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6-7 JULIO 2023

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First line treatment (for mRCC)

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UNIVERSITÀ CATTOLICA del Sacro Cuore

Comprehensive Cancer Center

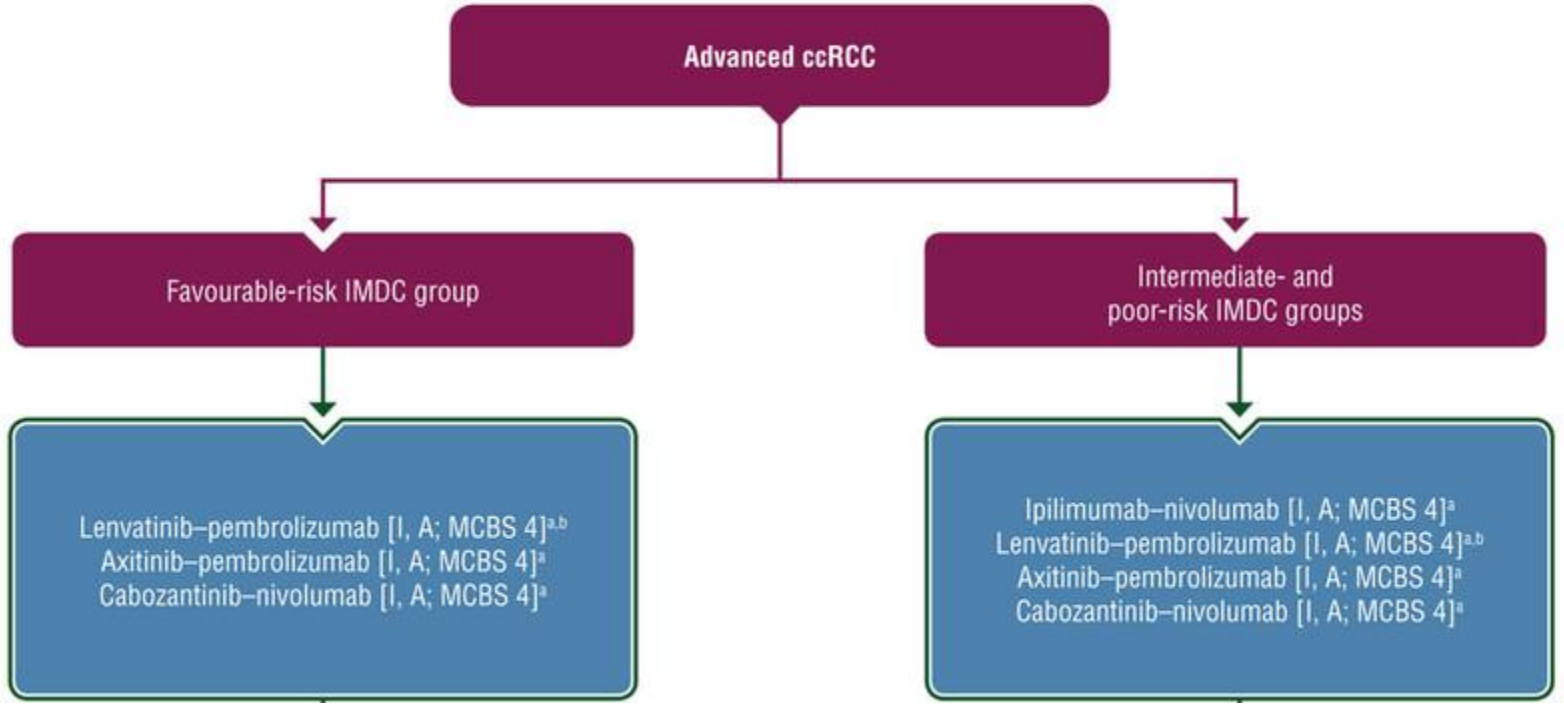
Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Conflicts of interest

Type of support	Sponsor
Advisory board	Astellas, BMS, Ipsen, Janssen, Merk, MSD, Pfizer, Sanofi, Bayer, EISAI.
Consultant	Astellas, Ipsen, Merk, MSD, Pfizer, EISAI
Research support (inst)	BMS, Pfizer
PI clinical trial	BMS, Exelixis, Ipsen, Lilly, MSD, Seagen.

Guidelines are enough or is it not all like that?



eUpdate – Renal Cell Carcinoma Treatment Recommendations
Published: 28 September 2021. Authors: ESMO Guidelines Committee available at esmo.org

My questions about first line:

- Are all combos equal?
- Is the expected benefit the same for each prognostic group?
- If there are, what are the reasons for these differences?
- How can we improve the management of the first line?

What we know about doublets?

Study and outcome	CheckMate214[1] Ipi/nivo vs Su	KeyNote426[2] Axi/pem vs Su	CheckMate9ER[3] Cabo/nivo vs Su	CLEAR[4] Len/pem vs Su
Patients	550 vs. 546	432 vs. 429	323 vs. 328	355 vs. 357
mFU (mos)	67.7	67.0	44.0	49.8
IMDC (F vs. I vs. P) (%)*	23 vs. 61 vs. 17	32 vs. 55 vs. 13	23 vs. 58. vs 19	27 vs. 64 vs. 9
mPFS (mos) HR (95%CI	12.3 vs. 12.3 0.86 (0.73-1.01)	15.7 vs. 11.1 0.69 (0.59-0.81)	16.6 vs. 8.4 0.58 (0.48-0.71)	23.9 vs. 9.2 0.47 (0.38-0-57)
mOS (mos) HR (95%CI	55.7 vs. 38.4 0.72 (0.62-0.85)	47.2 vs. 40.8 0.84 (0.71-0.99)	49.5 vs. 35.5 0.70 (0.56-0.87)	53.7 vs. 54.3 0.79 (0.63-0.99)
24mos OS (%)	71 vs. 61	73 vs. 65	70 vs. 60	80.4 vs. 69.6
ORR (%)	39 vs. 32	60.6 vs. 39.6	55.7 vs. 28.4	71.3 vs. 36.7
mDOR	NR vs. 24.8	23.6 vs. 15.3	23.1 vs. 15.2	26.7 vs. 14.7

*experimental arm only

1. Motzer R, Cancer 2022
2. Rini B, ASCO 2023
3. Burotto M, ASCO-GU2023
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24mos OS (%)	71 vs. 61	73 vs. 65	70 vs. 60	80.4 vs. 69.6
ORR (%)	39 vs. 32	60.6 vs. 39.6	55.7 vs. 28.4	71.3 vs. 36.7
mDOR	NR vs. 24.8	23.6 vs. 15.3	23.1 vs. 15.2	26.7 vs. 14.7

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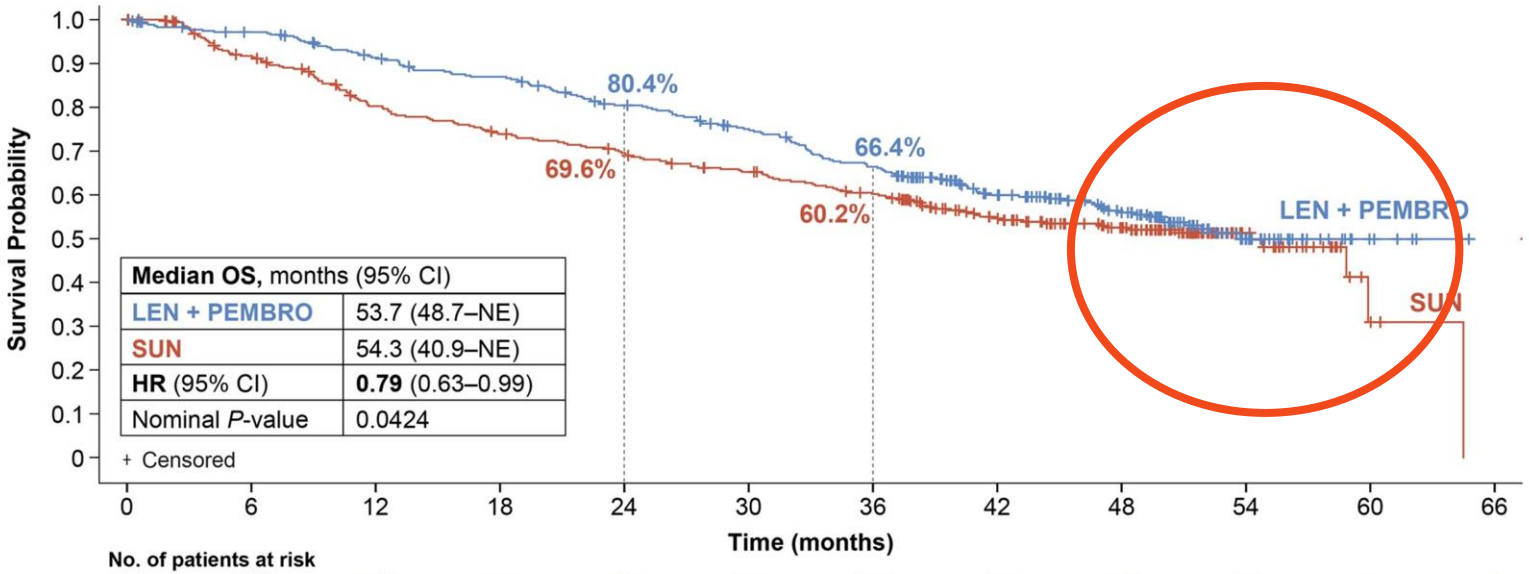
Why?

Final OS analysis



Median OS, months (95% CI)	
LEN + PEMBRO	53.7 (48.7–NE)
SUN	54.3 (40.9–NE)
HR (95% CI)	**0.79** (0.63–0.99)
Nominal *P*-value	0.0424

No. of patients at risk

355	338	313	296	269	245	216	158	117	34	5	0
357	308	264	242	226	208	188	145	108	33	3	0

At median OS follow-up time (IQR) of **49.8 months** (41.4–53.1) in the lenvatinib plus pembrolizumab group and **49.4 months** (41.6–52.8) in the sunitinib group, 308 target OS events had occurred (lenvatinib plus pembrolizumab, 149 events; sunitinib, 159 events). The HR and 2-sided 95% CI for lenvatinib plus pembrolizumab vs sunitinib were estimated by a stratified Cox proportional hazards model with Efron's method for ties, stratified by geographic region and MSKCC prognostic groups.

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PRESENTED BY: Thomas E. Hutson

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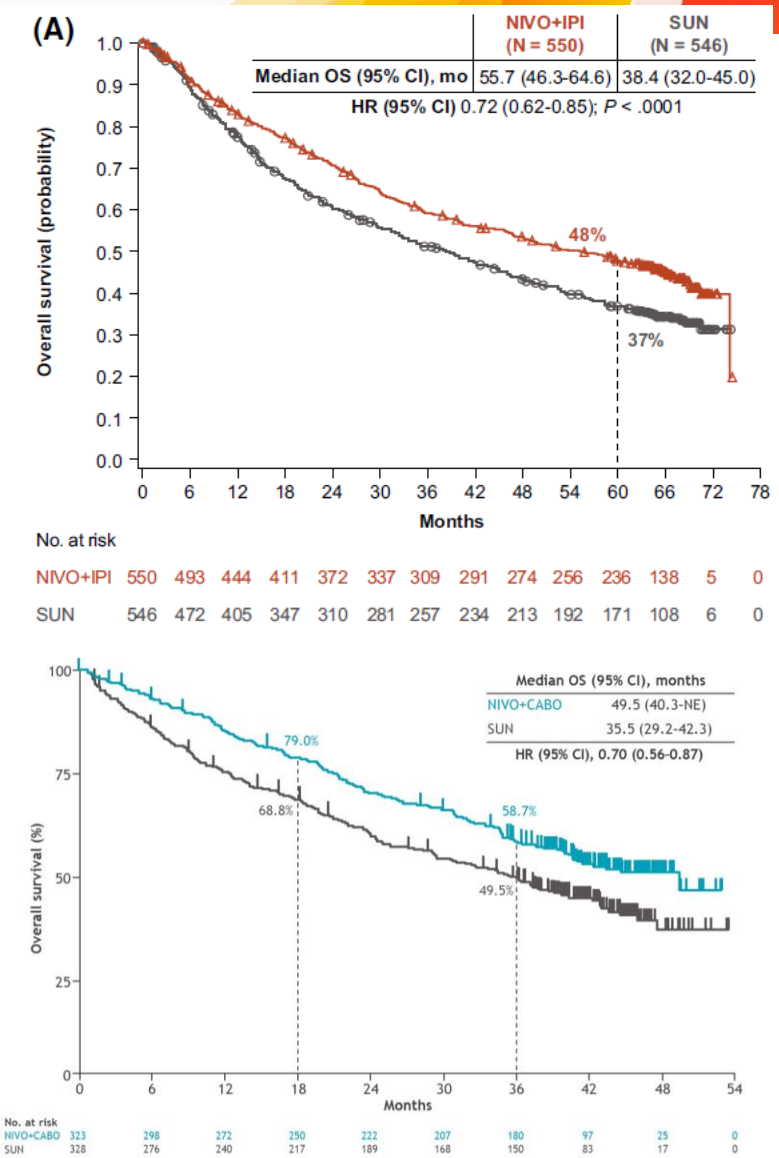
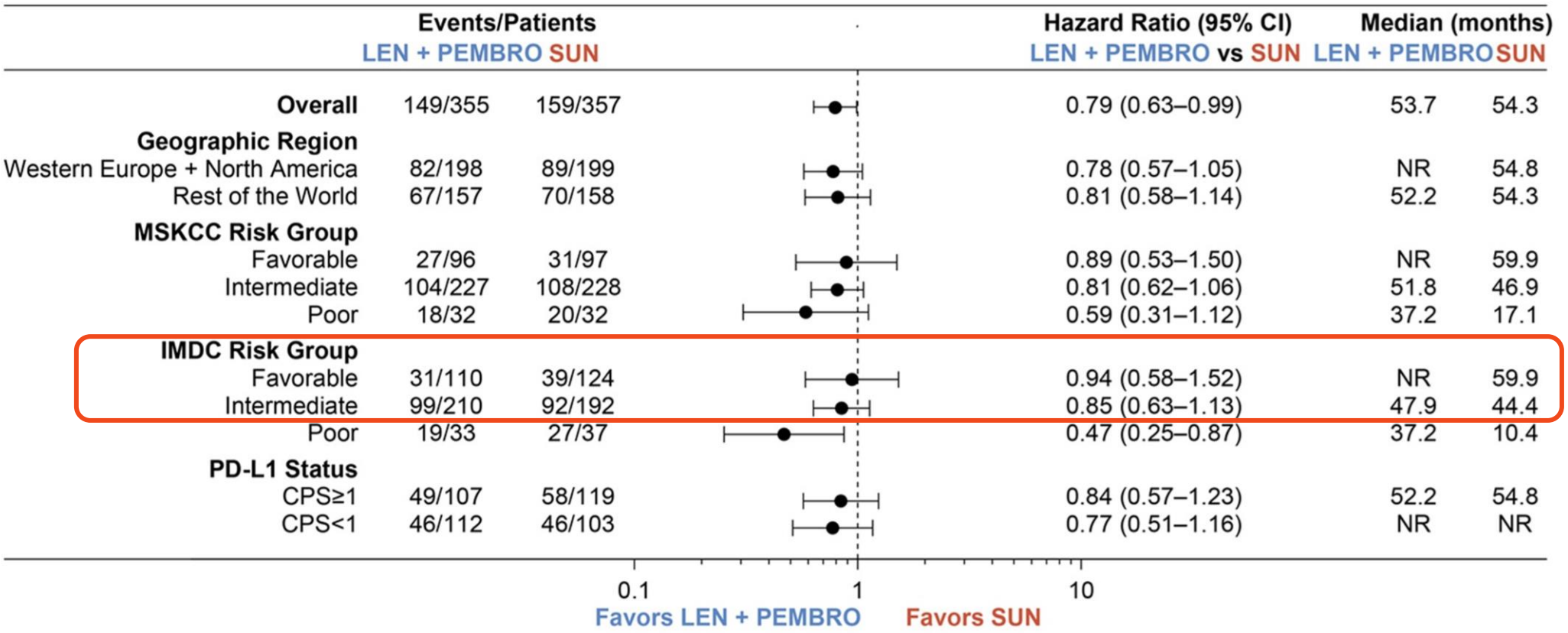


Why?

	Events/Patients LEN + PEMBRO	Events/Patients SUN	Hazard Ratio (95% CI) LEN + PEMBRO vs SUN	Median (months) LEN + PEMBRO	Median (months) SUN
Overall	149/355	159/357	0.79 (0.63–0.99)	53.7	54.3
Geographic Region					
Western Europe + North America	82/198	89/199	0.78 (0.57–1.05)	NR	54.8
Rest of the World	67/157	70/158	0.81 (0.58–1.14)	52.2	54.3
MSKCC Risk Group					
Favorable	27/96	31/97	0.89 (0.53–1.50)	NR	59.9
Intermediate	104/227	108/228	0.81 (0.62–1.06)	51.8	46.9
Poor	18/32	20/32	0.59 (0.31–1.12)	37.2	17.1
IMDC Risk Group					
Favorable	31/110	39/124	0.94 (0.58–1.52)	NR	59.9
Intermediate	99/210	92/192	0.85 (0.63–1.13)	47.9	44.4
Poor	19/33	27/37	0.47 (0.25–0.87)	37.2	10.4
PD-L1 Status					
CPS≥1	49/107	58/119	0.84 (0.57–1.23)	52.2	54.8
CPS<1	46/112	46/103	0.77 (0.51–1.16)	NR	NR



What we know about doublets in favorable prognosis?

Table 1 – Initial and updated results for OS for patients with IMDC favourable prognosis enrolled in phase 3 trials investigating anti-PD-1/PD-L1–based combinations over sunitinib in mRCC

Trial	Initial analysis		Latest update	
	mFU (mo)	HR for OS (95% CI)	mFU (mo)	HR for OS (95% CI)
CheckMate-214 [1]	25.2	0.83 (0.35–1.97)	67.7	0.94 (0.65–1.37)
Javelin Renal 101 [3]	9.9	0.80 (0.33–1.96)	13.0 [a]	0.81 (0.34–1.96)
KeyNote-426 [4]	12.8	1.06 (0.60–1.86)	42.8	1.17 (0.76–1.80)
CheckMate-9ER [5]	18.1	0.84 (0.35–1.97)	32.9	1.03 (0.55–1.92)
CLEAR [6]	26.6	1.15 (0.55–2.40)	33.7	1.22 (0.66–2.26)

CI = confidence interval; HR = hazard ratio; IMDC = International mRCC Database Consortium; mFU = median follow-up; mRCC = metastatic renal cell carcinoma; OS = overall survival.
[a] Minimum follow-up.

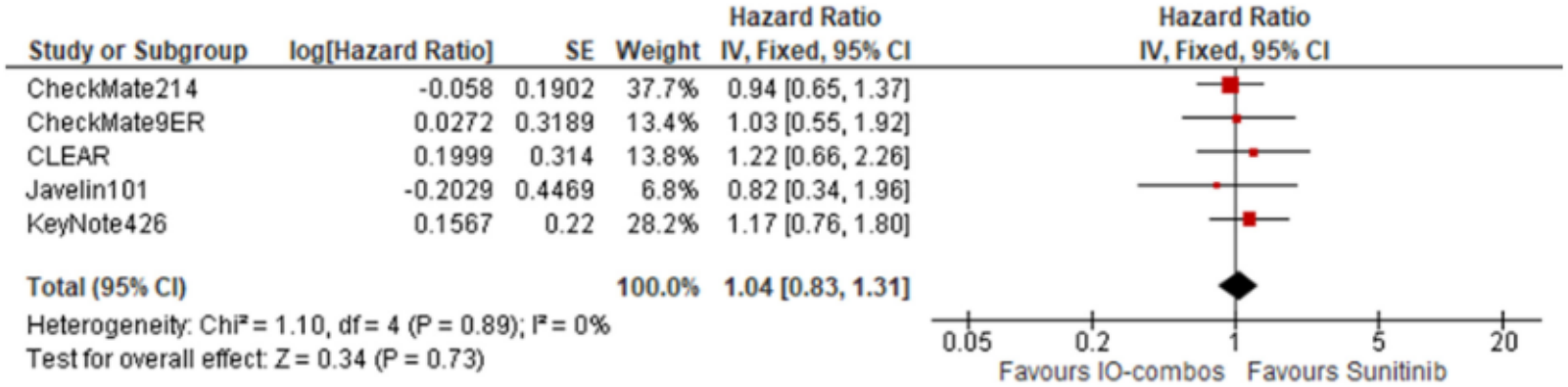


Fig. 1 – Meta-analysis of data for overall survival for patients with IMDC favourable prognosis enrolled in phase 3 trials investigating anti-PD-1/PD-L1–based combinations over sunitinib in mRCC. IMDC = International mRCC Database Consortium; mRCC = metastatic renal cell carcinoma; SE = standard error; CI = confidence interval; IV = inverse variance; df = degrees of freedom; IO = immunotherapy.

Ciccarese C, Iacovelli R. Eur Urol. 2023 Feb;83(2):e45-e46.

What we know about doublets in favorable prognosis?

Study and outcome	CheckMate214[1] Ipi/nivo vs Su	KeyNote426[2] Axi/pem vs Su	CheckMate9ER[3] Cabo/nivo vs Su	CLEAR[4] Len/pem vs Su
Patients	125 vs. 124	136 vs. 131	74 vs. 72	110 vs. 124
mFU (mos)#	67.7	67.0	44.0	49.8
IMDC (F vs. I vs. P) (%)*	23 vs. 61 vs. 17	32 vs. 55 vs. 13	23 vs. 58. vs 19	27 vs. 64 vs. 9
mPFS (mos) HR (95%CI	12.4 vs. 28.9 1.60 (1.13 – 2.26)	20.7 vs. 17.9 0.76 (0.57 – 1.02)	21.4 vs. 13.9 0.75 (0.50 – 1.13)	28.6 vs. 12.9 0.50 (0.35 – 0.71)
mOS (mos) HR (95%CI	74.1 vs. 68.4 0.94 (0.65 – 1.37)	60.3 vs. 62.4 1.10 (0.79 – 1.54)	NR vs. 40.7 1.07 (0.63 – 1.79)	NR vs. 59.9 0.94 (0.58 – 1.52)
24mos OS (%)	≈83 vs. 86	≈85 vs. 88	≈80 vs. 82	≈95 vs. 90
ORR (%)	30.0 vs. 52.0	68.8 vs. 50.4	66.2 vs. 44.4	NA

*experimental arm only
for all study population

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What do we not know about doublets in favorable prognosis?

Why the increased PFS did not translate in an OS benefit for patients with favourable prognosis?

What we know about doublets in intermediate-poor prognosis?

Study and outcome	CheckMate214[1] Ipi/nivo vs Su	KeyNote426[2] Axi/pem vs Su	CheckMate9ER[3] Cabo/nivo vs Su	CLEAR[4] Len/pem vs Su
Patients	425 vs. 422	294 vs. 298	249 vs. 256	243 vs. 229
mFU (mos)#	67.7	67.0	44.0	49.8
IMDC (F vs. I vs. P) (%)*	23 vs. 61 vs. 17	32 vs. 55 vs. 13	23 vs. 58. vs 19	27 vs. 64 vs. 9
mPFS (mos) HR (95%CI	11.6 vs. 8.3 0.73 (0.61 – 0.87)	13.8 vs. 8.3 0.68 (0.56 – 0.82)	16.4 vs. 7.1 0.55 (0.45 – 0.69)	22.1 vs. 5.9 0.43 (0.34 – 0.55)
mOS (mos) HR (95%CI	47.0 vs. 26.6 0.68 (0.58 – 0.81)	42.2 vs. 29.3 0.76 (0.62 – 0.93)	49.5 vs. 29.2 0.65 (0.51 – 0.83)	47.9 vs. 34.3 0.74 (0.57 – 0.96)
24mos OS (%)	≈68 vs. 55	≈68 vs. 55	≈70 vs. 55	≈75 vs. 60
ORR (%)	42.0 vs. 27.0	56.8 vs. 34.9	52.6 vs. 23.8	NA

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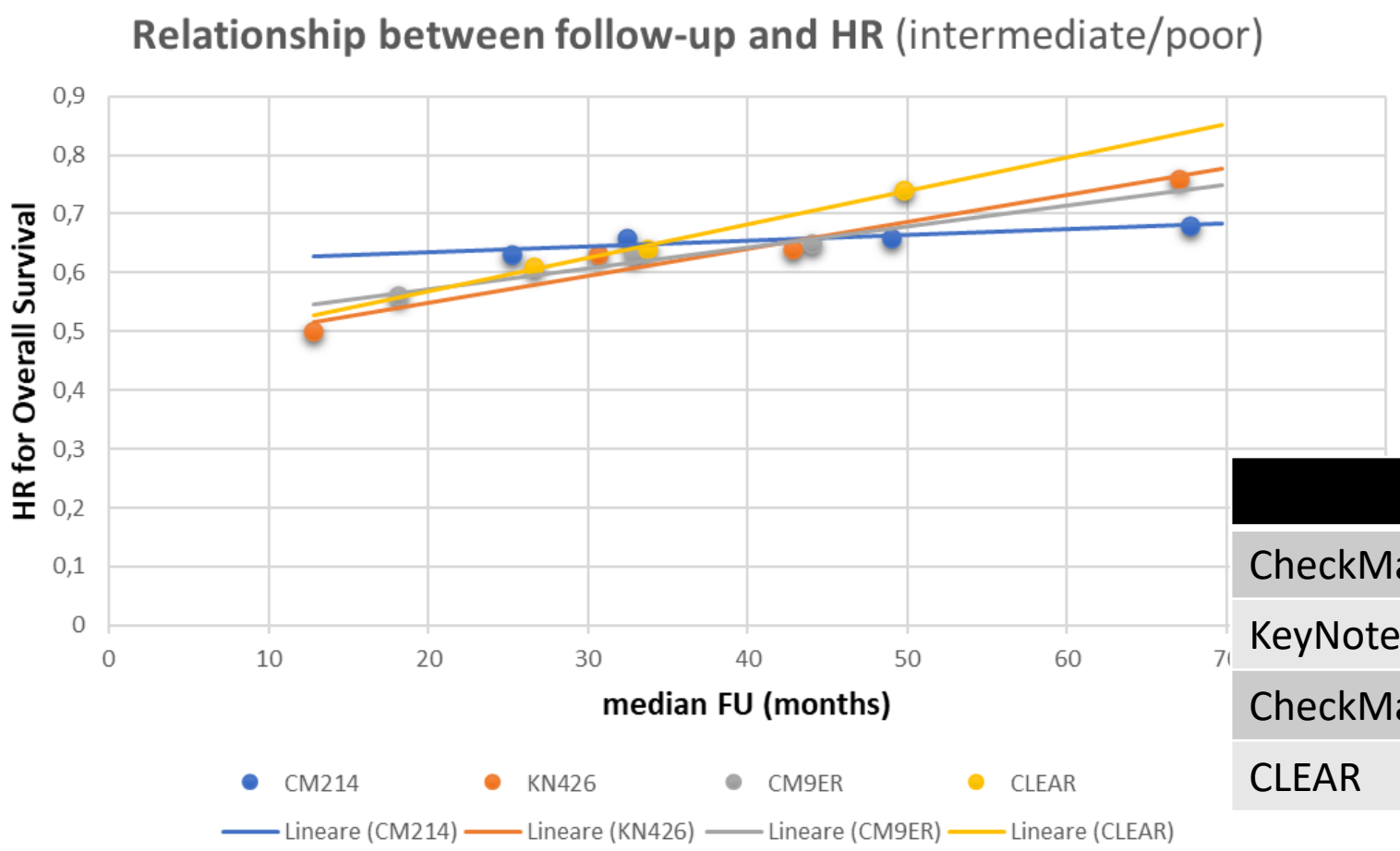
The follow up is affecting the OS magnitude of benefit



For each study, the HR for OS has been correlated to the median FU.

The increasing FU is correlated with the increasing HR for OS irrespectively of the type of combo.

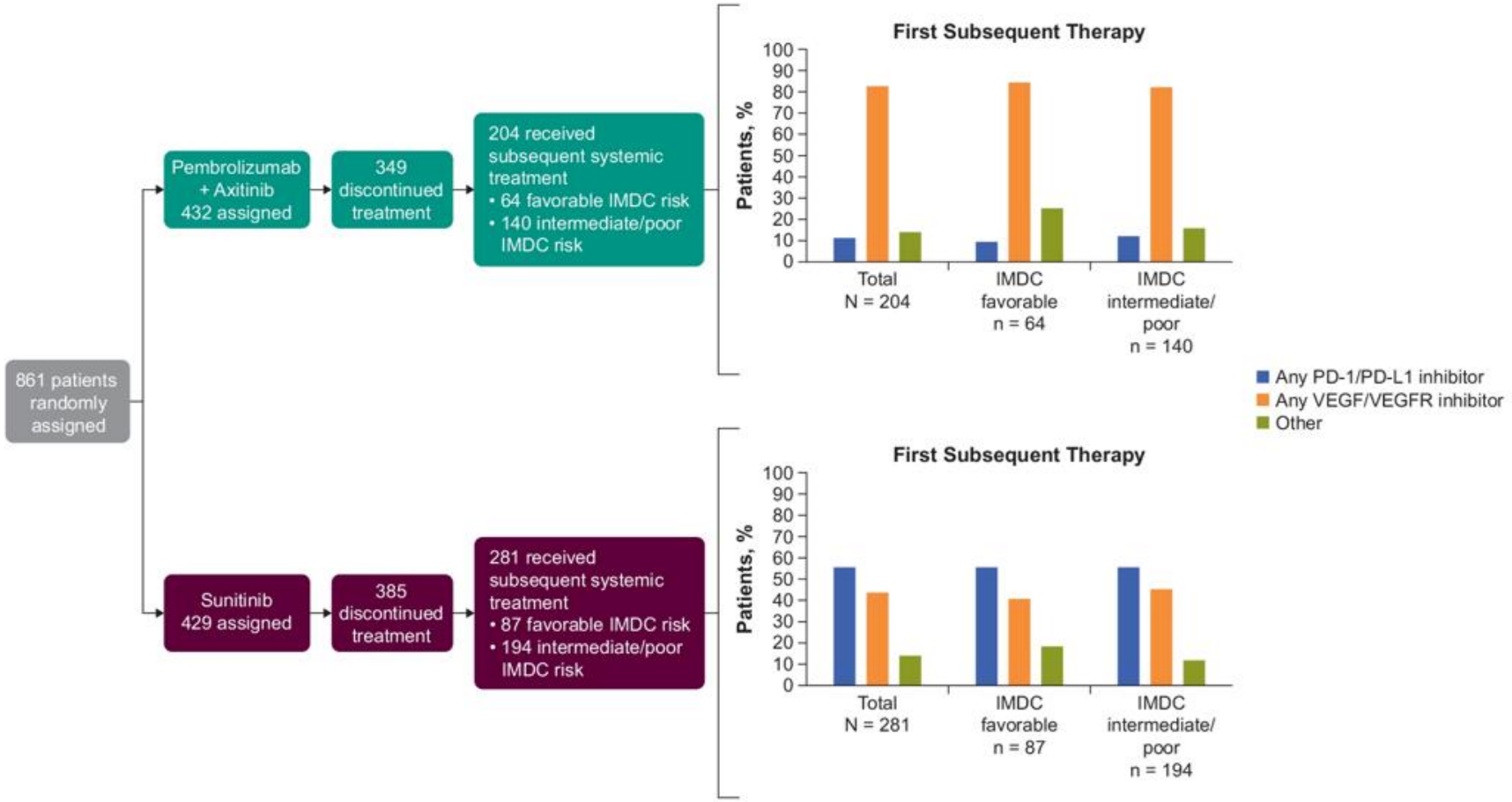
	Correlation (r_p)	P-value
CheckMate214	0.930	*0.035*
KeyNoteN426	0.977	*0.011*
CheckMate9ER	0.974	*0.073*
CLEAR	0.997	*0.026*

What we know about doublets in intermediate-poor prognosis?

Why the increased PFS did not translate in an OS benefit for patients with favourable prognosis?

Why the longer FUp is affecting the advantage in OS in patients with intermediate/poor prognosis?

Rate & quality of subsequent therapies in combo studies



The analysis of KeyNote426 confirms as patients in the control arm received more frequently anti-PD(L)1 therapies at progression.

Powles T, et al, ASCO 2022; abs 4513

Rate of subsequent therapies in combo studies

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Subsequent Systemic Tx (%)	55 vs. 68	62.2 vs. 73.9	25 vs. 41	51.0 vs. 68.9
Anti-VEGFR(%)		86.9 vs. 72.0	21 vs. 19	45.9 vs. 45.4
Anti-PD(L)1	13.5 vs. 45.6	26.6 vs. 80.0	7 vs. 31	15.8 vs. 54.6

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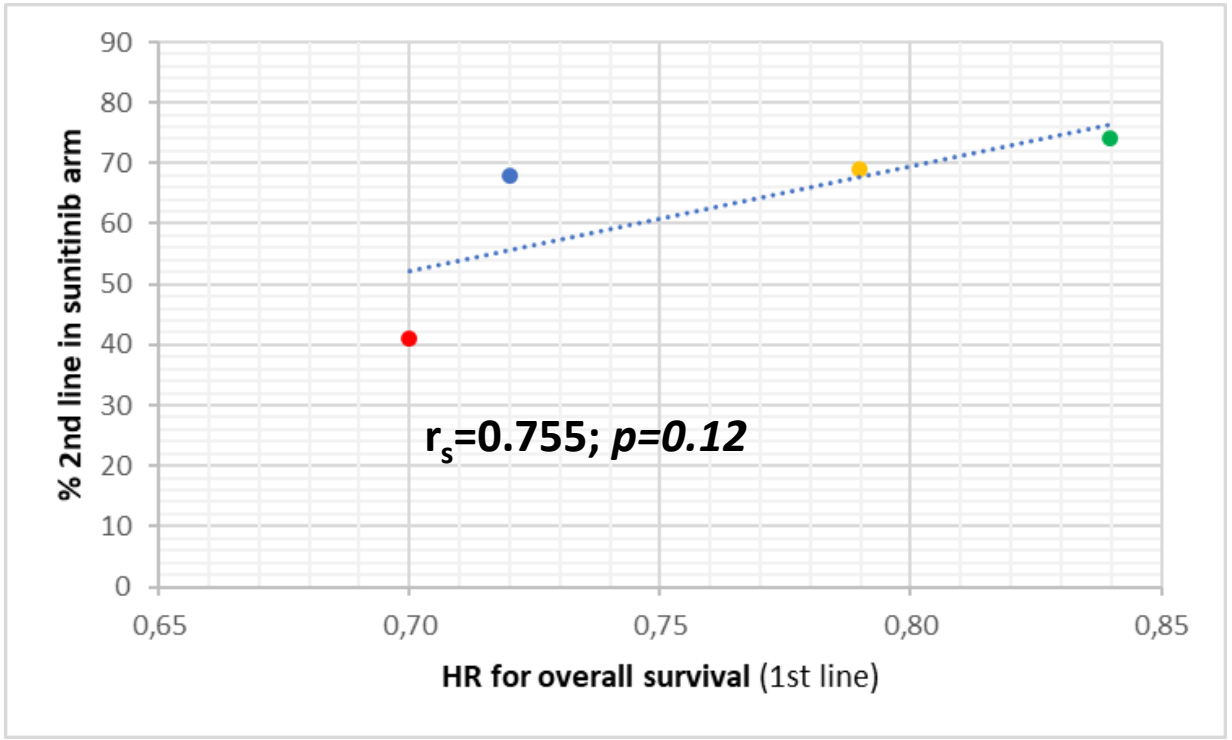
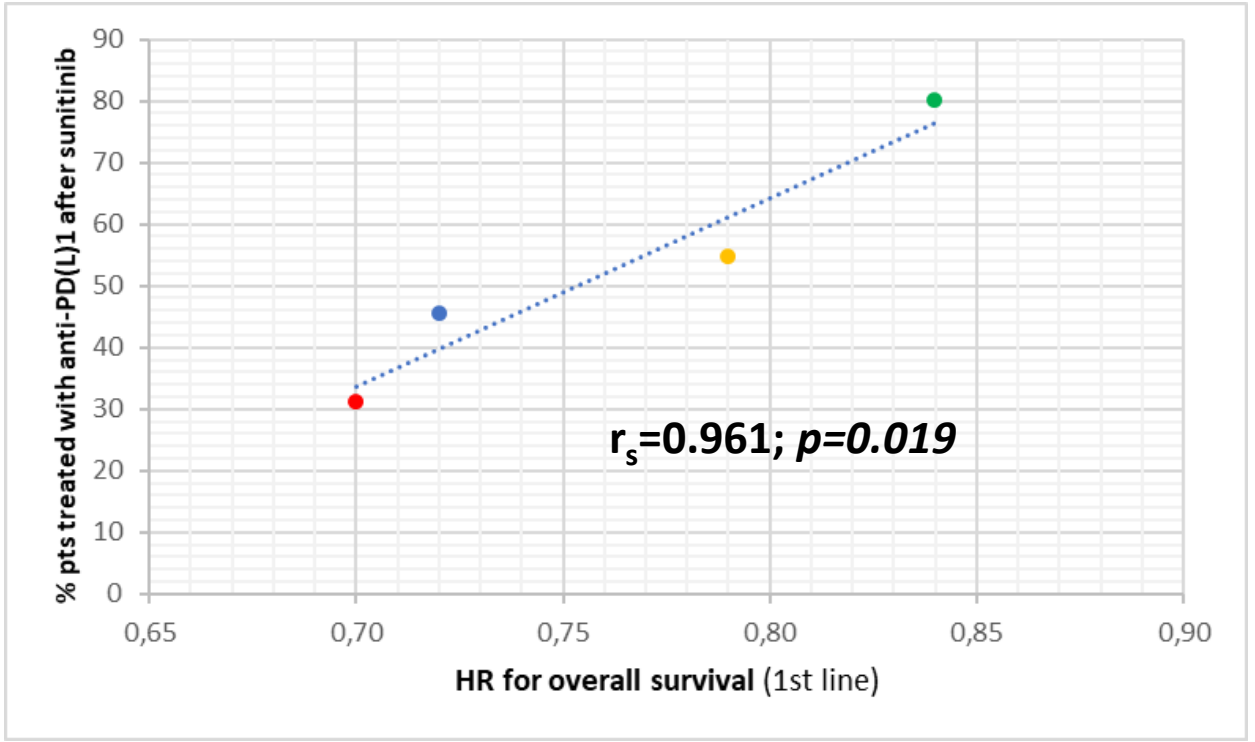
Correlation between rate & quality of second line





In the control arm, the second line immunotherapy affects the final HR for OS more than the absolute rate of patients who received subsequent therapies.

CheckMate214 KeyNote426 CheckMate9ER CLEAR

Follow up and rate of 2nd line IO affect HR for OS in combo studies

TKI-IO combo	HR for OS	Follow up (mos)	IO after sunitinib
KeyNote 426[2]	0.84	67.0	80.0%
CLEAR[4]	0.79	49.8	54.6%
CheckMate 9ER[3]	0.70	44.0	31.0%

IO-IO combo	HR for OS	Follow up	IO after sunitinib
CheckMate 214[1]	0.72	67.0	45.6%

Studies with worse HR have also the longer follow up and the higher rate of patients treated with IO after sunitinib.

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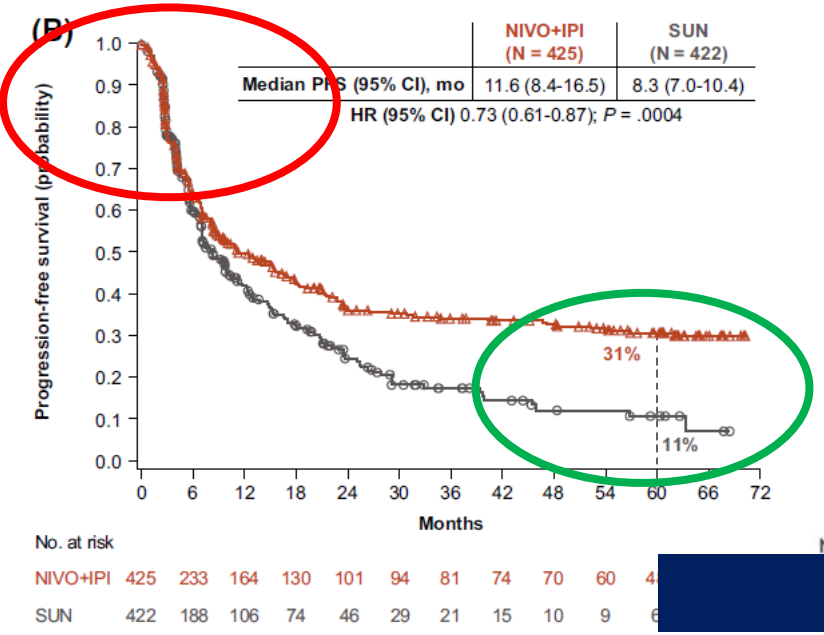
Conclusions about the current options for 1st line therapy

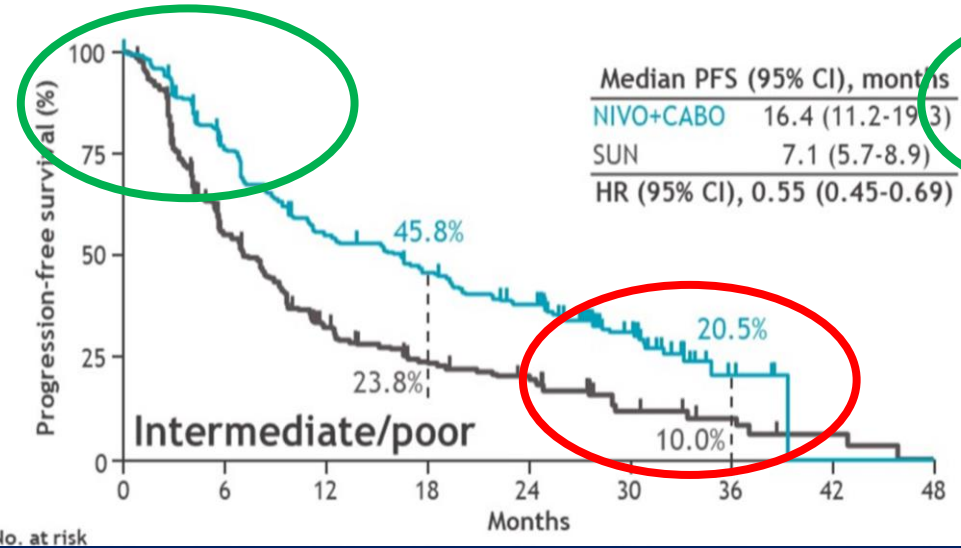
- Patients with **favourable prognosis do not require the use of the IO-based combo** in majority of cases.
- Patients with favourable prognosis **treated with sunitinib have similar OS** to those treated with combos because of their greater chance to receive immunotherapy in second line. Therefore, the **sequential therapy is a feasible strategy.**
- Patients with **intermediate/poor prognosis have the greatest benefit** from IO-based combos.
- Nevertheless, **the magnitude of benefit for IO-based combos is progressively decreasing** (probably) because of the increase of the follow up and of the number of patients who are receiving IO after sunitinib.
- Considering the difference in the length of follow up and rate/quality of subsequent lines, **any comparison between combos is useless.**

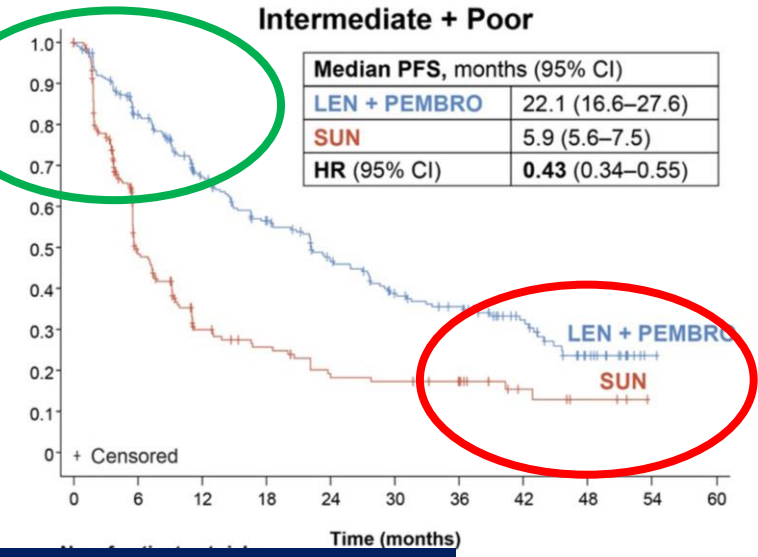
How can we choose?

It depends by your need…

High risk of primary progression for IO-IO compared to IO-TKI







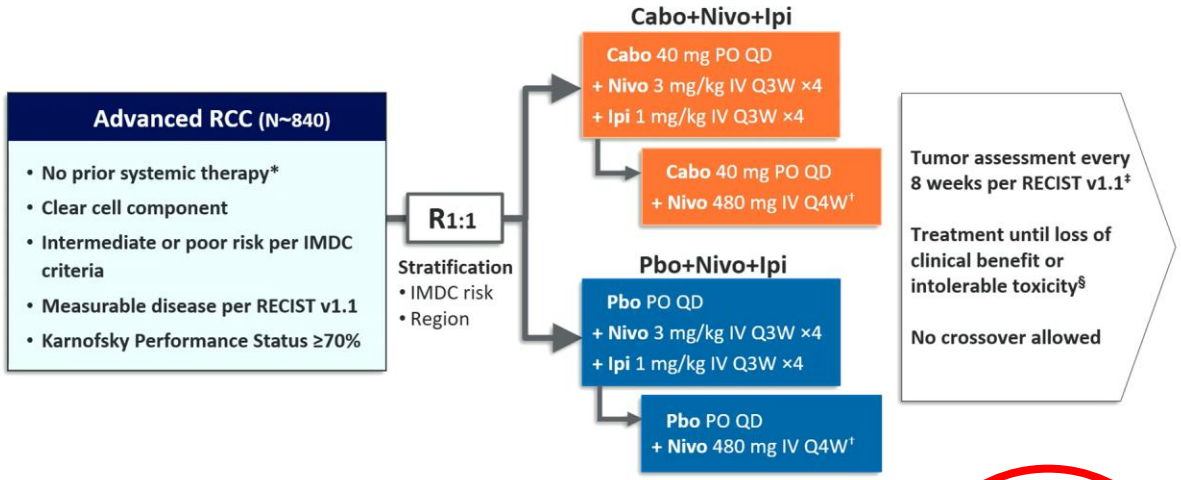
Longer disease control for IO-IO compared to IO-TKI

Next strategies in 1st line

- Intensification
- Immunestimulation (boost)
- Deintensification

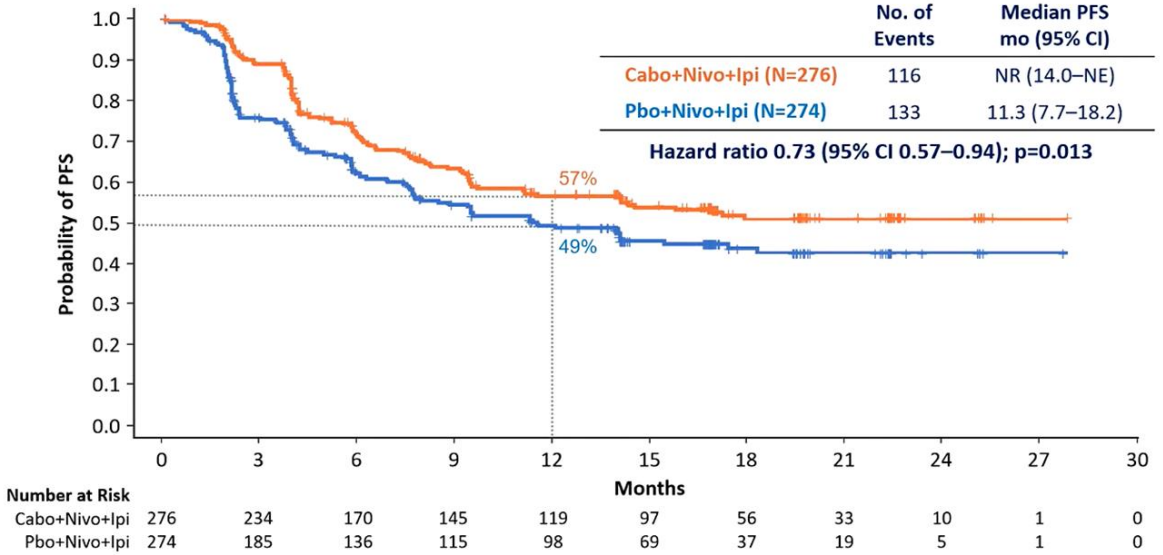
Next strategies for improvement of 1st line: intensification

COSMIC-313 Study Design



Study	CLEAR[1]	CM9ER[2]	KN426[3]	Cosmic313[4]
TRAE ≥ G3 (%)	71.6	61.0	66.9	73.0
Tx discontinuation	37,2	19,7	30,5	45,0
Tx delay/interruption	78,4	N:71,9 C:68,1	69,9	90,0
Dose reduction (TKI)	68,8	56,3	20,3	54,0
Use high dose steroids	NA	19,1	NA	58,0

Progression-Free Survival: Final Analysis (PITT Population)

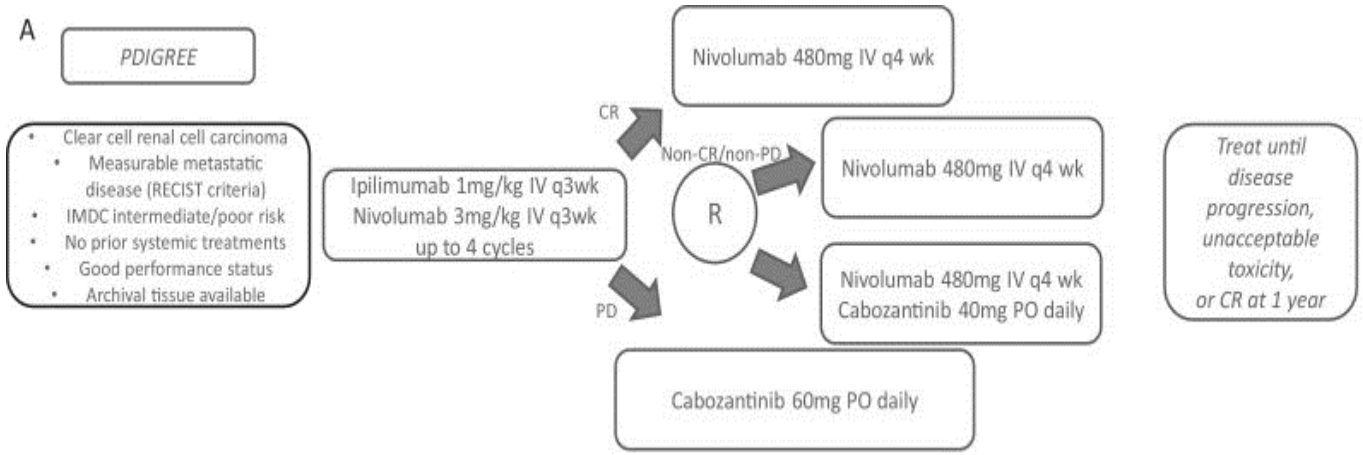


1. N Engl J Med 2021;384:1289-300.
2. N Engl J Med 2021;384:829-41.
3. N Engl J Med 2019;380:1116-27
4. Choueiri TK, ESMO 2022

Next strategies for improvement of 1st line: intensification

Doublet followed by doublet *(or a different way to be triplet!)*

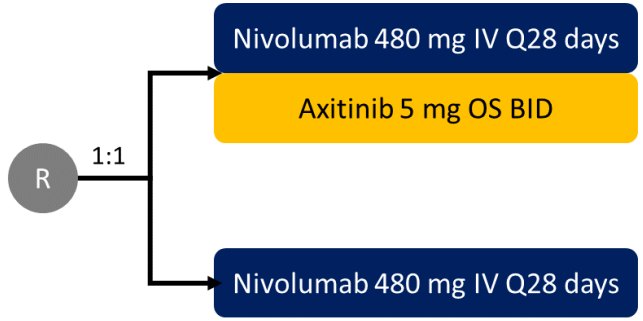
PDGREE trial



NCT03793166

AXIN trial

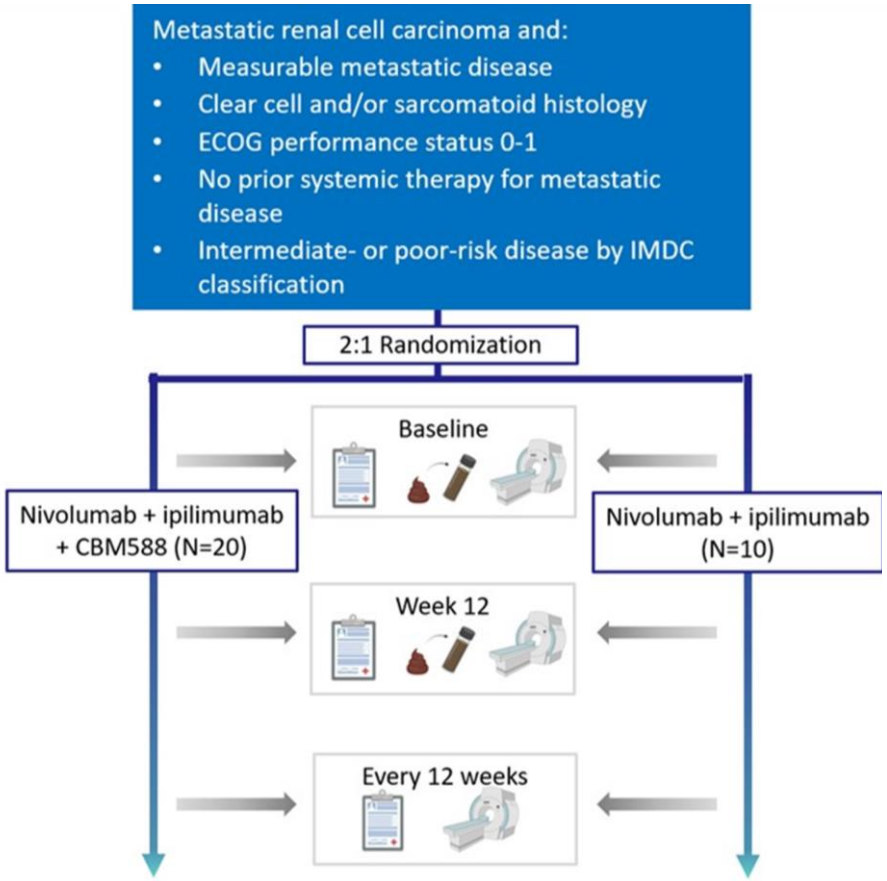
118 mRCC patients **after ipi/nivo induction** with
- ECOG=0-1
- Metastatic disease
- No PD & No RC
- No Immune tox ≥ G2

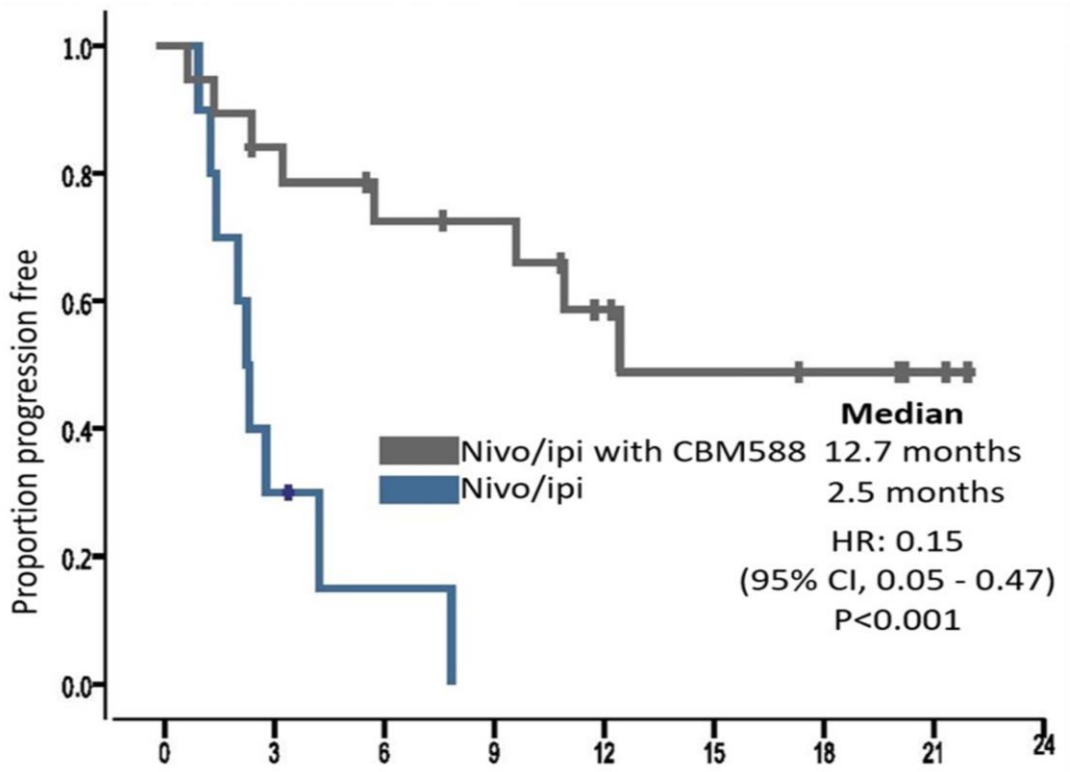


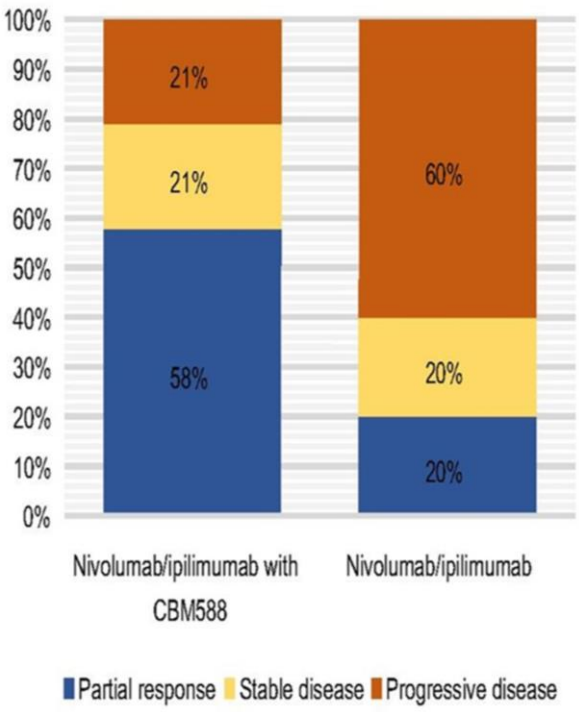
Endpoints:
Primary: *ORR*
Secondary: *mPFS, mOS; deepth of response, DOR, QoL, safety*

NCT05817903

Next strategies for improvement of 1st line: immunestimulation



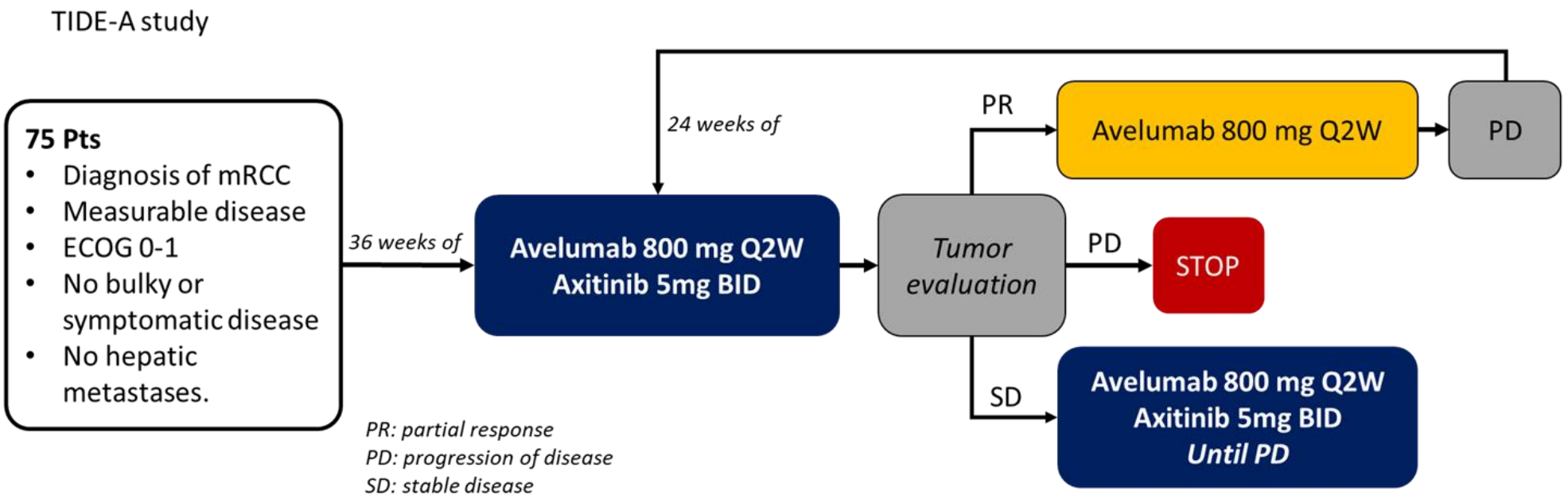




CBM588: Clostridium butyricum

Dizman N, et al. Nat Med. 2022; 28: 704–712.

Next strategies for improvement of 1st line: deintensification



Iacovelli et al. Presented at ASCO GU 2020 TPS762

Eudract CT number: 2019-004098-23
ClinicalTrials.gov Identifier: NCT04698213

Definitive conclusions:

- **First line** therapy is **the most important step** for the management of mRCC patient.
- The **choice** among the available therapies should be **based on clinical need** and symptomatic patients should be treated with one of the available IO-TKI combos.
- **Triplet therapy cannot be offered** considering toxicity and lack of OS benefit. Sequence of two doublets seems to be more reasonable and results are awaited.
- Next years will offer new data for a **tailored first line**, *please be patient!*