Updates in Kidney and Bladder Cancers

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Tulane University
SCHOOL OF MEDICINE
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Disclosures

Consultant (Institutional): Astellas; Eisai; Janssen, EMD Serono; Dendreon; Pfizer, Seattle Genetics, BMS, Bayer, Guardant Health
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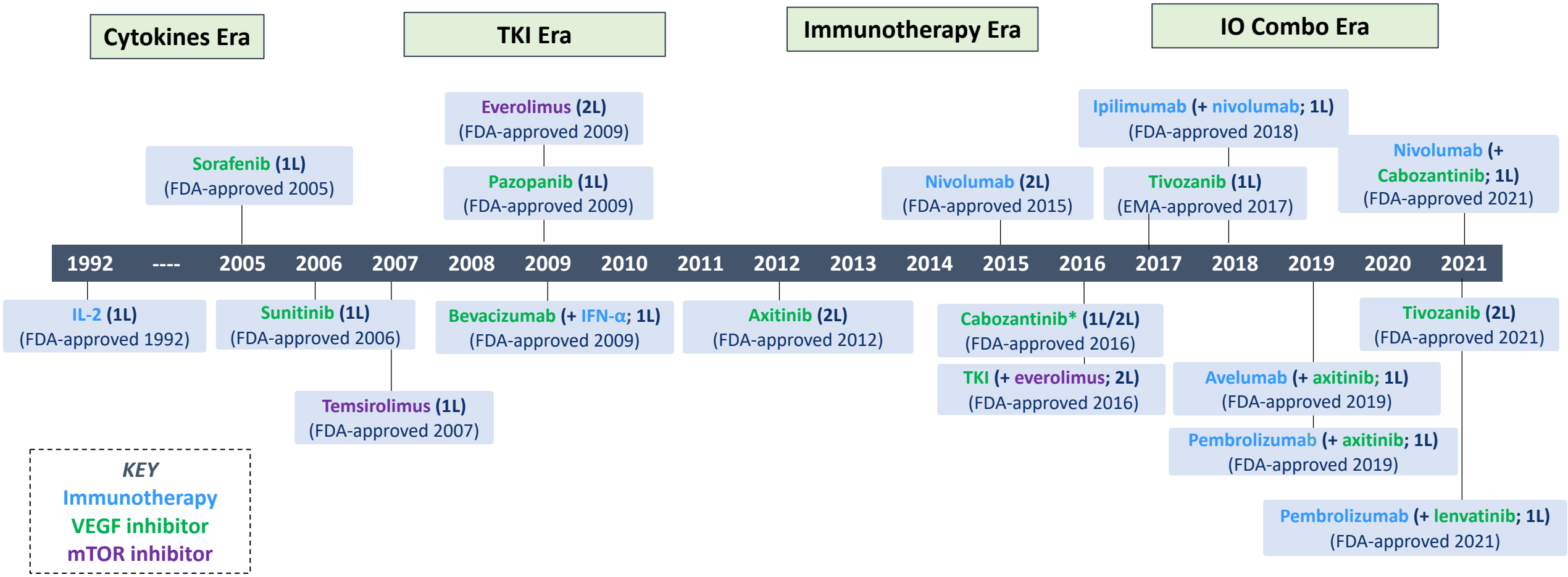
Renal Cell Cancer

Evolution of Systemic Therapy in Metastatic RCC



1L = first line; 2L= second line; IFN-α = interferon alpha; IL = interleukin; IO = immunotherapy; mTOR, mammalian target of rapamycin;TKI = tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR-2 = VEGF receptor-2

*Cabozantinib inhibits VEGFR-2, but also c-MET and AXL.22.

Dizman N, et al. *Nature Reviews Nephrol.* 2020;16:435–451.

Food and Drug Administration. Drug Approvals and Databases. https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases.

Advanced Renal Cancer – First Line

Updated Results From Front-Line IO-Combination Trials

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
HR mOS, months	**0.72** 55.7 vs 38.4	**0.73** 45.7 vs 40.1	**0.70** 37.7 vs 34.3	**0.72** NR vs NR
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%	**90%** vs. 79% **74%** vs. 66%	**86%** vs. 76% **70%** vs 60%	**90%** vs 79% (est.) **79%** vs. 70%
HR mPFS, months	**0.86** **12.3** vs 12.3	**0.68** **15.7** vs 11.1	**0.56** **16.6** vs 8.3	**0.39** **23.9** vs 9.2
ORR, %	**39** vs 32	**60** vs 40	**56** vs 28	**71** vs 36
CR, %	**12** vs 3	**10** vs 4	**12** vs 5	**16** vs 4
Med f/u, months	**67.7**	**42.8**	**32.9**	**33.7**
Primary PD, %	**18**	**11**	**6**	**5**

1. Consistent OS benefit; medians immature for IO/TKIs
2. IO/TKIs with more tumor shrinkage; higher ORR, longer PFS and less early PD
3. Ipi/Nivo has the most durable benefit at 5 years -IO/TKI data immature

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HRQoL Summary of Randomized Phase 3 First-Line Combination Studies in cc Renal Cell Carcinoma

	CHECKMATE-214[1]		KEYNOTE-426[2]		CHECKMATE-9ER[3]		CLEAR[4]			
	N=847		N=861		N=651		N=1069			
HRQoL Tools	Nivolumab + Ipilimumab	vs. Sunitinib	Axitinib + Pembrolizumab	vs. Sunitinib	Cabozantinib + Nivolumab	vs. Sunitinib	Lenvatinib + Pembrolizumab	vs. Sunitinib	Lenvatinib + Everolimus	vs. Sunitinib
	Intermediate and Poor Risk Only		All Risk Groups		All Risk Groups		All Risk Groups			
FKSI-19	✓				✓					
FKSI-DRS			=				=		=	
EORTC QLQ-C30			=				=		=	
FACT-G	✓									
EQ-5D-3L	✓		=		✓		=		=	

1. Lancet Oncol 2019; 20: 297–310; 2. Bedke J. et al., 35th Annual EAU Congress -July 2020 (via https://www.urotoday.com)3. Cella D et al., JCO 39, no. 6_suppl (February 20, 2021) 285; 4. Motzer R et al., JCO 39, 2021 (suppl 15; abstr 4502).

Presented By: Andrea B. Apolo, MD
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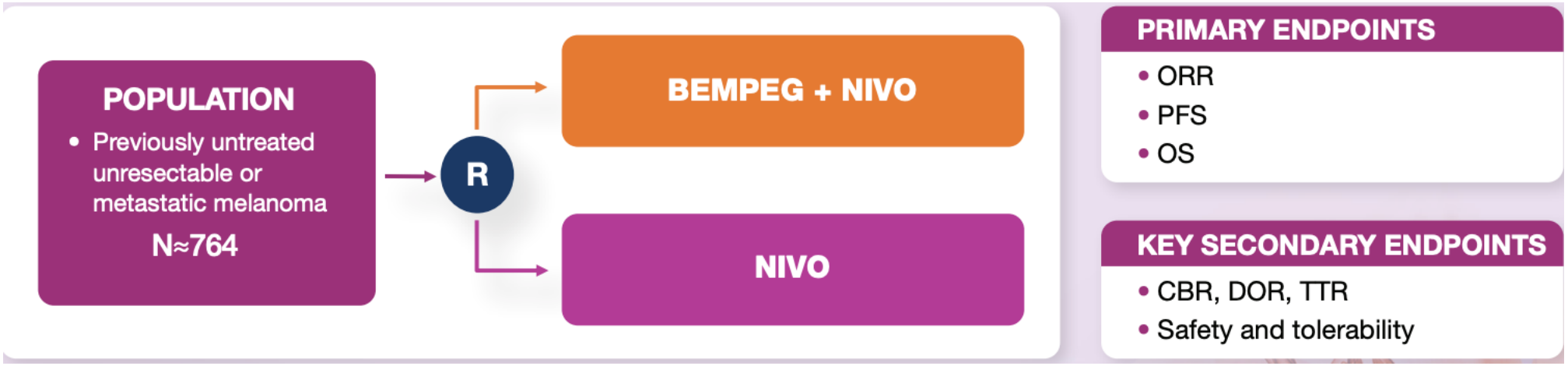
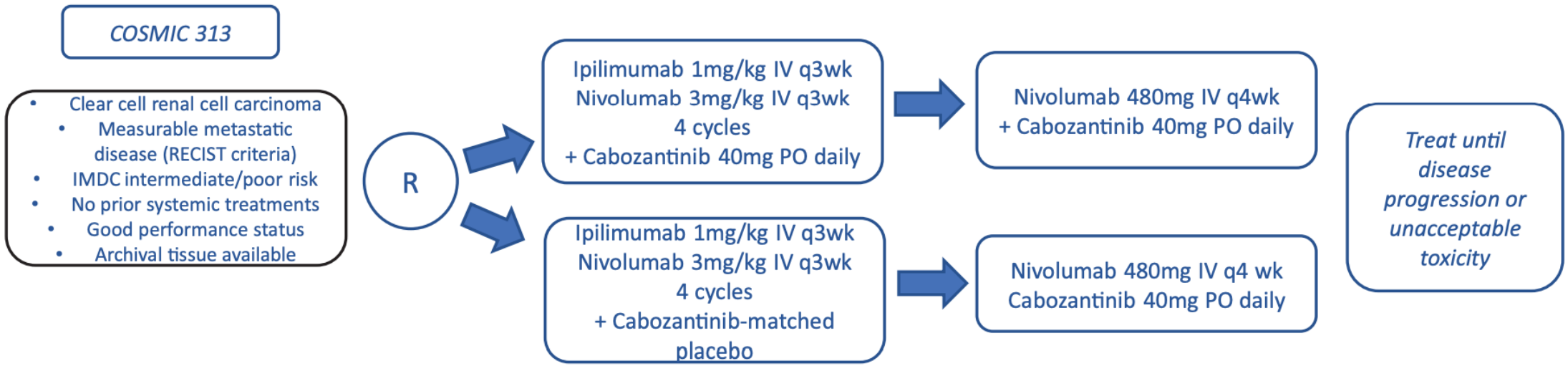
PIVOT-09 and COSMIC 313





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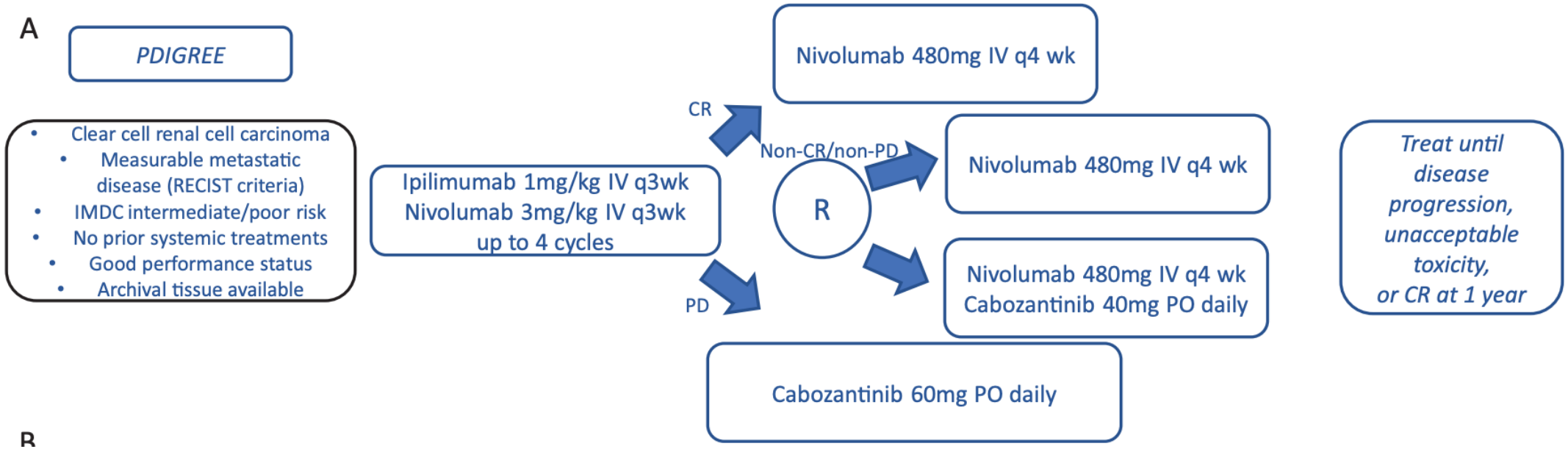

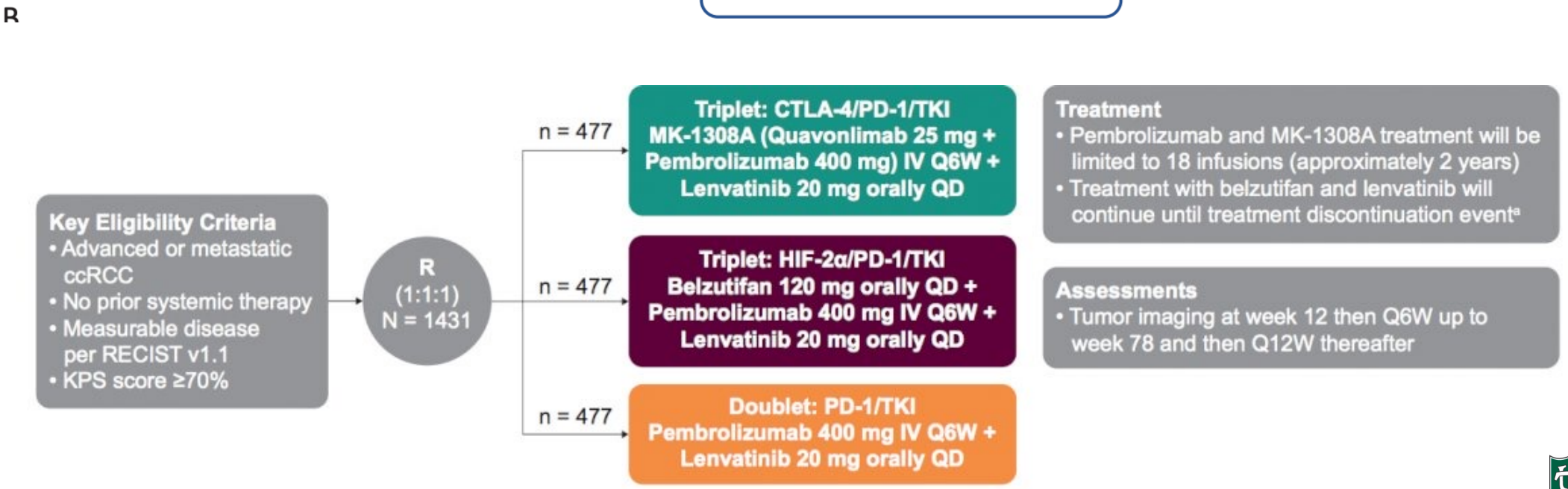

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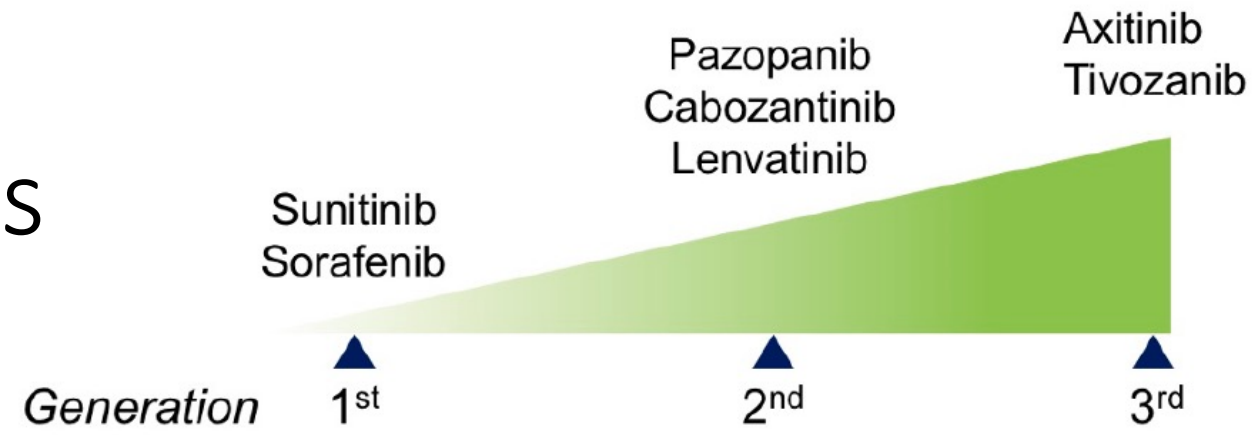
Second Line and Beyond

VEGF-TKI Properties



- Increased potency
- and/or VEGFR selectivity
- Favorable PK

Higher generation

PD Properties

Drug name	Selectivity	Generation	Potency (IC_{50}, nM)						Other targets
			VEGFR-1	VEGFR-2	VEGFR-3	PDGFR-β	c-Kit	FGFR-1	
Tivozanib	Yes	III	0.2–30	0.2–6.5	0.2–15	1.7–49	1.6–78	530	RET, FGFR-2/3
Axitinib	Yes	III	0.1–1.2	0.2–0.3	0.1–0.3	1.6–1.7	1.6–1.7	231	PDGFRα
Pazopanib	Yes	II	7–15	8–30	2–47	14–215	2.4–74	14–80	PDGFRα
Lenvatinib	No	II	1.3	0.74	0.71	NR	11	22	PDGFRα, RET, FGFR-2/4
Cabozantinib	No	II	12.2	0.04–14.0	6	575	4.6–752	NA	c-MET, RET, AXL, FLT3, TRKB, TIE-2
Sunitinib	No	I	2–21	10–38	3–30	8–75	1–40	437–880	PDGFRα, RET, FLT3, CSF-1R
Sorafenib	No	I	9	28–90	7–20	68	68–1862	64–580	RET, FLT3, RAF

IC_{50}: concentration required for 50% inhibition. The comparison of the pharmacological potencies among VEGFR-TKIs should be done with caution due to different assays and conditions used (e.g., inhibition of recombinant receptor tyrosine kinase activity in cell-free kinase assays or VEGF-induced phosphorylation of intracellular VEGFR in cell-based assays). NR: not reported. References: [16,18,44,94–98].

Fogli S, et al. Cancer Treat Rev. 2020;84:101966.

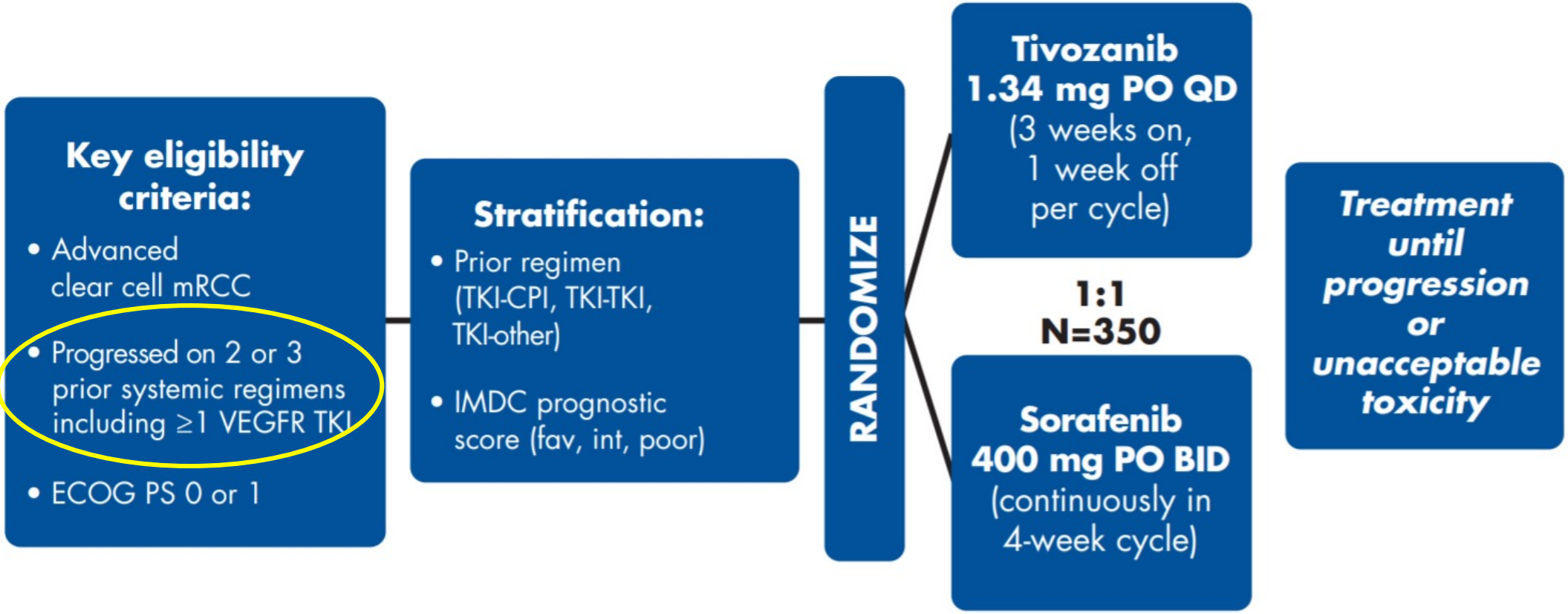
Second-Line Therapy: Preferred NCCN Recommendations

	Nivolumab vs evero[2] N = 821	Cabozantinib vs evero[3] N = 658	Lenvatinib + evero vs lenvatinib or evero[4] N = 153
Trial	Phase 3 CM-025	Phase 3 METEOR	Phase 2 Study 205
Patient population	TKI-refractory (72% 1 prior)	TKI-refractory (71% 1 prior)	TKI-refractory (100% 1 prior)
Primary end point	OS	PFS (IRC)	PFS (INV)
Risk, favorable/int/poor	35/49/16	45/42/12	24/37/39
ORR, %	25	17	43
PFS, mo	4.6	7.4 (HR 0.51; 95% CI, 0·41–0·62; P <.0001)	14.6 (HR, 0.40; 95% CI, 0.24-0.68; P = .0005 vs evero)
OS, mo	25.0 (HR, 0.73; 95% CI, 0.57-0.93; P =.002)	21.4	25.5
Dose reductions	N/A	62%	71%
AE discontinuation	8%	12%	24%
Toxicity	18% G3 1% G4 (tx-related)	71% G3/4	57% G3 14% G4

AE, adverse event; discontinuation; evero, everolimus; tx, treatment.

1. Rini et al., *Lancet*. 2011;378:1931; 2. Motzer et al., *N Engl J Med*. 2015;373:1803;
3. Choueiri et al., *Lancet Oncol.* 2016;17:917-927; 4. Motzer et al., *Lancet Oncol*. 2015;16:1473

Phase 3 TIVO-3: Study Design



Primary endpoint: PFS (BICR)
Secondary endpoints: OS, ORR, DOR, and safety

Verzoni E, et al. ASCO 2021. Abstract 4546.

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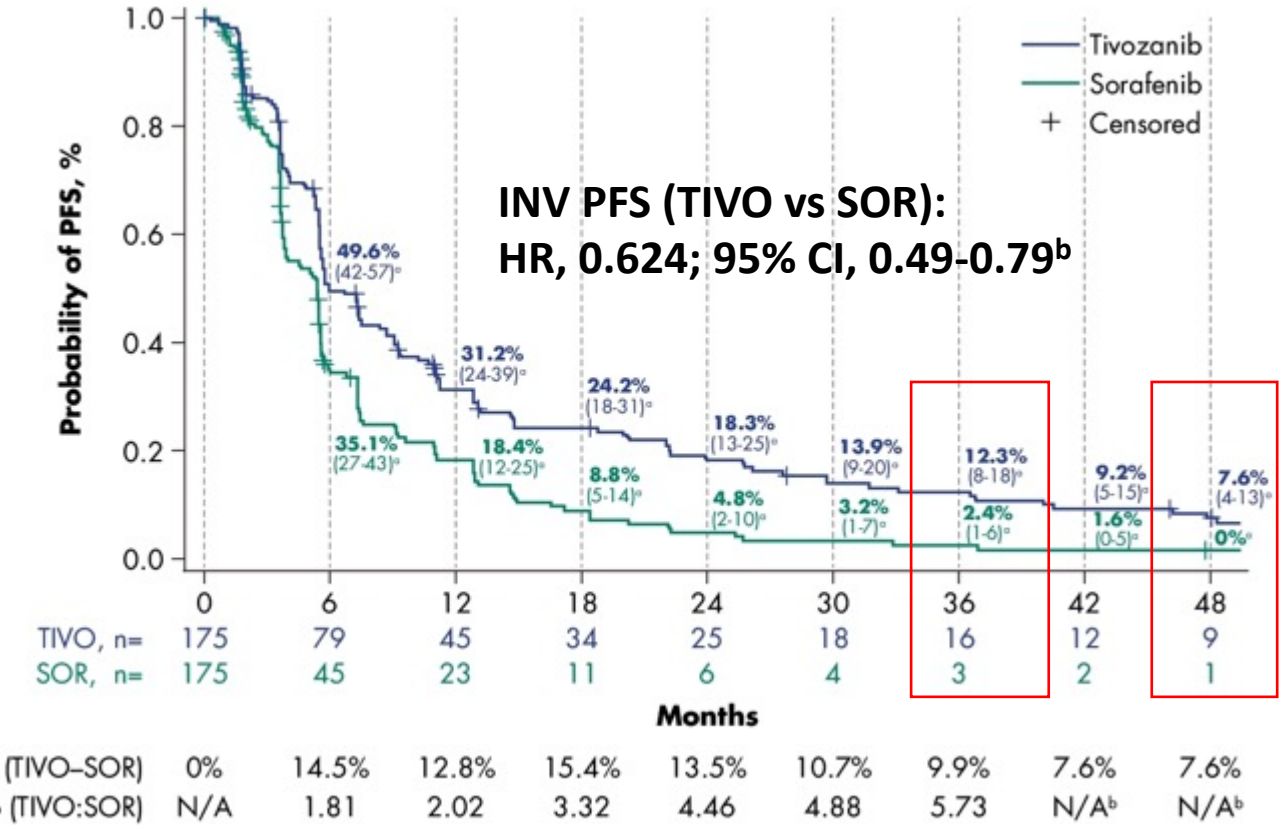
TIVO-3: Landmark Rates of Long-Term PFS (ITT[a])— INV Assessment



INV PFS (TIVO vs SOR):
HR, 0.624; 95% CI, 0.49-0.79[b]

A clinically relevant proportion of patients were alive and progression free at 3 and 4 years after initiating TIVO therapy compared with SOR, and this difference was consistent across all clinical and demographic subgroups evaluated

Subgroup	TIVO n	SOR n	12-month PFS, %		24-month PFS, %		36-month PFS, %		48-month PFS, %	
			TIVO	SOR	TIVO	SOR	TIVO	SOR	TIVO	SOR
Prior treatment										
Any immunotherapy	47	44	27.0	18.6	19.1	3.7	9.8[c]	NE	6.5	NE
TKI-TKI only	79	80	31.6	9.8	18.6	2.0	13.5	NE	NE	NE
No immunotherapy	128	131	32.7	18.3	18.1	5.1	13.0	2.0	7.9	NE

a. Results include the ITT population, with censoring for missing assessments and discontinuation without PD.
b. Data cut-off: May 24, 2021.

Atkins MB, et al. ASCO GU 2022. Abstract 362.

TIVO-3: Safety

	Tivozanib (n=173)*			Sorafenib (n=170)*		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Hypertension	46 (27%)	35 (20%)	0	23 (14%)	23 (14%)	0
Diarrhoea	57 (33%)	3 (2%)	0	81 (48%)	15 (9%)	1 (1%)
Fatigue	50 (29%)	6 (4%)	0	28 (16%)	8 (5%)	0
Decreased appetite	42 (24%)	6 (4%)	0	35 (21%)	3 (2%)	1 (1%)
Dysphonia	40 (23%)	1 (1%)	0	13 (8%)	0	0
Asthenia	36 (21%)	8 (5%)	0	28 (16%)	6 (4%)	0
Nausea	33 (19%)	0	0	21 (12%)	4 (2%)	0
Stomatitis	32 (18%)	3 (2%)	0	28 (16%)	4 (2%)	0
Palmar-plantar erythrodysesthesia syndrome	27 (16%)	1 (1%)	0	61 (36%)	17 (10%)	0
Hypothyroidism	23 (13%)	1 (1%)	0	10 (6%)	0	0
Vomiting	13 (8%)	1 (1%)	0	17 (10%)	3 (2%)	0
Decreased weight	14 (8%)	1 (1%)	0	23 (14%)	3 (2%)	0
Rash	6 (4%)	0	0	31 (18%)	12 (7%)	1 (1%)
Alopecia	5 (3%)	0	0	35 (21%)	1 (1%)	0
Pruritus	1 (1%)	0	0	17 (10%)	0	0

Rini BI, et al. *Lancet Oncol*. 2020;21:95-104.

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Key Inclusion Criteria

- Metastatic clear cell RCC
- Measurable disease per irRECIST[1]
- Disease progression after PD-1/PD-L1 treatment:
  - ≥ 2 doses of anti-PD-1/PD-L1
  - Defined by RECIST v1.1; confirmed ≥ 4 weeks

Study Treatment

Lenvatinib[a]
20 mg/day PO
+
Pembrolizumab[b]
200 mg/3 weeks IV

Primary End Point[c]

- Objective response rate at week 24

Secondary End Points

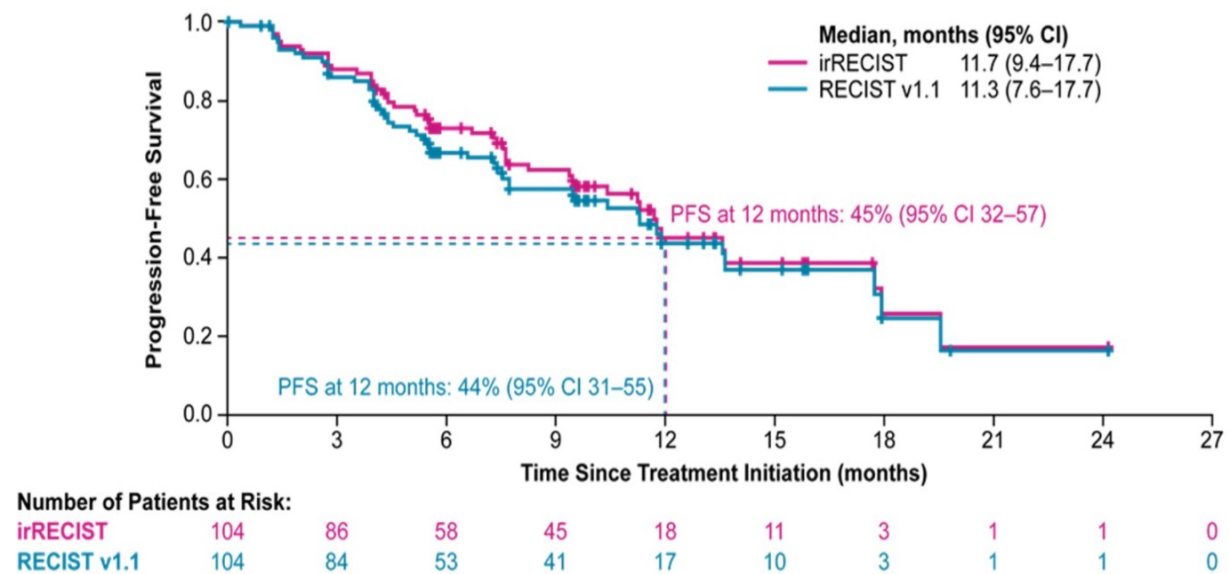
- Objective response rate[c]
- Progression-free survival[c]
- Overall survival
- Safety and tolerability

Tumor Response by Investigator Assessment

Parameter	irRECIST N = 104	RECIST v1.1[a] N = 104
ORR at week 24, % (95% CI)	51 (41–61)	–
ORR, % (95% CI)	55 (45–65)	52 (42–62)
Best objective response, %		
Partial response	55	52
Stable disease	36	38
Progressive disease	5	6
Not evaluable	5	5
Median DOR, months (95% CI)	12 (9–18)	12 (9–18)

[a] Up to 10 target lesions could be selected (up to 5 per organ).

PFS Kaplan–Meier Curves by irRECIST[a] and RECIST v1.1[a,b]



Lee at al, ASCO 2021

CONTACT-03 and TINIVO-2

- Histologically confirmed advanced, metastatic ccRCC or nccRCC
- Radiographic progression during or following ICI treatment

R
1:1

N ≈ 500

Atezolizumab *IV*
1200 mg q3w
+
Cabozantinib *po*
60 mg qd

Cabozantinib *po*
60 mg qd

No crossover allowed

Treatment until loss of clinical benefit or unacceptable toxicity

Survival follow-up

N = 326

- Histologically / cytologically confirmed recurrent/metastatic RCC
- ECOG PS 0 or 1
- Progressed following immediate prior immunotherapy treatment in first or second line
- Stratified by IMDC and prior TKI

Randomize 1:1

Tivozanib + Nivolumab

Tivozanib

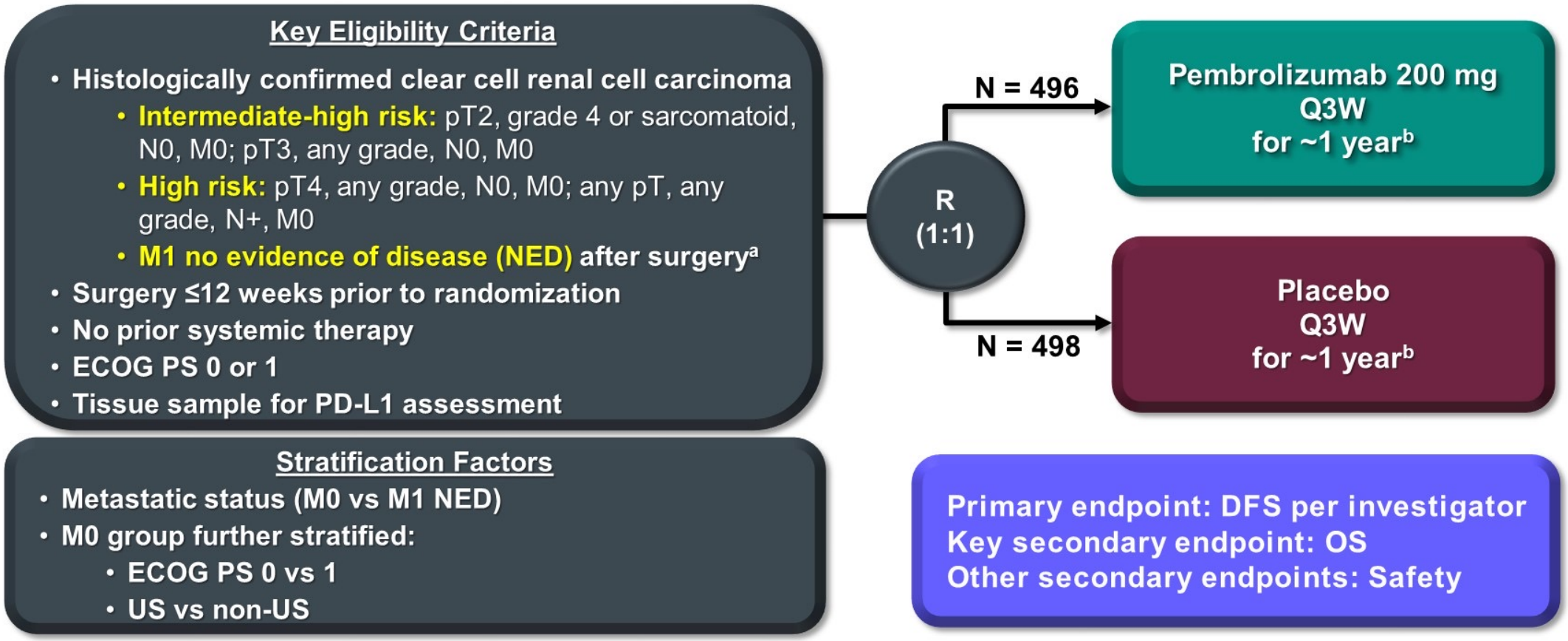
Treatment Until Progression

Endpoints

- Primary: PFS
- Secondary: OS, ORR, DoR, Safety and Tolerability

Renal Cell Cancer – Adjuvant

KEYNOTE-564 (NCT03142334) Study Design



- Median (range) time from randomization to cutoff: 30.1 (20.8−47.5) months

Q3W, every 3 weeks.
[a]M1 NED: no evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy; [b]≤17 cycles of treatment were equivalent to ~1 year.
Data cutoff date: June 14, 2021.

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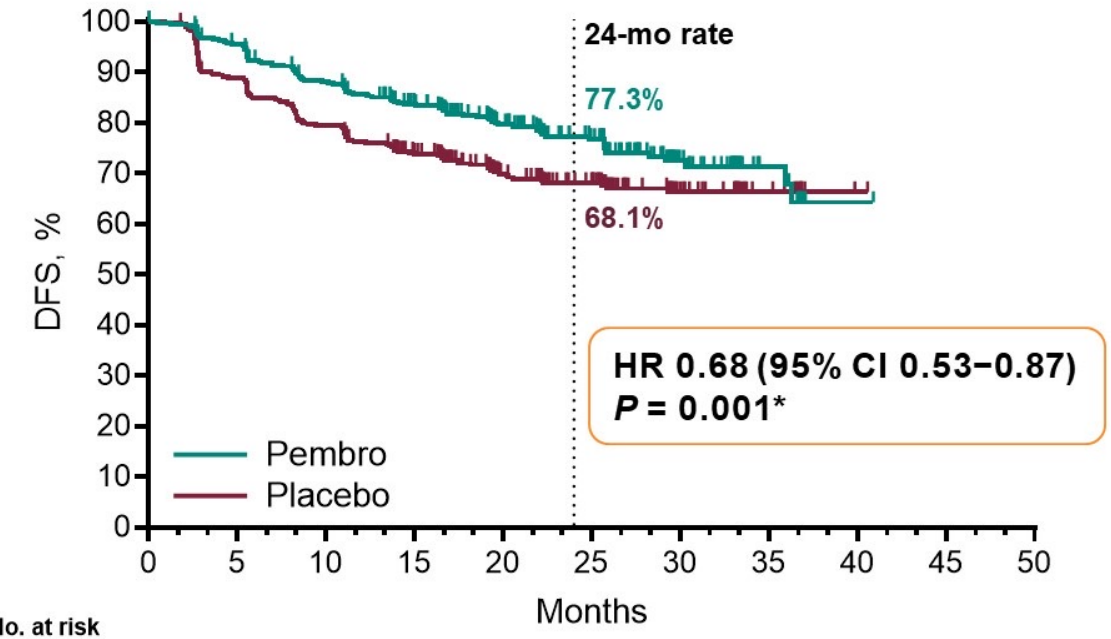
Primary Endpoint: DFS, ITT Population

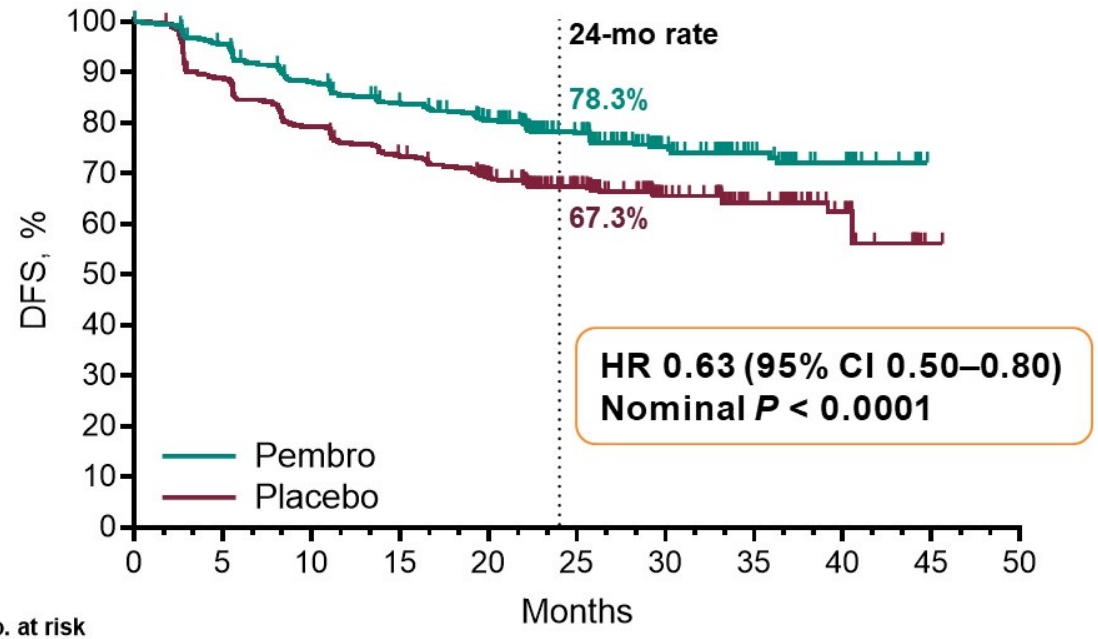
Primary Analysis: 24.1 mo Follow-Up



No. at risk											
Pembro	496	457	414	371	233	151	61	21	1	0	0
Placebo	498	436	389	341	209	145	56	19	1	0	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	109	NR (NR–NR)
Placebo	151	NR (NR–NR)

Updated Analysis: 30.1 mo Follow-Up



No. at risk											
Pembro	496	458	416	389	361	255	135	77	37	0	0
Placebo	498	437	389	356	325	230	125	74	33	1	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

* denotes statistical significance.

ITT population included all randomized participants. DFS, disease-free survival; NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

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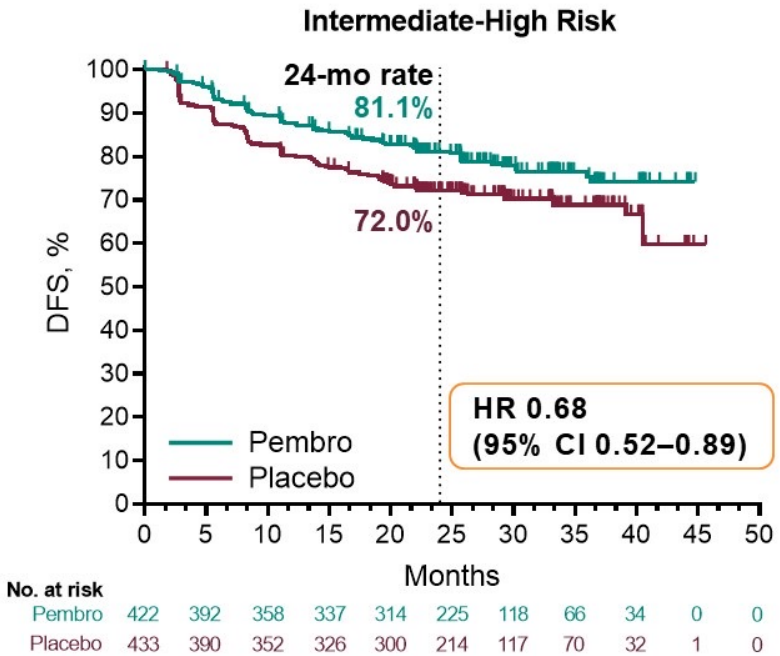
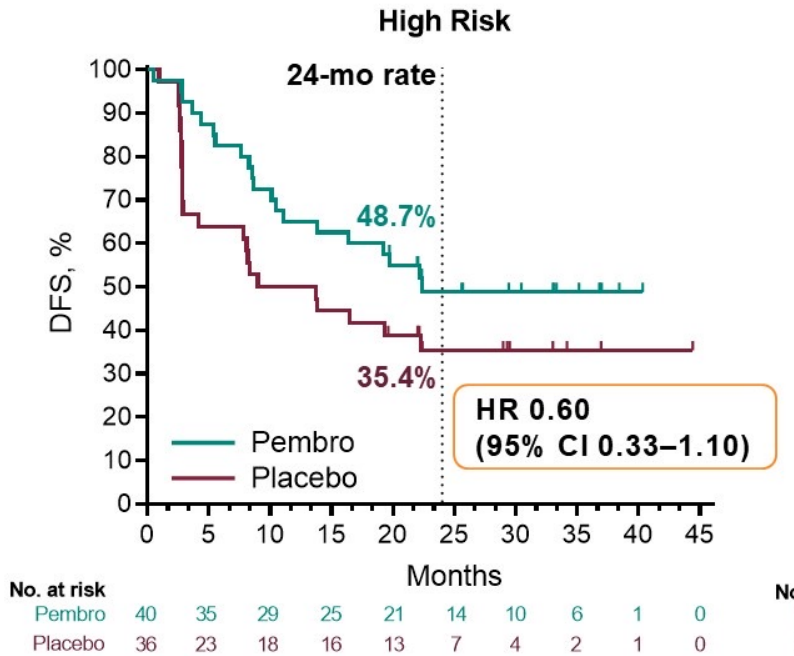
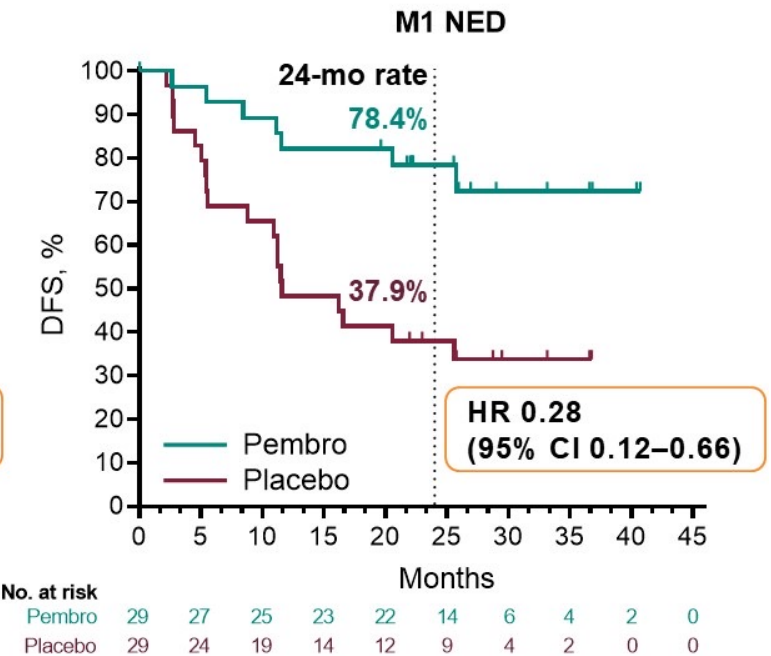
DFS by Recurrence Risk Subgroups



	Pts w/ Event	Median, mo (95% CI)
Pembro	87	NR (NR–NR)
Placebo	127	NR (40.5–NR)



	Pts w/ Event	Median, mo (95% CI)
Pembro	20	22.4 (11.1–NR)
Placebo	23	11.4 (2.9–NR)



	Pts w/ Event	Median, mo (95% CI)
Pembro	7	NR (25.7–NR)
Placebo	19	11.6 (5.6–NR)

Intermediate-high risk: pT2, grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0;
High risk: pT4, any grade, N0, M0; or pT any stage, any grade, N+, M0;
M1 NED: No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy.
DFS, disease-free survival; NR, not reached. Data cutoff date: June 14, 2021.

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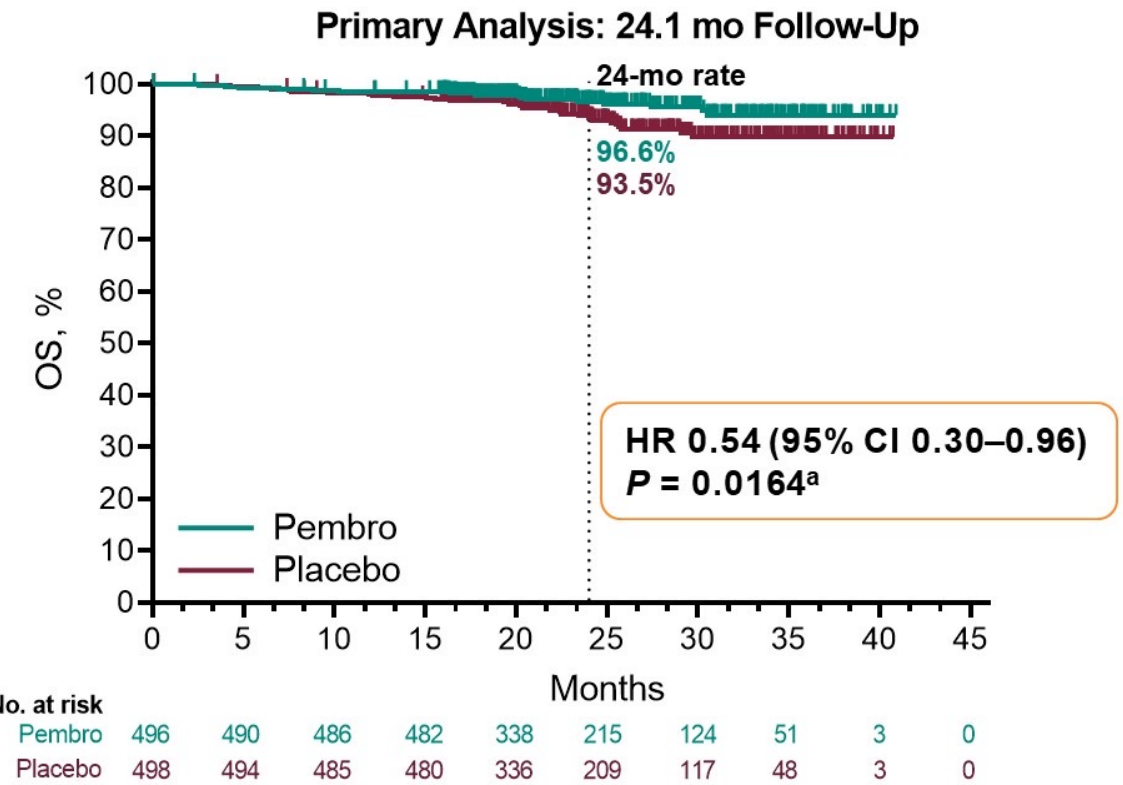
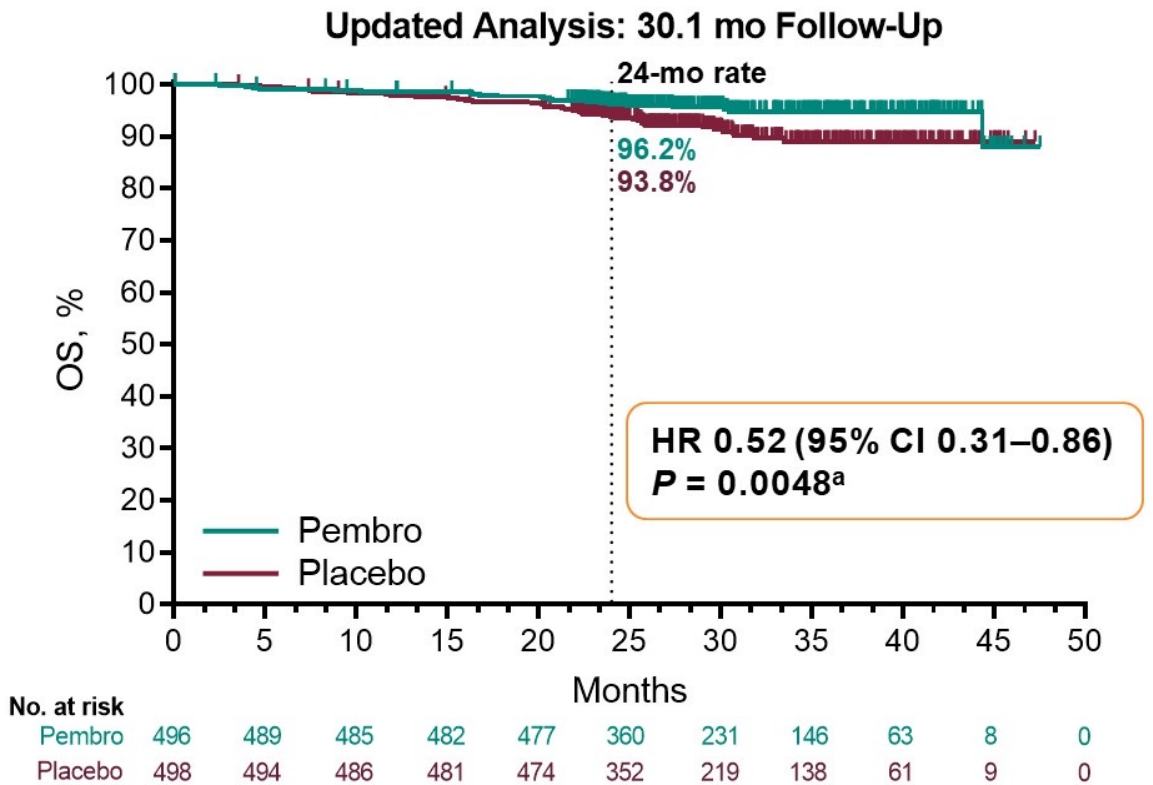
Key Secondary Endpoint: OS, ITT Population



	Pts w/ Event	Median, mo (95% CI)
Pembro	18	NR (NR–NR)
Placebo	33	NR (NR–NR)



	Pts w/ Event	Median, mo (95% CI)
Pembro	23	NR (NR–NR)
Placebo	43	NR (NR–NR)

[a]Did not cross prespecified p-value boundary for statistical significance.
ITT population included all randomized participants. NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

Studies of Adjuvant IO in RCC

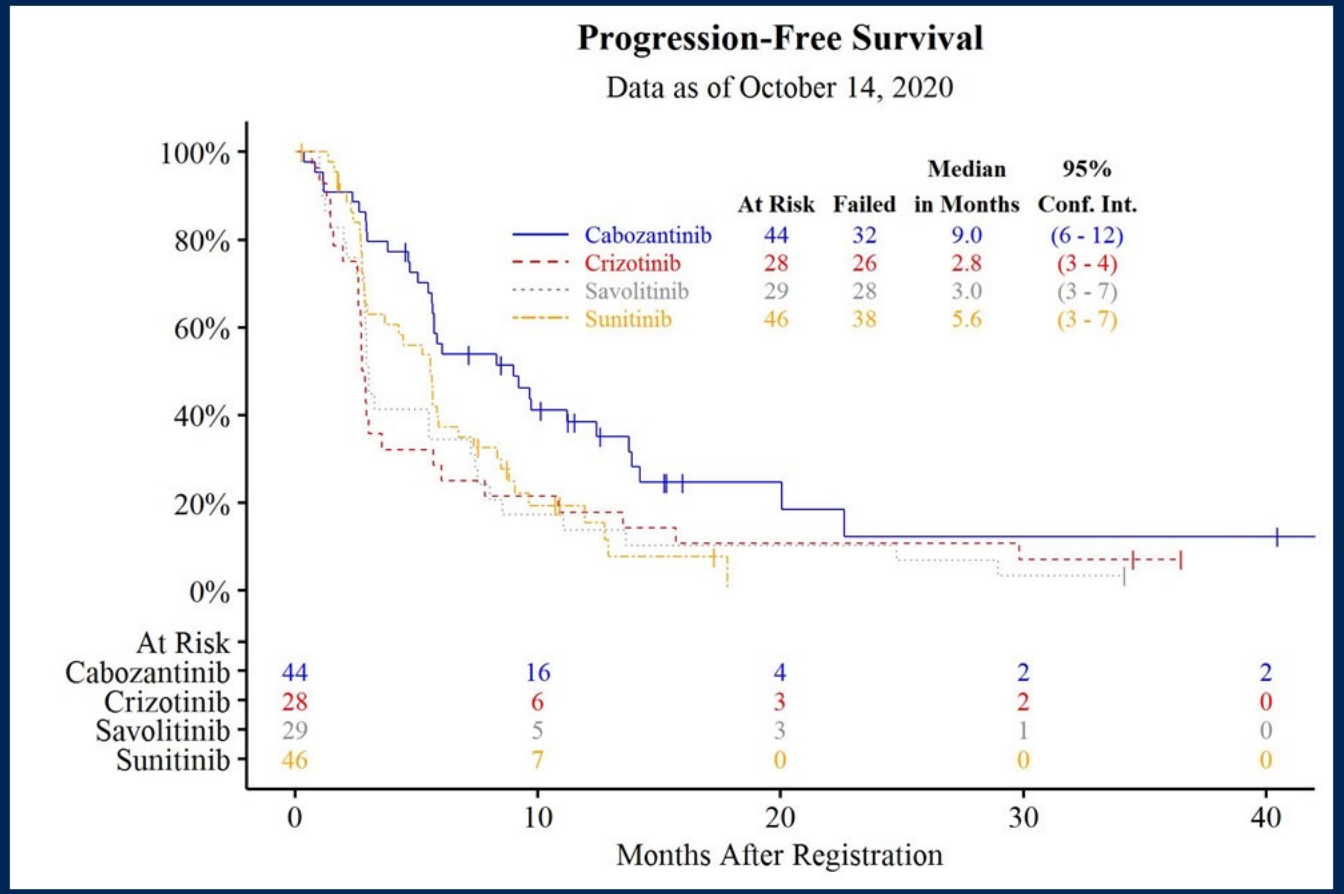
Trial	Sample Size	Inclusion Criteria	Treatment	Primary Endpoint	Expected Results
Keynote-564[1]	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell	Pembrolizumab vs placebo	DFS	**ASCO 2021 ASCO GU 2022**
IMmotion010[2]	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo	DFS	1/2022
CheckMate-914[3]	1600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs. nivolumab + placebo vs placebo *(6 months)*	DFS	1/2023
PROSPER RCC[4]	766	T2Nx, TxN1, TxNxM1 (resected to NED); any RCC histology	Nivolumab vs observation	EFS	11/2023
RAMPART[5]	1750	Leibovich score 3-11; any RCC histology	Durvalumab + tremelimumab vs durvalumab vs observation	DFS, OS	7/2024

*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy.
DFS, disease-free survival; EFS, event-free survival; NED, no evidence of disease; RCC, renal cell carcinoma; OS, overall survival.
1. Choueiri TK et al. *N Engl J Med*. 2021;385:683-694. 2. NCT03024996. 3. NCT03138512. 4. NCT03055013. 5. NCT03288532.

Non-Clear Cell Renal Cell Carcinoma

PAPMET
Results: Progression-Free Survival

Primary Endpoint



- Cabozantinib significantly prolonged PFS relative to sunitinib (HR 0.60 (95%CI 0.37-0.97 [1-sided P-value=0.019])

Study Design

Key Inclusion Criteria
- Advanced or metastatic ncRCC
- Measurable disease per RECIST v1.1
- 0–1 prior lines of systemic therapy

Study Treatment

Cabozantinib
40 mg PO daily

+

Nivolumab
240 mg IV every 2 weeks
(or 480 mg IV 4 weeks)

Primary Endpoint
- ORR by RECIST

Secondary Endpoints
- PFS by RECIST
- PFS by irRECIST
- OS
- Safety and tolerability

This is a single center, open-label, phase 2 study (NCT03635892) including patients treated with 0 or 1 prior systemic therapies in non-clear cell RCC with select histologies[1]:

- Cohort 1: papillary[2], unclassified, or translocation-associated RCC (N=40)
- Cohort 2: chromophobe RCC (N=7)

Cohort 1 was a single-stage design that met its primary endpoint (N=20) and was expanded to produce more precise estimates of ORR (total N=40). Cohort 2 was a Simon two-stage design that closed early.

[1]Histopathology was prospectively reviewed at MSKCC and retrospectively reviewed/confirmed by dedicated GU pathologist (YC)
[2]Papillary included unclassified with papillary features, high grade/type 1 papillary, and FH-deficient/type 2 papillary

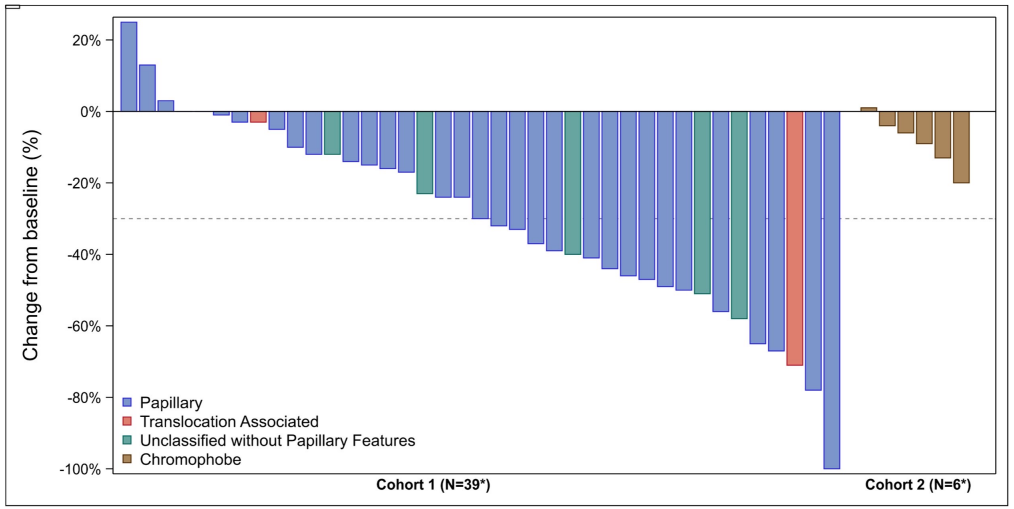
ncRCC, non-clear cell renal cell carcinoma, ORR, objective response rate; RECIST, Response Evaluation Criteria In Solid Tumors v1.1; irRECIST, immune-related Response Evaluation Criteria In Solid Tumors; PO, orally; IV, intravenously; PFS, progression-free survival; OS, overall survival

Summary of Efficacy Outcomes

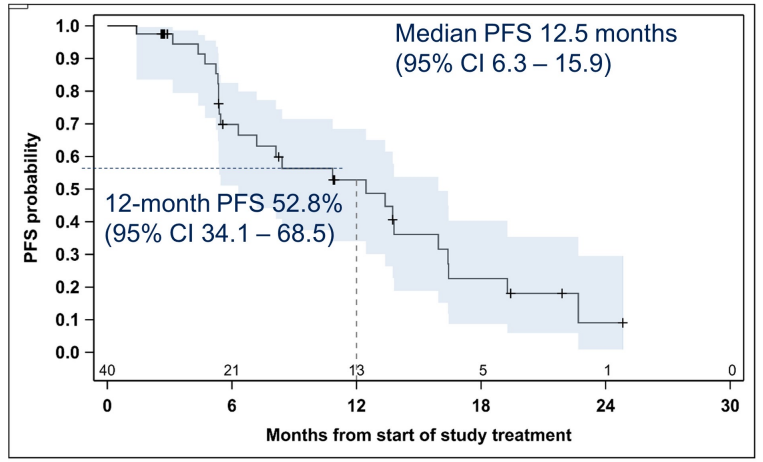
	Cohort 1 (N=40)	Cohort 2 (N=7)
Objective response rate (95% CI)	47.5% (31.5, 63.9)	0% (0, 41.0)
Best response – n (%)		
Partial response	19 (47%)	0 (0%)
Stable disease	20 (50%)	5 (71%)
Progressive disease	1 (3%)	1 (14%)
Not Evaluable	0 (0%)	1 (14%)
Disease control rate (95% CI)	97.5% (86.8, 99.9)	71.4% (29.0, 96.3)
Clinical benefit rate (95% CI)	75.0% (58.8, 87.3)	57.1% (18.4, 90.1)
Median progression-free survival, months (95% CI)	12.5 (6.3, 15.9)	*
Median duration of response, months (95% CI)	13.6 (9.7, 19.8)	†

*Median PFS not calculated due to small numbers of patients.
†No responders in cohort to calculate DOR

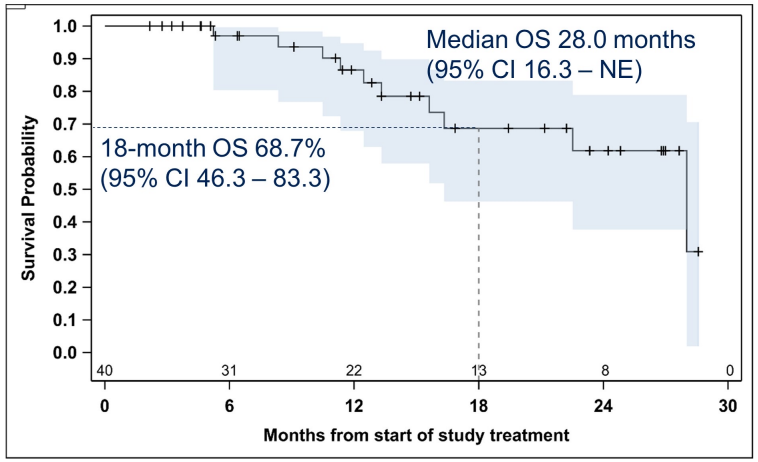
Maximum Change in Target Lesions by Histology



PFS by RECIST Kaplan-Meier Curve of Cohort 1 (Papillary/unclassified/translocation-associated)



OS Kaplan-Meier Curve of Cohort 1



Summary Points

- Primary renal tumors respond to systemic therapy with IO-based therapy (but less than metastatic sites)
- The gold-standard for mRCC is an IO-based combination (TKI monotherapy is the exception, not the rule!)
- TKI is the current SOC (includes novel agents, ie tivozanib). IO rechallenge might play a role: CONTACT3 and TINIVO2 will confirm
- nccRCC (papillary, uncl, transl ++) might benefit from IO-TKI (cabo/nivo)
- The benefit of adjuvant IO seems associated with the higher risk of recurrence/progression

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Urothelial Carcinoma

Platinum and Cisplatin Eligibility Criteria[1-4]

Platinum-Ineligible 10% to 15%	Platinum-Eligible (85-90%)

Platinum-Ineligible Criteria	Cisplatin-Ineligible Criteria (~35%)
Proposed consensus definition (Gupta JCO 2019)[2] One of the following 5 parameters to be used to define "platinum-ineligible" • ECOG PS ≥3 • CrCl <30 ml/min • Peripheral neuropathy ≥ grade 3 • NYHA Class III heart failure • ECOG PS 2 and CrCl <30 ml/min	**Proposed working group cisplatin ineligibility criteria (Galsky JCO 2011)[3]** At least one of the following • WHO or ECOG PS of 2 or Karnofsky PS of 60% to 70% • CrCl <60 mL/min • CTCAE v4 grade ≥2 audiometric hearing loss • CTCAE v4 grade ≥2 peripheral neuropathy • NYHA Class III heart failure

1. Internal resource: 1L UC Landscape and Patient Journey: US Report 07.30.2019. 2. Gupta S. et al, *J Clin Oncol.* 2019;37(Suppl 7s):abst 451. 3. Galsky MD, et al, *J Clin Oncol.* 2011;29: 2432-2438. 4. Kantar Health, Utilization and number of months of first-line systemic therapy, metastatic bladder cancer, United States, 2019

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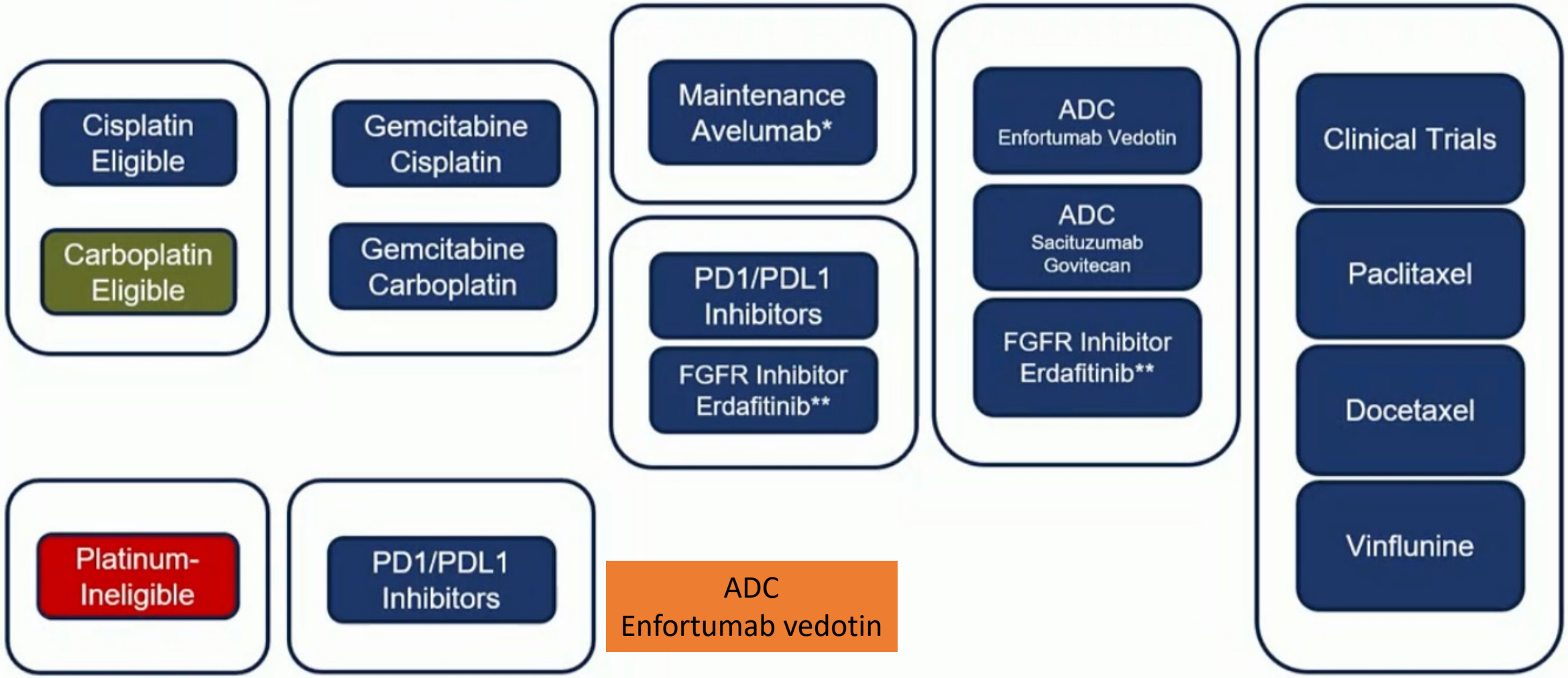
Treatment Landscape of mUC in 2021



*Disease control on platinum-based chemotherapy; ** FGFR 2/3 alterations, no prior Erdafitinib. ADC - Antibody Drug Conjugates

First-line mUC – platin-eligible

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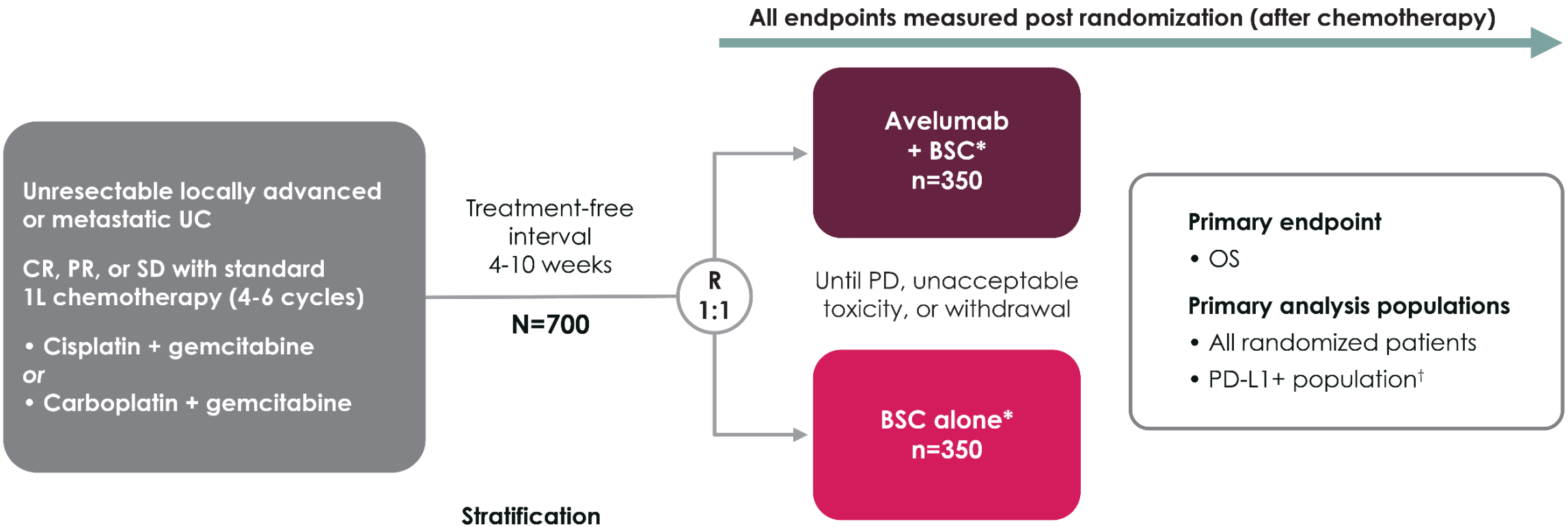
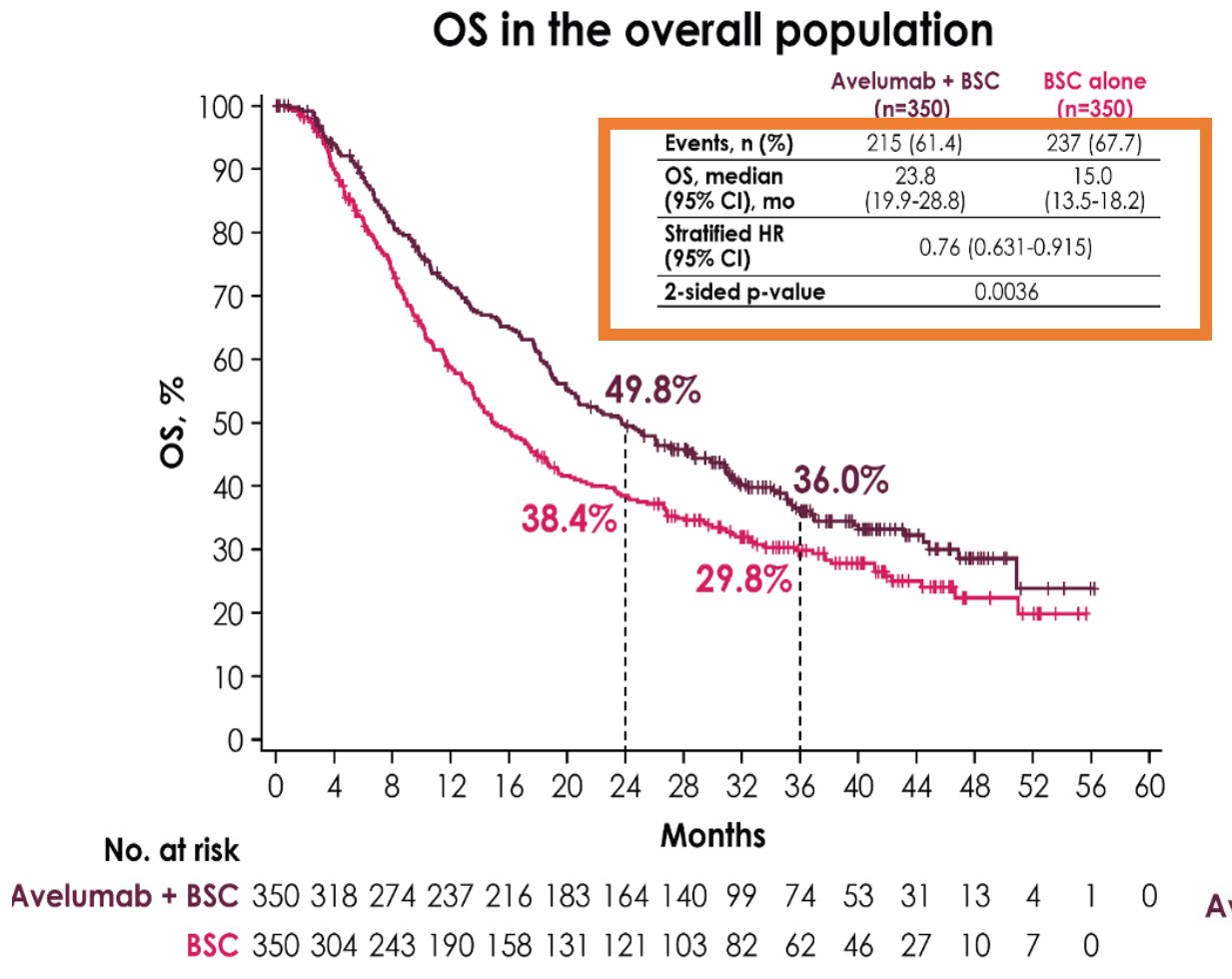
JAVELIN Bladder 100 Phase III Study

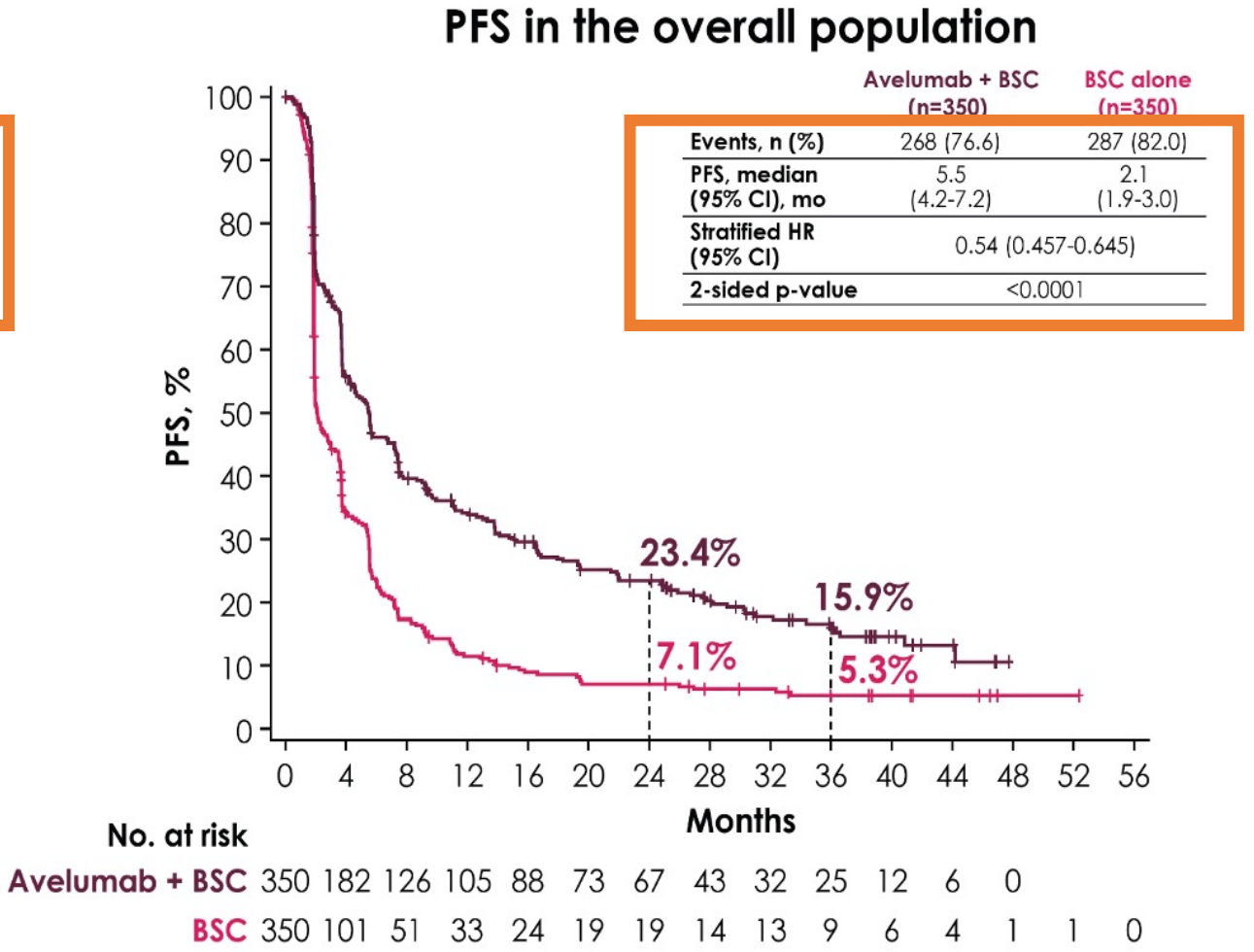


Data cutoff date: June 2021
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable. †Assessed using the Ventana SP263 assay.
1L, first line; BSC, best supportive care; CR, complete response; PR, partial response; OS, overall survival; PD, progressive disease; R, randomization; SD, stable disease; UC, urothelial carcinoma.

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

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





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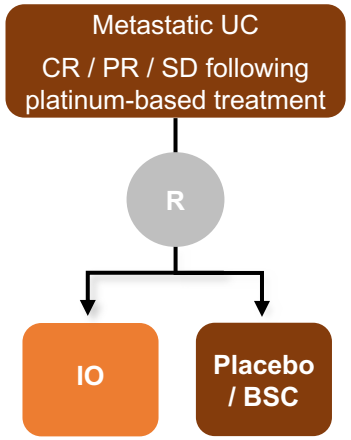
Current First-line Metastatic UC Maintenance and Combination Trials

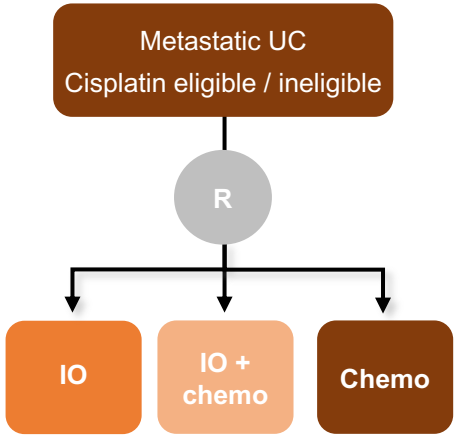
Treatment Strategies with the Potential to Impact Standard of Care

Maintenance



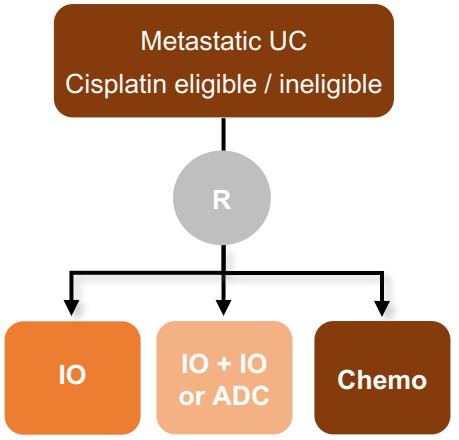
JB100 [NCT02603432]	avelumab	BSC	OS
HOOSIER [NCT02500121]	pembro	placebo	6-mo PFS

Chemo + IO



~~**KN361**~~ [NCT02853305]	pembro	pembro + chemo	chemo	OS, PFS
CM901 [NCT03036098]	--	nivo + chemo*	chemo	OS, PFS
~~**IMvigor130**~~ [NCT02807636]	atezo	atezo + chemo	chemo	OS, PFS, safety
NILE† [NCT03682068]	durva	durva + chemo	chemo	OS, PFS

IO + IO/ IO + ADC



~~**DANUBE**~~ [NCT02516241]	durva	durva + treme	chemo	OS
CM901 [NCT03036098]	--	nivo + ipi	chemo	OS, PFS
EV-302 [NCT04223856]	pembro	pembro + EV + chemo	chemo	OS, PFS
NILE† [NCT03682068]	durva	durva + treme + chemo	chemo	OS, PFS

~~Study~~ Study has read out with negative results on one or more endpoints

†NILE is a 3-arm trial comparing durva + CT to durva + treme + CT to CT alone; including features of IO + CT, as well as IO doublet therapy.

*For cisplatin-eligible patients only.

1L, first-line; ADC, antibody-drug conjugate; atezo, atezolizumab; BSC, best supportive care; EV, enfortumab vedotin; chemo, chemotherapy; CR, complete response; durva, durvalumab; IO, immuno-oncology; ipi, ipilimumab; OS, overall survival; nivo, nivolumab; pembro, pembrolizumab; PFS, progression-free survival; PR, partial response; R, randomisation; SD, stable disease; SoC, standard of care; treme, tremelimumab; UC, urothelial carcinoma. NCT entries available at https://clinicaltrials.gov/ [Accessed August 2020].

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First-line mUC – cisplatin ineligible

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Enfortumab vedotin + Pembrolizumab (EV-103)

Long Term Results and Durability Updates from ASCO 2021

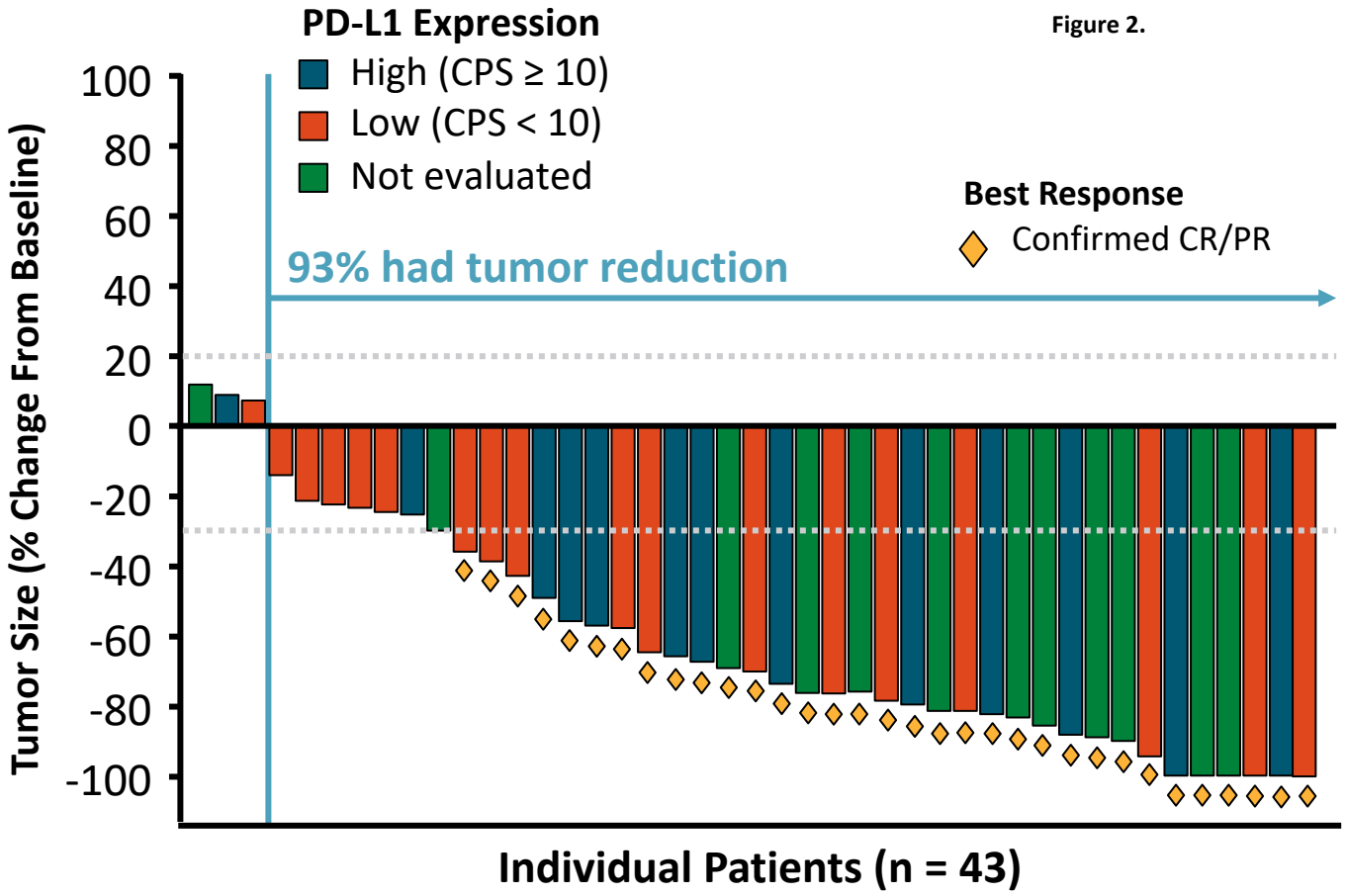
- Updated data with 24.9 months median follow-up (Data cut-off: October 2020)

Figure 1.

Best Overall Response	All Patients (N = 45)
Confirmed ORR, n (%) [95% CI] CR, n (%) PR, n (%)	**33 (73.3) [58.1–85.4]** 7 (15.6) 26 (57.8)
SD	9 (20.0)
PD	1 (2.2)
ORR in patients with liver metastasis, n/N (%)	8/14 (57.1)
ORR by PD-L1 status, n/N (%) High expression Low expression	 11/14 (78.6) 12/19 (63.2)
Additional Efficacy @ ASCO 2021	**All Patients (N = 45)**
Median DOR, months, (95% CI)	25.6 (8.3, –)
DCR, %	93.3
Median PFS, months, (95% CI)	12.3 (8.0, –)
24 mo. OS Rate, %, (95% CI)	56.3 (39.8-69.9)

1. Presented by TW Friedlander at ASCO 2021 Annual Meeting June 4-8, 2021. Abstract 4528.

Figure 2.



2. Rosenberg. ASCO 2020. Abstr 5044. Rosenberg. ASCO GU 2020. Abstr 441.

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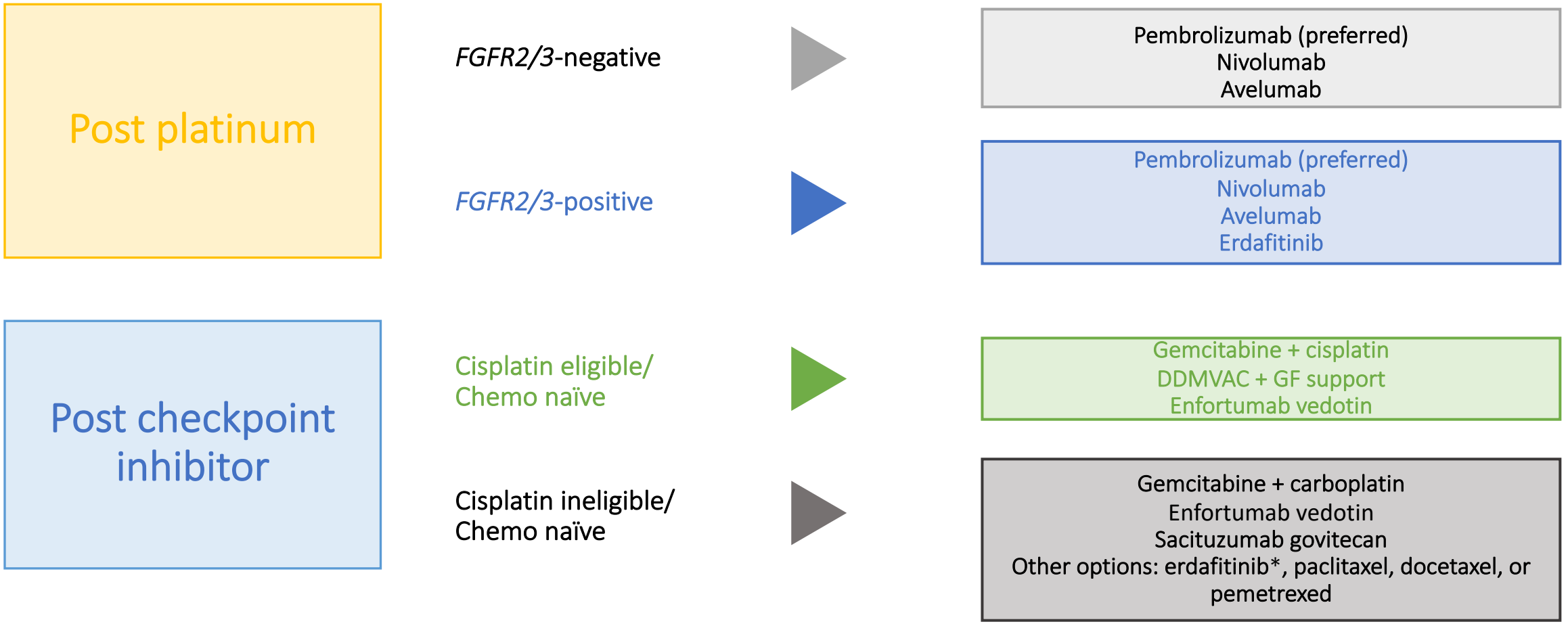
Second-Line Systemic Treatment for mUC



* If *FGFR2/3* positive

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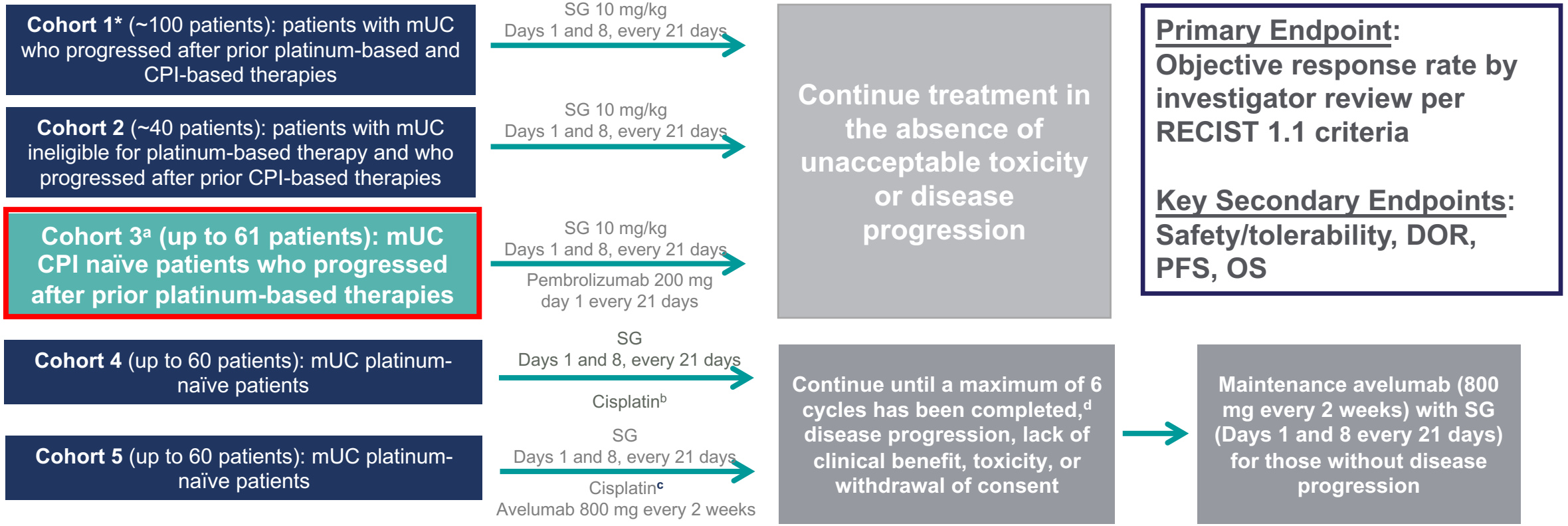
TROPHY-U-01 Is a Registrational, Open-Label, Multicohort Phase 2 Trial in Patients With mUC



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

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

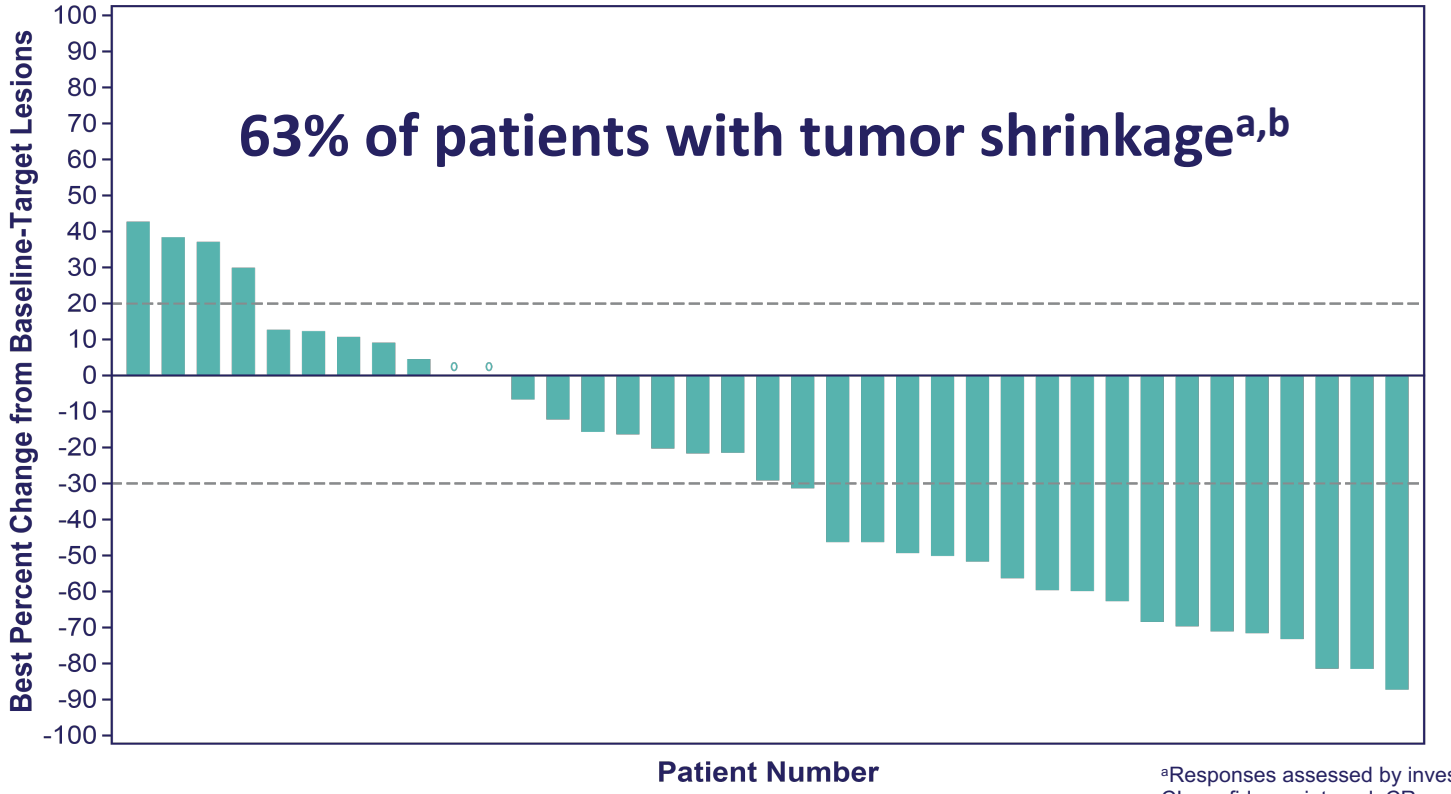
[a]Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. [b]In patients with CrCl ≥60 mL/min; [c]In patients with creatinine clearance 50–60 mL/min. [d]For patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 2 weeks beginning cycle 1, day 1 and every 2 weeks thereafter) followed by SG on days 1 and 8 every 21 days.
CBR, clinical benefit rate; CPI, checkpoint inhibitor; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.

1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

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

TROPHY-U-01 Cohort 3: Overall Response and Best % Change From Baseline in Tumor Size

- Median follow-up: 5.8 months (data cutoff date: 2021-09-24)
- Median time to response: 2 months (1.3–2.8; n=14)
- Median DOR not yet reached: N/A (2.80-N/A)
- Median PFS (95% CI), 5.5 months (1.7–NR); median OS, not reached



	Cohort 3[a] (N=41)
Objective response rate (CR + PR), n (%) [95%CI]	**14 (34) [20.1-50.6]**
Objective response rate (CR + PR), evaluable patients, n (%)	14 (38)
Best overall response, n (%)	
CR	1 (2)
PR	13 (32)
SD	11 (27)
SD ≥ 6 months	*4 (10)*
PD	12 (29)
Not assessed	4 (10)
Clinical Benefit Rate (CR + PR + SD), n (%) [95%CI]	25 (61) [44.5-75.8]

[a]Responses assessed by investigator in the intent-to-treat population. [b]Patients without post-baseline assessments are not shown here.
CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

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

Localized UC

CheckMate 274

Study design

- CheckMate 274 is a phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

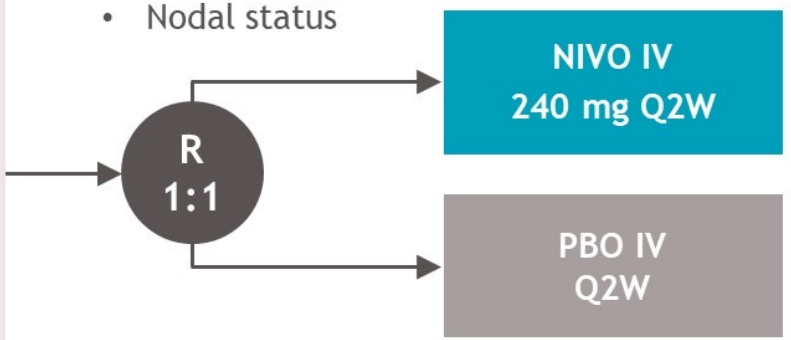
N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors

- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status



Treat for up to 1 year of adjuvant therapy

Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

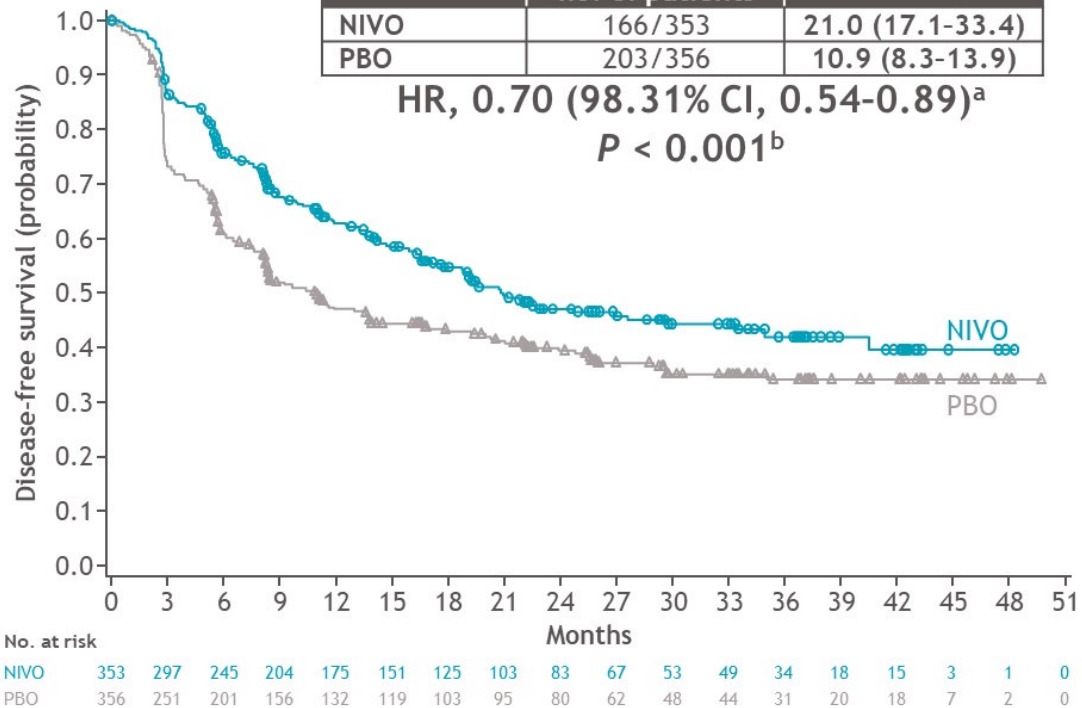
[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IHC, immunohistochemistry; ITT, intent-to-treat; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; R, randomized.

Disease-free survival

ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	166/353	21.0 (17.1-33.4)
PBO	203/356	10.9 (8.3-13.9)

HR, 0.70 (98.31% CI, 0.54-0.89)[a]
P < 0.001[b]



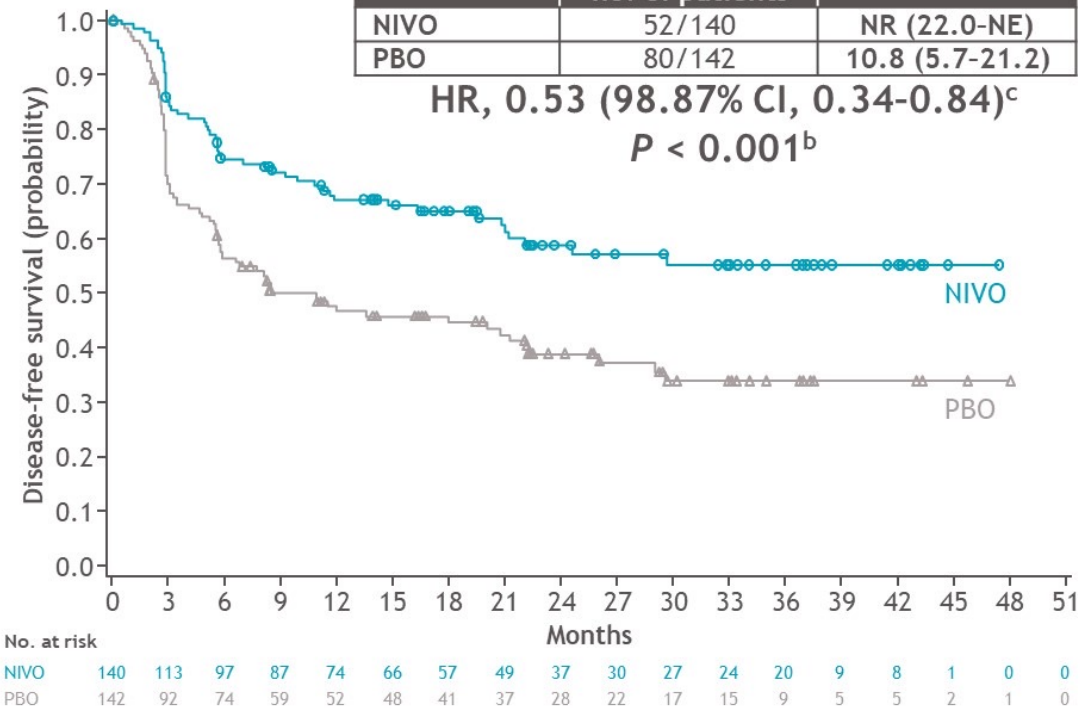
No. at risk

NIVO	353	297	245	204	175	151	125	103	83	67	53	49	34	18	15	3	1	0
PBO	356	251	201	156	132	119	103	95	80	62	48	44	31	20	18	7	2	0

PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	52/140	NR (22.0-NE)
PBO	80/142	10.8 (5.7-21.2)

HR, 0.53 (98.87% CI, 0.34-0.84)[c]
P < 0.001[b]



No. at risk

NIVO	140	113	97	87	74	66	57	49	37	30	27	24	20	9	8	1	0	0
PBO	142	92	74	59	52	48	41	37	28	22	17	15	9	5	5	2	1	0

Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

Disease-free survival

FDA approves nivolumab for adjuvant treatment of urothelial carcinoma

On August 19, 2021, the Food and Drug Administration approved nivolumab [redacted] for the adjuvant treatment of patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection.

Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

Summary Points

- PD(L)-1 play a role in localized and advanced UC
- ADC-IO combinations are promising
- Long-term Fup data supports the use of IO earlier in the course of the disease
- Optimal sequencing is unclear

Thank You!!

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