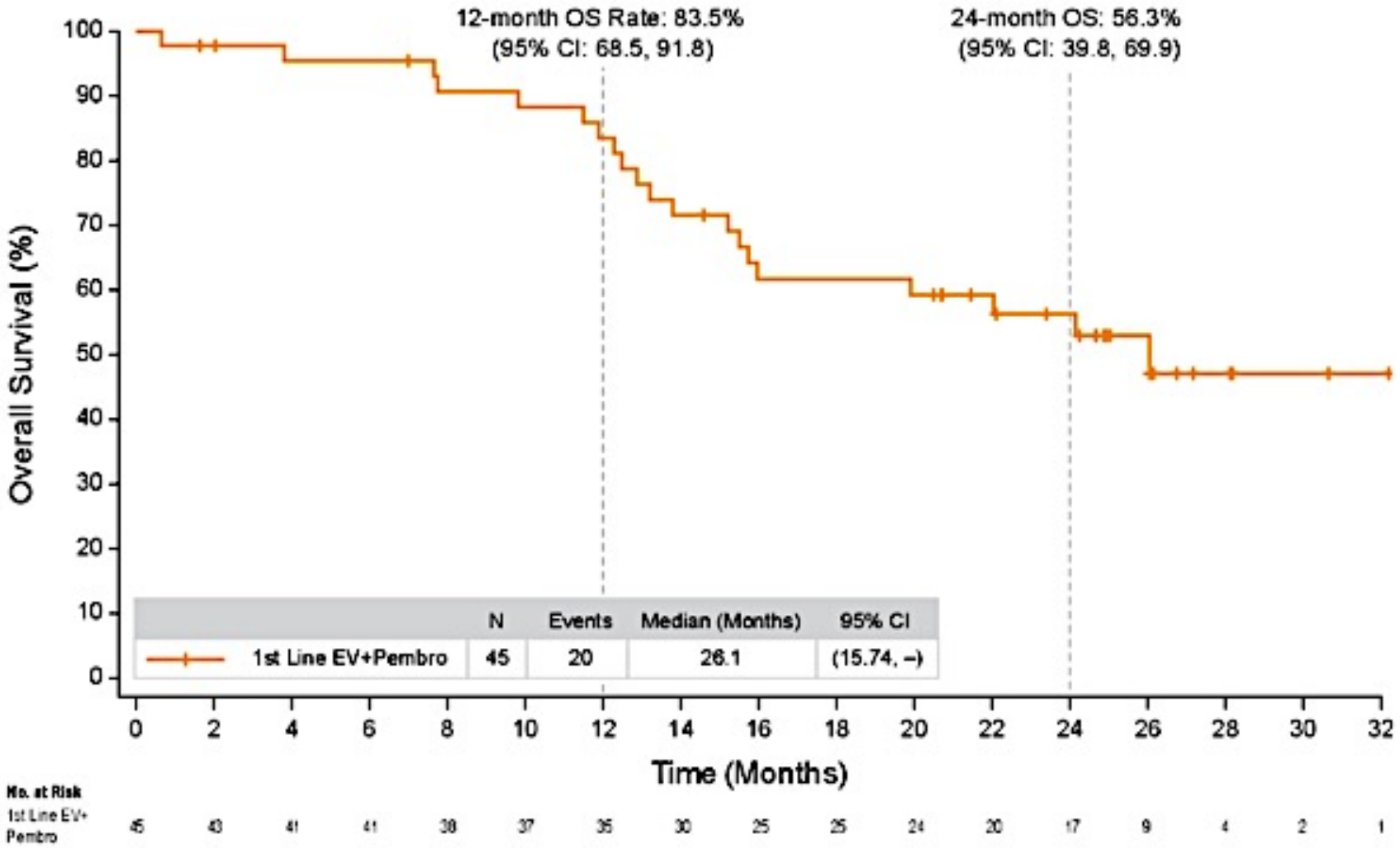


Hoimes CJ et al. J Clin Oncol 2023 Jan 1;41(1):22-31.

Enfortumab Vedotin Patient Selection

- Responses in liver consistently 40%
- Studies of EV/Pembrolizumab are in cisplatin-ineligible patients
  - EV-302 is a randomized trial of EV/Pembrolizumab vs std chemo in both cisplatin eligible and ineligible patients
- Will similar results be seen with platinum-based chemotherapy followed by avelumab in lymph node only metastatic disease?

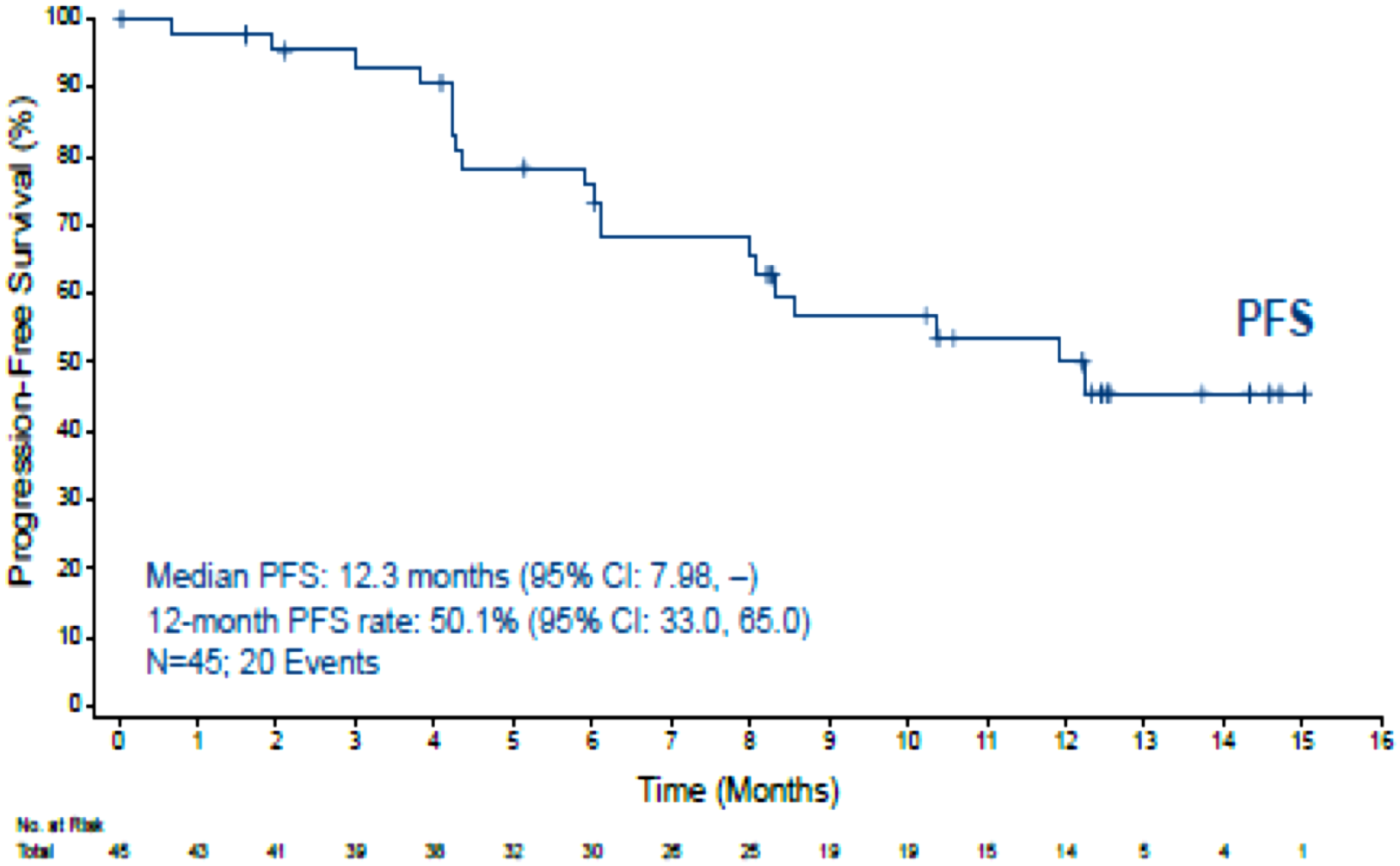
EV-103: Updated Survival Data



Median survival 26.1 months with a median follow-up of 24.9 months

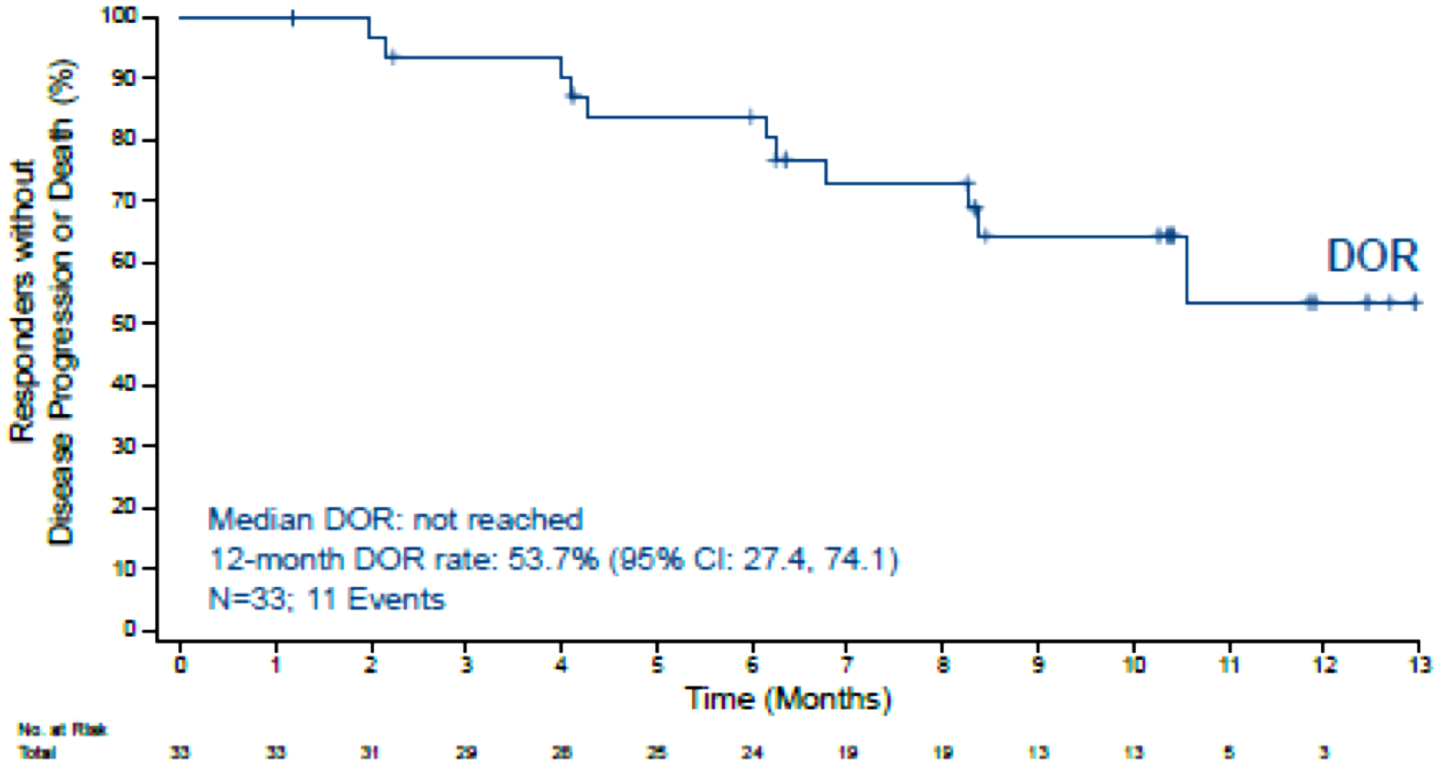
Hoimes CJ et al. J Clin Oncol 2023 Jan 1;41(1):22-31.

Progression-Free Survival



Rosenberg et al. Genitourinary Cancers Symposium 2020;Abstract 441.

Duration of Response



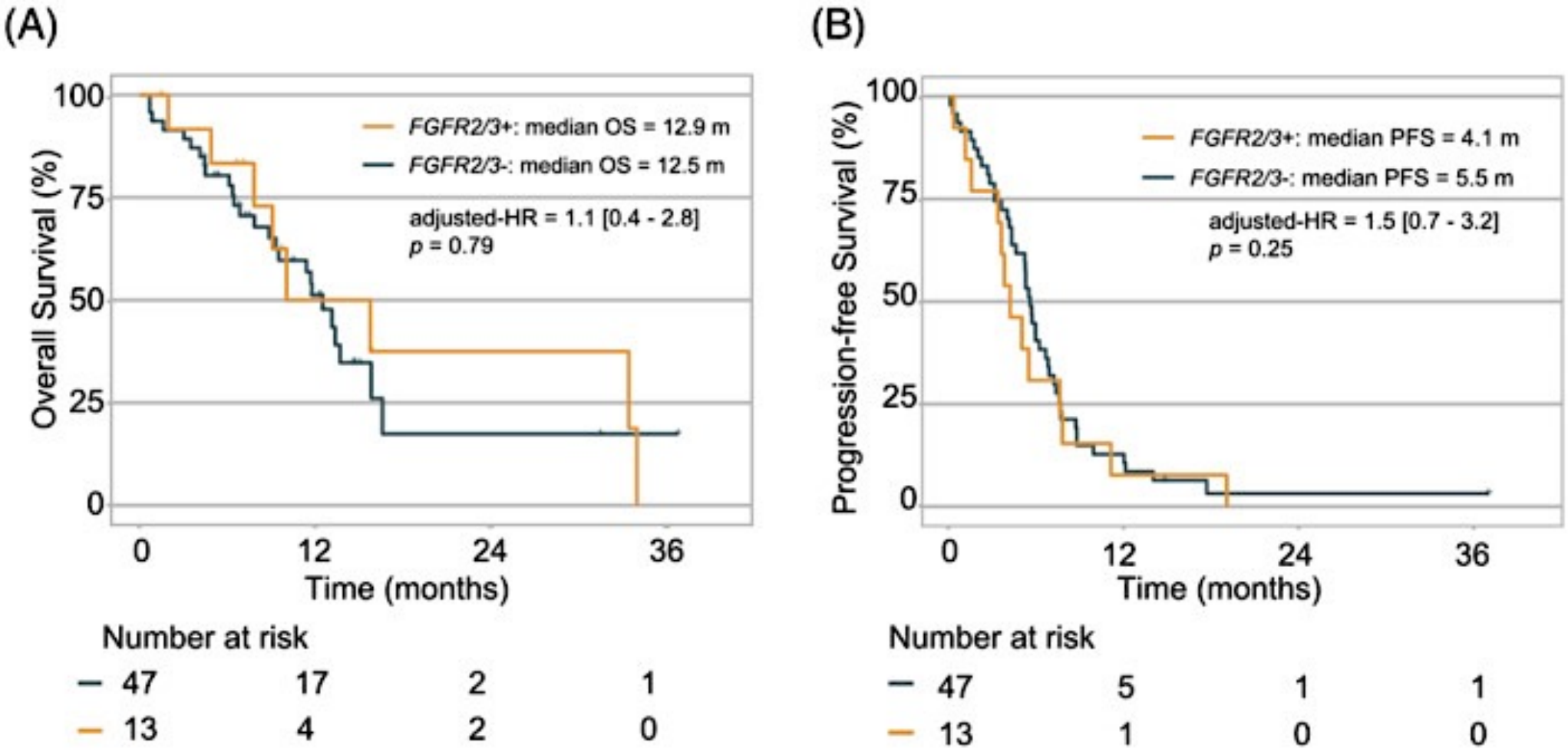
- Median DOR has not been reached with a median follow-up of 10.4 months
  - DOR (range: 1.2, 12.9+ months)
- Out of the 33 responders,
  - 18 (55%) had an ongoing response
  - 11 (33%) had progressed or died
  - 4 (12%) had started a new antitumor treatment before progressive disease

Rosenberg et al. Genitourinary Cancers Symposium 2020;Abstract 441.

QUESTION 3

How do you generally sequence enfortumab vedotin, erdafitinib and sacituzumab govitecan for patients with mUBC who are eligible to receive all of these agents?

EV in FGFR2/3+ patients

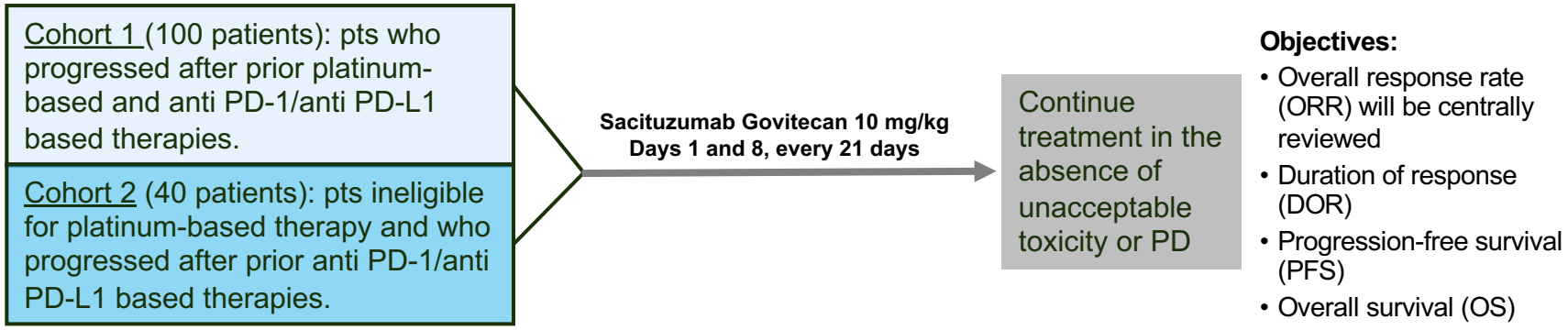


Abib BJUI Compass 2022

TROPHY-U-01 (IMMU-132-06) Study

A Phase II Open Label, Study of IMMU-132 in Metastatic Urothelial Cancer After Failure of Platinum-based Regimen or Anti-PD-1/ PD-L1 Based Immunotherapy

- Results from the Study-01 basket trial warranted further investigation in a dedicated phase 2 trial.
- TROPHY-U-01 (NCT03547973) is an international, single-arm, open-label, phase 2 trial evaluating the antitumor activity and safety of sacituzumab govitecan in 140 pts with advanced UC.



NCT Trial Number: 03547973
PD-1, programmed cell death-1; PD-L1, programmed death ligand-1.

View TROPHY-U-01 Poster on Feb 15th TPS #495; Poster Board #N5

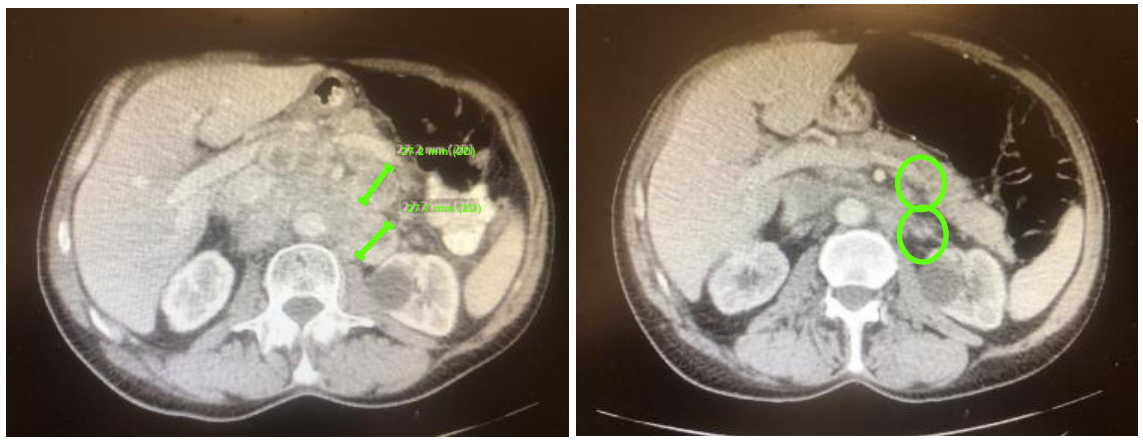
Case: Retroperitoneal Lymph Node Metastasis

- 61 year-old male with past medical history of G1 neuropathy and RLE edema, with target lesions consisting of periportal, retroperitoneal, and mesenteric adenopathy

- Refractory to adjuvant tx: Cisplatin/gemcitabine
- Prior metastatic regimens:
  - Atezolizumab (24 mon)
  - Enfortumab vedotin (8 mon)
  - Pemetrexed (3 mon)

- **Confirmation of PR after cycle 4 with SG treatment[a]**
  - **No worsening of neuropathy reported**
  - **Significant reduction in lower extremity edema**
  - **On treatment for 7 mon and ongoing at time of data cut-off**

Images provided by Daniel P. Petrylak from the Yale School of Medicine, New Haven, CT



Baseline CT

Follow-up CT
(after 10 cycles of SG)

70% reduction of target lesions

[a]Assessed by investigator using RECISTv1.1.
CT, computed tomography; G1, grade 1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; RLE, right leg extremity; SG, sacituzumab govitecan.

Sequencing of Urothelial Agents

- No randomized data comparing outcomes.
- Drugs are apparently non cross resistant
- Selection based on efficacy, route of administraton, and toxicities

QUESTION 4

What is the optimal first-line therapy for patients with metastatic renal cell carcinoma (mRCC), and how does this vary based on risk status, symptomatology and other factors?

Frontline Renal Cell Carcinoma Landscape

	KEYNOTE-426 (Axi/Pembro)	CheckMate 9ER (Cabo/Nivo)	JAVELIN Renal 100 (Axi/Avelumab)	IMmotion 151 (Bevacizumab/Atezolizumab)	CheckMate-214 (Nivolumab/Ipilimumab)	COSMIC-313 (Cabozantinib/Nivo/Ipi)
mOS, months HR (CI);	NR vs 35.7 **0.68** (0.55-0.85);	NR vs NR **0.60** (0.40–0.89);	NR vs NR **0.79** (0.62-1.03)	33.6 vs 34.9 **0.93** (0.76-1.14)	NR vs 38.4 **0.69** (0.59-0.81)	Not reported
Landmark OS at 12 mo Landmark OS at 24 mo	**90%** vs. 79% **74%** vs. 66%	**87%** vs. 78% (est) NA	**86%** vs. 82% (est) **70%** vs. 65% (est)	**82%** vs. 79% (est) **63%** vs. 60%	**84%** vs 79% (est) **56%** vs 48% (est)	Not reported
mPFS, months HR (CI)	**15.4** vs 11.1 0.71 (0.60–0.84)	**16.6** vs 8.3 0.51 (0.41–0.64)	**13.8** vs 7.0 0.69 (0.57-0.83)	**11.2** vs 8.4 0.83 (0.70-0.97)	**12.2** vs 12.3 **0.89** (0.76-1.05)	**NR** vs 11.3 **0.73** (0.57-0.94)
ORR, %	**60** vs 40	**56** vs 27	**53** vs 27	**37** vs 33	**39** vs 32	**43** vs 36
CR, %	**9** vs 3	**8** vs 5	**4** vs 2	**5** vs 2	**11** vs 3	3 vs 3
Med f/u, months	**30.6**	**18.1**	**19.3**	**24**	**48**	17.7
Prognostic risk, % Favorable Intermediate Poor	 32 55 13	 23 58 19	 21 61 16	 20 69 12	 23 61 17	Not reported
Randomization period	Oct 2016 – Jan 2018	July 2017–May 2019	March 2016 – Dec 2017	May 2015 – Oct 2016	Oct 2014—Feb 2016	Not reported
Subsequent systemic therapy for sunitinib arm	Overall (69%) IO (48%)	Overall (40%) IO (29%)	Overall (51%) IO (36%)	NR	Overall (64.1%) IO (38.6%)	Not applicable

Rini BI et al. *N Engl J Med*. 2019;380(12):1116-1127; Choueiri TM et al. 2020 ESMO Virtual Meeting. Abstract 6960_PR. Motzer RJ et al. *N Engl J Med*. 2018;378(14):1277-1290; Rini BI et al. *Lancet. 2019;* Albiges L et al. *ESMO Open.* 2020;5:e001079; Choueiri T et al. ESMO 2022;Abstract LBA8.

Caveats about Front Line Therapy for Metastatic RCC

- Longest Follow-up: Ipilimumab/nivolumab-tail to survival curve (30%)
- Quickest response: IO/TKI
- Sites of disease: Bone favor Cabozantinib
- Comorbidities: Hypertension with TKI

QUESTION 5

How do you generally sequence available therapies for mRCC that has progressed on front-line immunotherapy and/or a TKI?

TKI Therapy Following Immune Checkpoint Blockade

TABLE 1. Activity of Targeted Therapy Following Immune Checkpoint Blockade

Author	Study	Agents	No. of Patients	ORR	PFS/TTF
Ornstein et al[5]	Prospective; phase II	Axitinib, dose titrated	38	45%	8.8 months
Choueiri et al[6]	Subgroup; phase III, METEOR	Cabozantinib/everolimus	32	22%	NR/4.1 months
Rini et al[7]	Subgroup; phase III, TIVO-3	Tivozanib	47	NR	7.3 months
Singh et al[8]	Retrospective	Cabozantinib	86	36%	6.5 months
Wiele et al[9]	Retrospective	Lenvatinib +/– everolimus	40	30%	4.2 months
Hamieh et al[10]	Retrospective	Lenvatinib + everolimus	5	40%	NR
Shankar et al[11]	Retrospective	VEGF TKI	70	41%	13.2 months
Powles et al[12]	Retrospective	VEGF TKI	70	28%	6.4 months
Hammers et al[13]	Retrospective	VEGF TKI	56	13%	6.9 months
Ravi et al[14]	Retrospective	VEGF TKI	56	33%	8.0 months
Choueiri et al[15]	Retrospective	VEGF TKI	55	30%	3.7/5.4 months*
Choueiri et al[16]	Retrospective	VEGF TKI	33	36%	8 months
Tykodi et al[17]	Retrospective	VEGF TKI	33	29%	6.4 months

Abbreviations: ORR, overall response rate; PFS, progression-free survival; TTF, time to treatment failure; NR, not reported; TKI, tyrosine kinase inhibitor.

*Following immune checkpoint blockade-VEGF and ipilimumab-nivolumab combination, respectively.