Selection of Rx for **RCC- Adjuvant** & **1st line Rx** in metastatic disease

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ADJUVANT Rx

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Kidney Cancer

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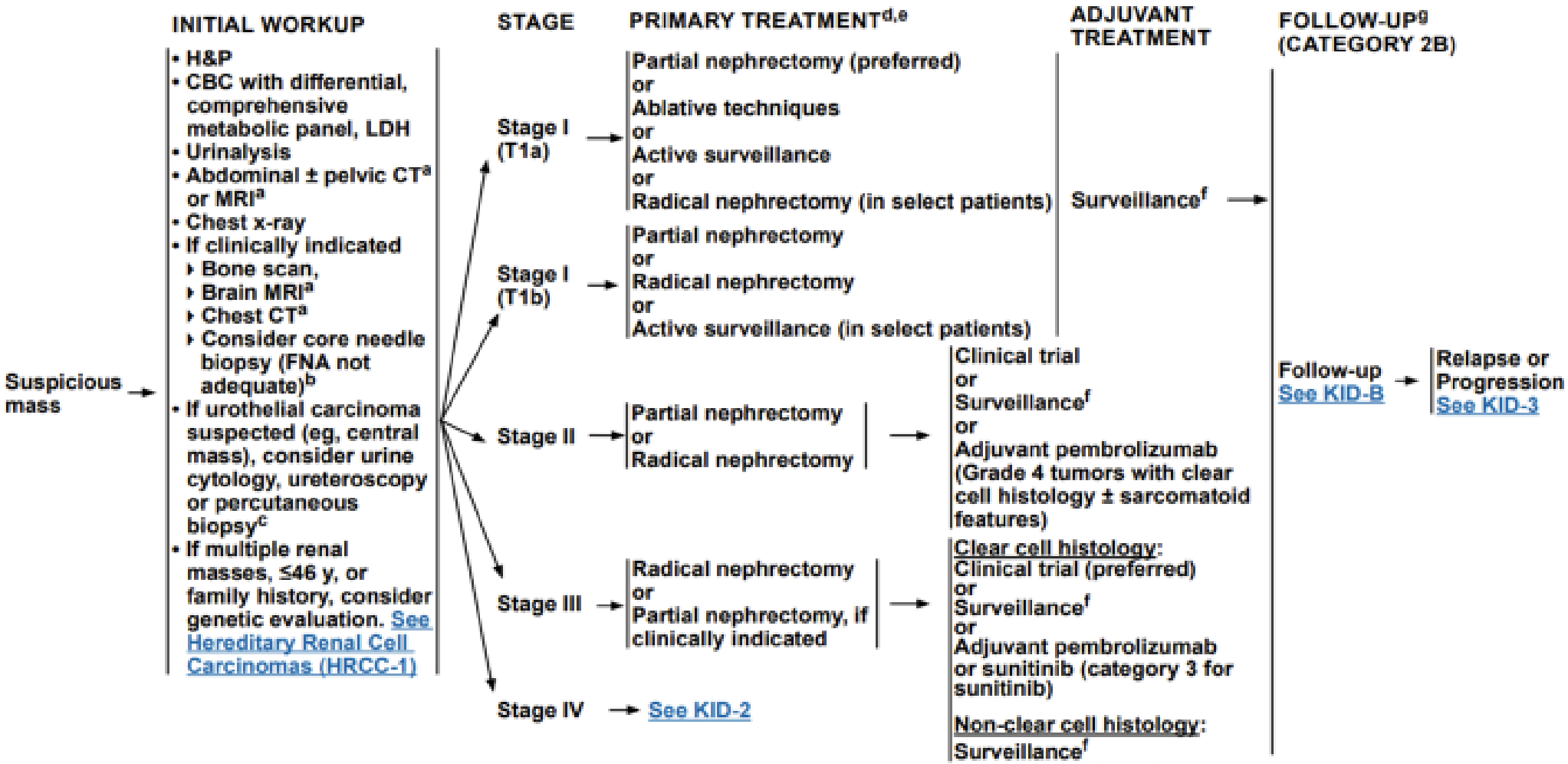


TKI ADJUVANT TRIALS

Trial	Therapy	N	Histology	Stage	Starting Dose	Minimum Dose	Significant Difference? DFS	Significant Difference? OS*
ASSURE[1]	Sunitinib Sorafenib Placebo	1943	79% ccRCC ccRCC was Primary endpt	> pT1b, G3-4, or N+	50 or 37.5 mg (Su)/ 400 mg (So)	25 mg (Su)/40 mg (So)	No	No
S-TRAC[2,3]	Sunitinib Placebo	615	ccRCC	> pT3b or N+	**50 mg**	**37.5 mg**	Yes	No
PROTECT[4,5]	Pazopanib Placebo	1538	ccRCC or mostly ccRCC	pT2 (G3-4), ≥ pT3, or N+	600 mg	400 mg	No	No

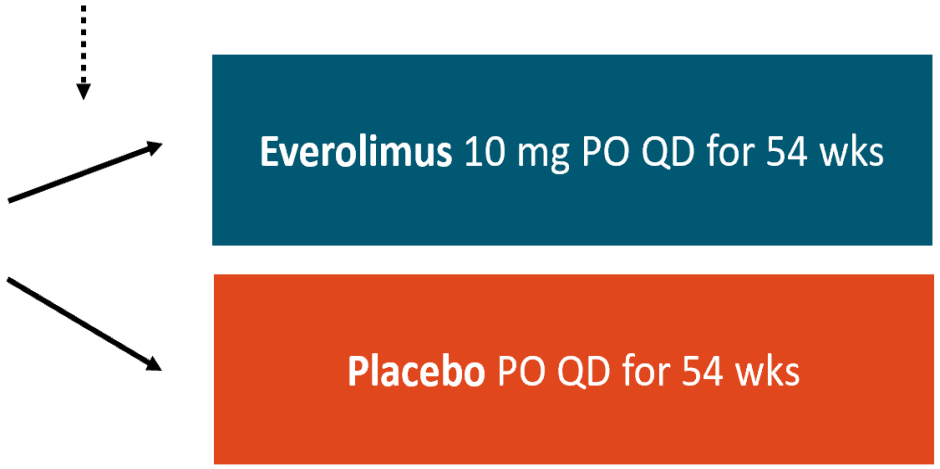
*Studies included OS as secondary endpoint and may not be powered to show an improvement.

EVEREST: Everolimus vs Placebo for Patients With RCC After Nephrectomy or Partial Nephrectomy

- Multicenter, randomized phase III trial of everolimus vs placebo for patients with pathologically intermediate high–risk or very high–risk RCC after nephrectomy

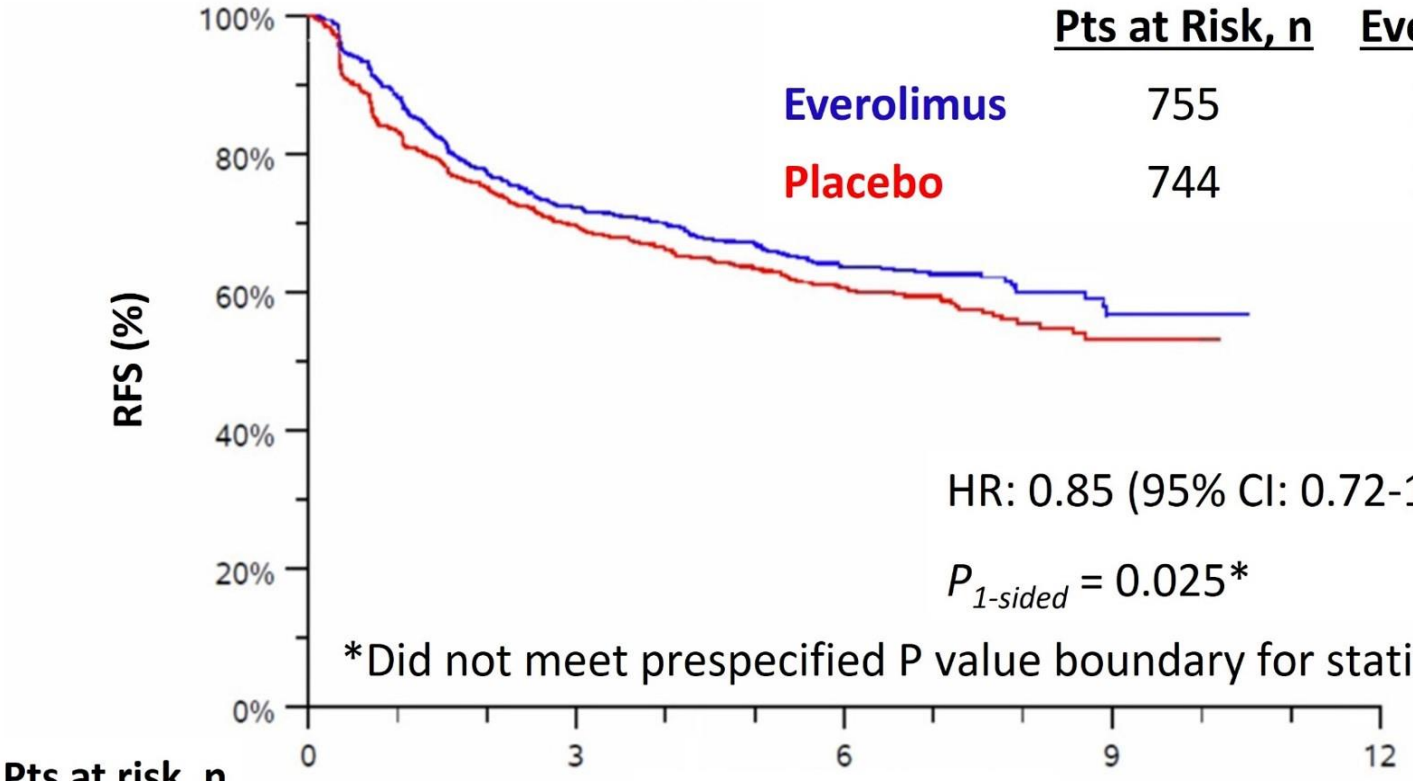
Stratified risk (intermediate high risk vs very high risk), histologic subtype (clear cell vs non–clear cell), and performance status (0 vs 1)

Patients with histologically confirmed RCC, clear cell or non–clear cell allowed, **within 12 weeks of full surgical resection** including any clinically positive nodes; **NED** (negative margins, no evidence of residual or metastatic RCC on CT scan after nephrectomy and within 28 days before enrolment); **TNM stage pT1b G3-4, pT2 and G, or any N+**; pathologically either intermediate high–risk or very high–risk disease
(N = 1545)



- **Primary endpoint**: recurrence-free survival
- **Secondary endpoints**: OS, safety

EVEREST: Recurrence-Free Survival with Everolimus vs Placebo After Nephrectomy or Partial Nephrectomy



	Pts at Risk, n	Events, n	5-Yr Estimate
Everolimus	755	262	67%
Placebo	744	294	63%

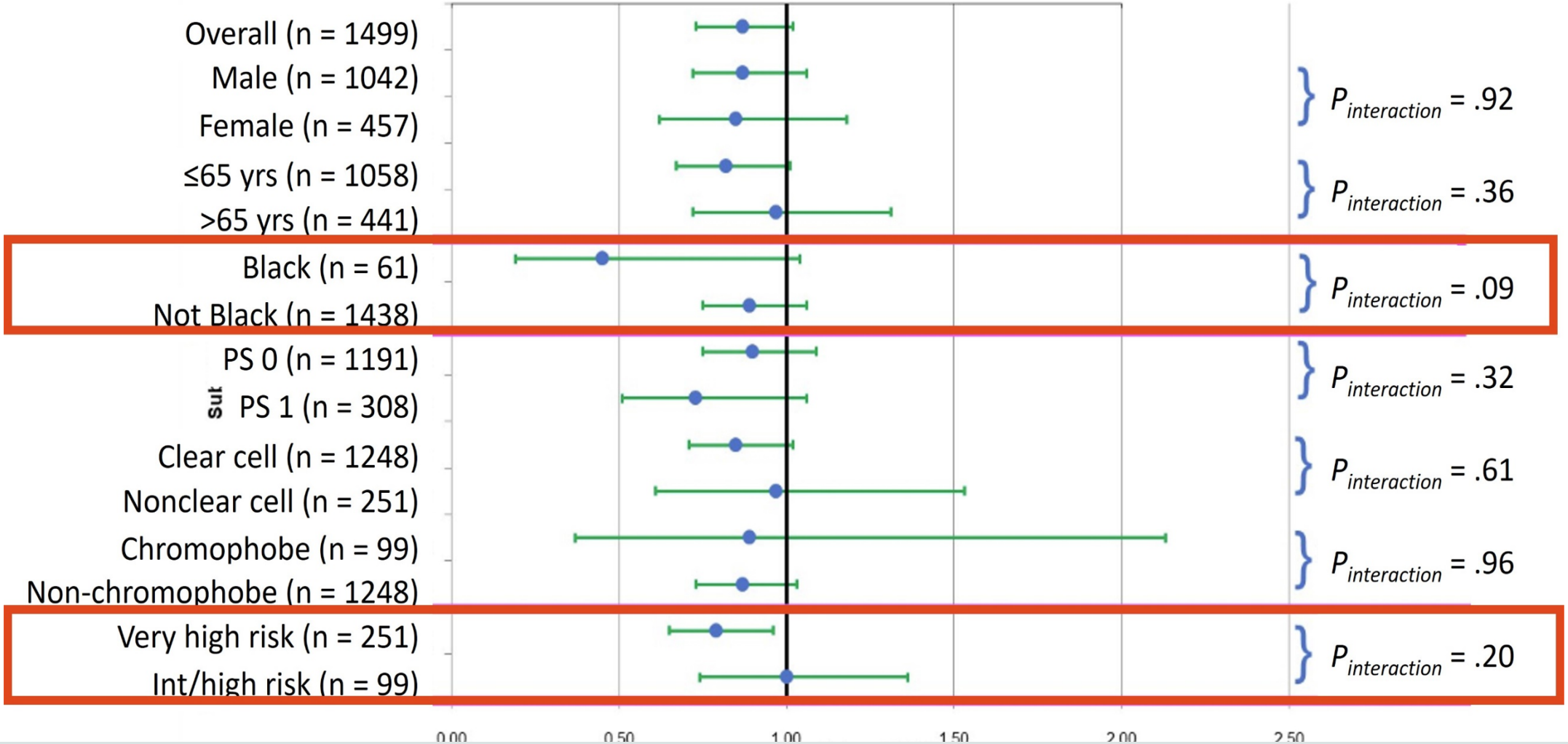
HR: 0.85 (95% CI: 0.72-1.00)

$P_{1\text{-sided}} = 0.025$*

*Did not meet prespecified P value boundary for statistical significance

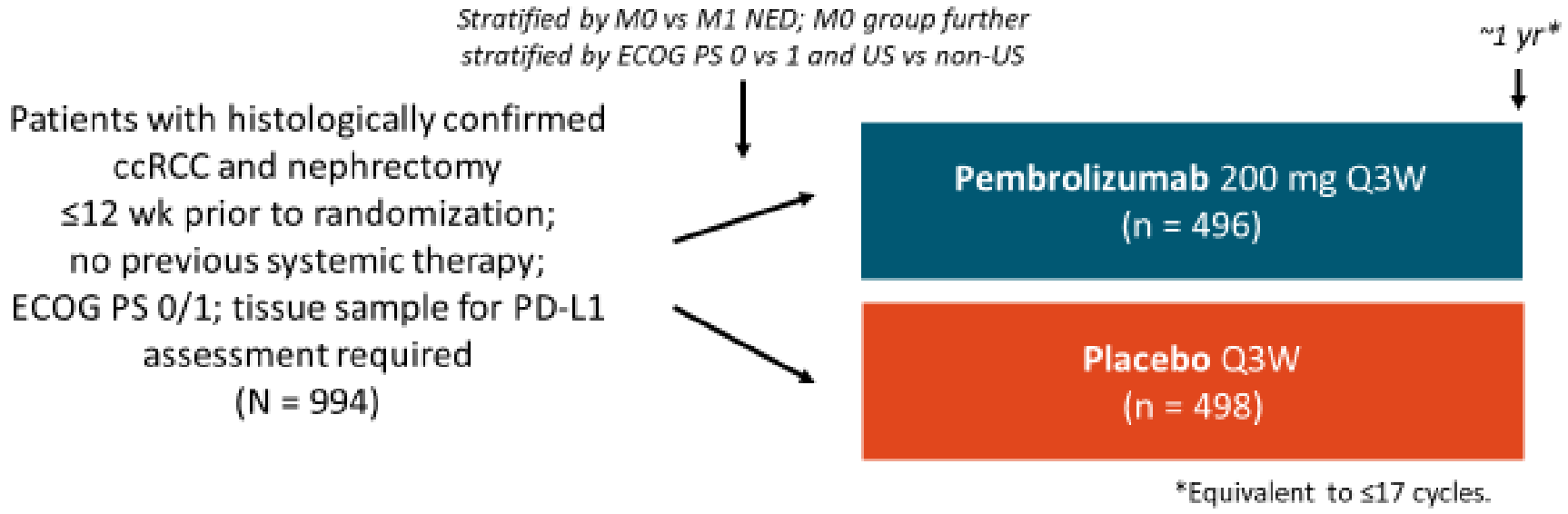
Pts at risk, n					
Everolimus	755	543			
Placebo	744	533	445	293	96

EVEREST: Everolimus vs Placebo for Patients With RCC After Nephrectomy or Partial Nephrectomy



KEYNOTE-564 30-Mo Follow-up: Adjuvant Pembrolizumab vs Placebo for ccRCC

- Multicenter, randomized, double-blind phase III trial of adjuvant therapy



- Primary endpoint: DFS per investigator
  - Met in first interim analysis
- Secondary endpoints: OS, safety
  - *P* value boundary for OS significance: .0000095

KEYNOTE-564: Eligibility Criteria

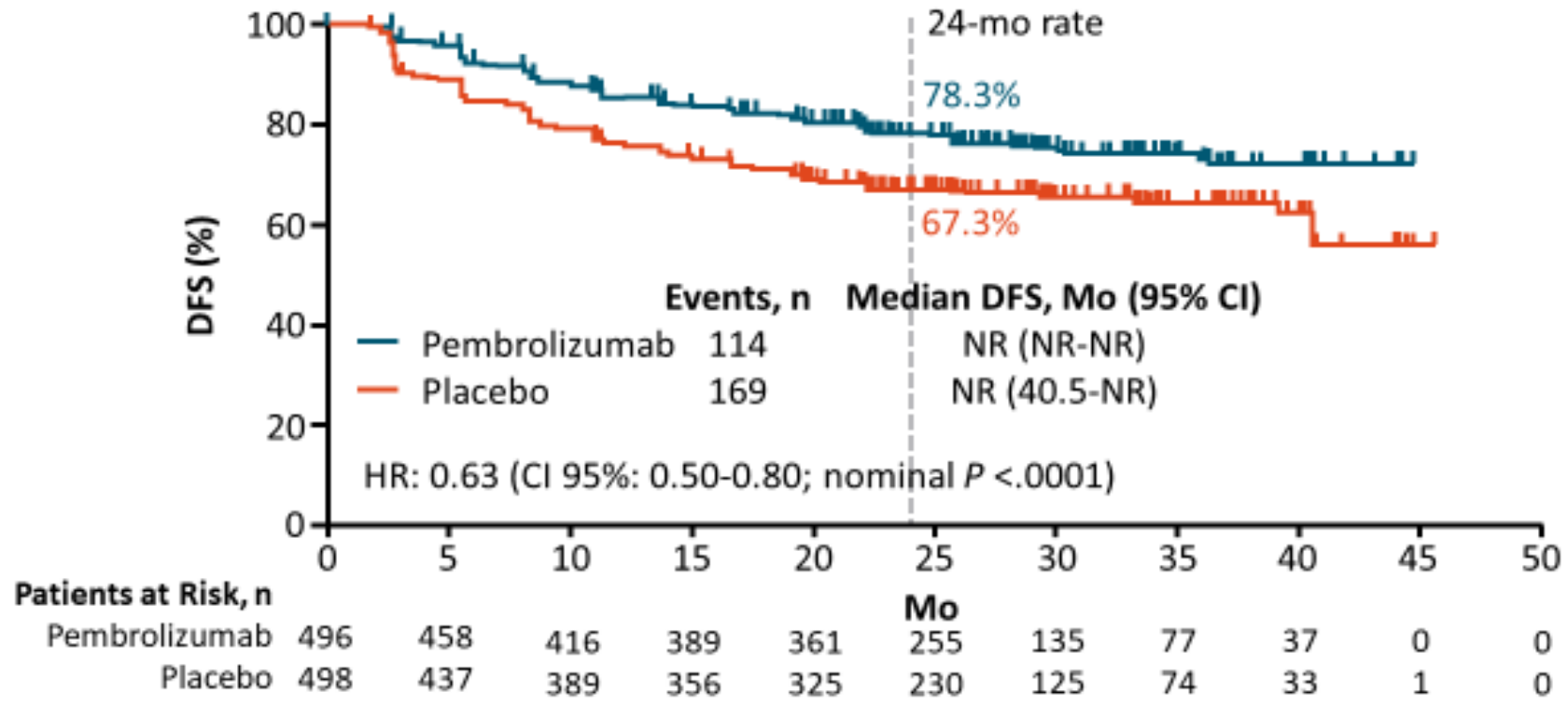
Histologically confirmed clear-cell RCC with:

1. **Intermediate-risk to high-risk disease**
   - pT2, grade 4 or sarcomatoid differentiation with N0, M0
   - pT3, any grade with N0, M0
2. **High-risk disease**
   - pT4, any grade with N0, M0
   - Any pT, any grade with N+, M0
3. **M1 no evidence of disease** with M1 disease in addition to primary tumor at diagnosis, and complete resection at time of nephrectomy or within 1 yr after nephrectomy

Choueiri. ASCO GU 2022. Abstr 290. NCT03142334.

Slide credit: clinicaloptions.com

KEYNOTE-564 30-Mo Follow-up: DFS in ITT Population (Primary Endpoint)



Choueiri. ASCO GU 2022. Abstr 290.

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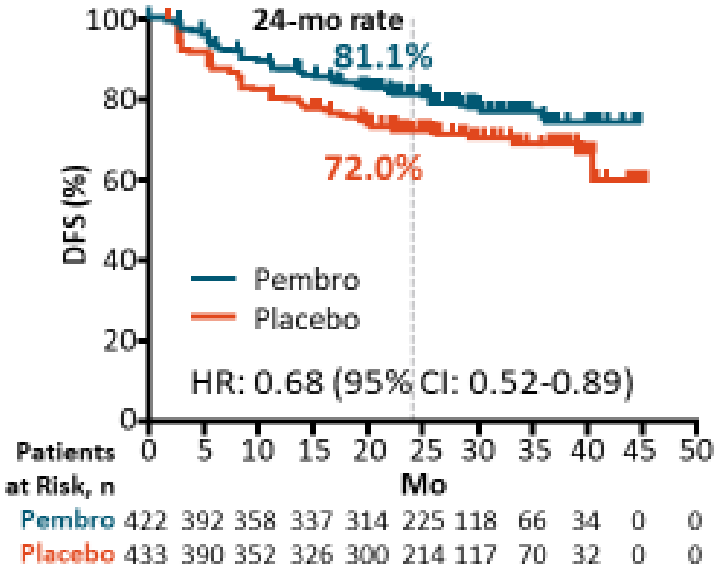
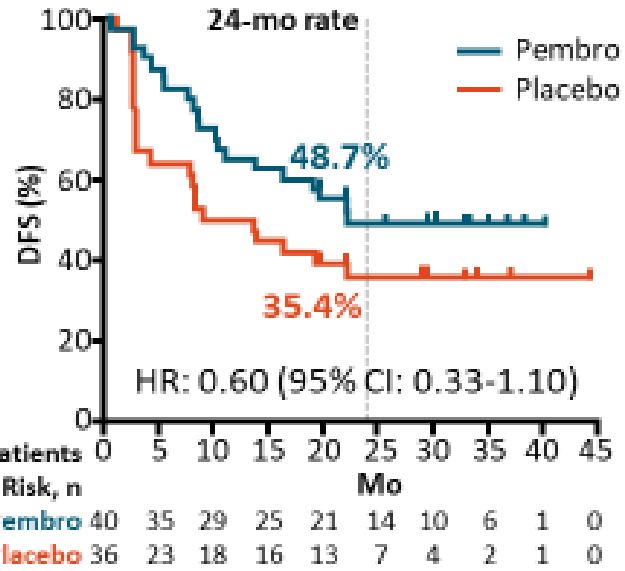
KEYNOTE-564 30-Mo Follow-up: DFS by Recurrence Risk

Intermediate-High Risk



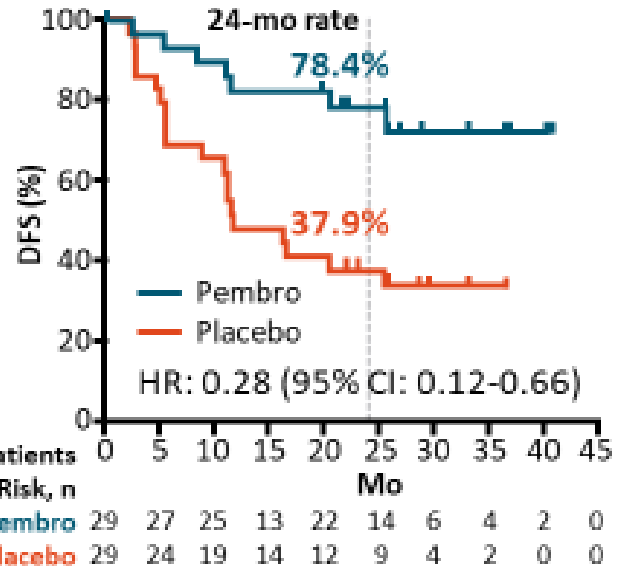
	Events	Median DFS, Mo (95% CI)
Pembro (n = 422)	87	NR (NR-NR)
Placebo (n = 433)	127	NR (40.5-NR)

High Risk



	Events	Median DFS, Mo (95% CI)
Pembro (n = 40)	20	22.4 (11.1-NR)
Placebo (n = 36)	23	11.4 (2.9-NR)

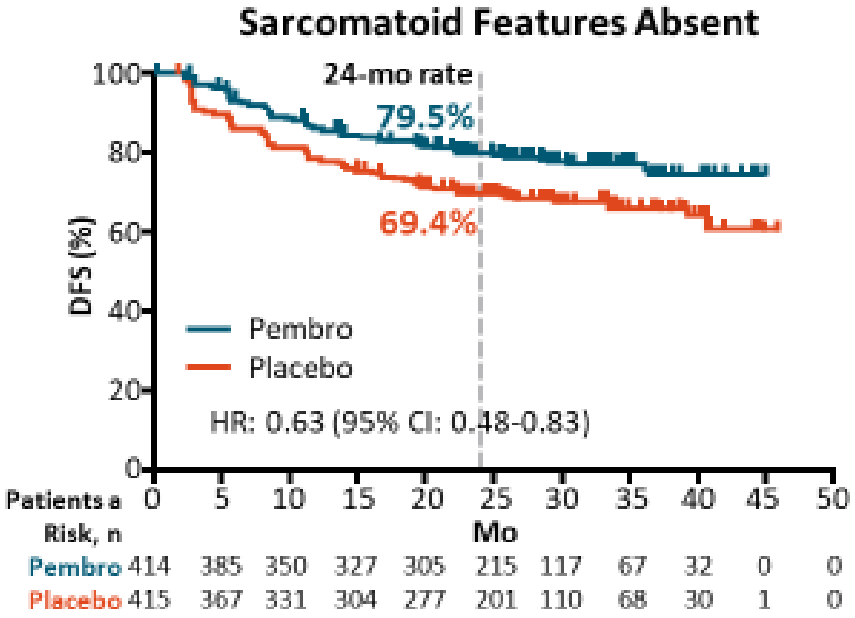
M1 NED



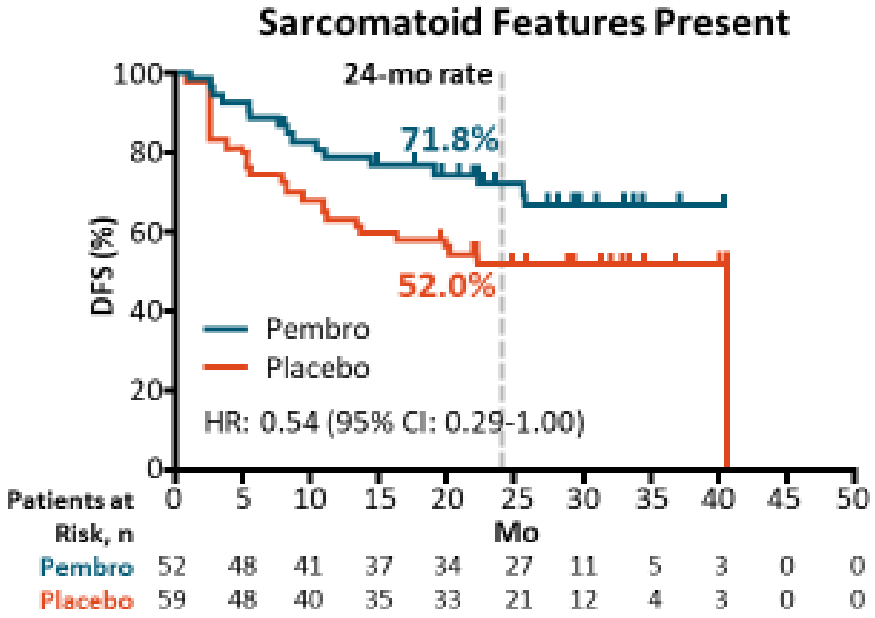
	Events	Median DFS, Mo (95% CI)
Pembro (n = 29)	7	NR (25.7-NR)
Placebo (n = 29)	19	11.6 (5.6-NR)

Choueiri. ASCO GU 2022. Abstr 290.

KEYNOTE-564 30-Mo Follow-up: DFS by Sarcomatoid Status



	Events	Median DFS, Mo (95% CI)
Pembro (n = 414)	88	NR (NR-NR)
Placebo (n = 415)	133	NR (NR-NR)



	Events	Median DFS, Mo (95% CI)
Pembro (n = 52)	16	NR (NR-NR)
Placebo (n = 59)	29	40.5 (11.3-NR)

Choueiri. ASCO GU 2022. Abstr 290.

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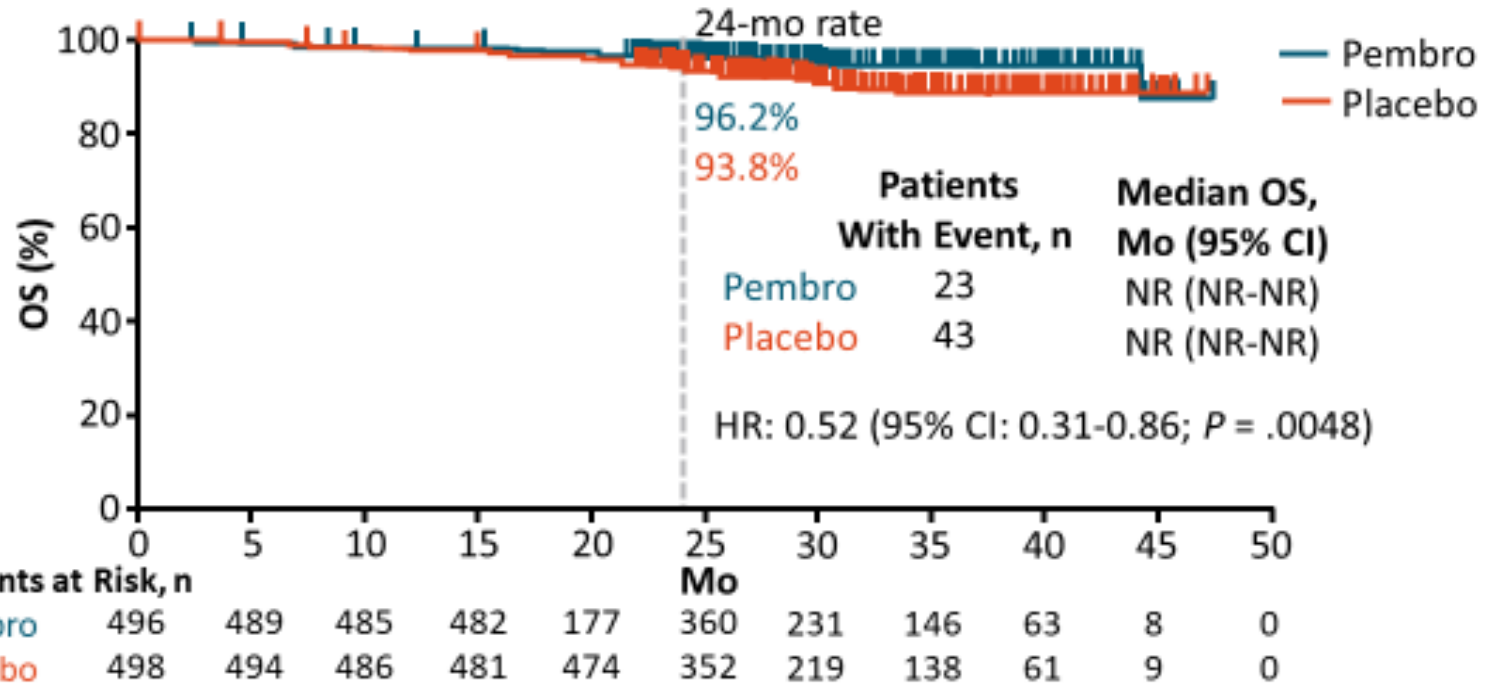
KEYNOTE-564 30-Mo Follow-up: OS in ITT Population



- Comparison did not meet criteria for statistical significance in this analysis
- Final OS analysis will be conducted after ~200 OS events have occurred

Choueiri. ASCO GU 2022. Abstr 290.

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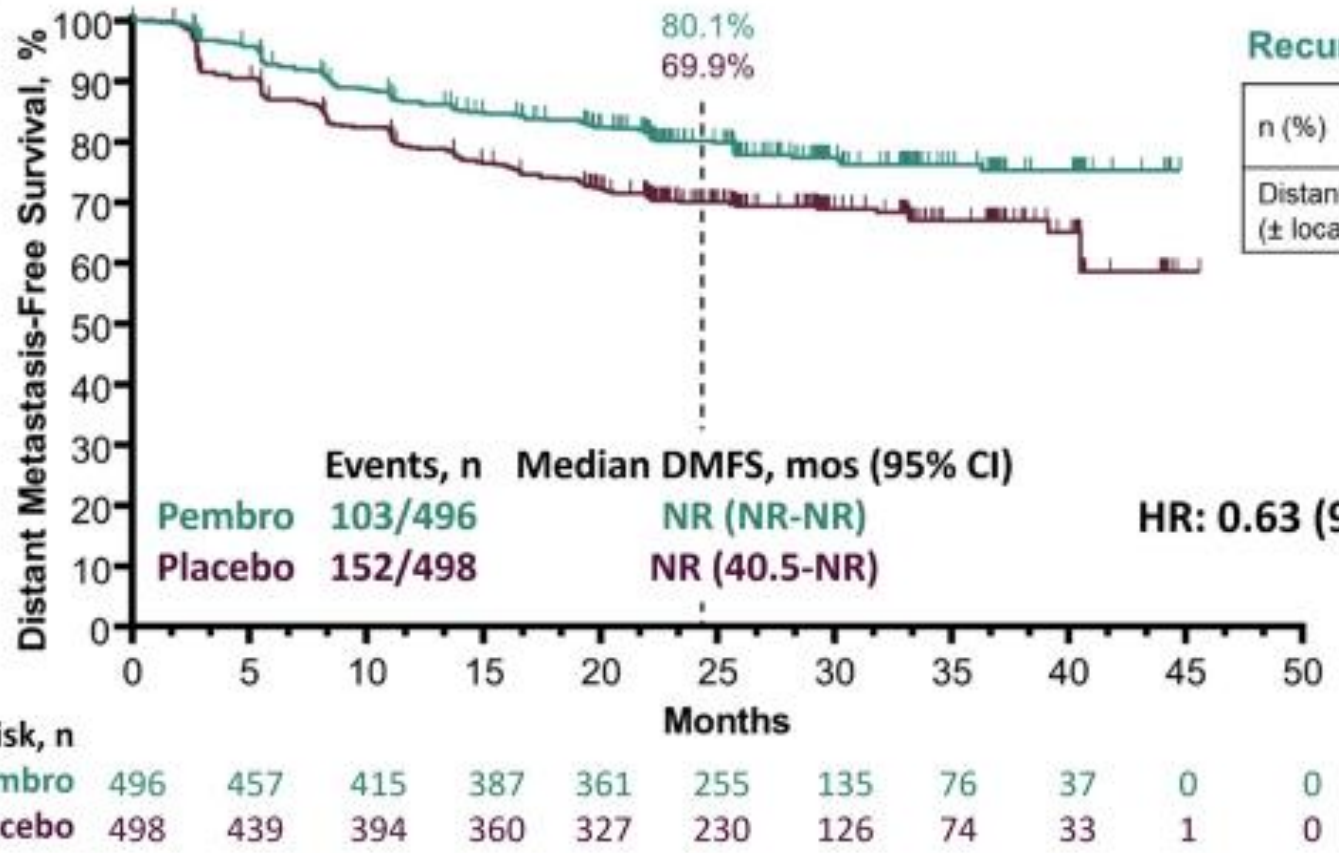
KEYNOTE-564 Expanded Efficacy Analysis: Distant Metastasis-Free Survival in ITT Population



Recurrence events

n (%)	Pembrolizumab n = 496	Placebo n = 498
Distant (± local)	95 (19.2)	140 (28.1)

Choueiri. ASCO 2022. Abstr 4512.

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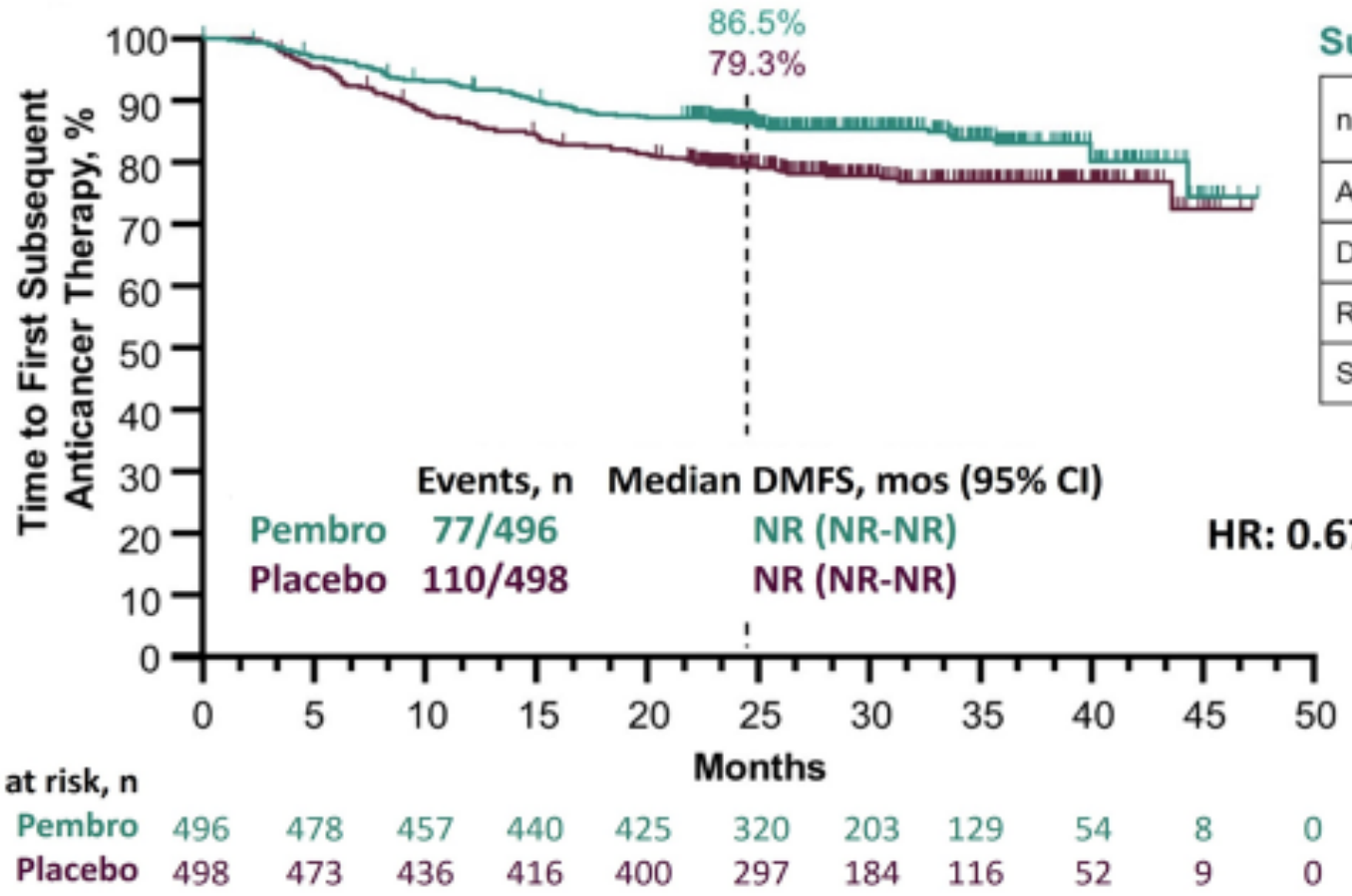
ASCO 2022 Update

KEYNOTE-564 Expanded Efficacy Analysis: Time to First Subsequent Therapy in ITT Population



Subsequent therapy

n (%)	Pembrolizumab n = 496	Placebo n = 498
Any	84 (17.5)	124 (24.9)
Drug therapy	67 (13.5)	99 (19.9)
Radiation therapy	17 (3.4)	19 (3.8)
Surgery	23 (4.6)	36 (7.2)

HR: 0.67 (95% CI: 0.50-0.90)

Choueiri. ASCO 2022. Abstr 4512.

Slide credit: clinicaloptions.com

Trial	Sample Size	Inclusion Criteria	Treatment	Duration	Primary Endpoint	Met Primary Endpoint?
KEYNOTE-564	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell	Pembrolizumab vs placebo	12 months	DFS	**YES**
IMmotion010	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo	12 months	DFS	No
CheckMate-914	1,600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs nivolumab + placebo vs placebo	6 months	DFS	No (Part A) Part B pending
PROSPER	766	T2Nx, TxN1, TxNxM1 (resected to NED); any RCC histology	Nivolumab vs active monitoring	10 doses total (1 preop)	EFS	No
RAMPART	1,750	Leibovich score 3-11; any RCC histology	Durvalumab + tremelimumab vs durvalumab vs active monitoring	12 months	DFS, OS	Pending 7/2024
LITESPARK-022	1,600	pT2G4/sarcomatoid, pT3, pT4, pTxN1, pTxNxM1 (resected to NED) clear cell	Belzutifan + pembrolizumab vs pembrolizumab	12 months	DFS	Pending

*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy
CPI = checkpoint inhibitors; EFS = event-free survival; NED = no evidence of disease; OS = overall survival.

Future Directions and Unanswered Questions

- **Duration** needed for adjuvant therapy for resected or radiated oligometastatic disease is still unknown: Is 1 yr enough or too much?
- **Intensity** of adjuvant therapy for resected or radiated oligometastatic disease is still unknown: Is monotherapy enough?
- **Risks** are more toxicity and overtreating or undertreating patients
- **Types of trials needed:** Validation of ctDNA, methylated DNA immunoprecipitation, or angiogenic immune signature trials are ideal for this space
- Use the best technology to identify who will progress, who will respond

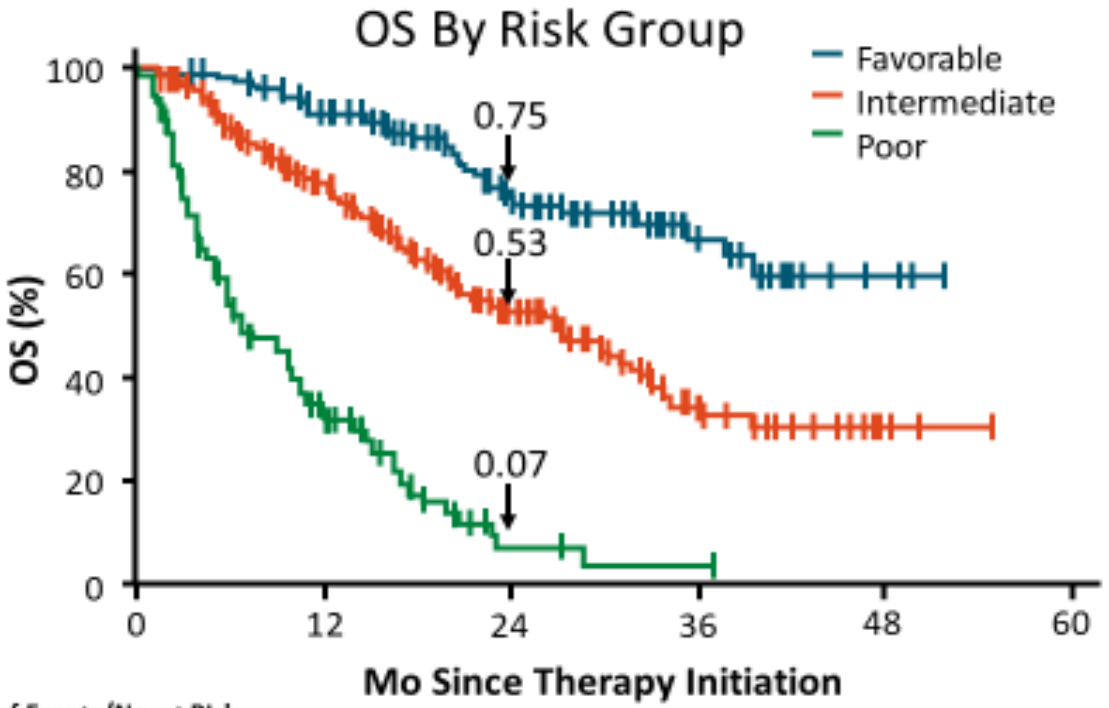
1st Line Rx in advanced RCC

Understanding the Role of Risk in the Treatment of Metastatic RCC

IMDC Criteria for Metastatic RCC

Karnofsky performance score <80%
Time from initial diagnosis to targeted Tx <1 yr
Hemoglobin <LLN
Calcium >10mg/dL
Platelet count >ULN
Neutrophil count >ULN

- Favorable: 0 risk factors
- Intermediate: 1-2 risk factors
- Poor: 3+ risk factors

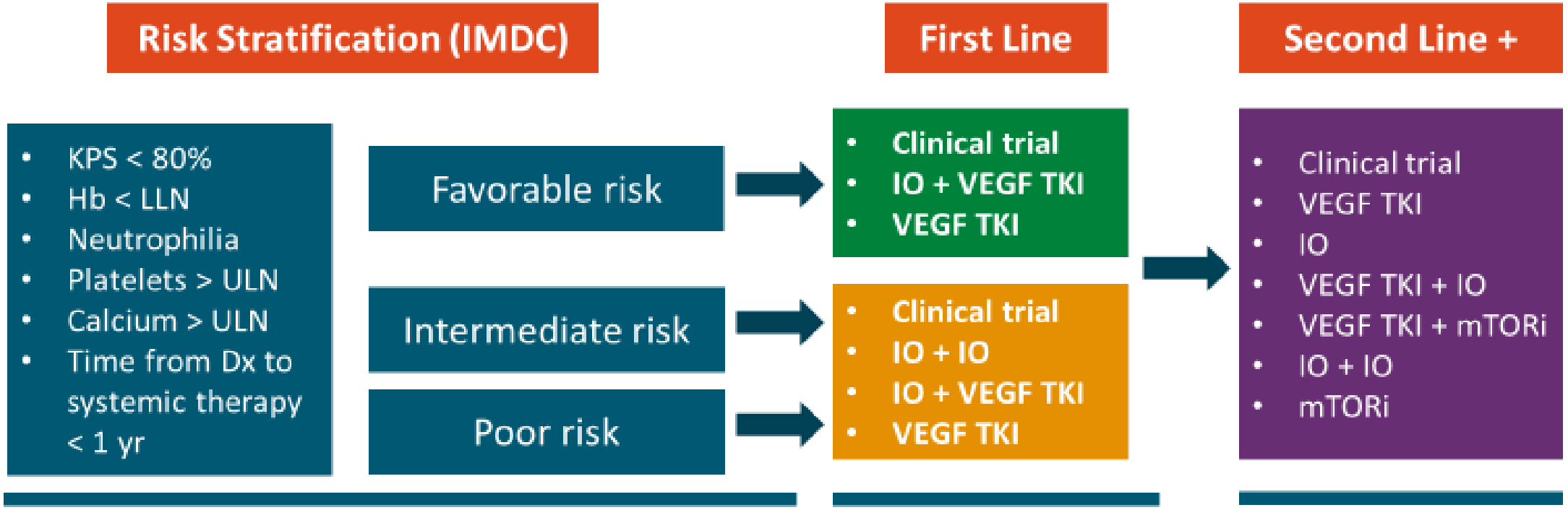


No. of Events/No. at Risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

International Kidney Cancer Coalition. Heng. JCO. 2009;27:5794.

Slide credit: clinicaloptions.com

Advanced Renal Cell Carcinoma: Current Therapeutic Landscape



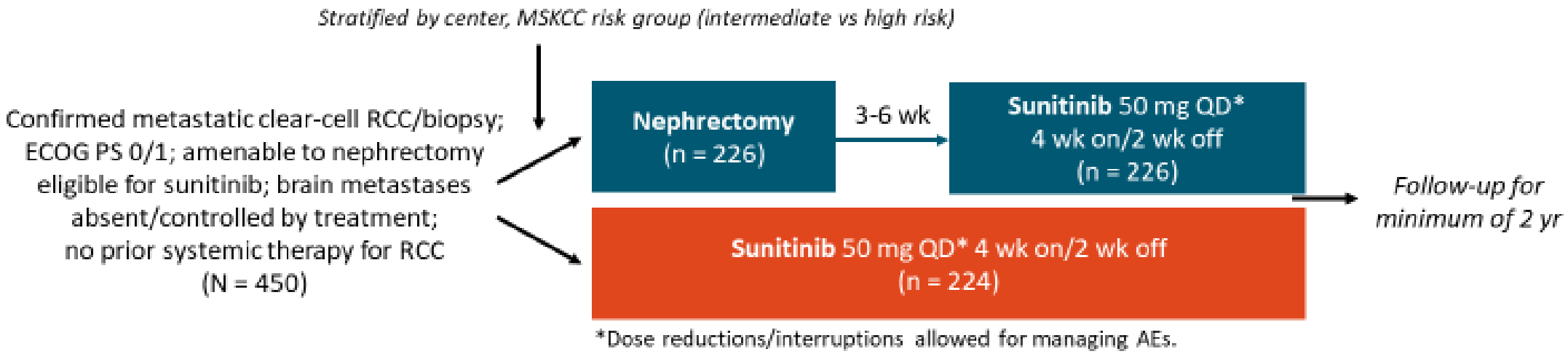
Courtesy of Jaime R. Merchan, MD.

Adapted from: Motzer RJ, Jonasch E, Agarwal, N, et al. NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer, Version 4.2022. Accessed May 31, 2022. To view the most recent version, visit NCCN.org.

Slide credit: clinicaloptions.com

CARMENA: Prospective, Multicenter, Open-Label, Randomized Phase III Noninferiority Study

- Multicenter, randomized, open-label noninferiority phase III trial

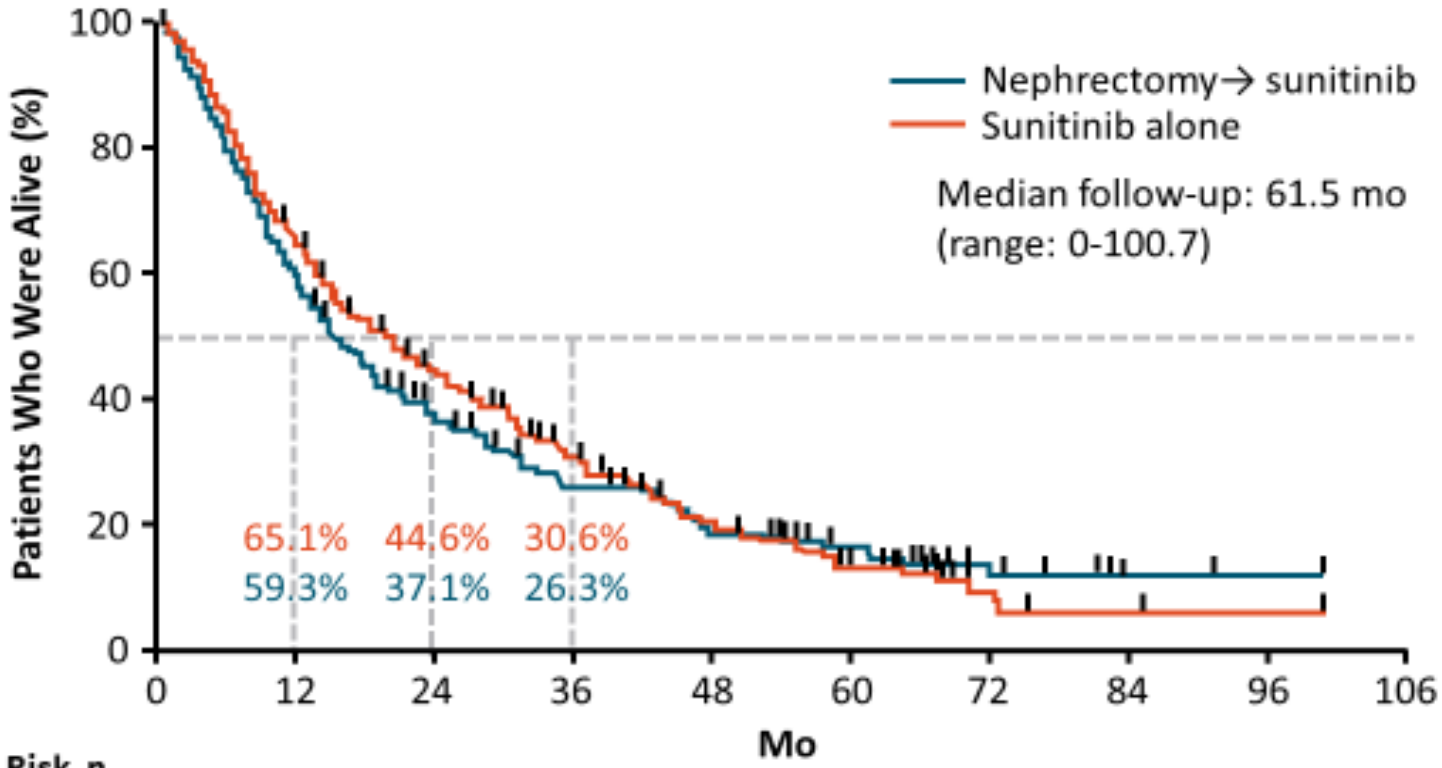


- Primary endpoint: OS
- Secondary endpoints: PFS, ORR (RECIST v1.1), clinical benefit, safety

Méjean. ASCO 2018. Abstr LBA3. Méjean. NEJM. 2018;379:417.

Slide credit: clinicaloptions.com

CARMENA: Overall Survival (ITT)



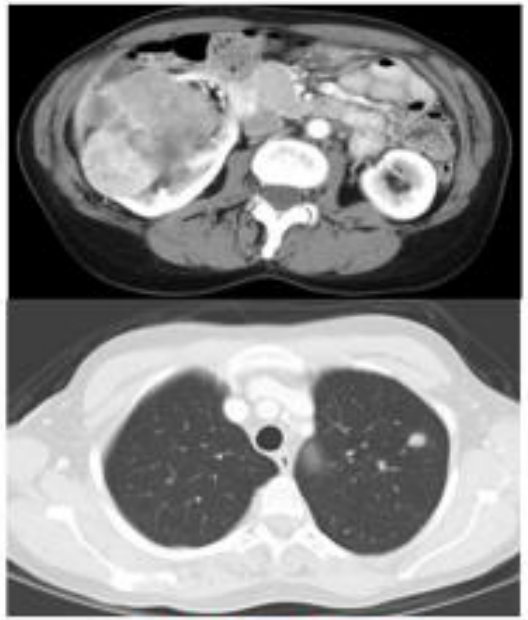
Patients at Risk, n										
Nephrectomy→ sunitinib	226	132	74	47	30	18	8	2	1	0
Sunitinib alone	224	144	90	51	29	16	5	2	1	0

Méjean. ASCO 2019. Abstr 4508.

Slide credit: clinicaloptions.com

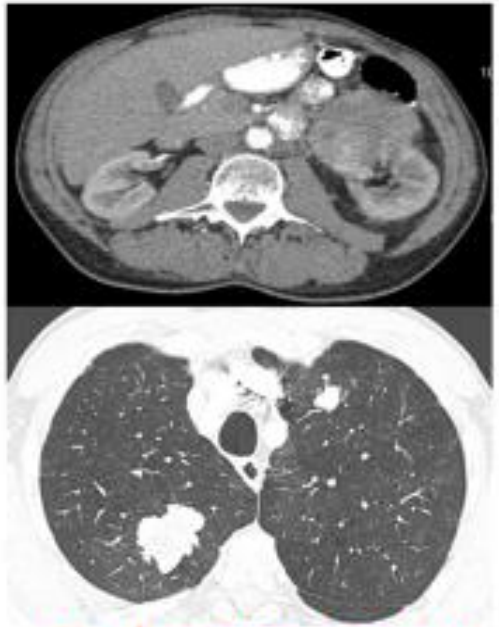
Considerations for Nephrectomy

PS 0
Minimal extrarenal disease



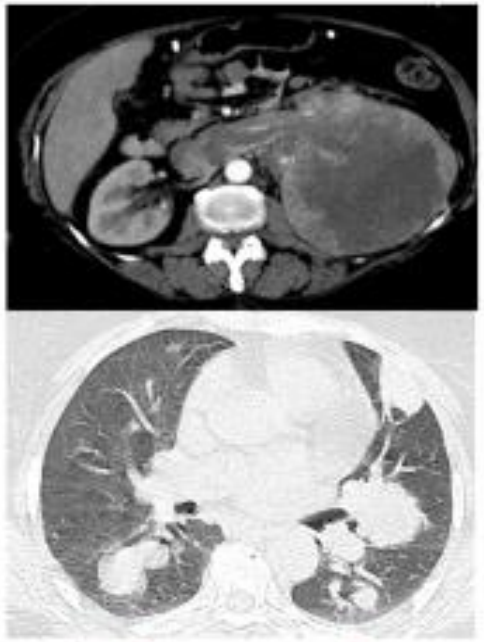
Nephrectomy makes sense

PS 0/1
Intermediate risk
Moderate extrarenal disease



Nephrectomy may or may not be indicated

Poor PS, poor risk
Large primary
Extensive extrarenal disease



Nephrectomy does not make sense

Slide credit: clinicaloptions.com

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Kidney Cancer

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

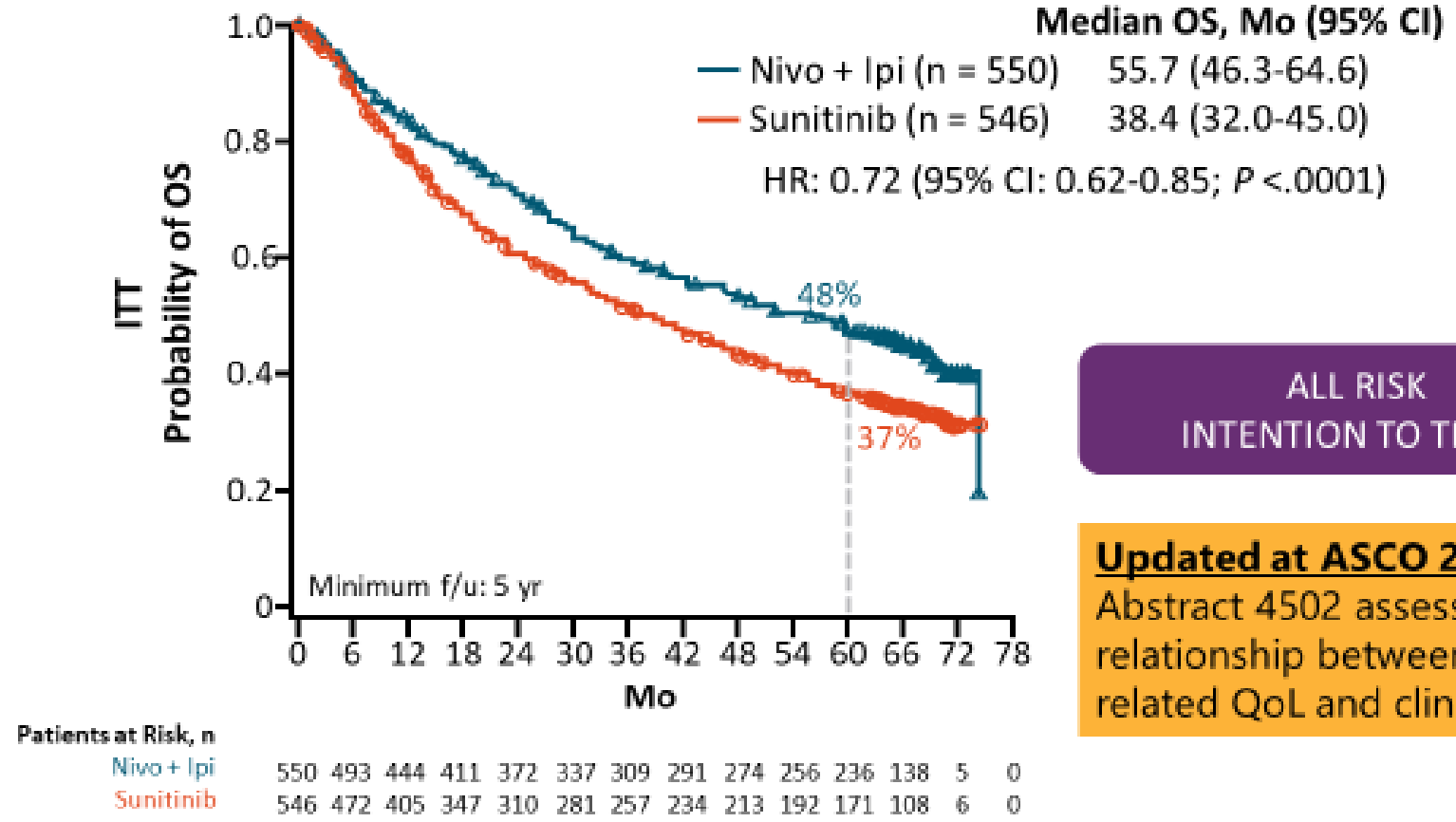
FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cabozantinib (category 1) • Lenvatinib + everolimus (category 1) • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] • Axitinib + avelumab[b] (category 3)	• Everolimus • Bevacizumab[f] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Sorafenib (category 3) • Temsirolimus[e] (category 2B)

CheckMate 214: Nivolumab + Ipilimumab vs Sunitinib for Untreated Advanced RCC



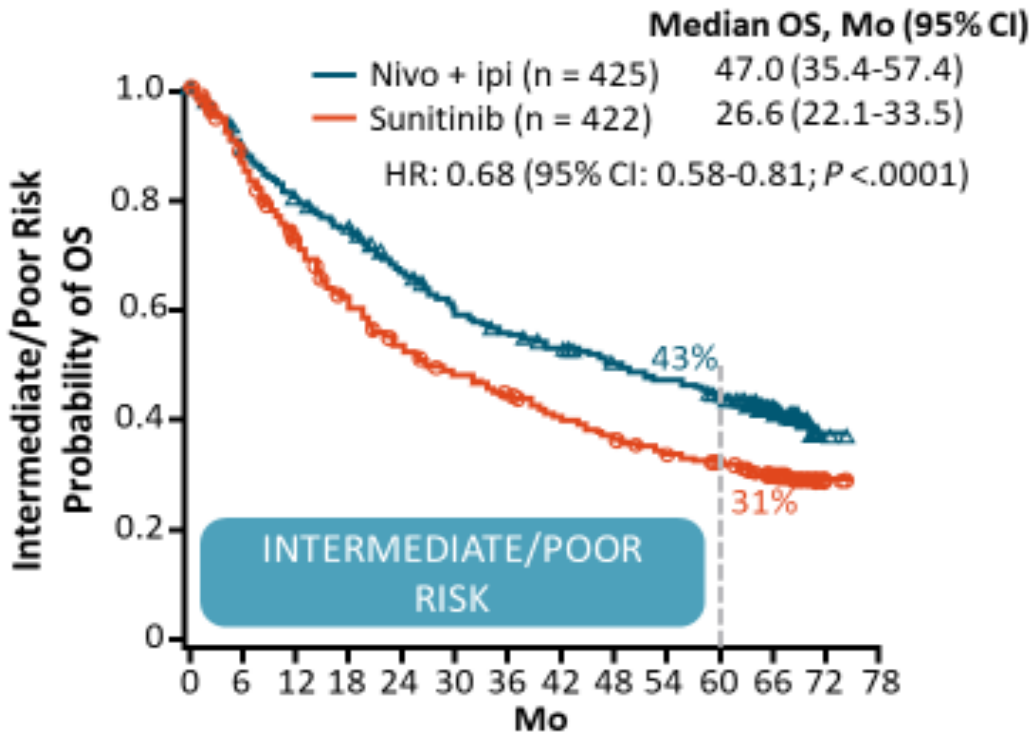
ALL RISK
INTENTION TO TREAT

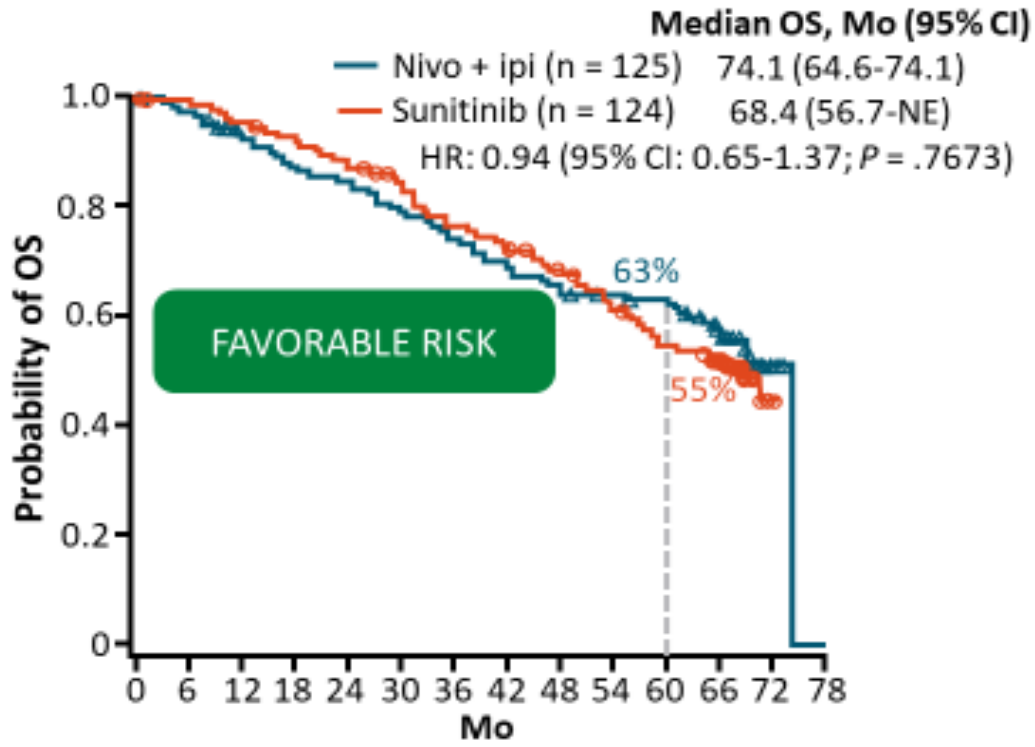
Updated at ASCO 2022:
Abstract 4502 assessing relationship between health-related QoL and clinical outcomes

Motzer. ESMO 2021. Abstr 661P.

Slide credit: clinicaloptions.com

CheckMate 214: Nivolumab + Ipilimumab vs Sunitinib for Untreated Advanced RCC





Patients at Risk, n

Nivo + ipi	425	372	332	306	270	241	220	207	196	181	163	79	2	0
Sunitinib	422	353	291	237	206	184	169	151	137	125	112	58	3	0

Patients at Risk, n

Nivo + ipi	125	121	112	105	102	96	89	84	78	75	73	59	3	0
Sunitinib	124	119	114	110	104	97	88	83	76	67	59	50	3	0

Minimum f/u: 5 yr

Motzer. ESMO 2021. Abstr 661P.

Slide credit: clinicaloptions.com

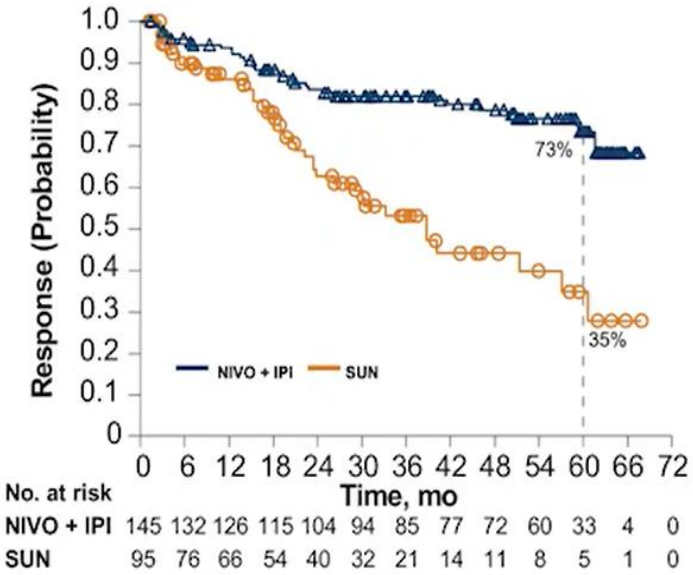
Responses at 5-Year Follow-Up[a,1]

	ITT		Intermediate/ Poor Risk		Favorable Risk	
	NIVO + IPI (n = 550)	SUN (n = 546)	NIVO + IPI (n = 425)	SUN (n = 422)	NIVO + IPI (n = 125)	SUN (n = 124)
Confirmed ORR, %	39	32	42	27	30	52
CR, %	12	3	11	2	13	6
mDOR, mo	NR	24.8	NR	19.7	61.5	33.2
Ongoing response, %	63	50	64	50	59	52

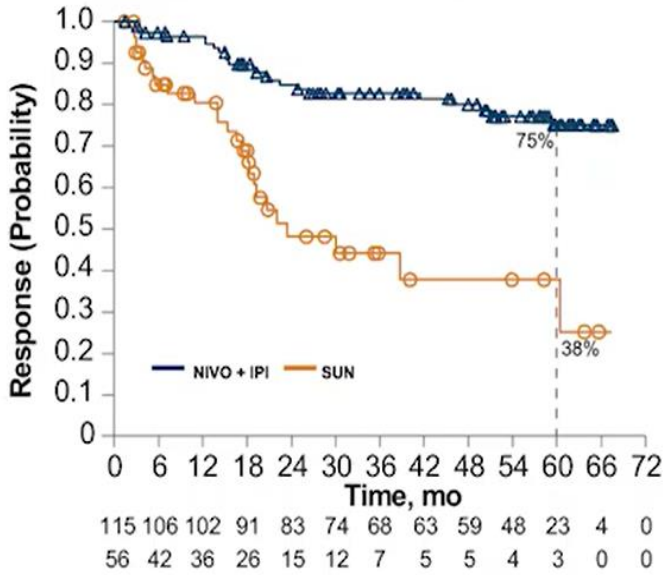
- A higher proportion of patients achieved CR with NIVO + IPI vs SUN regardless of risk
- More patients achieved CR and their disease did not subsequently progress with NIVO + IPI
- Median DOR was notably longer with NIVO + IPI in all three populations

Response Outcomes in Patients With Long-Term Survival of ≥ 5 years

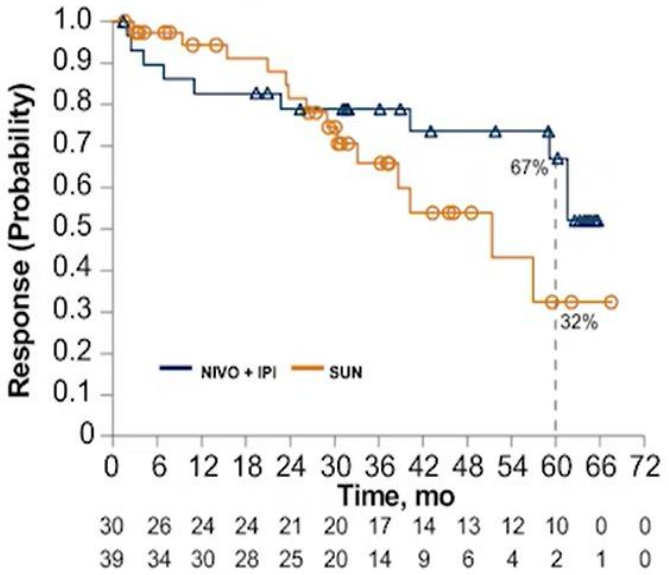
All Patients With LTS



I/P Patients With LTS

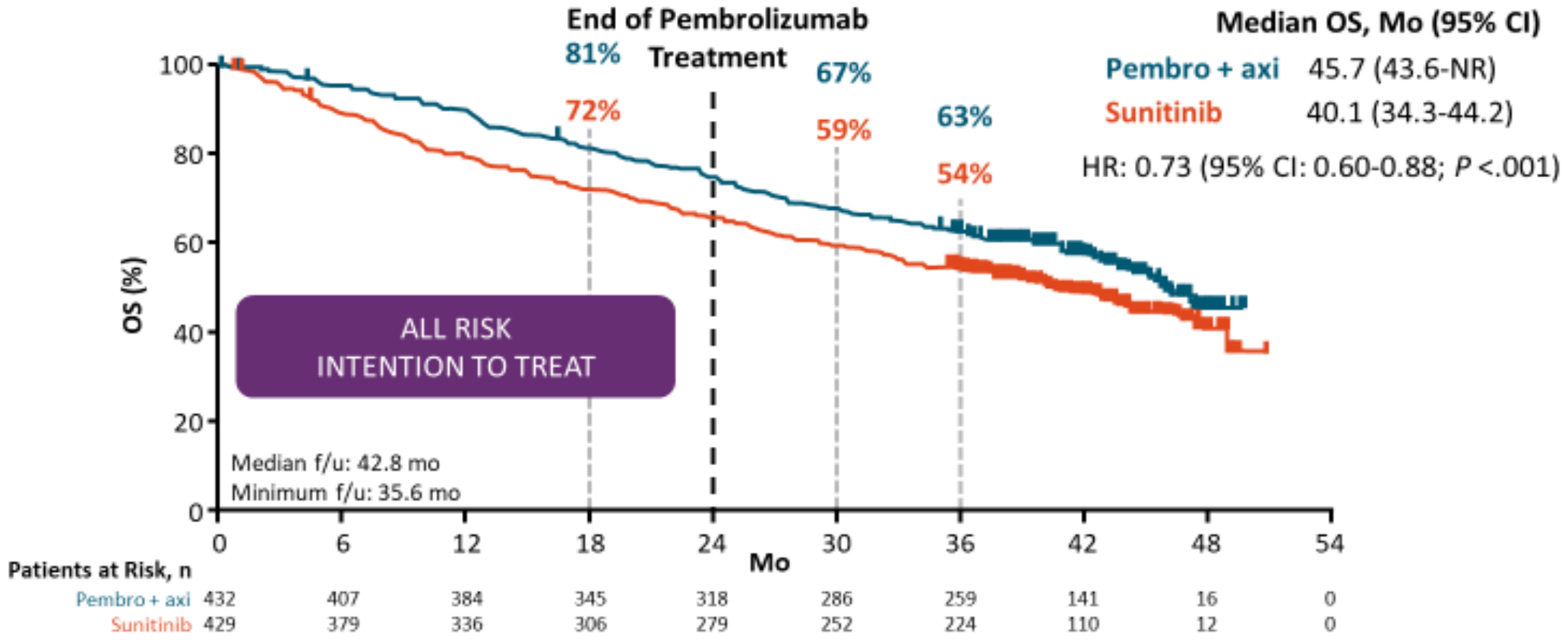


FAV Patients With LTS



	All Patients With LTS		I/P Patients With LTS		FAV Patients With LTS	
	NIVO + IPI (n = 236)	SUN (n = 171)	NIVO + IPI (n = 163)	SUN (n = 112)	NIVO + IPI (n = 73)	SUN (n = 59)
Confirmed ORR, % (95% CI)	61 (55-68)	56 (48-63)	71 (63-77)	50 (40-60)	41 (30-53)	66 (53-78)
CR	56 (24)	15 (9)	40 (25)	7 (6)	16 (22)	8 (14)
	NIVO + IPI (n = 145)	SUN (n = 95)	NIVO + IPI (n = 115)	SUN (n = 56)	NIVO + IPI (n = 30)	SUN (n = 39)
Ongoing response, n (%)	112 (77)	56 (59)	92 (80)	31 (55)	20 (67)	25 (64)
Median DOR (95% CI), mo	NR (NE)	38.7 (26.3-60.4)	NR (NE)	23.5 (18.2-60.4)	NR (59.0-NE)	51.4 (33.2-NE)

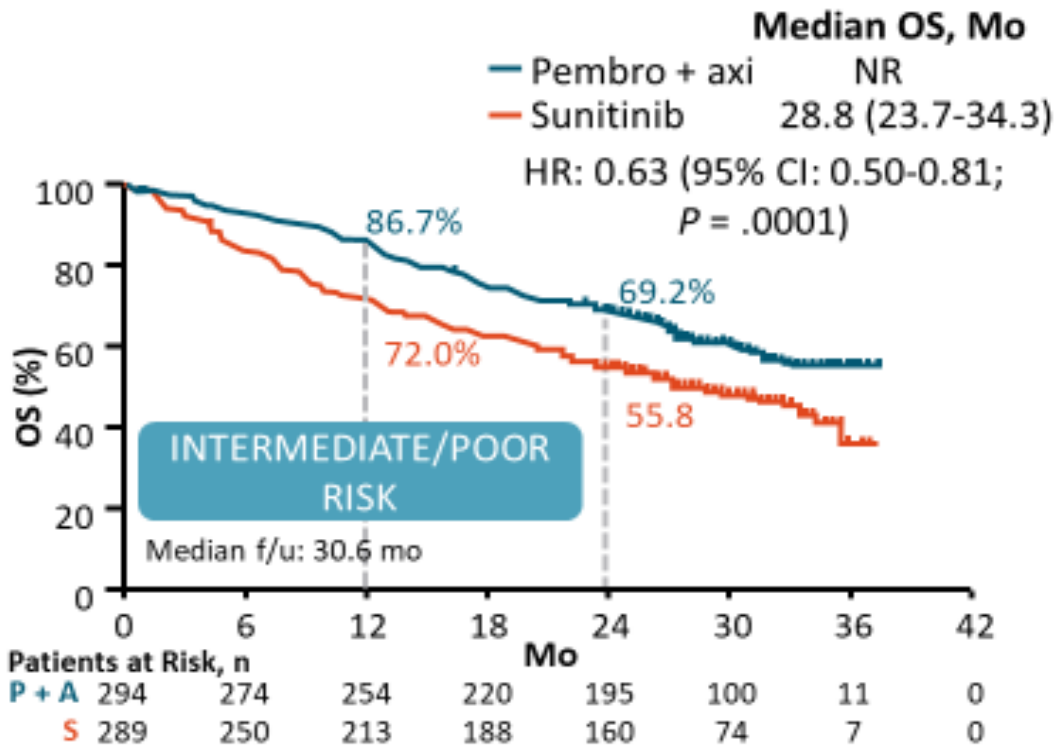
KEYNOTE-426: First-line Pembrolizumab + Axitinib vs Sunitinib in Advanced or Metastatic RCC

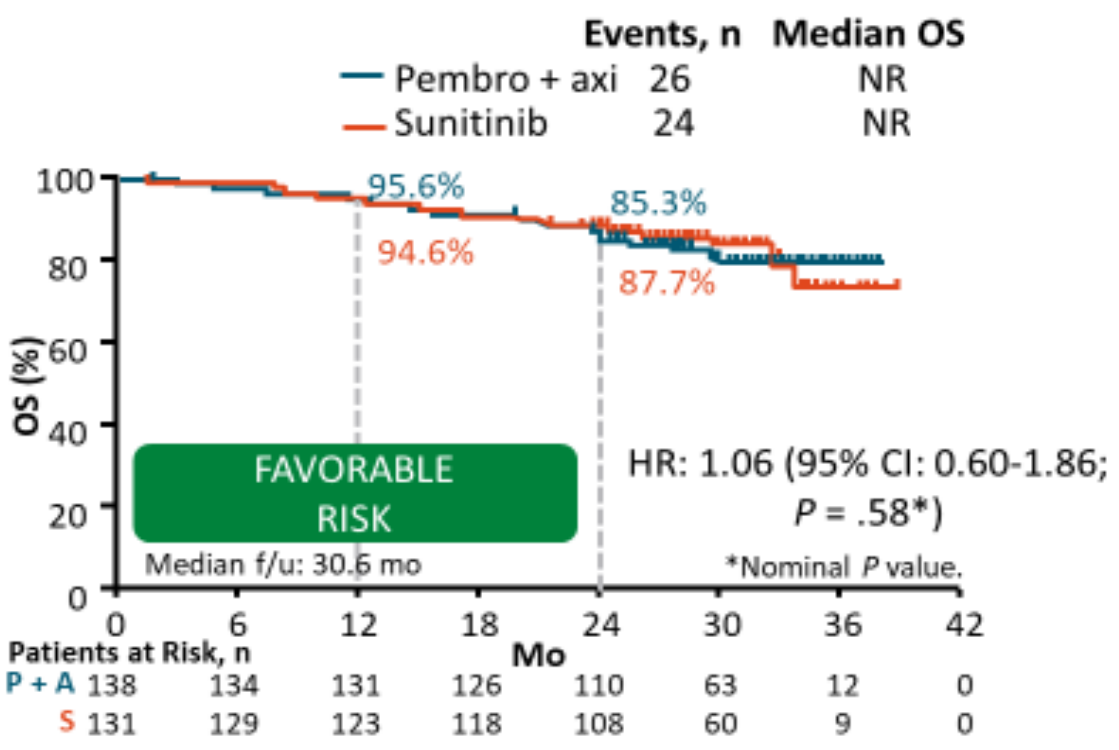


Rini. ASCO 2021. Abstr 4500.

Slide credit: clinicaloptions.com

KEYNOTE-426: First-line Pembrolizumab + Axitinib vs Sunitinib in Advanced or Metastatic RCC

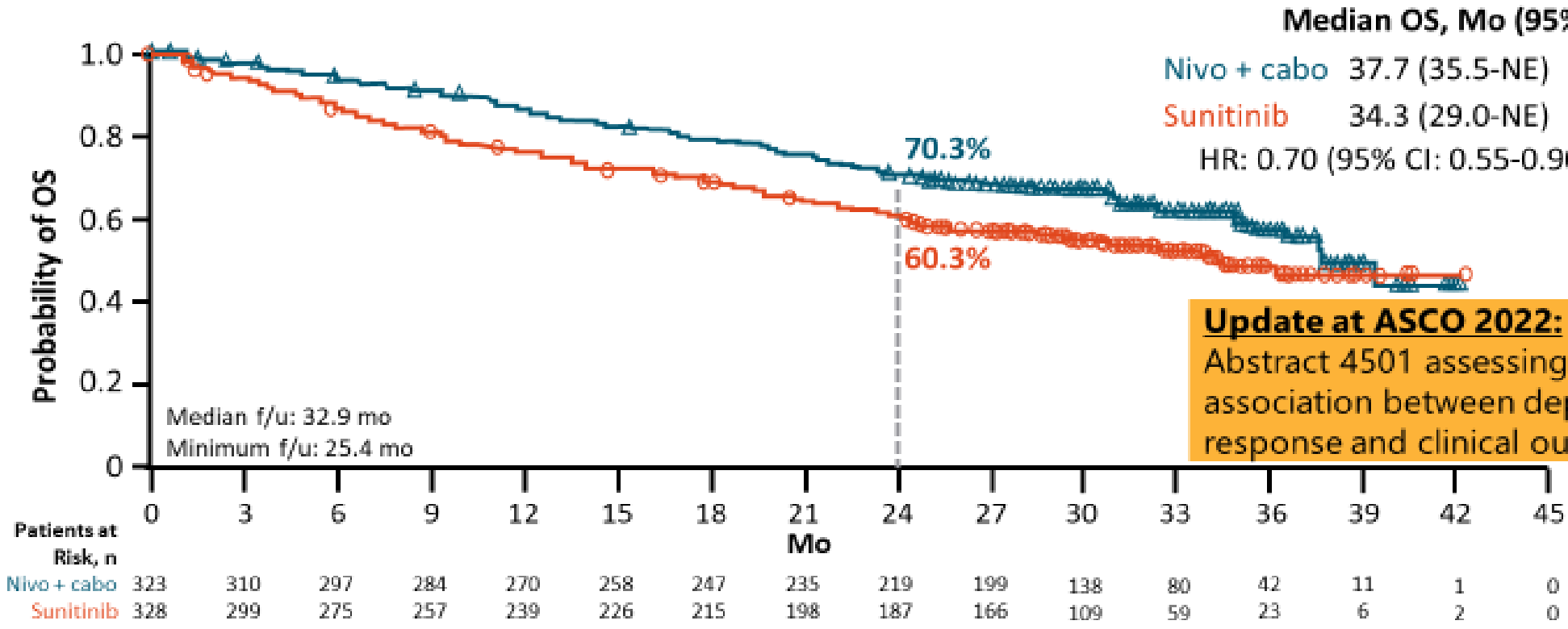




Powles. Lancet Oncol. 2020;21:1563.

Slide credit: clinicaloptions.com

CheckMate 9ER: First-line Nivolumab + Cabozantinib vs Sunitinib in Advanced or Metastatic RCC

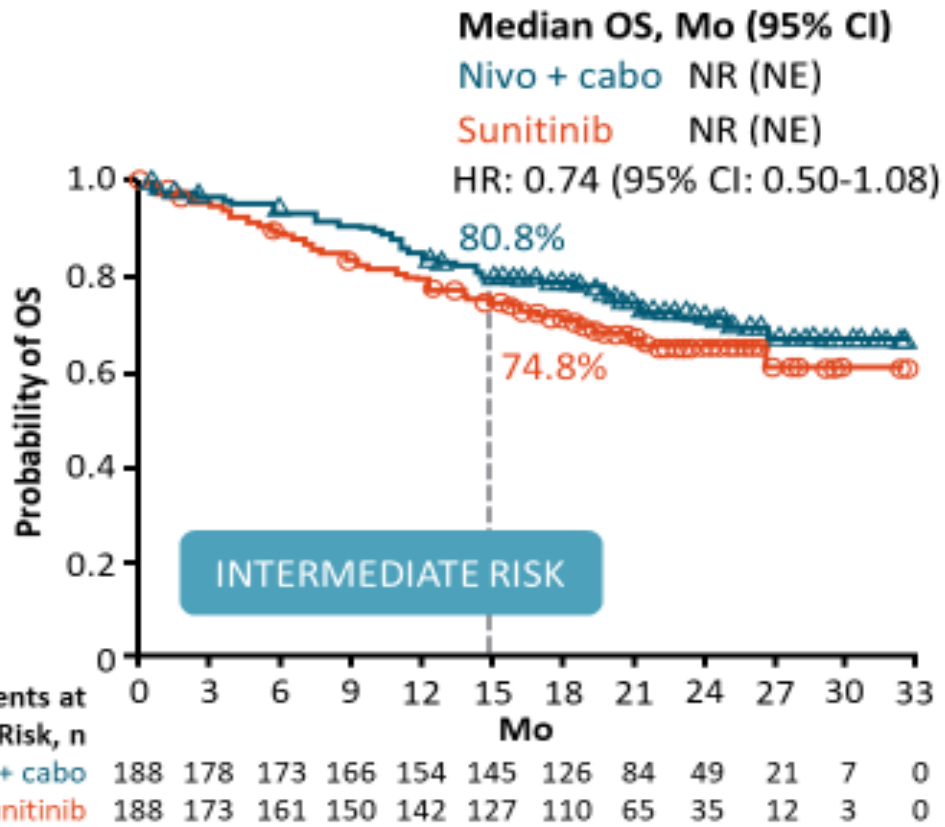


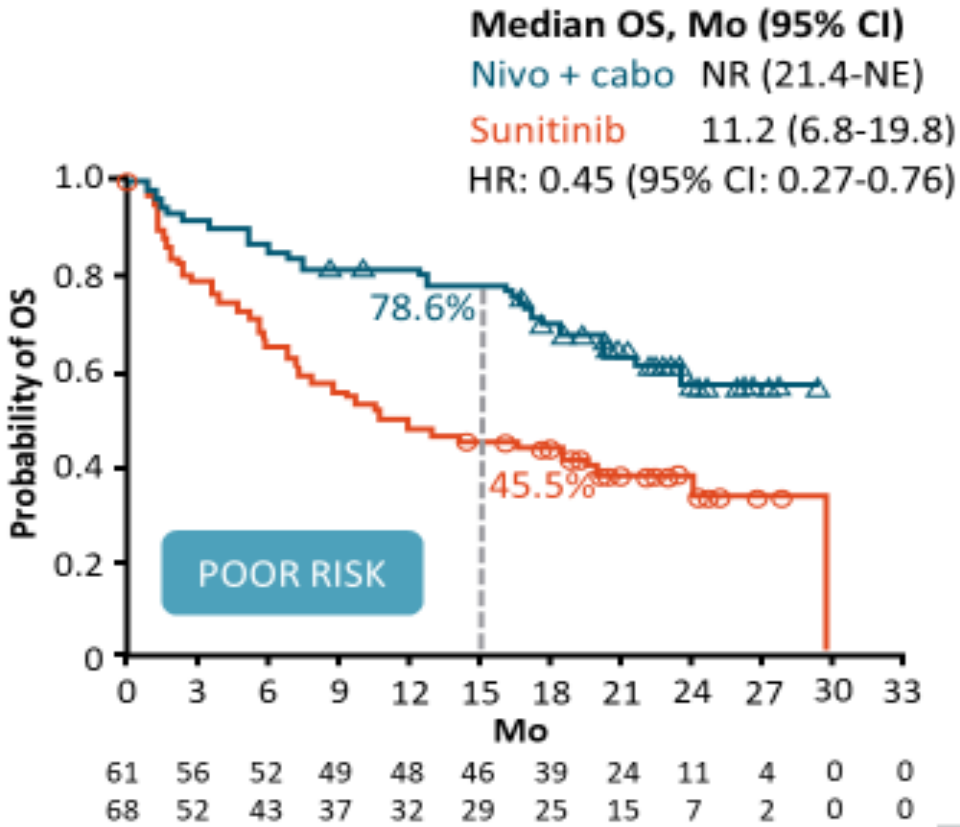
Update at ASCO 2022:
Abstract 4501 assessing association between depth of response and clinical outcomes

Powles. ASCO GU 2022. Abstr 350.

Slide credit: clinicaloptions.com

CheckMate 9ER: First-line Nivolumab + Cabozantinib vs Sunitinib in Advanced or Metastatic RCC



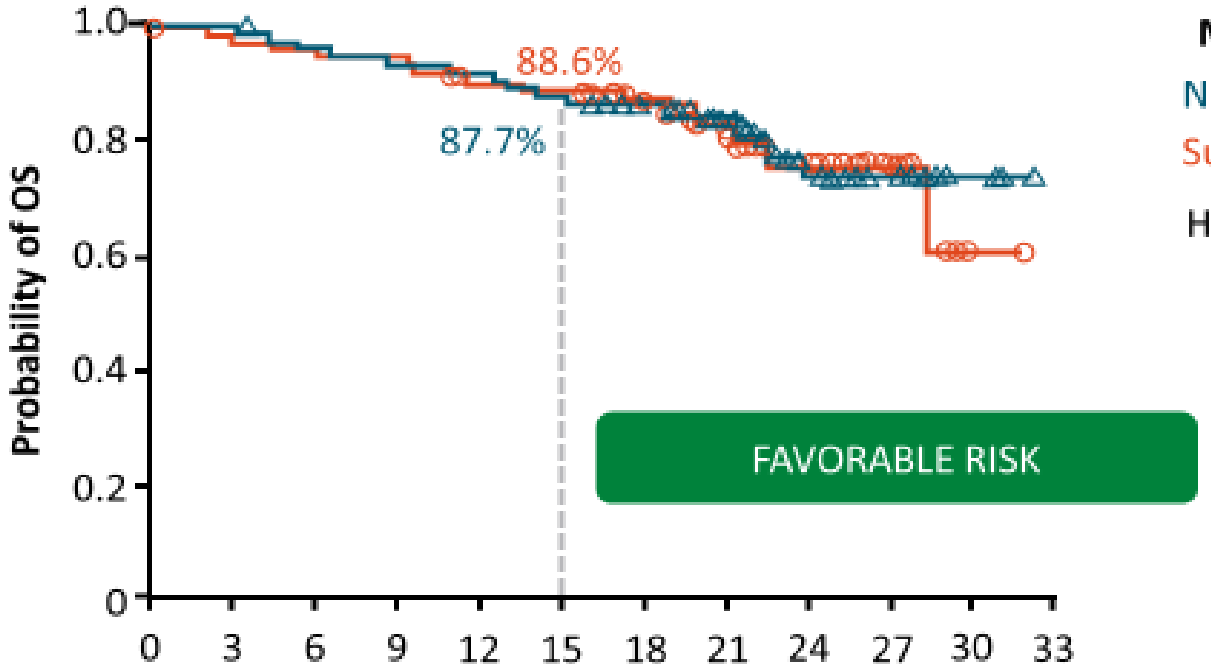


Median f/u: 23.5 mo (ITT)
Minimum f/u: 16.0 mo

Apolo. ASCO 2021. Abstr 4553.

Slide credit: clinicaloptions.com

CheckMate 9ER: First-line Nivolumab + Cabozantinib vs Sunitinib in Advanced or Metastatic RCC



Median OS, Mo (95% CI)

Nivo + Cabo NR (NE)

Sunitinib NR (28.4-NE)

HR: 0.94 (95% CI: 0.46-1.92)

Patients at Risk, n

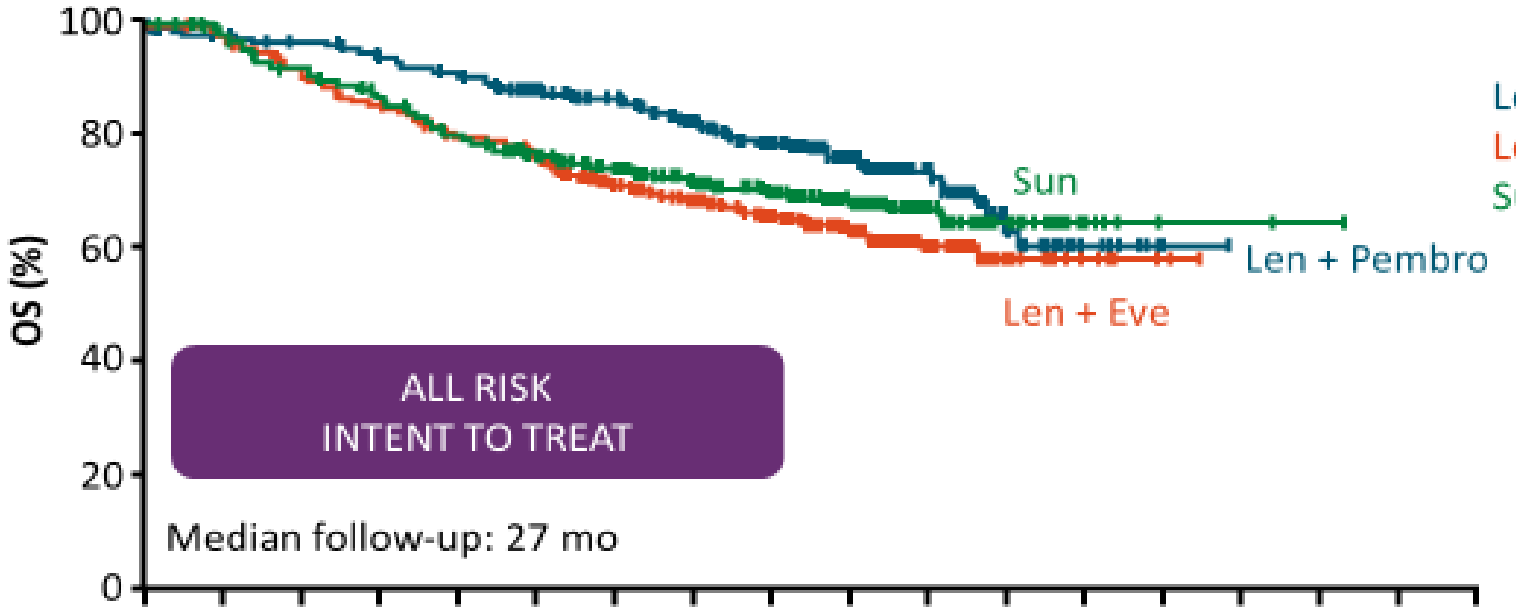
Nivo + Cabo	74	74	70	68	67	64	55	39	24	15	3	0
Sunitinib	72	70	68	67	62	61	54	38	20	8	1	0

Median f/u: 23.5 mo (ITT)
Minimum f/u: 16.0 mo

Apolo. ASCO 2021. Abstr 4553.

Slide credit: clinicaloptions.com

CLEAR: First-line Lenvatinib + Pembrolizumab or Everolimus vs Sunitinib in Advanced RCC



Patients at Risk, n	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
	Mo																	
Len + pembro	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0			
Len + eve	357	346	321	299	277	246	205	183	154	109	46	22	8	2	0			
Sunitinib	357	332	307	289	264	236	207	186	169	112	60	25	7	2	2	1	0	

Median OS, Mo (95% CI)

Len + pembro	NR (33.6-NE)
Len + eve	NR (NE)
Sunitinib	NR (NE)

Len + Pembro vs Sunitinib:
HR: 0.66 (95% CI: 0.49-0.88; *P* = .005)

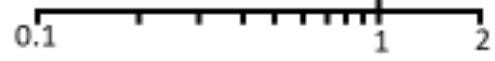
Len + Eve vs Sunitinib:
HR: 1.15 (95% CI: 0.88-1.50; *P* = .3)

Motzer. ASCO GU 2021. Abstr 269. Motzer. NEJM. 2021;384:1289.

Slide credit: clinicaloptions.com

CLEAR: OS in Patient Subgroups

		Events/Participants		HR (95% CI)
		Len + Pembro	Sunitinib	
Overall		80/355	101/357	0.66 (0.49-0.88)
Age	▪ <65 yr	41/194	57/225	0.63 (0.41-0.95)
	▪ ≥65 yr	39/161	44/132	0.61 (0.40-0.95)
Sex	▪ Male	59/255	71/275	0.70 (0.49-0.99)
	▪ Female	21/100	30/82	0.54 (0.30-0.94)
Geographic region	▪ W. Europe and NA	46/198	57/199	0.68 (0.46-1.00)
	▪ Rest of world	34/157	44/158	0.63 (0.40-0.99)
PD-L1 status	▪ ≥1	28/107	36/119	0.76 (0.46-1.27)
	▪ <1	21/112	31/103	0.50 (0.28-0.89)
IMDC risk group	▪ Favorable	14/110	15/124	1.15 (0.55-2.40)
	▪ Intermediate	56/210	60/192	0.72 (0.50-1.05)
	▪ Poor	10/33	25/37	0.30 (0.14-0.64)
Prior nephrectomy	▪ Yes	50/262	66/275	0.71 (0.49-1.03)
	▪ No	30/93	35/82	0.52 (0.31-0.86)
Sarcomatoid features	▪ Yes	9/28	7/21	0.91 (0.32-2.58)
	▪ No	71/327	94/336	0.64 (0.47-0.87)

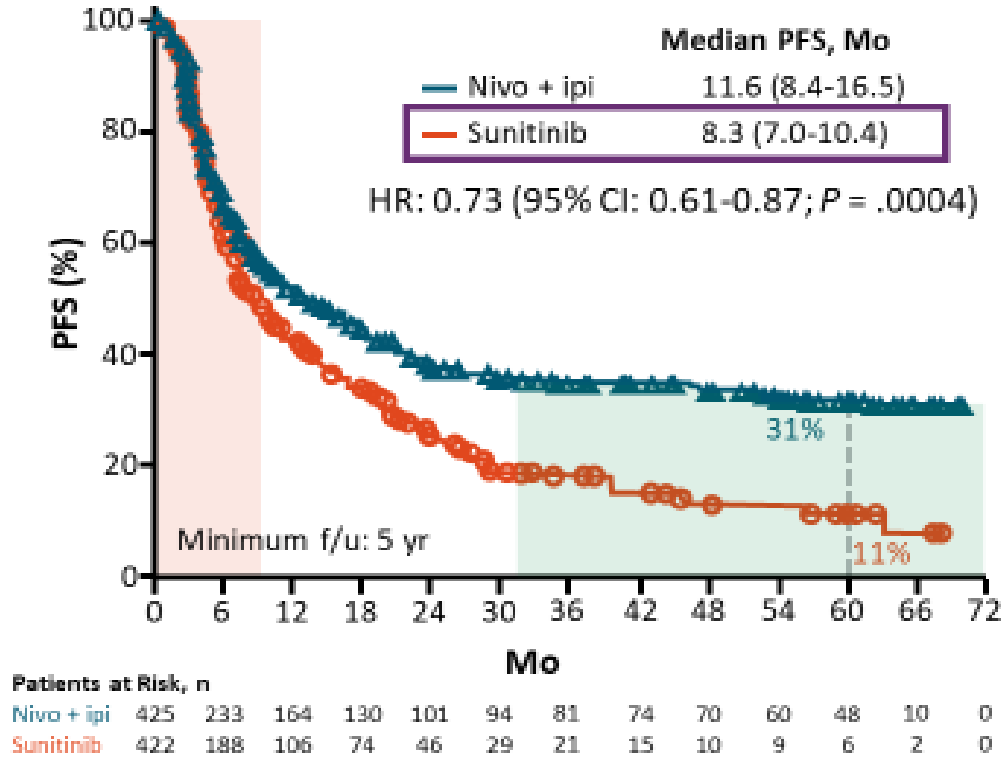


Motzer. ASCO GU 2021. Abstr 269.

Slide credit: clinicaloptions.com

PFS for IMDC Intermediate-/Poor-Risk Disease

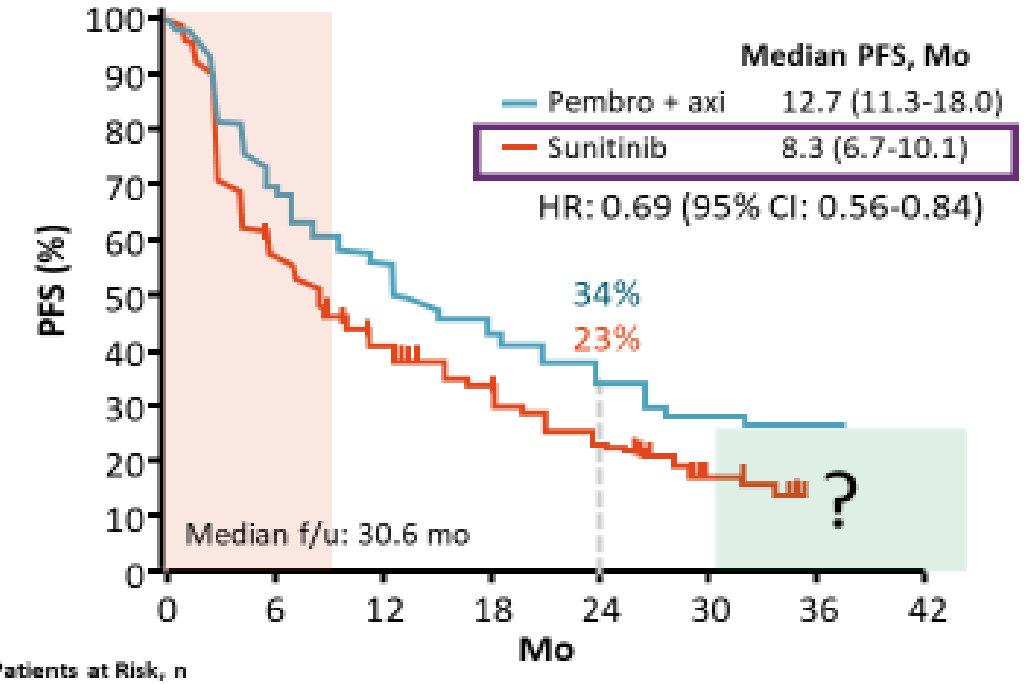
CheckMate 214: Nivo + Ipi vs Sunitinib (n = 847)[1]



Patients at Risk, n

Nivo + ipi	425	233	164	130	101	94	81	74	70	60	48	10	0
Sunitinib	422	188	106	74	46	29	21	15	10	9	6	2	0

KEYNOTE-426: Axitinib + Pembro vs Sunitinib (n = 592)[2]



Patients at Risk, n

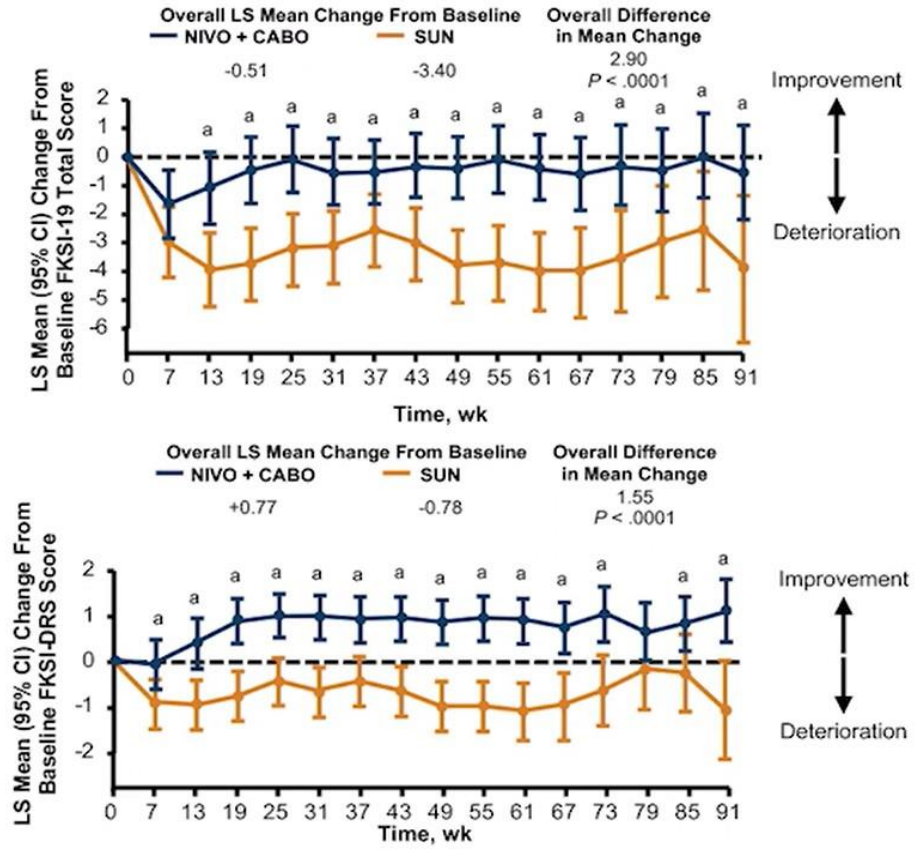
Pembro + axi	294	189	146	113	68	23	2	0
Sunitinib	298	149	93	66	35	11	0	0

1. Motzer. ESMO 2021. Abstr 661P. 2. Powles. Lancet Oncol. 2020;21:1563.

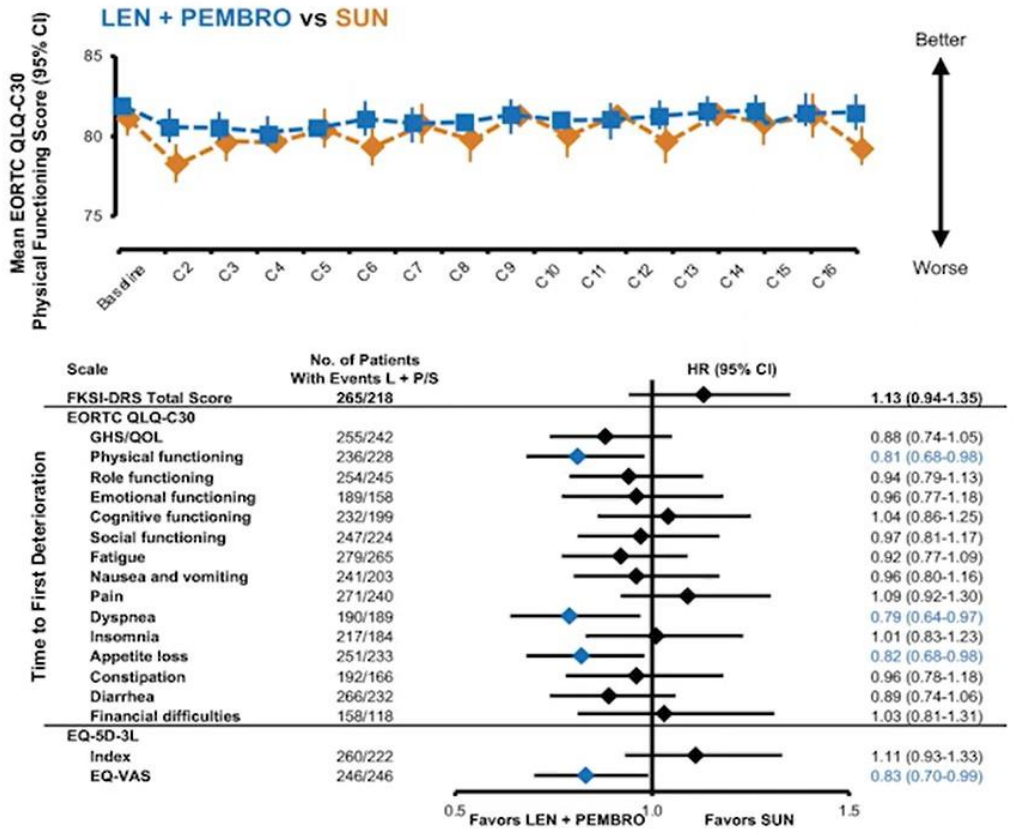
Slide credit: clinicaloptions.com

Patient Perspectives: Patient-Reported Outcomes

CheckMate -9ER[1,2]



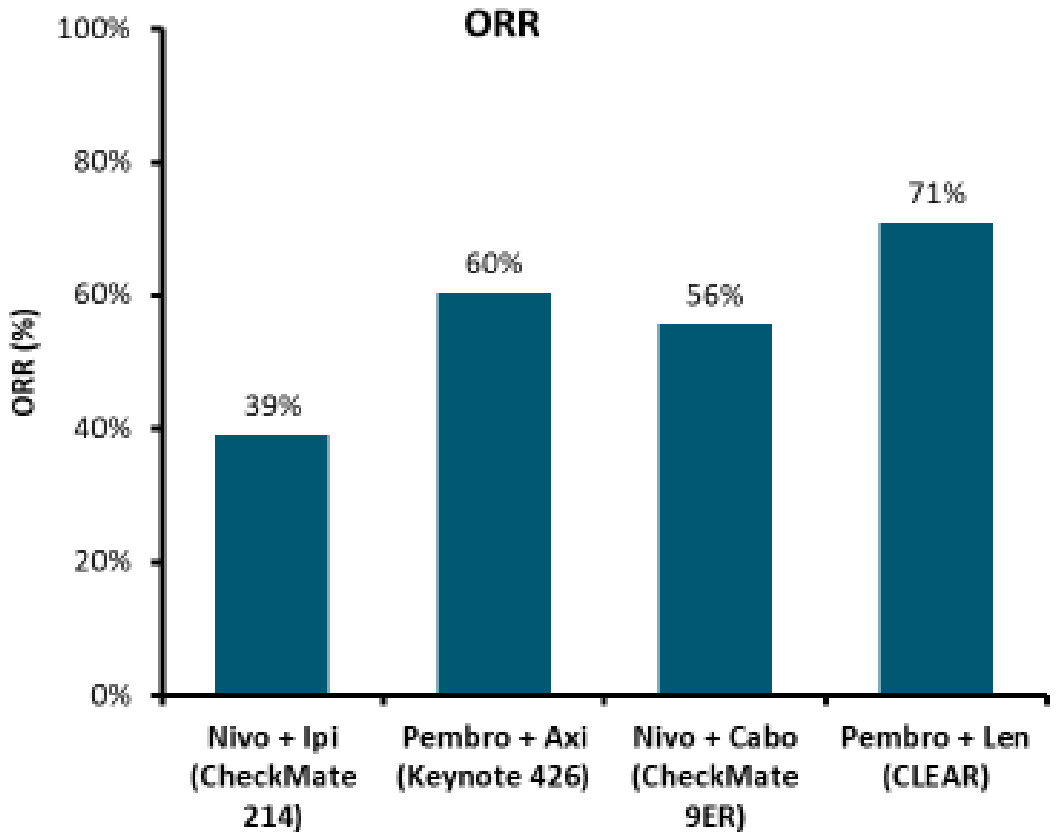
CLEAR[3]

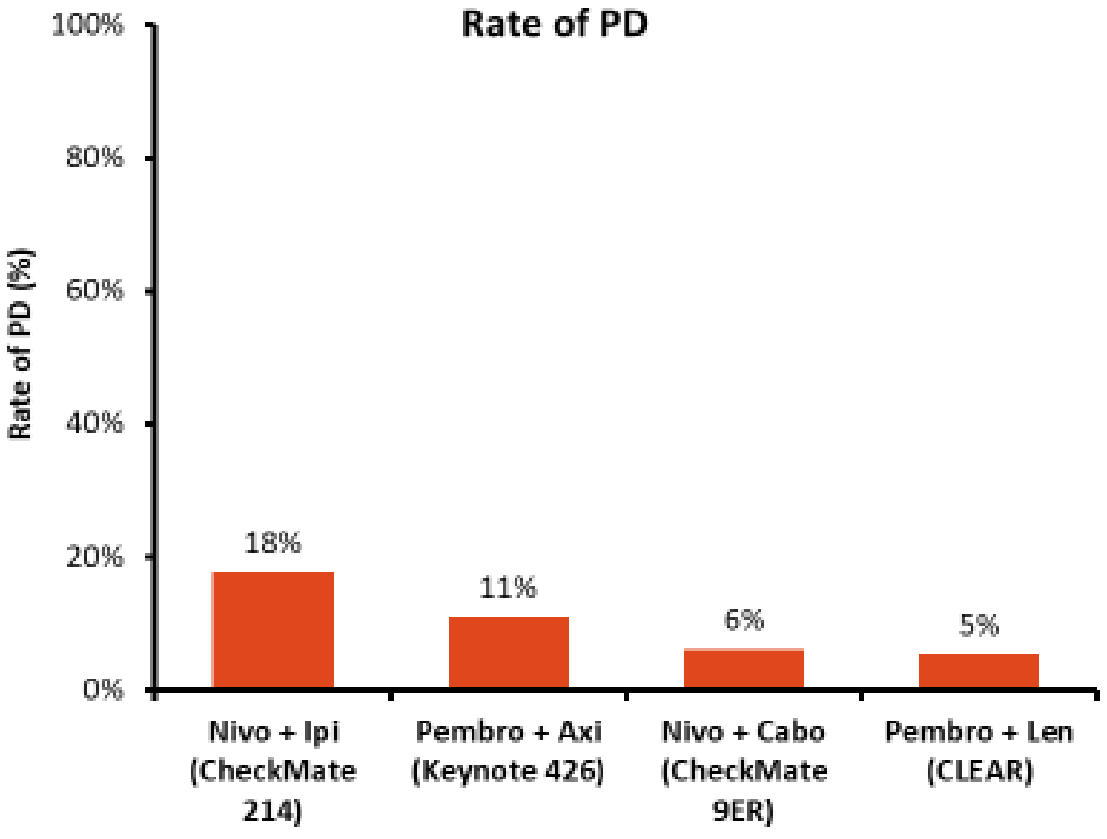


[a] Between-arm difference was statistically significant at this time point ($P < .05$).

1. Cella D et al. ASCO GU 2021. Abstract 285. 2. Cella D et al. ASCO 2021. Abstract 6567. 3. Motzer RJ et al. ASCO 2021. Abstract 4502.

Cross-Trial Comparison of Response in ITT Population





Motzer. ESMO 2021. Abstr 661P. Rini. ASCO 2021. Abstr 4500.
Motzer. ASCO GU 2022. Abstr 350. Motzer. ASCO GU 2021. Abstr 269.

Slide credit: clinicaloptions.com

First-Line IO Combination Trials in mRCC

	CheckMate -214 (NIVO + IPI vs SUN)[1] (n = 550 vs n = 546)	KEYNOTE-426 (PEMBRO + AXI vs SUN)[2] (n = 432 vs n = 429)	CheckMate -9ER (NIVO + CABO vs SUN)[3] (n = 323 vs n = 328)	CLEAR (LEN + PEMBRO vs SUN)[4] (n = 355 vs n = 357)
mOS, mo **HR (CI)**	55.7 vs 38.4 0.72 (0.62-0.85)	45.7 vs 40.1 0.73 (0.60-0.88)	NR vs 29.5 0.66 (0.50-0.87)	NR vs NR 0.66 (0.49-0.88)[a,5]
mPFS, mo **HR (CI)**	12.3 vs 12.3 0.86 (0.73-1.01)	15.7 vs 11.1 0.68 (0.58-0.80)	17.0 vs 8.3 0.52 (0.43-0.64)	23.9 vs 9.2 0.39 (0.32-0.49)
ORR, %	39 vs 32	60 vs 40	55 vs 27	71 vs 36
CR, %	12 vs 3	10 vs 4	9 vs 4	16 vs 4
Med f/u, mo	67.7	42.8	23.5	27
FDA Approved	✓	✓	✓	✓


thank
you