Frontline Immunotherapy in Advanced Kidney and Urothelial Cancer

UCDAVIS COMPREHENSIVE CANCER CENTER

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NCI Comprehensive Cancer Center
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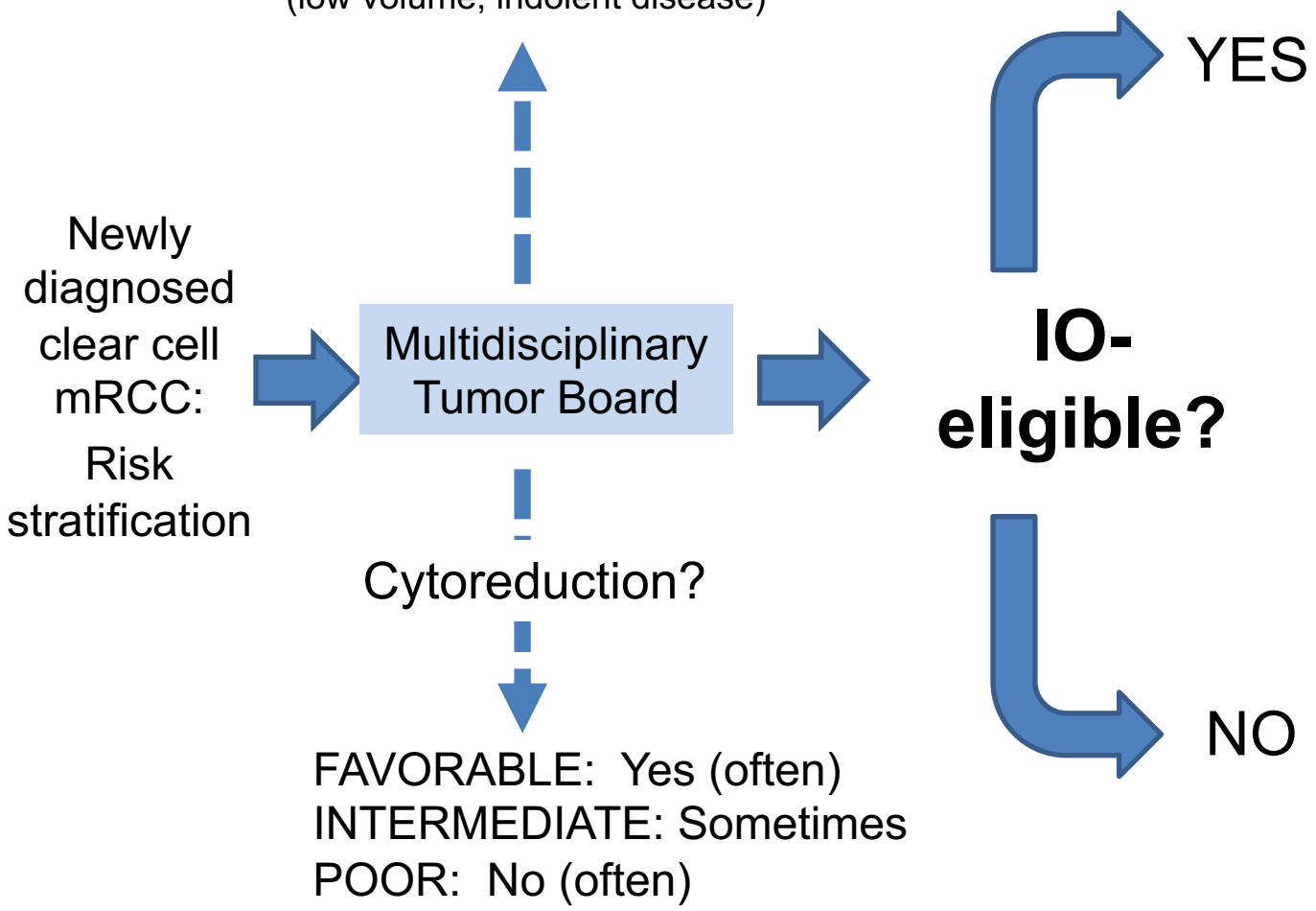
mRCC Decision Tree



IO-Based Combo

ALL RISK GROUPS:
Pembrolizumab-Axitinib
Nivolumab-Cabozantinib
Pembrolizumab-Lenvantinib
(Avelumab-Axitinib)

INTERMEDIATE or POOR RISK:
Nivolumab-Ipilimumab

Single agent IO

SELECTED PATIENTS:
Pembrolizumab
Nivolumab

Cost, convenience, physician experience, and patient preference apply

TKI

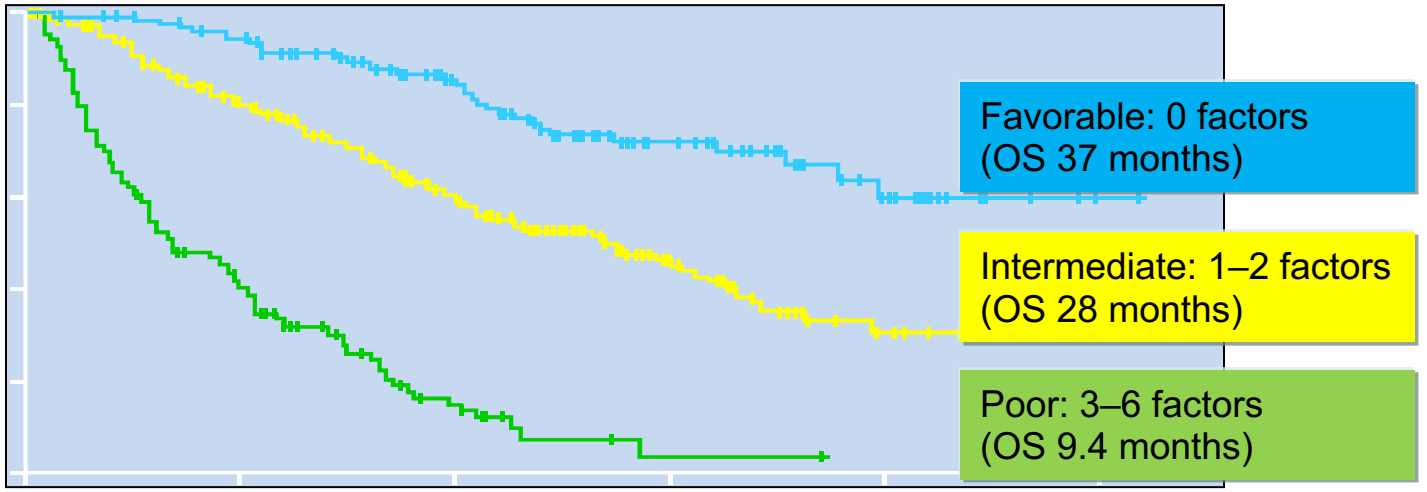
FAVORABLE:
Sunitinib, Pazopanib

INTERMEDIATE or POOR:
Cabozantinib

Risk Stratification in mRCC

- **N = 645 patients with mRCC treated with VEGF-targeted therapy**
  - Sunitinib (61%); Sorafenib (31%); Bevacizumab (8%)

- **Predictors for OS:**
  - Time from diagnosis to treatment*
  - Hemoglobin*
  - Calcium*
  - Performance status*
  - Neutrophil count
  - Platelet count



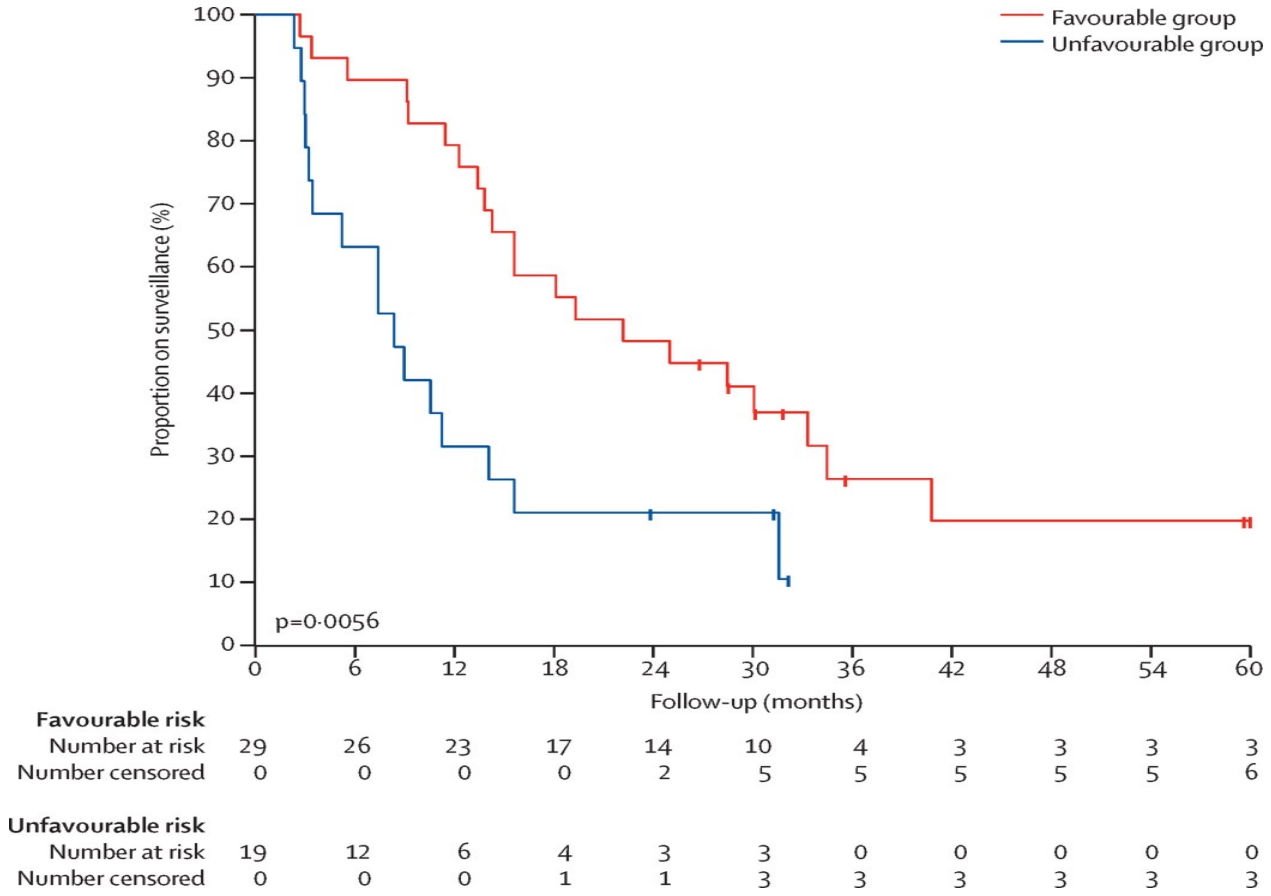
Risk Group	Number of Risk Factors	Median Survival Time
Favorable Risk (n=133)	0	37 months
Intermediate Risk (n=292)	1-2	28.5 months
Poor Risk (n=139)	>2	9.4 months

* Components of MSKCC prognostic criteria

Heng DY et al. *J Clin Oncol*. 2009;27(34):5794-5799.

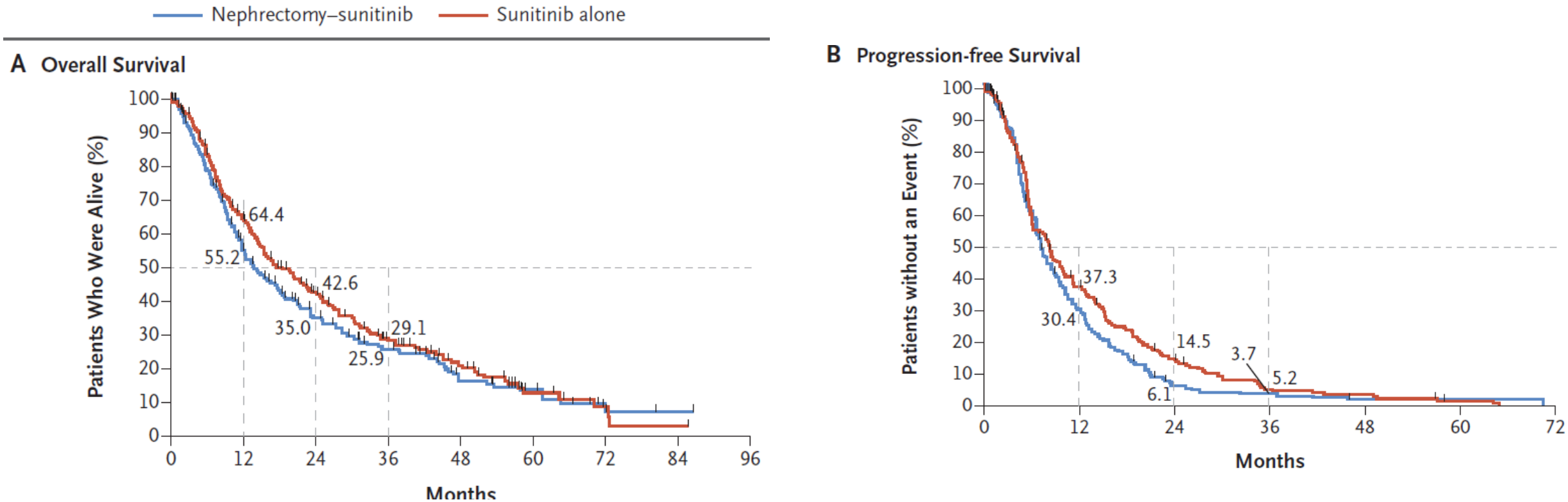
Who Are Candidates for Active Surveillance?

- Phase II trial of 52 asymptomatic mRCC patients
- Radiographic assessments:
  - Baseline, q3 months in year 1; q4 months in year 2; q6 months thereafter
- Median time-to-treatment initiation (TTI) for symptomatic disease was 14.9 months
  - Poor risk group expectedly had shorter TTI
  - 22 patients died: all from mRCC
- Median OS = 38.6 months



Rini BI et al. *Lancet Oncol*. 2016;17(9):1317-1324.

Who Should Undergo Cytoreductive Nephrectomy (CN) in mRCC?: Phase III Trial of Sunitinib With or Without CN

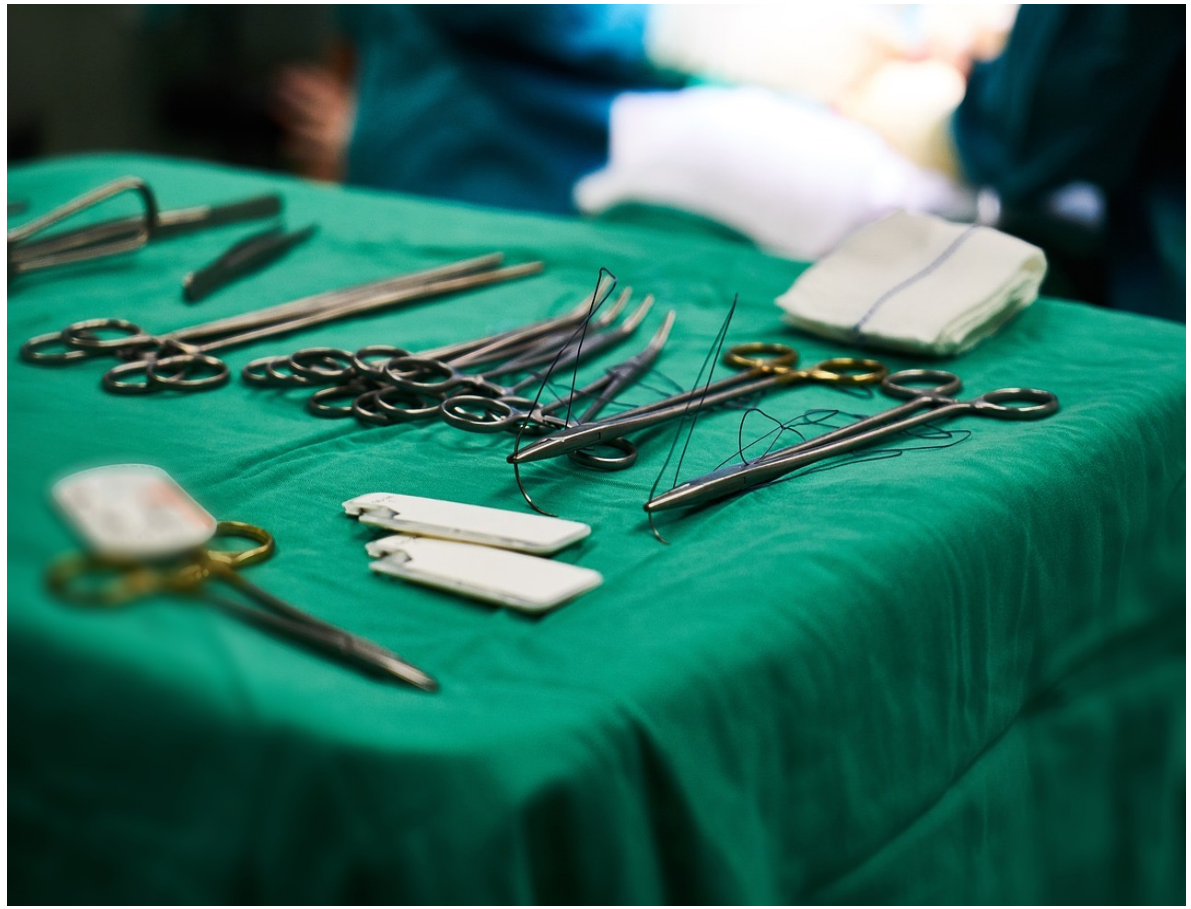


"Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were classified as having intermediate risk or poor-risk disease."

Méjean A et al. *N Engl J Med*. 2018;379(5):417-427.

Who Should Undergo Cytoreductive Nephrectomy?

- Decision must be individualized according to risk
  - Avoid reflexive decisions
  - Seek multidisciplinary input
  - Most favorable risk and some intermediate risk patients remain candidates
    - Large and/or symptomatic primary tumors, low volume metastatic disease
  - Many intermediate and nearly all poor risk patients start systemic therapy first



Lara PN Jr et al. *JAMA Oncol*. 2019;5(2):171-172.

Who Should Undergo Metastasectomy in mRCC?

- Highly selected patients
- Quality of evidence limited to retrospective studies
- Clinical features associated with benefit:
  - Good performance status
  - Isolated/oligometastatic disease
  - Disease-free interval post-nephrectomy >2 years
  - Absence of lymph node involvement
  - Lung-only disease

Ouzaid I et al. *Eur Urol Oncol*. 2019;2(2):141-149.

Systemic Frontline mRCC Therapy: Standard-of-Care 2023

- Immunotherapy-based combination therapy is SOC
  - Most mRCC patients should be considered for combination therapy
  - Immunotherapy-TKI combinations (for all risk groups)
    - Pembrolizumab-Axitinib
    - Nivolumab-Cabozantinib
    - Pembrolizumab-Lenvantinib
    - Avelumab-Axitinib
  - All-immunotherapy doublet (for intermediate/poor risk groups)
    - Nivolumab-Ipilimumab

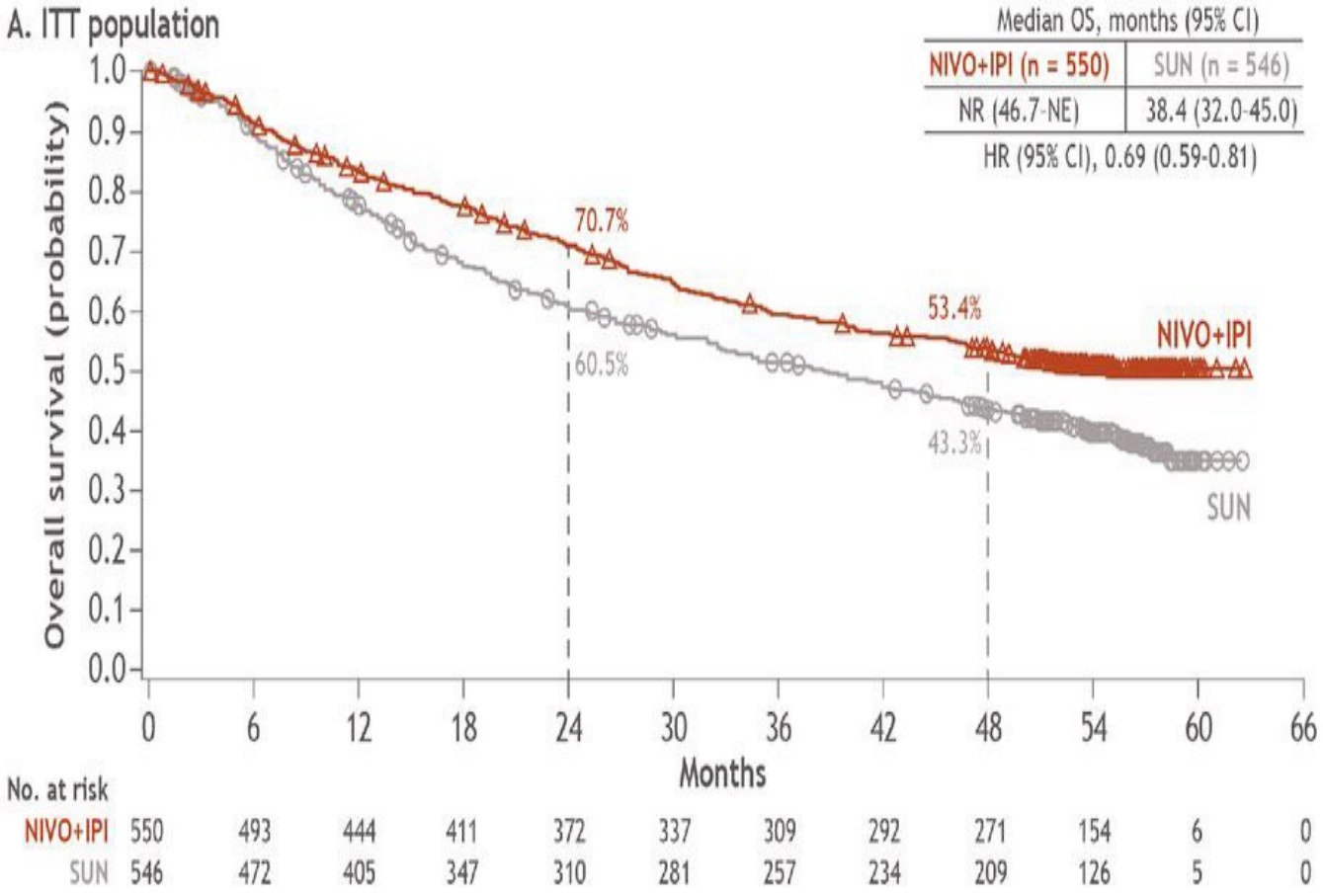
Frontline RCC Combination Therapy* vs. Sunitinib: Scorecard

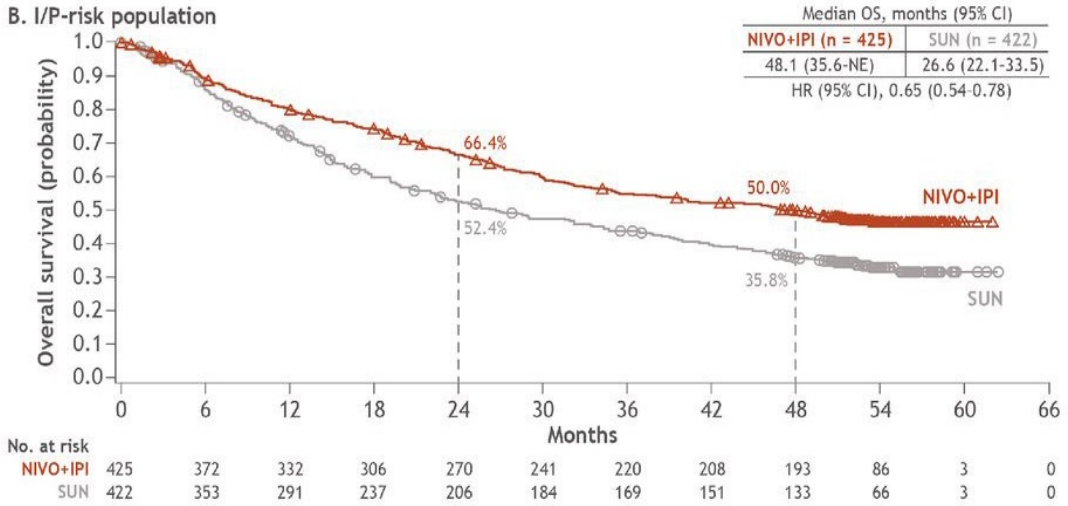
Trial and Regimen	CM 214	KN 426	CM-9ER	CLEAR
	Nivo/Ipi	Pembro/Axi	Nivo/Cabo	Pembro/Lenva
Prognostic Group: Fav/Int/Poor (%)	23/61/17	32/55/13	23/58/19	31/60/9
Overall Response Rate	39% vs. 32%	60% vs. 40%	56% vs. 27%	71% vs. 36%
Complete Response Rate	11% vs. 3%	9% vs. 3%	8% vs. 5%	16% vs. 4%
Median PFS, months	12.2 vs. 12.3	15.4 vs. 11.1	16.6 vs. 8.3	23.9 vs. 9.2
PFS Hazard Ratio [95% CI]	0.89 [0.76-1.05] (0.74 for Int/Poor)	0.71 [0.6-0.84]	0.51 [0.41-0.64]	0.39 [0.32-0.49]
Median OS, months	NR vs. 38.4	NR vs. 35.7	NR vs. NR	NR vs. NR
OS Hazard Ratio [95% CI]	0.69 [0.59-0.81] (0.65 for Int/Poor)	0.68 [0.55-0.85]	0.60 [0.40-0.89]	0.66 [0.49-0.88]

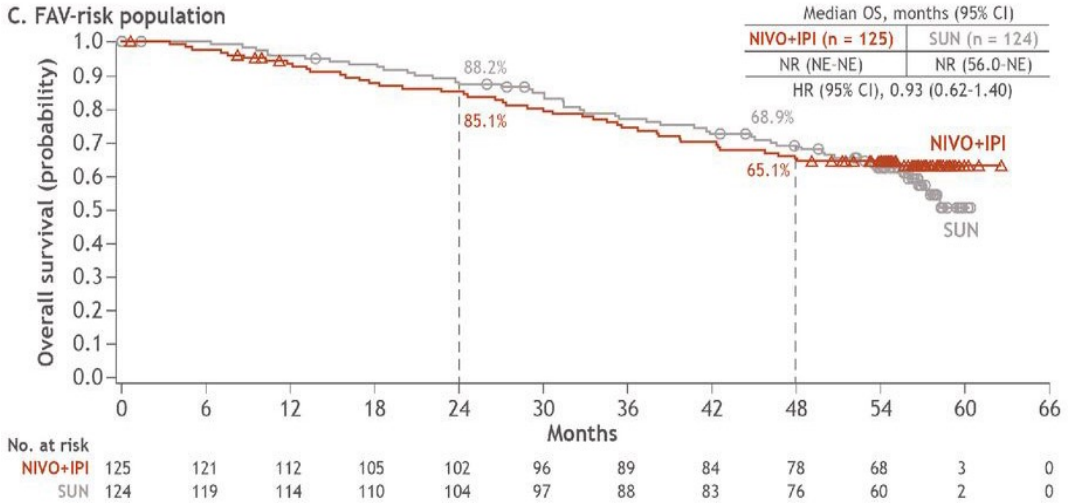
*Includes only trials that resulted in a positive OS benefit for the combination arm; NR, not reached

Albiges L et al. *ESMO Open*. 2020;5(6):e001079; Powles T et al. *Lancet Oncol*. 2020;21(12):1563-1573; Choueiri TK et al. *Ann Oncol*. 2020;31(S4):S1159; Motzer R et al. *N Engl J Med*. 2021;384:1289-1300.

CheckMate 214 - Nivo/Ipi vs. Sunitinib: 4-year Follow-up







Albiges L et al. *ESMO Open*. 2020;5(6):e001079

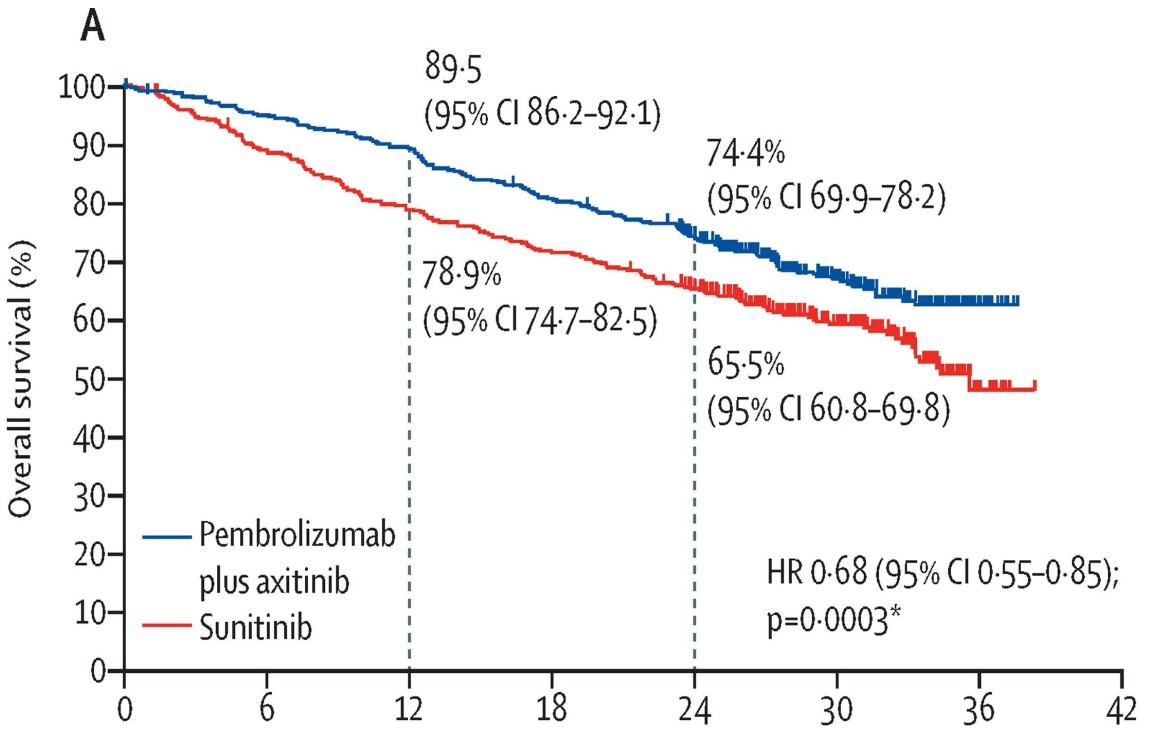
CheckMate 214: Safety

Safety parameters; patients, n (%)	All treated patients			
	NIVO+IPI (N=547)		SUN (N=535)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs	514 (94)	262 (48)	521 (97)	343 (64)
All treatment-related AEs (any grade >20% in either arm)				
Fatigue	209 (38)	24 (4)	266 (50)	51 (10)
Pruritus	169 (31)	3 (<1)	50 (9)	0
Diarrhoea	155 (28)	21 (4)	284 (53)	31 (6)
Rash	126 (23)	10 (2)	70 (13)	0
Nausea	110 (20)	8 (1)	208 (39)	7 (1)
Hypothyroidism	90 (16)	2 (<1)	143 (27)	1 (<1)
Decreased appetite	76 (14)	7 (1)	135 (25)	6 (1)
Vomiting	61 (11)	4 (<1)	116 (22)	10 (2)
Dysgeusia	26 (5)	0	118 (22)	1 (<1)
Stomatitis	25 (5)	0	151 (28)	14 (3)
Mucosal inflammation	15 (3)	1 (<1)	155 (29)	15 (3)
Hypertension	12 (2)	4 (<1)	220 (41)	91 (17)
Palmoplantar erythema	6 (1)	1 (<1)	234 (44)	50 (9)
All treatment-related select AEs[a]				
Gastrointestinal	163 (30)	28 (5)	284 (53)	31 (6)
Hepatic	107 (20)	48 (9)	79 (15)	20 (4)
Skin	279 (51)	22 (4)	308 (58)	55 (10)
Endocrine	180 (33)	38 (7)	168 (31)	1 (<1)
Pulmonary	38 (7)	6 (1)	2 (<1)	0
Renal	56 (10)	7 (1)	48 (9)	6 (1)

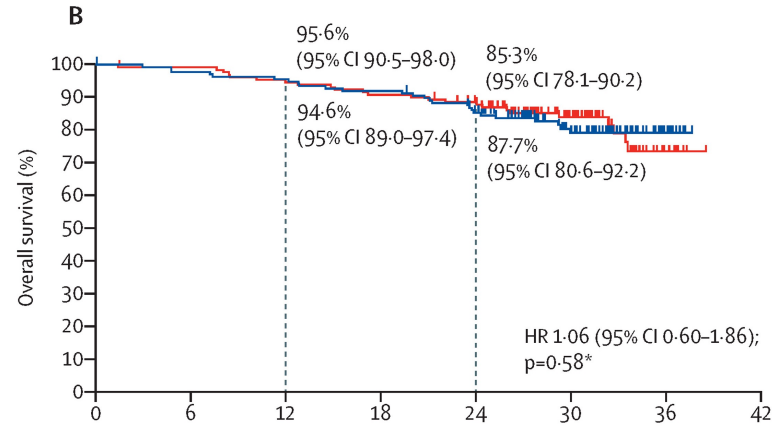
Albiges L et al. *ESMO Open*. 2020;5(6):e001079

KEYNOTE-426 - Pembro/Axitinib vs. Sunitinib

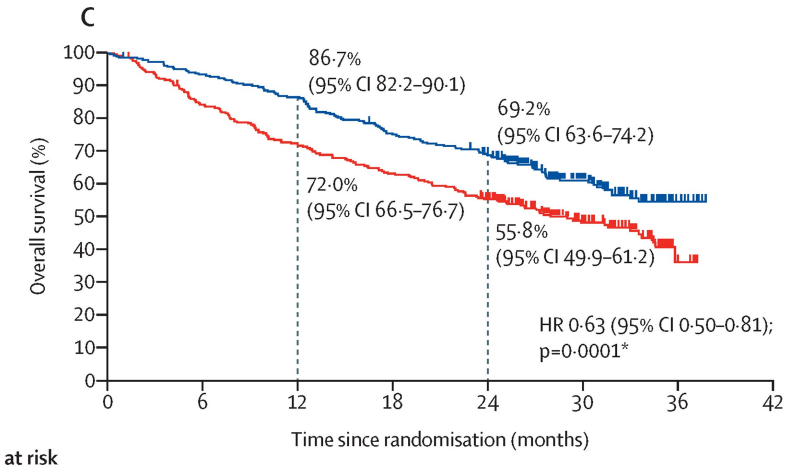
Median follow-up time = 30.6 months



Number at risk (number censored)								
Pembrolizumab plus axitinib	432 (0)	408 (2)	385 (2)	346 (3)	305 (17)	163 (135)	23 (267)	0 (290)
Sunitinib	429 (0)	379 (3)	336 (3)	306 (3)	268 (14)	134 (129)	16 (235)	0 (251)



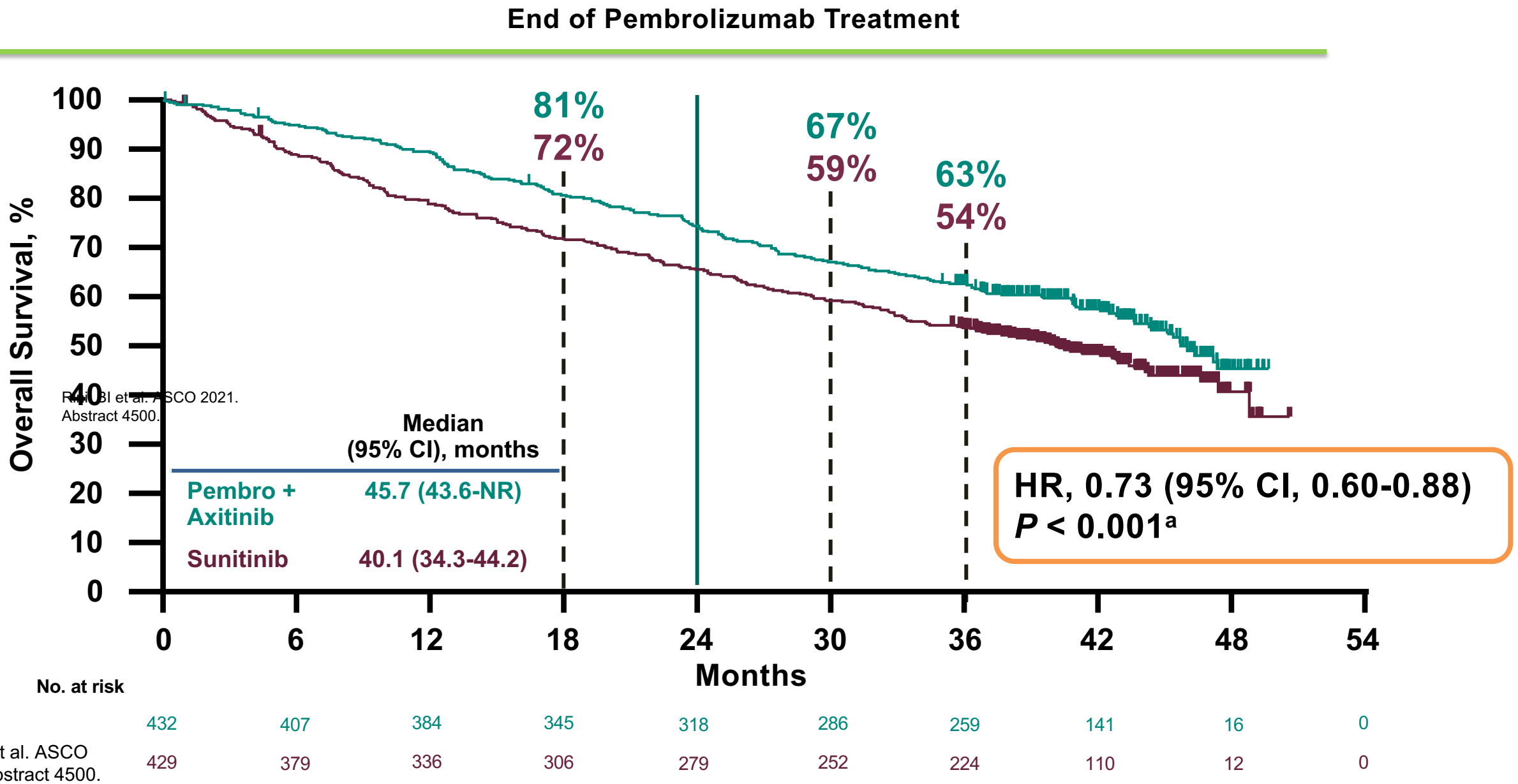
Number at risk (number censored)								
Pembrolizumab plus axitinib	138 (0)	134 (1)	131 (1)	126 (1)	110 (8)	63 (49)	12 (100)	0 (112)
Sunitinib	131 (0)	129 (1)	123 (1)	118 (1)	108 (7)	60 (51)	9 (98)	0 (107)



Number at risk (number censored)								
Pembrolizumab plus axitinib	294 (0)	274 (1)	254 (1)	220 (2)	195 (9)	100 (86)	11 (167)	0 (178)
Sunitinib	298 (0)	250 (2)	213 (2)	188 (2)	160 (7)	74 (78)	7 (137)	0 (144)

Powles T et al. *Lancet Oncol*. 2020;21(12):1563-1573

KEYNOTE-426 (42-month follow-up): OS in the ITT Population

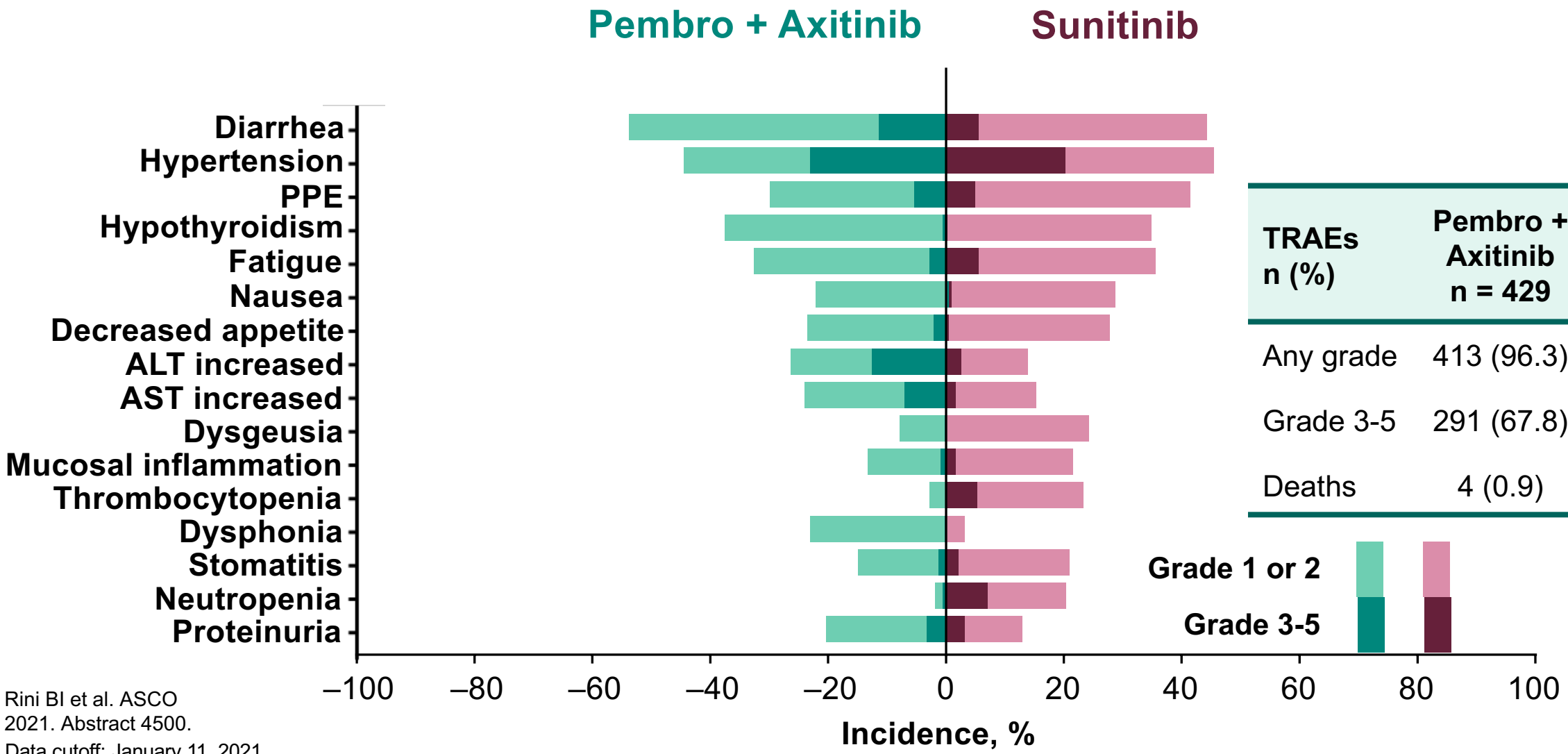


Rini BI et al. ASCO 2021. Abstract 4500.

Rini BI et al. ASCO 2021. Abstract 4500.

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 11, 2021.

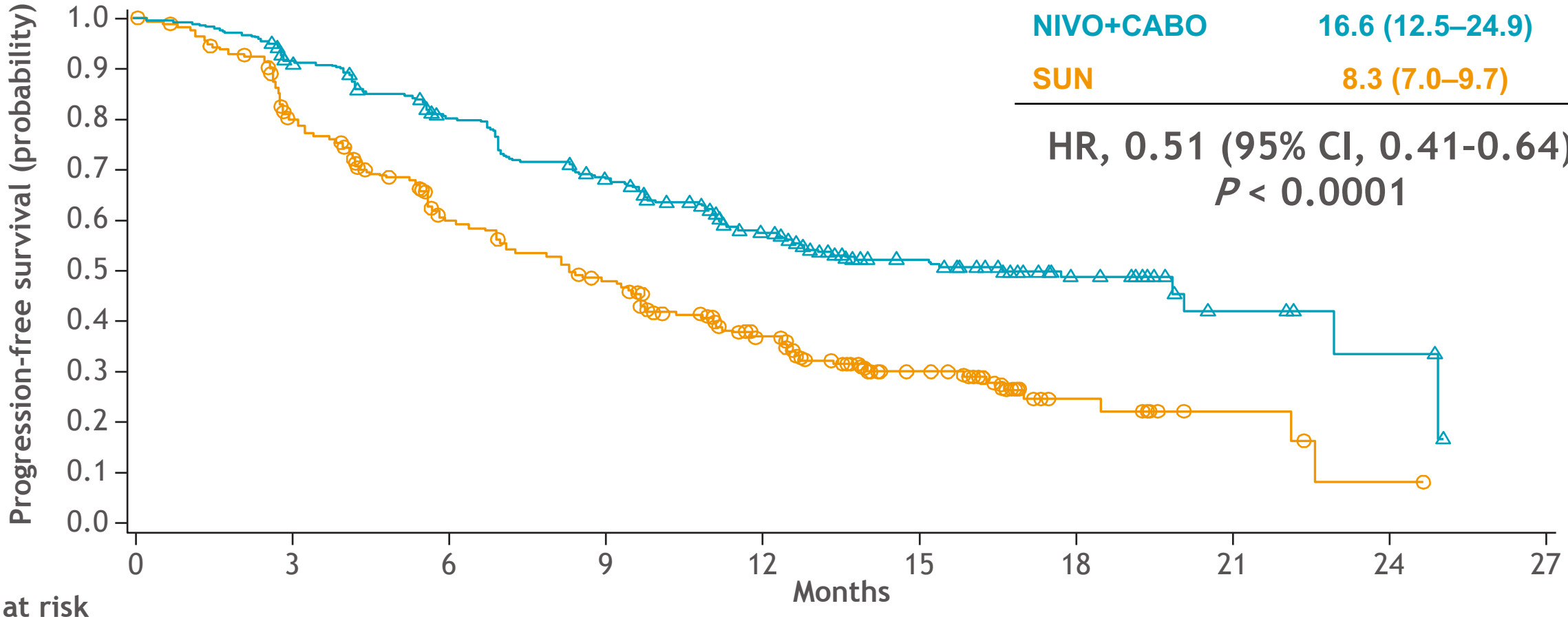
KEYNOTE-426 Treatment-Related Adverse Events Incidence ≥20% Within Either Treatment Arm



TRAEs n (%)	Pembro + Axitinib n = 429	Sunitinib n = 425
Any grade	413 (96.3)	415 (97.6)
Grade 3-5	291 (67.8)	271 (63.8)
Deaths	4 (0.9)	7 (1.6)

Rini BI et al. ASCO 2021. Abstract 4500.
Data cutoff: January 11, 2021.

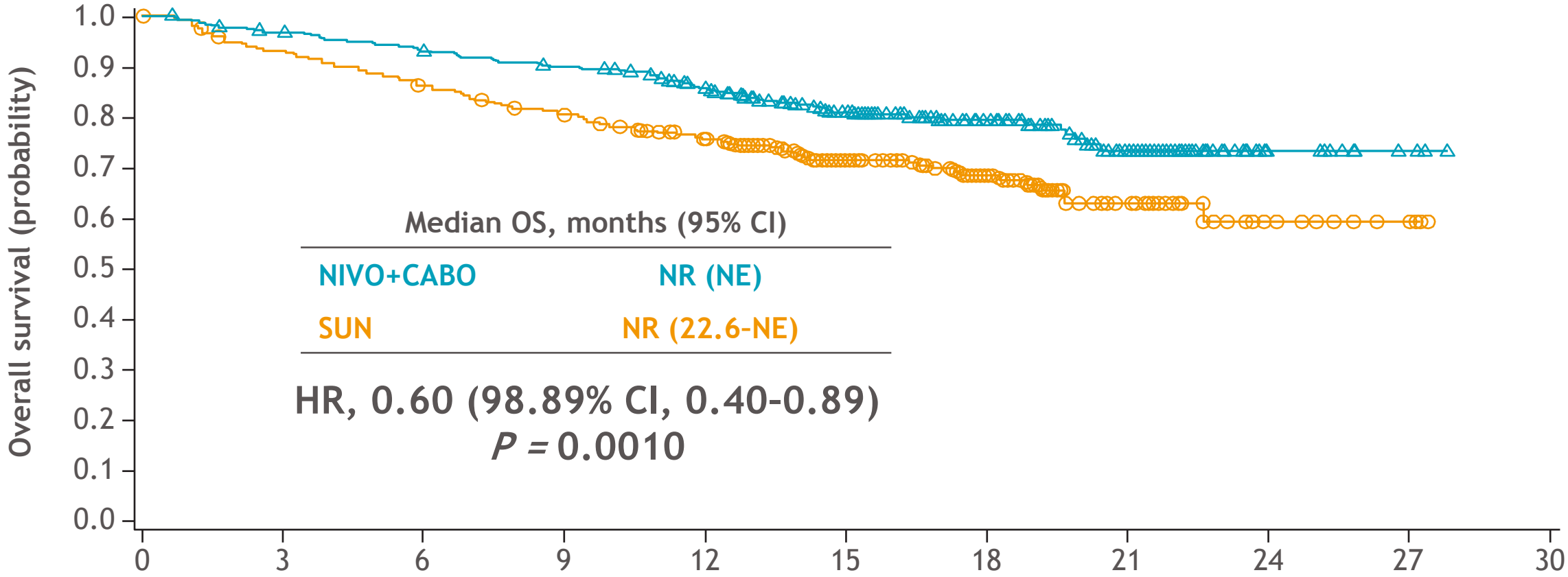
CheckMate 9ER Phase III: Progression-free Survival per BICR



Minimum study follow-up, 10.6 months.

Choueiri TK et al. *Ann Oncol*. 2020;31(S4):S1159.

CheckMate 9ER: Overall Survival



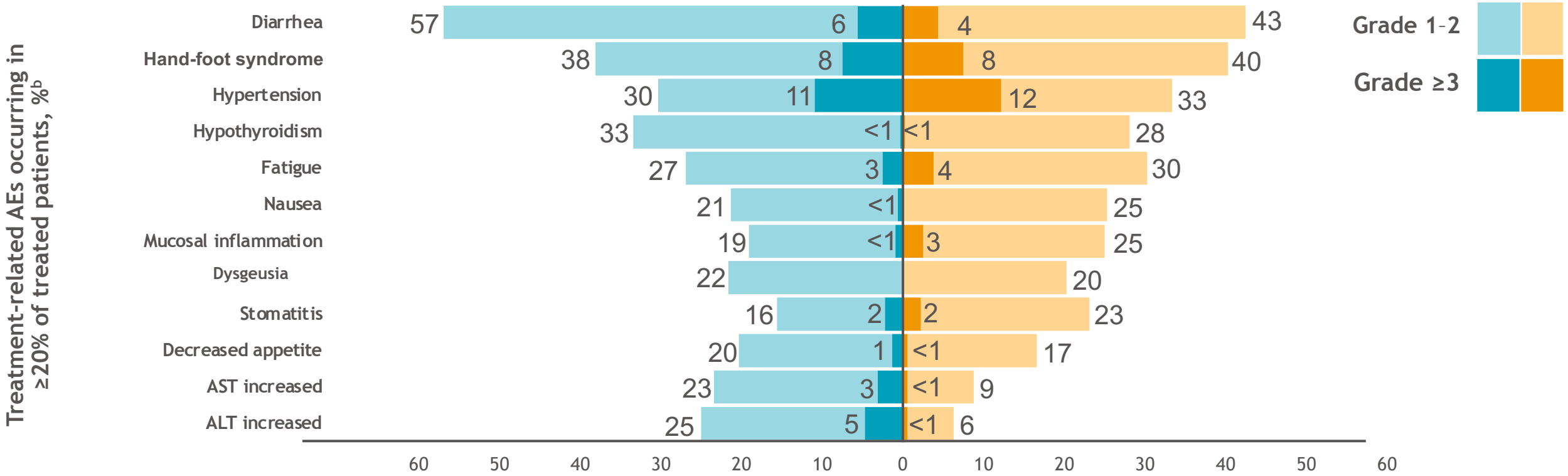
No. at risk											
NIVO+CABO	323	308	295	283	259	184	106	55	11	3	0
SUN	328	296	273	253	223	154	83	36	10	3	0

Minimum study follow-up, 10.6 months.
NE, not estimable; NR, not reached.

Choueiri TK et al. *Ann Oncol*. 2020;31(S4):S1159.

CheckMate 9ER: Safety Summary

	NIVO+CABO, n = 320		SUN, n = 320	
Events, %[a]	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
All-cause AEs	100	75	99	71
Treatment-related AEs	97	61	93	51



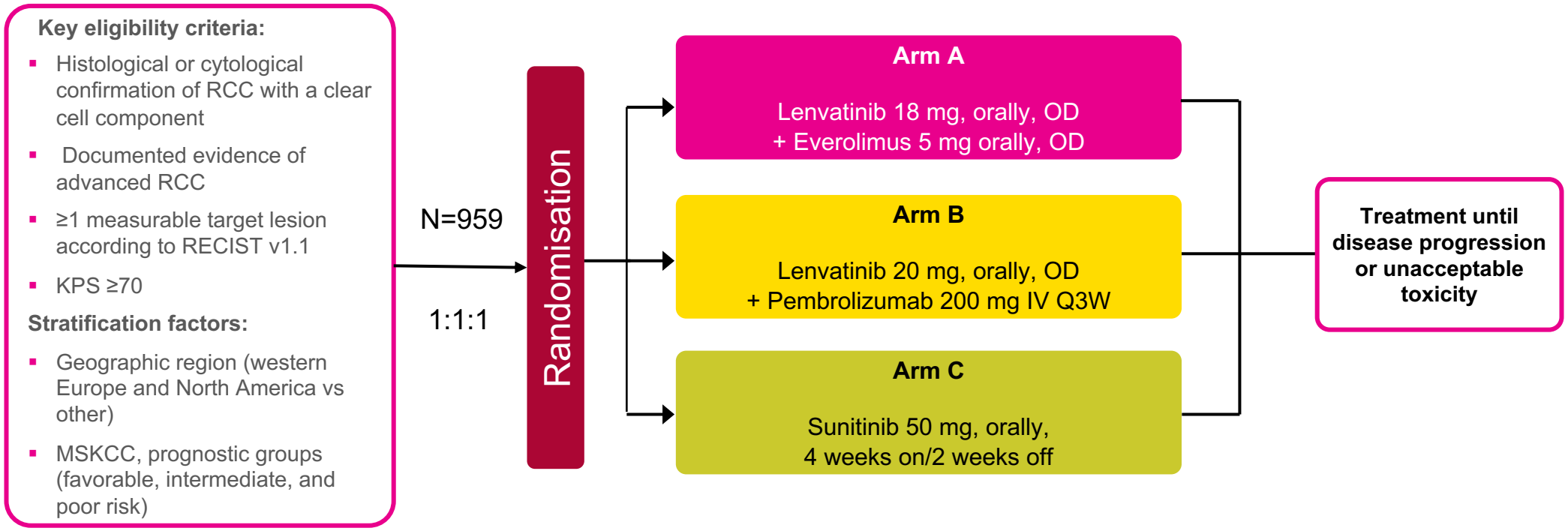
[a]Includes events that occurred on therapy or within 30 days after the end of the treatment period of all treated patients. Treatment-related deaths per investigator: NIVO+CABO n = 1 (small intestine perforation), SUN n = 2 (pneumonia, respiratory distress); [b]Total bar represents treatment-related AEs of any grade ≥ 20% in either treatment arm; of these events, none were grade 5.

Choueiri TK et al. *Ann Oncol*. 2020;31(S4):S1159.

CLEAR Trial: Pembrolizumab/Lenvatinib vs. Sunitinib

Design: Multicentre, open-label, randomised, Phase 3 trial in first-line mRCC

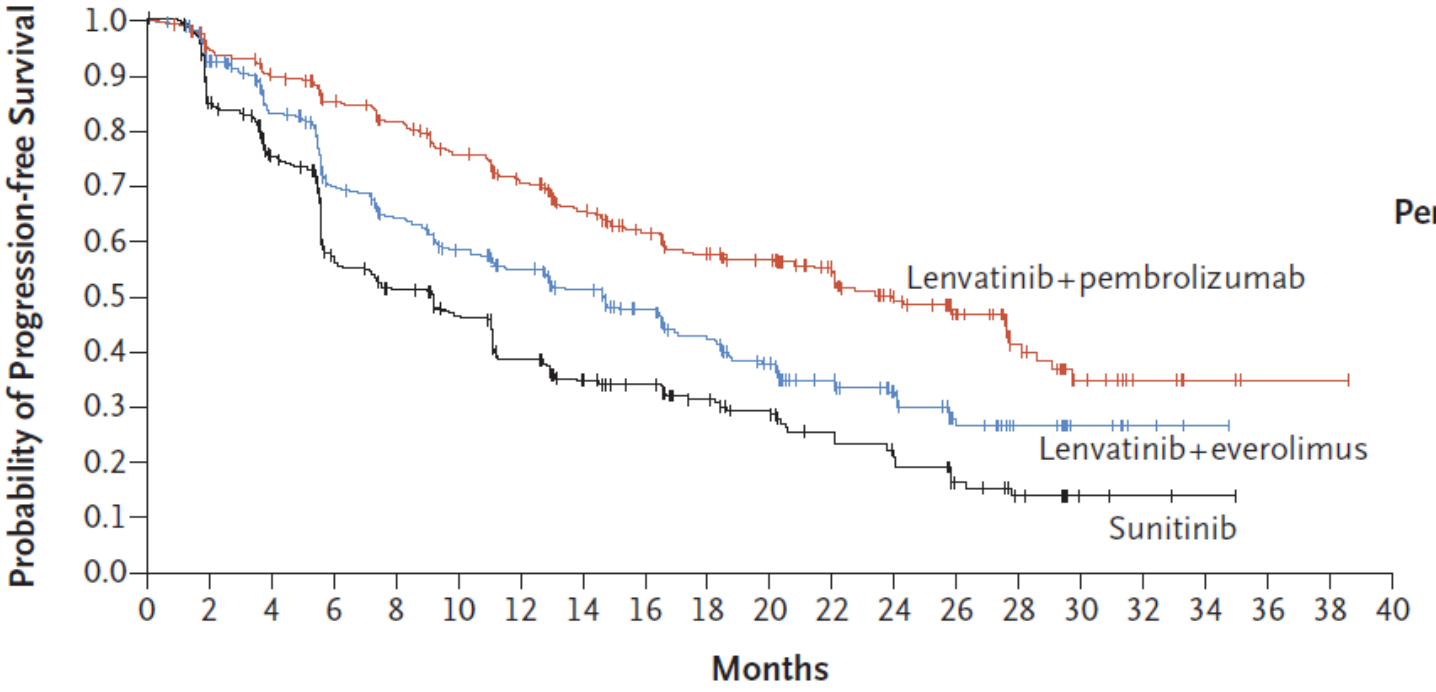
Primary endpoint: Progression-free survival (PFS) by independent review



Motzer R et al. *N Engl J Med*. 2021;384:1289-1300.

CLEAR Trial: Pembrolizumab/Lenvatinib or Lenvatinib/Everolimus vs. Sunitinib

A Kaplan–Meier Analysis of Progression-free Survival



Median Progression-free Survival (95% CI)	*mo*
Lenvatinib+ Pembrolizumab	23.9 (20.8–27.7)
Lenvatinib+ Everolimus	14.7 (11.1–16.7)
Sunitinib	9.2 (6.0–11.0)

Hazard ratio for disease progression or death (lenvatinib+ pembrolizumab vs. sunitinib), 0.39 (95% CI, 0.32–0.49); P<0.001

Hazard ratio for disease progression or death (lenvatinib+ everolimus vs. sunitinib), 0.65 (95% CI, 0.53–0.80); P<0.001

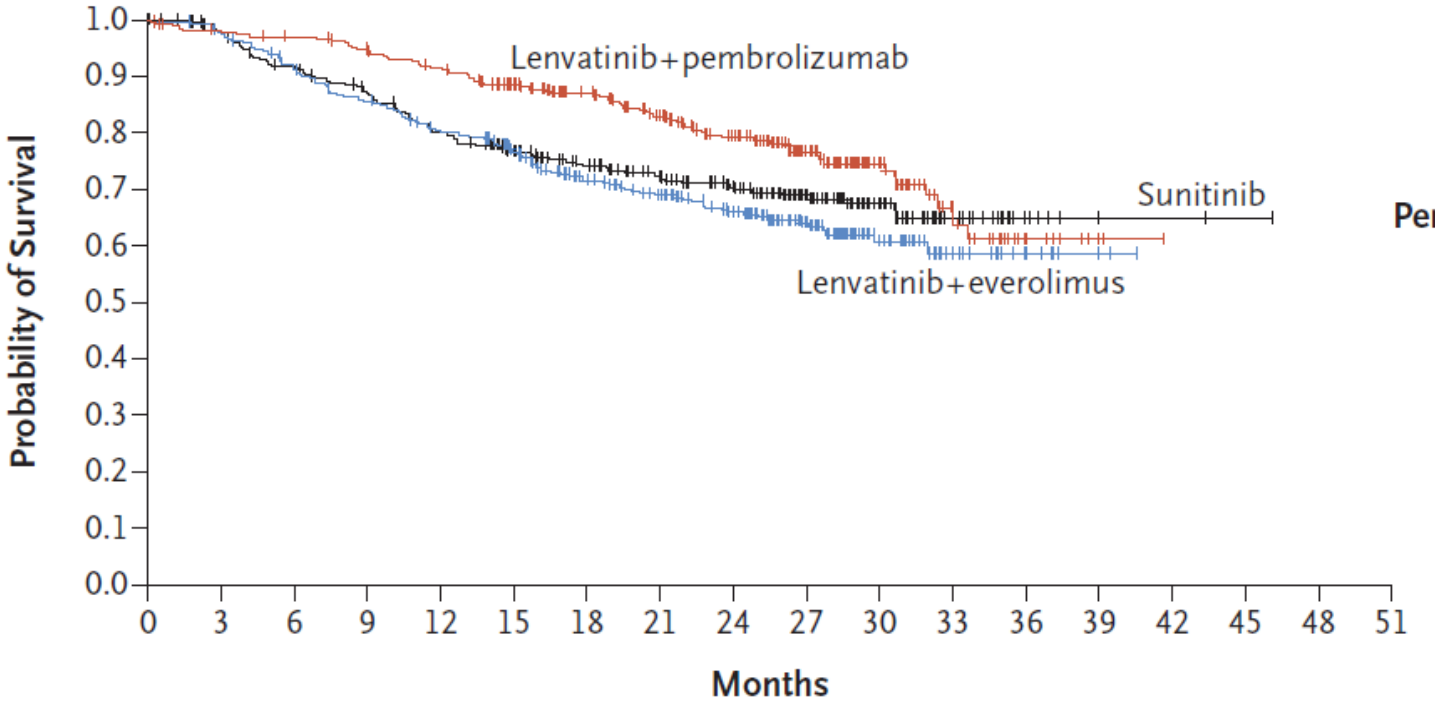
No. at Risk

Lenvatinib+pembrolizumab	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Lenvatinib+everolimus	357	305	259	207	185	163	149	125	105	85	70	53	37	20	13	7	3	1	0		
Sunitinib	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0		

Motzer R et al. *N Engl J Med*. 2021;384:1289-1300.

CLEAR Phase III Trial: Pembrolizumab/Lenvantinib or Lenvantinib/Everolimus vs. Sunitinib

A Kaplan–Meier Analysis of Overall Survival



	Median Overall Survival (95% CI)
	mo
Lenvatinib+ Pembrolizumab	NR (33.6–NE)
Lenvatinib+ Everolimus	NR (NE–NE)
Sunitinib	NR (NE–NE)

Hazard ratio for death (lenvatinib+ pembrolizumab vs. sunitinib), 0.66 (95% CI, 0.49–0.88); P=0.005

Hazard ratio for death (lenvatinib+ everolimus vs. sunitinib), 1.15 (95% CI, 0.88–1.50); P=0.30

No. at Risk

Lenvatinib+pembrolizumab	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0		
Lenvatinib+everolimus	357	346	321	299	277	246	205	183	154	109	46	22	8	2	0		
Sunitinib	357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

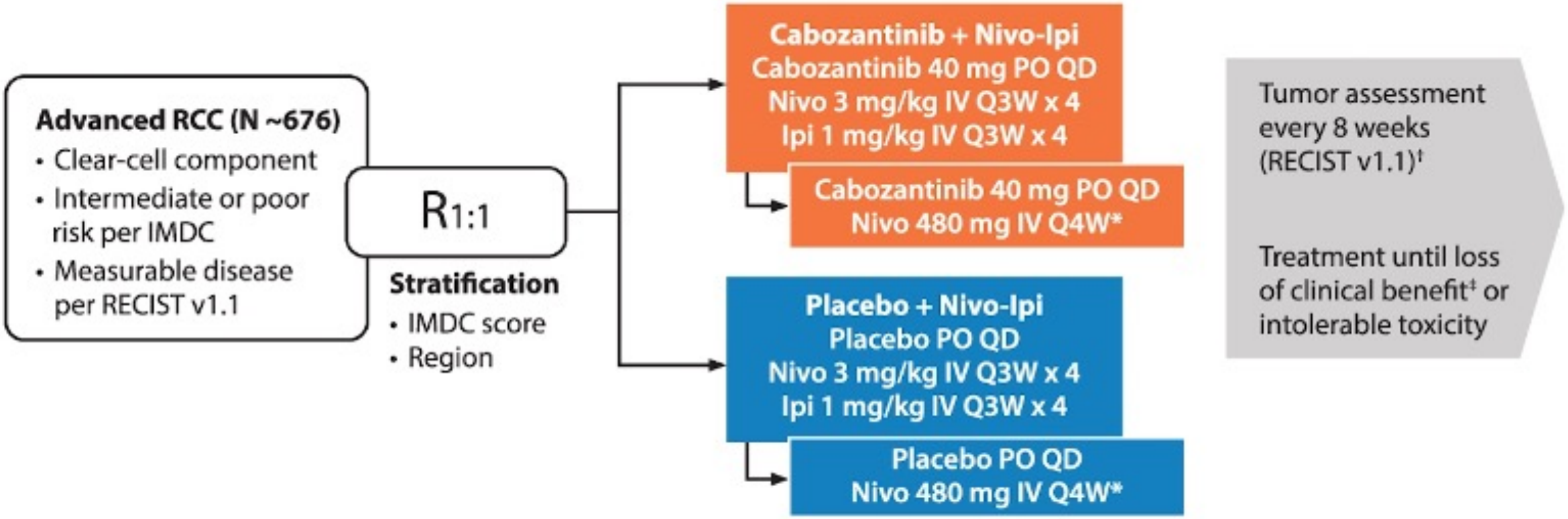
Motzer R et al. *N Engl J Med*. 2021;384:1289-1300.

Table 3. Adverse Events of Any Cause That Emerged or Worsened during Treatment in at Least 25% of the Patients in Any Treatment Group.*

Event	Lenvatinib plus Pembrolizumab (N=352)		Lenvatinib plus Everolimus (N=355)		Sunitinib (N=340)	
	Any Grade	Grade ≥3†	Any Grade	Grade ≥3†	Any Grade	Grade ≥3†
	number of patients (percent)					
Any event	351 (99.7)	290 (82.4)	354 (99.7)	295 (83.1)	335 (98.5)	244 (71.8)
Diarrhea	216 (61.4)	34 (9.7)	236 (66.5)	41 (11.5)	168 (49.4)	18 (5.3)
Hypertension	195 (55.4)	97 (27.6)	162 (45.6)	80 (22.5)	141 (41.5)	64 (18.8)
Hypothyroidism‡	166 (47.2)	5 (1.4)	95 (26.8)	2 (0.6)	90 (26.5)	0
Decreased appetite	142 (40.3)	14 (4.0)	144 (40.6)	22 (6.2)	105 (30.9)	5 (1.5)
Fatigue	141 (40.1)	15 (4.3)	149 (42.0)	27 (7.6)	125 (36.8)	15 (4.4)
Nausea	126 (35.8)	9 (2.6)	141 (39.7)	9 (2.5)	113 (33.2)	2 (0.6)
Stomatitis	122 (34.7)	6 (1.7)	169 (47.6)	22 (6.2)	131 (38.5)	7 (2.1)
Dysphonia	105 (29.8)	0	84 (23.7)	2 (0.6)	14 (4.1)	0
Weight decrease	105 (29.8)	28 (8.0)	116 (32.7)	26 (7.3)	31 (9.1)	1 (0.3)
Proteinuria	104 (29.5)	27 (7.7)	121 (34.1)	29 (8.2)	43 (12.6)	10 (2.9)
Palmar–plantar erythrodysesthesia syndrome	101 (28.7)	14 (4.0)	81 (22.8)	10 (2.8)	127 (37.4)	13 (3.8)
Arthralgia	99 (28.1)	5 (1.4)	76 (21.4)	5 (1.4)	52 (15.3)	1 (0.3)
Rash	96 (27.3)	13 (3.7)	88 (24.8)	1 (0.3)	47 (13.8)	2 (0.6)
Vomiting	92 (26.1)	12 (3.4)	113 (31.8)	10 (2.8)	68 (20.0)	5 (1.5)
Constipation	89 (25.3)	3 (0.9)	73 (20.6)	1 (0.3)	64 (18.8)	0
Dysgeusia	43 (12.2)	1 (0.3)	59 (16.6)	0	95 (27.9)	1 (0.3)

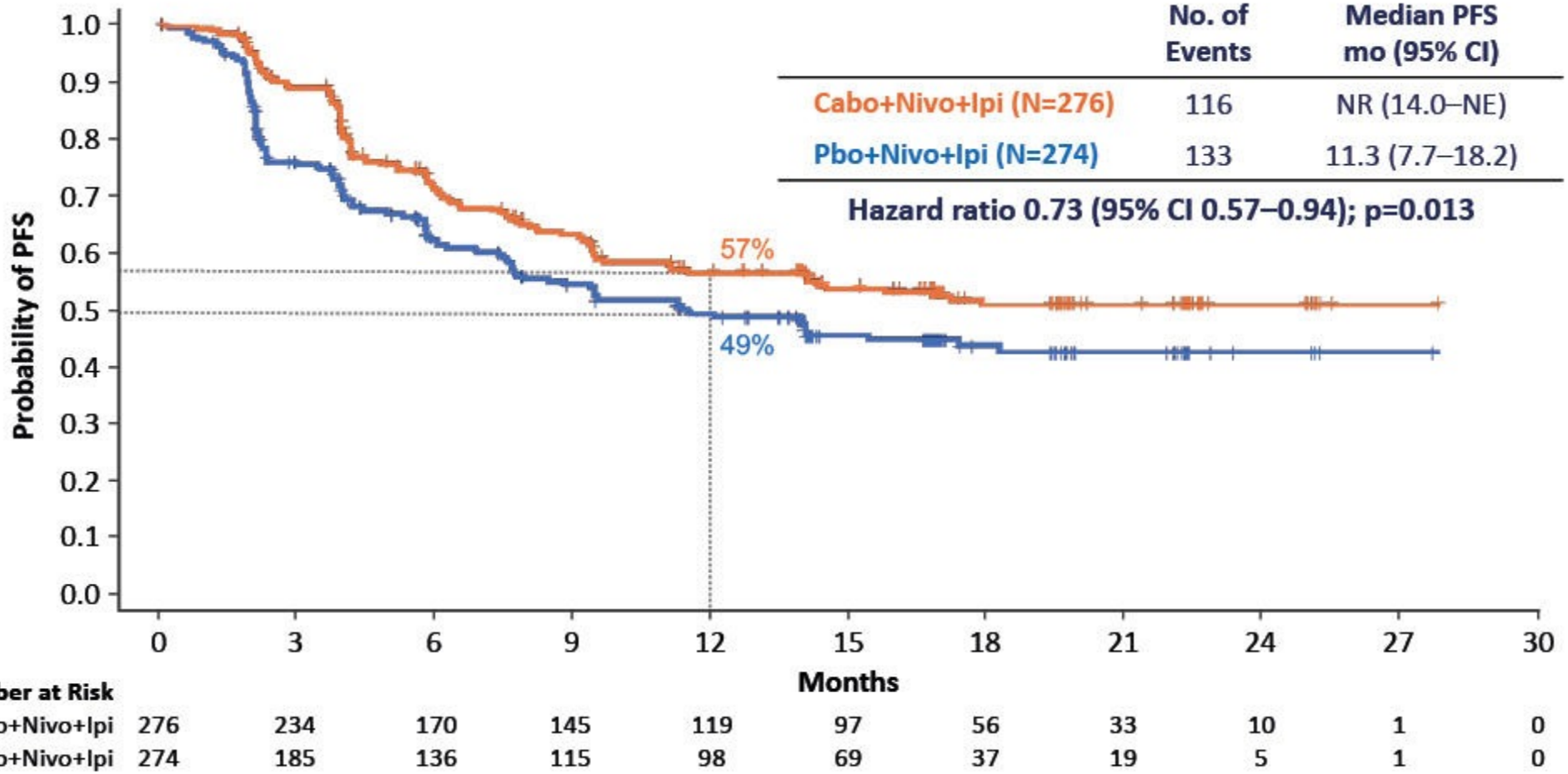
Motzer R et al. *N Engl J Med*. 2021;384:1289-1300.

COSMIC 313: Nivo/Ipi +/- Cabozantinib in mRCC



Choueiri, ESMO 2022

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

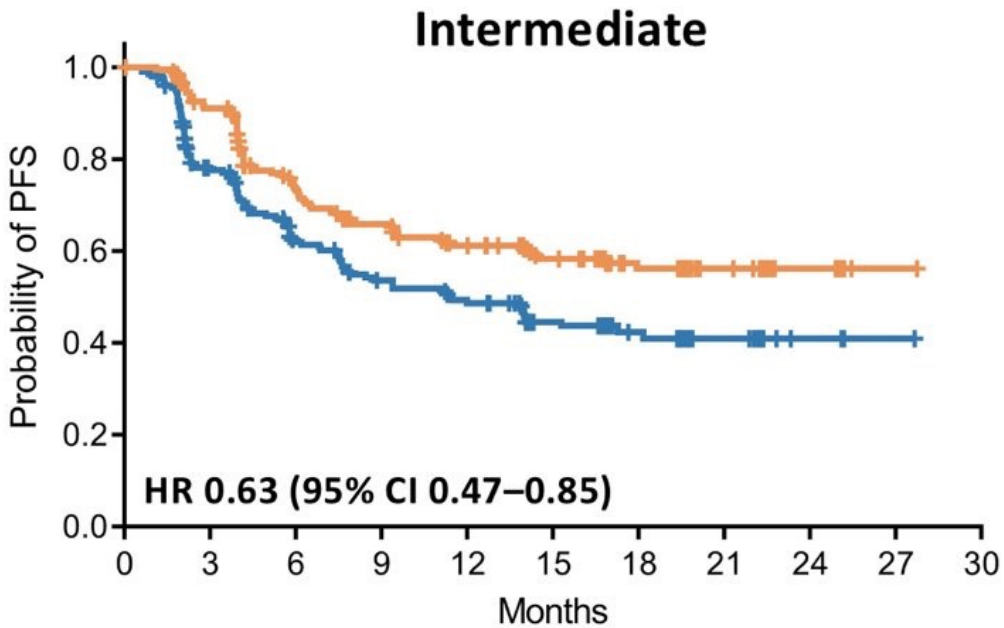
Number at Risk											
Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

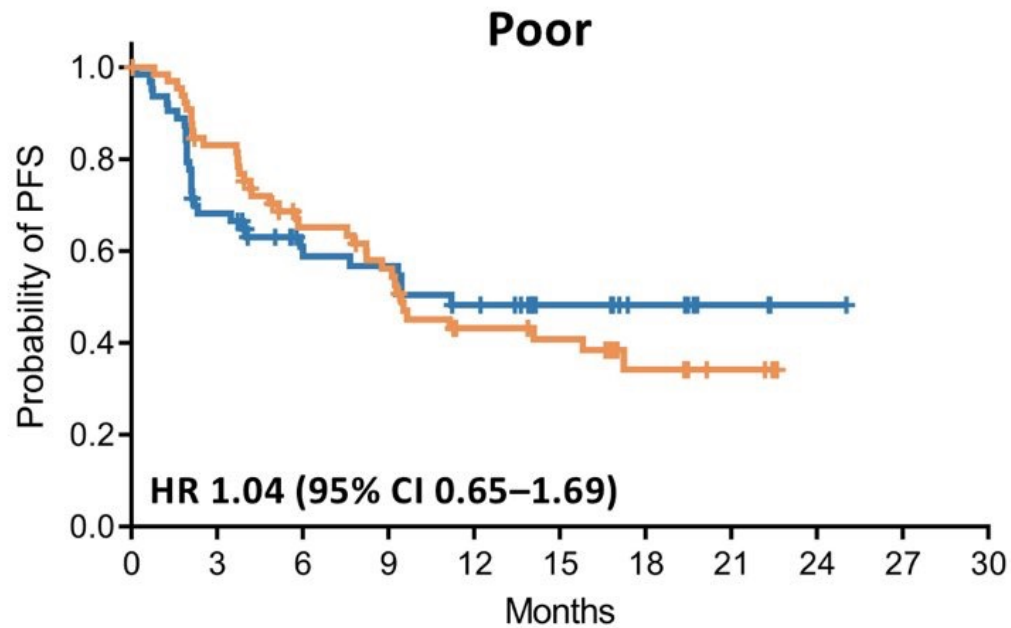
PFS per RECIST v1.1 by BIRC.
Data cut-off: Aug 23, 2021

PITT – PFS Intent To Treat

Choueiri, ESMO 2022

PFS by IMDC Risk Group (PITT Population)





	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=209)	79	NR (16.9–NE)
Pbo+Nivo+Ipi (N=208)	103	11.4 (7.6–17.3)

	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=67)	37	9.5 (7.8–17.3)
Pbo+Nivo+Ipi (N=66)	30	11.2 (4.0–NE)

PFS per RECIST v1.1 by BIRC. IMDC risk group is per IxRS.

Data cut-off: 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

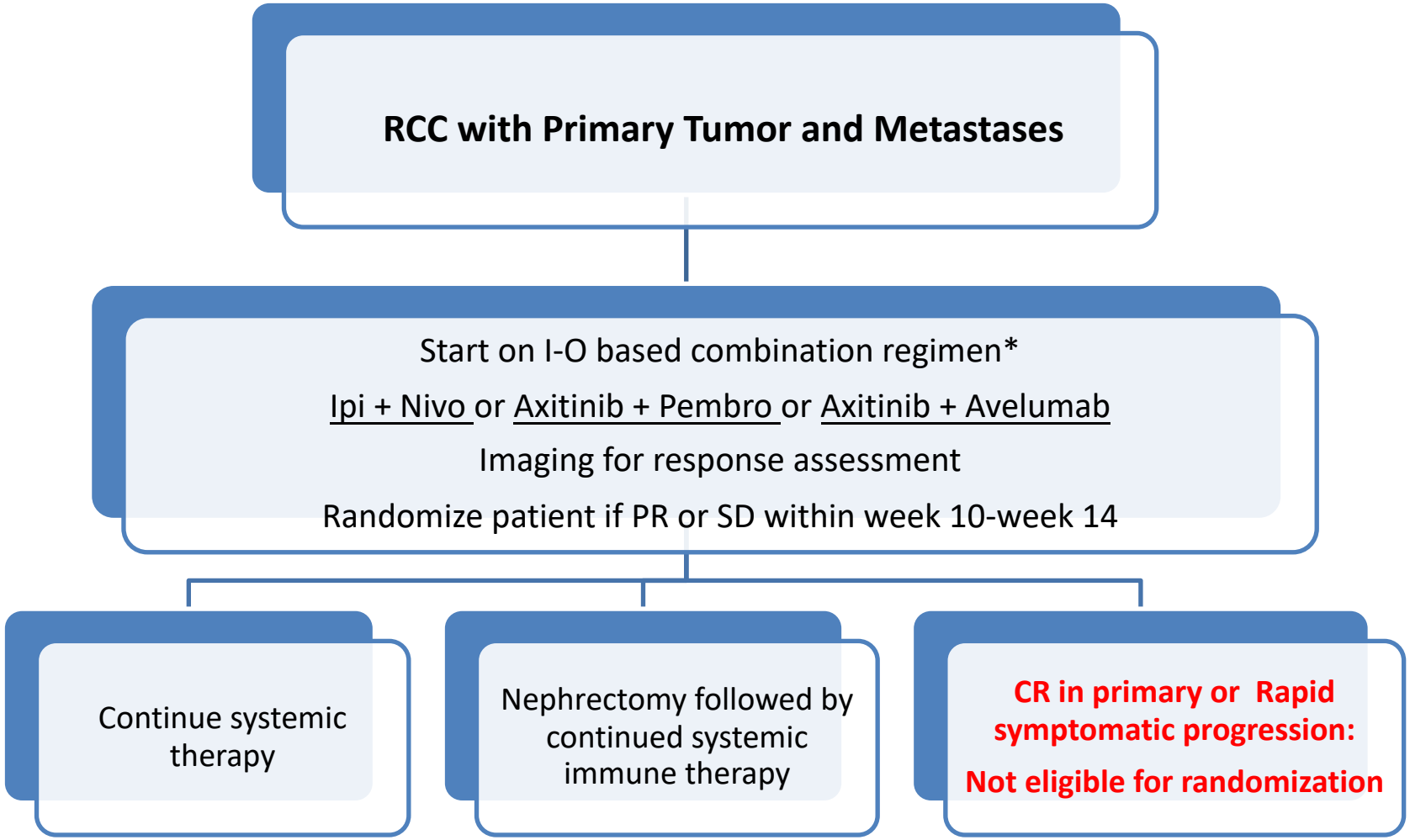
COSMIC 313: Safety

	Nivo/Ipi + Placebo	Nivo/Ipi + Cabozantinib
Grade 3-4 TRAEs	41%	73%
TRAEs leading to discontinuation	5%	12%

Three patients in both treatment arms had grade 5 TRAEs: GI hemorrhage, hepatic failure and respiratory failure in the triplet arm and renal failure, myocarditis and sudden death in the doublet arm.

Choueiri, ESMO 2022

SWOG 1931/PROBE Trial
Primary Endpoint: Overall Survival



*Pembro/Len and Nivo/Cabo to be added as options

PIs: Kim & Vaishampayan

Who Is NOT Eligible for Immunotherapy?

- Active autoimmune disease
- History of solid organ transplantation
- Supraphysiologic corticosteroids
- Chronic immunosuppressive therapy
- Personal preference (e.g., refuses IV therapy)

Frontline mRCC:
Who Gets Checkpoint Inhibitor <u>Monotherapy</u>?

Answer: A few patients…

- Ineligible for (or refuse) VEGFR-TKI containing combination
- Averse to ipilimumab

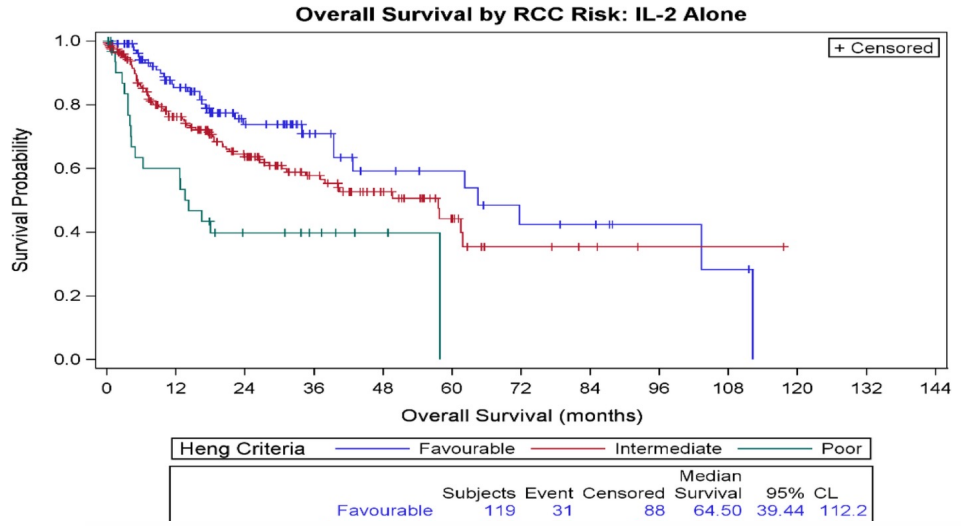
	Number of ccRCC patients	ORR (95% CI)	PFS, months(95% CI)
Pembrolizumab	110	33.6% (24.8–43.4)	6.9 (5.1–NR)
Nivolumab	123	36.4% (27.4-46.1)	8.3 (5.5-10.9)

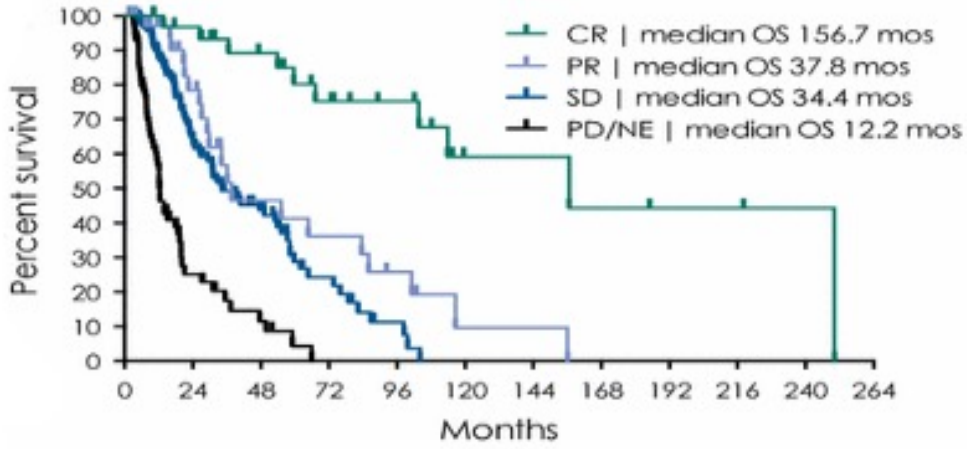
Tykodi SS et al. *J Clin Oncol.* 2019;37(suppl 15):4570; Donskov F et al. *Ann Oncol*. 2018;29(suppl 8):3762; Atkins MB et al. *J Clin Oncol*. 2020;38(suppl 15):5006.

Frontline mRCC:
Who Gets HD IL-2 Monotherapy?

***Answer*: Almost no one**

- HD IL-2 still listed as monotherapy option in some guidelines
  - Reserved for robust patients with excellent PS and normal end-organ function
  - Long term survival observed, particularly those with favorable/int risk and/or CR
- Requirement for inpatient care and high toxicity limits routine use of HD IL-2





Fishman JA et al. *Clin Infect Dis*. 2019;69(6):909-920; Stenehjem DD et al. *Cancer Immunol Immunother*. 2016;65(8):941-949.

Frontline mRCC:
Who Gets mTORi Monotherapy?

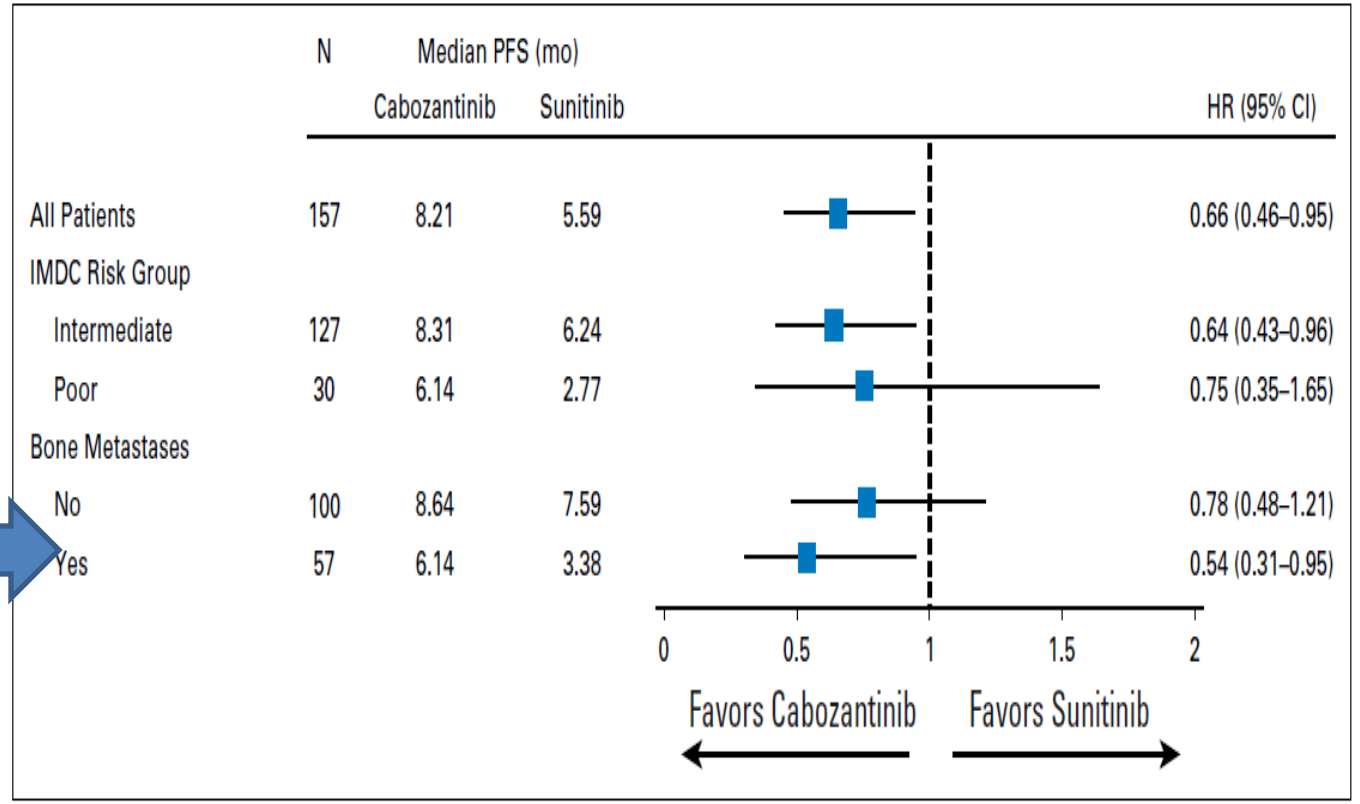
***Answer*: No one**

- Temsirolimus monotherapy is FDA approved for frontline mRCC
- Original registration trial was in a “poor risk” subset (composite criteria)
- In era of more active, life-prolonging therapies…

There is little justification for routine frontline temsirolimus use

Frontline mRCC:
Who Gets VEGFR-TKI Monotherapy?

1. Ineligible for IO
2. Refuses IO
3. Intolerant of IO
4. Selected patient subsets
   - Bone-only metastases? (Cabozantinib)
   - Non-clear cell histology (Papillary RCC)
   - Selected patients with favorable risk

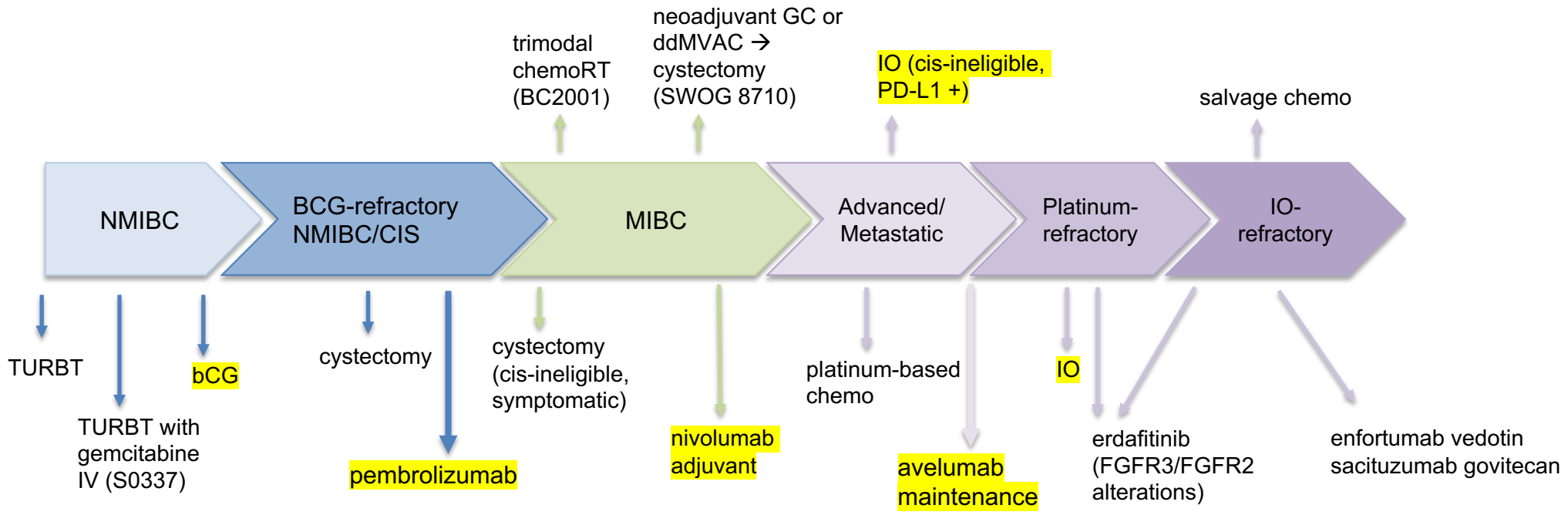


Choueiri TK et al. *J Clin Oncol*. 2017;35(6):591-597.

Summary: Frontline mRCC Therapy

- Key steps for the practicing clinician:
  - Risk stratify
  - Seek multidisciplinary input
  - Consider active surveillance and cytoreduction
  - Assess for immunotherapy eligibility
- Combination immunotherapy-based therapy is SOC for most
- Monotherapy is limited to a small (and diminishing) subset
- Clinical trial participation, where appropriate

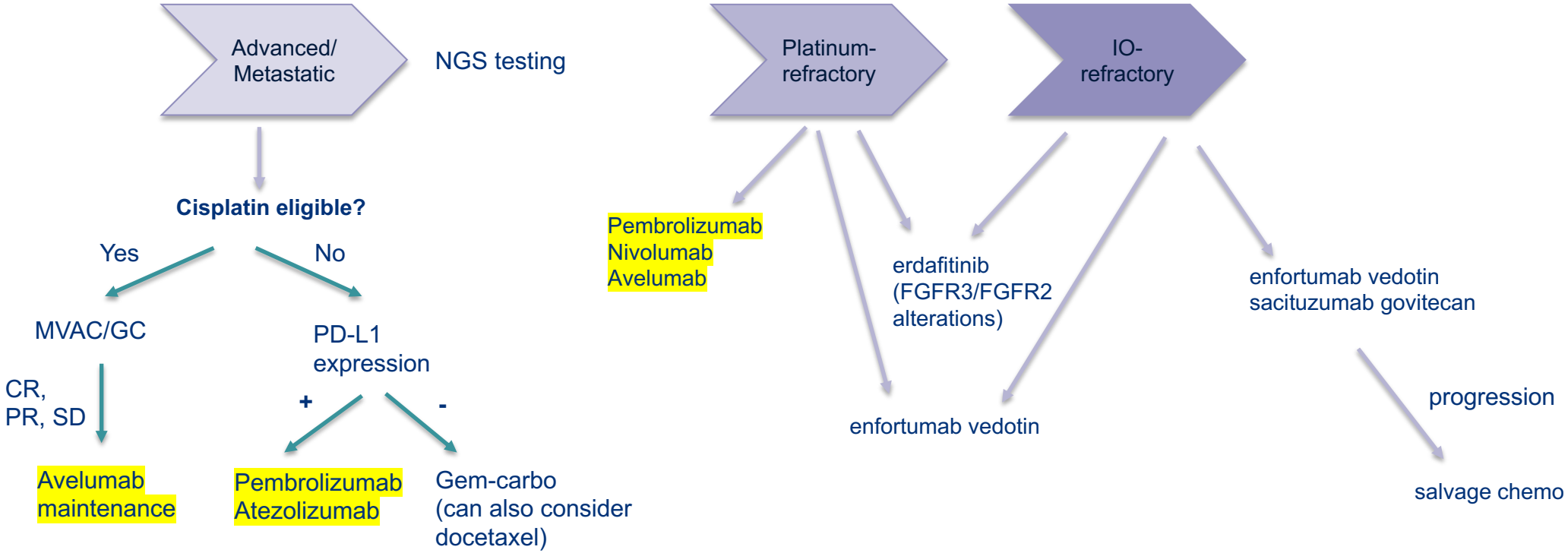
Bladder Cancer Treatment* Spectrum



In 2022, the US FDA's accelerated approvals for **Durvalumab** (*2nd line after PD on platinum therapy*) and **Atezolizumab** (*PD during or after platinum-based chemotherapy, or within 12 months of adjuvant or neoadjuvant chemotherapy*) were voluntarily withdrawn after failure of confirmatory trials

*Clinical trial consideration is always an option

Treatment of Advanced Metastatic Urothelial Carcinoma*



*Clinical trial consideration is always an option

Questions?

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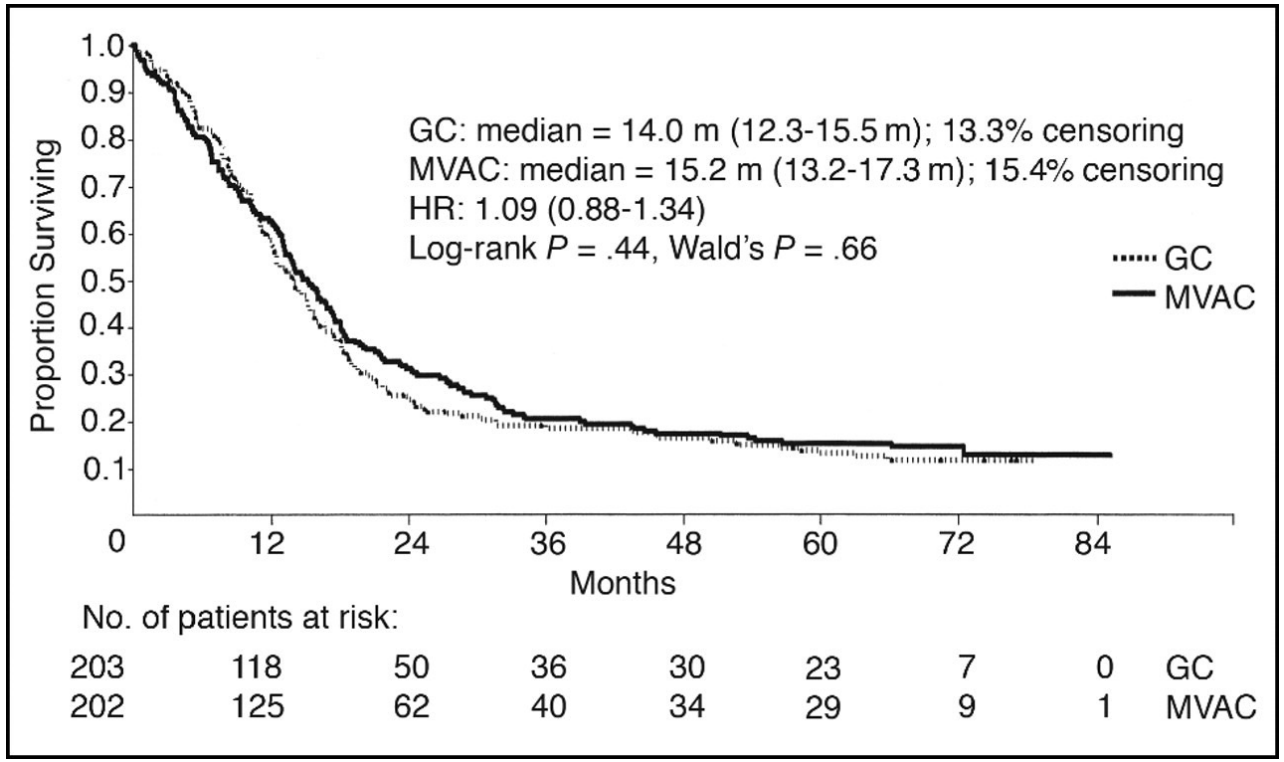
Back Up Slides

Treatment of advanced/metastatic disease

Advanced/ Metastatic → Platinum-refractory → IO-refractory



- **Cisplatin eligible?**
- Phase III non-inferiority trial of:
  - ddMVAC (MTX, vinblastine, doxorubicin, cisplatin) **vs**
  - gemcitabine + cisplatin

Results: met non-inferiority

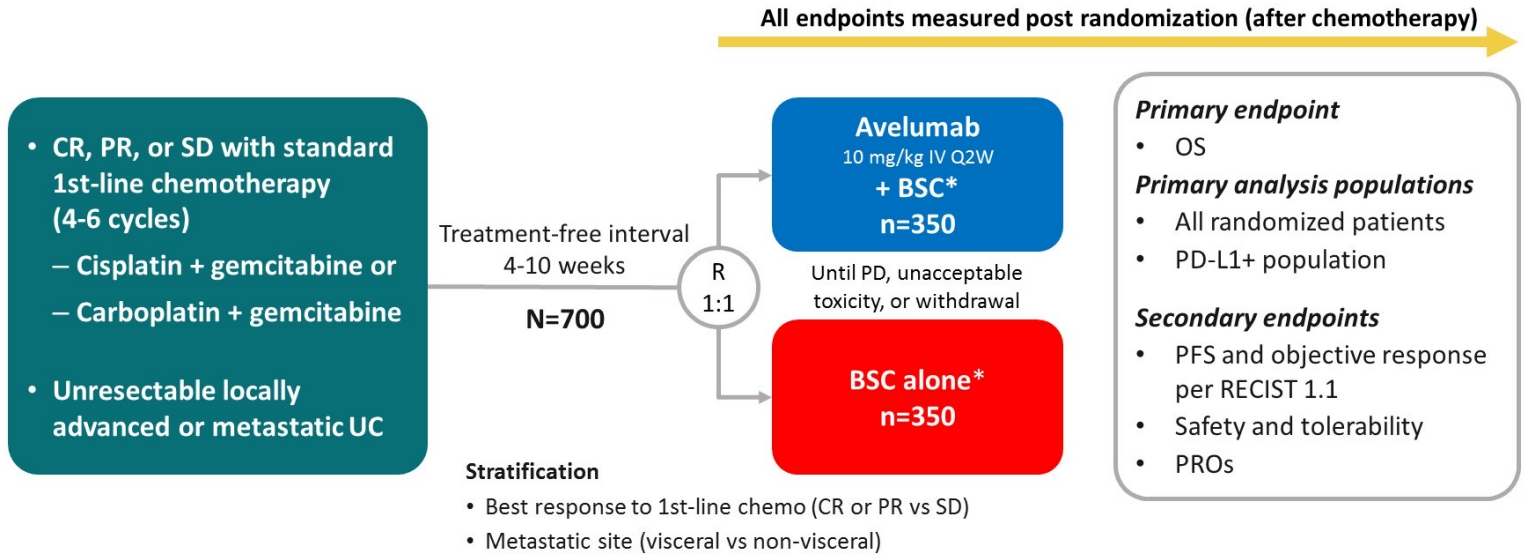
- median OS: 14 vs 15.2 months
- ~10-15% of patients have long-term survival with cisplatin-based regimen

von der Maase et al, JCO 2005

Next steps in patients who respond to platinum chemo

Advanced/ Metastatic → Platinum-refractory

JAVELIN Bladder 100 study design (NCT02603432)

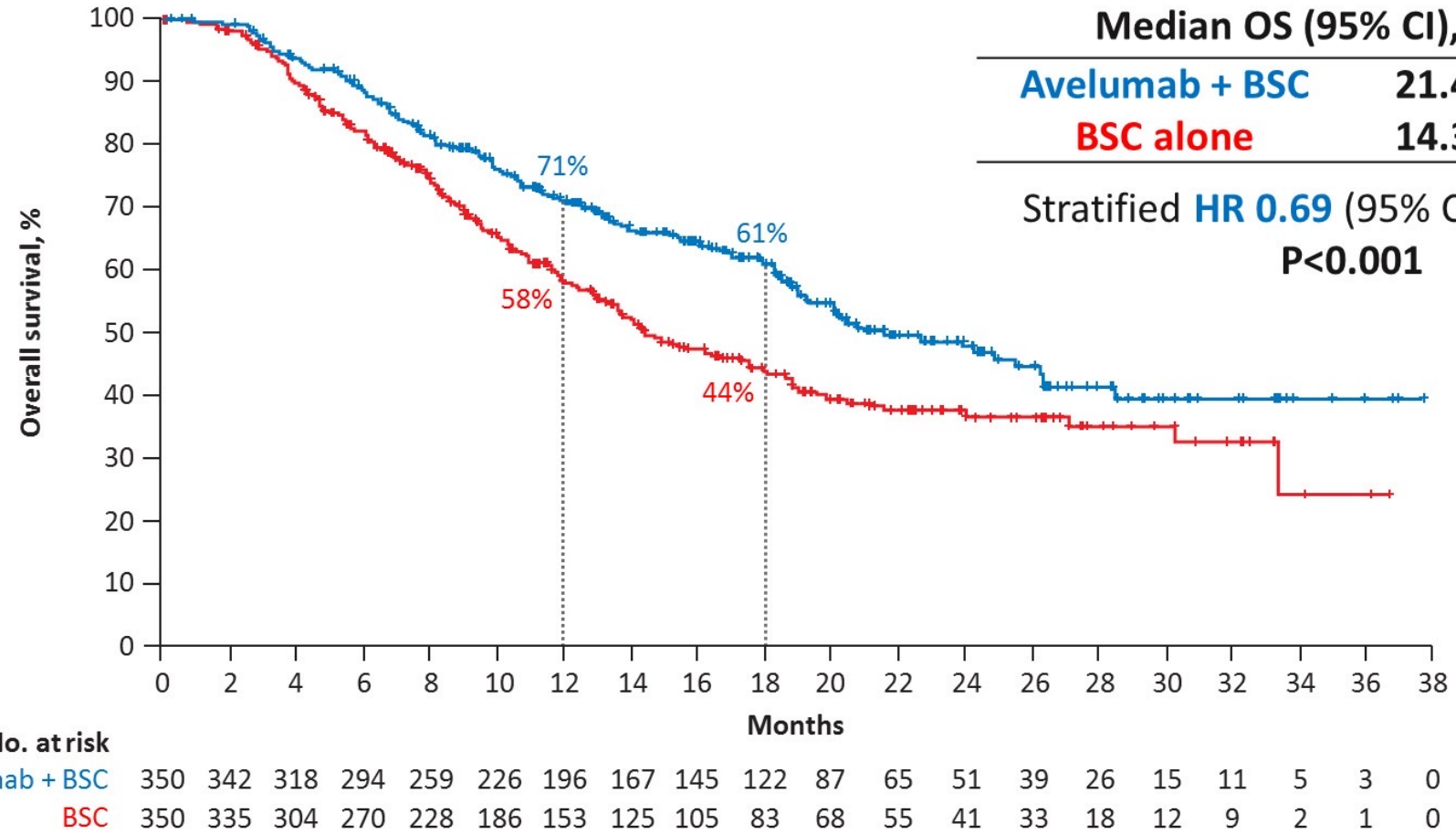


PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

BSC, best supportive care; **CR,** complete response; **IV,** intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W,** every 2 weeks; **R**, randomization; **RECIST 1.1,** Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

OS in the overall population



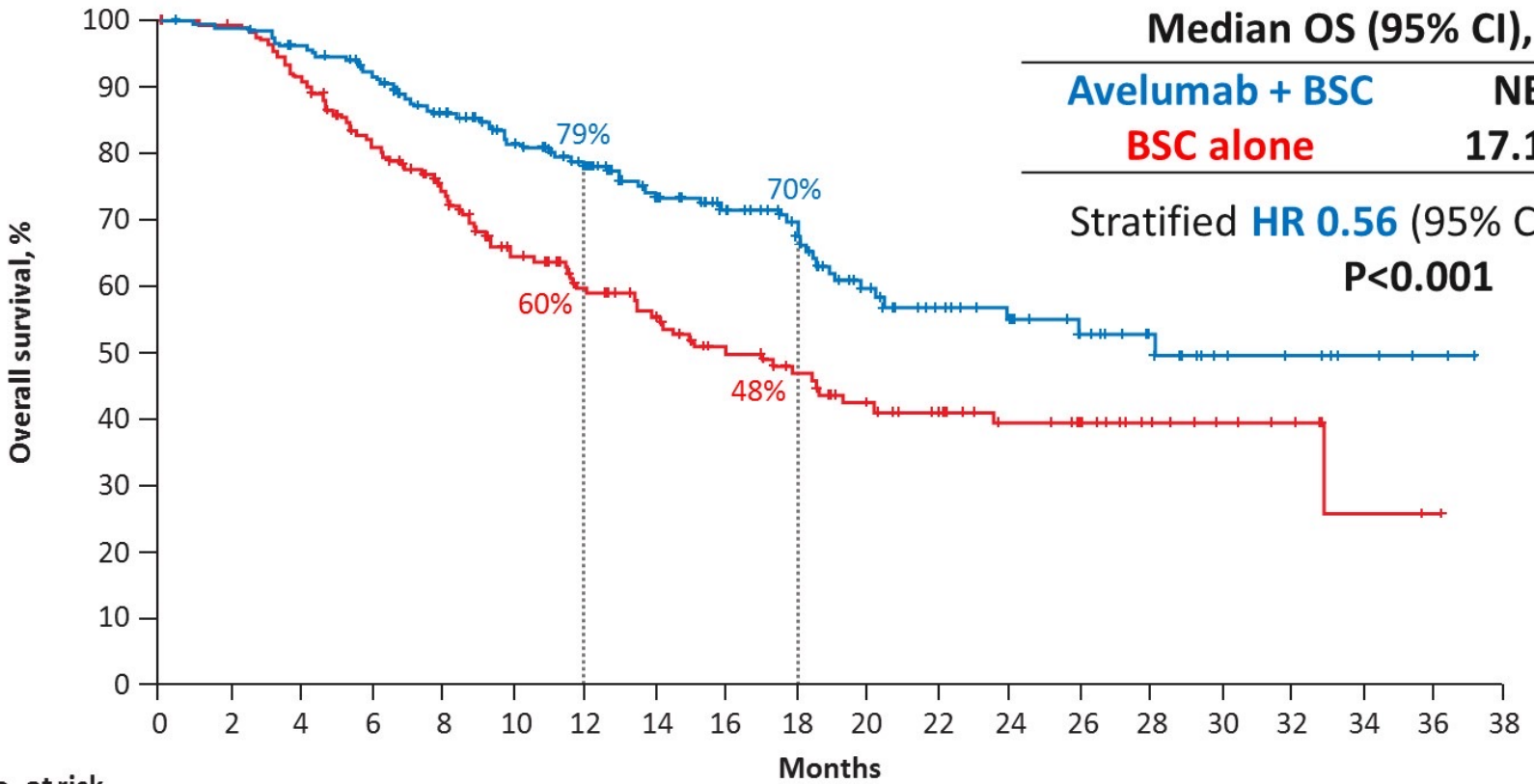
Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

Stratified **HR 0.69** (95% CI, 0.56, 0.86)

P<0.001

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

OS in the PD-L1+ population



Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.3, NE)
BSC alone	**17.1** (13.5, 23.7)

Stratified **HR 0.56** (95% CI, 0.40, 0.79)

P<0.001

No. at risk																				
Avelumab + BSC	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
BSC	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). **NE**, not estimable

Cisplatin-ineligible patients- IMvigor210 Cohort 1

IMvigor210:
- Inoperable locally advanced or metastatic urothelial carcinoma
- Predominantly UC histology
- Tumor tissue evaluable for PD-L1 testing[a]

Cohort 1 (N = 119): 1L cisplatin ineligible → Atezolizumab 1200 mg IV q3w until RECIST v1.1 progression

Cohort 2: Platinum-treated mUC → Atezolizumab 1200 mg IV q3w until loss of clinical benefit

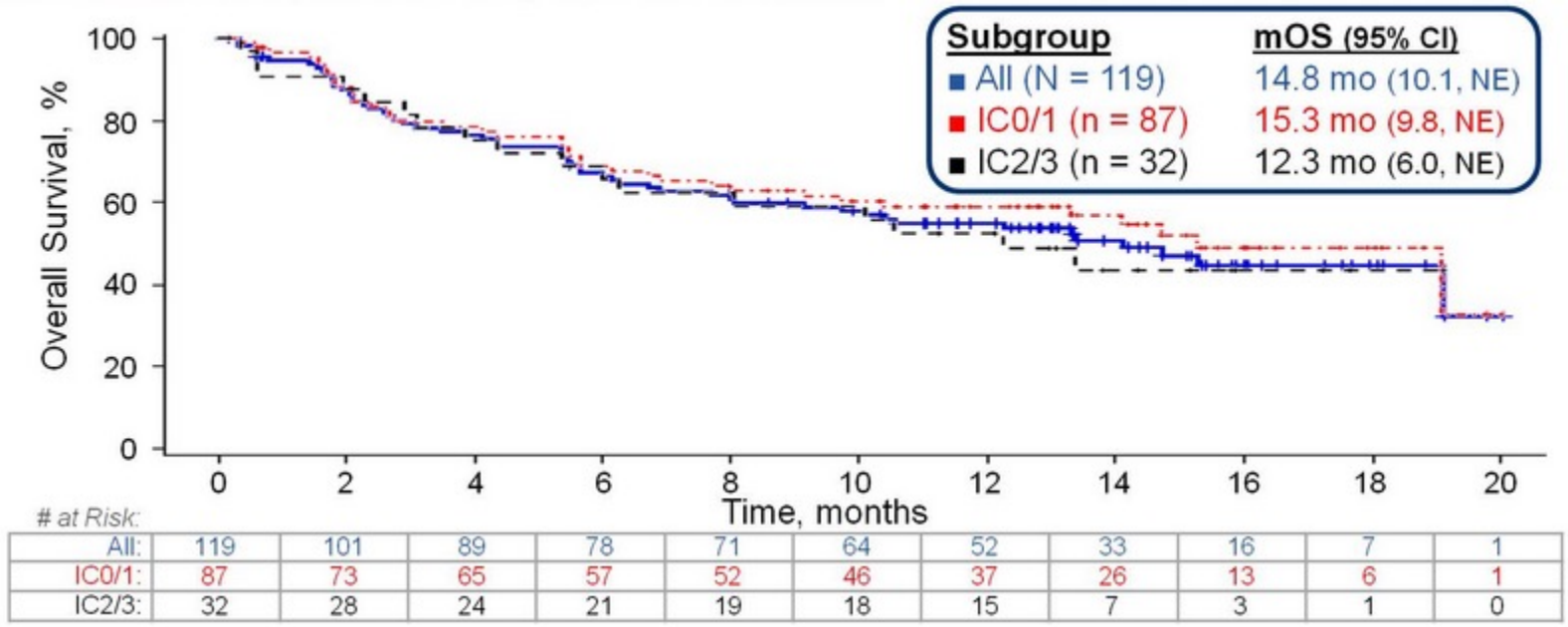
Cohort 1–specific inclusion criteria
- No prior treatment for mUC (> 12 mo since perioperative chemo)
- ECOG PS 0-2
- Cisplatin ineligibility[1] based on ≥ 1 of the following:
  - Renal impairment: GFR < 60 and > 30 mL/min[b]
  - ≥ Grade 2 hearing loss or peripheral neuropathy
  - ECOG PS 2

Primary endpoint
- Confirmed ORR: RECIST v1.1 (per central IRF)

Key secondary endpoints
- DOR, PFS, OS, safety

IC 0: < 1%
IC 1: 1 - < 5%
IC2/3: ≥ 5%

ORR: 24%
- ORR in IC2/3: 28%



# at Risk:											
All:	119	101	89	78	71	64	52	33	16	7	1
IC0/1:	87	73	65	57	52	46	37	26	13	6	1
IC2/3:	32	28	24	21	19	18	15	7	3	1	0

AV Balar et al, ASCO 2016

Cisplatin-ineligible patients- KEYNOTE-052

- Objective Response Rate: 29%

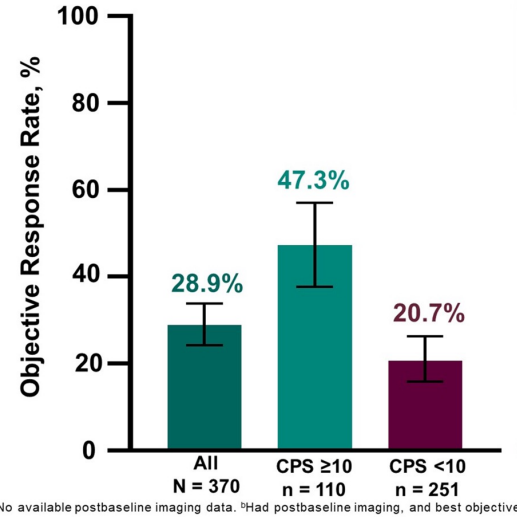
Key Eligibility Criteria

- Histologically or cytologically confirmed locally advanced/metastatic UC of the renal pelvis, ureter, bladder, or urethra
- Measurable disease based on RECIST v1.1 per independent central review
- No prior systemic chemotherapy for UC[a]
- Ineligible for cisplatin-based chemotherapy
- ECOG PS 0-2

→ N = 370 → Pembrolizumab 200 mg IV Q3W → Disease status and tumor response assessed by CT/MRI 9 weeks after first Pembrolizumab dose, then Q6W for 12 months and Q12W thereafter[b]

- Primary end point: confirmed ORR per RECIST v1.1 by independent radiology review
- Secondary end points: PFS and DOR per RECIST v1.1 by independent radiology review, OS, safety
- End points analyzed for the overall population, patients with PD-L1 CPS ≥10 and CPS <10[c]

Confirmed ORR per RECIST v1.1

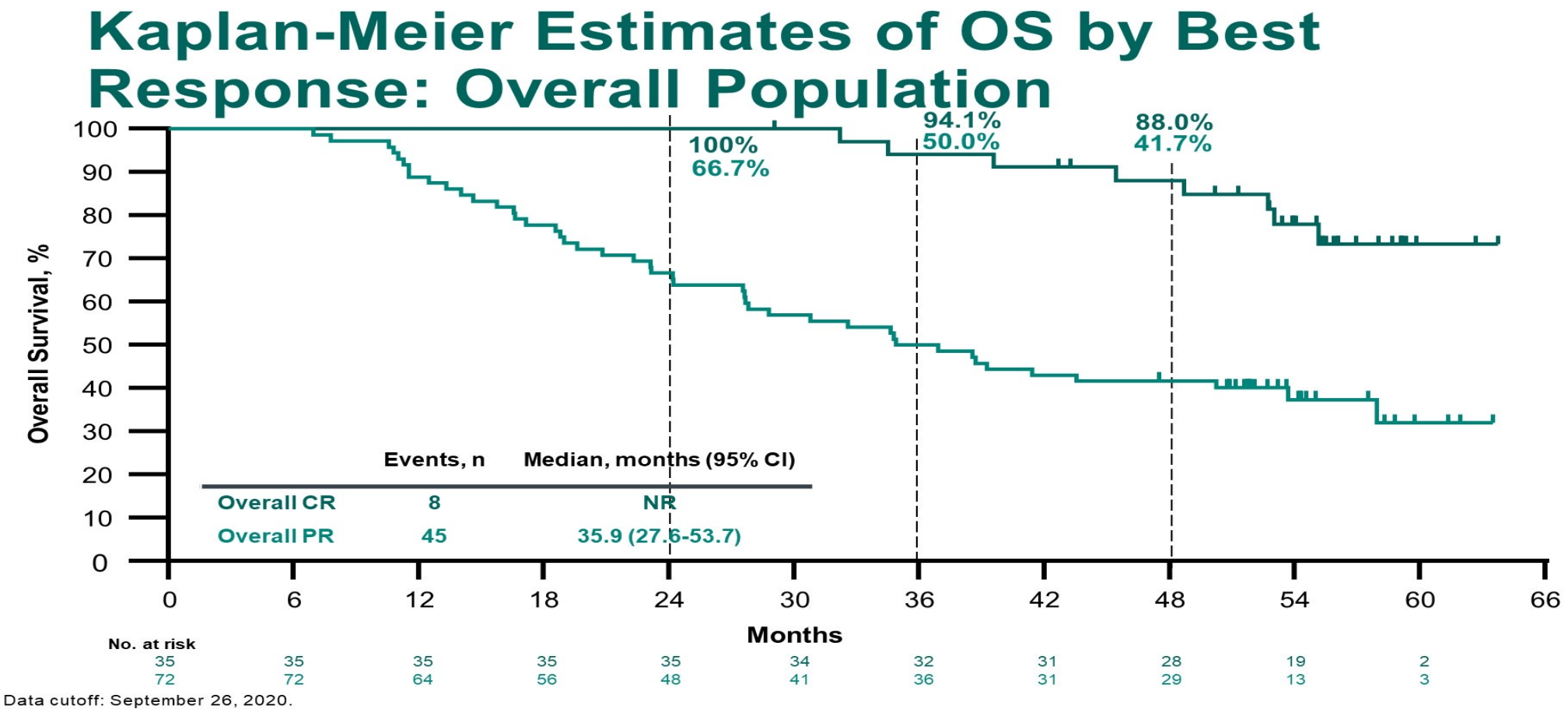


Best Response n (%)	All Patients N = 370	CPS ≥10 n = 110	CPS <10 n = 251
CR	35 (9.5)	23 (20.9)	10 (4.0)
PR	72 (19.5)	29 (26.4)	42 (16.7)
SD	67 (18.1)	22 (20.0)	44 (17.5)
PD	155 (41.9)	30 (27.3)	121 (48.2)
NA[a]	32 (8.6)	6 (5.5)	25 (10.0)
NE[b]	9 (2.4)	0 (0)	9 (3.6)

[a]No available postbaseline imaging data. [b]Had postbaseline imaging, and best objective response was determined to be NE by RECIST v1.1. Data cutoff: September 26, 2020.

O'Donnell et al, ASCO 2019

KEYNOTE-052 – survival in responders

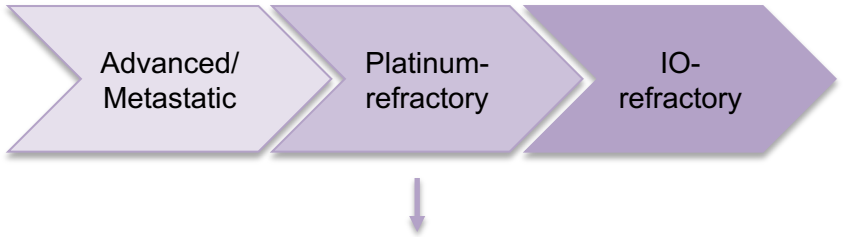


Data cutoff: September 26, 2020.

Caveat in cisplatin-ineligible patients

- Follow-up Phase III studies (IMVigor130, KEYNOTE-361) showed that PD-L1 low status → decreased OS
- Approach to cisplatin-ineligible patients:
  - PD-L1 expression
    - CPS ≥ 10% (pembrolizumab)
    - PD-L1 IC ≥ 5% (atezolizumab)
  - Chemotherapy candidacy
    - if patient is absolutely not a chemotherapy candidate, IO can be considered

Treatment of platinum-refractory disease



Agent	n	ORR	ORR by PD-L1 status
~~**Atezolizumab**~~	467	13.4%	PD-L1 IC2/IC3: 23%
Avelumab	44	17%	PD-L1 ≥5%: 24% PD-L1 low: 14%
~~**Durvalumab**~~	191	17.8%	PD-L1 ≥ 25%: 27.6% PD-L1 low/negative: 5.1%
Nivolumab	270	20.7%	PD-L1 >5%: 28.4% PD-L1 <5%: 23.8% PD-L1 <1%: 16.1%
Pembrolizumab	270	21.1%	PD-L1 ≥10%: 20.3%

* due to negative OS results from randomized Phase III IMvigor211 and DANUBE studies, the respective pharma sponsors have voluntary withdrawn approval of atezolizumab and durvalumab