Immunotherapy for the Treatment of Renal Cell and Bladder Carcinoma

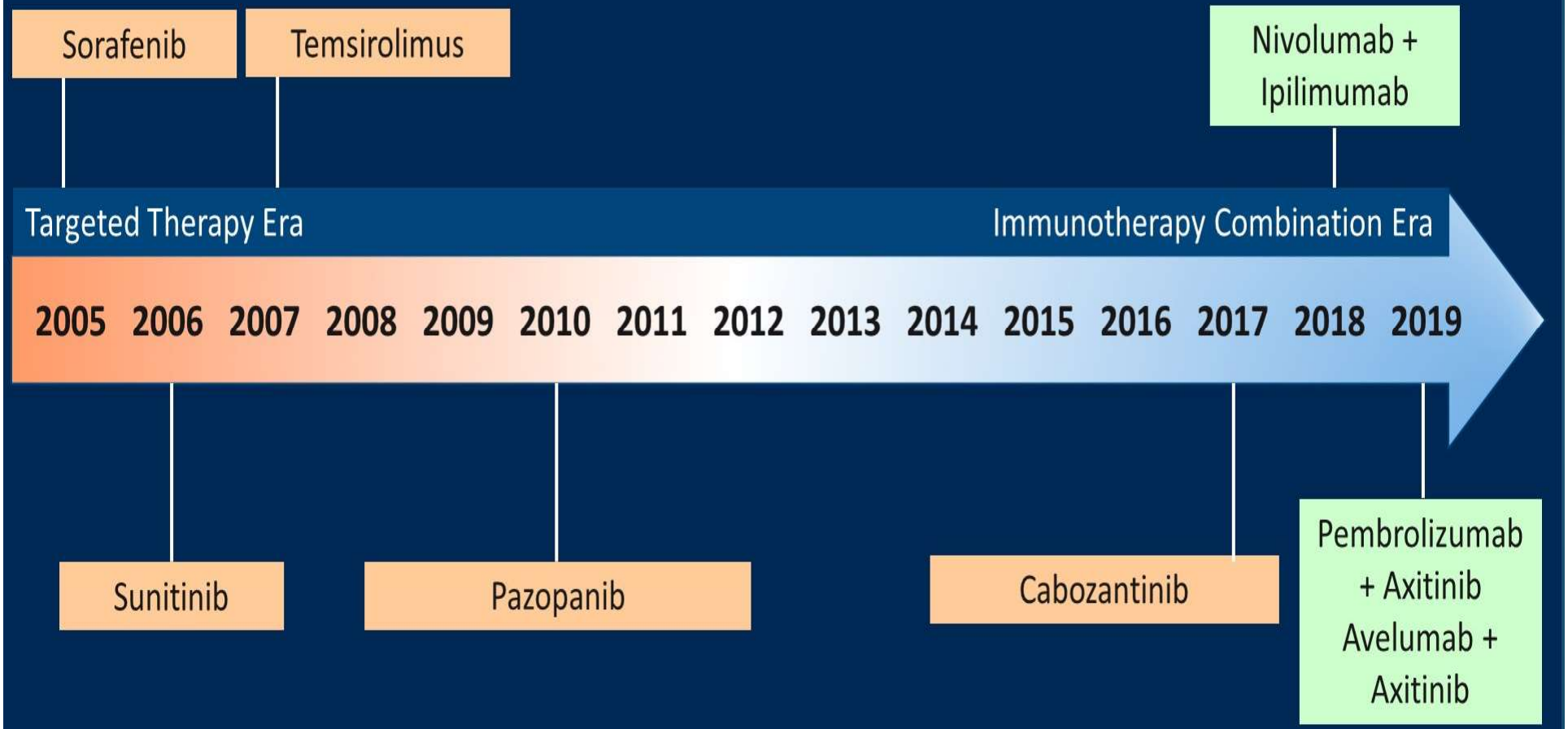
Alan J. Koletsky, MD

Eugene and Christine Lynn Cancer Institute
Clinical Associate Professor
Charles E Schmidt College of Medicine
Florida Atlantic University

Boca Raton, FL

Clinical Management of Renal Cell Carcinoma in 2020

First-Line Treatment Landscape for RCC



RCC=Renal cell carcinoma; Adapted from Rana McKay ASCO 2019

Prognostic Models for Metastatic RCC: MSKCC and IMDC*

Risk Group	Favorable	Intermediate	Poor
No. of risk factors			
MSKCC[1]	**0**	**1-2**	**3-5**
IMDC[2]	**0**	**1-2**	**3-6**
Distribution of risk groups (%)			
MSKCC[3]	**19%**	**59%**	**22%**
IMDC[4]	**19%**	**55%**	**26%**
Median OS (months)			
MSKCC[1]	**29.6**	**13.8**	**4.9**
IMDC[3]	**43.2**	**22.5**	**7.8**
2-yr OS rate (%)			
MSKCC[1]	**55%**	**31%**	**6%**
IMDC[2]	**75%**	**53%**	**7%**
Predicted 2-yr OS rate post 1L VEGF tx (%)[3]			
MSKCC	**70%**	**42%**	**9%**
IMDC	**70%**	**47%**	**12%**

*MSKCC: patients treated with IFN-alfa; IMDC: patients treated with VEGF-targeted agent

MSKCC Risk Factors:[1]

1. Interval from diagnosis to treatment of <1 year
2. Karnofsky PS <80%
3. Corrected serum calcium > the ULN
4. Serum hemoglobin < the LLN
5. Serum LDH >1.5 times the ULN

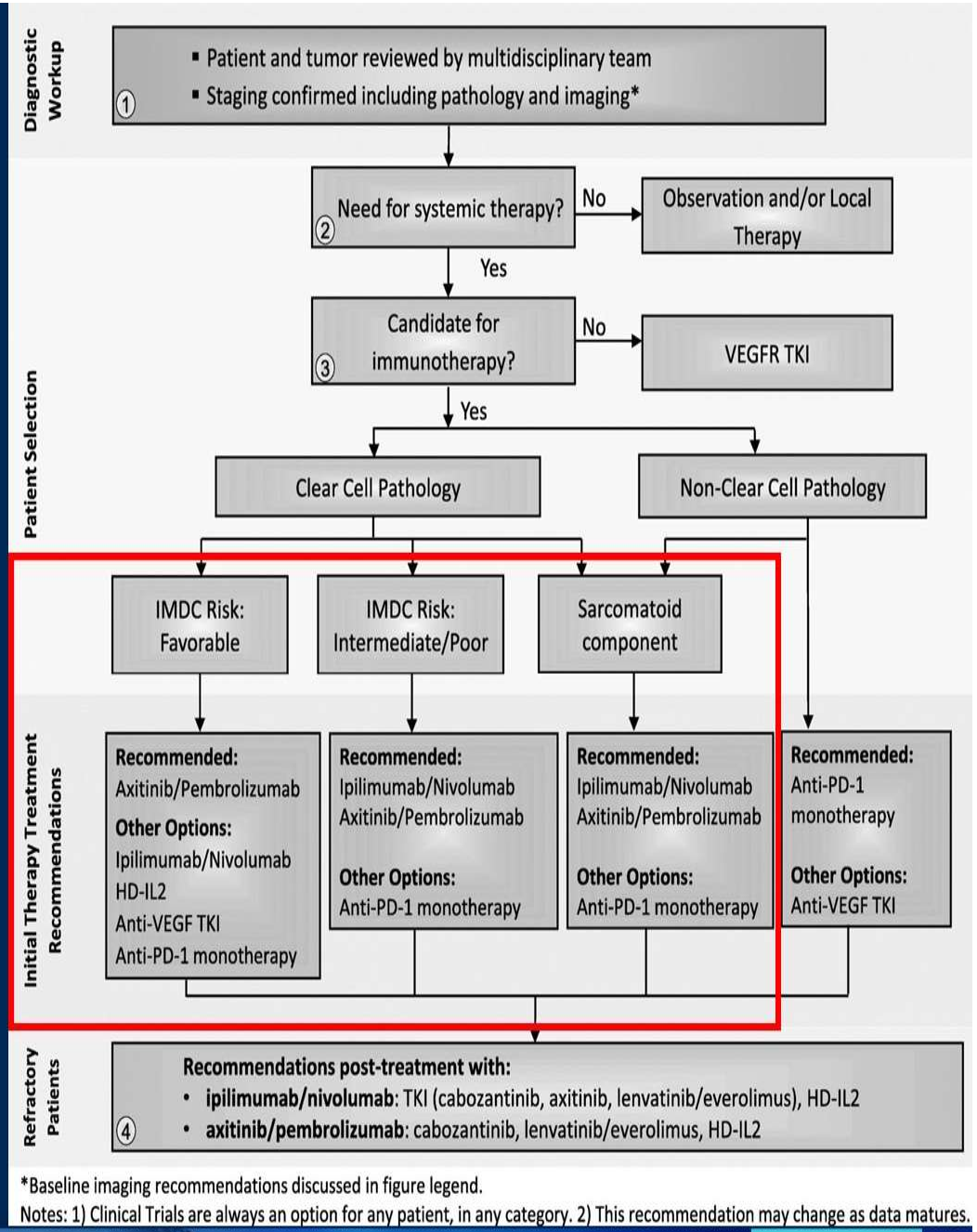
IMDC Risk Factors:[2]

1. Interval from diagnosis to treatment of <1 year
2. Karnofsky PS <80%
3. Corrected serum calcium > the ULN
4. Serum hemoglobin < the LLN
5. Absolute neutrophil count > than ULN
6. Platelets > the ULN

*MSKCC: patients treated with IFN-alfa; IMDC: patients treated with VEGF-targeted agent; LLN = lower limit of normal; ULN = upper limit of normal

1. Motzer RJ et al. J Clin Oncol. 2002;20:289-296; 2. Heng D et al. J Clin Oncol. 2009;27:5794-5799; 3. Heng D et al. Lancet Oncol. 2013;14:141-148;
4. Ko JJ et al. Br J Cancer. 2014;110:1917-1922.

SITC Guidelines Kidney Cancer



*Baseline imaging recommendations discussed in figure legend.

Notes: 1) Clinical Trials are always an option for any patient, in any category. 2) This recommendation may change as data matures.

Brian I. Rini et al. J Immunother Cancer 2019;7:354

First Line Therapies 2020

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Kidney Cancer

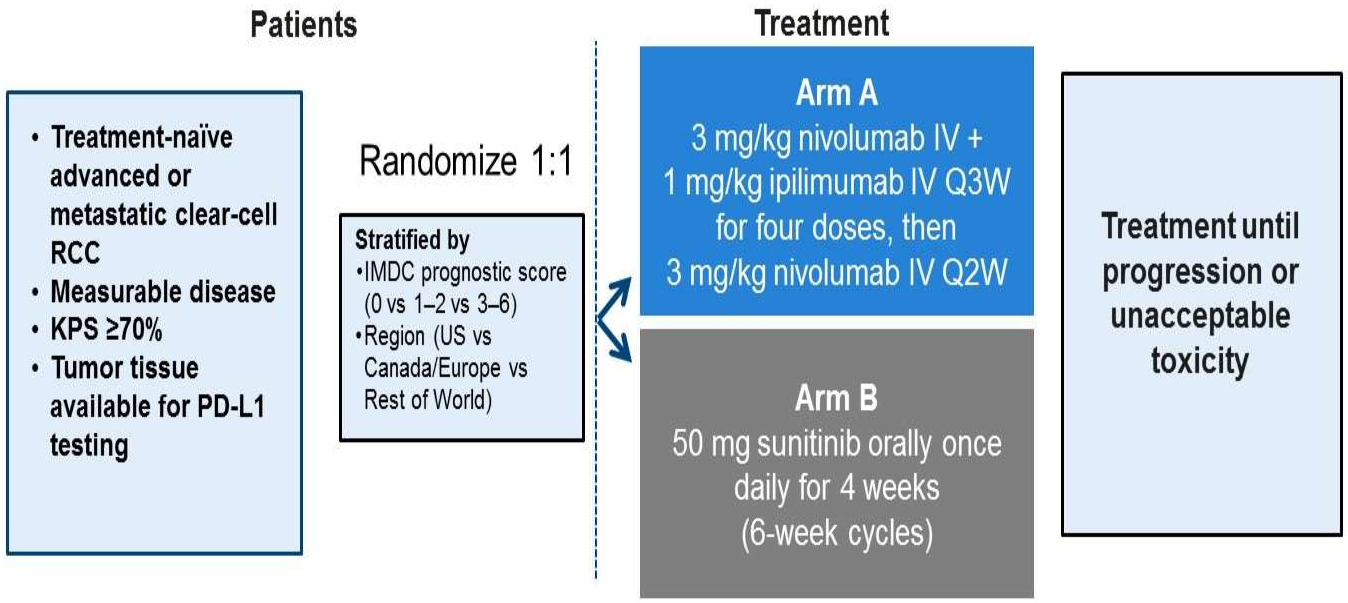
NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable[a]	• Axitinib + pembrolizumab • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab	• Active surveillance[b] • Axitinib (category 2B) • High-dose IL-2[c]
Poor/ intermediate[a]	• Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (category 2B) • High-dose IL-2[c] • Temsirolimus[d]

PD1/CTLA4
CheckMate 214: Study Design



Statistical analyses

Split alpha of 0.05:

0.001 for ORR, 0.009 for PFS, and 0.04 for OS

Primary Endpoints: In IMDC intermediate- and poor-risk patients

ORR (per independent radiology review committee, IRRC)

PFS (per IRRC)

OS

Escudier et al ESMO 2017

ORR Intermed/poor (Checkmate 214)

Outcome	N = 847	
	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	**42 (37–47)**	**27 (22–31)**
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	9[b]	1[b]
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine/not reported	8	12
Duration of response, median (95% CI), months	Not reached (21.8–NE)	18.2 (14.8–NE)
Patients with ongoing response, %	72	63

Escudier et al ESMO 2017

Statistical analyses

Split alpha of 0.05:

0.001 for ORR, 0.009 for PFS, and 0.04 for OS

Primary Endpoints: In IMDC intermediate- and poor-risk patients

ORR (per independent radiology review committee, IRRC)

PFS (per IRRC)

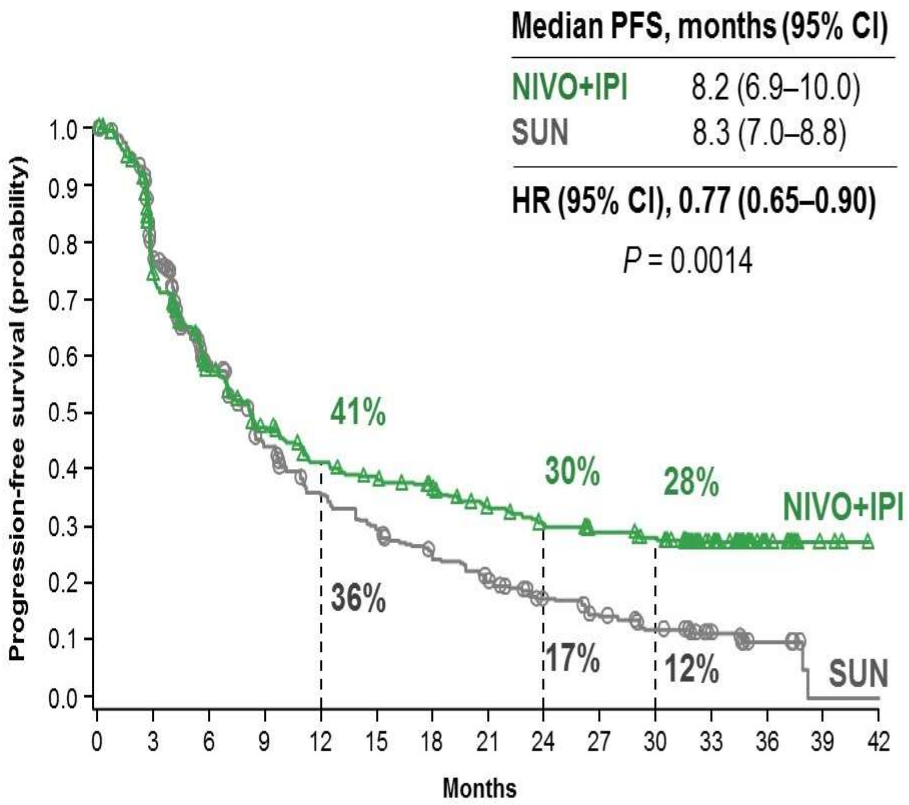
OS

Escudier et al ESMO 2017

PRESENTED AT: Genitourinary Cancers Symposium
Slides are the property of the author, permission required for reuse.
PRESENTED BY: #GU20

PFS (30 months follow up)

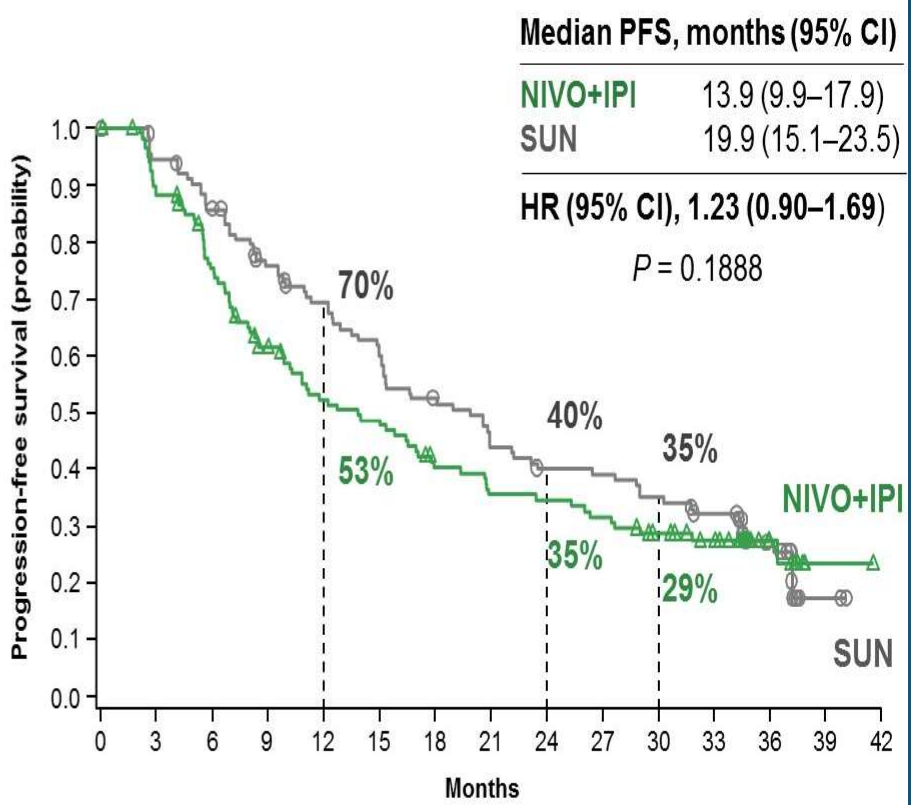
Intermediate/poor risk



No. at risk

NIVO+IPI	425	296	218	173	147	135	125	106	95	87	81	48	17	3	0
SUN	422	295	200	142	111	93	75	60	44	34	26	16	6	0	0

Favorable risk



No. at risk

NIVO+IPI	125	107	88	69	57	53	42	37	36	33	27	22	8	1	0
SUN	124	109	98	83	74	64	55	46	41	40	36	31	15	2	0

Tannir et al GU ASCO 2019

OS (30 months follow up)

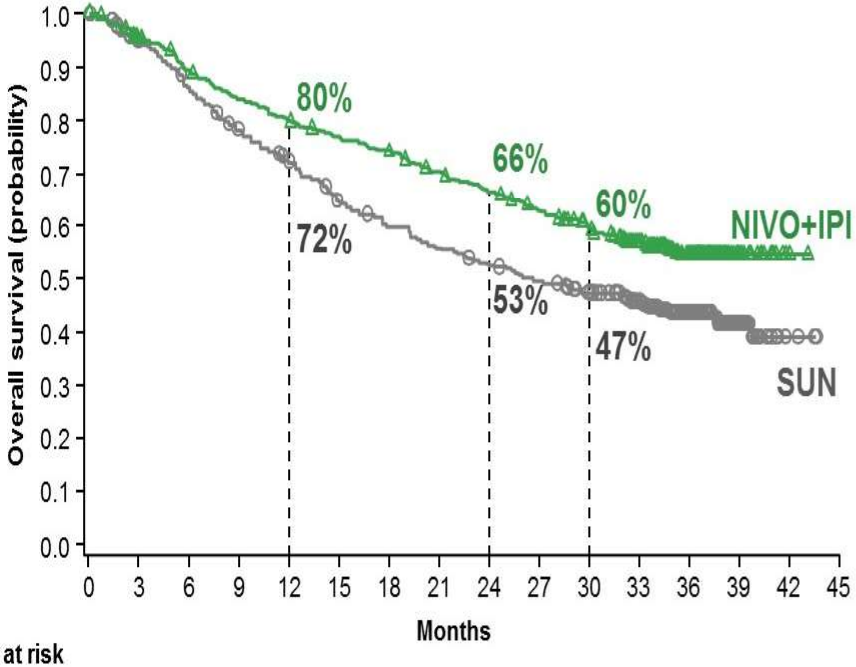
Intermediate/poor risk

Median OS, months (95% CI)

NIVO+IPI	NR (35.6–NE)
SUN	26.6 (22.1–33.4)

HR (95% CI), 0.66 (0.54–0.80)

P < 0.0001



No. at risk

NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

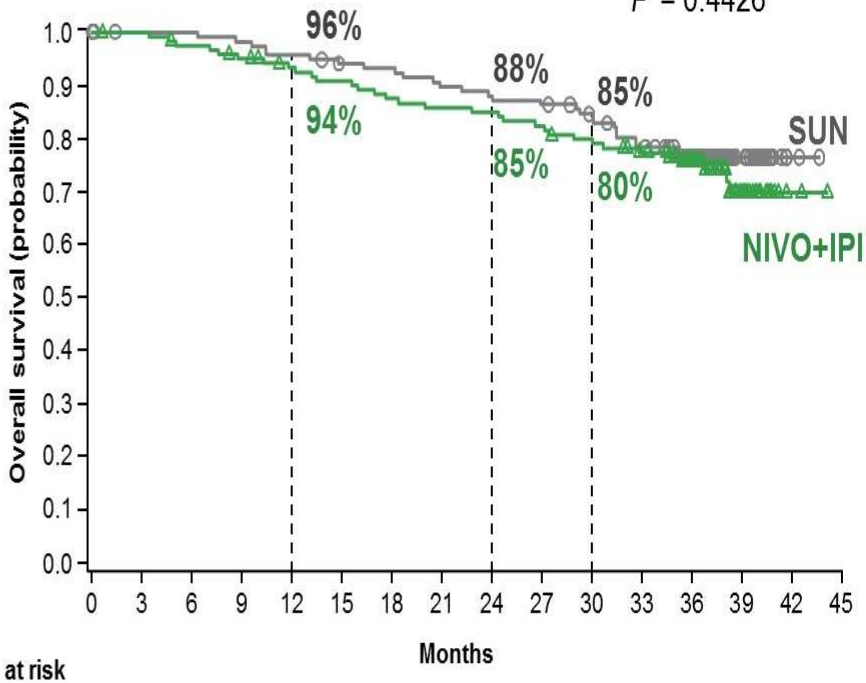
Favorable risk

Median OS, months (95% CI)

NIVO+IPI	NR (NE)
SUN	NR (NE)

HR (95% CI), 1.22 (0.73–2.04)

P = 0.4426

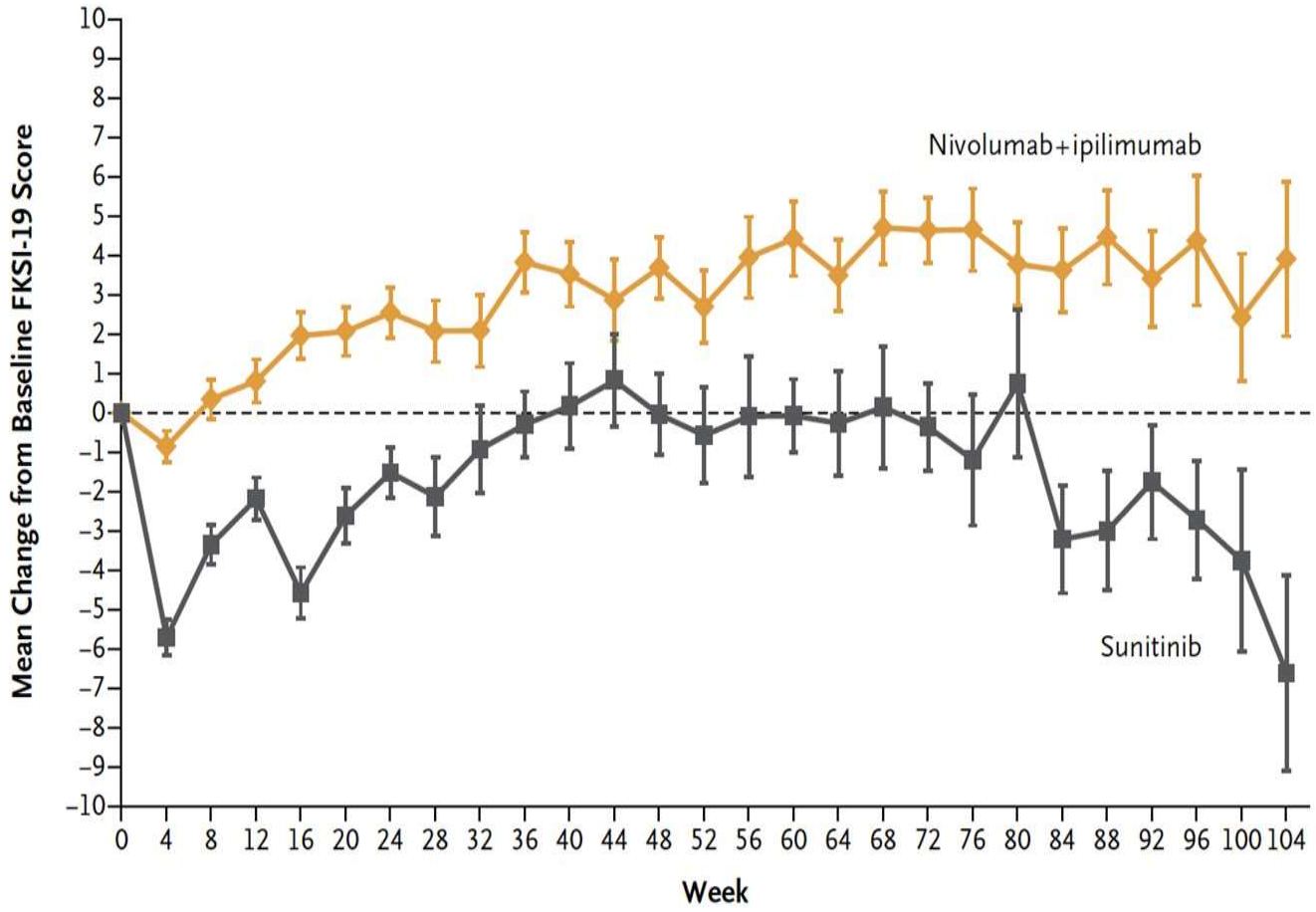


No. at risk

NIVO+IPI	125	124	120	116	111	108	104	102	101	98	94	88	71	24	2	0
SUN	124	119	119	117	114	110	109	105	103	101	96	88	70	26	2	0

Tannir et al GU ASCO 2019

QoL (Checkmate 214)

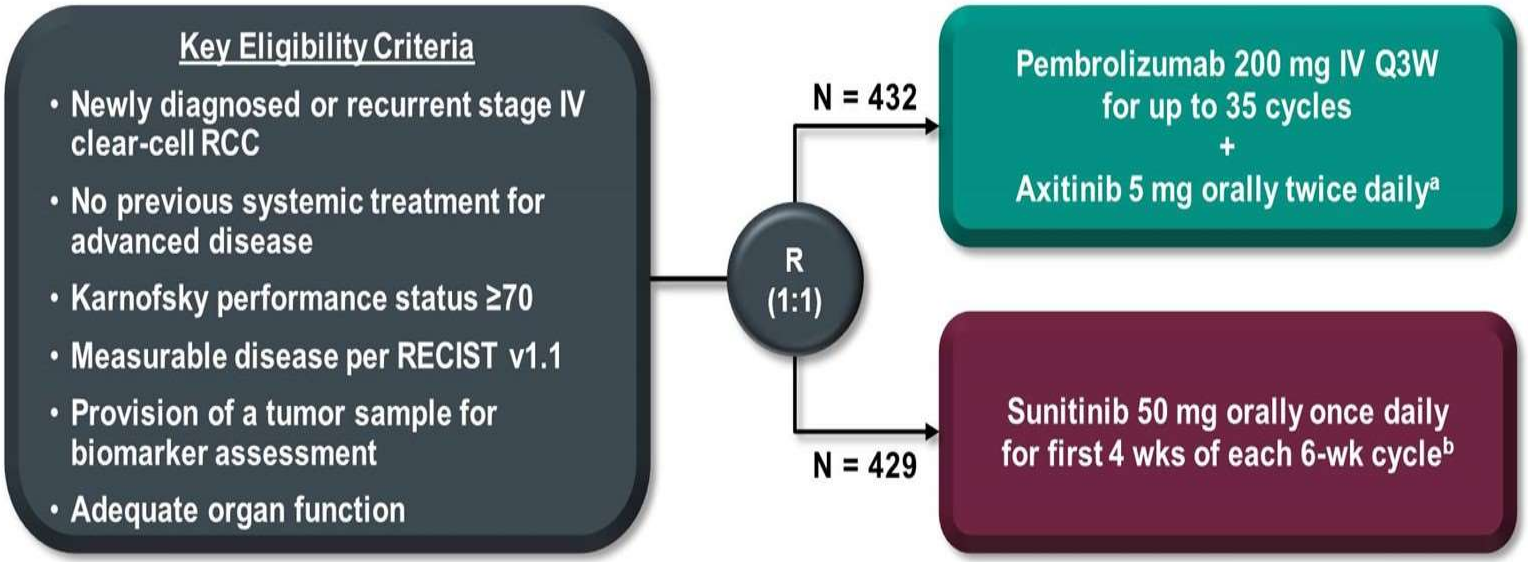


No. at Risk

Nivolumab+ipilimumab	425	347	281	239	212	180	166	152	143	139	125	108	76	44
Sunitinib	422	371	284	221	184	147	127	113	104	93	80	64	43	26

Escudier et al ESMO 2017

KEYNOTE-426 Study Design



Stratification Factors

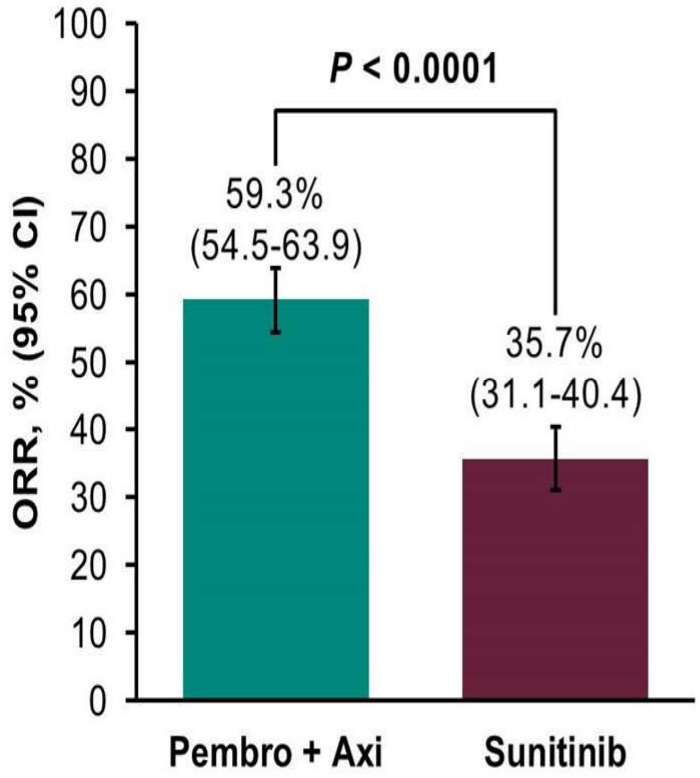
- IMDC risk group (favorable vs intermediate vs poor)
- Geographic region (North America vs Western Europe vs ROW)

End Points

- **Dual primary:** OS and PFS (RECIST v1.1, BICR) in ITT
- **Key secondary:** ORR (RECIST v1.1, BICR) in ITT
- **Other secondary:** DOR (RECIST v1.1), PROs, safety

[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.
[b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).

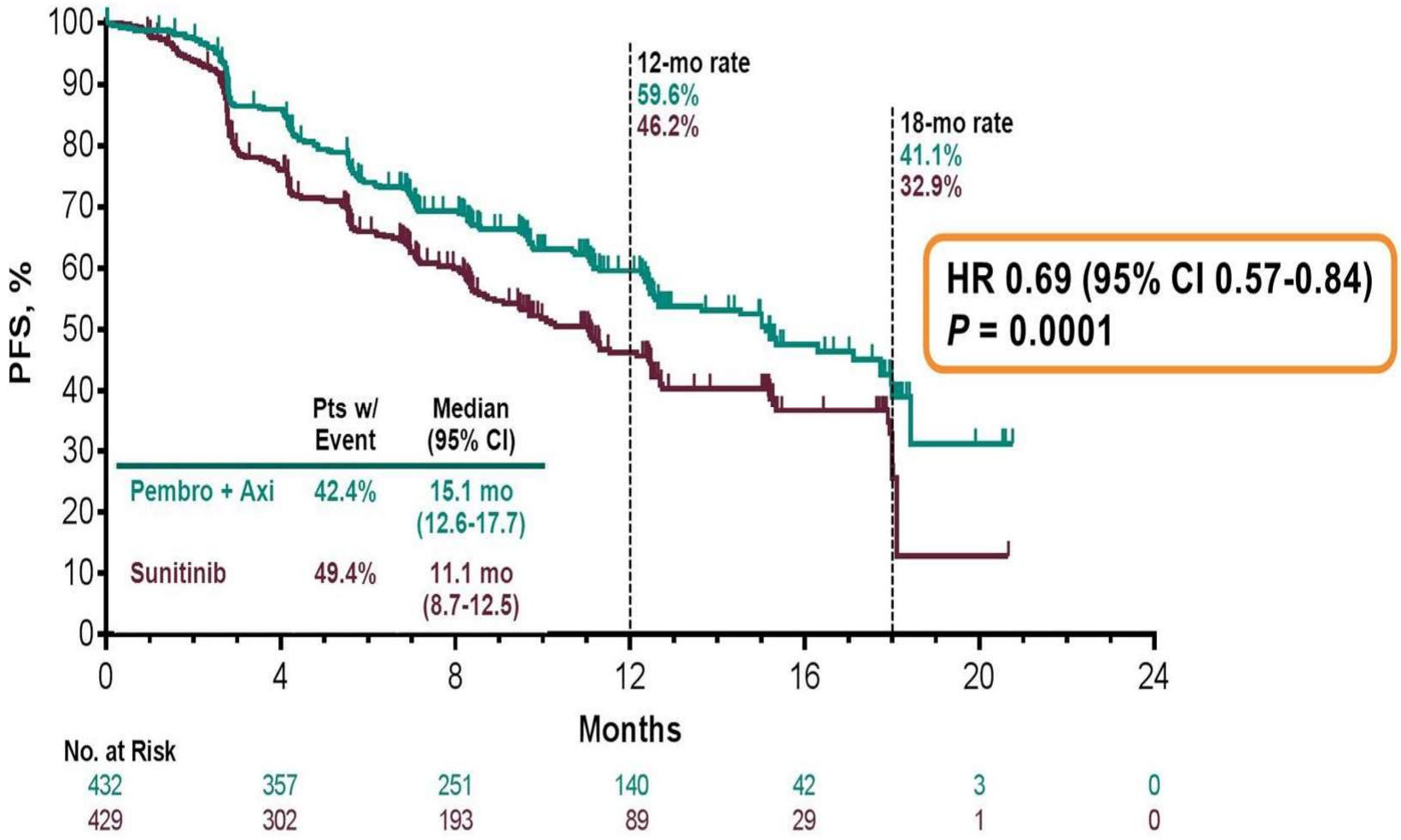
Confirmed Objective Response Rate



Best Response	Pembro + Axi N = 432	Sunitinib N = 429
CR	25 (5.8%)	8 (1.9%)
PR	231 (53.5%)	145 (33.8%)
SD	106 (24.5%)	169 (39.4%)
PD	47 (10.9%)	73 (17.0%)
NE[a]	8 (1.9%)	6 (1.4%)
NA[b]	15 (3.5%)	28 (6.5%)
Response Duration	**N = 256**	**N = 153**
Median (range), mo	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

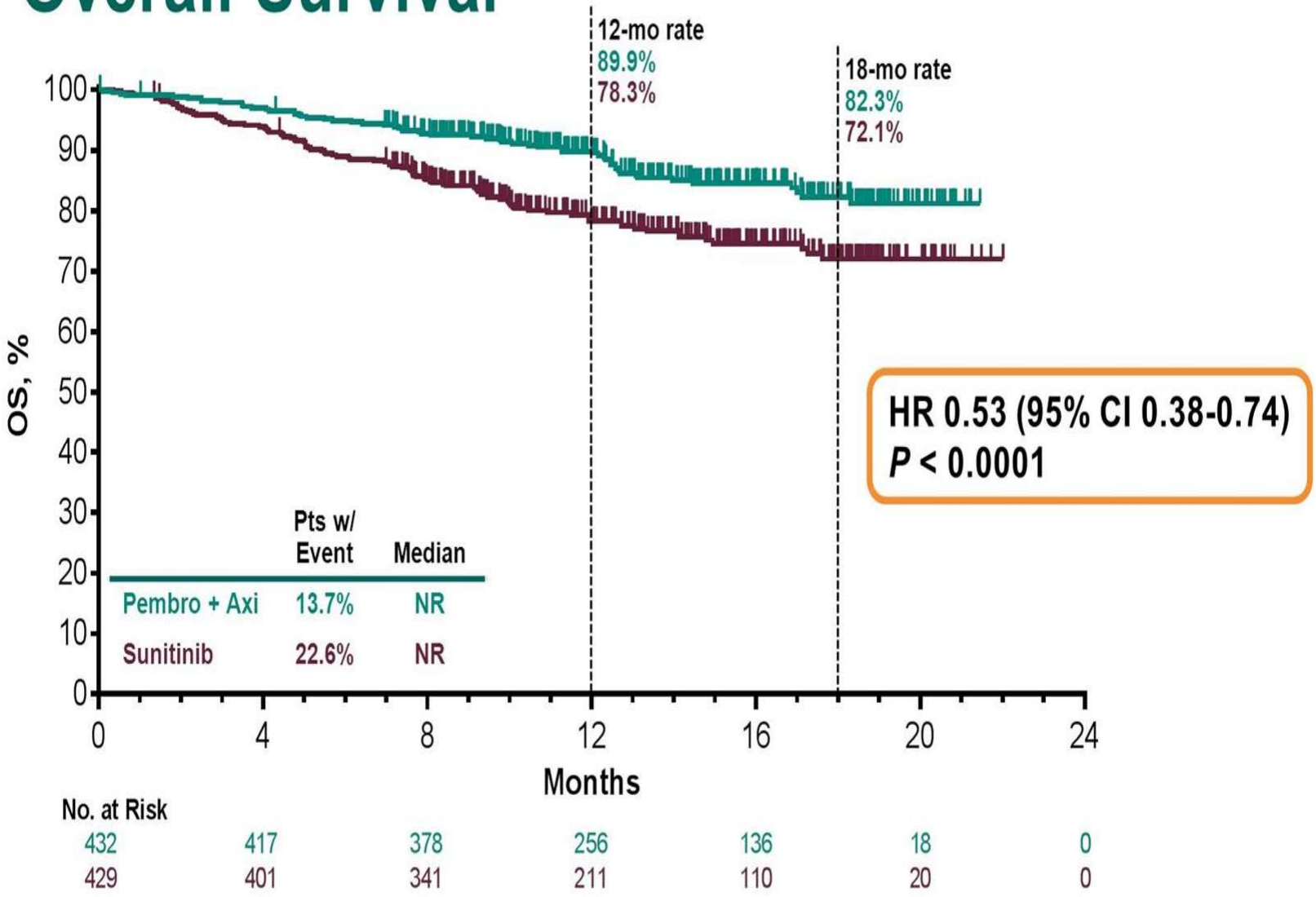
[a]Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR. [b]Patients who did not have ≥1 post-baseline imaging assessment.
Data cutoff date: Aug 24, 2018.

Progression-Free Survival



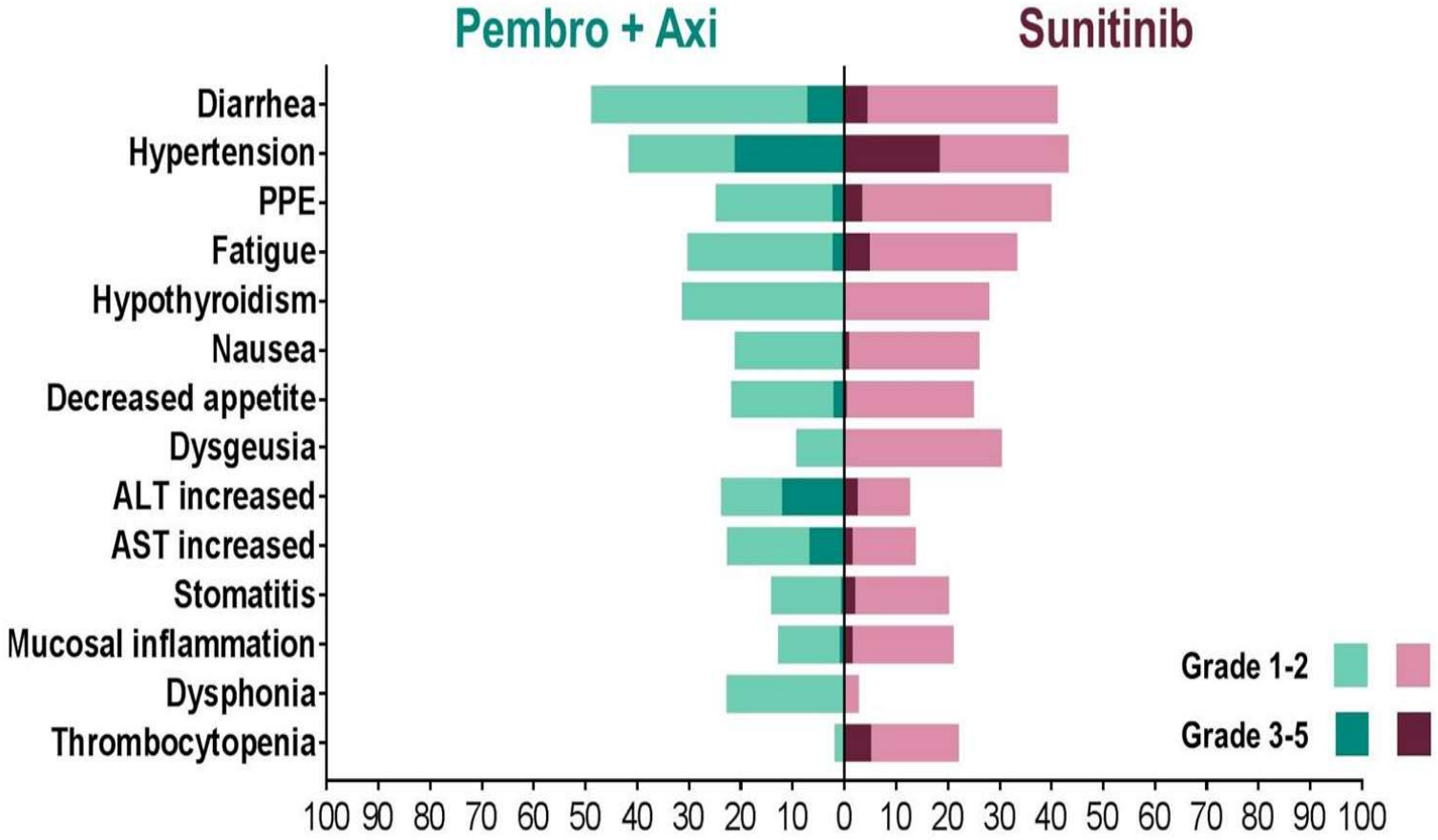
Data cutoff date: Aug 24, 2018.

Overall Survival



Data cutoff date: Aug 24, 2018.

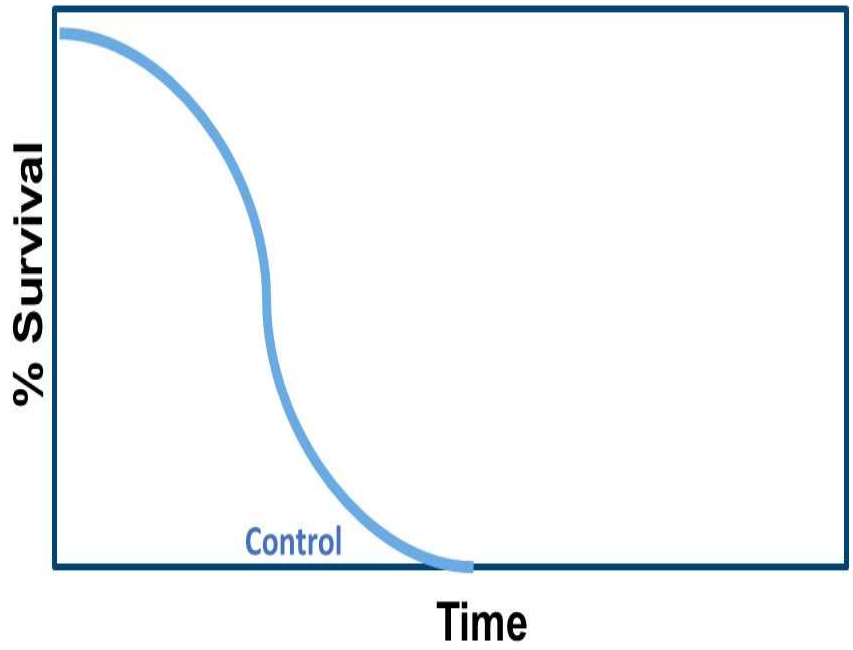
Treatment-Related Adverse Events: Incidence ≥20%



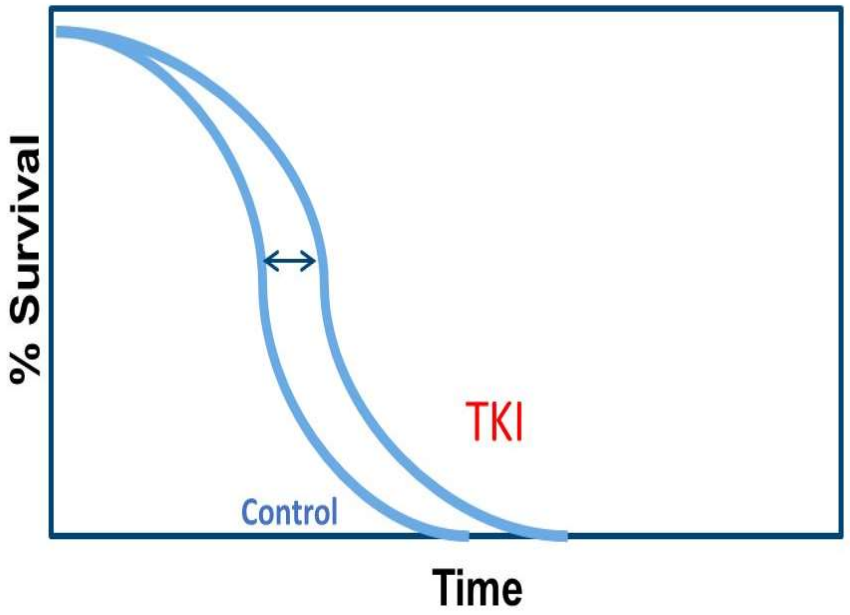
Events are shown in order of decreasing incidence in the total population.
PPE, palmar-plantar erythrodysesthesia.
Data cutoff date: Aug 24, 2018.

IO/IO vs IO/TKI

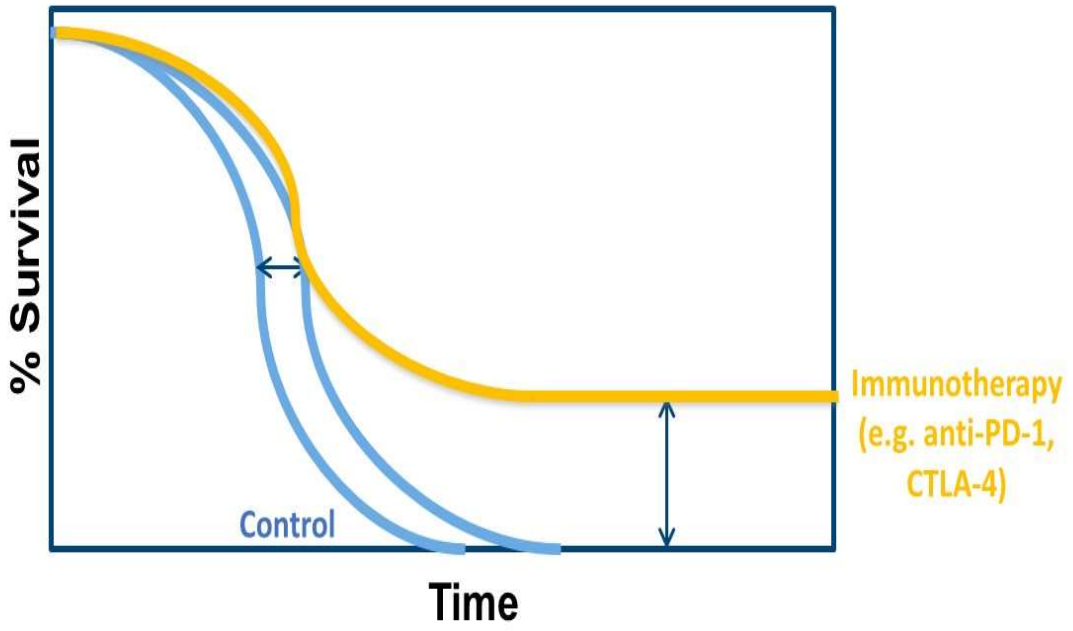
Improving Survival With Immunotherapy



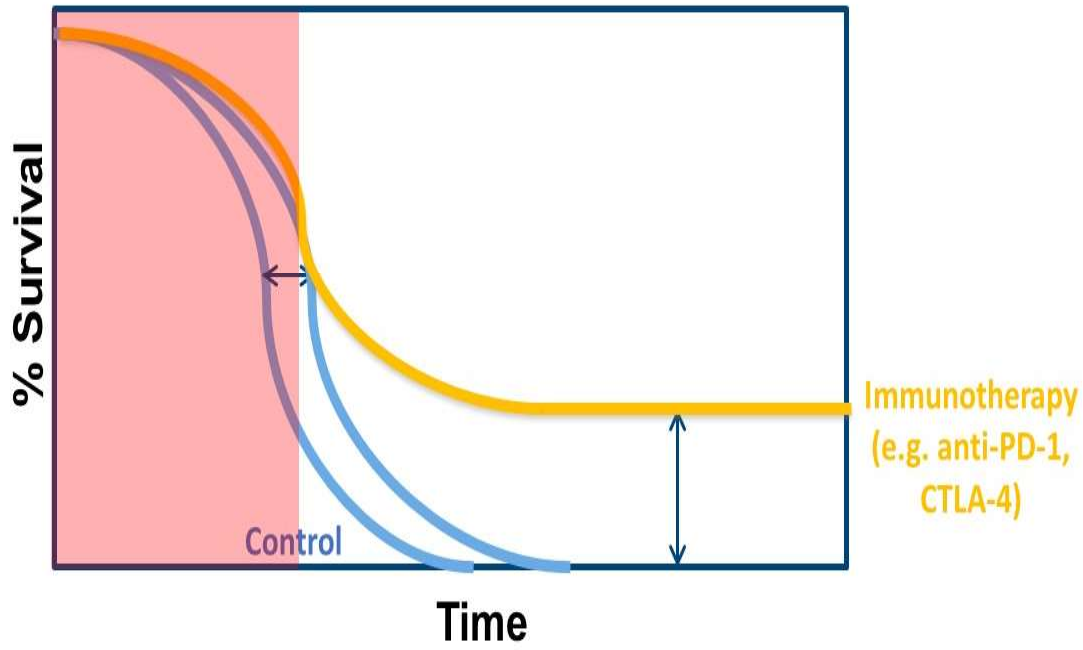
Improving Survival With Immunotherapy



Improving Survival With Immunotherapy

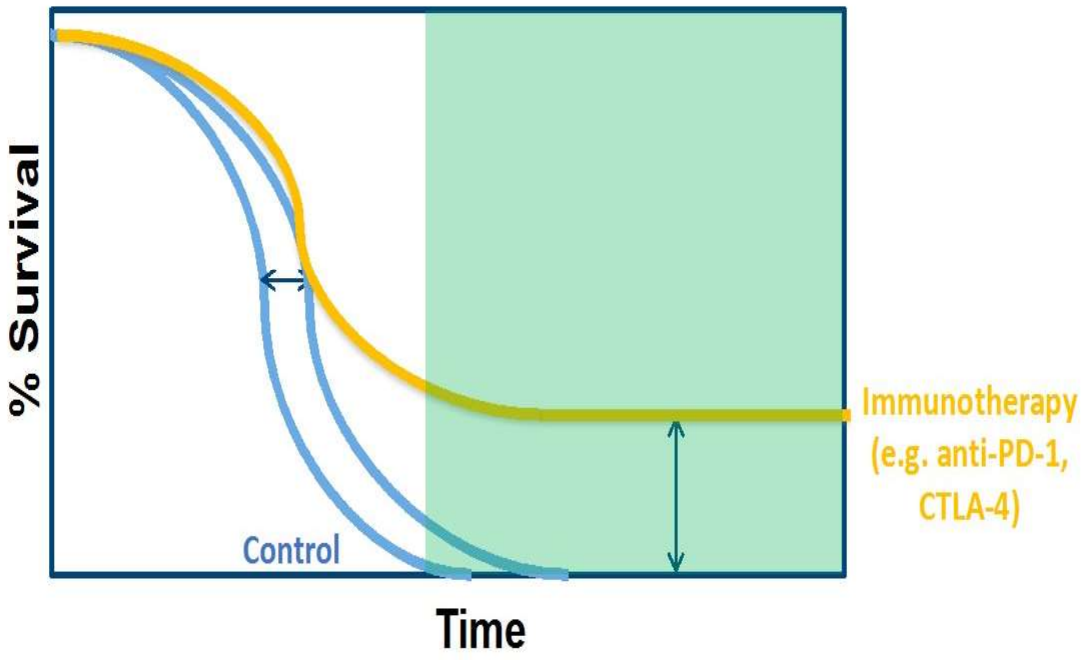


Improving Survival With Immunotherapy



Early Treatment Goal

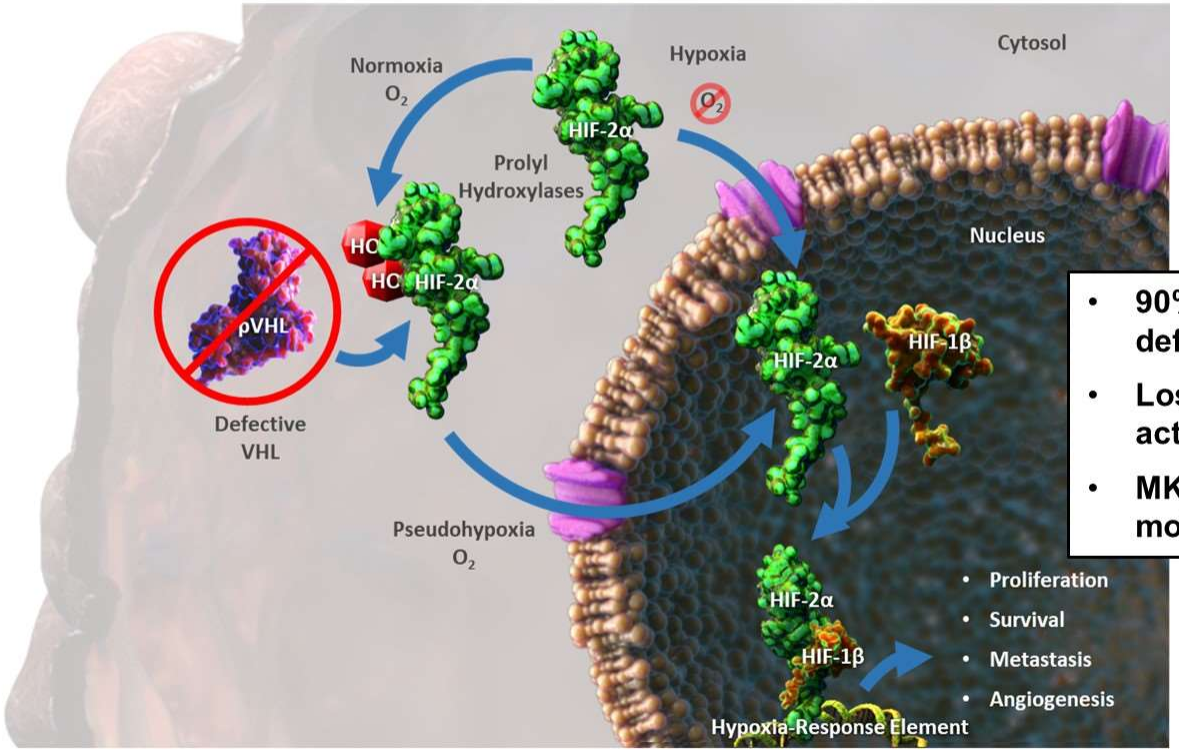
Improving Survival With Immunotherapy



Early Treatment Goal

Long Term Outcome

pVHL Deficiency Results in HIF-2α Activation



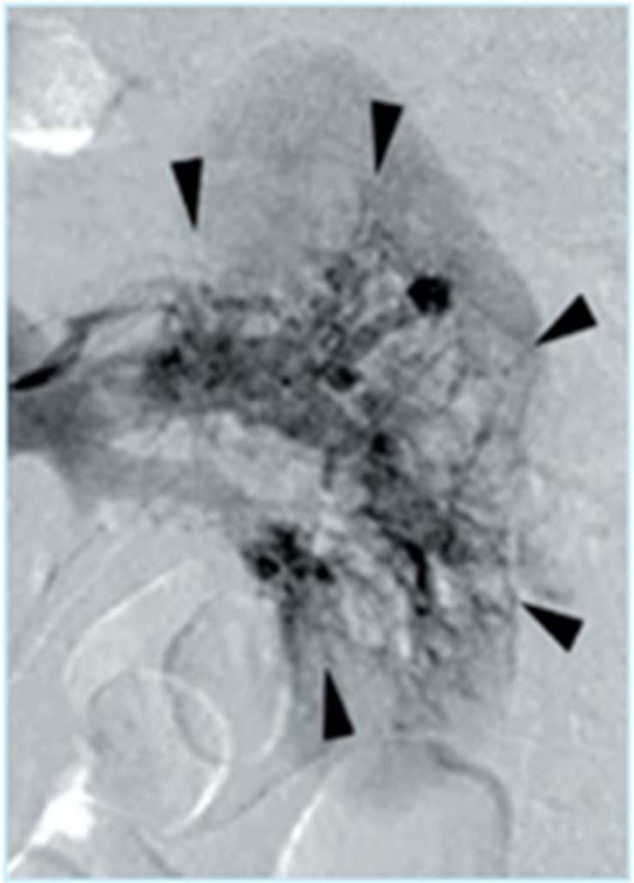
The Nobel Prize in Physiology or Medicine 2019

- 90% of patients with sporadic ccRCC have defective pVHL[1,2]
- Loss of pVHL function results in constitutive activation of HIF-2α[2]
- MK-6482 is a potent, selective, small molecule HIF-2α inhibitor

HIF-2α, hypoxia-inducible factor 2α; pVHL, protein product of the Von Hippel-Lindau tumor suppressor gene; VHL, Von Hippel-Lindau tumor suppressor.

1. Shen C, Kaelin WG Jr. *Semin Cancer Biol*. 2013;23:18-25. 2. Sato Y et al. *Nat Genet*. 2013;45:860-867.

Increased VEGF and Angiogenesis in RCC

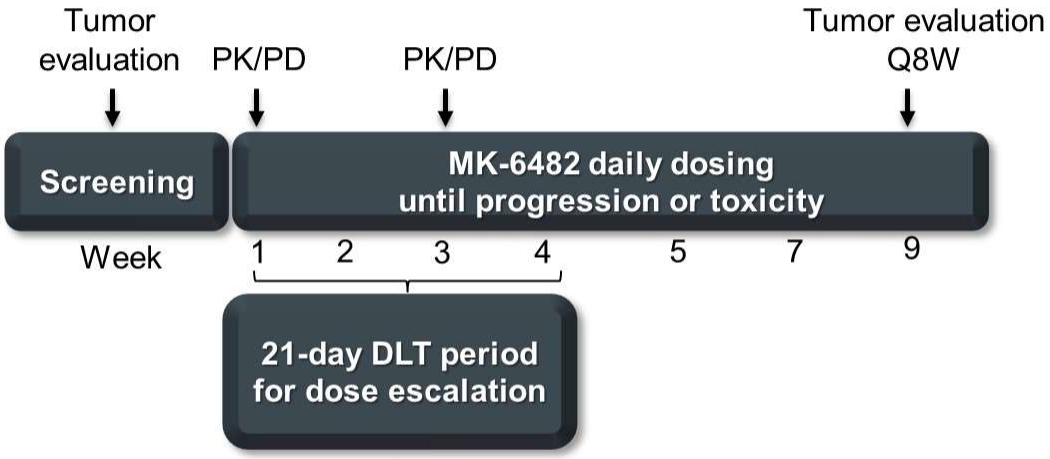


RCC is a highly vascularized tumor[1,2]

VEGF expression has been shown to be higher in RCC tumors compared to normal kidney tissue due to the persistent presence of HIF[2]

1. Hutson TE et al. ASCO Annual Meeting Education Session. 2010; Izawa JI et al. CMAJ. 2001;164:662.

Study Design (NCT02974738)



- Dose-escalation cohort for patients with advanced solid tumors
- Dose-expansion cohort for patients with advanced ccRCC who previously received ≥1 therapy
  - Key end points: Safety, ORR, duration of response, PFS

- Dose of 120 mg QD selected for further clinical development from the dose-escalation cohort
- **55 patients with previously treated advanced ccRCC enrolled at 120 mg PO QD in the dose-expansion cohort**
  - 39 (71%) discontinued
    - Most common reason was disease progression: 55%
  - 16 (29%) have treatment ongoing
- Median (95%CI) follow-up:
  - 13.0 (11.0-13.8) months

Data cutoff: May 15, 2019.

Baseline Clinical Characteristics

Characteristics	All Patients N = 55	IMDC Risk Category		
		Favorable n = 5	Intermediate n = 40	Poor n = 10
Age, median (range), years	62 (39-75)	61 (50-71)	62 (39-75)	59 (41-75)
Sex, n (%)				
Female	11 (20)	3 (60)	7 (18)	1 (10)
Male	44 (80)	2 (40)	33 (82)	9 (90)
Prior systemic therapies, median (range), n	3 (1-9)	3 (1-5)	3 (1-6)	3 (2-9)
Prior systemic therapies, n (%)				
1	9 (16)	1 (20)	8 (20)	0 (0)
2	12 (22)	1 (20)	9 (23)	2 (20)
≥3	34 (62)	3 (60)	23 (58)	8 (80)
Prior anticancer therapies, n (%)				
VEGF/VEGFR	51 (93)	5 (100)	36 (90)	10 (100)
Immune checkpoint inhibitor	40 (73)	3 (60)	29 (73)	8 (80)
Investigational/other	15 (27)	2 (40)	10 (25)	3 (30)
mTOR inhibitor	12 (22)	1 (20)	8 (20)	3 (30)
Cytokine	7 (13)	0 (0)	4 (10)	3 (30)

- 37 patients (67%) received anti–PD-1 and anti–VEGF agents

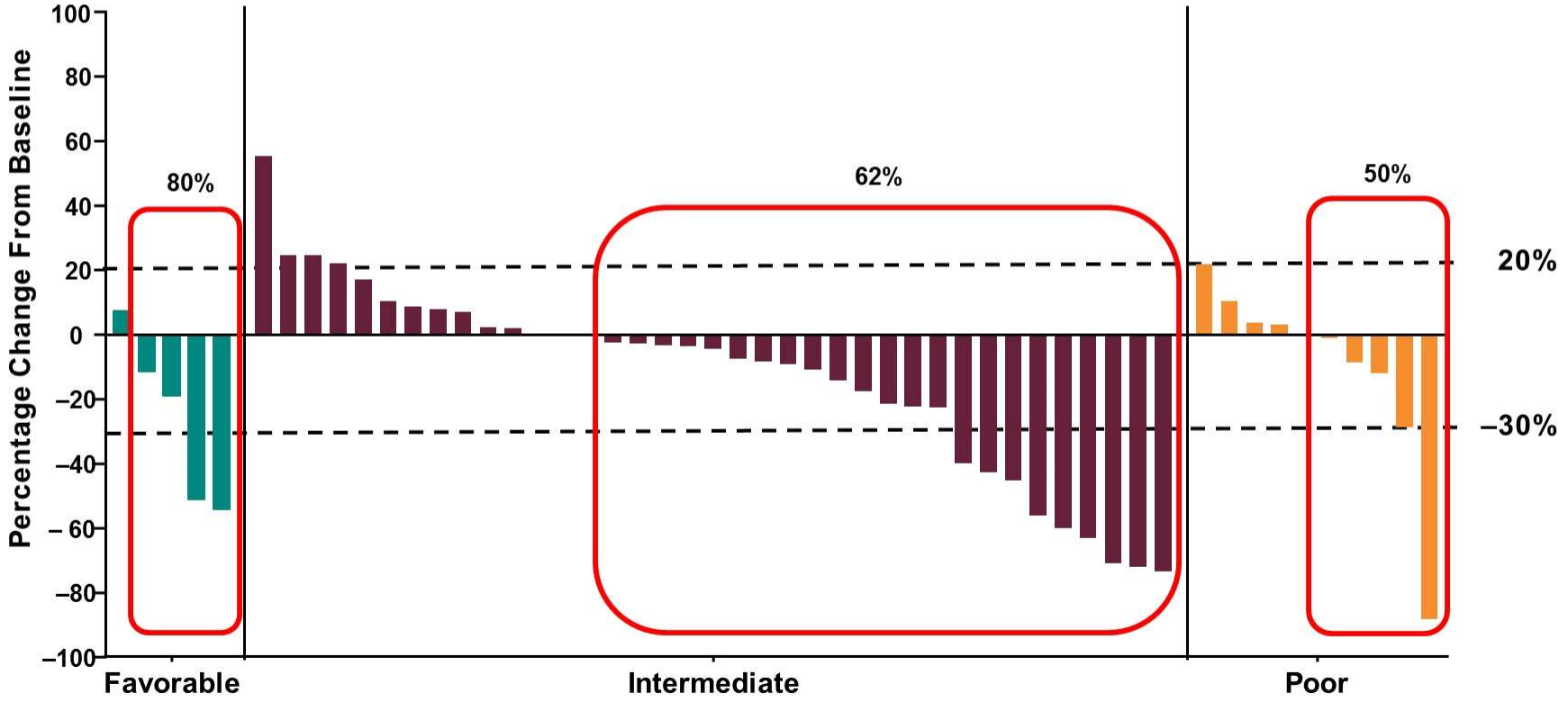
Data cutoff: May 15, 2019.

Best Confirmed Objective Response by RECIST v1.1 per Investigator Assessment

Efficacy Parameter, n (%) [95%CI]	All Patients N = 55	IMDC Risk Category		
		Favorable n = 5	Intermediate n = 40	Poor n = 10
ORR	13 (24) [13-37]	2 (40)	10 (25)	1 (10)
PR	13 (24)	2 (40)	10 (25)	1 (10)
SD	31 (56)	3 (60)	22 (55)	6 (60)
Disease control rate (CR + PR + SD)	44 (80)	5 (100)	32 (80)	7 (70)
PD	9 (16)	0 (0)	7 (18)	2 (20)
Nonevaluable	2 (4)	0 (0)	1 (2)	1 (10)

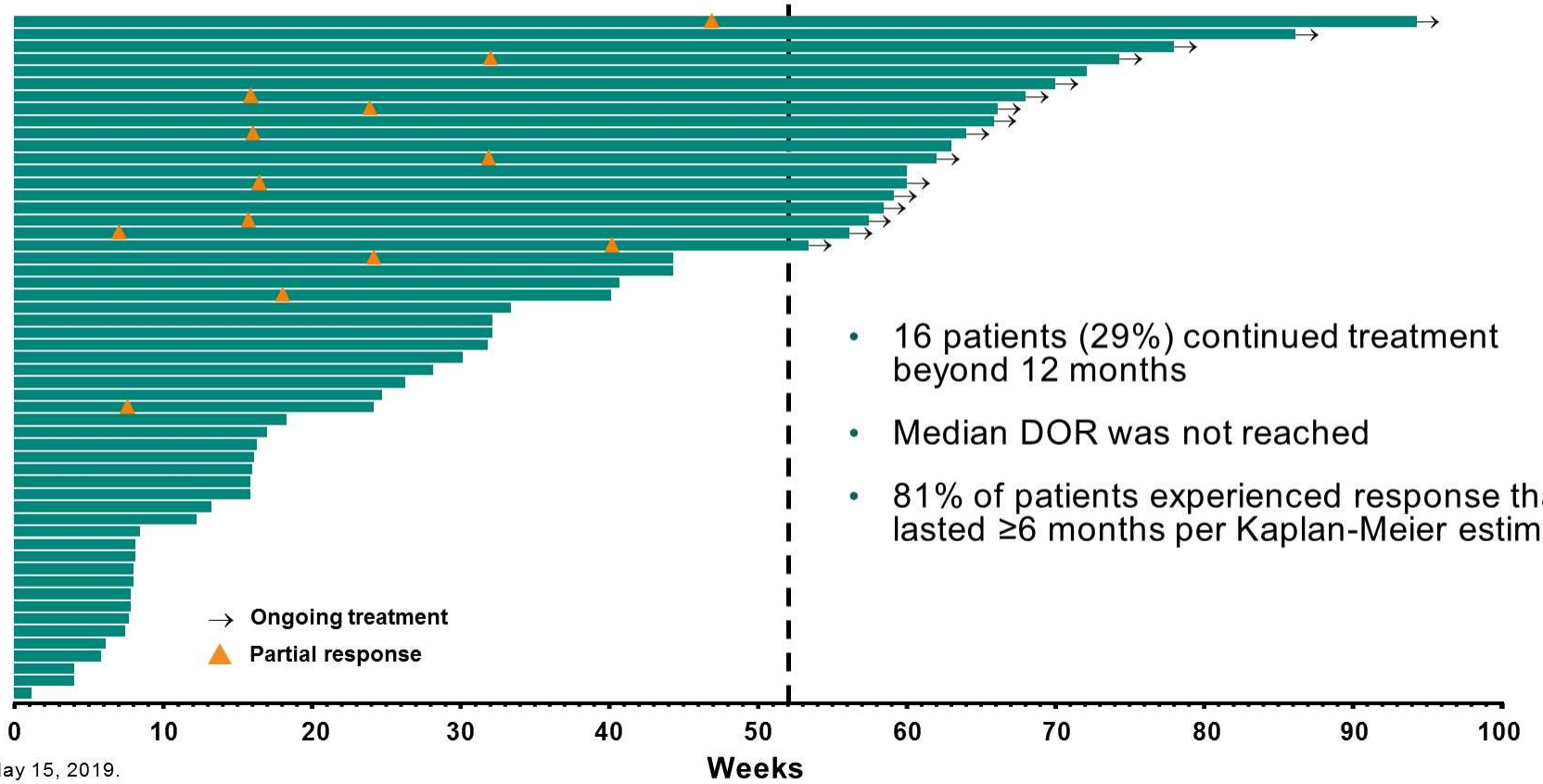
Data cutoff: May 15, 2019.

Maximum Change From Baseline in Target Lesions: By IMDC Risk Category[a]



[a]Includes patients who had a baseline and a postbaseline assessment (n = 52).
Data cutoff: May 15, 2019.

Duration of Treatment: All Patients



- 16 patients (29%) continued treatment beyond 12 months
- Median DOR was not reached
- 81% of patients experienced response that lasted ≥6 months per Kaplan-Meier estimate

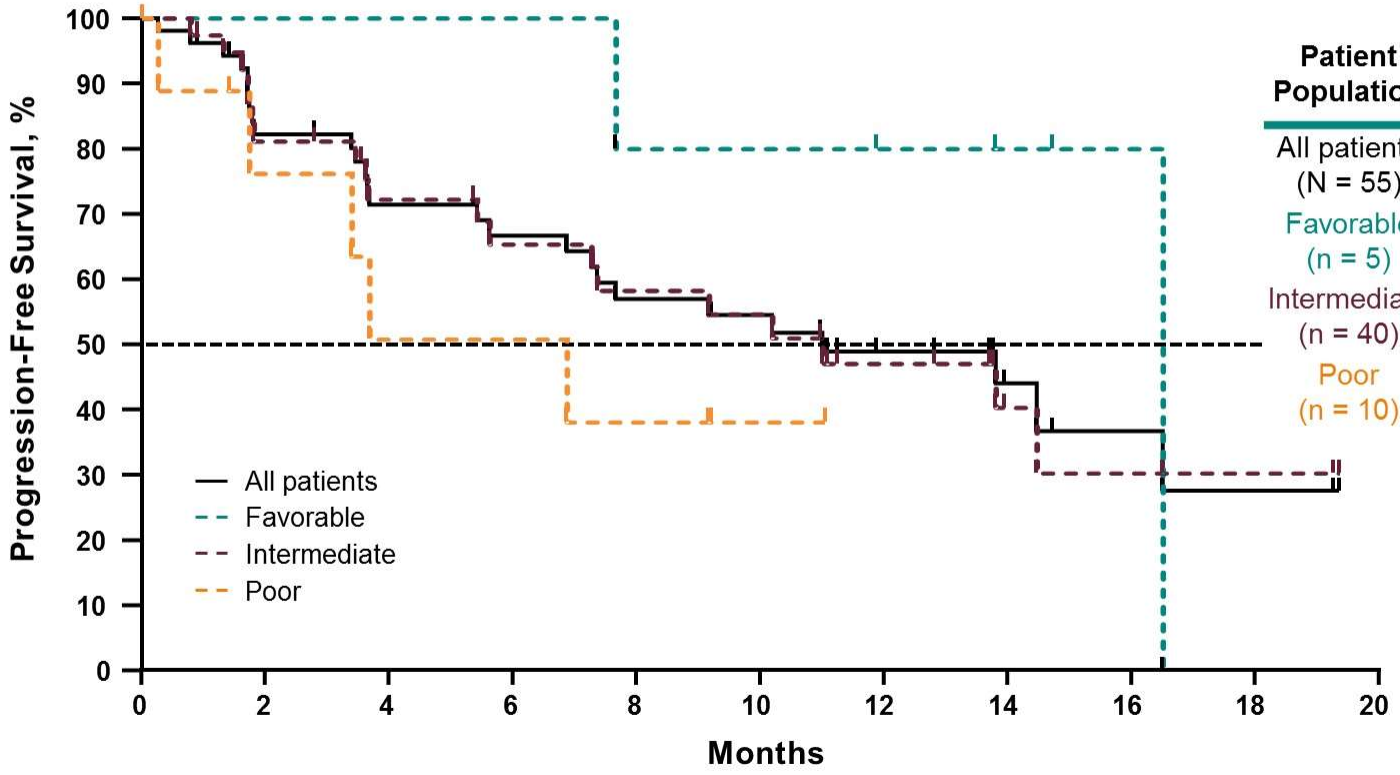
Data cutoff: May 15, 2019.

All-Cause Adverse Events ≥20%

AE, n (%)	MK-6482 N = 55				
	Grade 1/2	Grade 3	Grade 4	Grade 5	All Grades
Anemia	27 (49)	14 (26)	0 (0)	0 (0)	41 (75)
Fatigue	34 (62)	3 (6)	—	—	37 (67)
Dyspnea	23 (42)	3 (6)	—	—	26 (47)
Nausea	17 (31)	1 (2)	—	—	18 (33)
Cough	17 (31)	0 (0)	—	—	17 (31)
Edema peripheral	16 (29)	0 (0)	—	—	16 (29)
Vomiting	16 (29)	0 (0)	—	—	16 (29)
Headache	13 (24)	1 (2)	—	—	14 (26)
Hypoxia	6 (11)	8 (15)	—	—	14 (26)
Arthralgia	13 (24)	0 (0)	—	—	13 (24)
Dizziness	13 (24)	0 (0)	—	—	13 (24)
Blood creatinine increased	11 (20)	1 (2)	—	—	12 (22)
Diarrhea	12 (22)	0 (0)	—	—	12 (22)
Constipation	11 (20)	0 (0)	—	—	11 (20)
Hyperkalemia	10 (18)	1 (2)	—	—	11 (20)

Data cutoff: May 15, 2019.

Progression-Free Survival[a]



Patient Population	Median PFS, months	12-Month PFS Rate, %
All patients (N = 55)	11.0	49
Favorable (n = 5)	16.5	80
Intermediate (n = 40)	11.0	47
Poor (n = 10)	6.9	Not reached

[a]Per Kaplan-Meier estimates.
Data cutoff: May 15, 2019.

Conclusions

- MK-6482 is well tolerated and has a favorable safety profile
  - Anemia and hypoxia are on-target toxicities
- After a median follow-up of 13.0 months, promising clinical activity was observed in patients with heavily pretreated advanced ccRCC
  - 62% of patients received ≥3 prior lines of therapy
  - ORR, 24% (95%CI: 13%-37%)
  - Median DOR not yet reached; 81% had a response ≥6 months
  - Median PFS (95%CI) was 11 months (6-17); 12-month PFS rate was 49%
  - Clinical activity was observed across IMDC risk categories
- A MK-6482 monotherapy phase 3 trial is ongoing in previously treated patients with advanced ccRCC (NCT04195750)

Clinical Management of Urothelial Bladder Cancer in 2020

Commonly Raised Questions in Treating Patients with Metastatic Bladder and Upper Tract Urothelial Cancers

-- Is there a preferred neoadjuvant regimen for patients with muscle-invasive bladder cancer?

-- Is there a preferred checkpoint inhibitor for patients on or following platinum based chemotherapy?

-- Should re discontinue checkpoint inhibitors in patients with metastatic bladder cancers who have a complete response to Rx?

-- Following progression on platinum-based chemotherapy and checkpoint inhibitors, what therapeutic options are available?

Neoadjuvant Chemotherapy Regimens (NAC)

The most popular (NAC) regimens, Cisplatinum-Gemcitabine and dd-MVAC have never

- been directly compared in a neoadjuvant clinical trial
- Retrospective studies suggest that ddMVAC is superior to Cis-Gemcitabine
- Zargar et al: Of 319 patient treated with NAC followed by radical cystectomy, those who received dd-MVAC had a higher pathologic response rates (pTNO and T1N0) and OS compared with Cis-Gem
- Peyton CC et al: In a cross-sectional analysis of 1,113 post-cystectomy patients, those receiving ddMVAC had a higher likelihood of tumor downstaging and pC (41.3%) than those receiving Cis-Gem (24.5%)
- Early data suggest that replacing NAC with check point inhibitors (atezolizumab and pembrolizumab) appear promising

Sargar H et al: J Urol 199; 1452-1458,2018
Peyton CC et al: JAMA Onc 4:1535-1542,2018

Should checkpoint inhibitors (CPI'S) be discontinued in patients with metastatic bladder cancer who achieve a CR ?

-- CPI trials in urothelial cancers have included a small percentage of patients who achieved durable CR's

-- Most trials limit duration lf treatment to 2 years but in practice most patients continue treatment until disease progression or intolerable toxicity

--Data from melanoma trials suggest that durable CR's can be obtained after CPI discontinuation (KEYNOTE-001)

-- in KEYNOTE-006, 86% of patients who completed 2 years of pembrolizumab were progression free at 20 months

-- A retrospective analysis examined long-term outcomes in various solid tumors (including bladder cancer) after discontinuation or PD-1 or PD-L1 Approximately 67% of patients with cancer other than melanoma

I

Is there a preferred checkpoint inhibitor for patients with metastatic bladder cancer who progress on or after platinum-based chemotherapy?

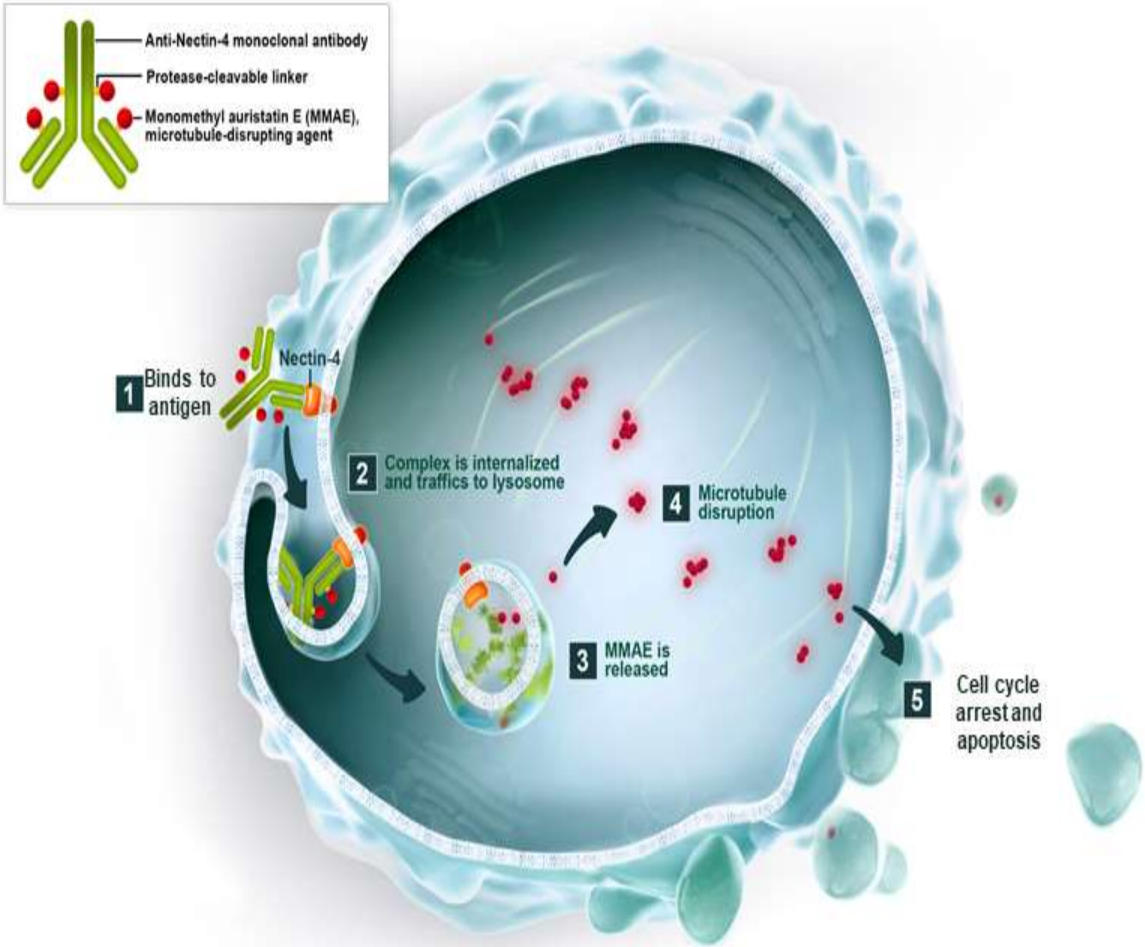
US-FDA-approved immune checkpoint inhibitors in metastatic UC

Drug	Relevant study	Target immune checkpoint protein	No. of final enrolled patients	Dosage	Design	ORR (%)	CR (%)	Median OS (mo)	Grade 3–4 TRAEs (%)
Second-line treatment (in platinum-refractory cases)									
Atezolizumab (Tecentriq)	IMvigor210, cohort 2 [20]	PD-L1	310	1,200 mg, 3 weeks	Phase II	14.5	5.0	7.9	16.0
Pembrolizumab (Keytruda)	KEYNOTE-045 [25]	PD-1	521	200 mg, 3 weeks	Phase III	21.1	6.0	10.3	15.0
Nivolumab (Opdivo)	CheckMate-275 [26]	PD-1	265	3 mg/kg, 2 weeks	Phase II	19.6	2.3	8.7	18.0
Durvalumab (Imfinzi)	NCT01693562 [27]	PD-L1	191	10 mg/kg, 2 weeks	Phase I/II	17.8	3.7	18.2	6.8
Avelumab (Bavencio)	NCT01772004 [28]	PD-L1	249	10 mg/kg, 2 weeks	Phase Ib	17.0	6.0	6.5	8.0
First-line treatment (in cisplatin-ineligible patients)									
Atezolizumab (Tecentriq)	IMvigor210, cohort 1 [29]	PD-L1	119	1,200 mg, 3 weeks	Phase II	23.0	9.2	15.9	16.0
Pembrolizumab (Keytruda)	KEYNOTE-052 [30]	PD-1	370	200 mg, 3 weeks	Phase II	24.0	5.0	-	15.0

US-FDA, United States Food and Drug Administration; UC, urothelial carcinoma; ORR, objective response rate; CR, complete response rate; OS, overall survival; TRAE, treatment-related adverse event; PD-L1, programmed cell death-ligand-1; PD-1, programmed cell death 1 receptor.

Following progression of platinum based chemotherapy and check point inhibitors , what therapeutic options are available

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 Pharma Inc.

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

Advanced and Metastatic Urothelial Carcinoma Has a High Unmet Need

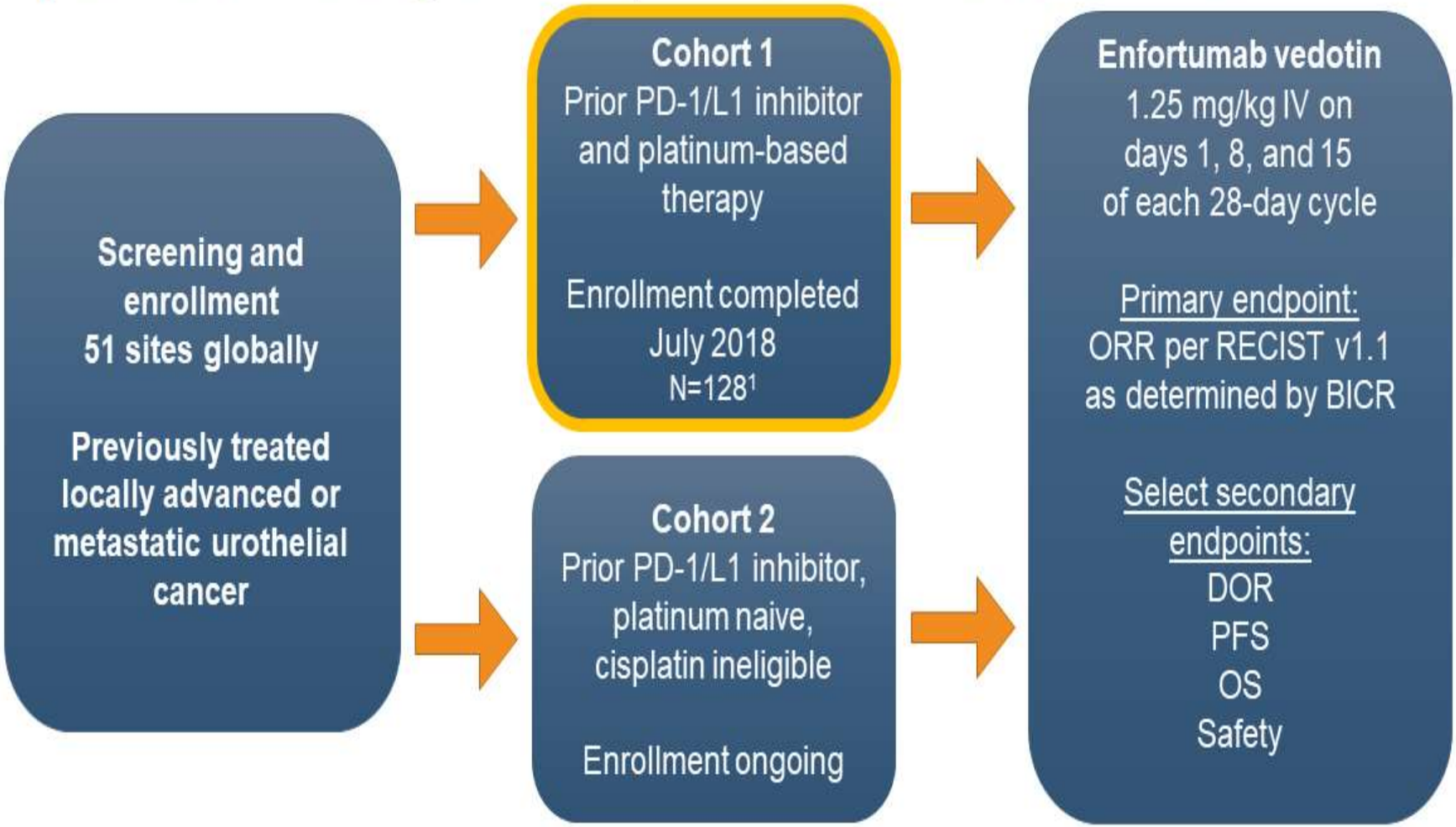
- For most patients, first-line therapy remains platinum-based combination chemotherapy
- Response rates to second-line PD-1/L1 inhibitors range from 13%-21% with few options once patients progress[1,2]
- Single agent chemotherapy shows limited activity post-platinum and post-PD-1/L1 inhibitors (ORR ~11%)[3]
- In a phase 1 study, enfortumab vedotin, an antibody-drug conjugate, showed an ORR of 45% in patients with prior PD-1/L1 inhibitors[4]
  - Based on the phase 1 data, the FDA granted enfortumab vedotin breakthrough designation

[1] Bellmunt J, et al. N Engl J Med. 2017;376:1015-26; [2] Powles T, et al. Lancet. 2018;391:748-57; [3] Petrylak DP et al. Lancet. 2017;390:2266-77; [4] Rosenberg JE, et al. J Clin Oncol. 2019;37:377.

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

SeattleGenetics | Astellas

EV-201: Single-Arm, Pivotal Phase 2 Trial



[1] 3 patients did not receive enfortumab vedotin treatment: one each due to clinical deterioration, patient decision, and low hemoglobin after enrollment

BICR=blinded independent central review; DOR=duration of response; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

EV-201: Cohort 1 Key Eligibility Criteria

- Histologically documented urothelial carcinoma, including squamous differentiation or mixed cell types
- Metastatic disease or locally advanced that is not resectable
- Progression during or following most recent treatment
- Previously treated with platinum-based chemotherapy and a PD-1/L1 inhibitor
- Measurable disease by RECIST v1.1
- ECOG PS ≤1
- No uncontrolled diabetes mellitus[1]
- No ongoing sensory or motor neuropathy ≥Grade 2
- No active CNS metastases

[1]Hemoglobin A1C (HbA1c) ≥8% or HbA1c of 7% to <8% with associated diabetes symptoms, polyuria or polydipsia, that were not otherwise explained

CNS= Central Nervous System; ECOG PS= Eastern Cooperative Oncology Group Performance Status; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

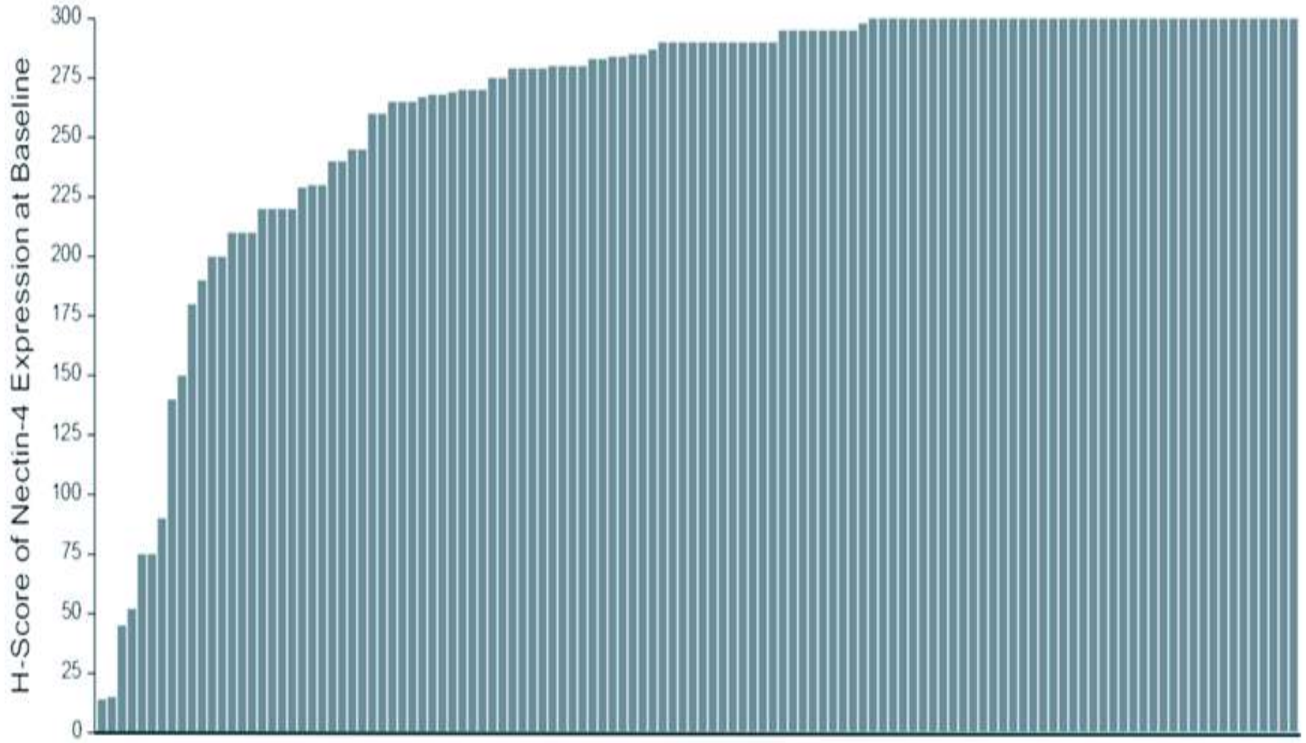
EV-201: Cohort 1 Demographics and Disease Characteristics

	Patients (N=125)
Age, years	
Median (min, max)	69 (40, 84)
≥75 years, n (%)	34 (27)
Male sex, n (%)	88 (70)
Primary tumor location, n (%)	
Bladder/other	81 (65)
Upper tract	44 (35)
ECOG PS of 1, n (%)	85 (68)
≥2 Bellmunt adverse prognostic factors	52 (42)
Metastasis sites, n (%)	
Lymph nodes only	13 (10)
Visceral disease	112 (90)
Liver	50 (40)
PD-L1 status by combined positive score[2]	
<10	78/120 (65)
≥10	42/120 (35)
Number of prior systemic therapies[1], median (range)	3 (1, 6)

[1] Patients with 1 prior therapy had platinum and a PD-1/L1 inhibitor in combination; [2] Five patients were not evaluable for PD-L1

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

EV-201: Cohort 1 Nectin-4 Expression



Cohort 1 (n=120)[1]

Nectin-4 expression was detected in all patients tested

Median H-score 290 (range: 14–300)

[1] Five patients did not have adequate tissue for Nectin-4 testing

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

EV-201: Cohort 1 Objective Response Rate with Enfortumab Vedotin

ORR per RECIST v 1.1 assessed by BICR	Patients (N=125) n (%)
Confirmed objective response rate	**55 (44)**
95% confidence interval[1]	(35.1, 53.2)
Best overall response per RECIST (v. 1.1)	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable[2]	12 (10)

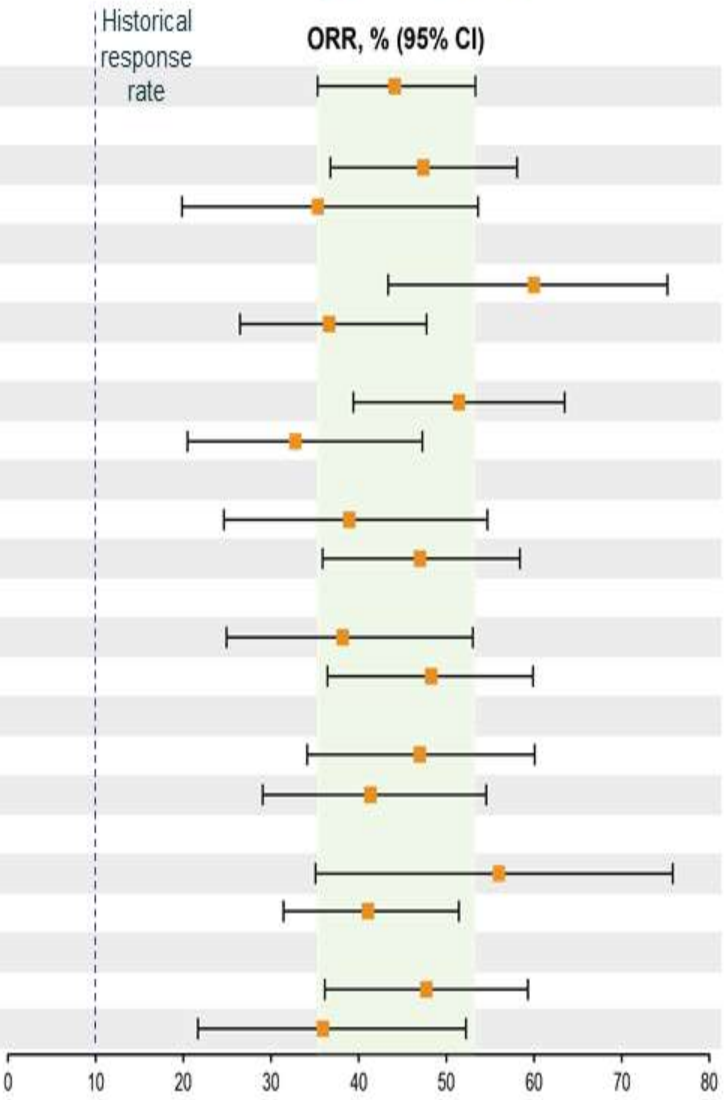
[1] Computed using the Clopper-Pearson method

[2] Includes 10 patients who discontinued study prior to post-baseline response assessment, 1 patient who had uninterpretable post-baseline assessment, and 1 patient whose post-baseline assessment did not meet the minimum interval requirement for stable disease

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

EV-201: Cohort 1 Responses by Subgroup per BICR

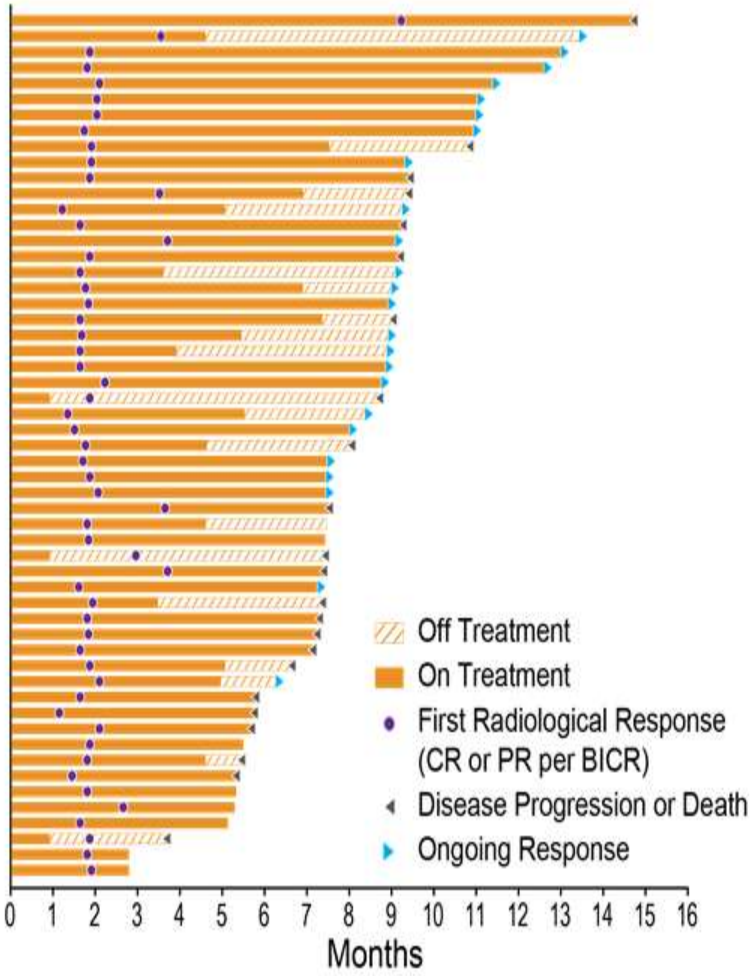
Subgroup	n/N	% (95% CI)
Overall	55/125	44 (35.1, 53.2)
Age		
<75	43/91	47 (36.7, 58.0)
≥75	12/34	35 (19.7, 53.5)
ECOG performance status, n (%)		
Grade 0	24/40	60 (43.3, 75.1)
Grade 1	31/85	36 (26.3, 47.6)
Bellmunt risk score[1]		
0–1	37/72	51 (39.3, 63.3)
≥2	17/52	33 (20.3, 47.1)
Primary tumor sites		
Upper tract	17/44	39 (24.4, 54.5)
Bladder/Other	38/81	47 (35.7, 58.3)
Liver metastasis		
Yes	19/50	38 (24.7, 52.8)
No	36/75	48 (36.3, 59.8)
Number of prior therapies in metastatic UC setting		
1–2	29/62	47 (34.0, 59.9)
≥3	26/63	41 (29.0, 54.4)
Best response to prior PD-1/L1[2]		
Responder	14/25	56 (34.9, 75.6)
Non-responder	41/100	41 (31.3, 51.3)
PD-L1 expression[3]		
CPS <10	37/78	47 (36.0, 59.1)
CPS ≥10	15/42	36 (21.6, 52.0)



[1] Bellmunt risk score was not available for 1 patient; [2] Anti-PD-1 or anti-PD-L1 therapy; [3] Five patients were not evaluable for PD-L1 expression levels.

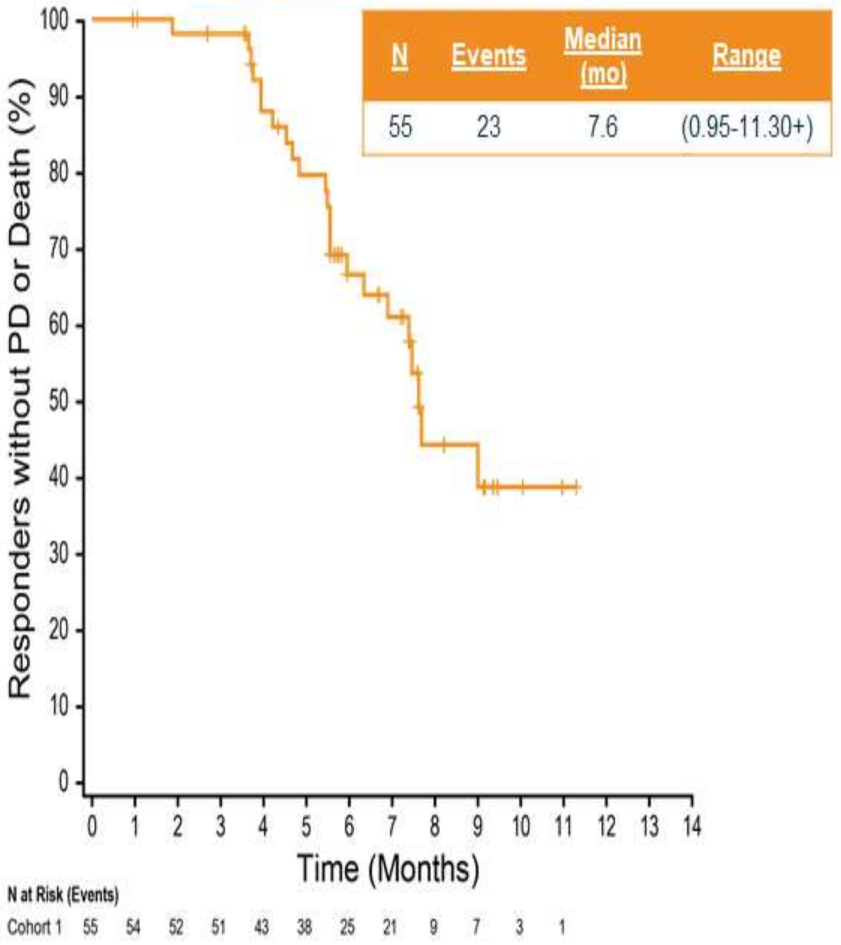
Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

EV-201: Cohort 1 Duration of Response with Enfortumab Vedotin



Median time to response: 1.8 mo (range: 1.2–9.2)
Most responses identified at first assessment

Duration of Response

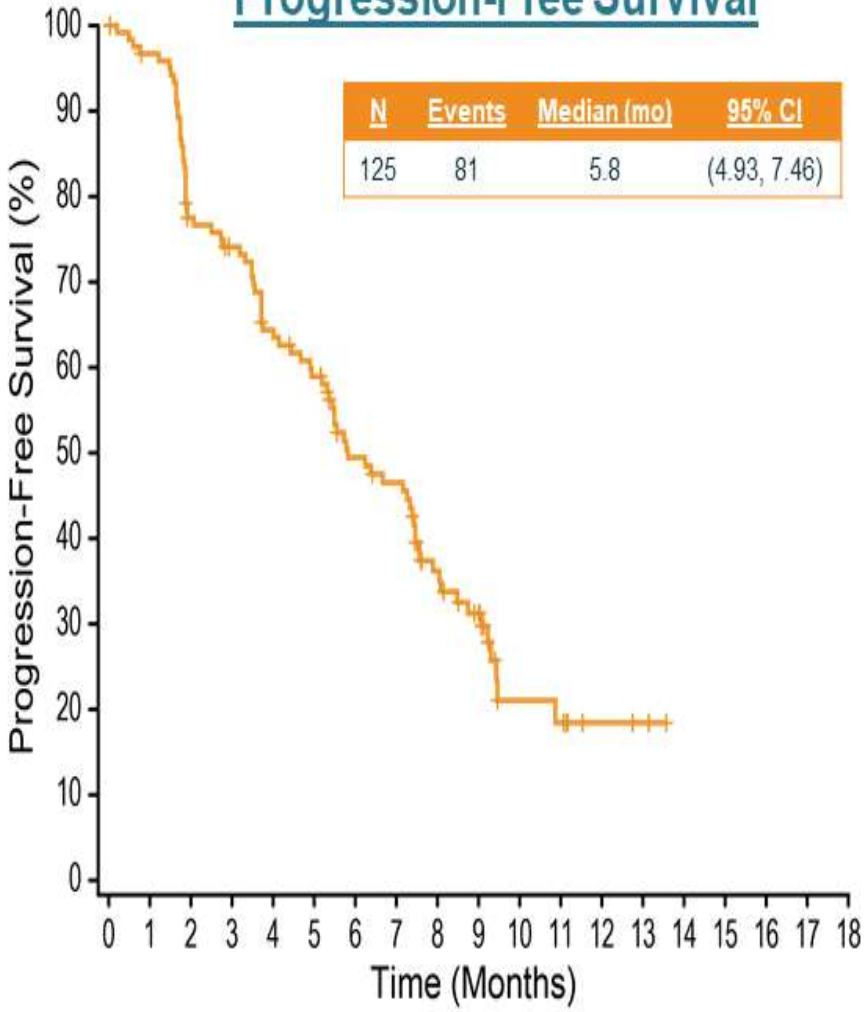


Median duration of response: 7.6 mo (range: 0.95–11.30+)
44% of responders still being followed

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

EV-201: Cohort 1 Kaplan-Meier Estimates of Survival

Progression-Free Survival



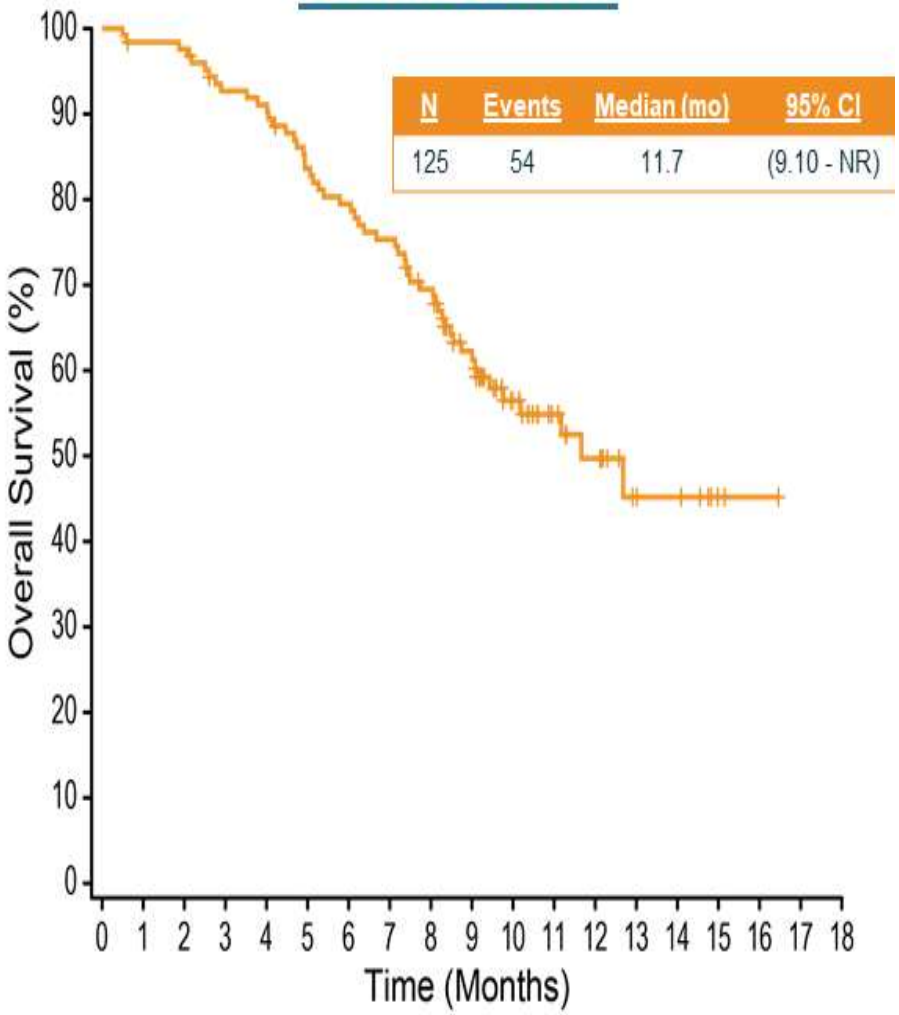
N	Events	Median (mo)	95% CI
125	81	5.8	(4.93, 7.46)

N at Risk (Events)

Cohort 1	125	116	91	84	72	65	51	47	30	22	8	7	3	2

Petrylak DP, et al. J Cl

Overall Survival



N	Events	Median (mo)	95% CI
125	54	11.7	(9.10 - NR)

N at Risk (Events)

Cohort 1	125	122	121	113	111	101	96	91	82	61	36	24	18	9	8	2	1

EV-201: Cohort 1 Treatment-Related Adverse Events

- Treatment-related AEs lead to few discontinuations (12%)
  - The most common was peripheral sensory neuropathy (6%)
- 1 treatment-related death was reported by the investigator
  - Interstitial lung disease
    - Confounded by high-dose corticosteroid use and suspected *pneumocystis jiroveci* pneumonia

Treatment-related AEs in ≥20% of patients (any Grade) or ≥5% (Grade 3)	Patients (N=125) n (%)	
	Any Grade	≥Grade 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	–
Decreased appetite	55 (44)	1 (1)
Peripheral sensory neuropathy	50 (40)	2 (2)
Dysgeusia	50 (40)	–
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Weight decreased	28 (22)	1 (1)
Dry skin	28 (22)	0
Rash maculo-papular	27 (22)	5 (4)
Anemia	22 (18)	9 (7)
Neutropenia	13 (10)	10 (8)

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

Summary

- High unmet need for patients with advanced and metastatic urothelial carcinoma
- Enfortumab vedotin is the first novel therapeutic to demonstrate clinical benefit in patients who progressed after platinum chemotherapy and a PD-1/L1 inhibitor
  - 44% response rate (CR 12%) and 7.6 months median duration of response
  - Responses observed across all subgroups and irrespective of response to prior PD-1/L1 inhibitor or presence of liver metastases
  - Tolerable with a manageable safety profile
  - EV-201 results are highly consistent with the phase 1 EV-101 trial in the same patient population
  - These data support submission to the FDA for accelerated approval
- If approved, enfortumab vedotin has the potential to become a new standard of care in patients who have progressed after platinum and PD-1/L1 inhibitors

Ongoing enfortumab vedotin trials: **EV-201:** Cohort 2 enrolling cisplatin-ineligible patients without prior platinum (NCT03219333); **EV-301:** Randomized phase 3 trial of EV vs. SOC post-platinum and a PD-1/L1 inhibitor (NCT03474107); **EV-103:** EV in combination with pembrolizumab and/or chemotherapy (NCT03288545)

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

Study EV-103: Durability Results of Enfortumab Vedotin Plus Pembrolizumab for Locally Advanced or Metastatic Urothelia Carcinoma

- **Jonathan E. Rosenberg[1], Thomas W. Flaig[2], Terence W. Friedlander[3], Matthew I. Milowsky[4], Sandy Srinivas[5], Daniel P. Petrylak[6], Jaime R. Merchan[7], Mehmet A. Bilen[8], Anne-Sophie Carret[9], Nancy Yuan[9], Carolyn Sasse[10], Christopher J. Hoimes[11]**

Locally Advanced or Metastatic Urothelial Carcinoma in First Line Setting

- Carboplatin-based regimens for cisplatin ineligible patients are associated with poor outcomes in the first-line (1L) setting
- The FDA recently granted accelerated approval to enfortumab vedotin-ejfv, a Nectin-4 directed antibody-drug conjugate*
- PD-1/PD-L1 inhibitor responses have promising durability, but 1L indication is restricted to patients with high PD-L1 expression or platinum ineligibility[2,3]
- Initial data from Study EV-103, enfortumab vedotin + pembrolizumab had encouraging activity for this platinum-free approach in cisplatin-ineligible patients[4]
- We present the first durability, PFS and OS data of enfortumab vedotin + pembrolizumab in 1L as well as an update on safety and efficacy

- Adults with locally advanced or metastatic urothelial cancer who have previously received a PD1/L1 inhibitor and a platinum-containing chemotherapy in the nedoadjuvant/adjuvant, locally advanced or metastatic setting. This indication is approved under accelerated approval based on tumor response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

[1]Grande et al. *Ann Oncol.* 2019;30(Suppl 5):Abstract LBA14_PR; [2]Balar et al. *J Clin Oncol.* 2017;35:6(Suppl):284; [3]Balar et al. *Lancet*. 2017;389(10064):67-76; [4]Hoimes et al.
Ann Oncol. 2019;30(Suppl 5):Abstract 9010.

EV-103 – First-line Cohorts of Enfortumab Vedotin + Pembrolizumab

Enfortumab vedotin 1.25 mg/kg + pembrolizumab (200 mg) in 1L cisplatin-ineligible la/mUC patients (N=45)

Patient Population

Locally Advanced or Metastatic Urothelial Carcinoma

Dose Escalation[1]

enfortumab vedotin + pembrolizumab

cisplatin-ineligible

(n=5)

Dose Expansion Cohort A

enfortumab vedotin + pembrolizumab

cisplatin-ineligible

(n=40)

Dosing: Enfortumab vedotin on days 1 and 8 and pembrolizumab on day 1 of every 3-week cycle

Enfortumab vedotin exposure: Comparable to enfortumab vedotin monotherapy on 4-week schedule (Days 1, 8, and 15)[2]

Primary endpoints: safety and tolerability

Key secondary endpoints: dose-limiting toxicities, ORR, DOR, PFS, OS

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

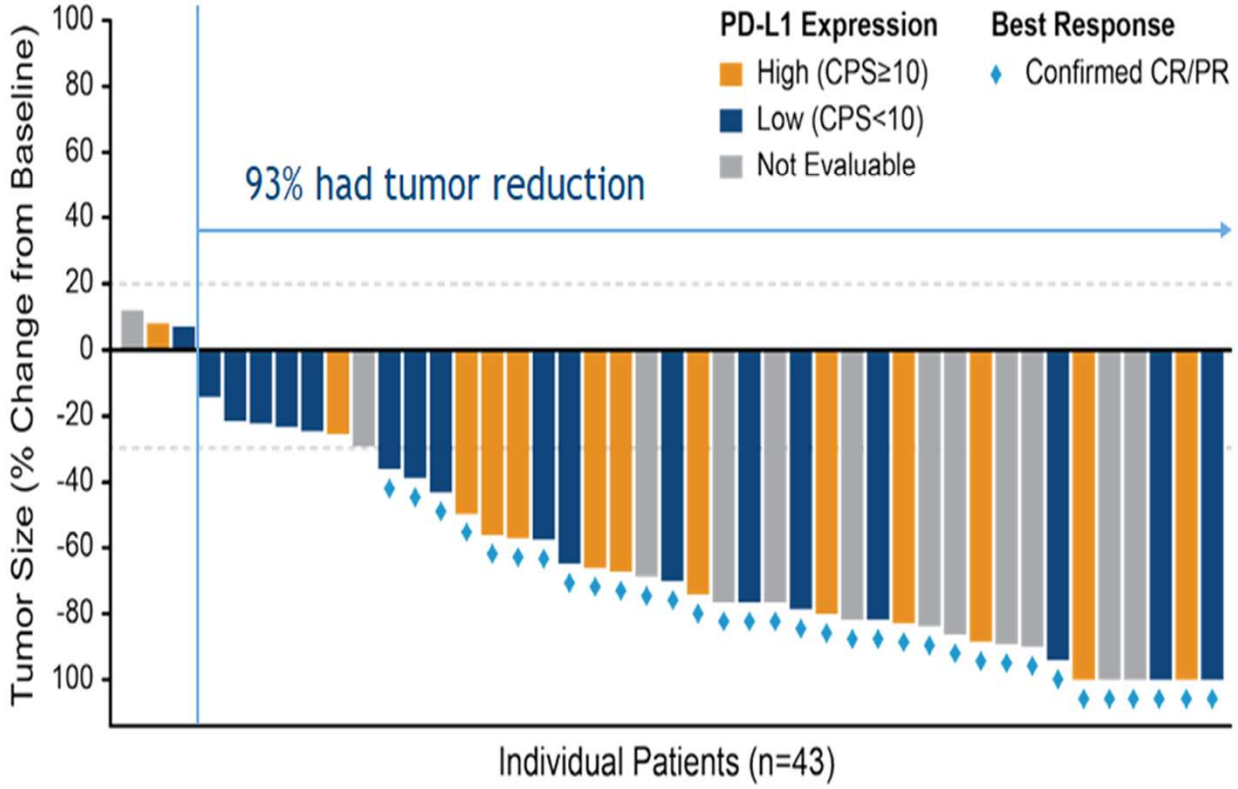
[2] Rosenberg et al. *J Clin Oncol.* 2019;37(29):2592-600.

Key Demographics and Disease Characteristics

Enfortumab vedotin 1.25 mg/kg + pembrolizumab in 1L setting 8 Oct 2019 data cut-off	Patients (N=45) n (%)
Male sex, n (%)	36 (80)
Age, yrs, Median (min, max)	69 (51, 90)
ECOG performance status, n (%)	
0	16 (36)
1	23 (51)
2	6 (13)
Primary tumor location, n (%)	
Lower tract	31 (69)
Upper tract	14 (31)
Metastasis sites, n (%)	
Lymph nodes only	4 (9)
Visceral disease	41 (91)
Liver	15 (33)
PD-L1 status by combined positive score,[1] n (%)	
<10	19 (42)
≥10	14 (31)
Not evaluable/Not available	12 (27)

[1] Unselected patient population; PD-L1 tested using the 22C3 PharmDx assay from Agilent/Dako

Maximal Target Lesion Reduction by PD-L1 status and Objective Response Rate per Investigator



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

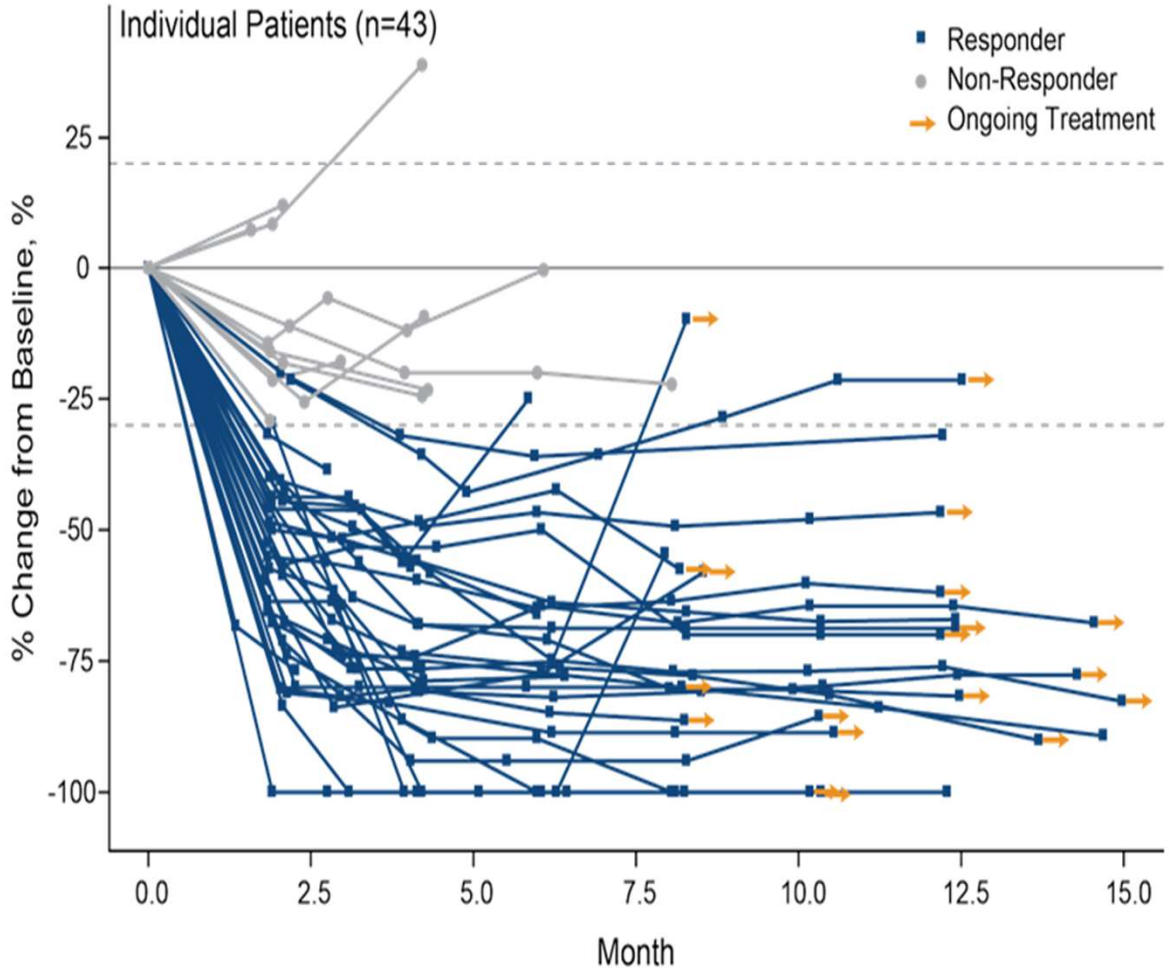
Best Overall Response Per RECIST v 1.1 by investigator (N=45)

- Responses observed regardless of PD-L1 expression level

Two patients did not have post-baseline response assessments before end-of-treatment: 1 withdrew consent and 1 died before any post-baseline response assessment. These patients are included in the full analysis set used to calculate ORR, but are not included in the figure above.

Horizontal lines at positive 20% and negative 30% denote thresholds for target lesions for disease progression and response, respectively.

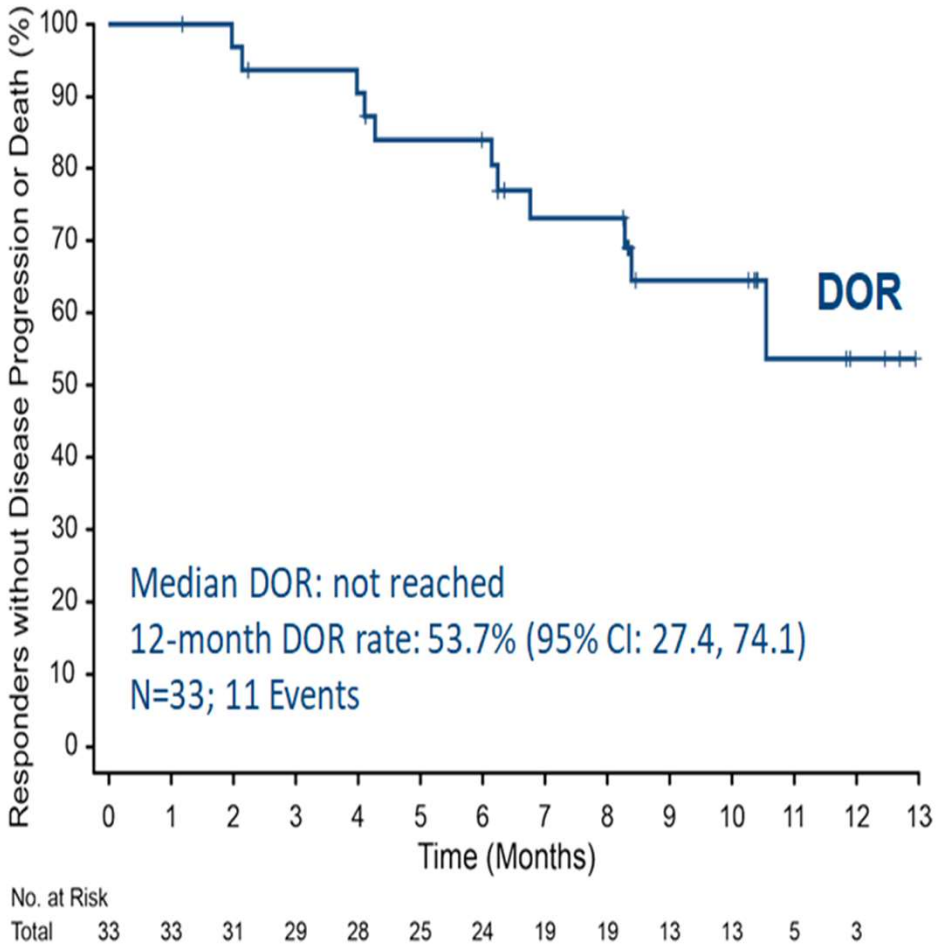
Percent Change from Baseline in Sum of Diameters of Target Lesions



- 88% of responses observed at first assessment (Week 9 ± 1 week)
- Median time to response = 2 months (range: 1.4 to 4.2 mo)

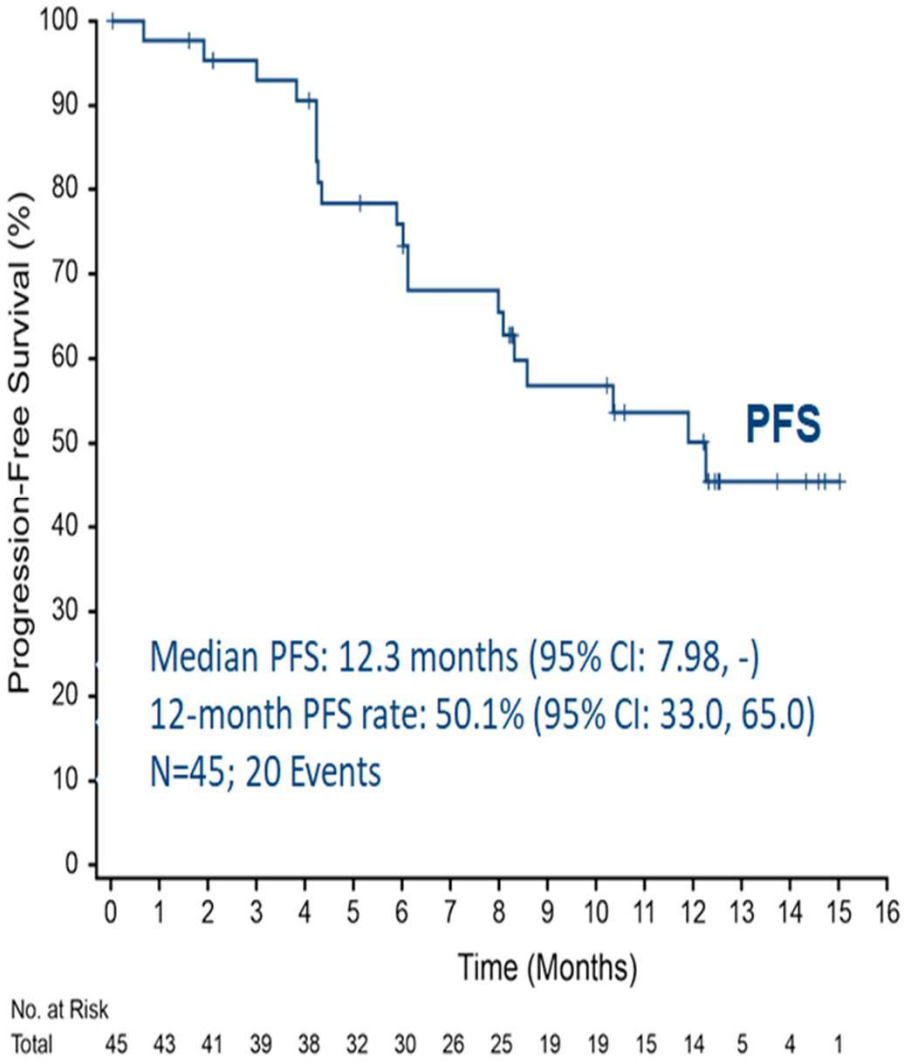
Two patients did not have post-baseline response assessments before end-of-treatment: 1 withdrew consent and 1 died before any post-baseline response assessment.
Horizontal lines at positive 20% and negative 30% denote thresholds for target lesions for disease progression and response, respectively.

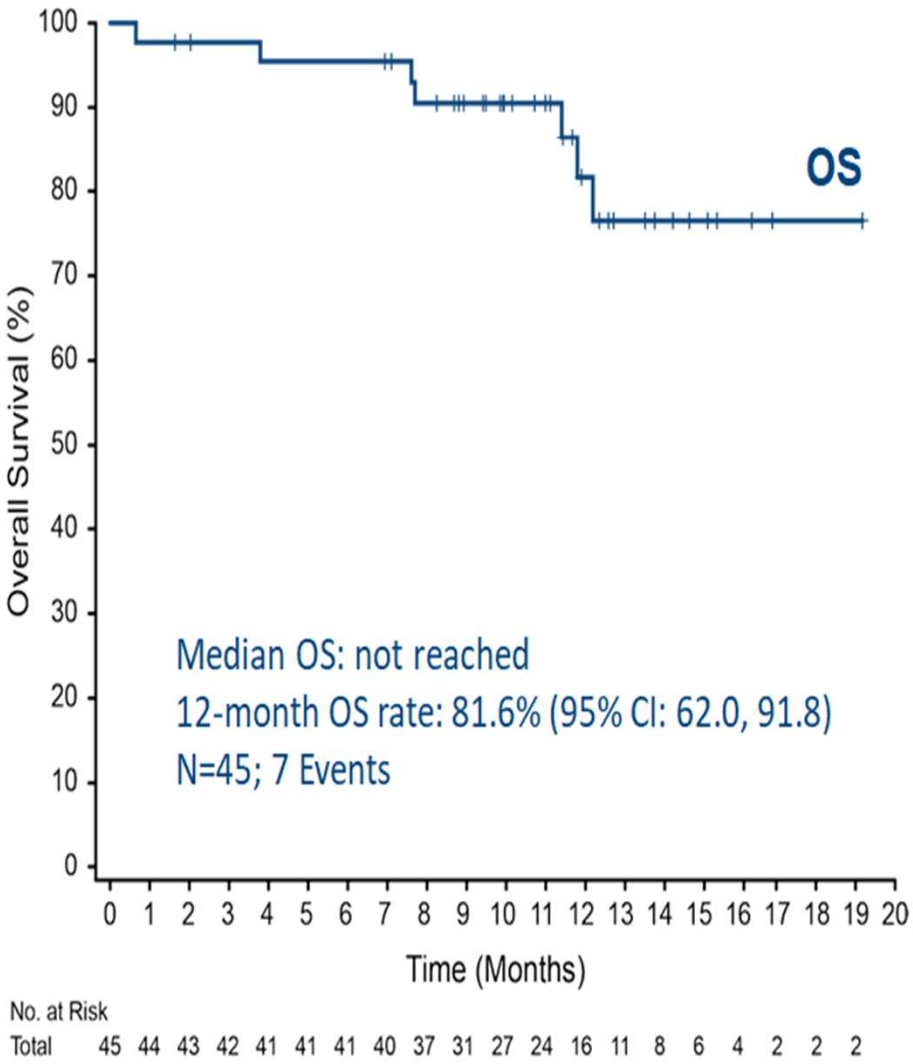
Duration of Response for Enfortumab Vedotin + Pembrolizumab



- With a median follow-up of 10.4 months, median DOR has not been reached
  - 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

Survival for Enfortumab Vedotin + Pembrolizumab





Treatment-Related Adverse Events (TRAE)

TRAEs by preferred term 8 Oct 2019 data cut-off	Patients (N=45) n (%)	
	Any Grade ≥20% of patients	≥Grade 3 ≥10% of patients
Overall	43 (96)	26 (58)
Fatigue	22 (49)	4 (9)
Alopecia	22 (49)	-
Peripheral sensory neuropathy	22 (49)	2 (4)
Diarrhea	20 (44)	3 (7)
Decreased appetite	17 (38)	0
Dysgeusia	15 (33)	-
Rash maculo-papular	14 (31)	4 (9)
Nausea	13 (29)	0
Pruritus	13 (29)	1 (2)
Anemia	9 (20)	3 (7)
Weight decreased	9 (20)	0
Lipase increased	8 (18)	8 (18)

- 7 patients had treatment-related serious AEs (16%)[1]
  - 6 patients had resolution
  - 1 treatment-related death as reported by investigator (2%)
    - Multiple organ dysfunction syndrome
- 6 discontinuations of enfortumab vedotin + pembrolizumab due to treatment-related AEs (13%)
  - Peripheral sensory neuropathy most common: 3 patients

[1] The only treatment-related serious event occurring in more than 1 patient was colitis (2 patients).

Treatment-Related Adverse Events of Clinical Interest (AECI)

- Rates of peripheral neuropathy, rash, and hyperglycemia similar to enfortumab vedotin monotherapy
- No new safety signal with the combination

AECI: categorized by related MedDRA terms	Patients (N=45) n (%)		Time to first onset (months) median (min, max)
	Any Grade	≥Grade 3[1]	Any Grade
Peripheral neuropathy	25 (56)	2 (4)	2.3 (1, 12)
Rash	28 (62)	6 (13)	0.7 (0, 12)
Hyperglycemia[2]	5 (11)	3 (7)	0.5 (0, 3)

AECI: determined by investigator	Patients (N=45) n (%)	
	Any Grade	≥Grade 3[1]
Immune-mediated AE requiring systemic steroids	13 (29)	8 (18)[3]

[1] No Grade 5 TRAE of Clinical Interest

[2] Blood glucose assessments were non-fasting.

[3] Grade 3 events: arthralgia, dermatitis bullous, pneumonitis, lipase increased, rash erythematous, rash maculo-papular, tubulointerstitial nephritis; Grade 4: dermatitis bullous, myasthenia gravis

Summary and Conclusions – EV-103 Enfortumab Vedotin + Pembrolizumab

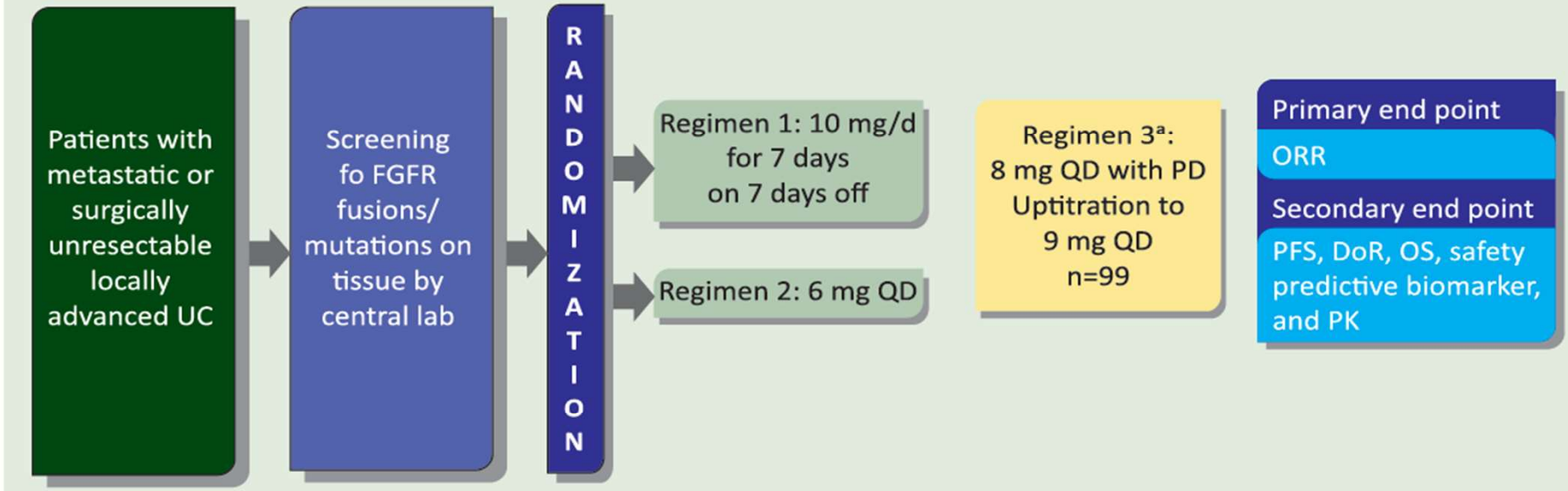
- **Patients with la/mUC in 1L who are ineligible for cisplatin-based therapies still represent a high unmet need**
- **Enfortumab vedotin + pembrolizumab demonstrates encouraging activity in 1L cisplatin-ineligible la/mUC patients**
  - High ORR (73.3%), with activity regardless of PD-L1 expression level
  - Favorable PFS trend; median PFS 12.3 months (95% CI: 7.98, -)
  - Median OS not reached; 81.6% OS rate at 12 months
  - Rapid responses (88% at first assessment); median DOR not reached (range 1.2, 12.9+ months)
- **Stable safety profile over time, immune-mediated AEs similar to pembrolizumab monotherapy**
  - No new safety signals with combination
  - Most common treatment-related adverse events: fatigue, alopecia, and peripheral sensory neuropathy
  - One treatment-related death of multiple organ dysfunction syndrome
- **Based on these results, further investigation of enfortumab vedotin + pembrolizumab as a platinum-free option is warranted in patients with untreated la/mUC**
- **The pivotal Phase 3 study EV-302 (NCT04223856) will evaluate enfortumab vedotin in combination with pembrolizumab +/- chemotherapy vs gemcitabine/platinum in patients with la/mUC in 1L setting**

Erdafitinib for Treatment of Patients with susceptible FGFR3 or FGFR2 genetic alterations

- Efficacy results for ORR, duration of response (DoR), progression-free survival (PFS), and OS as well as safety were analyzed by select baseline variables

- High-risk was defined as having at least 1 of the following characteristics:
  - o Age ≥75 years
  - o Eastern Cooperative Oncology Group performance status (ECOG PS) of 2
  - o Hemoglobin <10 g/dL
  - o Visceral metastases

Figure 1. BLC2001: study design



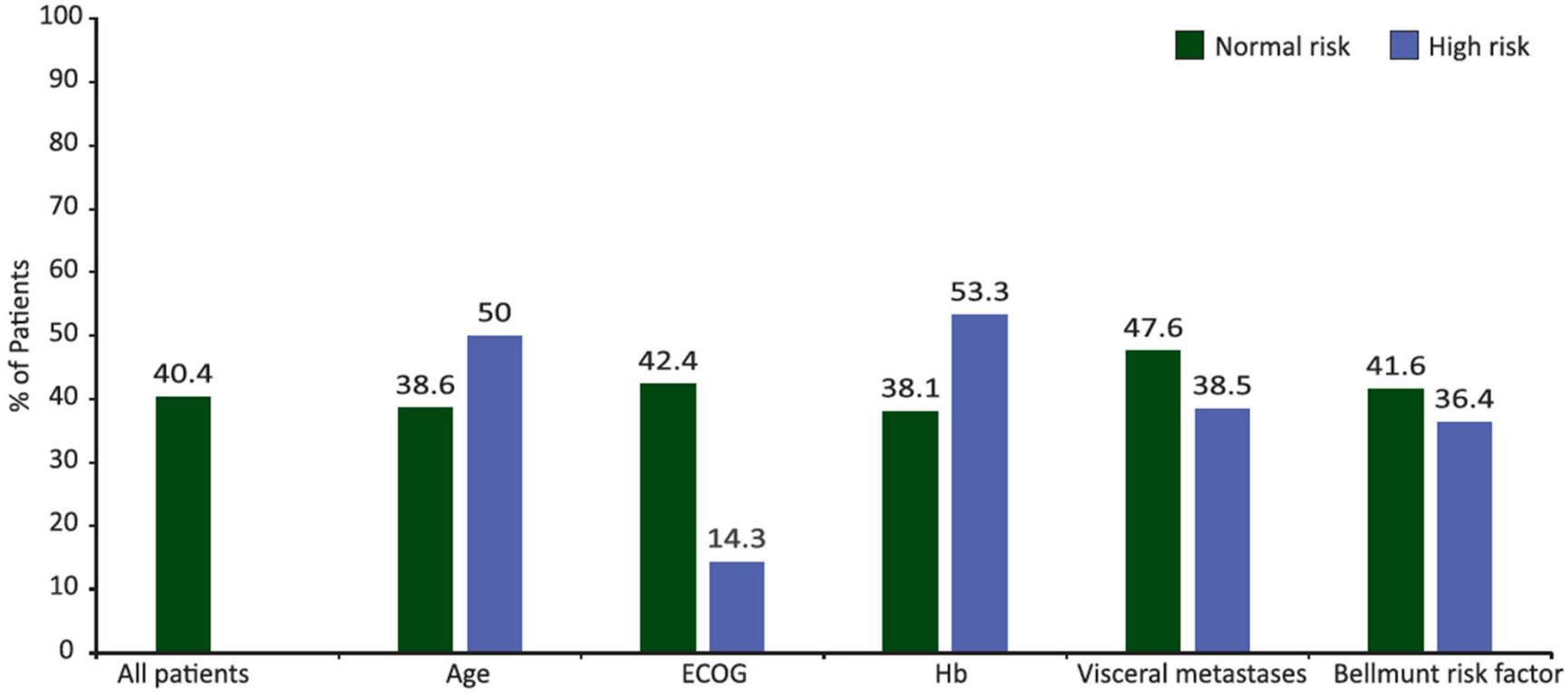
Patients

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

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

DoR, duration of response; FGFR, fibroblast growth factor receptor; OS, overall survival; PD, pharmacodynamics; PFS, progression free survival; PK, pharmacokinetics; QD, once daily, TRAEs, treatment-related adverse events; UC, urothelial carcinoma.

Figure 2. Investigator-assessed objective response rates



	All patients
n/N	40/99
95% CI	30.7, 50.7

<75 y	≥75 y
32/83	8/16
28.1, 49.9	24.7, 75.3

0-1	2
39/92	1/7
32.1, 53.1	0.4, 57.9

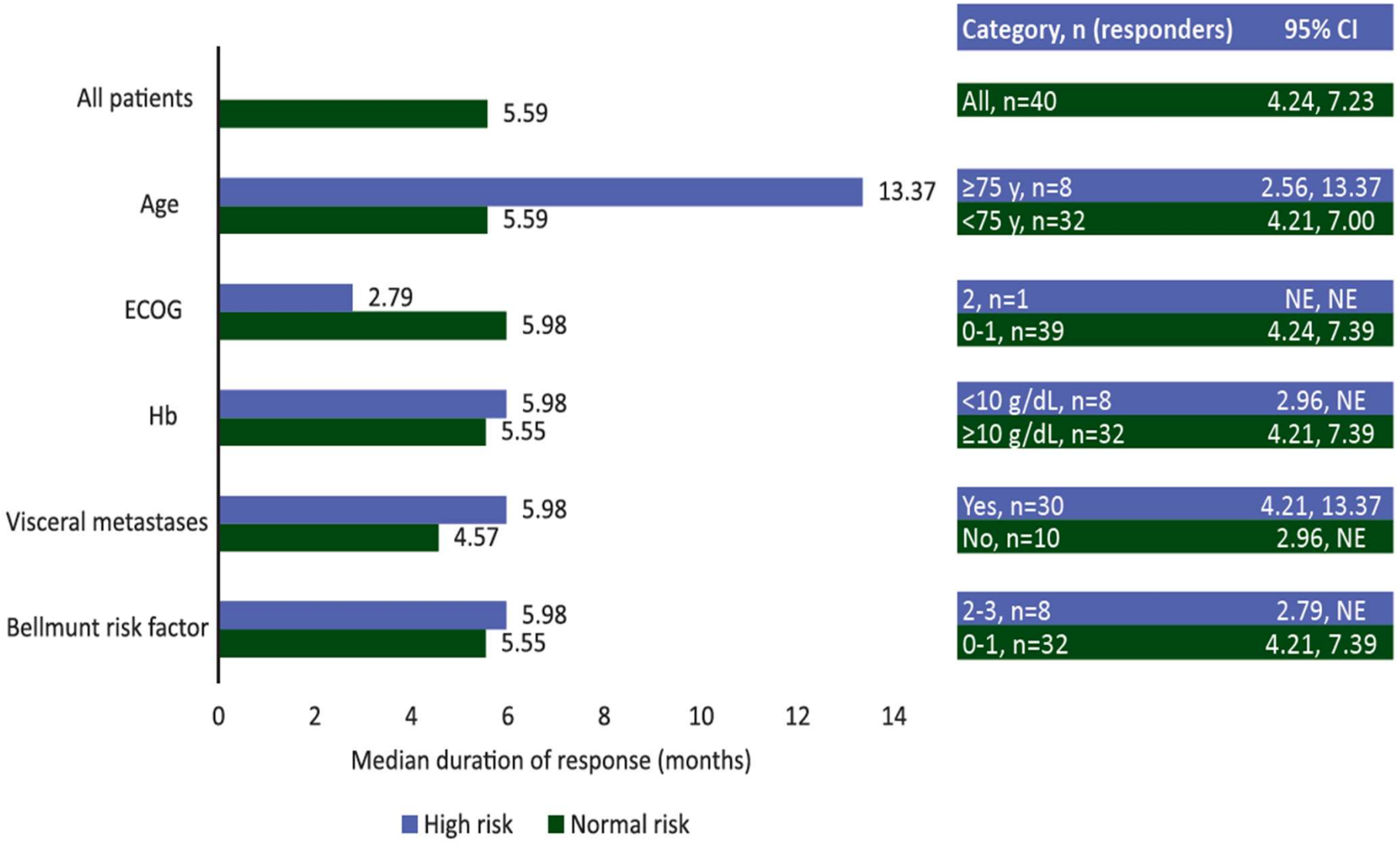
≥10 g/dL	<10 g/dL
32/84	8/15
27.7, 49.3	26.6, 78.7

No	Yes
10/21	30/78
25.7, 70.2	27.7, 50.2

0-1	2-3
32/77	8/22
30.4, 53.4	17.2, 59.3

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin

Figure 3. Duration of response



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; NE, not evaluable

RESULTS

Efficacy

- Investigator-assessed ORR was 40% in the primary analysis of all patients and >36% in all subgroups except for ECOG PS 2 (Figure 2)
  - ORR in the high-risk subgroups ranged from 14.3% to 53.3%
  - ORR reached 50% in 2 high-risk subgroups: patients age ≥75 years and those with hemoglobin <10 g/dL
- DoR was within the range of 5.5 to 6 months for most subgroups (Figure 3), the exceptions being:
  - Patients age ≥75 years, with DoR of 13.4 months
  - ECOG PS 2 and no visceral disease subgroups, with DoR of 2.8 months and 4.6 months, respectively
- In the primary analysis of all patients, median PFS was 5.52 months (95% CI 4.17, 5.95) and median OS was 13.80 months (95% CI 8.82, not evaluable)
  - Median PFS exceeded 5 months across all subgroups, except for the ECOG PS 2 and Bellmunt risk factor 2-3 subgroups (Figure 4)
  - OS data are immature but generally follow the trend of PFS, with medians exceeding 1 year in most subgroups (Figure 5)
    - In the high-risk subgroups based on age and visceral metastases, median OS reached or exceeded the 13.8-month median for the primary analysis of all patients

CONCLUSION

Although limited by small sample sizes and immature OS data:

- Common high-risk criteria (older age, lower hemoglobin, visceral disease, multiple Bellmunt risk factors) associated with adverse outcomes in UC patients with chemotherapy had no impact on ORR in patients treated with erdafitinib
- ECOG PS 2 was the only statistically significant risk factor with adverse PFS and OS effects in patients treated with erdafitinib, with trends for visceral metastases and Bellmunt risk factor 2-3
  - This may be related to the high discontinuation rate of erdafitinib in this group of patients
- Overall, the safety profile of erdafitinib was not adversely influenced by the presence of high-risk characteristics