Cancer du Rein:

RECOMMANDATIONS

S.ZAIDI M.OUKKAL
Oncologie Médicale
CHU BENI MESSOUS

RENAL CELL CARCINOMA

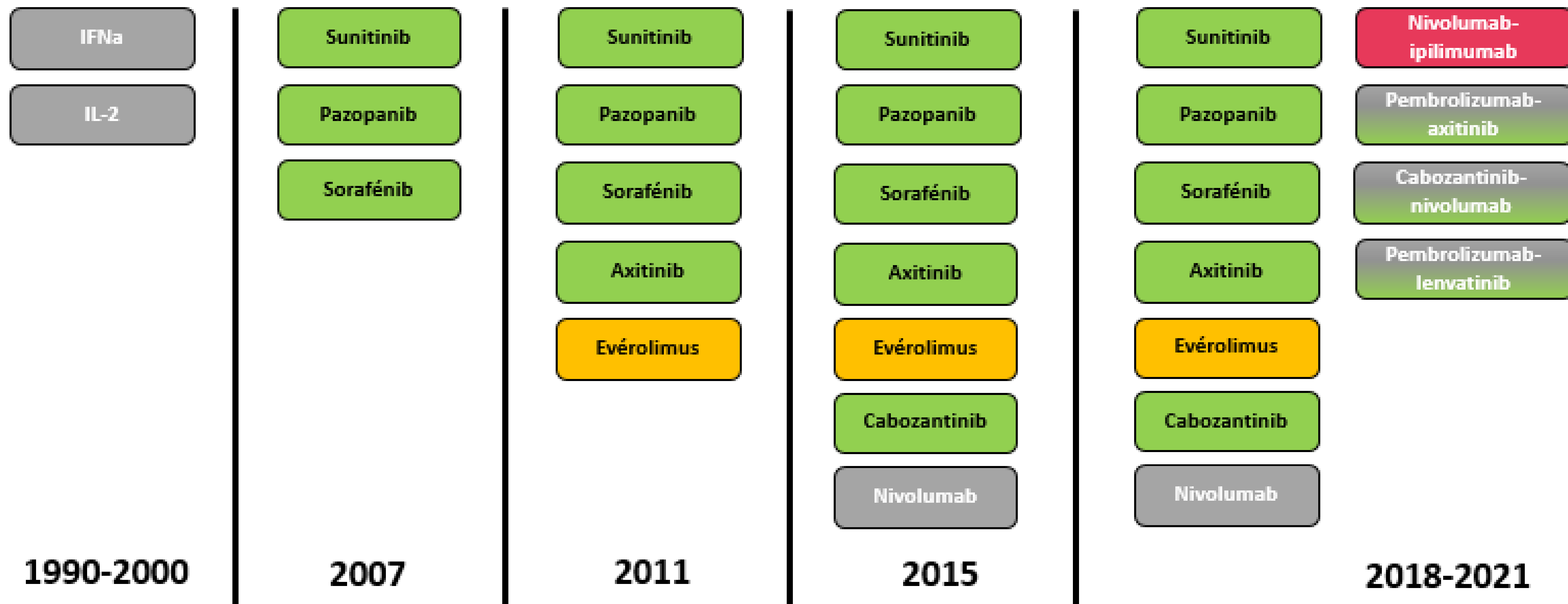
- Accounts for 5% and 3% of all adult malignancies in men and women, respectively
- Representing the 7th most common cancer in men and the 10th most common cancer in women

Management has greatly evolved recently

- **Metastatic setting**
  - **Cytoreductive nephrectomy**
  - **Systemic treatment changes**

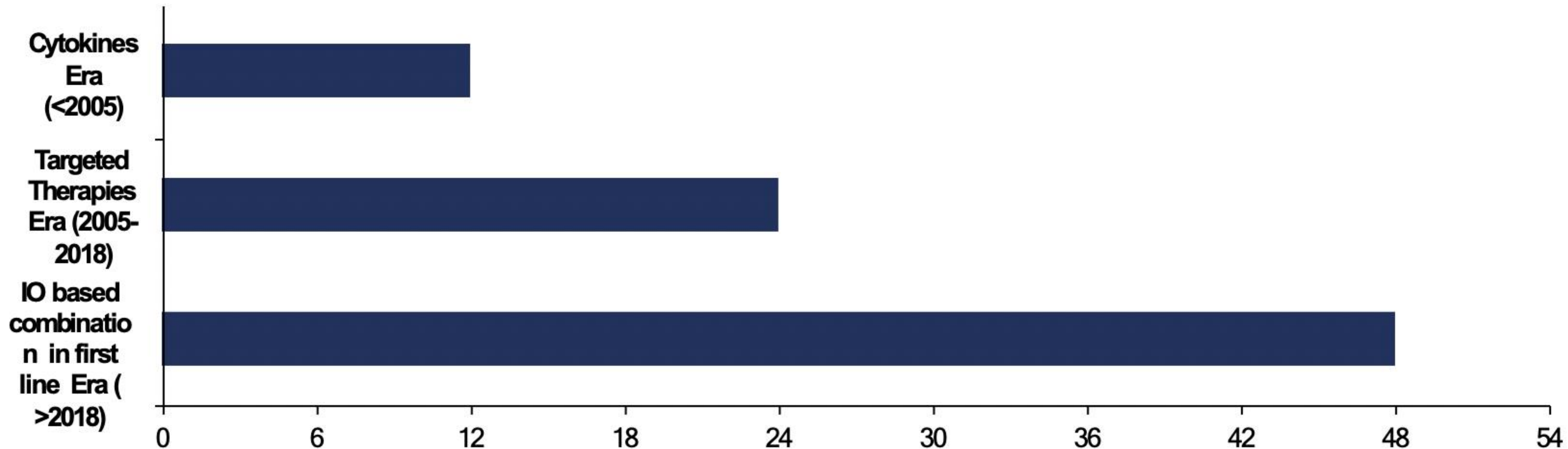
- **Localised disease:**
  - **Role for adjuvant CPI**

Arsenal thérapeutique riche dans le mRCC

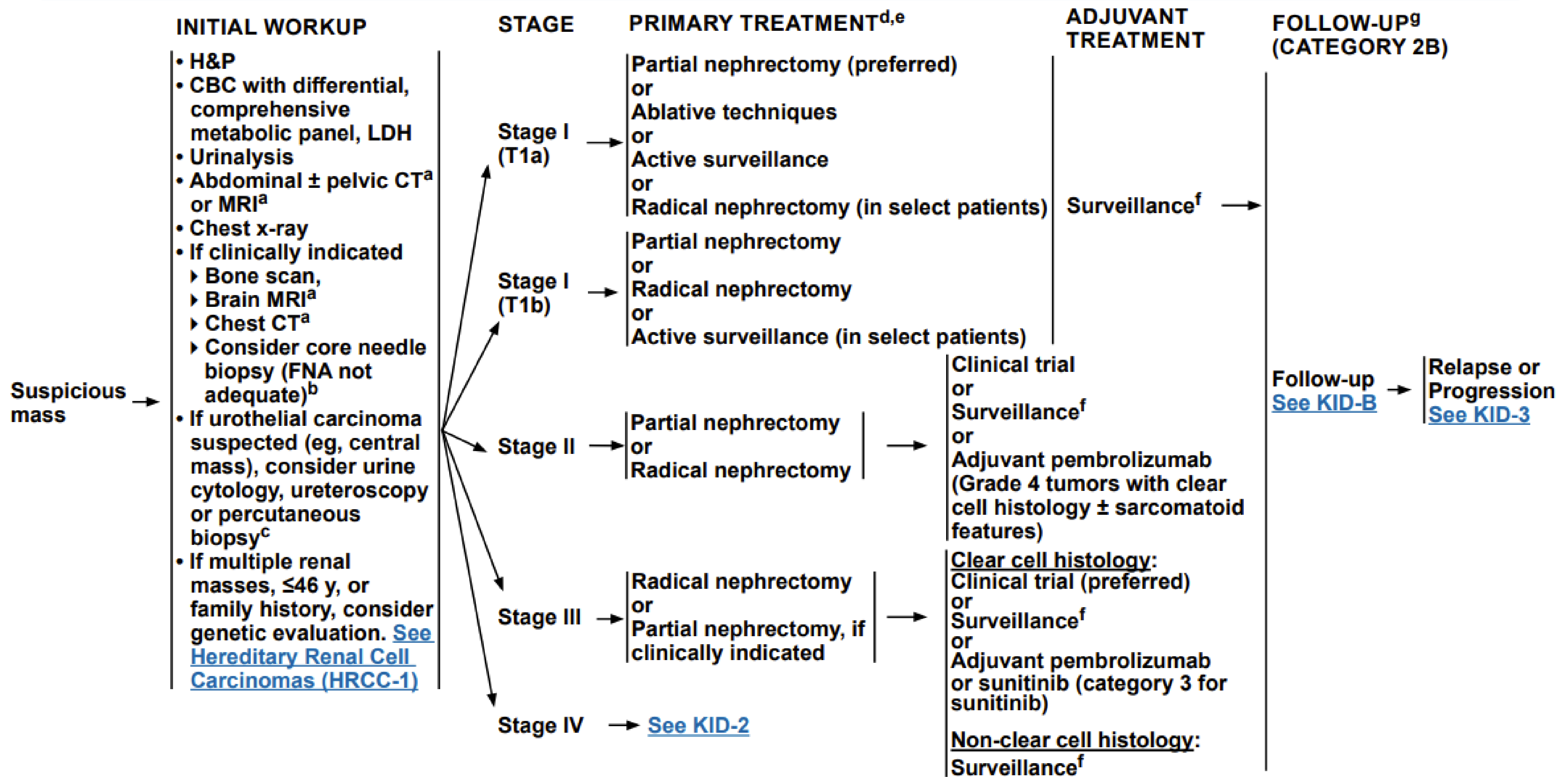


OVERALL SURVIVAL: CHANGES IN 20 YEARS

What has been achieved and need to be implemented routinely



RCC: Traitement Adjuvant



Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V4.2022. © National Comprehensive Cancer Network, Inc 2022. All rights reserved. Accessed May 31, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org.

Published Tyrosine Kinase Inhibitor Adjuvant Trials

Trial	Therapy	N	Histology	Stage	Starting Dose	Minimum Dose	Significant Difference?	
							DFS	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.

1. Haas. Lancet. 2016;387:2008. 2. Ravaud. NEJM. 2016;375:2246. 3. Motzer. Eur Urol. 2018;73:62. 4. Motzer. JCO. 2017;35:3916. 5. Motzer. Eur Urol. 2021;79:334.

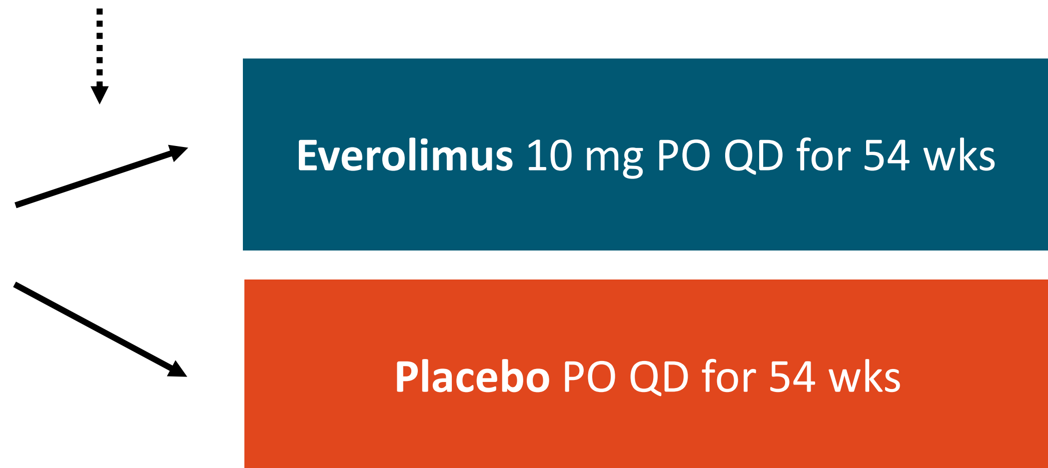
CCO
Slide credit: clinicaloptions.com

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)

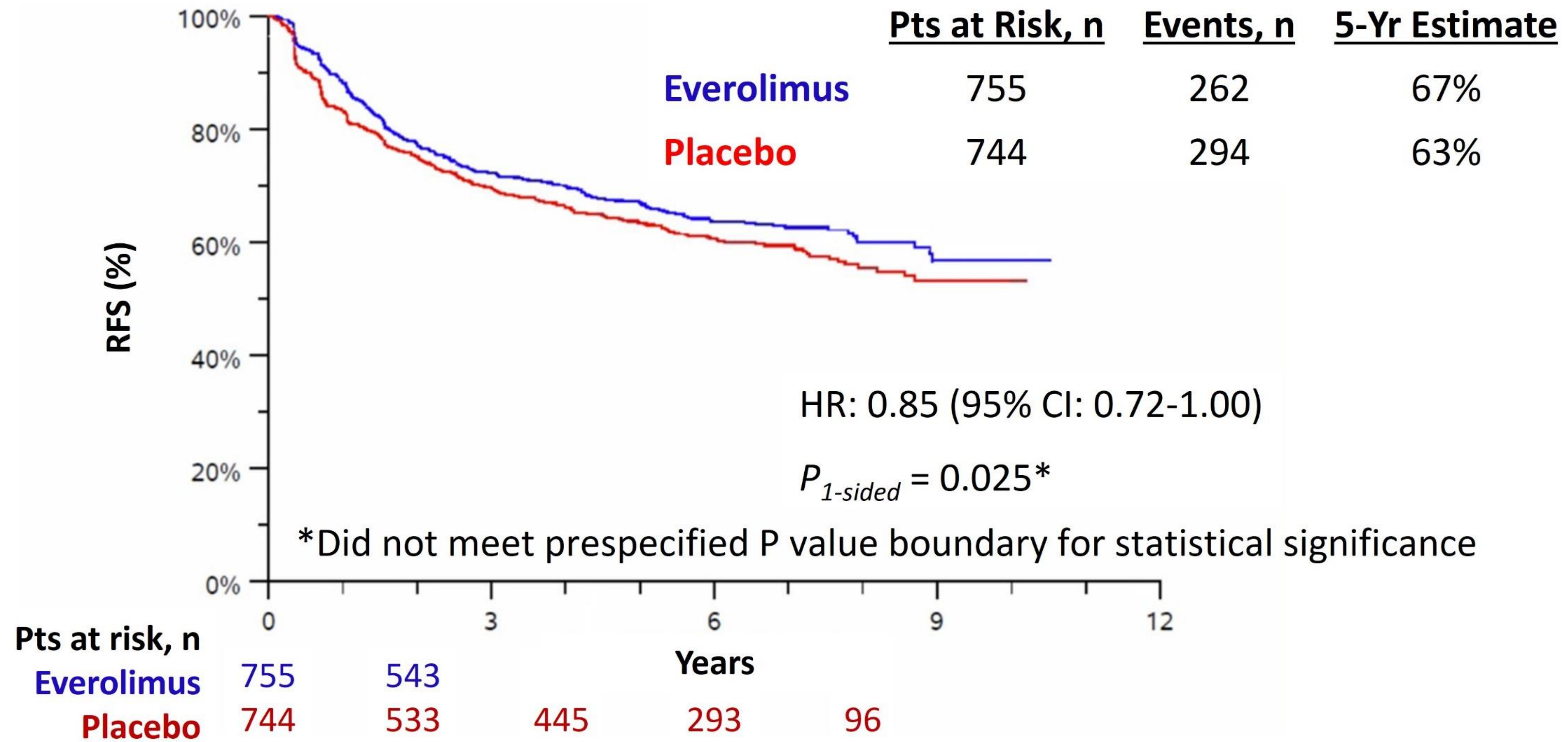


- **Primary endpoint**: recurrence-free survival
- **Secondary endpoints**: OS, safety

Ryan. ASCO 2022. Abstr LBA4500. NCT01120249.

CCO
Slide credit: clinicaloptions.com

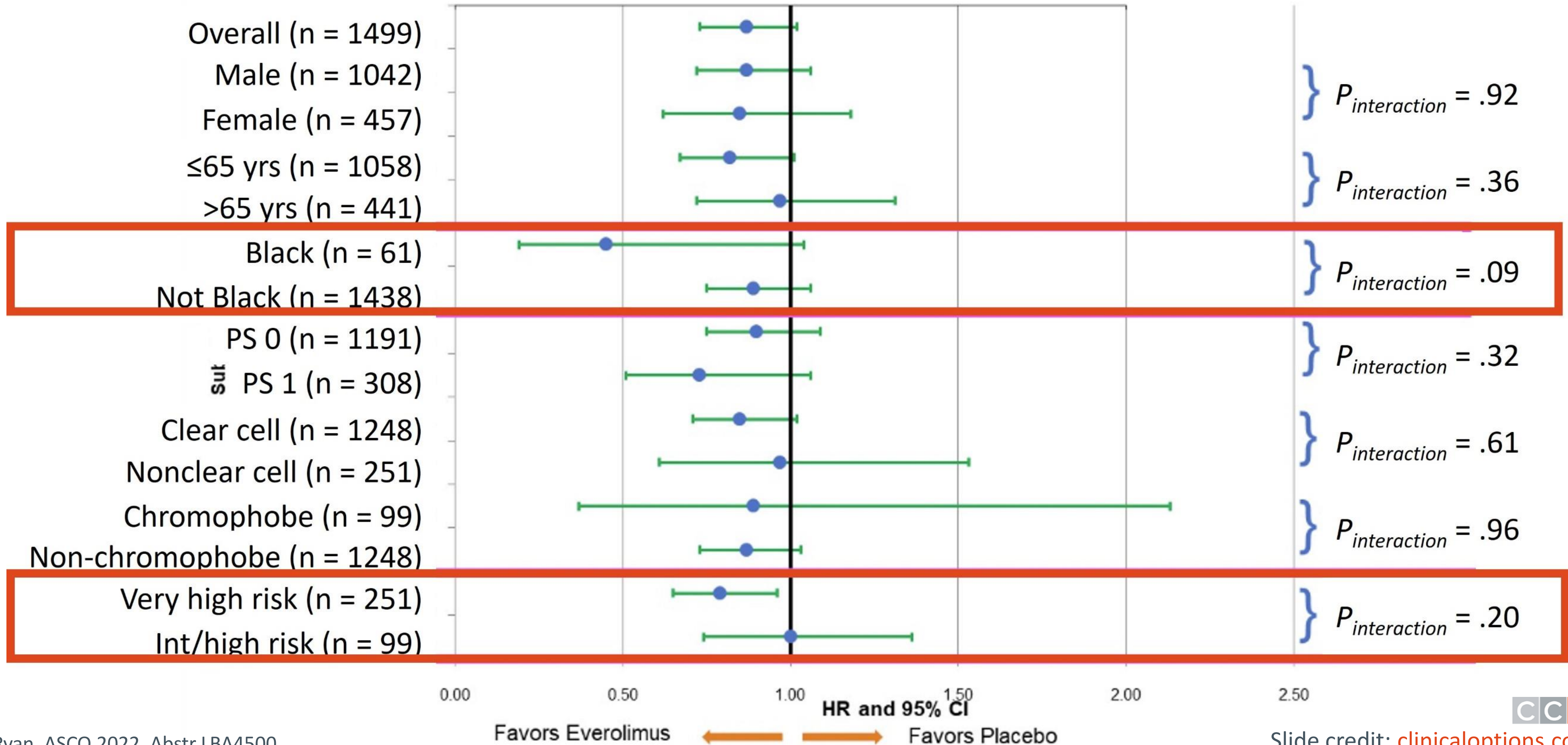
EVEREST: Recurrence-Free Survival with Everolimus vs Placebo After Nephrectomy or Partial Nephrectomy



Ryan. ASCO 2022. Abstr LBA4500.

Slide credit: clinicaloptions.com

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

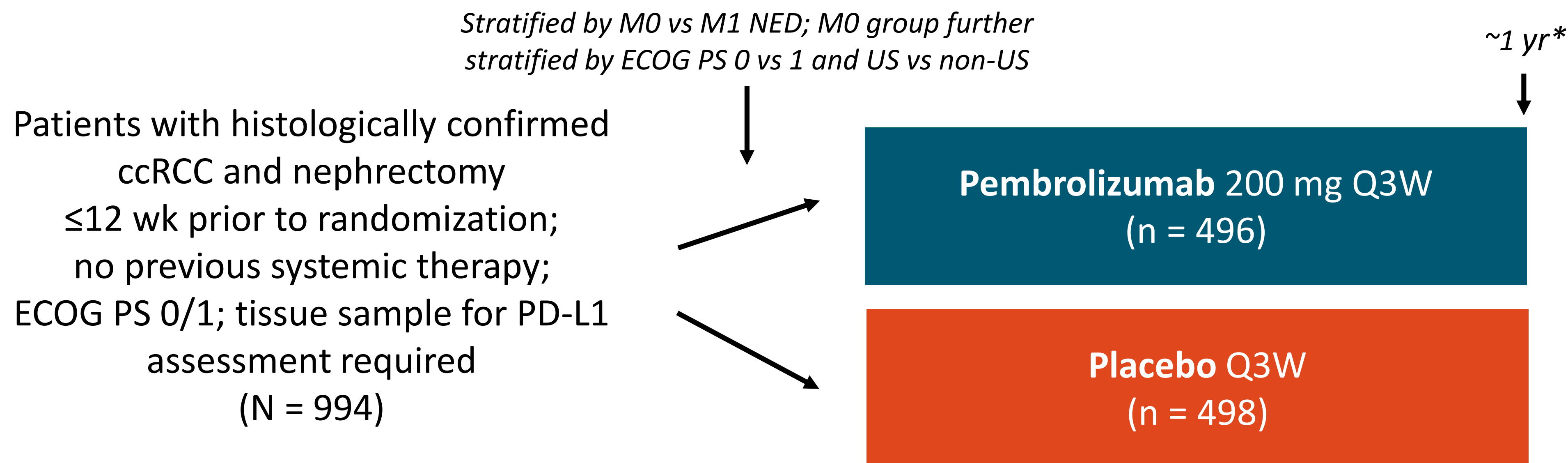


Ryan. ASCO 2022. Abstr LBA4500.

CCO
Slide credit: clinicaloptions.com

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

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



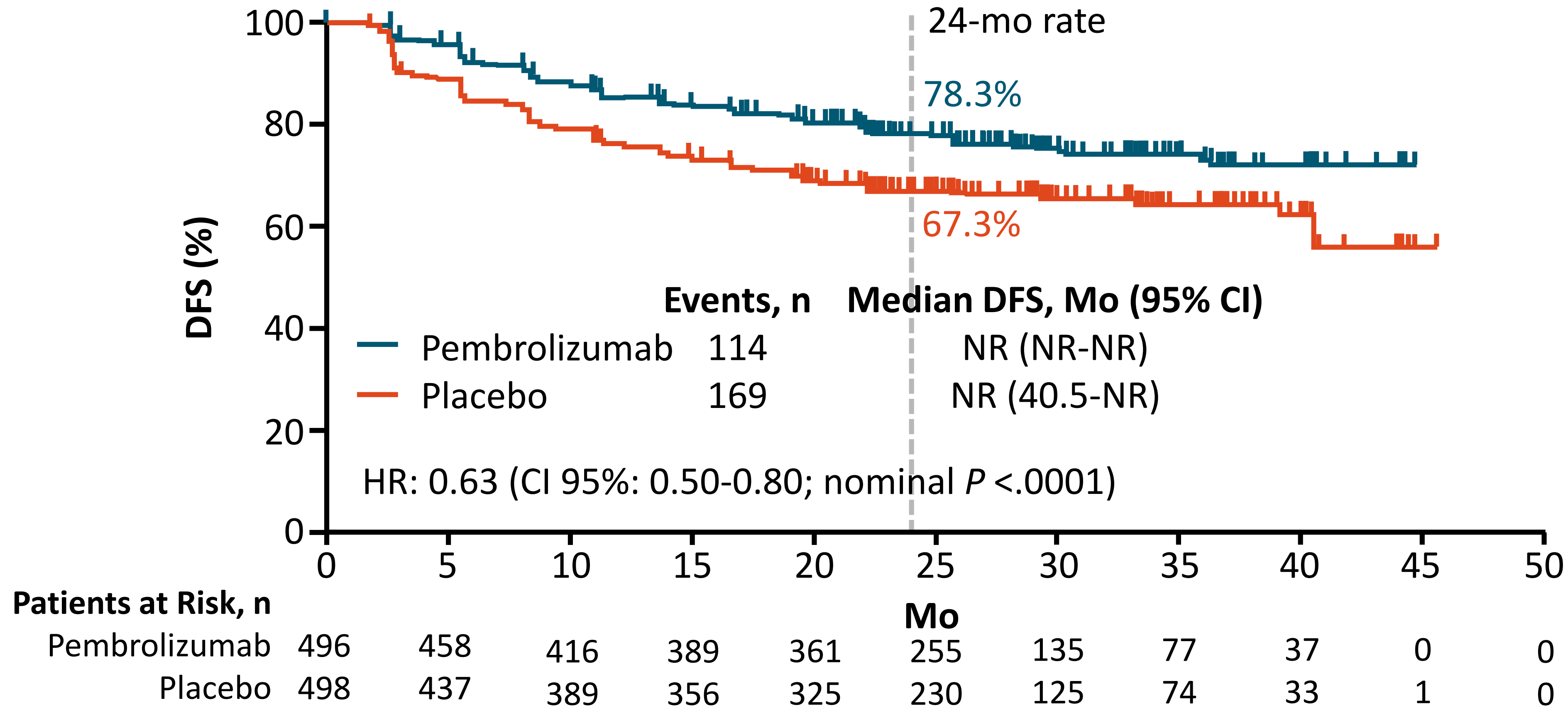
*Equivalent to ≤17 cycles.

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

Choueiri. ASCO GU 2022. Abstr 290. NCT03142334.

Slide credit: clinicaloptions.com

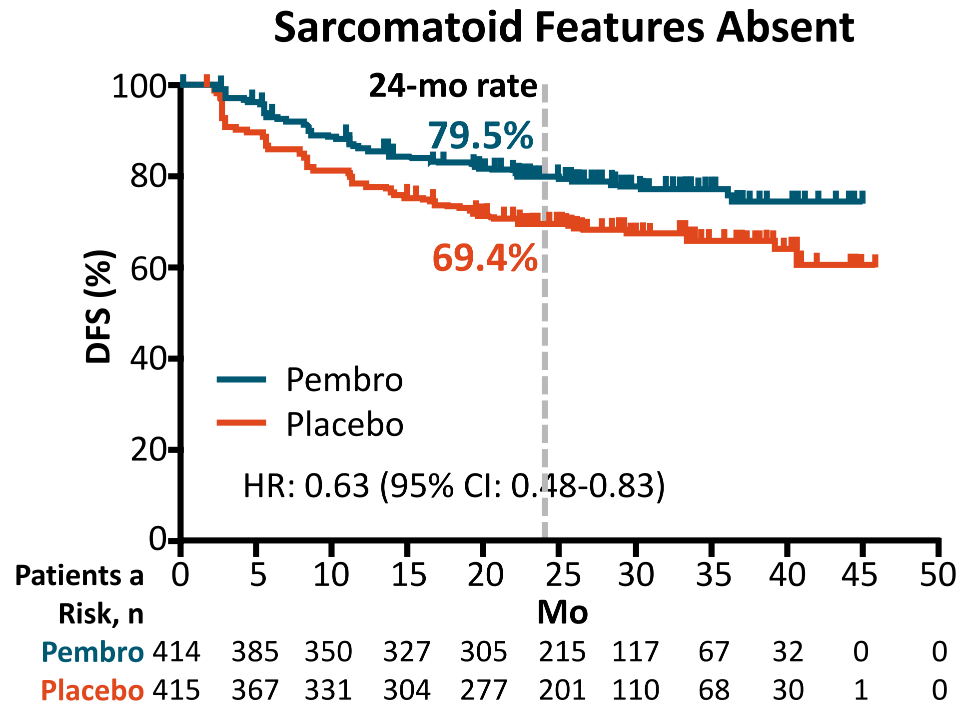
KEYNOTE-564 30-Mo Follow-up: DFS in ITT Population (Primary Endpoint)

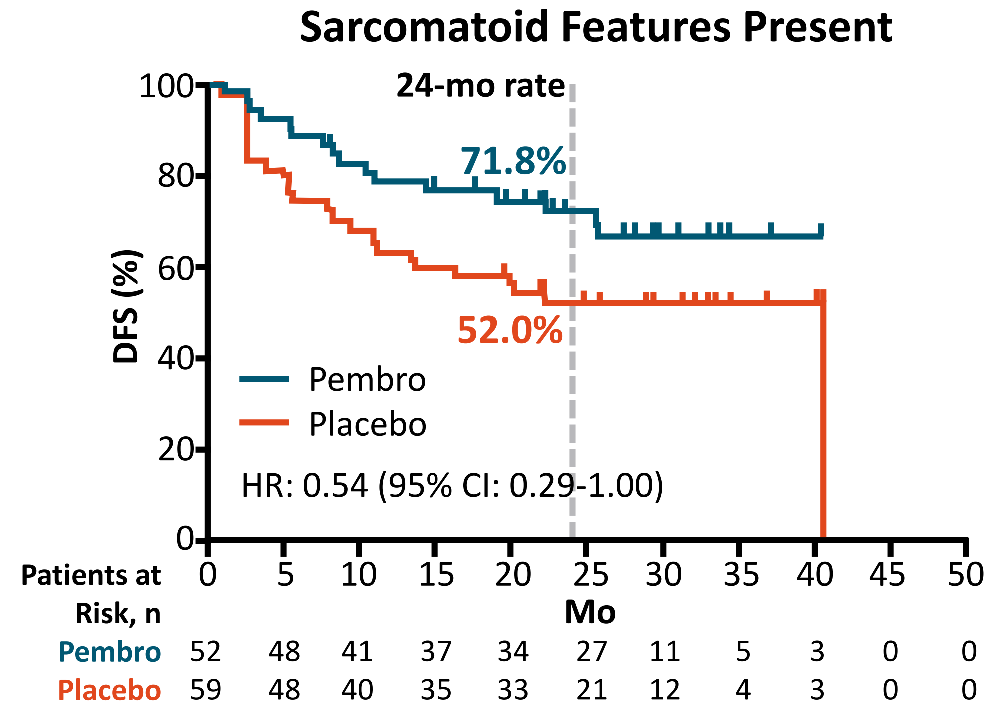


Choueiri. ASCO GU 2022. Abstr 290.

Slide credit: clinicaloptions.com

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





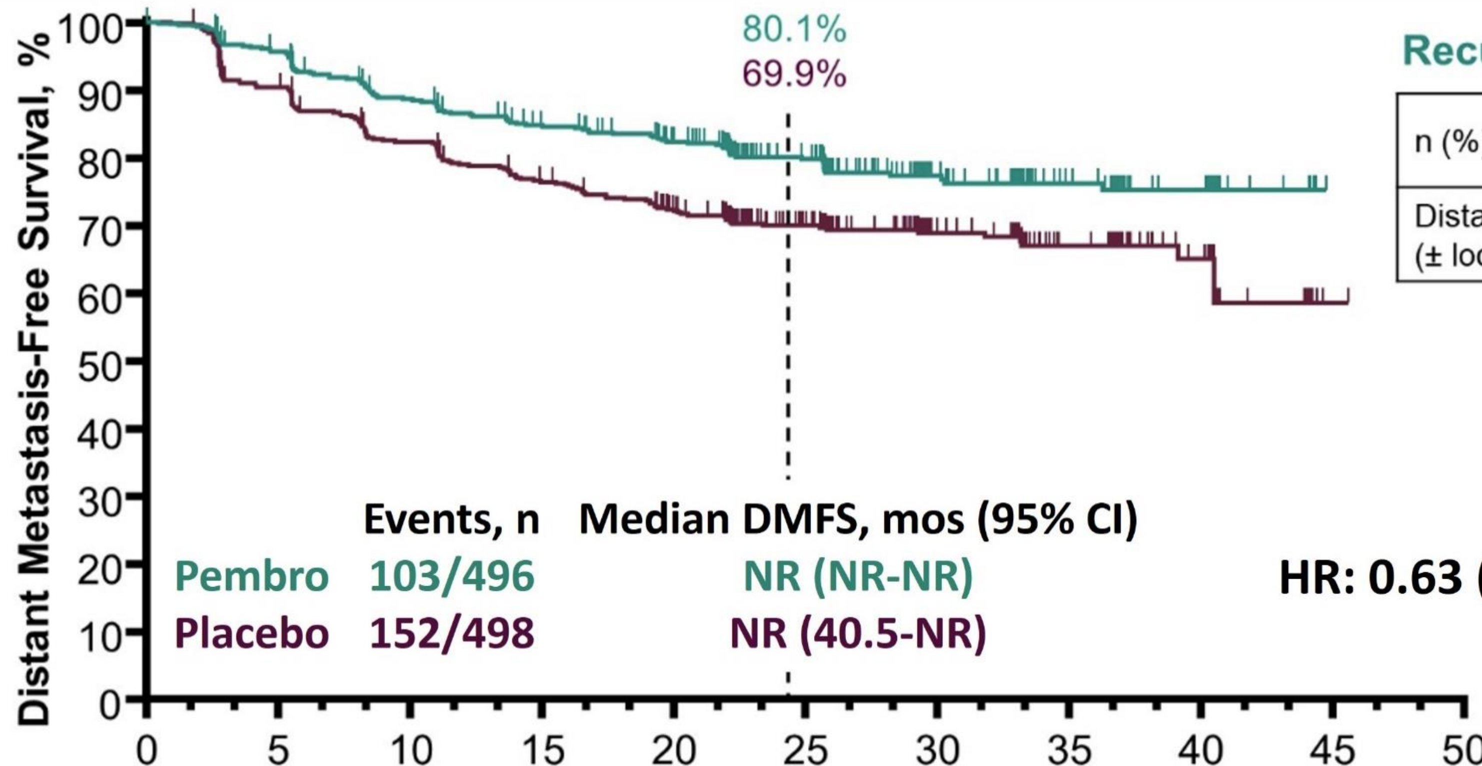
	Events	Median DFS, Mo (95% CI)
Pembro (n = 414)	88	NR (NR-NR)
Placebo (n = 415)	133	NR (NR-NR)

	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.

CCO
Slide credit: clinicaloptions.com

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)

HR: 0.63 (95% CI: 0.49-0.82)

Pts at risk, n

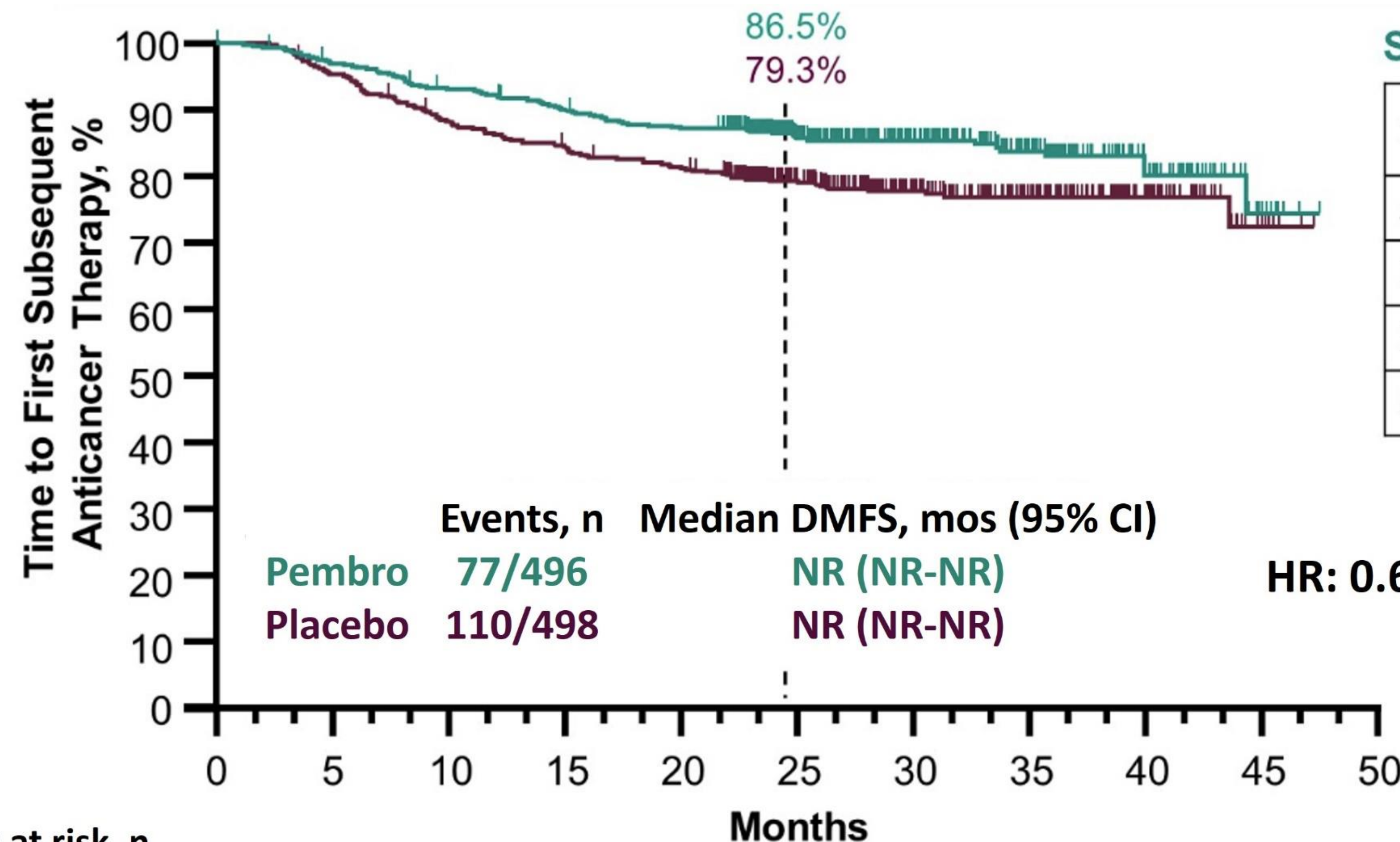
	0	5	10	15	20	25	30	35	40	45	50
Pembro	496	457	415	387	361	255	135	76	37	0	0
Placebo	498	439	394	360	327	230	126	74	33	1	0

Choueiri. ASCO 2022. Abstr 4512.

CCO
Slide credit: clinicaloptions.com

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)

Pts at risk, n											
Pembro	496	478	457	440	425	320	203	129	54	8	0
Placebo	498	473	436	416	400	297	184	116	52	9	0

Choueiri. ASCO 2022. Abstr 4512.

Slide credit: clinicaloptions.com

Questions sans réponses

- **Durée** necessaire de traitement en adjuvant : une année c'est suffisant ou pas?
- **Intensité** du traitement djuvant : la monothérapie est-elle suffisante?
- **Risque de toxicité** : sur-traitement ou sous-traitement?
- **Besoin de quels types d'essais :** Validation du ctDNA, signature immunologique ou angiogénique?
- Utiliser les meilleures technologies pour identifier ceux qui vont progresser de ceux qui vont répondre parmis les patients traités

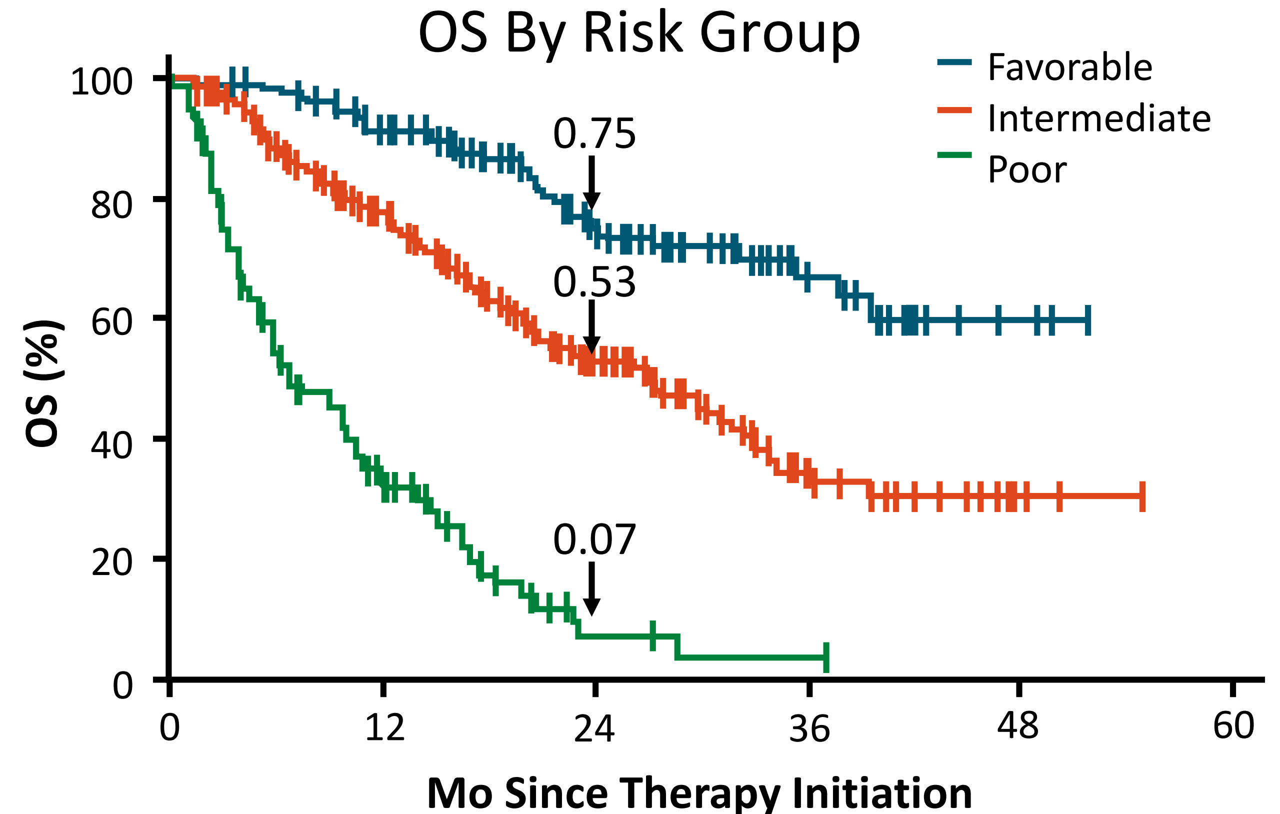
Première ligne de Treatment pour le RCC avancé

Rôle du Risque dans le Traitement du mRCC

IMDC Criteria for 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



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

CCO
Slide credit: clinicaloptions.com

Advanced Renal Cell Carcinoma: Current Therapeutic Landscape

Risk Stratification (IMDC)

- KPS < 80%
- Hb < LLN
- Neutrophilia
- Platelets > ULN
- Calcium > ULN
- Time from Dx to systemic therapy < 1 yr

Favorable risk

Intermediate risk

Poor risk

First Line

Favorable risk:

- **Clinical trial**
- **IO + VEGF TKI**
- **VEGF TKI**

Intermediate/poor risk:

- **Clinical trial**
- **IO + IO**
- **IO + VEGF TKI**
- **VEGF TKI**

Second Line +

- Clinical trial
- VEGF TKI
- IO
- VEGF TKI + IO
- VEGF TKI + mTORi
- IO + IO
- mTORi

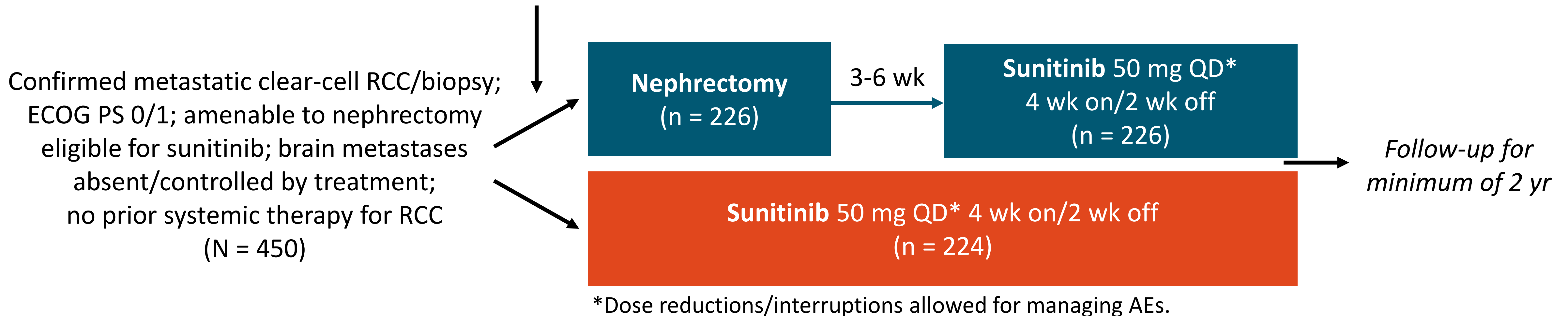
Courtesy of Jaime R. Merchan, MD.

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

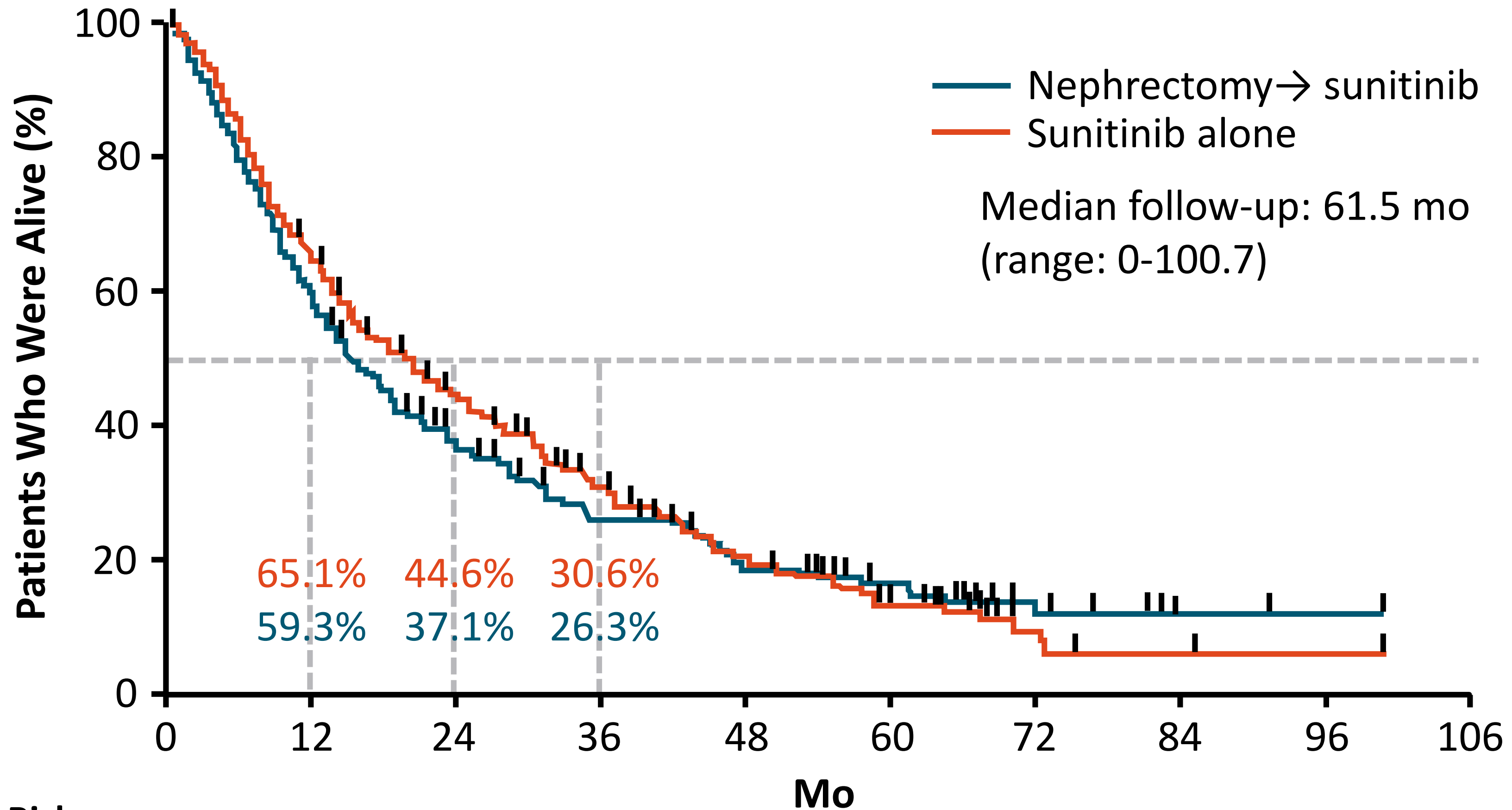
CARMENA: Prospective, Multicenter, Open-Label, Randomized Phase III Noninferiority Study

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



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

CARMENA: Overall Survival (ITT)

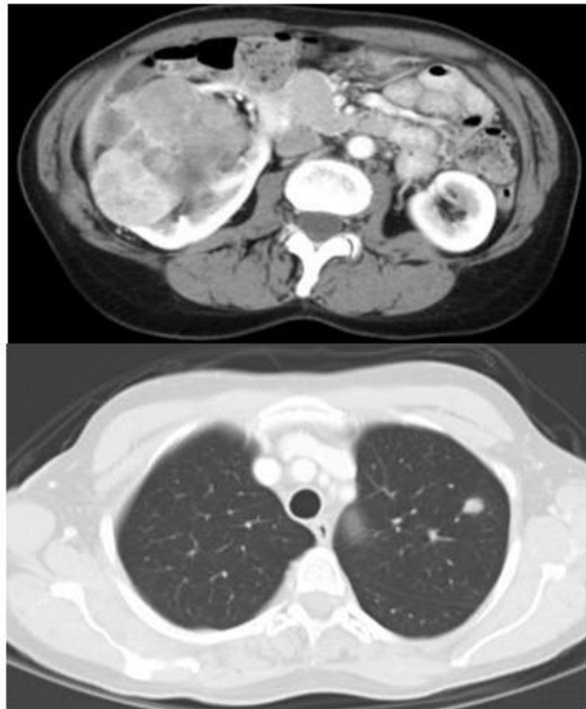


Méjean. ASCO 2019. Abstr 4508.

CCO
Slide credit: clinicaloptions.com

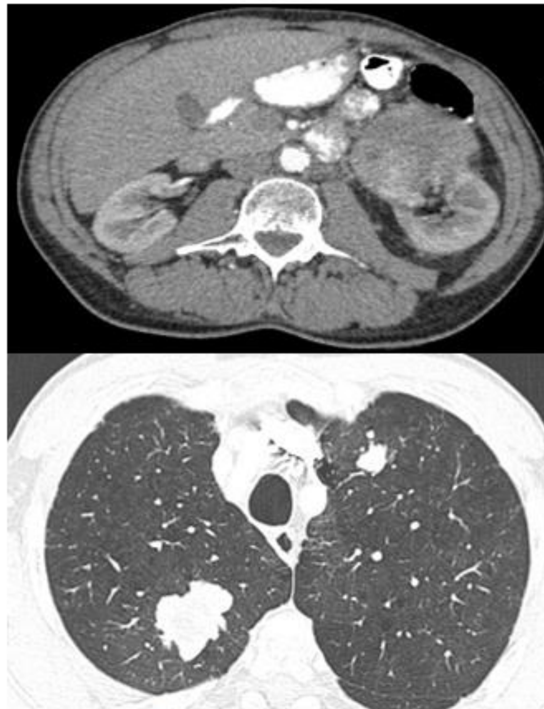
Considerations for Nephrectomy

PS 0
Minimal extrarenal disease



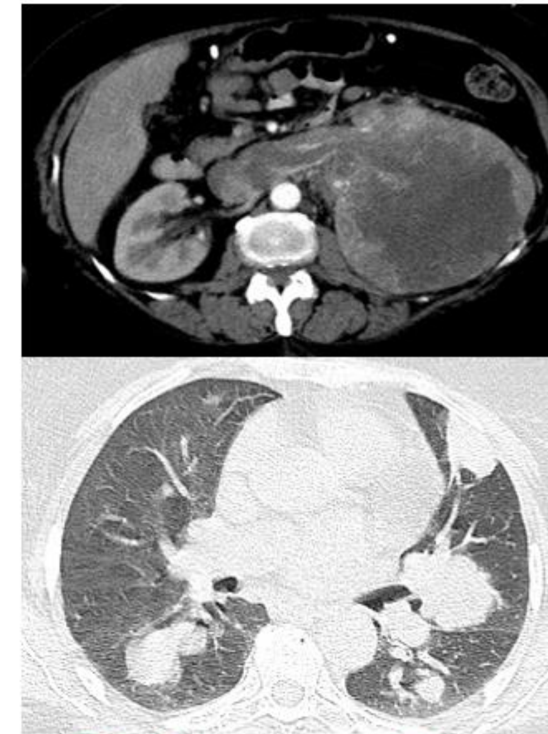
Nephrectomy makes sense

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

CCO
Slide credit: clinicaloptions.com

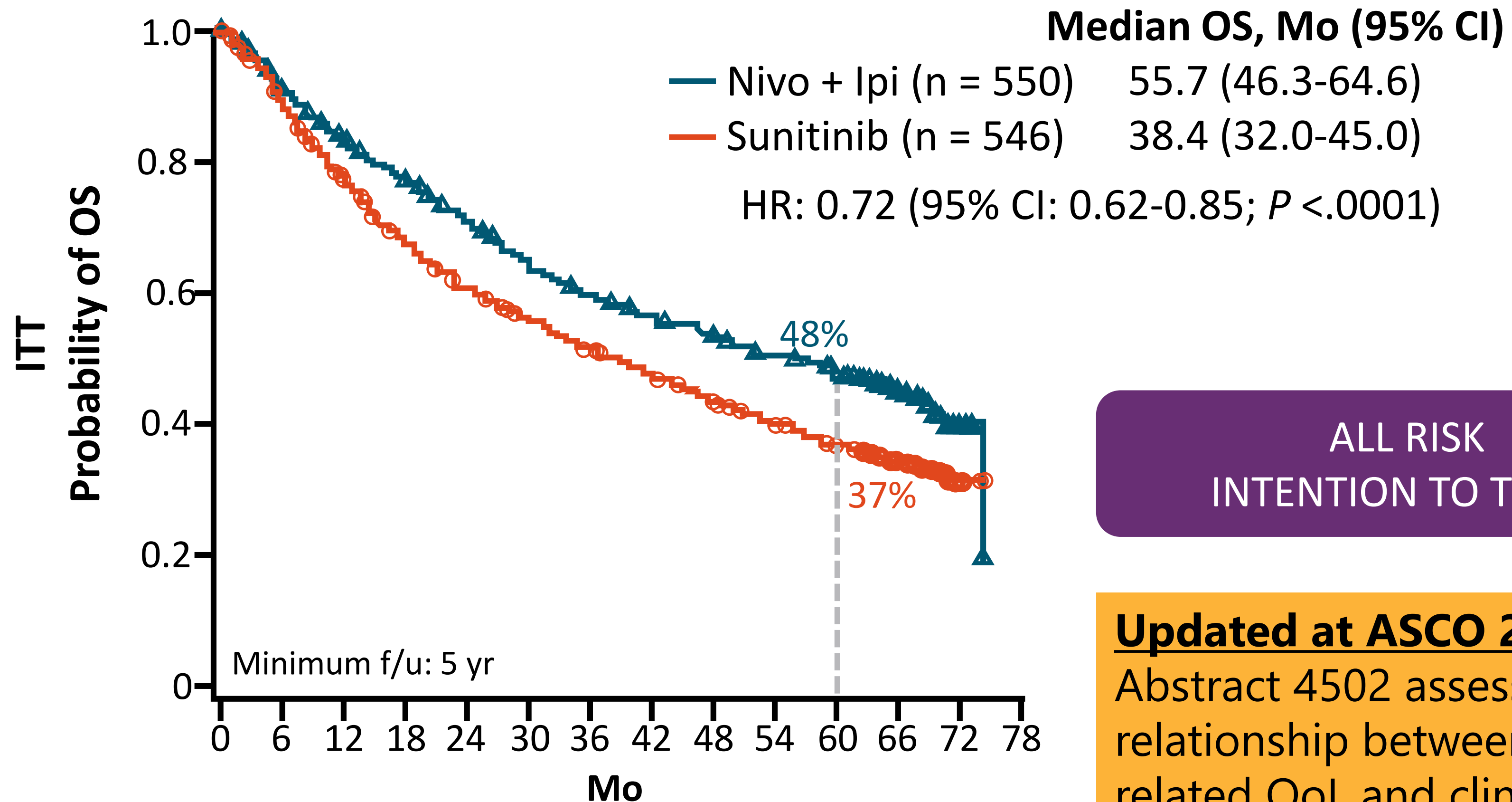
PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

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)

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V4.2022. © National Comprehensive Cancer Network, Inc 2022. All rights reserved. Accessed February 21, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org.

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



Patients at Risk, n														
Nivo + Ipi	550	493	444	411	372	337	309	291	274	256	236	138	5	0
Sunitinib	546	472	405	347	310	281	257	234	213	192	171	108	6	0

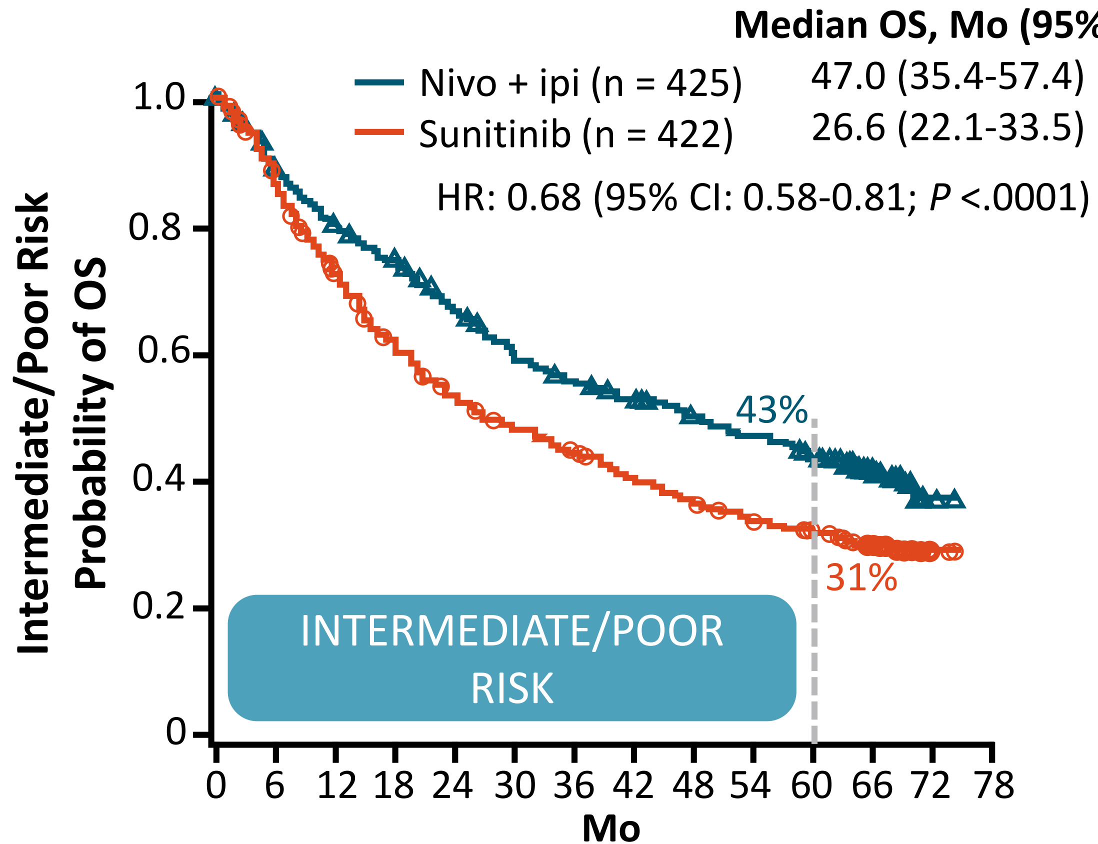
ALL RISK
INTENTION TO TREAT

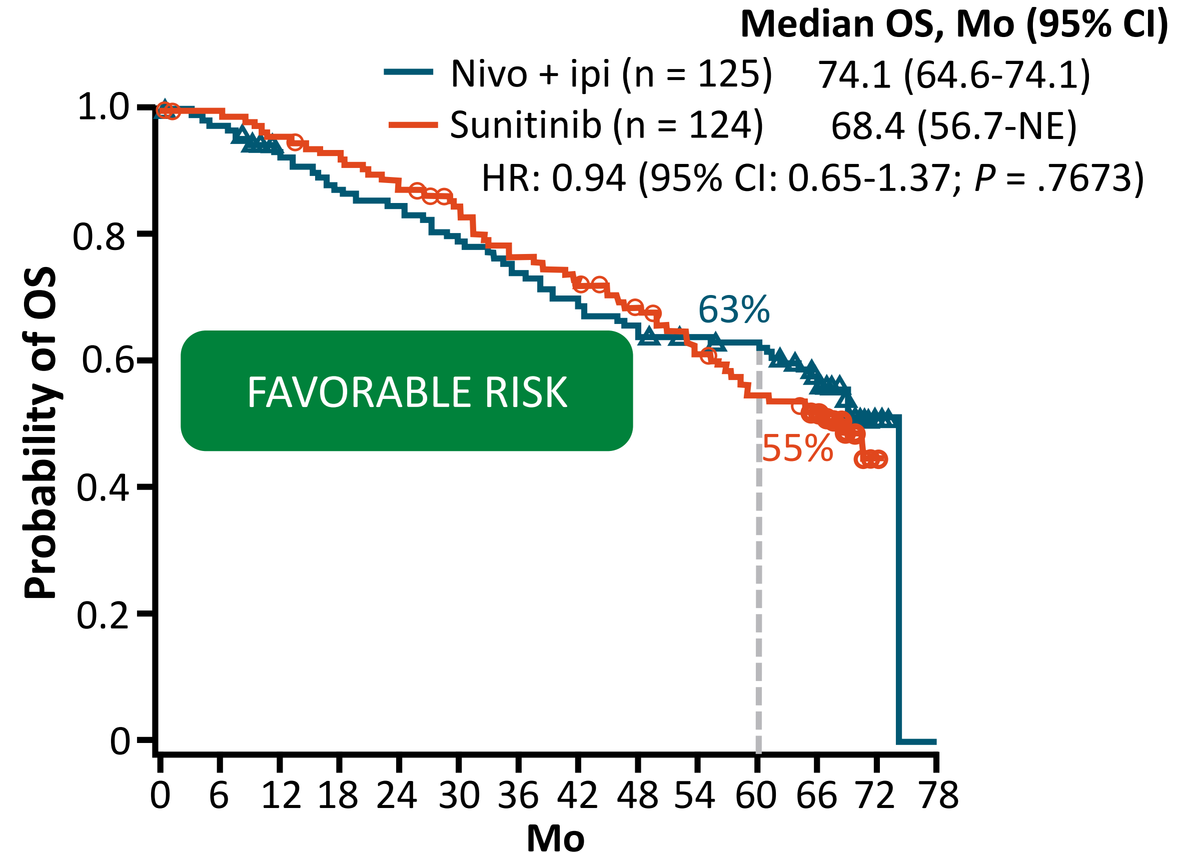
Updated at ASCO 2022:
Abstract 4502 assessing relationship between health-related QoL and clinical outcomes

Motzer. ESMO 2021. Abstr 661P.

CCO
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

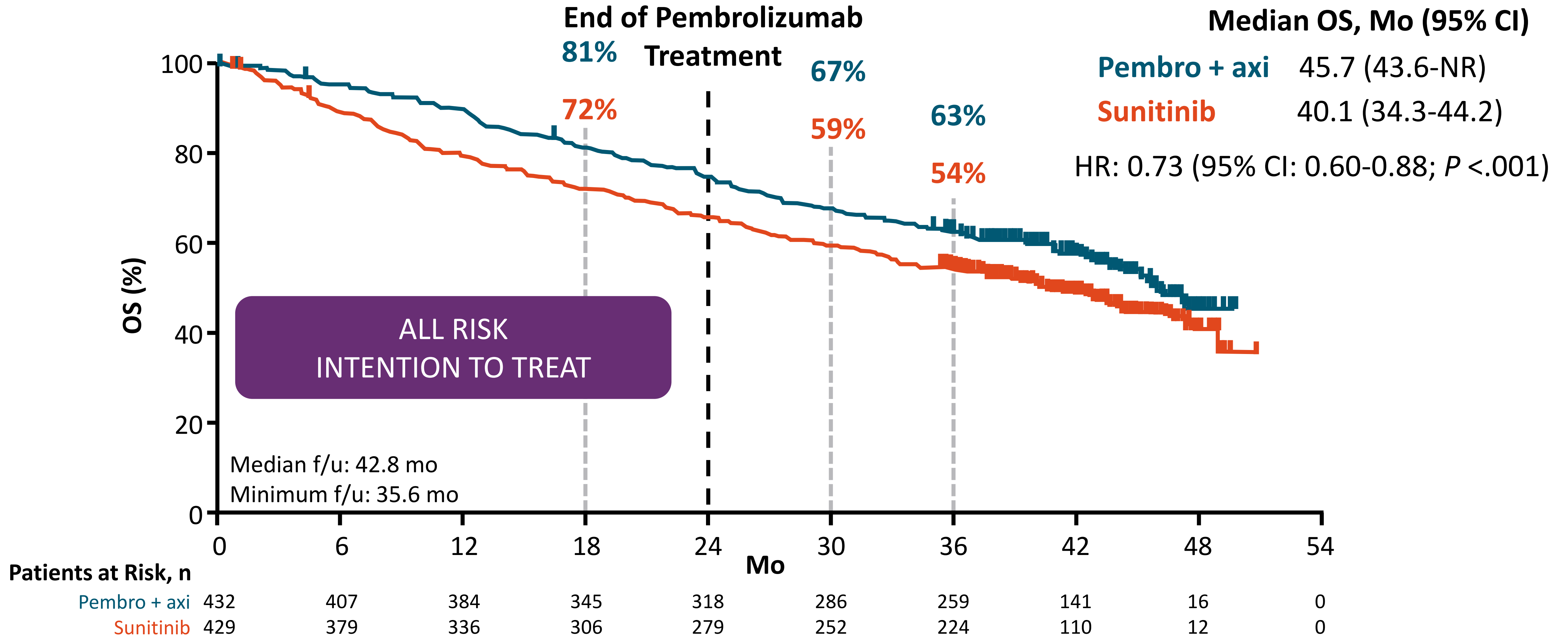
Nivo + ipi	125	121	112	105	102	96	89	84	78	75	73	59	3	0
Sunitinib	124	119	114	110	104	97	88	83	76	67	59	50	3	0

Minimum f/u: 5 yr

Motzer. ESMO 2021. Abstr 661P.

Slide credit: clinicaloptions.com

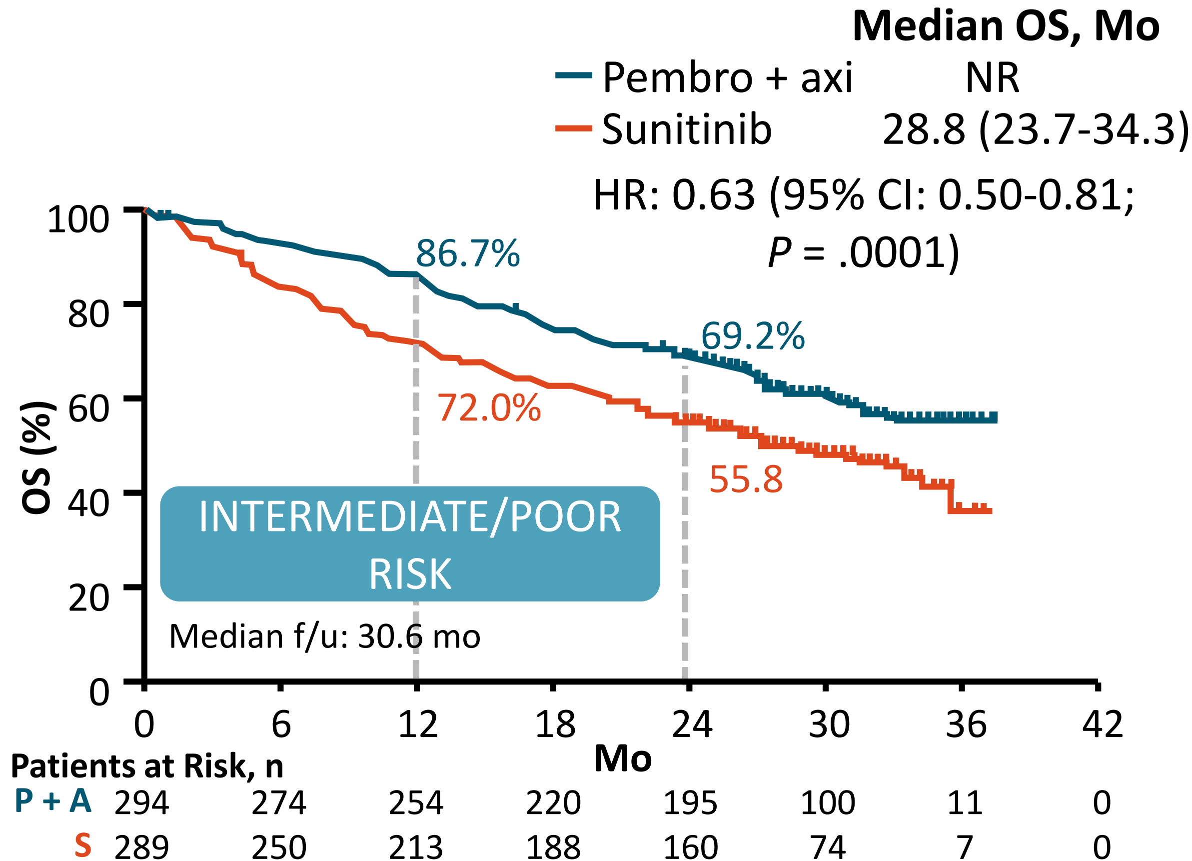
KEYNOTE-426: First-line Pembrolizumab + Axitinib vs Sunitinib in Advanced or Metastatic RCC

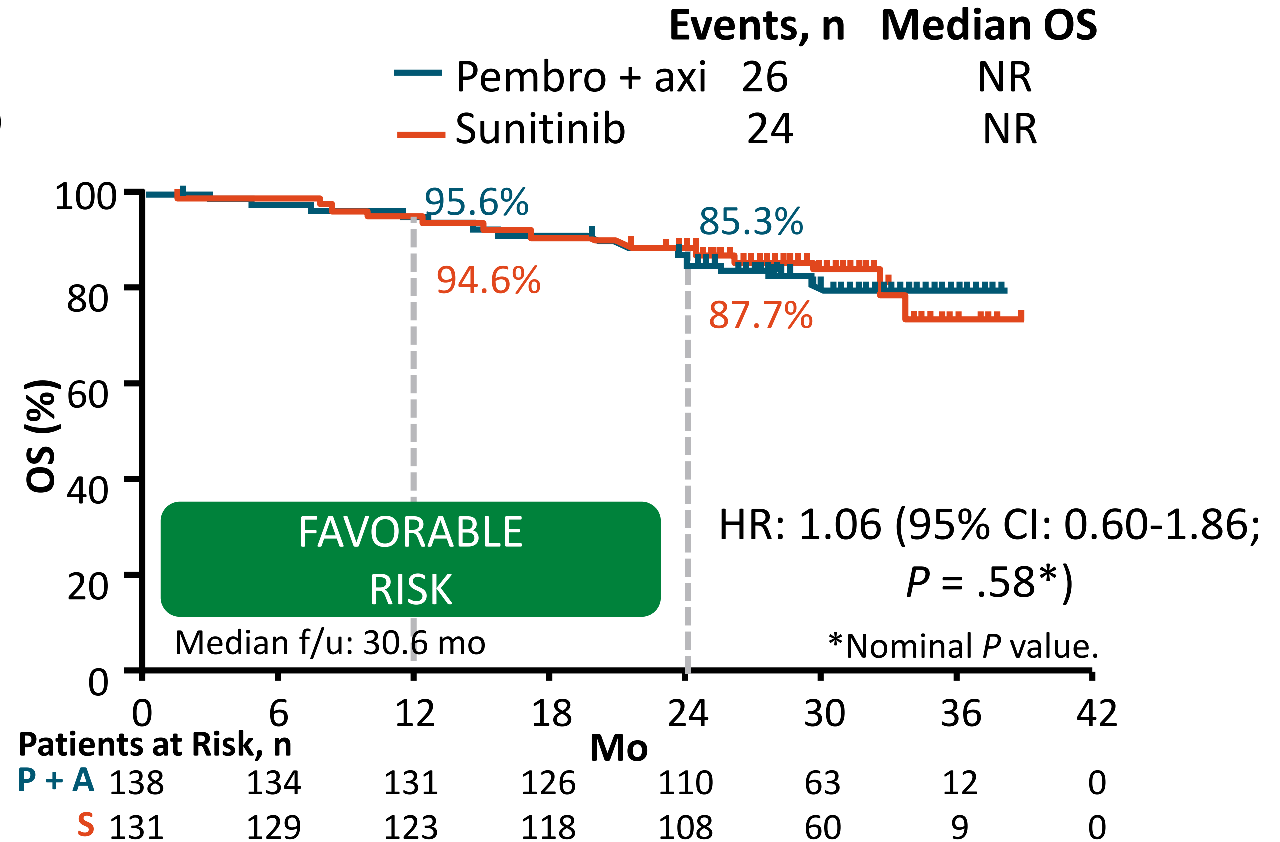


Rini. ASCO 2021. Abstr 4500.

Slide credit: clinicaloptions.com

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

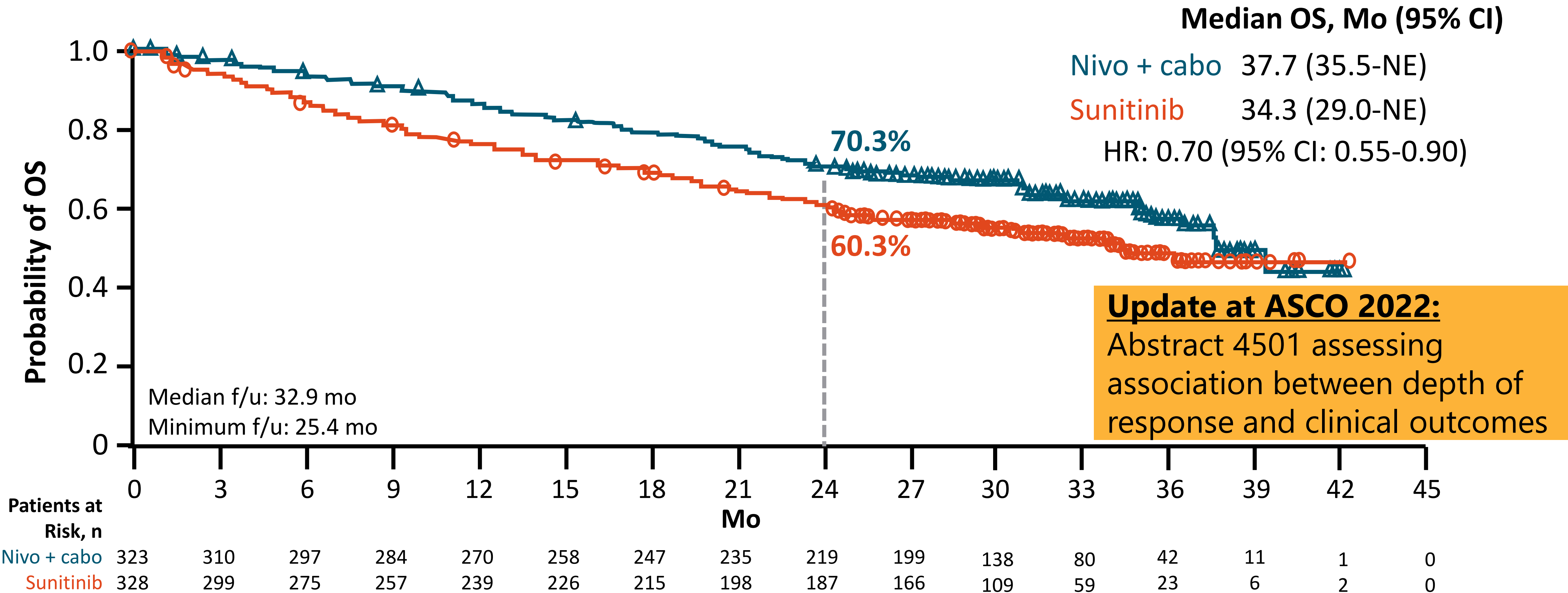




Powles. Lancet Oncol. 2020;21:1563.

Slide credit: clinicaloptions.com

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



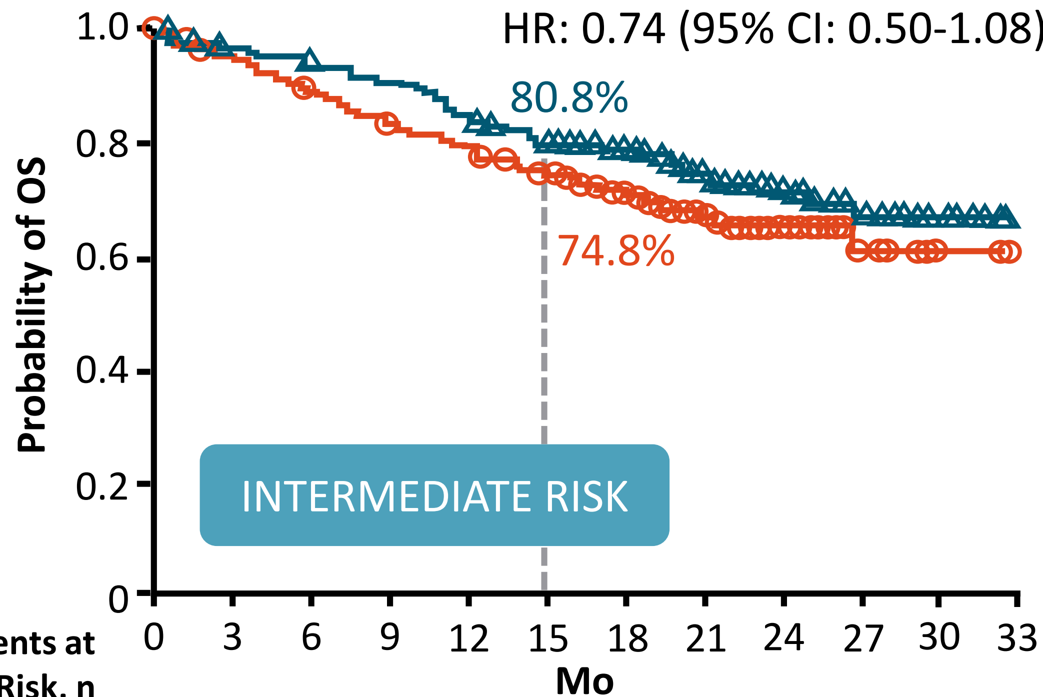
Powles. ASCO GU 2022. Abstr 350.

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

Median OS, Mo (95% CI)

Nivo + cabo	NR (NE)
Sunitinib	NR (NE)

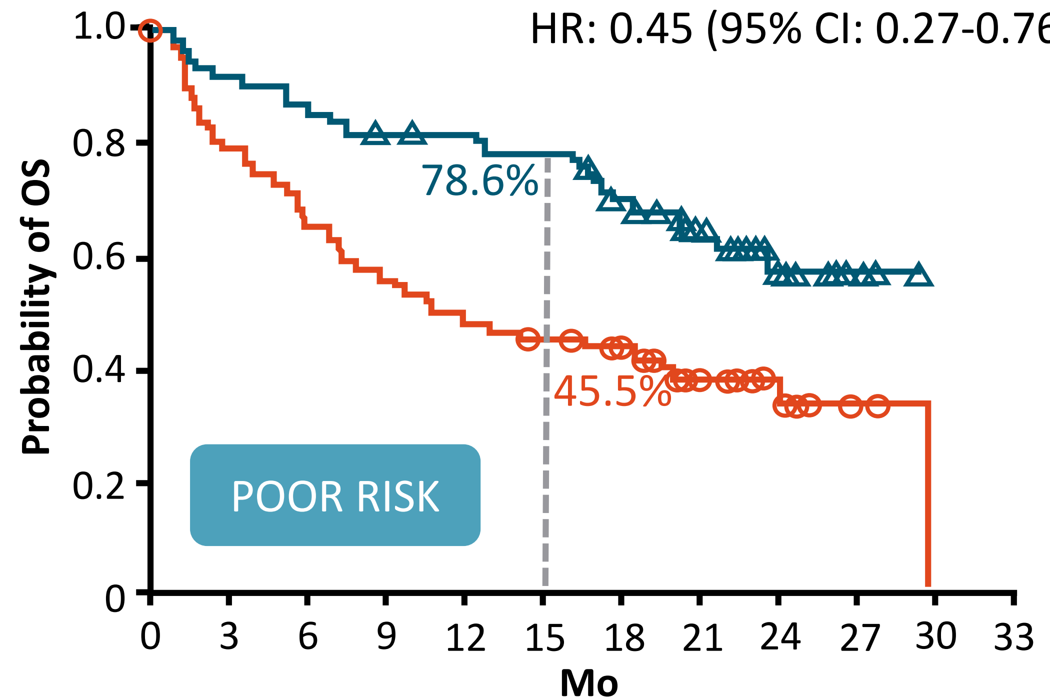
HR: 0.74 (95% CI: 0.50-1.08)



Median OS, Mo (95% CI)

Nivo + cabo	NR (21.4-NE)
Sunitinib	11.2 (6.8-19.8)

HR: 0.45 (95% CI: 0.27-0.76)



Patients at Risk, n

Intermediate risk:

	0	3	6	9	12	15	18	21	24	27	30	33
Nivo + cabo	188	178	173	166	154	145	126	84	49	21	7	0
Sunitinib	188	173	161	150	142	127	110	65	35	12	3	0

Poor risk:

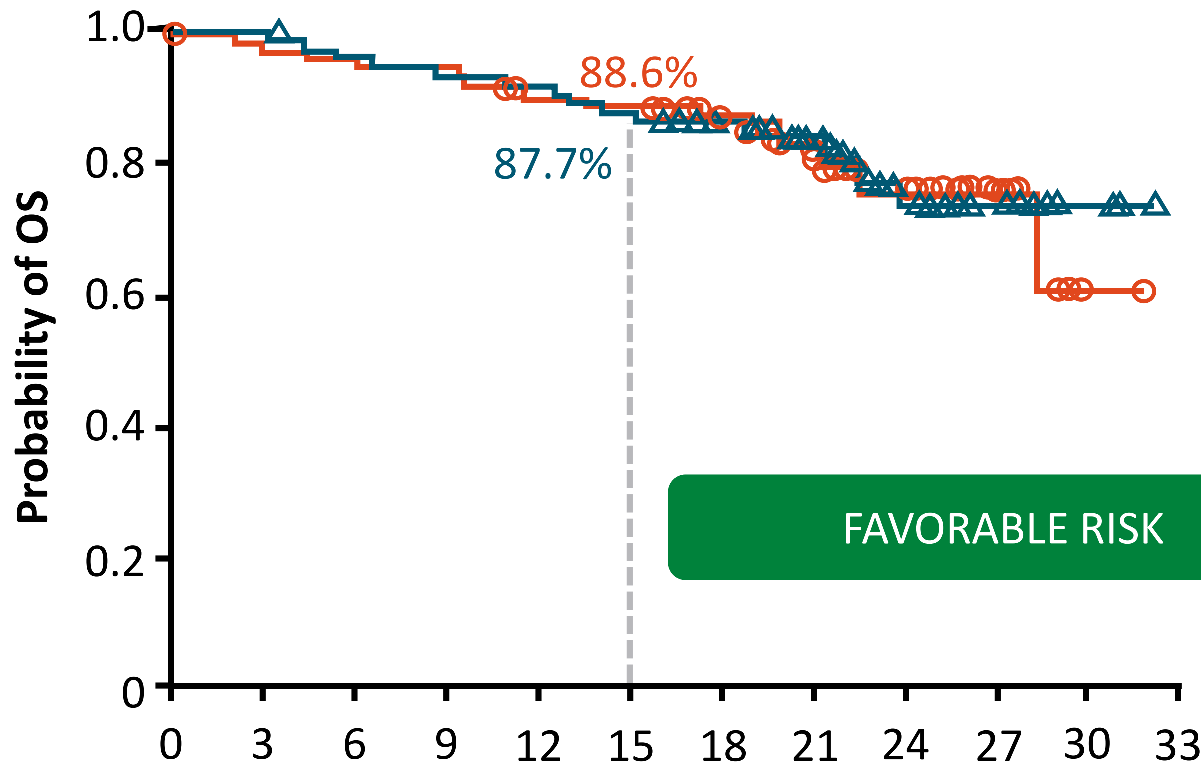
	0	3	6	9	12	15	18	21	24	27	30	33
Nivo + cabo	61	56	52	49	48	46	39	24	11	4	0	0
Sunitinib	68	52	43	37	32	29	25	15	7	2	0	0

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.

CCO
Slide credit: clinicaloptions.com

CLEAR: OS in Patient Subgroups

		Events/Participants Len + Pembro	Events/Participants Sunitinib	HR (95% CI)
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

SOME TAKE-AWAY MESSAGES

- ✓ Malgrés des taux de survie moindre comparés à ceux publiés dans la littérature,les résultats acompagant des traitement basés sur l'immunothérapie confirment le bénéfice en SG dans le ccRCC évolué.

- ✓ Pas de différence significative entre les combinations IO/IO vs IO/TKI en 1L dans les groupes à risque intermediaire / haut risque (la décision dépendra du volume tumoral, la toxicité atendue,, le cou et l'acces)

- ✓ Pour le groupe de bon pronostic,- surveillance, monotherapie sont des options raisonables en pratique courante

Merci pour vôtre attention