Novel Advanced in the Therapy of Kidney and Bladder Carcinomas

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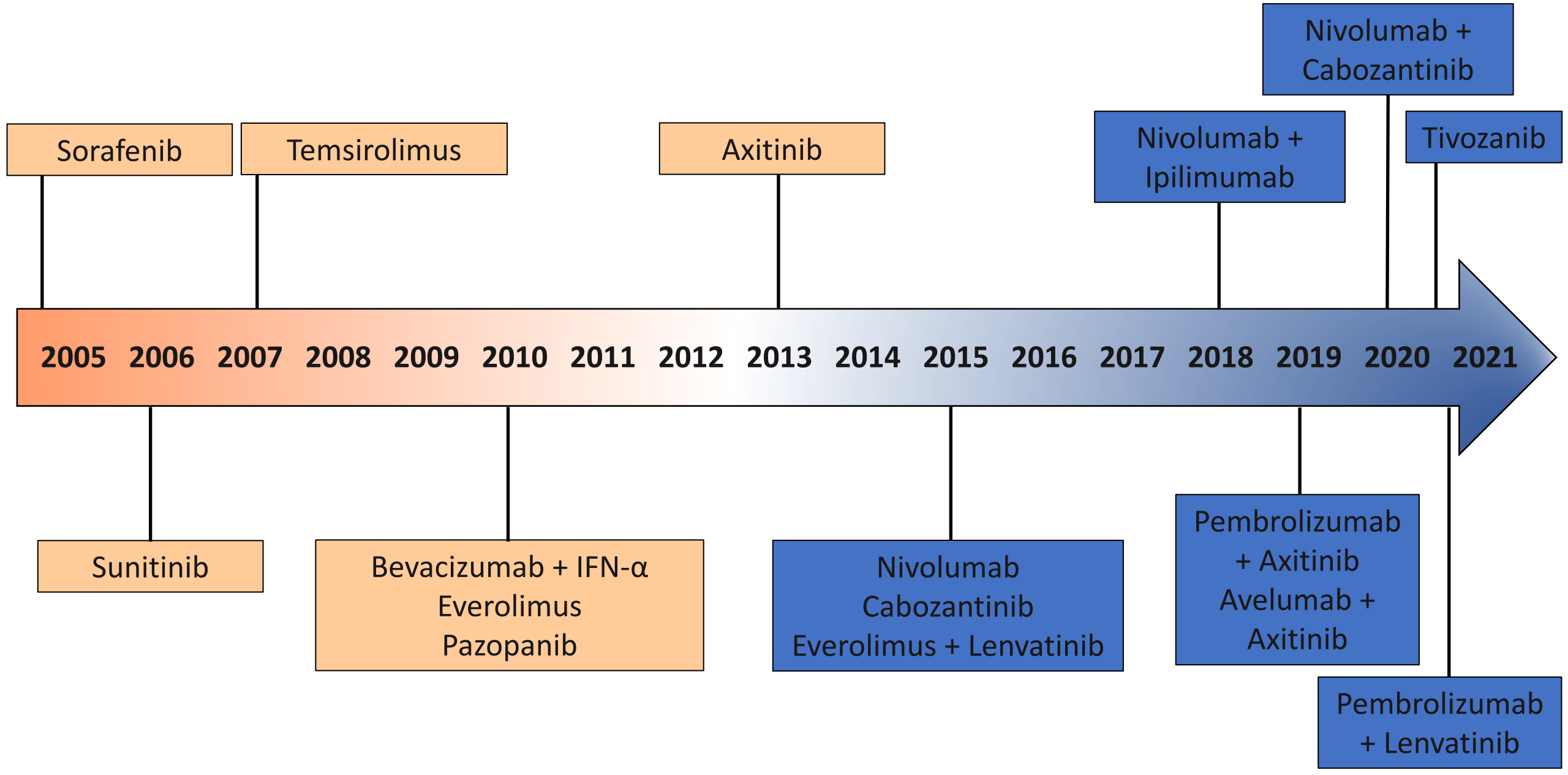
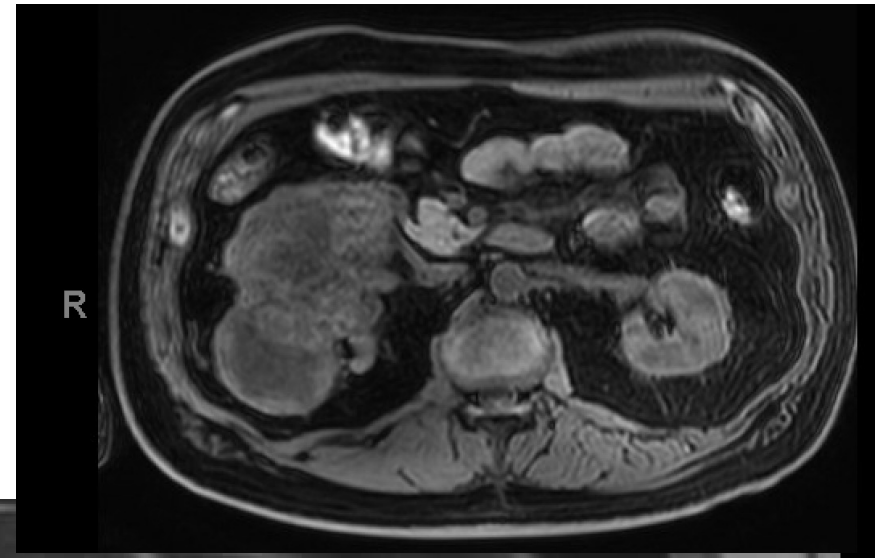
Treatment Landscape of Metastatic RCC

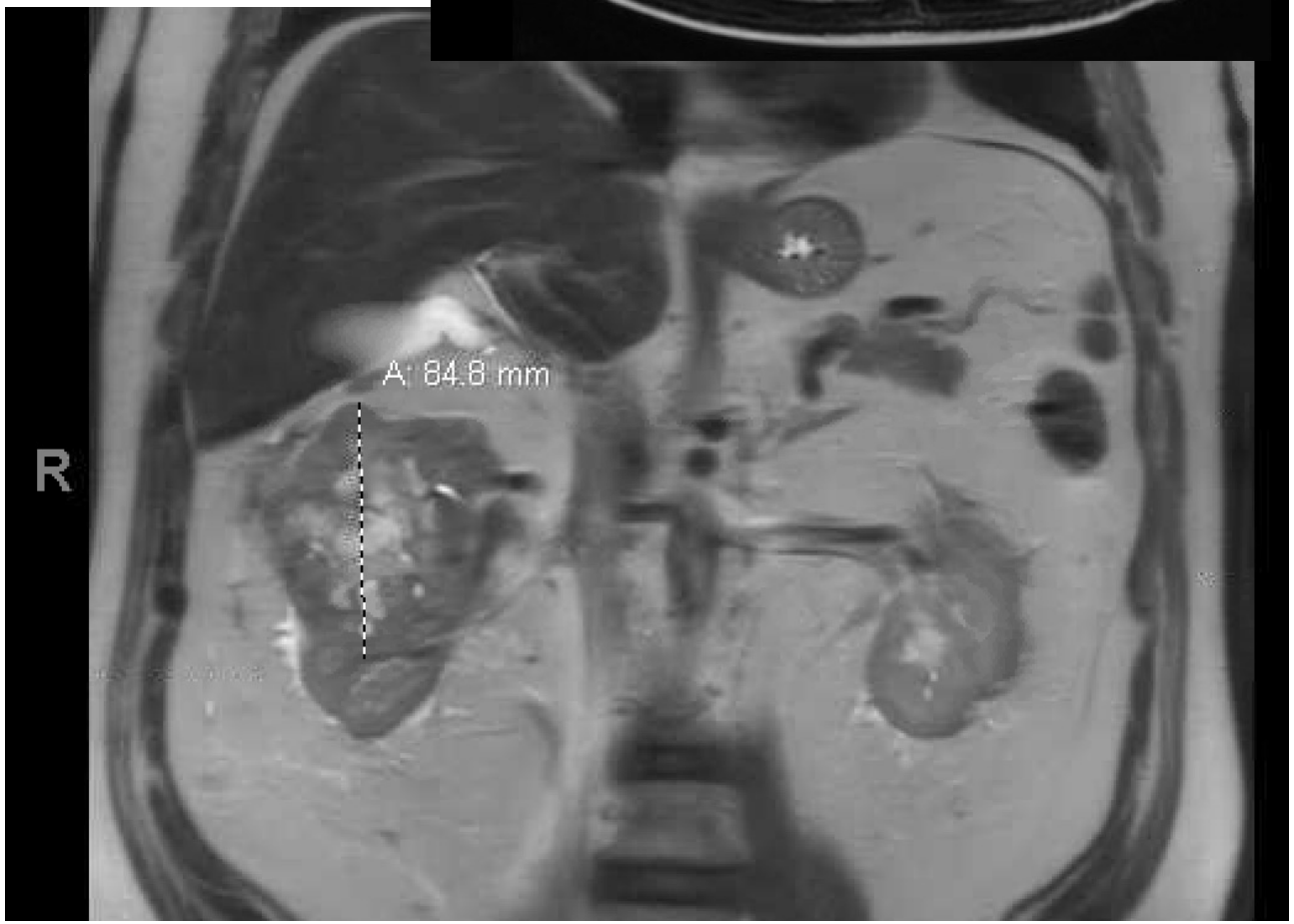


Clinical Case:

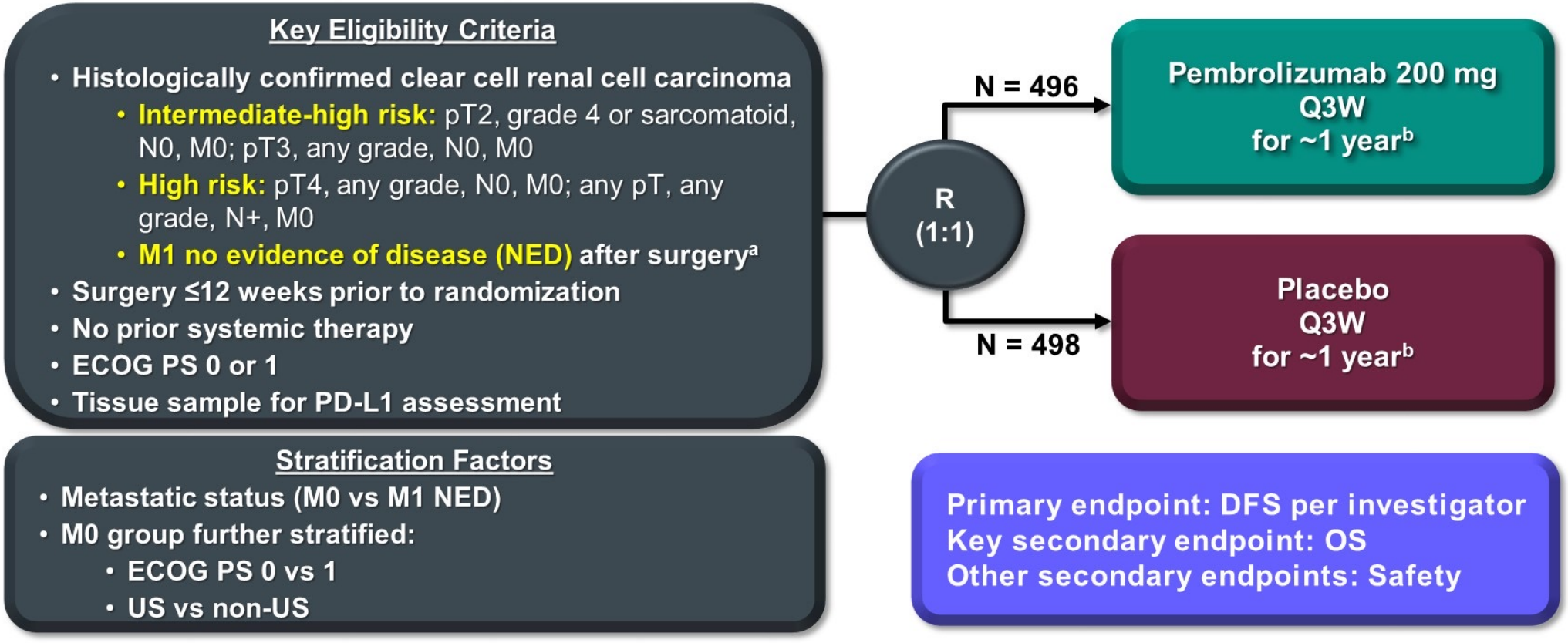
70-year-old man presented with gross hematuria

- CT shows 13cm R renal mass with hemorrhage into ureter and bladder
- R radical nephrectomy: pathology showed clear cell RCC, 11cm, extensive involvement of renal vein, renal sinus fat, rhabdoid and focal sarcomatoid differentiation, multifocal tumor necrosis; margins negative pT3aNxMx





KEYNOTE-564 (NCT03142334) Study Design

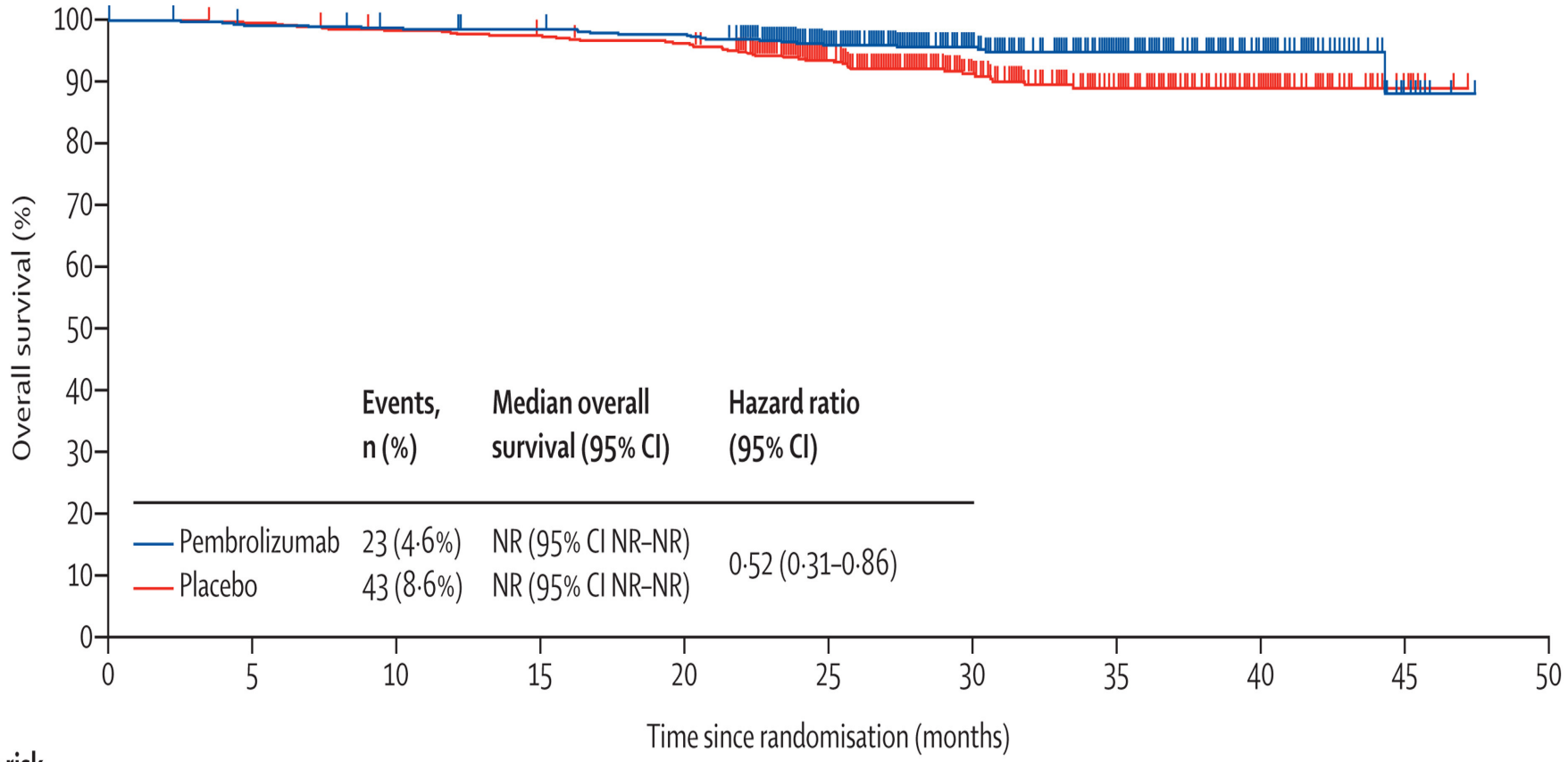


- Median (range) time from randomization to cutoff: 30.1 (20.8–47.5) months

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.

Choueiri TK, et al. *N Engl J Med*. 2021; 385(8):683-694.
Powles T, et al. *Lancet Oncol*. 2022;23(9):1133-1144.

Key Secondary Endpoint: OS, ITT Population



Number at risk (number censored)											
Pembrolizumab	496 (3)	489 (3)	485 (5)	482 (7)	477 (8)	360 (117)	231 (245)	146 (328)	63 (411)	8 (465)	0 (473)
Placebo	498 (0)	494 (2)	486 (4)	481 (5)	474 (6)	352 (115)	219 (241)	138 (317)	61 (394)	9 (446)	0 (455)

Powles T, et al. *Lancet Oncol*. 2022;23(9):1133-1144.

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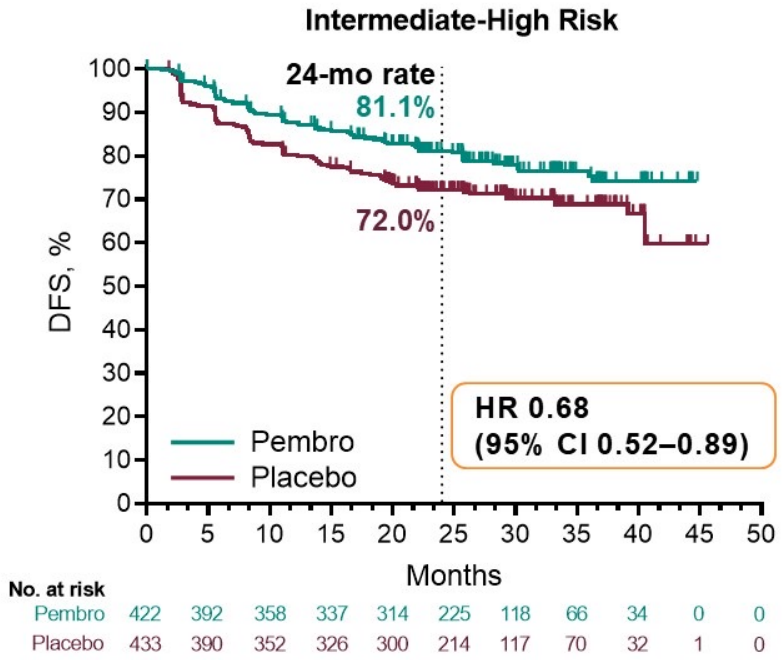
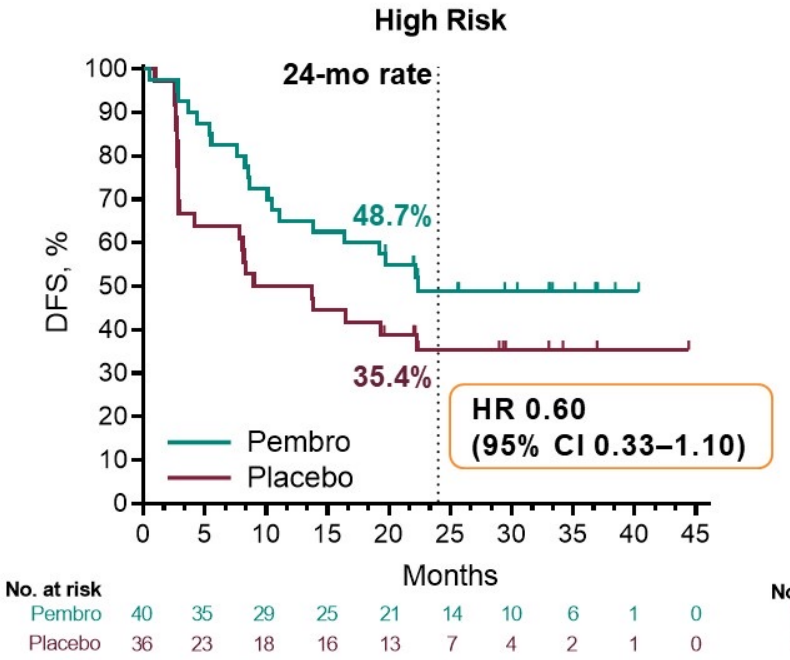
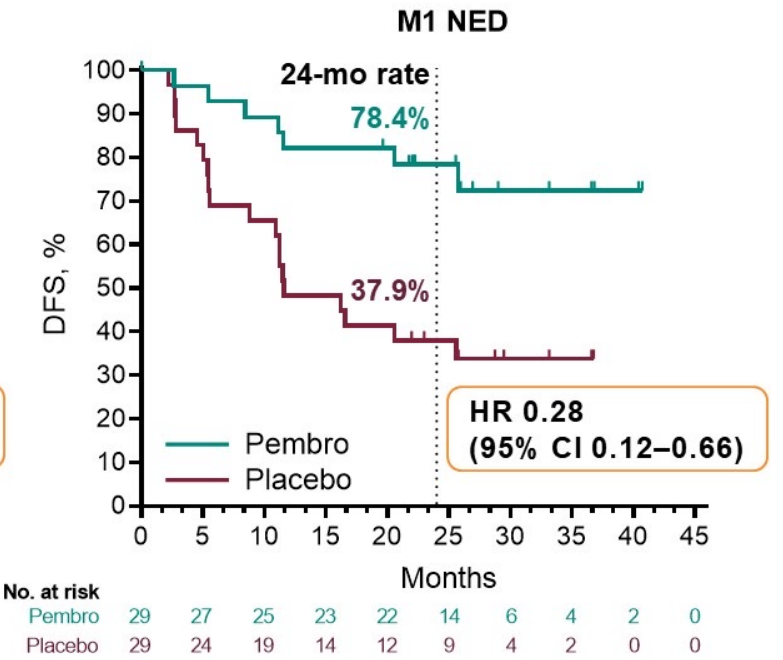
DFS by Recurrence Risk Subgroups



	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.

Powles T, et al. *Lancet Oncol*. 2022;23(9):1133-1144.

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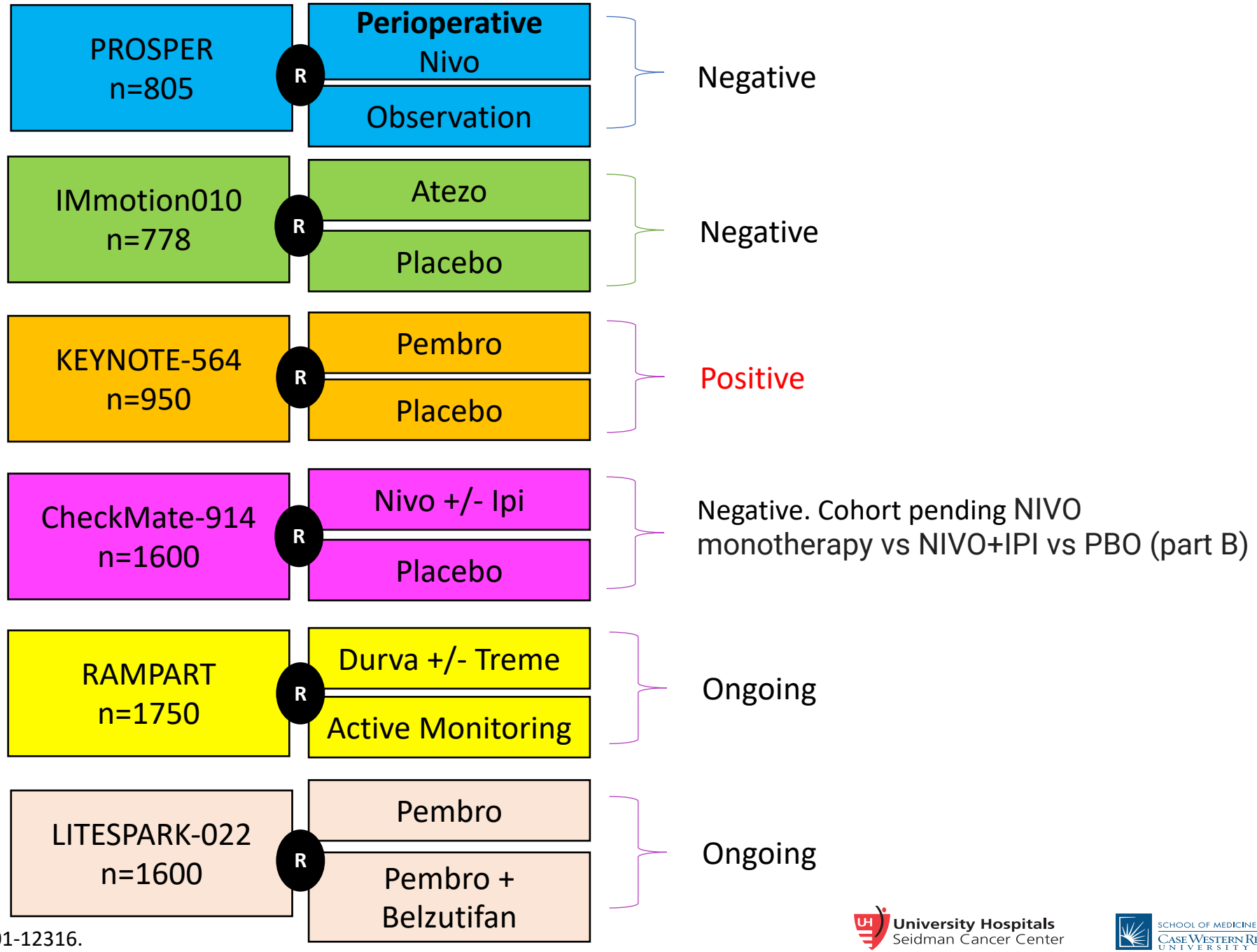
Adjuvant IO Trials

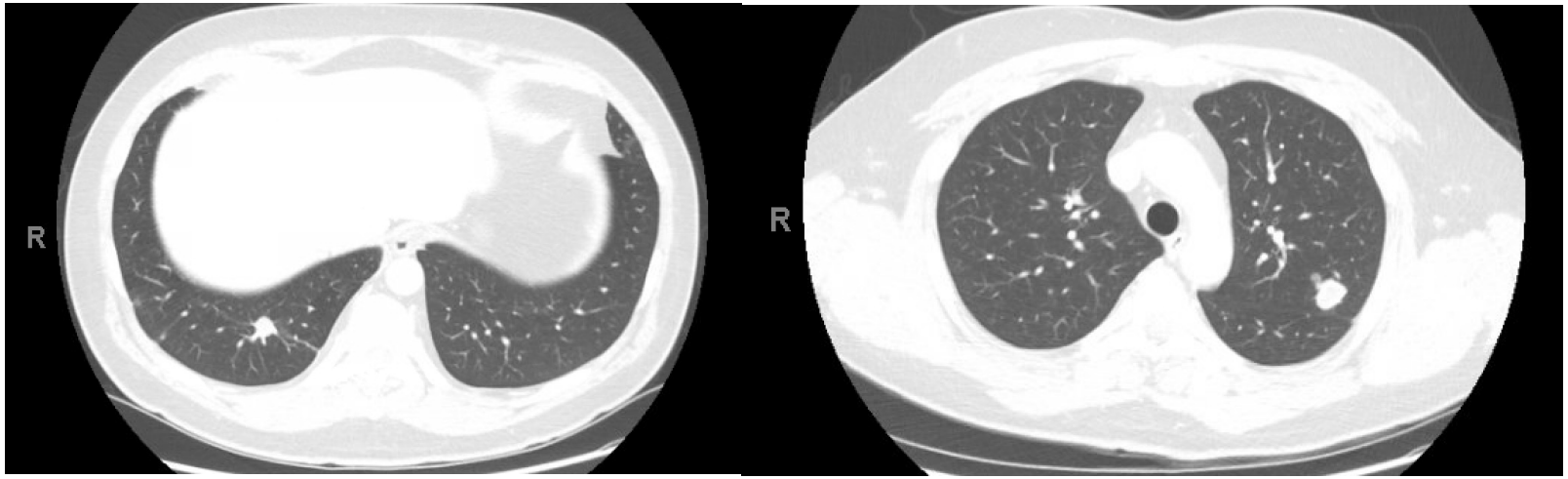


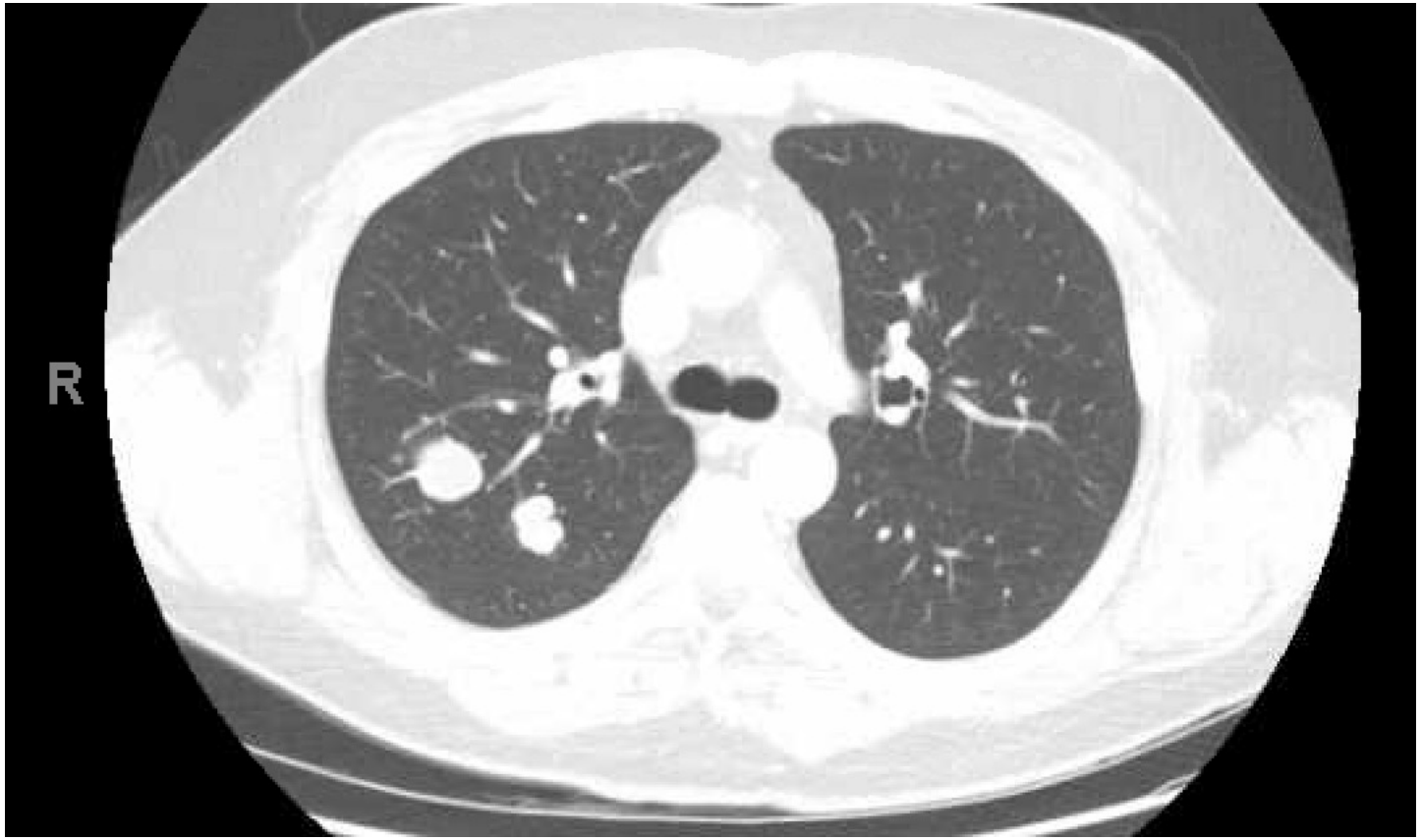
Tacconi EMC, et al. *Onco Targets Ther.* 2020;13:12301-12316.

Back to the Case…

70-year-old man presented with gross hematuria

- CT shows 13cm R renal mass with hemorrhage into ureter and bladder
- R nephrectomy: pathology showing clear cell RCC, 11cm, extensive involvement of renal vein, renal sinus fat, rhabdoid and focal sarcomatoid differentiation, multifocal tumor necrosis; margins negative pT3aNxMx
- Opted for surveillance
- 10 months later, on surveillance scans developed multifocal bilateral pulmonary nodules
- Labs are normal





The Latest Evidence-based Guidance for the Management of First-line Metastatic RCC

University Hospitals
Seidman Cancer Center

School of Medicine
Case Western Reserve University

Front Line Treatment Options in Metastatic RCC

IO-IO

- Nivolumab + Ipilimumab

IO-VEGF

- Pembrolizumab + Axitinib
- Avelumab + Axitinib
- Nivolumab + Cabozantinib
- Pembrolizumab + Lenvatinib

VEGF

- Cabozantinib
- Sunitinib
- Pazopanib

Frontline Immunotherapy Combination Studies

Baseline Characteristics

Variable		Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Avelumab + Axitinib Javelin 101 n=886	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib n=1096
IMDC Risk Group	Favorable	23%	33%	21%	23%	32%
	Intermediate	61%	56%	62%	58%	54%
	Poor	17%	13%	16%	19%	10%
Previous Nephrectomy		81%	83%	80%	69%	73%
PD-L1 Expression ≥1%		24% (Dako PD-L1 28-8; Tumor)	60% (Agilent Tech PD-L1 22C3; CPS)	63% (Ventana PD-L1 SP263; Immune)	25% (Dako PD-L1 28-8; Tumor)	31% (Agilent Tech PD-L1 22C3; CPS)
Primary Endpoint		ORR, PFS, OS in Int/Poor (IRC)	OS, PFS (IRC)	OS, PFS in PD-L1+ (IRC)	PFS (IRC)	PFS (IRC)

Motzer RJ, et al. *N Engl J Med*. 2018;378(14):1277-1290.
Rini BI, et al. *N Engl J Med*. 2019;380(12):1116-1127.
Motzer RJ, et al. *N Engl J Med*. 2019;380(12):1103-1115.
MotzerRJ, et al. *N Engl J Med*. 2021;384(14):1289-1300.

IMDC=International Metastatic RCC Database Consortium; PD-L1=Programmed Death Ligand 1; CPS=Combined positive score (TC+IC positive/TC all); ORR=Objective response rate; PFS=Progression-free survival; OS=Overall survival; Int=Intermediate; IRC=Independent review committee.

Summary of Select Immunotherapy Combination Trials

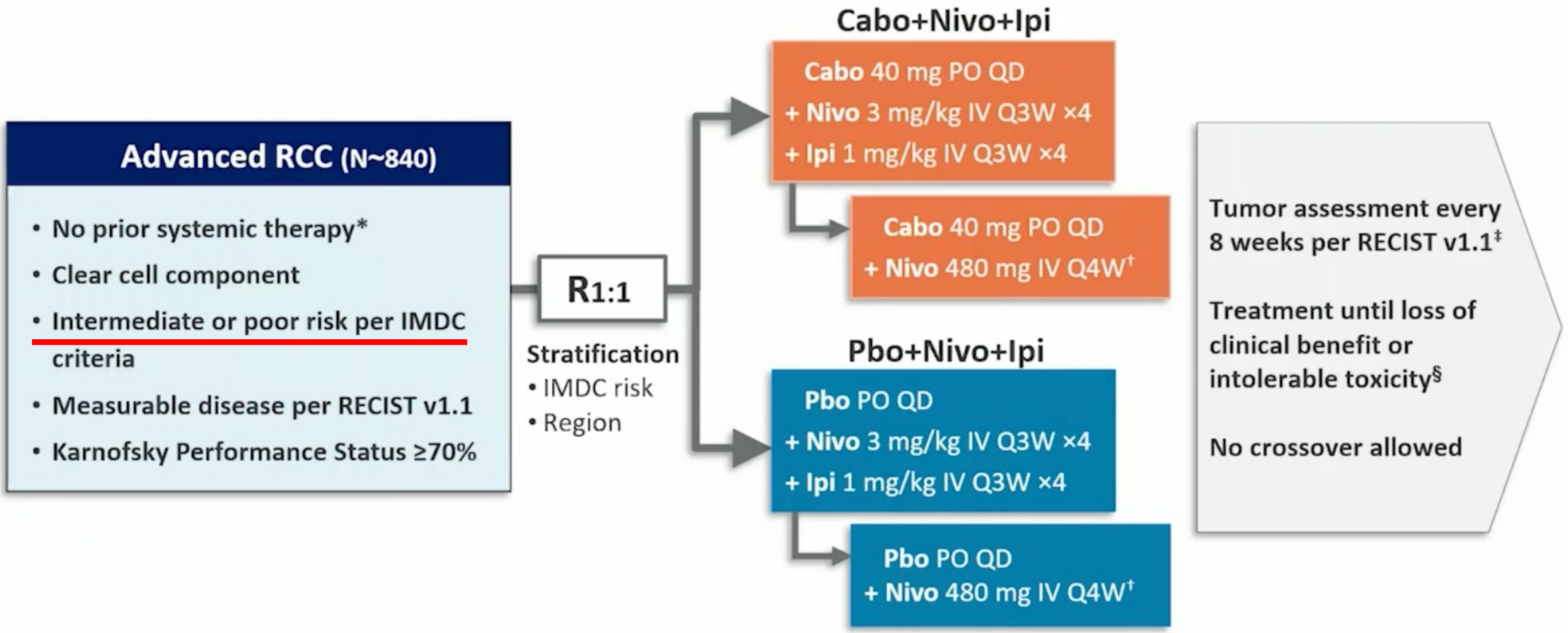
	Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib Clear n=1096
Follow-up, mo	67.7 (median)	42.8 (median)	32.9 (median)	33.7 (median)
Median PFS, mo	12.3	15.7	16.6	23.9
PFS HR	0.86	0.68	0.56	0.39
Median OS, mo	55.7	45.7	37.7	NR
12-month OS, %	83	90	86	90
24-month OS, %	71	74	70	79
OS HR	0.72	0.73	0.70	0.72
ORR, %	39	60	56	71
CR, %	12	10	12	16
PD, %	18	11	6	3

Motzer RJ, et al. *N Engl J Med*. 2018;378(14):1277-1290.
Rini BI, et al. *N Engl J Med*. 2019;380(12):1116-1127.
Motzer RJ, et al. *N Engl J Med*. 2019;380(12):1103-1115.
MotzerRJ, et al. *N Engl J Med*. 2021;384(14):1289-1300.

Not Intended for Direct Comparison

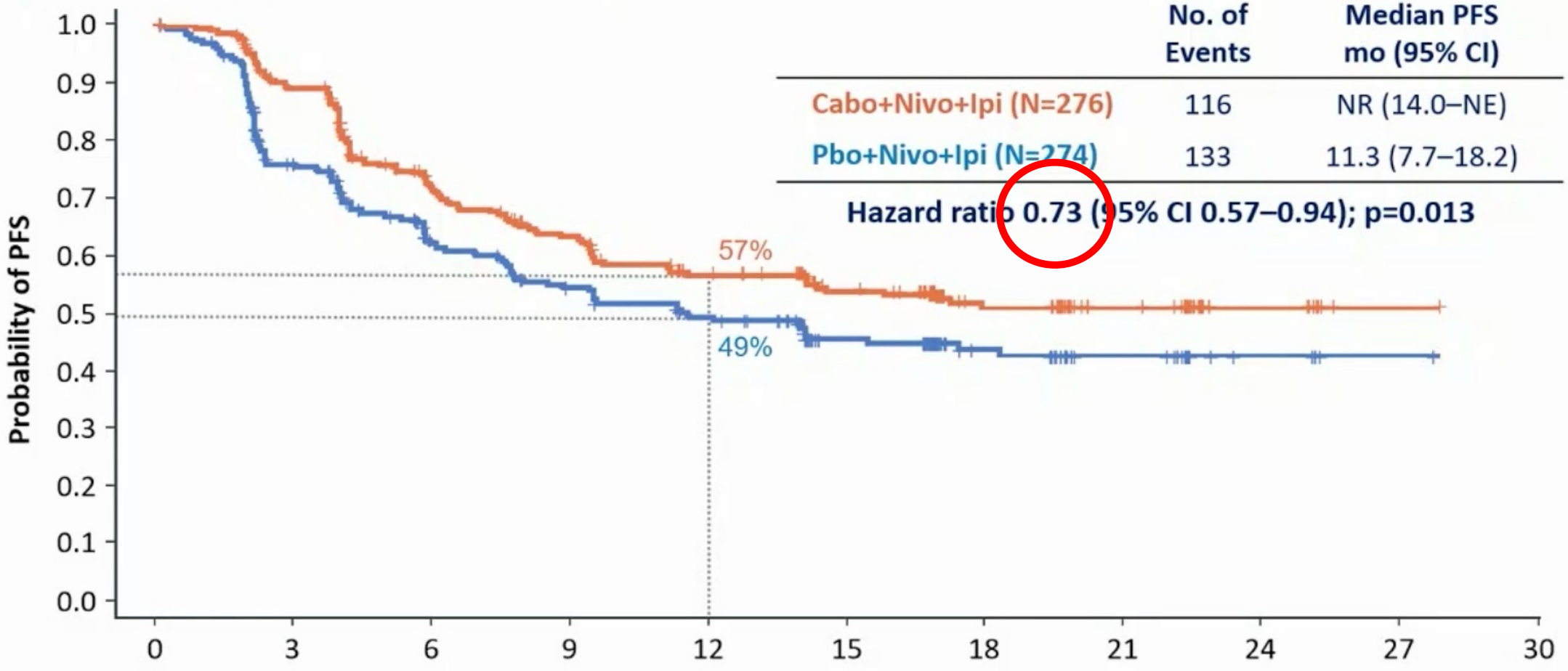
Mo=months; PFS=Progression-free survival; HR=Hazard ratio; ORR=Objective response rate; CR=Complete response rate; PD=Progressive disease rate; TTR=Time to response; DOR=Duration of response.

COSMIC-313 Study Design



*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. §Discontinuation of one agent did not mandate discontinuation of all agents.

Progression-Free Survival: Final Analysis (PITT Population)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=276)	116	NR (14.0–NE)
Pbo+Nivo+Ipi (N=274)	133	11.3 (7.7–18.2)

Hazard ratio 0.73 (95% CI 0.57–0.94); p=0.013

Number at Risk

Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

PFS per RECIST v1.1 by BIRC.

Date of the 249th event: Aug 23, 2021

Tumor Response (PITT Population)

	Cabo+Nivo+Ipi (N=276)	Pbo+Nivo+Ipi (N=274)
Objective response rate (95% CI), %	43 (37.2–49.2)	36 (30.1–41.8)
Best overall response, n (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Not evaluable	15 (5)	21 (8)
Disease control rate, %	86	72
Median time to objective response (range), mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI), mo	NR (20.2–NE)	NR (NE–NE)

Tumor response per RECIST v1.1 by BIRC
Disease control rate = complete response + partial response + stable disease

Data cut-off: Jan 31, 2022

What about Toxicity?

	Nivolumab + Ipilimumab CheckMate-214 n=1096 Minimum Follow-Up 48 mo	Pembrolizumab + Axitinib Keynote 426 n=861 Minimum Follow-Up 23 mo	Nivolumab + Cabozantinib CheckMate-9ER n=651 Median Follow-Up 23.5 mo	Pembrolizumab + Lenvatinib Clear n=1096 Median Follow-Up 26.6 mo
TRAE Grade 3-5	48%	67%	62%	82%
TRAE leading to D/C (either/both drugs)	22.1%*	27.7%/6.5%#	23.4%/6.6%	29% pembrolizumab 26% lenvatinib 13% both
HD Corticosteroid	29%	27%	21%	Not reported
TR deaths, n (%)	8 (1.5%)	4 (0.9%)	1 (0.3%)	15 (4.2%)

Motzer RJ, et al. *N Engl J Med*. 2018;378(14):1277-1290.
Rini BI, et al. *N Engl J Med*. 2019;380(12):1116-1127.
Motzer RJ, et al. *N Engl J Med*. 2019;380(12):1103-1115.
MotzerRJ, et al. *N Engl J Med*. 2021;384(14):1289-1300.

*From minimum 42 month follow-up. #From median 16.6 month follow-up.
Mo=Months; TRAE=Treatment-related adverse events; D/C=Discontinue; HD=high dose; TR=Treatment-related.

What about Quality of Life?

	CheckMate-214		Keynote-426		Checkmate-9ER		Clear		
	Nivolumab + Ipilimumab	Sunitinib	Pembrolizumab + Axitinib	Sunitinib	Nivolumab + Cabozantinib	Sunitinib	Pembrolizumab + Lenvatinib	Lenvatinib + Everolimus	Sunitinib
	Intermediate/Poor		All Risk		All Risk		All Risk		
FKSI-19	↑				↑				
FKSI-DRS			=		↑		=/↑	=/↓	
EQ-5D-3L	↑		=		↑		=/↑	=/↓	
EORTC QLQ-C30			=				=/↑	=/↓	
FACT-G	↑								

FKSI-19=Functional Assessment of Cancer Therapy—Kidney Symptom Index; FKSI-DRS=Functional Assessment of Cancer Therapy-Disease related symptoms; EPRTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; FACT-G=Functional Assessment of Cancer Therapy—General.

Motzer RJ, et al. *N Engl J Med*. 2018;378(14):1277-1290.
Rini BI, et al. *N Engl J Med*. 2019;380(12):1116-1127.
Motzer RJ, et al. *N Engl J Med*. 2019;380(12):1103-1115.
MotzerRJ, et al. *N Engl J Med*. 2021;384(14):1289-1300.

Second Line and Beyond

National Comprehensive Cancer Network®

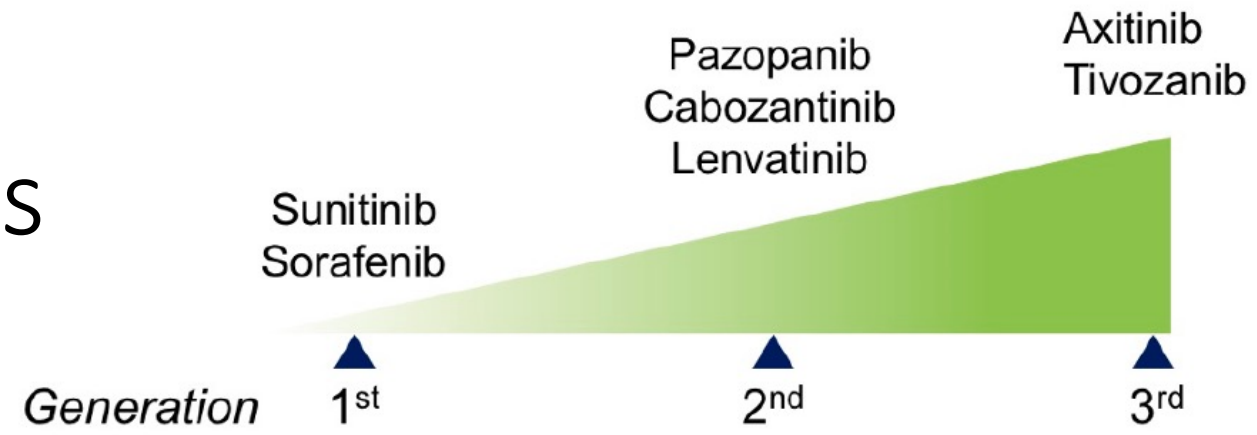
NCCN Guidelines Version 4.2023
Kidney Cancer

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)				
Immuno-oncology (IO) Therapy History Status	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**	
IO Therapy Naïve	• None	• Axitinib + pembrolizumab[b] • Cabozantinib • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + everolimus • Lenvatinib + pembrolizumab[b] • Nivolumab[b]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[f] • Belzutifan (category 2B) • Bevacizumab[g] (category 2B)	• High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Cabozantinib • Lenvatinib + everolimus • Tivozanib[f]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Everolimus • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib	• Belzutifan (category 2B) • Bevacizumab[g] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)

[a] See Risk Models to Direct Treatment (IMDC criteria or MSKCC Prognostic Model) (KID-D).
[b] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[c] Rini BI, et al. Lancet Oncol 2016;17:1317-1324. Harrison MR, et al. Cancer 2021;127:2204-2212. Bex A. Cancer 2021;127:2184-2186.
[d] Patients with excellent performance status and normal organ function.
[e] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, et al. N Engl J Med 2007;356:2271-2281.
[f] For patients who received ≥2 prior systemic therapies.
[g] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

* Belzutifan is only FDA-approved only for the treatment of VHL-associated RCC, CNS hemangioblastomas, or pNET not requiring immediate surgery.

VEGF-TKI Properties



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

Higher generation

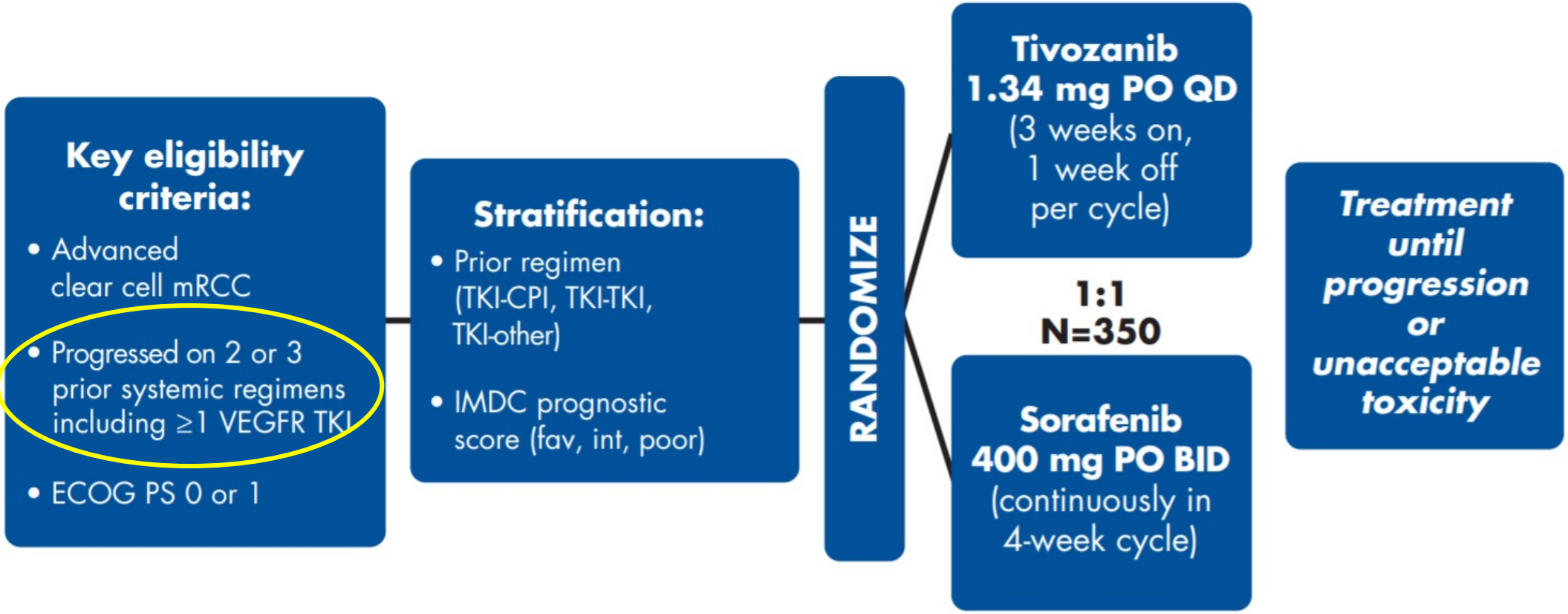
PD Properties

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.

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.

Phase 3 TIVO-3: Baseline Characteristics

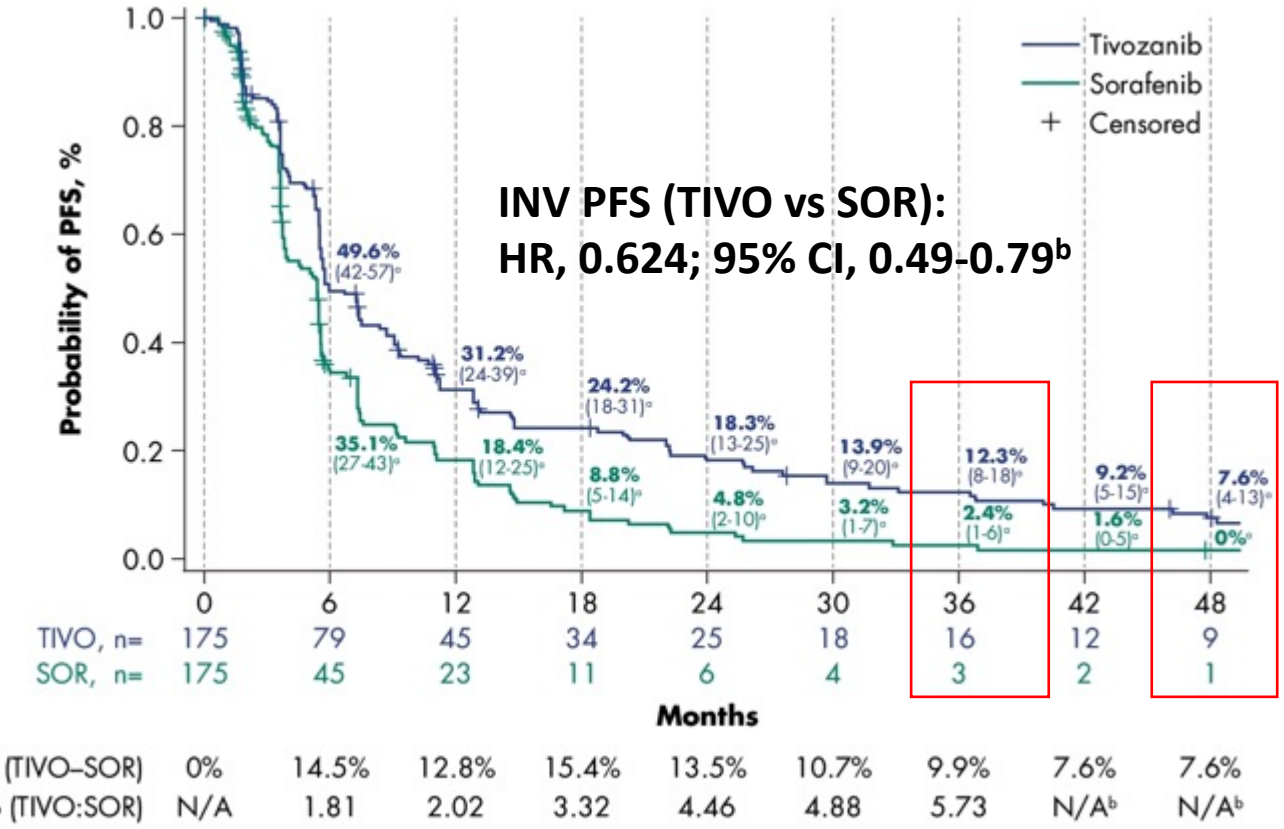
Characteristics	Tivozanib (N=175)	Sorafenib (N=175)
Median age, years	62	64
Male, %	72	73
IMDC Prognostic Risk, %		
Favorable	19	21
Intermediate	62	60
Poor	18	19
ECOG Performance Status, % (0/1)	(49/50)	(47/48)
Region, % (NA/EU)	(18/82)	(15/85)
Prior Lines of Therapy, % (2/3)	(62/38)	(59/41)
Prior Treatment Regimen, %		
TKI-PD1	27	25
TKI-TKI	45	46
TKI-Other	28	29

- Age: 35% between age 65 and 75; 10% were over 75
- Time from initial diagnosis: 50 months, both arms
- Time from most recent relapse: 1 month, both arms

Data cutoff: Jan 15, 2021

Verzoni E, et al. ASCO 2021. Abstract 4546. Escudier B, et al. ASCO 2021. Abstract e16553.

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

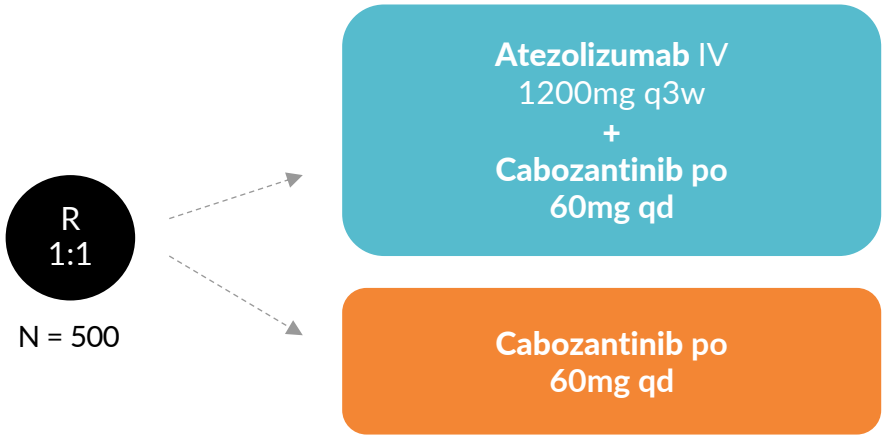
a. Results include the ITT population, with censoring for missing assessments and discontinuation without PD.
b. Data cut-off: May 24, 2021.

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

CONTACT-03

Negative Trial

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



No crossover allowed

Treatment until progression

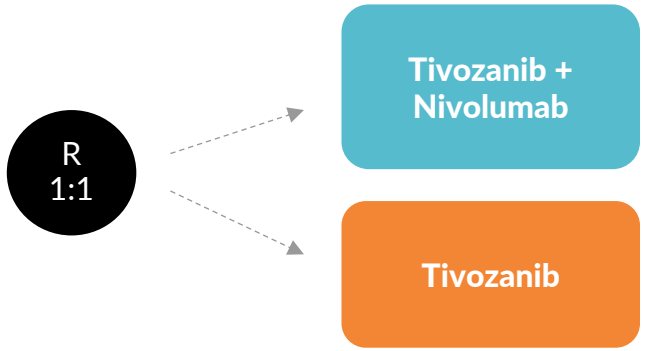
- Primary endpoint: PFS, OS
- Secondary endpoint: PFS, ORR, DoR, Safety and Tolerability

Fully Enrolled

TINIVO-2

Complete enrollment Summer 20212

- 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



Treatment until progression

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

Actively Recruiting

Summary Points

- The gold-standard for mRCC is an IO-based combination (TKI monotherapy is the exception, not the rule!)
- Primary renal tumors respond to systemic therapy with IO-based therapy (but less than metastatic sites)
- 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

Urothelial Carcinoma

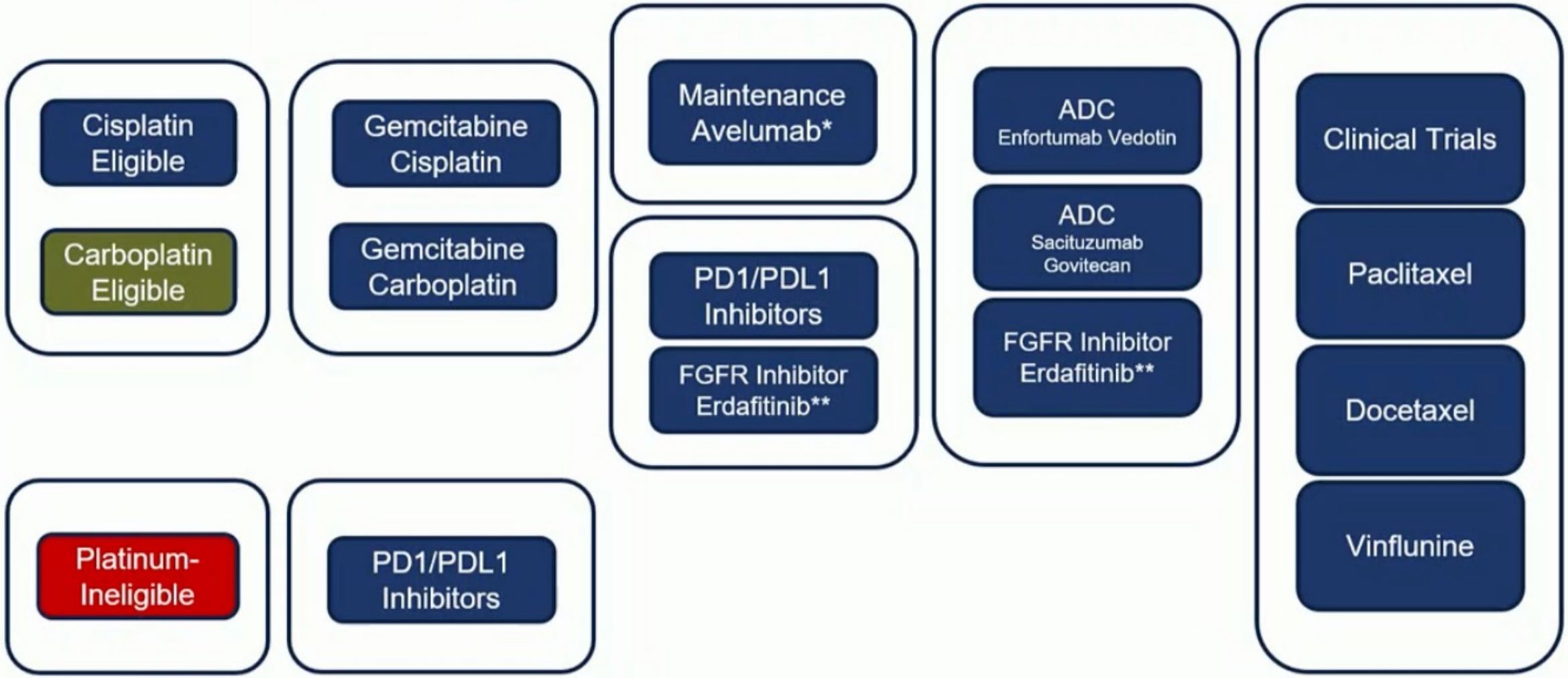
Platinum and Cisplatin Eligibility Criteria[1-4]

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

Treatment Landscape of mUC in 2021 (And Pre-ASCO GU 2023)



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

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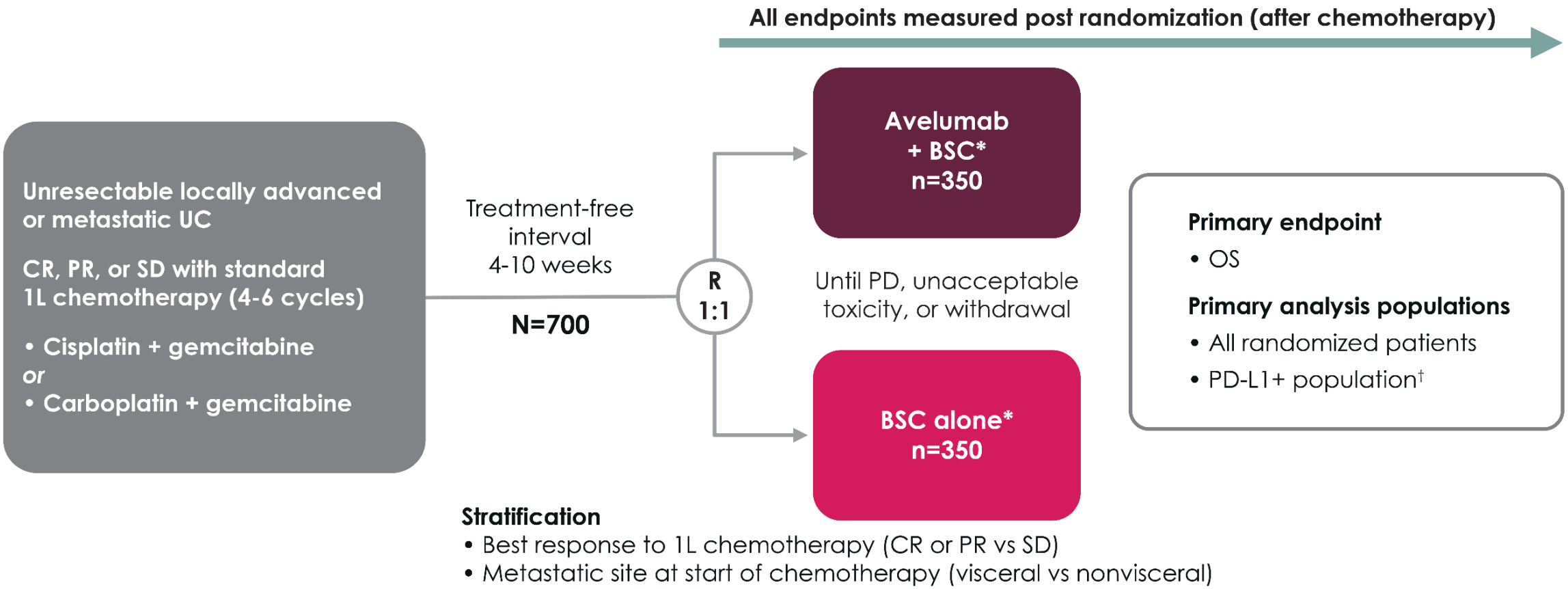
Srikala Sridhar MD, MSc

First-line mUC – platin-eligible

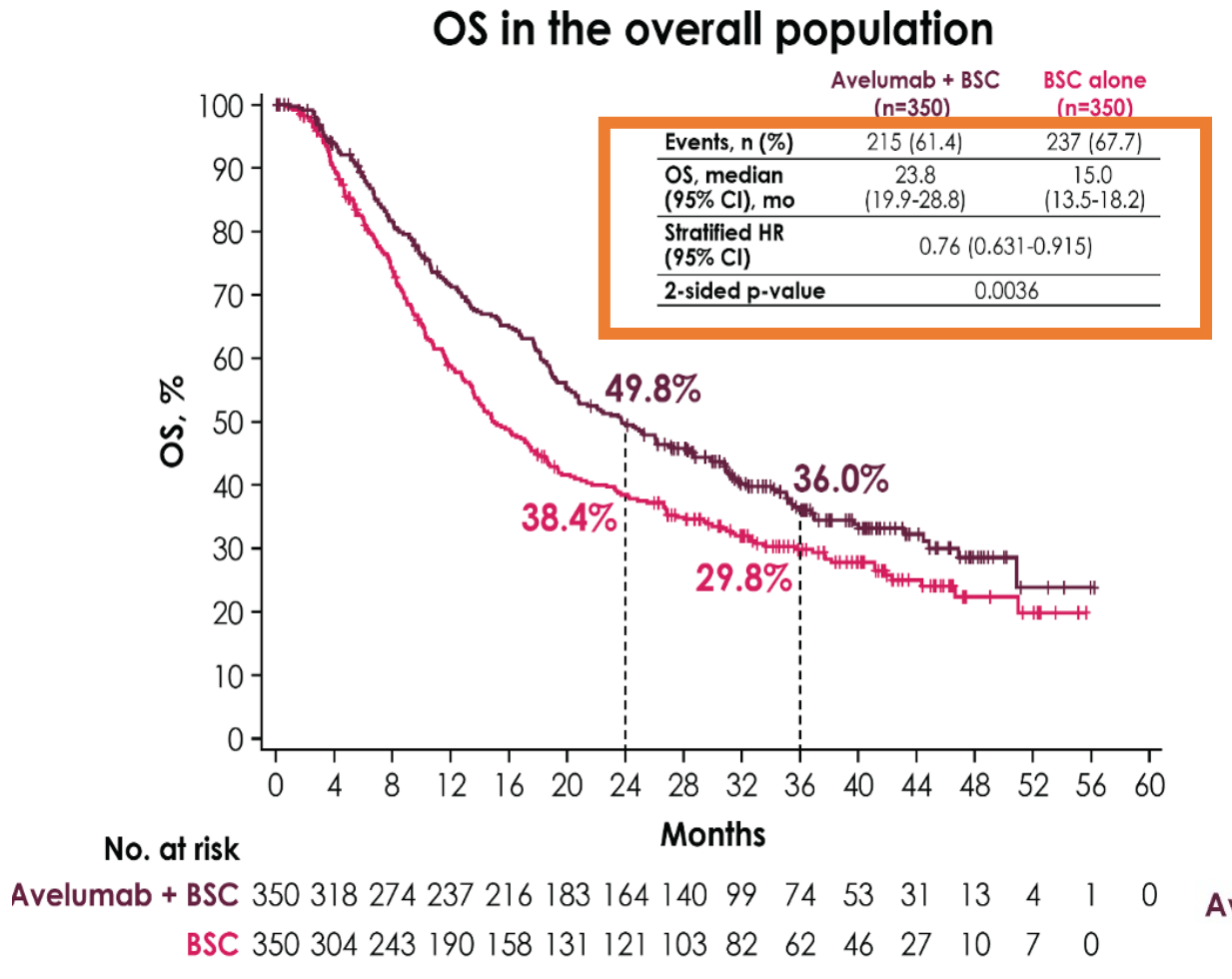
JAVELIN Bladder 100 Phase III Study

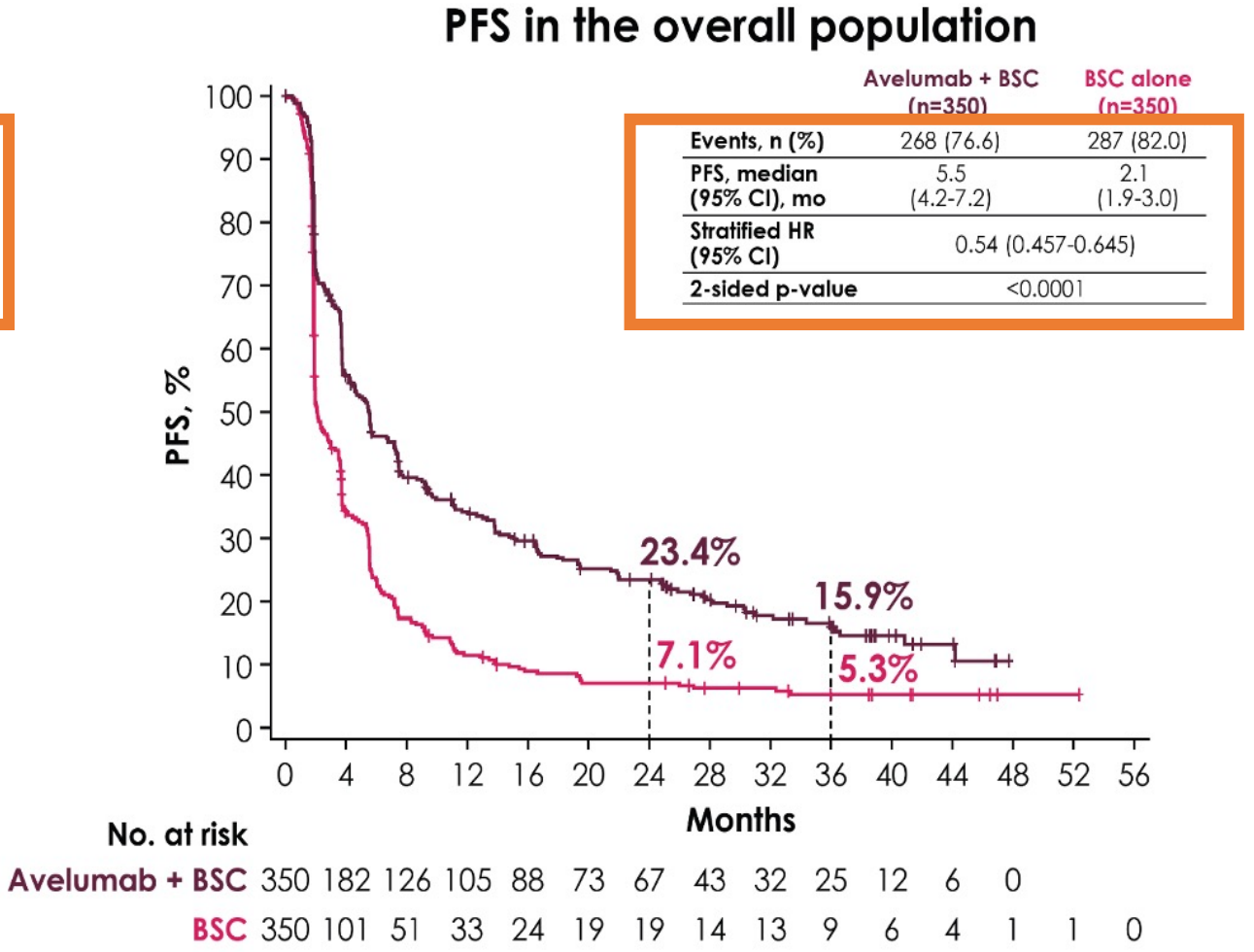


Data cutoff date: June 2021
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable. †Assessed 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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First-line mUC – cisplatin ineligible

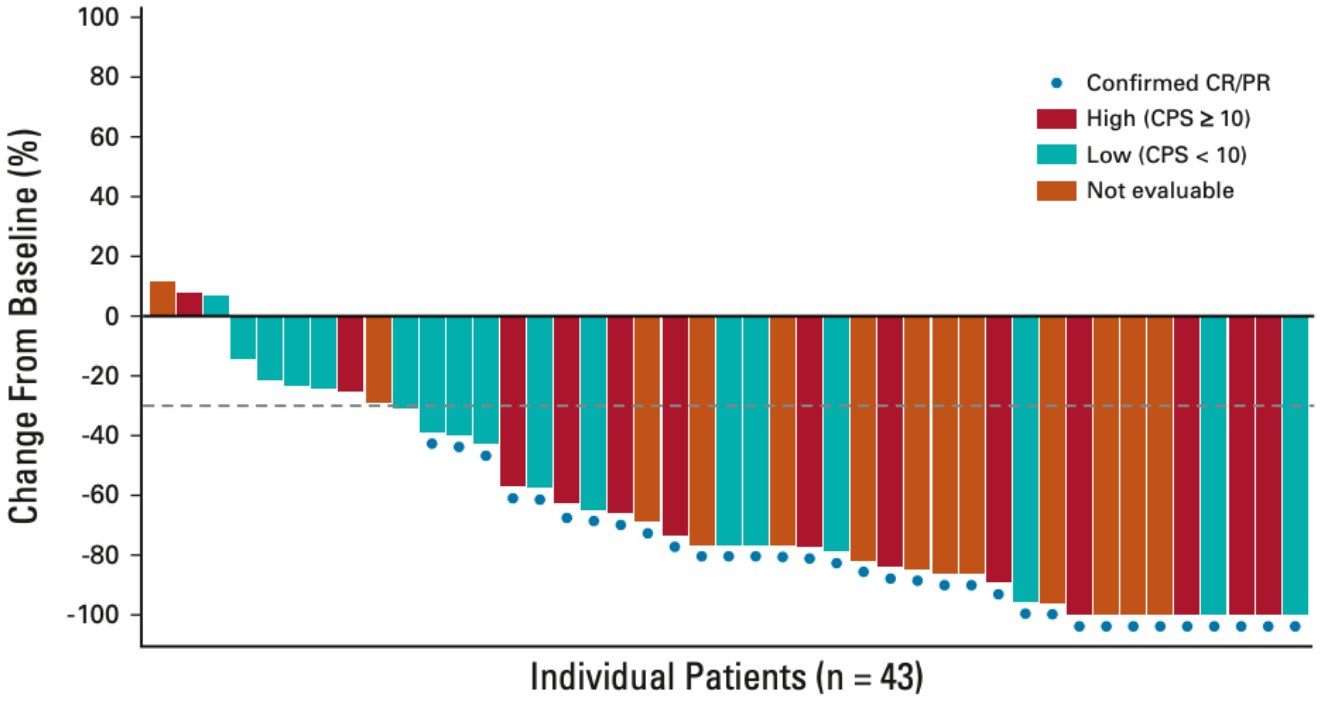
Enfortumab vedotin + Pembrolizumab (EV-103)

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.

Hoimes et al, JCO 2023

Enfortumab vedotin + Pembrolizumab (EV-103)

Long Term Results and Durability Updates from ASCO 2021

- Updated d
  (Data cut-

Figure 1.

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

FDA grants accelerated approval to enfortumab vedotin-ejfv with pembrolizumab for locally advanced or metastatic urothelial carcinoma

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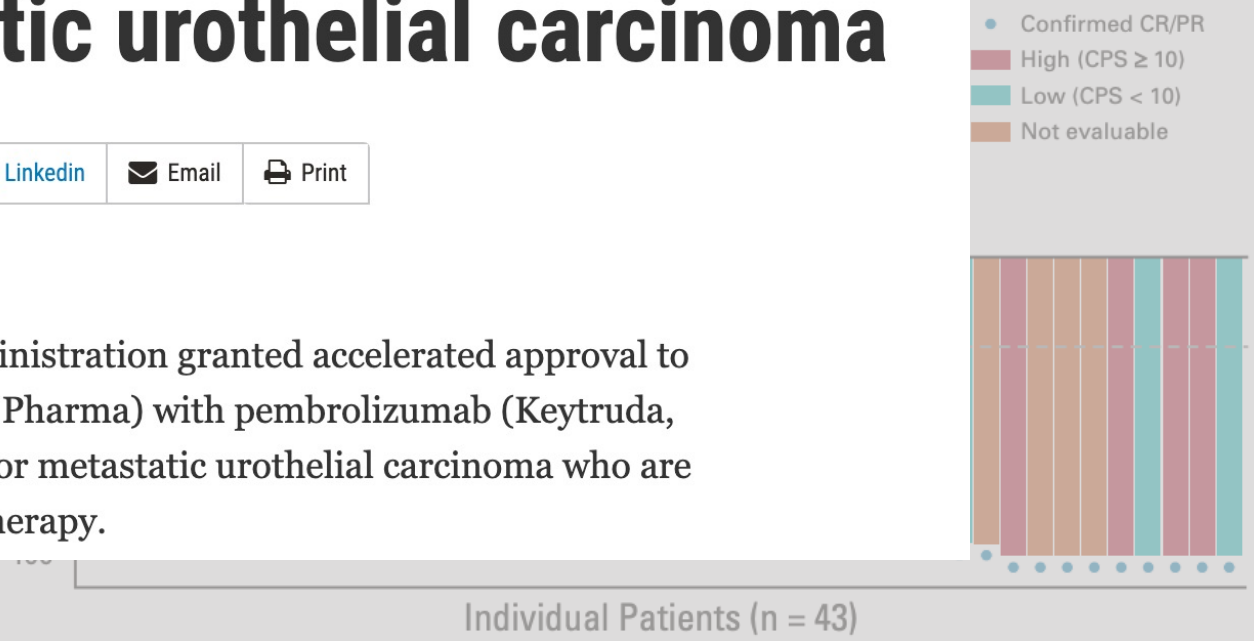
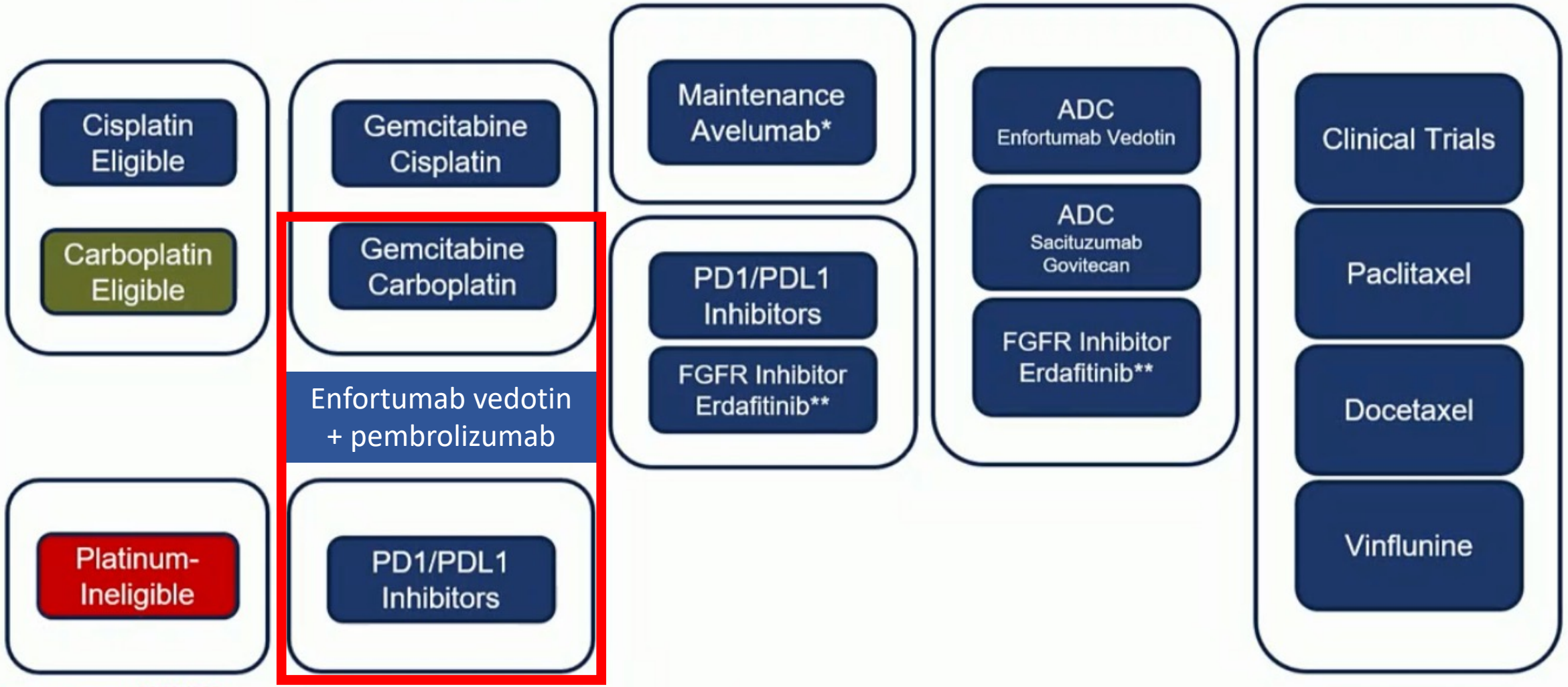
On April 3, 2023, the Food and Drug Administration granted accelerated approval to enfortumab vedotin-ejfv (Padcev, Astellas Pharma) with pembrolizumab (Keytruda, Merck) for patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy.



Hoimes et al, JCO 2023

Treatment Landscape of mUC in 2021 (And Pre-ASCO GU 2023)



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

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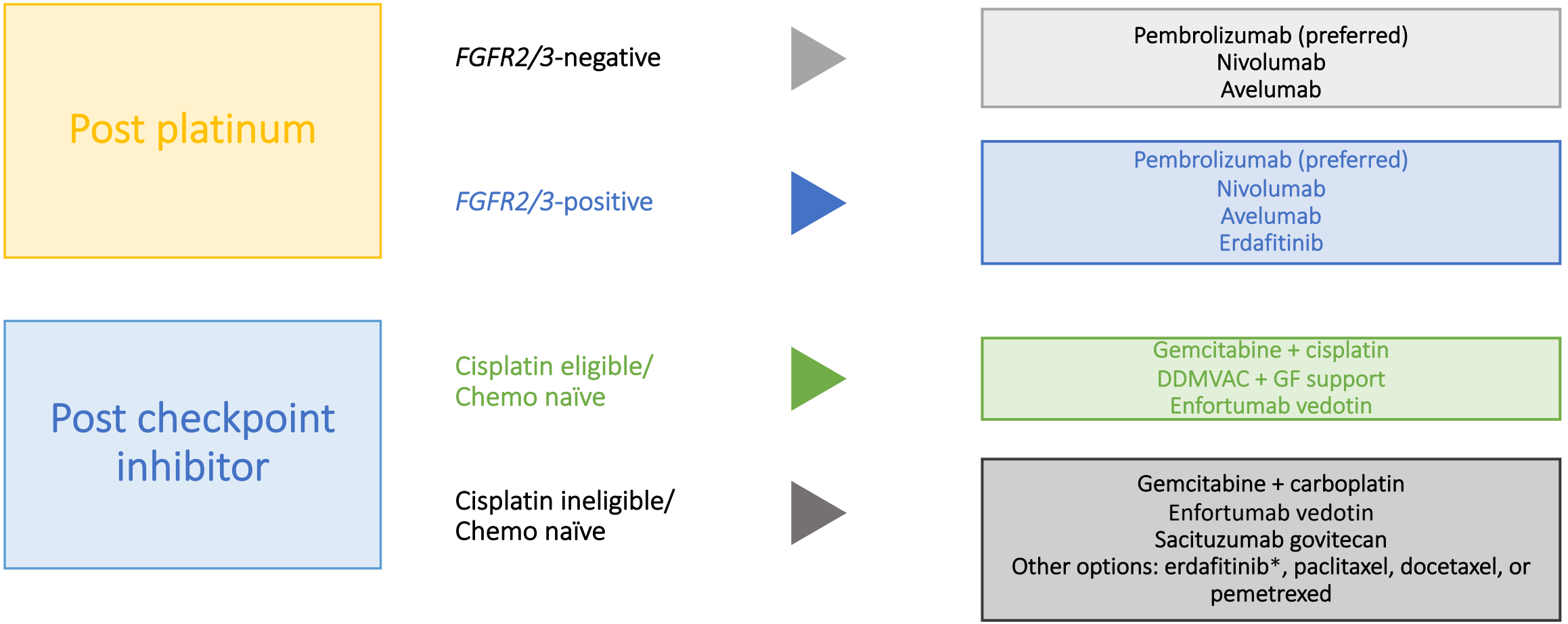
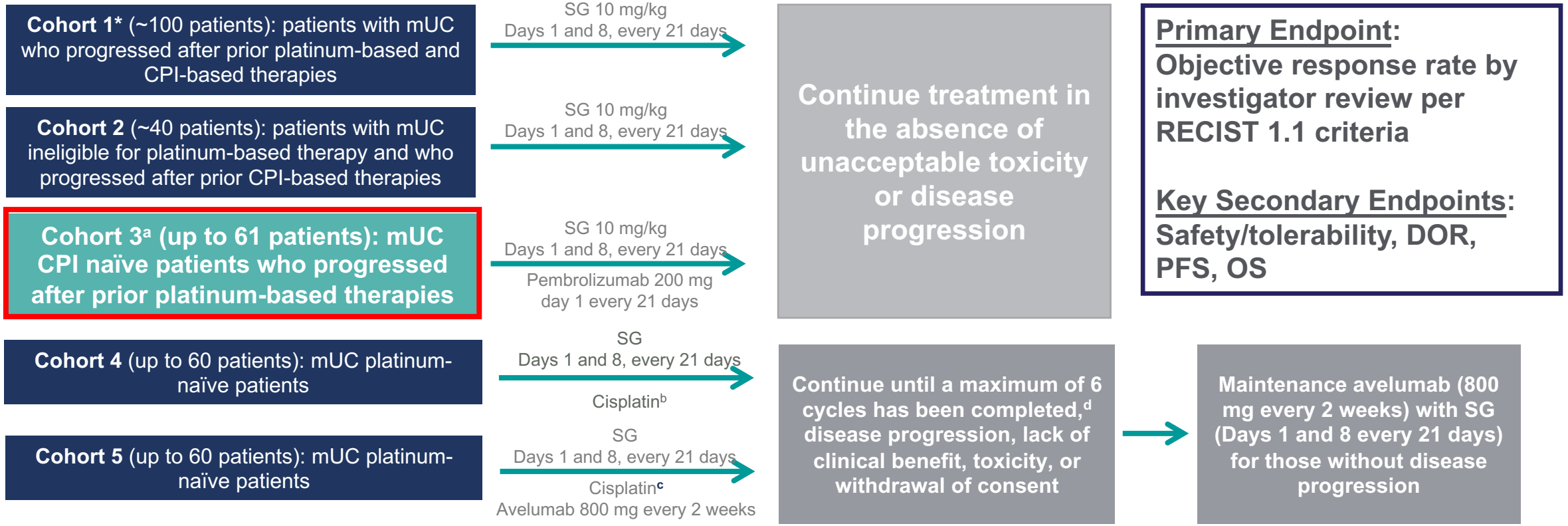
Second-Line Systemic Treatment for mUC



* If *FGFR2/3* positive

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]**

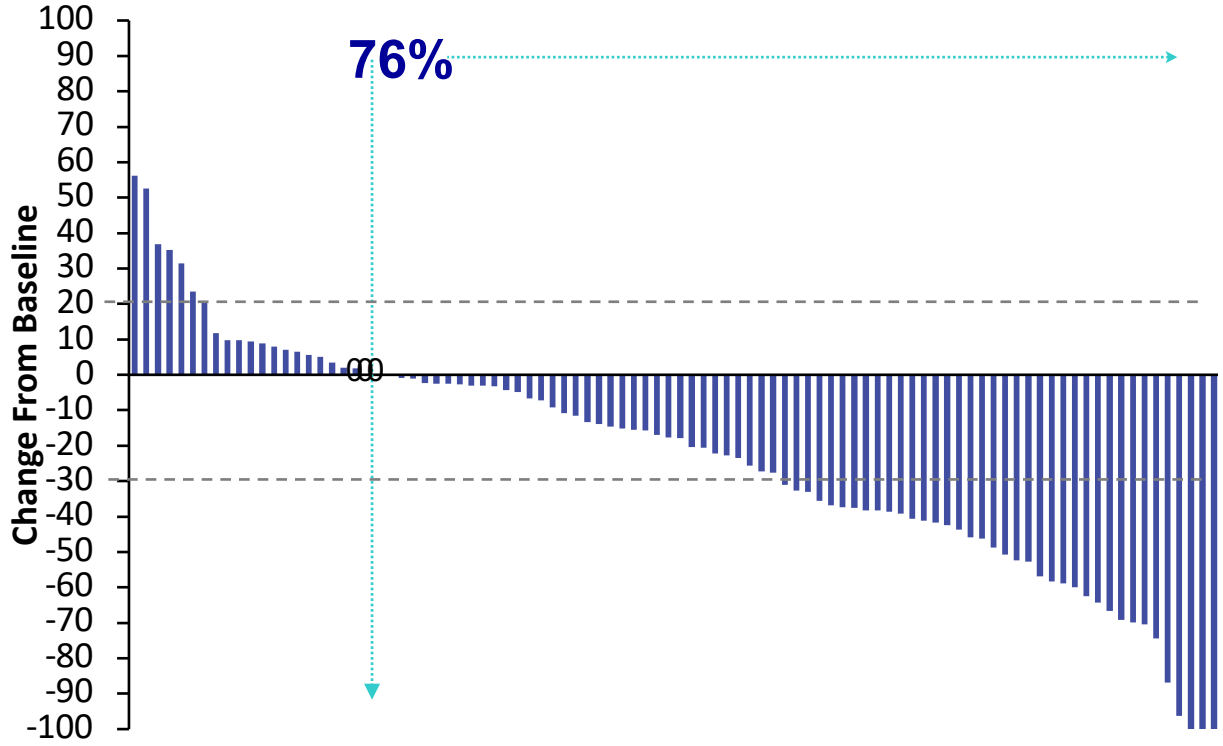
[a]Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. [b]In patients with CrCl ≥60 mL/min; [c]In patients with creatinine clearance 50–60 mL/min. [d]For patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 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 1: Response and Reduction in Tumor Size

Endpoint	Cohort 1 (N=113)
ORR, No. (%) [95% CI]	31 (27) [19, 37]
CR, No. (%)	6 (5)
PR, No. (%)	25 (22)
Median duration of response, mo [95% CI] (range)	5.9 [4.70, 8.60] (1.4–11.7)
Median time to onset of response, mo (range)	1.6 (1.2–5.5)



Assessments were per Blinded Independent Review Assessment, RECIST v1.1.

71/94 patients with at least one post-baseline target lesion measurement and accepted for central review. Fourteen patients had no post-treatment imaging, 1 patient lacked measurable lesions by central review, and 4 patients had poor image quality.

Loriot Y, et al. *Annal Oncol*. 2020;31(suppl 4):S1142-S1215 (LBA24).

University Hospitals Seidman Cancer Center

School of Medicine Case Western Reserve University

TROPHY-U-01 Cohort 1: Response and Reduction in Tumor Size

Endpoint
ORR, No. (%) [95
CR, No. (%)
PR, No. (%)
Median duration [95% CI] (range)
Median time to (range)

FDA grants accelerated approval to sacituzumab govitecan for advanced urothelial cancer

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On April 13, 2021, the Food and Drug Administration granted accelerated approval to sacituzumab govitecan ([redacted]) for patients with locally advanced or metastatic urothelial cancer (mUC) who previously received a platinum-containing chemotherapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor.

Assessments were per Blinded Independent Review Assessment, RECIST v1.1.

71/94 patients with at least one post-baseline target lesion measurement and accepted for central review. Fourteen patients had no post-treatment imaging, 1 patient lacked measurable lesions by central review, and 4 patients had poor image quality.

Loriot Y, et al. *Annal Oncol*. 2020;31(suppl 4):S1142-S1215 (LBA24).

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

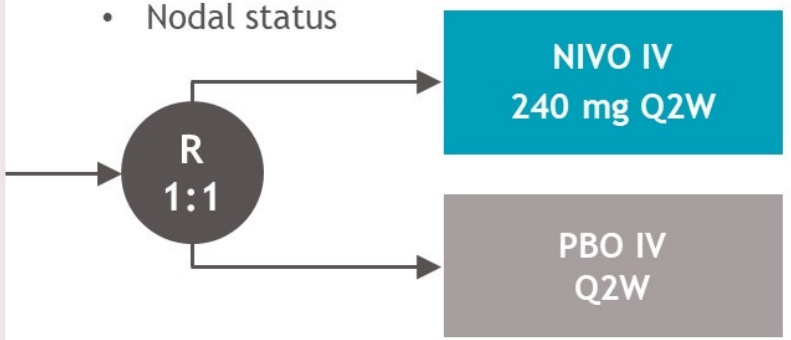
N = 709

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

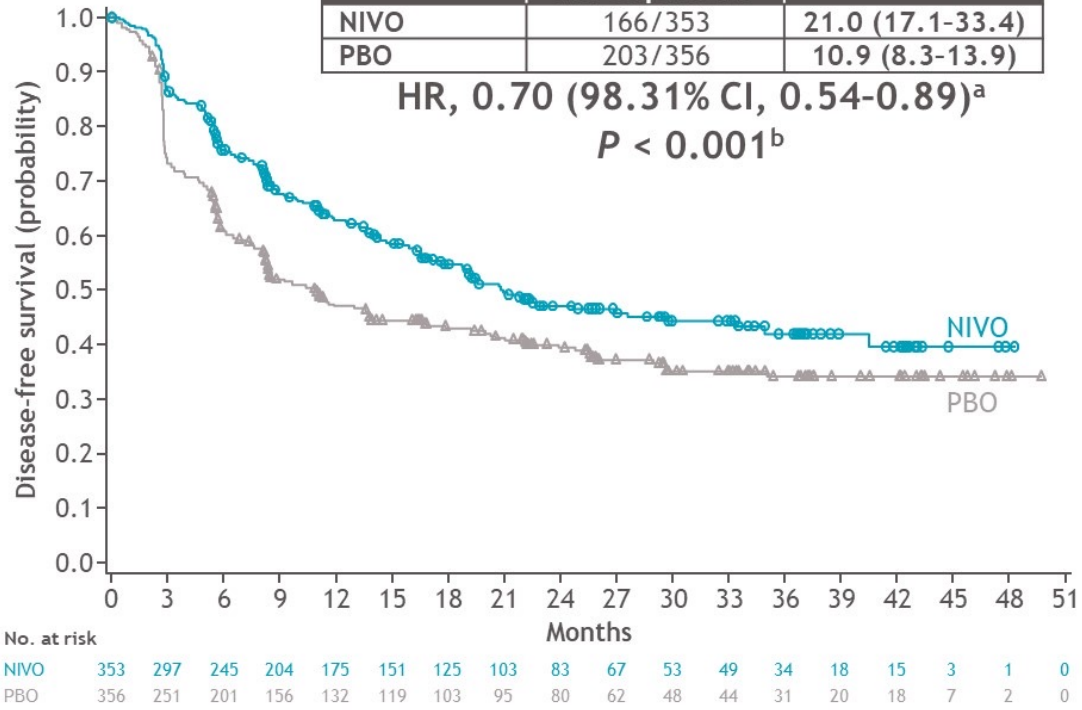
[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free 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)

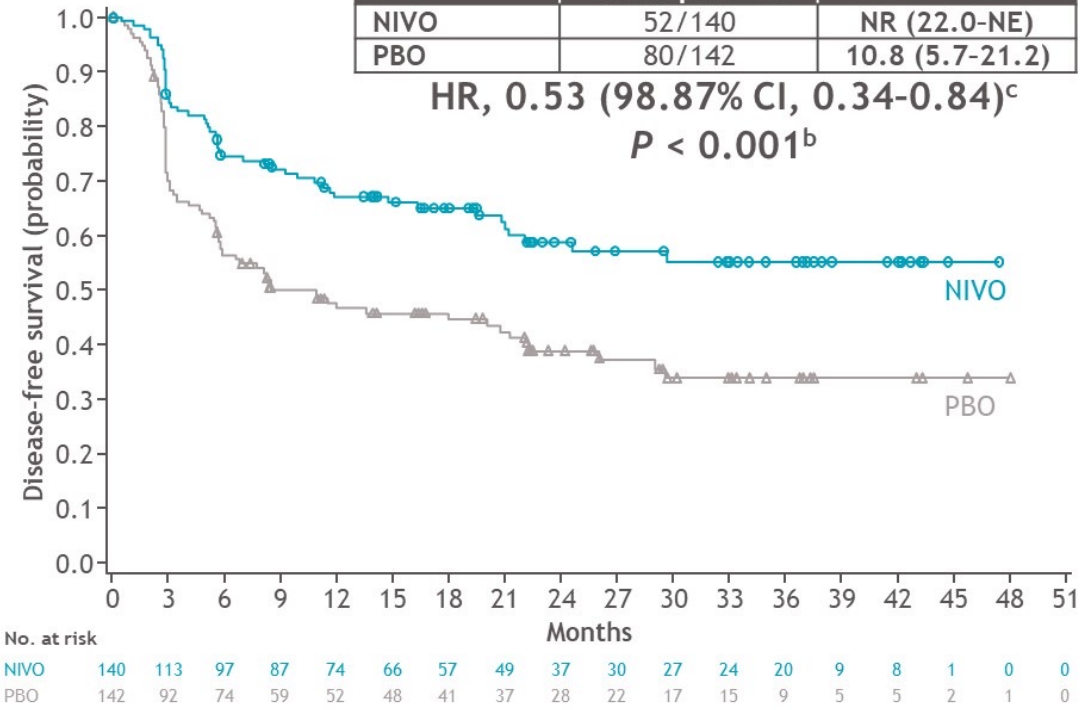
HR, 0.70 (98.31% CI, 0.54-0.89)[a]
P < 0.001[b]



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]



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