Mesa de Cáncer Renal: papel del tratamiento sistémico vs local

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Disclosures

- **Advisory Boards:**
  - MSD, BMS, Roche-Genentech, Janssen, Novartis, Bayer, Astellas
- **Research Funding:**
  - Roche-Genentech, Astellas, Pfizer
- **Travel expenses:**
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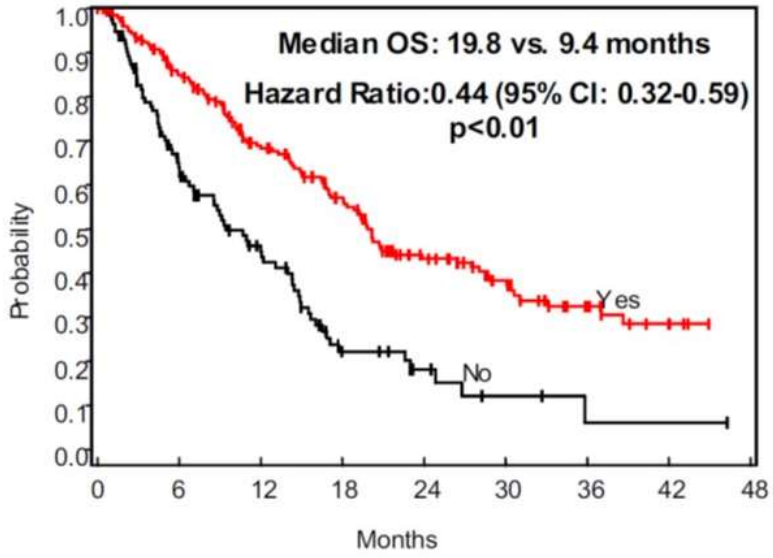
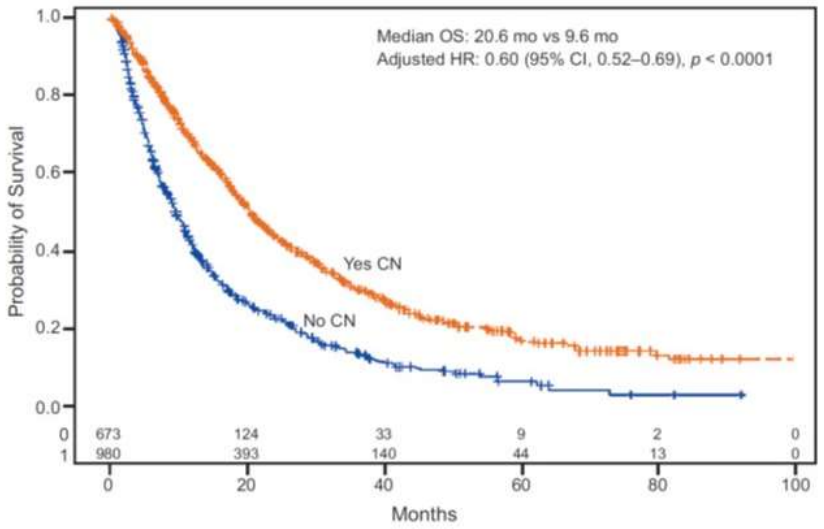
- **Clinical Trials:**
  - BMS, Roche-Genentech, Merck, EISAI, MSD, Gilead, Exelixis
- **Lectures:**
  - Astellas, Astra Zeneca, Janssen, MSD, Bayer, Pfizer, Eisai, Ipsen, Sanofi, Roche, BMS, Pierre Fabre, Merck

Targeted Therapy Era: Controversies and patients selection

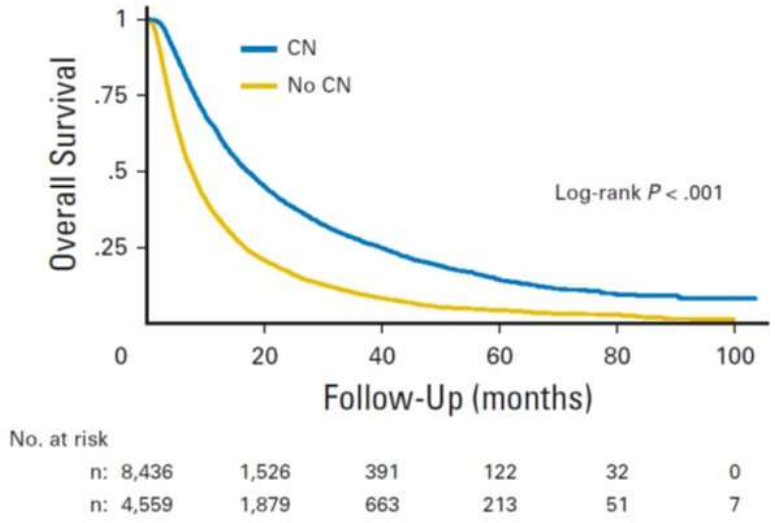
Choueiri et al, J Urol, 2011



Heng et al, Eur Urol, 2014



Hanna et al, JCO, 2016

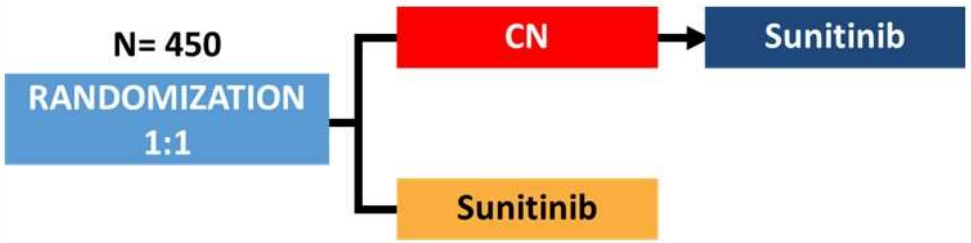


Caveats:

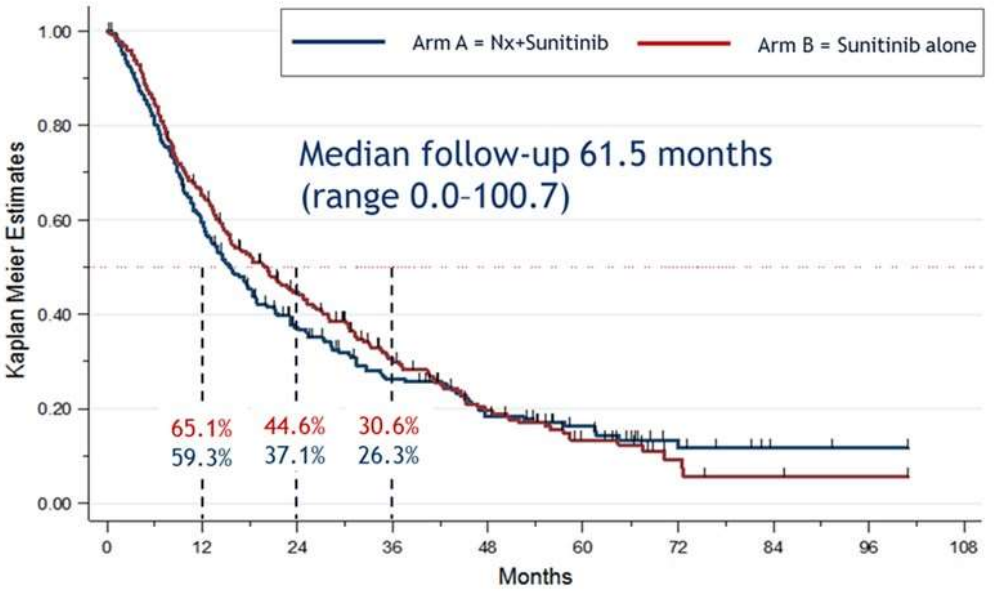
- Retrospective
- Inherent Selection Bias with CN

CARMENA-RCT: Gold Standard

Key Eligibility Criteria:
- Metastatic Clear Cell RCC
- Treatment-naive
- MSKCCC Int/Poor Risk Disease



Primary endpoint: Overall Survival
Design: Non-Inferiority (HR OS <1.20)
PI: Arnaud Méjean



Potential Caveats:

- Lower Median OS than expected in both arms
- Potential benefit to CN in patients w/ IMDC criteria= 1

Mejean et al. ASCO 2019
Motzer et al .NEJM 2018

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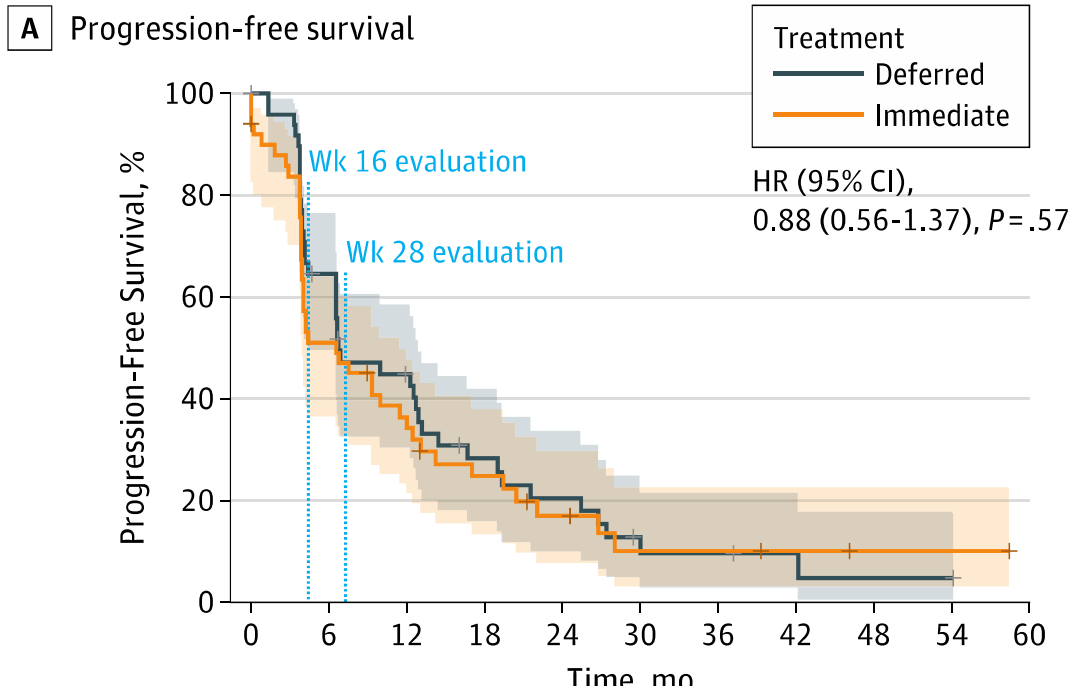
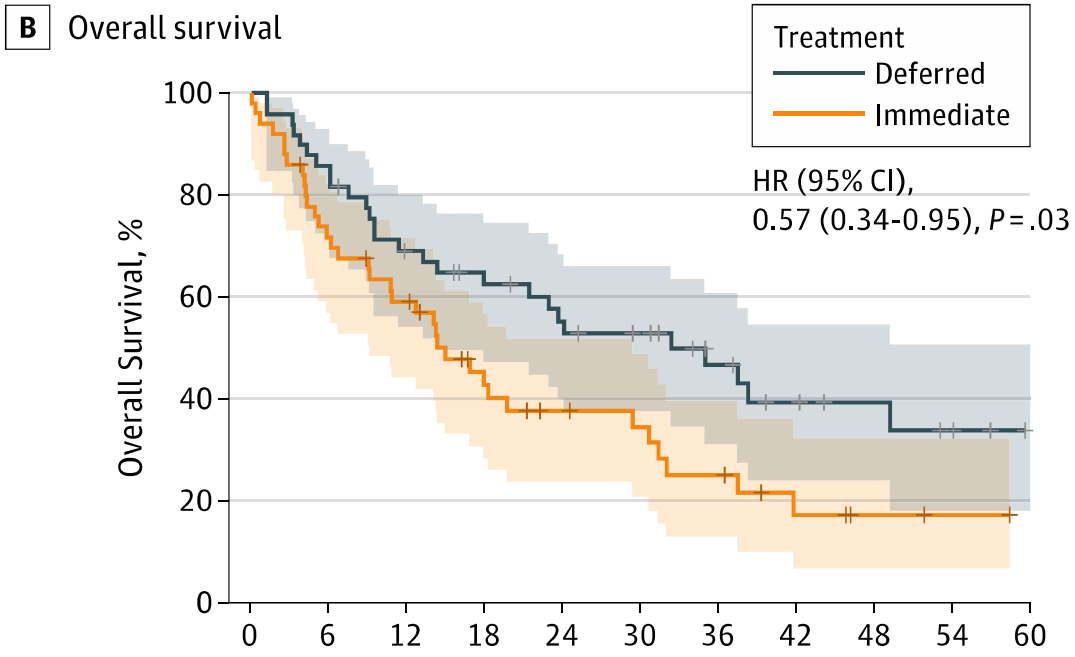
SURTIME trial





Bex et al. JAMA Oncol 2018

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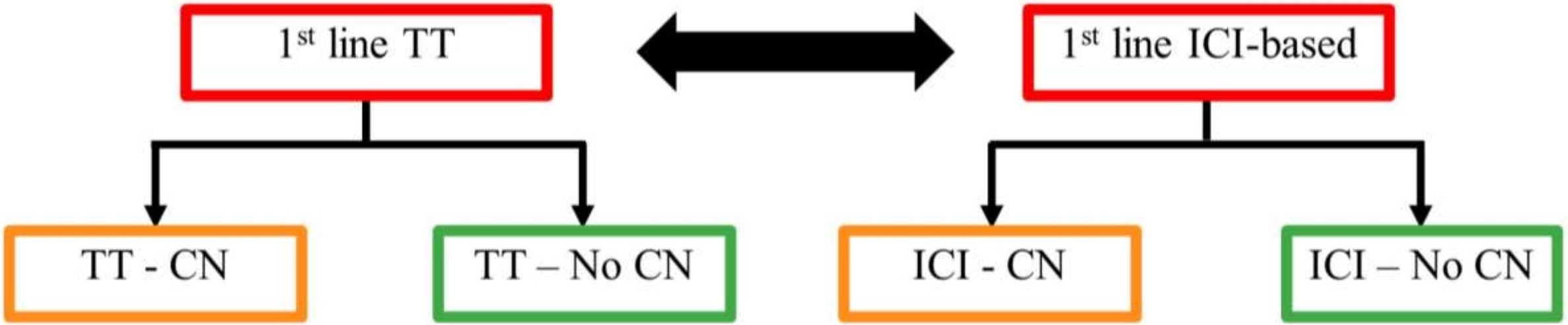
Questions today (2023)

1) Is there still a benefit to CN in the ICI Era?

2) How does this benefit compare to that in the TT Era?



Mejean et al. ASCO 2019
Motzer et al .NEJM 2018

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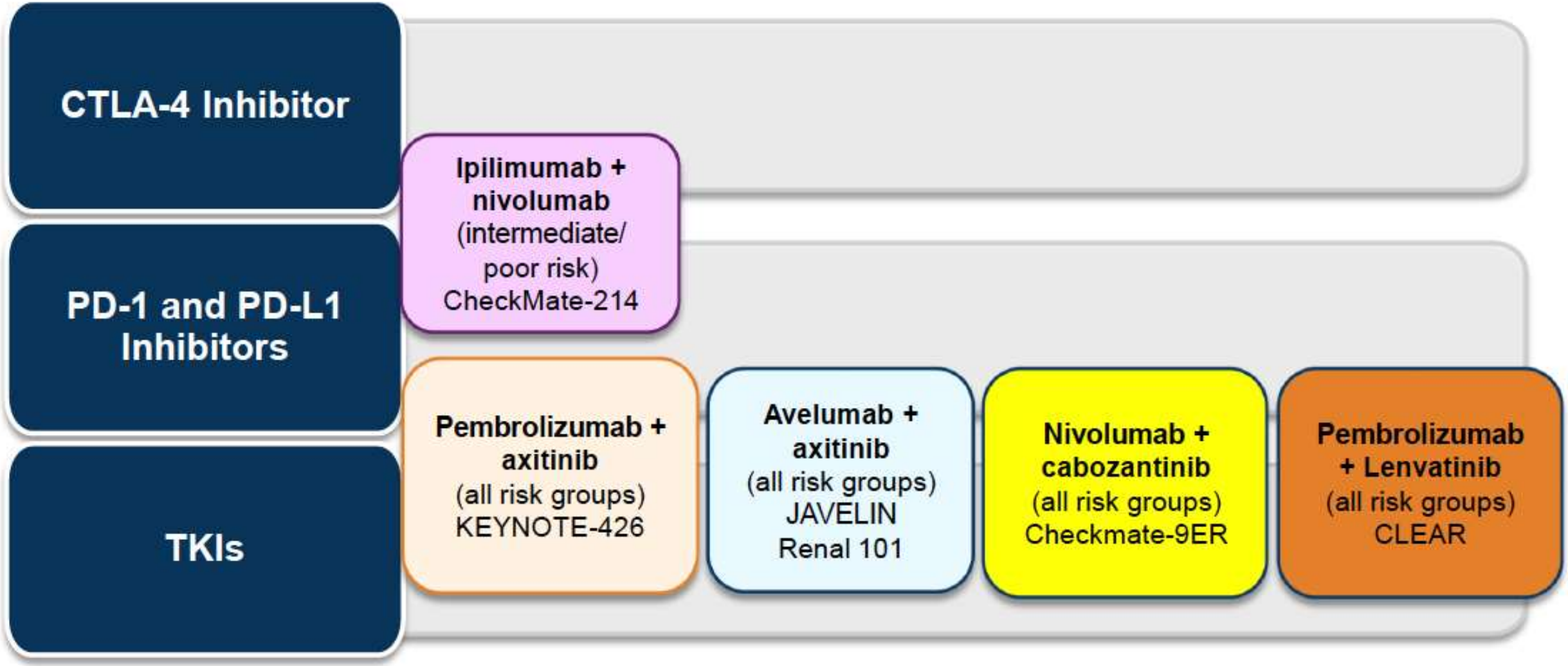
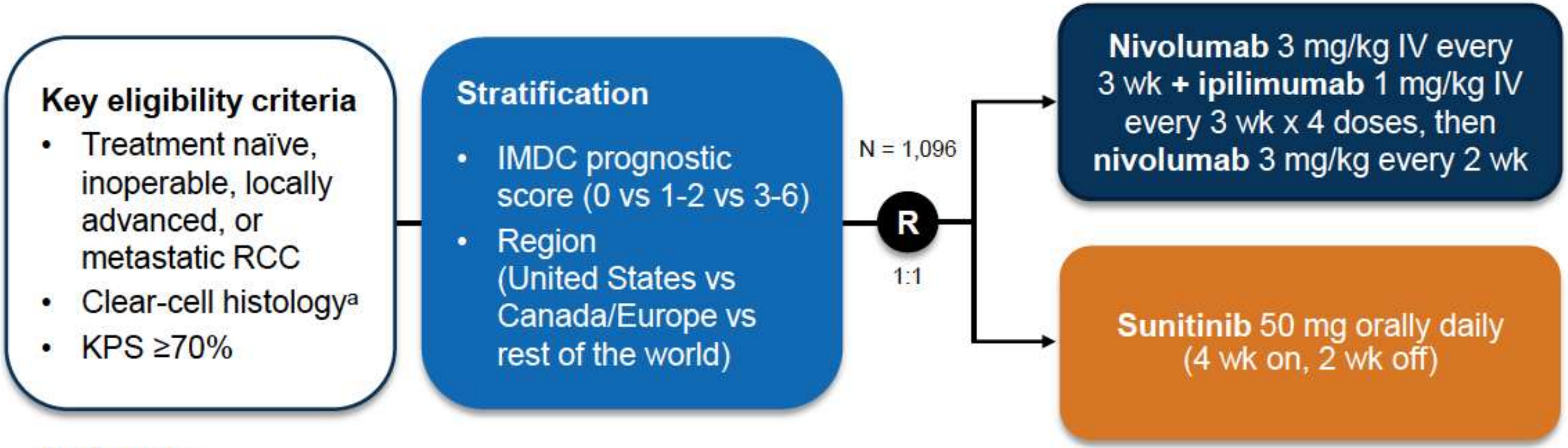
First-line combination therapies in advanced RCC



CheckMate-214: Nivolumab plus Ipilimumab in 1L mRCC



Endpoints

- **Coprimary:** PFS, OS, ORR (intermediate/poor risk)
- **Secondary:** PFS, OS, ORR (ITT)
- **Exploratory:** PFS, OS, ORR (favorable risk)

Escudier B, et al. ESMO 2017
Motzer R, et al. NEJM 2018
Motzer R, et al. Lancet Oncol 2019

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IO-VEGF combos in mRCC

*KEYNOTE 426[1]	Treatment-naive clear-cell RCC (N = 861)	**Pembrolizumab** 200 mg IV Q3W + **Axitinib** 5 mg PO BID **Sunitinib** 50 mg PO QD (4/2)	1º EP: PFS/OS
JAVELIN Renal 101[2]	Treatment-naive clear-cell RCC (N = 886)	**Avelumab** 10 mg/kg IV Q2W + **Axitinib** 5 mg PO BID in 6-wk cycles **Sunitinib** 50 mg PO (4/2)	1º EP: PFS/OS PD-L1⁺ pts
*CM 9ER[3]	Treatment-naive clear cell RCC (N = 651)	**Nivolumab** 240 mg Q2W IV + **Cabozantinib** 40mg PO QD **Sunitinib** 50 mg (4/2)	1º EP: PFS
*CLEAR[4]	Treatment-naive clear cell RCC (N = 1069)	**Pembrolizumab** 200 mg Q3W IV + Lenvantinib 20mg PO QD **Everolimus** 5 mg PO QD + **Lenvatinib** 18 mg PO QD **Sunitinib** 50 mg (4/2)	1º EP: PFS/OS

*With OS at 1st analysis!

Rini B, et al .NEJM 2019; Motzer R, et al. NEJM 2019; Choueiri T, et al. NEJM 2021; Motzer R, et al. NEJM 2021

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Baseline characteristics in 1L mRCC phase III are different

	KEYNOTE-426[1]	CLEAR[2]	CheckMate 214[3]	CheckMate 9ER[4]
	Axi + Pembro N=432	Len + Pembro N=355	Nivo + Ipi N=550	Cabo + Nivo N=323
IMDC Risk Group, %				
Favorable	32	31	23	23
Intermediate	55	59	61	58
Poor	13	9	17	19
ECOG 0 % or KPS 90-100 %	80.3[5]	83	68.6 (I/P)[6]	80
Sarcomatoid features, %	18	8	14	11
Prior Nephrectomy, %	83	74	82	69
≥ 2 organs with metastasis, %	73	72	78	80
Liver Metastasis, %	15	17	18	23
Bone Metastasis, %	24	24	20	24

Rini B, et al .NEJM 2019; Motzer R, et al. NEJM 2021; Albiges L, et al. Ann Oncol 2020; Choueiri T, et al. NEJM 2021

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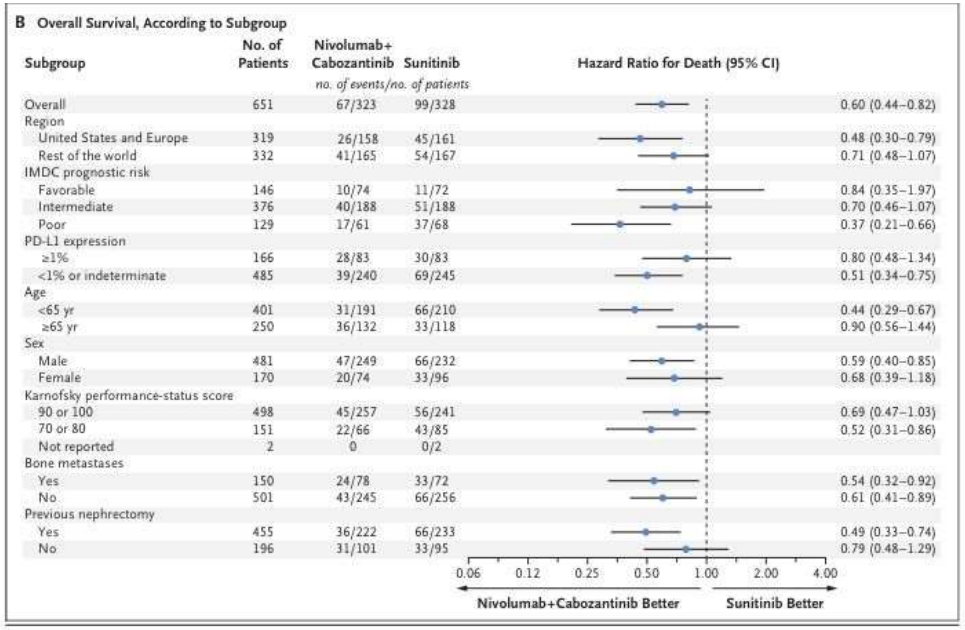
First line trials comparison: updated results after ASCO 2023

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
OS HR mOS, months	**0.72** 55.7 vs 38.4	**0.84** 47.2 vs 40.8	**0.70** 49.5 vs 35.5	**0.79** 53.7 v. 54.3
Landmark OS	**60%** at 3 years (est.) **48%** at 5 years	**63%** at 3 years **42%** at 5 years	**59%** at 3 years	**66%** at 3 years
PFS HR mPFS, months	**0.86** **12.3** vs 12.3	**0.69** **15.7** vs 11.1	**0.59** **16.6** vs 8.4	**0.47** **23.9** vs 9.2
Landmark PFS	32% (3 years; est.) 30% (5 years)	29% (3 years) 18% (5 years)	23% (3 years)	37% (3 years)
ORR, %	**39** vs 32	**61** vs 40	**56** vs 28	**71** vs 37
CR, %	**12** vs 3	**12** vs 4	**13** vs 5	**18** vs 4
Med f/u, months	**68**	**67**	**44**	**48**
Primary PD, %	**18**	**12**	**7**	**5**

Motzer R, et al. NEJM 2018; Motzer R, et al. ESMO 2021; Rini B, et al. ASCO 2023; Motzer R, et al. NEJM 2021; Burotto et al. CITIM 2023; Hudson T, et al. ASCO 2023

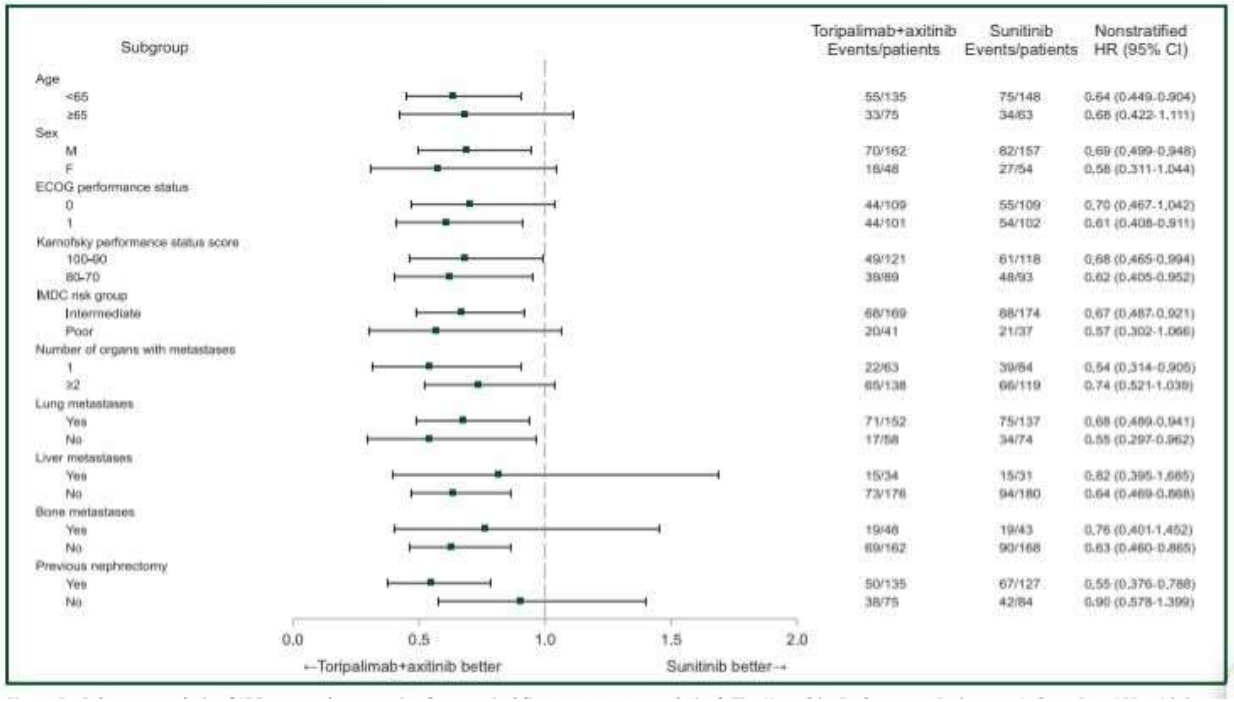
First line trials comparison: updated results after ASCO 2023

Subgroup	Nivolumab + Ipilimumab	Sunitinib	Hazard Ratio for Death (95% CI)
	no. of deaths/no. of patients		
Previous nephrectomy			
Yes	103/341	127/319	0.69 (0.53–0.89)
No	37/84	61/103	0.63 (0.42–0.94)



B Overall Survival, According to Subgroup

Subgroup	No. of Patients	Nivolumab+ Cabozantinib	Sunitinib	Hazard Ratio for Death (95% CI)
		no. of events/no. of patients		
Overall	651	67/323	99/328	0.60 (0.44–0.82)
Region				
United States and Europe	319	26/158	45/161	0.48 (0.30–0.79)
Rest of the world	332	41/165	54/167	0.71 (0.48–1.07)
IMDC prognostic risk				
Favorable	146	10/74	11/72	0.84 (0.35–1.97)
Intermediate	376	40/188	51/188	0.70 (0.46–1.07)
Poor	129	17/61	37/68	0.37 (0.21–0.66)
PD-L1 expression				
≥1%	166	28/83	30/83	0.80 (0.48–1.34)
<1% or indeterminate	485	39/240	69/245	0.51 (0.34–0.75)
Age				
<65 yr	401	31/191	66/210	0.44 (0.29–0.67)
≥65 yr	250	36/132	33/118	0.90 (0.56–1.44)
Sex				
Male	481	47/249	66/232	0.59 (0.40–0.85)
Female	170	20/74	33/96	0.68 (0.39–1.18)
Karnofsky performance-status score				
90 or 100	498	45/257	56/241	0.69 (0.47–1.03)
70 or 80	151	22/66	43/85	0.52 (0.31–0.86)
Not reported	2	0	0/2	
Bone metastases				
Yes	150	24/78	33/72	0.54 (0.32–0.92)
No	501	43/245	66/256	0.61 (0.41–0.89)
Previous nephrectomy				
Yes	455	36/222	66/233	0.49 (0.33–0.74)
No	196	31/101	33/95	0.79 (0.48–1.29)



Motzer R, et al. NEJM 2018; Motzer R, et al. ESMO 2021; Rini B, et al. ASCO 2023; Motzer R, et al. NEJM 2021; Burotto et al. CITIM 2023; Hudson T, et al. ASCO 2023

Clinical case Nº1

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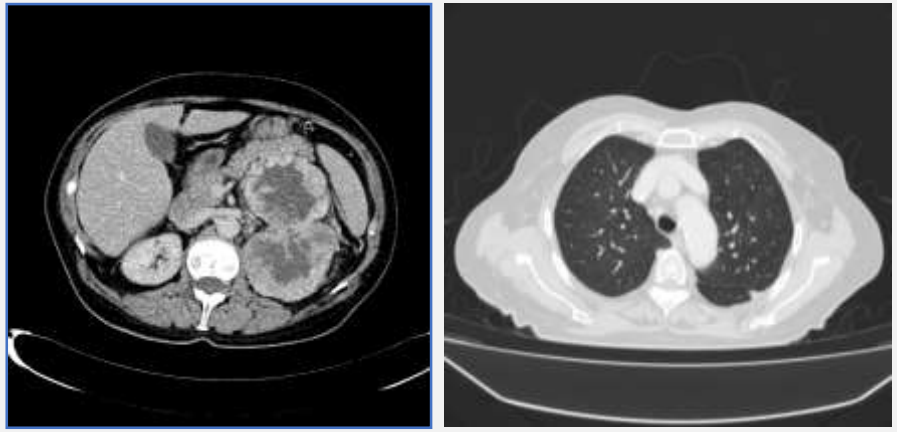
María

- White, female
- Age: 67 years
- ECOG: PS 1
- BMI: 28 kg/m2

Lifestyle: Single, lives alone
Employment status/job: Retired bank employee
Family history of cancer: Yes, father lung cancer (smoker)

Comorbidities:
DM2, hypothyroidism
Concomitant medications:
Alprazolam, levothyroxine, metformine

- **Asthenia, moderate pain**
- **Clear cell carcinoma T3N0M1**
- **Lung metastases**
- **Intermediate IMDC (1 factor)**



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Clinical case Nº2

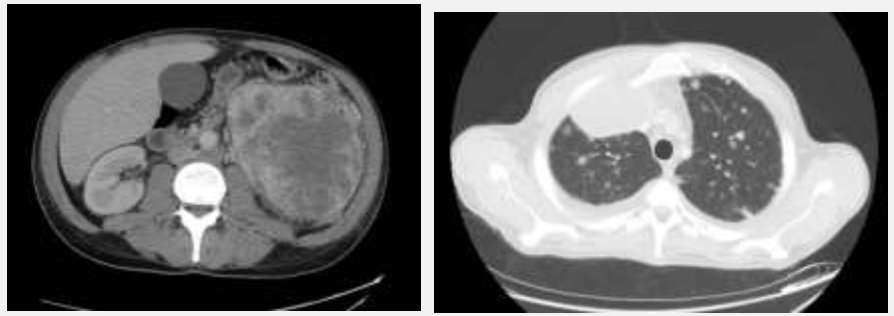
Guillermo

- White, male
- Age: 71 years
- ECOG: PS 1
- BMI: 24 kg/m2

Lifestyle: Married, 3 sons
Employment status/job: Builder employee
Family history of cancer: Yes, father prostate cancer (78y)

Comorbidities:
Hypertension, COPD, DM2
Concomitant medications:
Lisinopril, inhalers, Insulin

- **Moderate pain, weight loss**
- **Clear cell carcinoma with sarcomatoid component (20%)**
- **Lung & nodal metastases**
- **Poor-risk IMDC (3 factors)**



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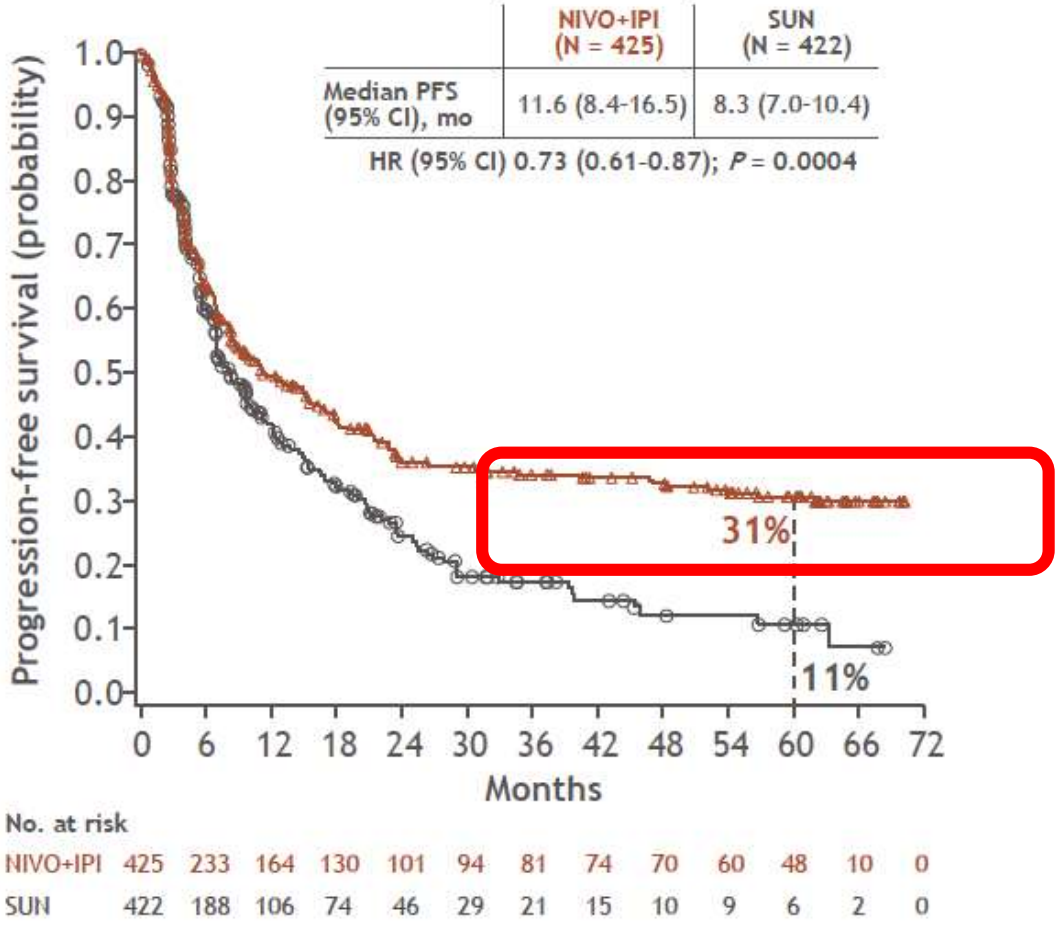
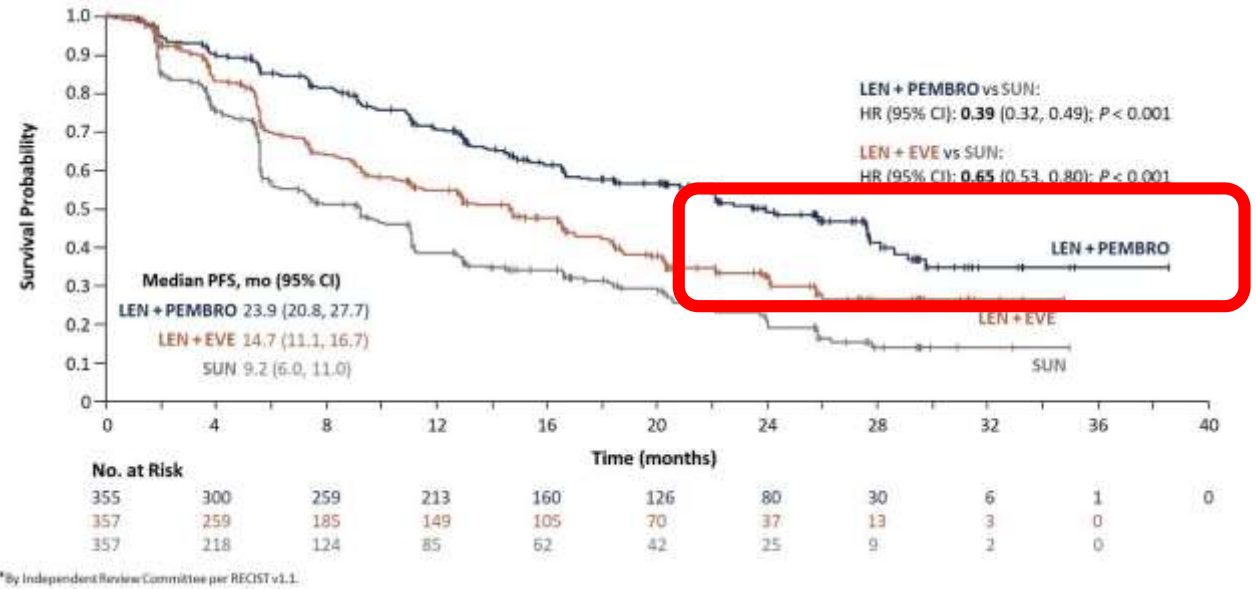
Durable responses





1. Motzer R, et al. NEJM 2018; 2. Motzer R, et al. Cancer 2022; 3. Motzer R, et al. NEJM 2021; 4. Porta C, et al. ESMO 2022; 5. Choueiri T, et al. NEJM 2021; 6. Motzer R, et al. Lancet Oncol 2022; 7. Rini B, et al. NEJM 2019; 8. Powles T, et al. Lancet Oncol 2020

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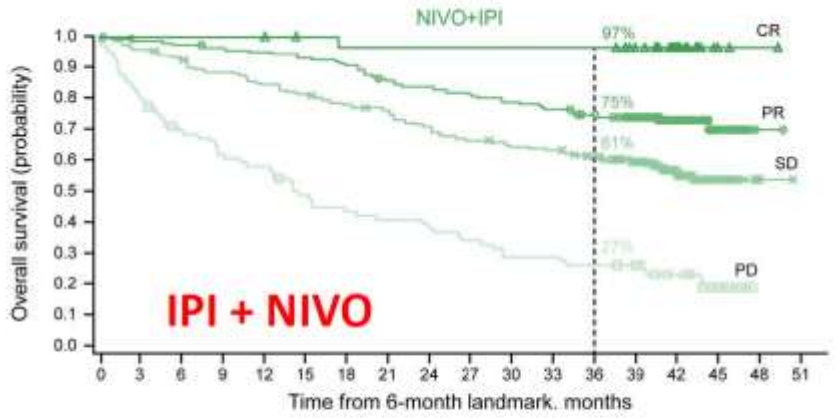
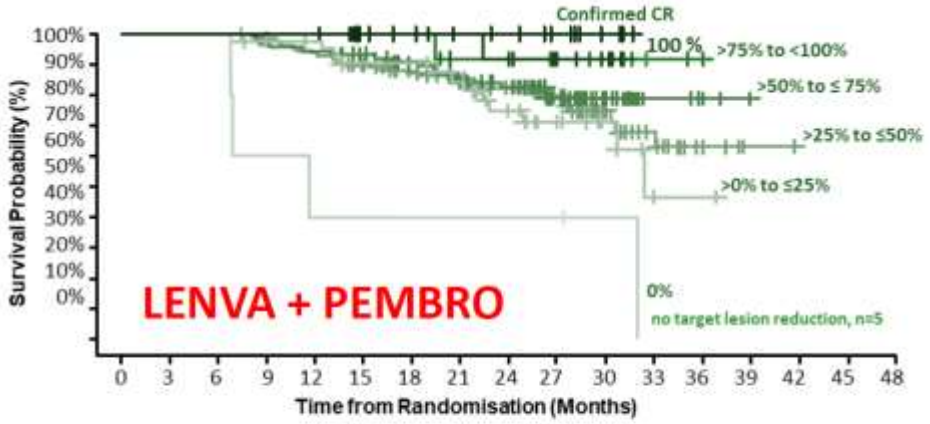
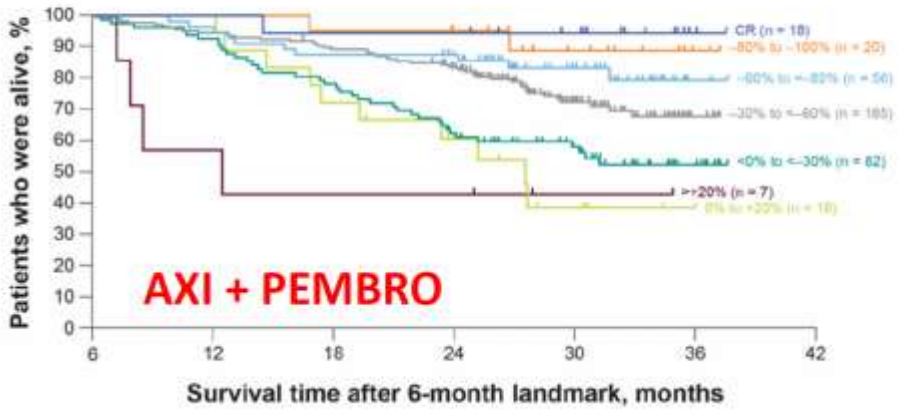
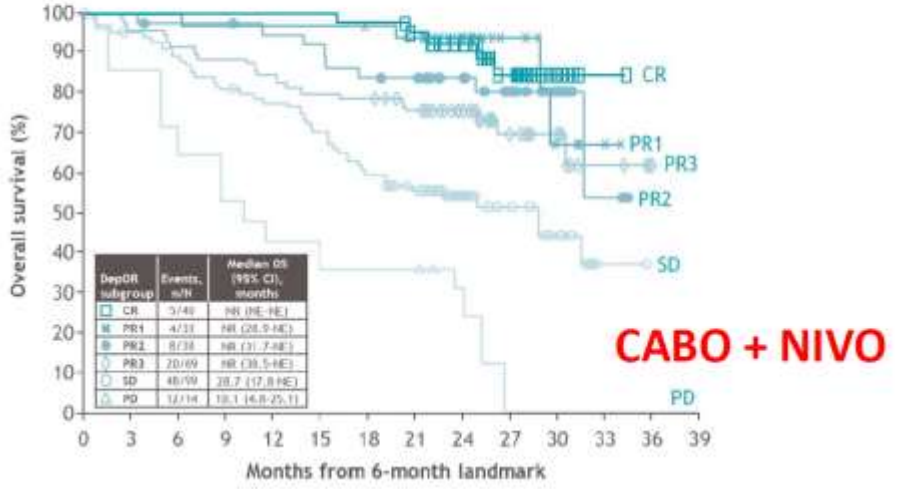
Association ORR with outcomes









1. Motzer R, et al. NEJM 2018; 2. Motzer R, et al. Cancer 2022; 3. Motzer R, et al. NEJM 2021; 4. Porta C, et al. ESMO 2022; 5. Choueiri T, et al. NEJM 2021; 6. Motzer R, et al. Lancet Oncol 2022; 7. Rini B, et al. NEJM 2019; 8. Powles T, et al. Lancet Oncol 2020; Suárez C, et al. ASCO 2022.

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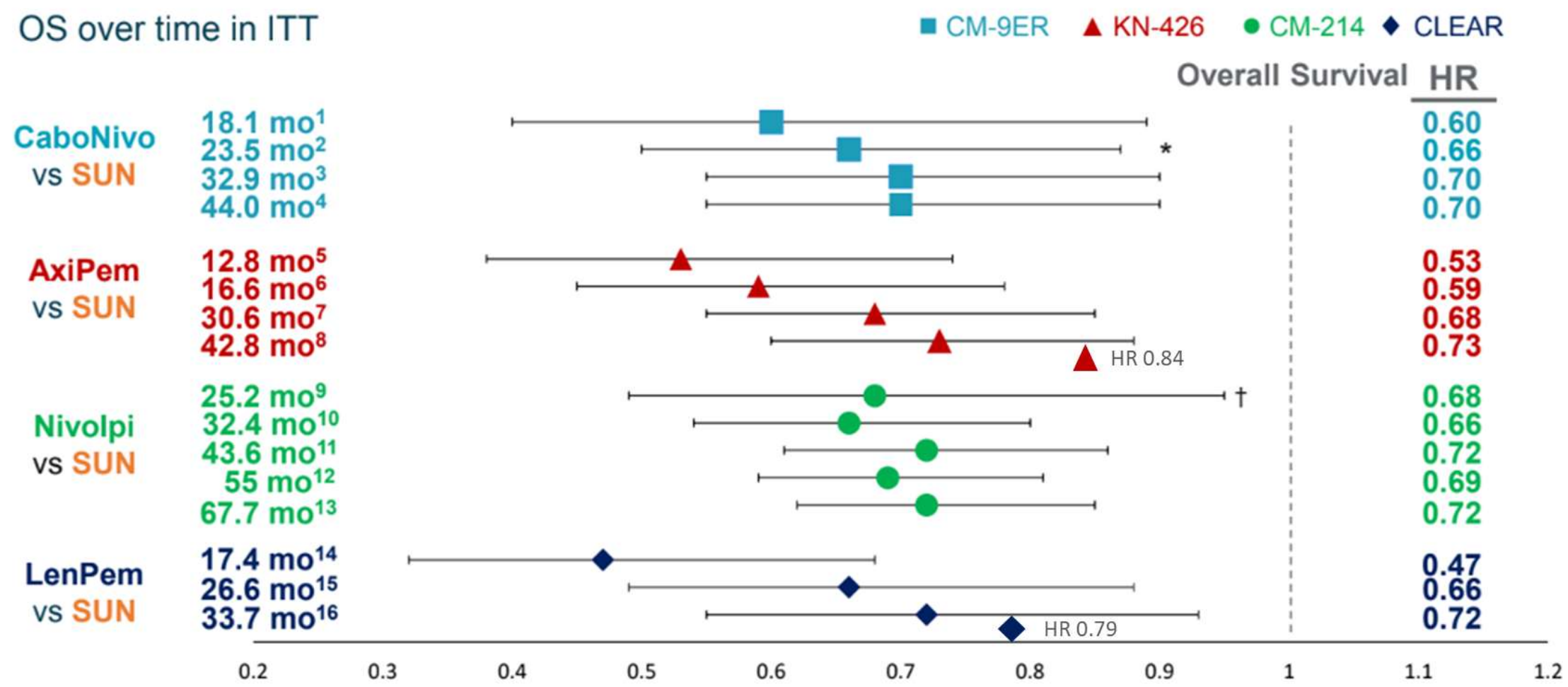
IO-VEGF combos in mRCC



Rini B, et al .NEJM 2019; Motzer R, et al. NEJM 2019; Choueiri T, et al. NEJM 2021; Motzer R, et al. NEJM 2021

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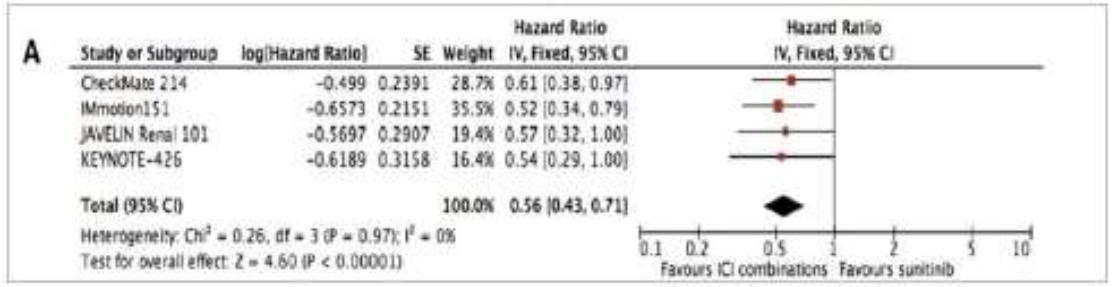
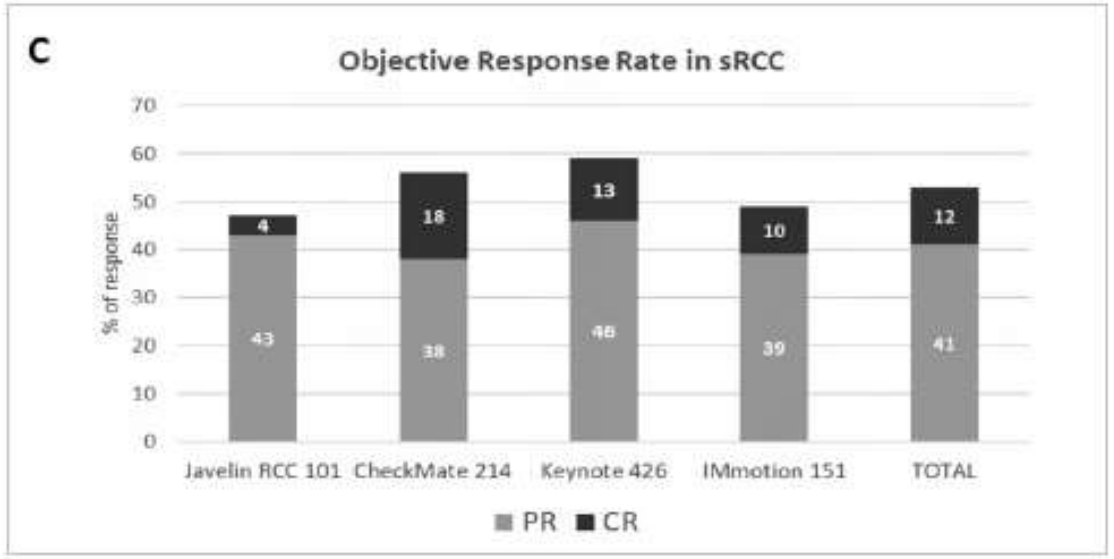
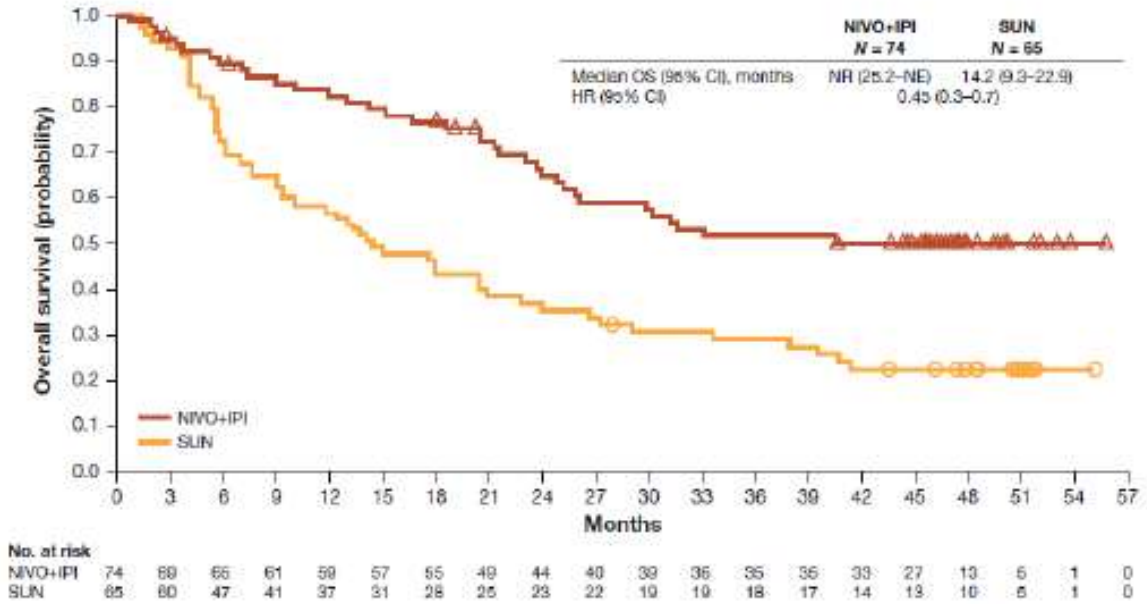
Meta-analisis showed superior outcome for IO-combos in sarcomatoid RCC







Iacovelli R, et al. Eur Urol Cancer 2020; Tannir N, et al. Clin Cancer Res 2021

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Long-term outcomes with Nivo-Ipi in sarcomatoid RCC

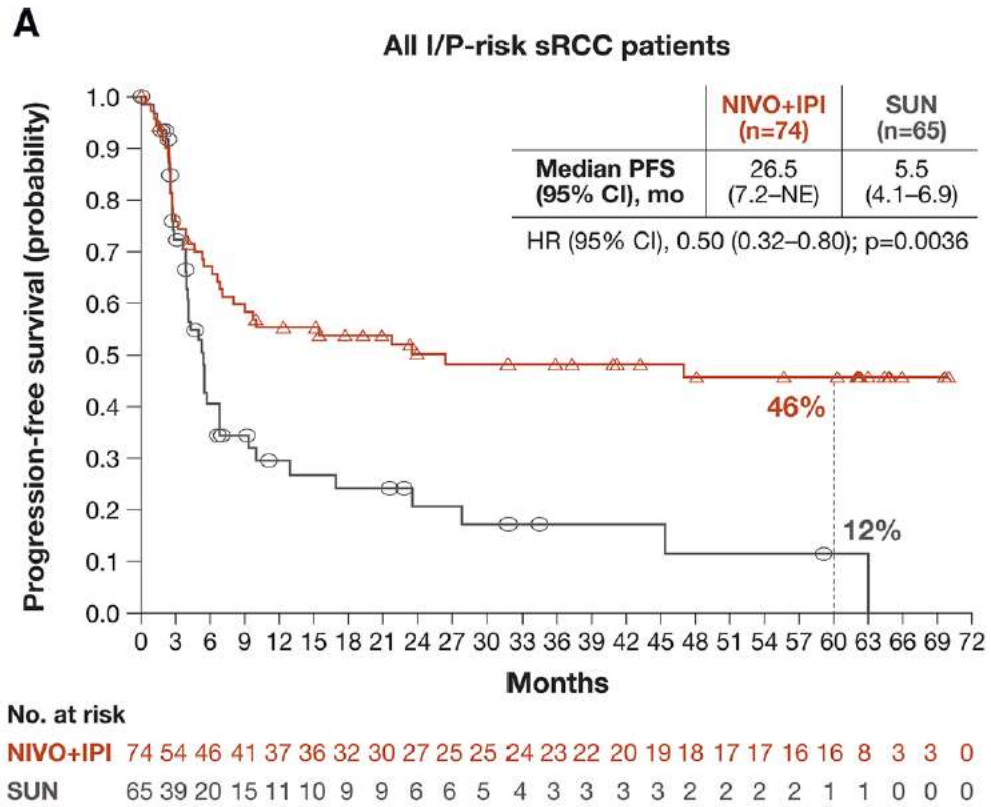
Table 2 Best overall confirmed response per RECIST V.1.1 in all patients with IMDC I/P-risk sRCC and by tumor PD-L1 expression levels

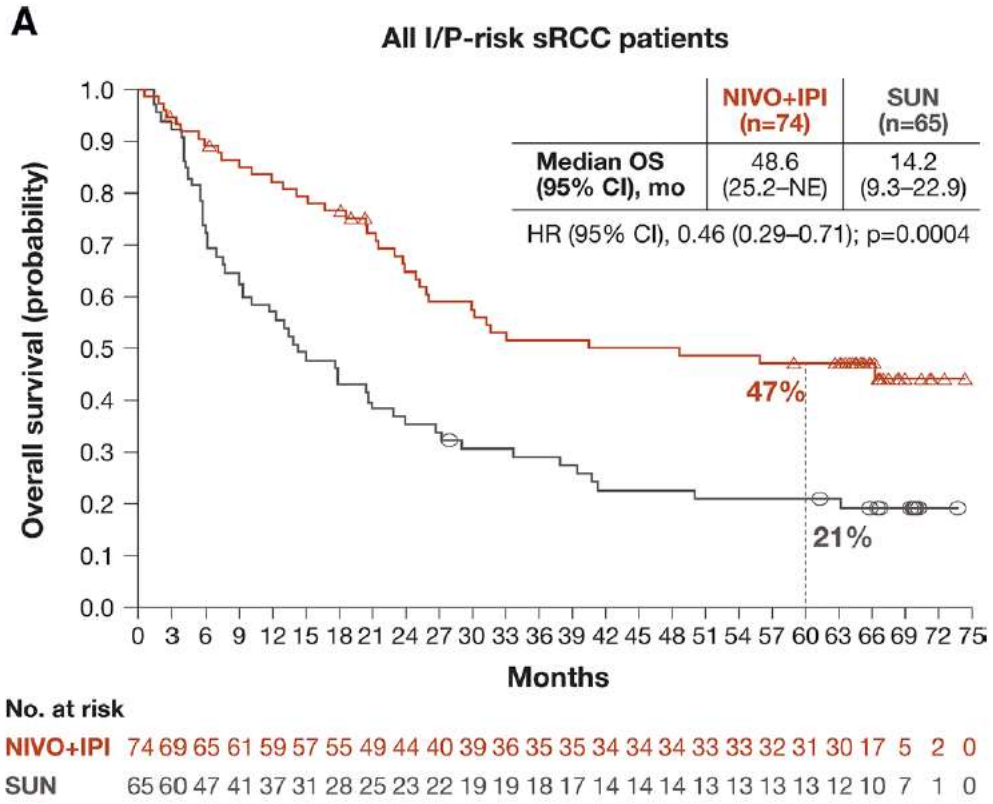
	Patients with I/P risk sRCC		Patients with I/P risk sRCC and PD-L1 ≥1		Patients with I/P risk sRCC and PD-L1 <1%	
	NIVO+IPI (n=74)	SUN (n=65)	NIVO+IPI (n=36)	SUN (n=33)	NIVO+IPI (n=35)	SUN (n=29)
Confirmed ORR (95% CI), %	60.8 (48.8 to 72.0)	23.1 (13.5 to 35.2)	69.4 (51.9 to 83.7)	24.2 (11.1 to 42.3)	54.3 (36.6 to 71.2)	20.7 (8.0 to 39.7)
P value	<0.0001		–		–	
Best overall response, n (%)						
Complete response	17 (23.0)	4 (6.2)	9 (25.0)	3 (9.1)	8 (22.9)	1 (3.4)
Partial response	28 (37.8)	11 (16.9)	16 (44.4)	5 (15.2)	11 (31.4)	5 (17.2)
Stable disease	8 (10.8)	28 (43.1)	4 (11.1)	13 (39.4)	4 (11.4)	13 (44.8)
Progressive disease	15 (20.3)	13 (20.0)	5 (13.9)	9 (27.3)	9 (25.7)	4 (13.8)
Unable to determine/not reported	6 (8.1)	9 (13.8)	2 (5.6)	3 (9.1)	3 (8.6)	6 (20.7)

I/P, intermediate/poor; NIVO+IPI, nivolumab plus ipilimumab; ORR, objective response rate; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; sRCC, sarcomatoid renal cell carcinoma; SUN, sunitinib.

Rini B, et al. J Immunother Cancer 2022

Long-term outcomes with Nivo-Ipi in sarcomatoid RCC

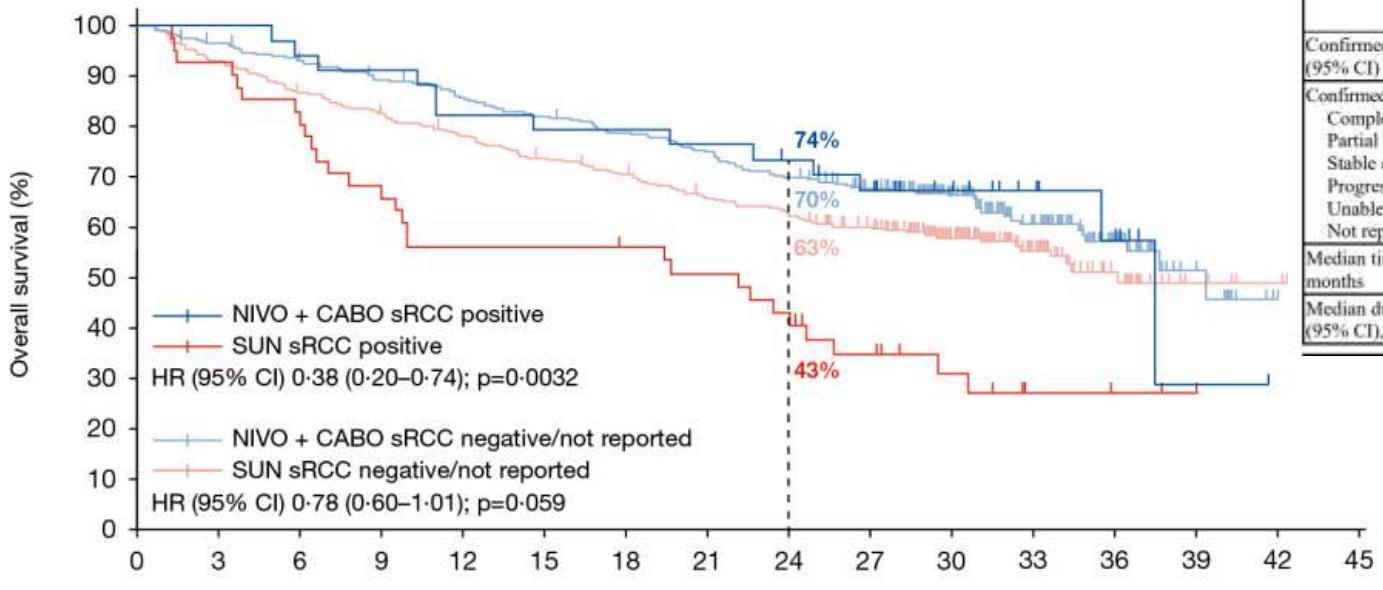




Rini B, et al. J Immunother Cancer 2022

Survival outcomes and ORR from phase III trial in patients with sRCC

A By sRCC status



Number at risk (number censored)																
NIVO + CABO sRCC positive	34 (0)	34 (0)	32 (0)	31 (0)	28 (0)	27 (0)	27 (0)	26 (0)	24 (1)	21 (2)	16 (7)	9 (14)	6 (16)	1 (20)	0 (21)	0 (21)
SUN sRCC positive	41 (0)	38 (0)	33 (0)	27 (0)	23 (0)	23 (0)	22 (1)	20 (1)	17 (1)	12 (3)	8 (6)	4 (9)	2 (11)	1 (12)	0 (13)	0 (13)
NIVO + CABO sRCC negative/not reported	289 (0)	276 (3)	265 (4)	253 (6)	242 (7)	231 (7)	220 (9)	209 (9)	195 (9)	178 (20)	122 (73)	71 (116)	36 (148)	10 (172)	1 (180)	0 (181)
SUN sRCC negative/not reported	287 (0)	261 (7)	242 (8)	230 (8)	216 (10)	203 (11)	193 (12)	178 (14)	170 (14)	154 (23)	101 (71)	55 (114)	21 (145)	5 (160)	2 (163)	0 (165)

Table S5: **Objective response in subgroups of clinical interest at baseline: sarcomatoid histology, metastasis**

Variable*	sRCC positive		sRCC negative/not reported	
	Nivolumab plus cabozantinib (n=34)	Sunitinib (n=41)	Nivolumab plus cabozantinib (n=289)	Sunitinib (n=287)
Confirmed objective response rate, % (95% CI)	59 (41–75)	22 (11–38)	55 (49–61)	29 (24–35)
Confirmed best overall response, n (%)				
Complete response	5 (15)	1 (2)	35 (12)	16 (6)
Partial response	15 (44)	8 (20)	125 (43)	68 (24)
Stable disease	10 (29)	10 (24)	95 (33)	124 (43)
Progressive disease	4 (12)	14 (34)	16 (6)	31 (11)
Unable to determine	0	8 (20)	18 (6)	47 (16)
Not reported	0	0	0	1 (<1)
Median time to response (IQR), months	2·8 (2·8–5·5)	3·9 (2·8–4·2)	2·8 (2·8–4·0)	4·4 (2·8–7·3)
Median duration of response (95% CI), months	NR (10·8–NE)	8·3 (2·8–15·2)	22·9 (18·6–27·6)	17·8 (10·9–23·5)

1. Motzer R, et al. NEJM 2018; 2. Motzer R, et al. Cancer 2022; 3. Motzer R, et al. NEJM 2021; 4. Porta C, et al. ESMO 2022; 5. Choueiri T, et al. NEJM 2021; 6. Motzer R, et al. Lancet Oncol 2022; 7. Rini B, et al. NEJM 2019; 8. Powles T, et al. Lancet Oncol 2020

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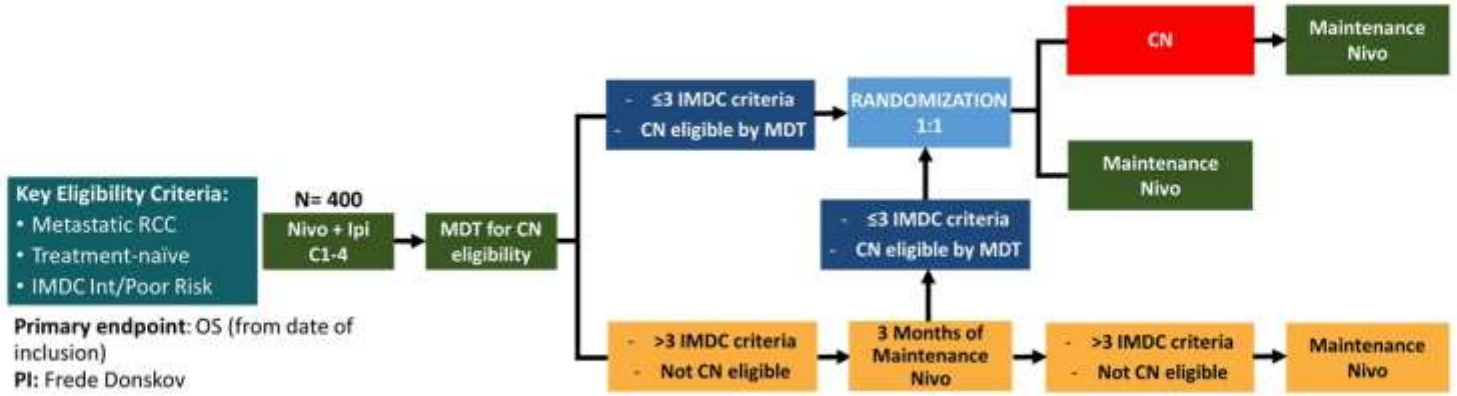
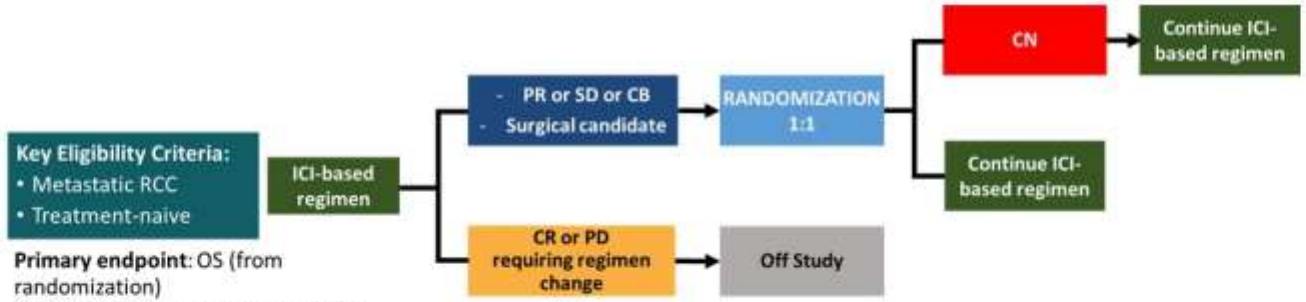
Ongoing studies

NORDIC-SUN (NCT03977571)



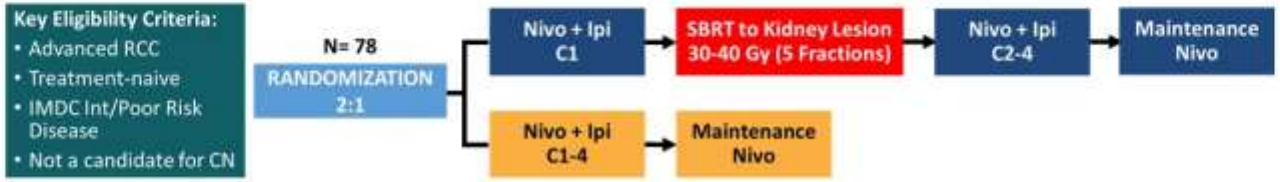
Primary endpoint: OS (from date of inclusion)
PI: Frede Donskov

PROBE Trial (SWOG – Under Development)



Primary endpoint: OS (from randomization)
PI: Ulka Vaishampayan & Hyung Kim

CYTOSHRINK (NCT04090710)



Primary endpoint: PFS
PI: Aly-Khan Lalani

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Key takeaways

- CN should rarely be performed in
  - Patients with poor risk disease.
  - Patients with rapidly progressive disease or high disease burden who need systemic therapy.

- Upfront CN should be considered in
  - Patients with Favorable/Intermediate risk disease who are candidates for active surveillance.
  - Candidates for oligo-metastasectomy → NED.
  - Symptomatic kidney masses.

- Deferred CN should be considered in patients with strong responses to systemic therapy.

Thanks

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