UT Southwestern
Harold C. Simmons
Comprehensive Cancer Center

NCI
Designated
Comprehensive
Cancer Center

Debate:
Dual Immunotherapy

Hans Hammers MD PhD
MATOS
March 21, 2025

NCCN Update

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Kidney Cancer

NCCN Guidelines Index
Table of Contents
Discussion

New preferred regimen designations

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0) OR RELAPSED 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) • Ipilimumab + nivolumab[b]	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Pazopanib • Sunitinib	• Active surveillance[1,2,3] • Axitinib (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)

Treatment for mRCC

1st Line

PD1 / CTLA4

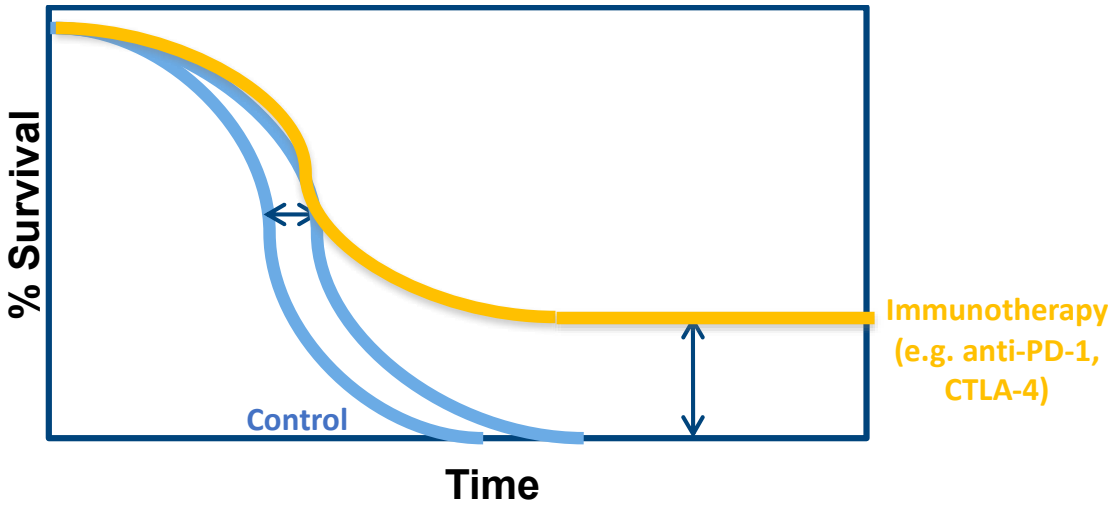
Immunotherapy:
Curative Potential

Subsequent Therapies

VEGF TKIs, HIF2 Inhibitors

Targeted Therapy:
Palliative

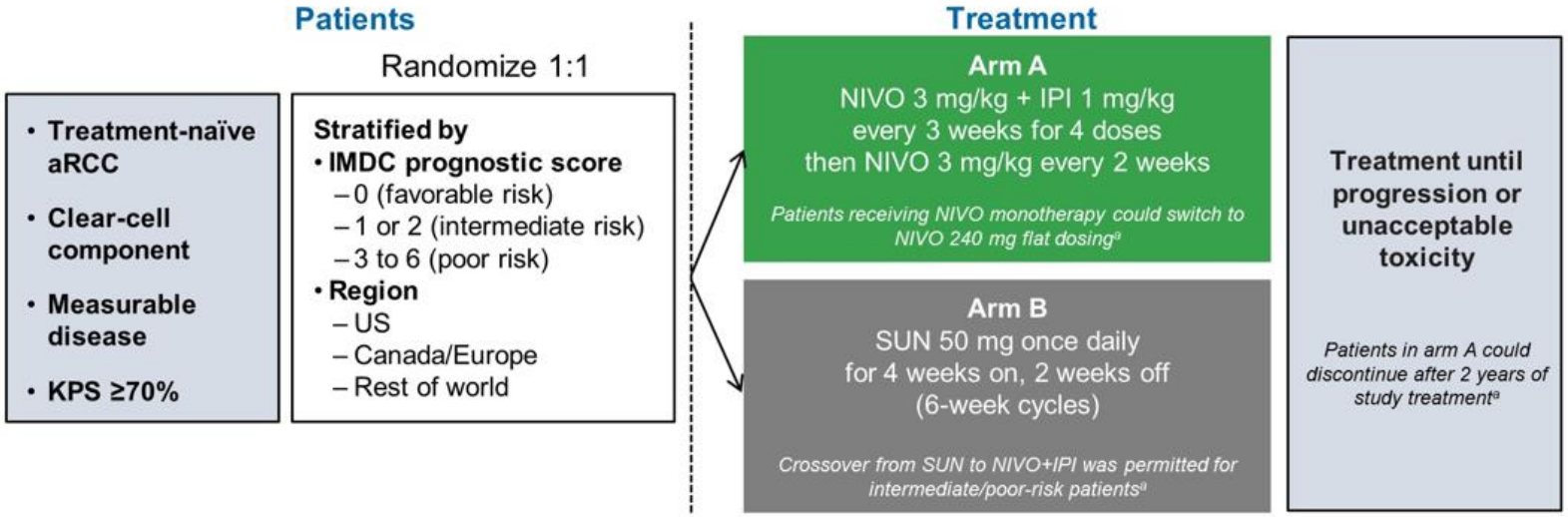
Goal of Immunotherapy



Early Treatment Goal

Long Term Outcome

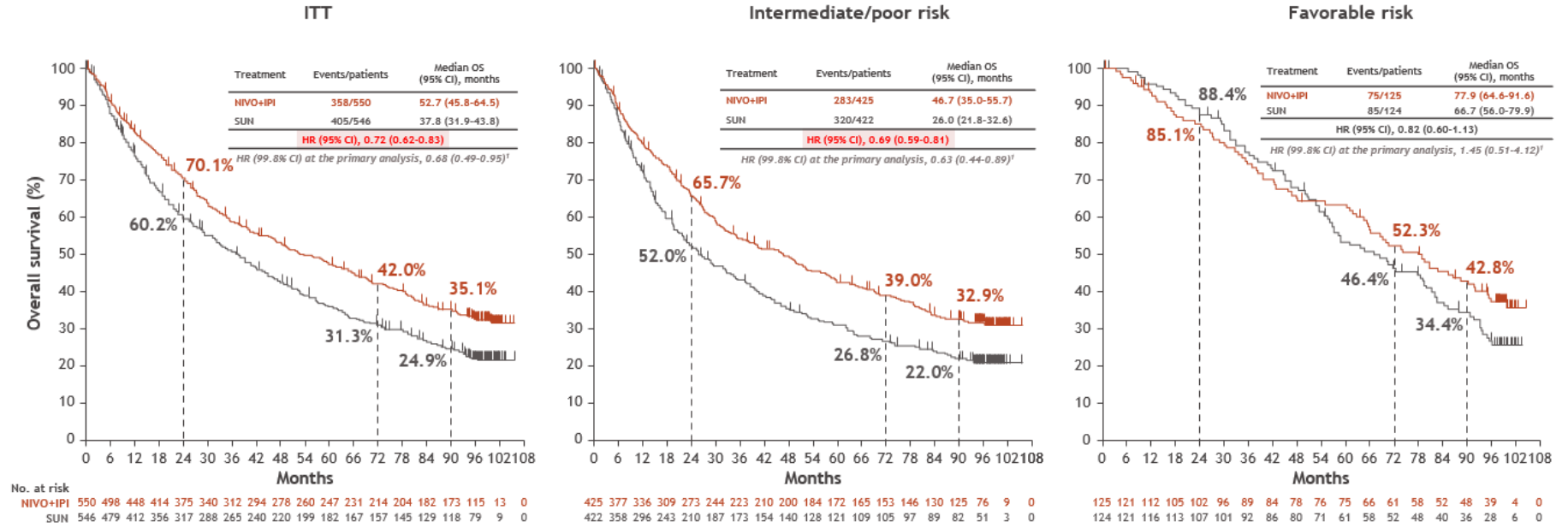
CheckMate-214: Study Design



Primary endpoint: **ORR (INV) in Intermediate/Poor Risk; OS (Intermediate/Poor Risk); PFS (Intermediate/Poor Risk)**

Secondary endpoints: ORR (INV) in any risk; OS (any risk), PFS (any risk)

Checkmate 214: Overall Survival
Median Follow-Up: 99.1 Months

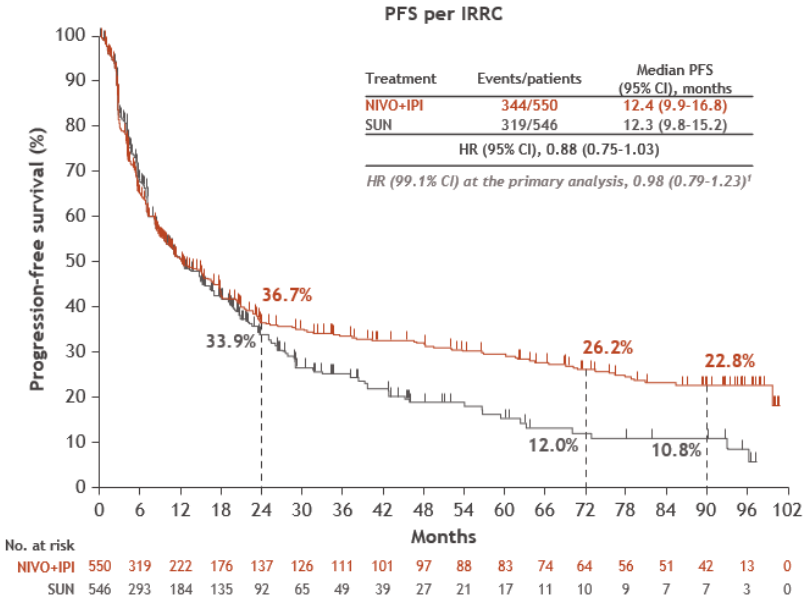


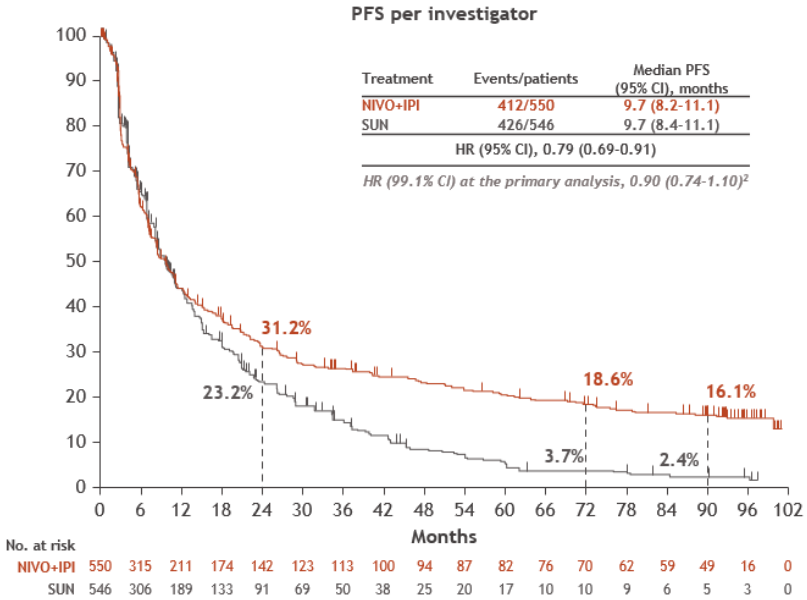
Tannir NM, et al. ASCO GU 2024. Abstract 363.

OS curves stay separated

OS curves for favorable risk separate

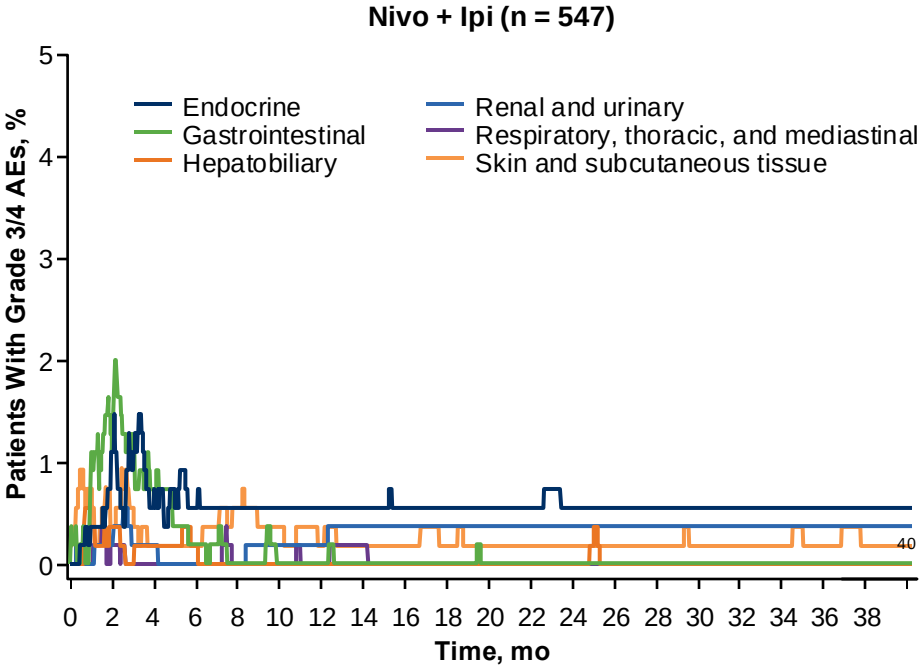
Checkmate-214: Progression-Free Survival
Median Follow-Up: 99.1 Months

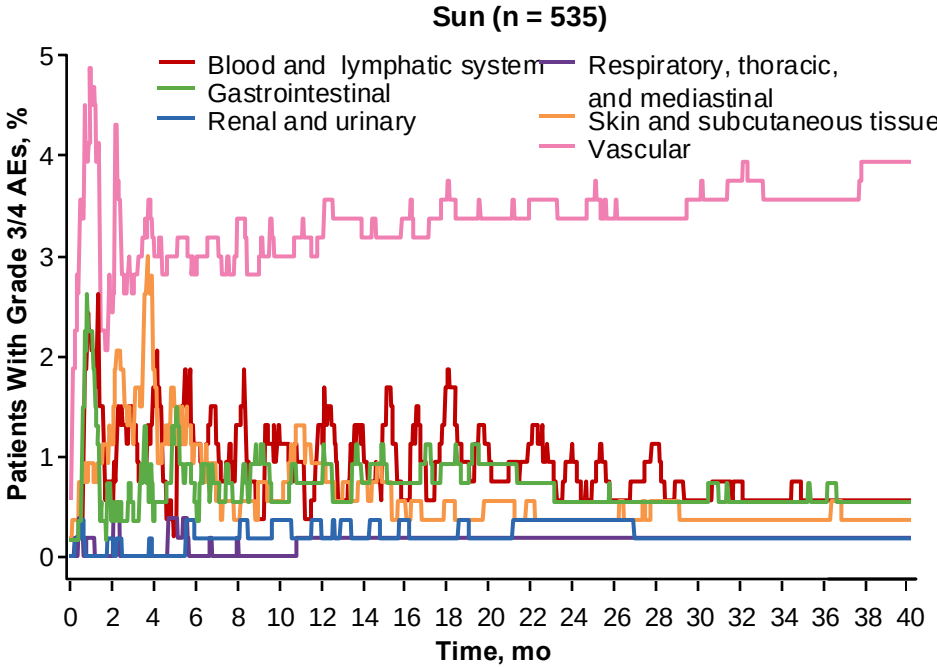




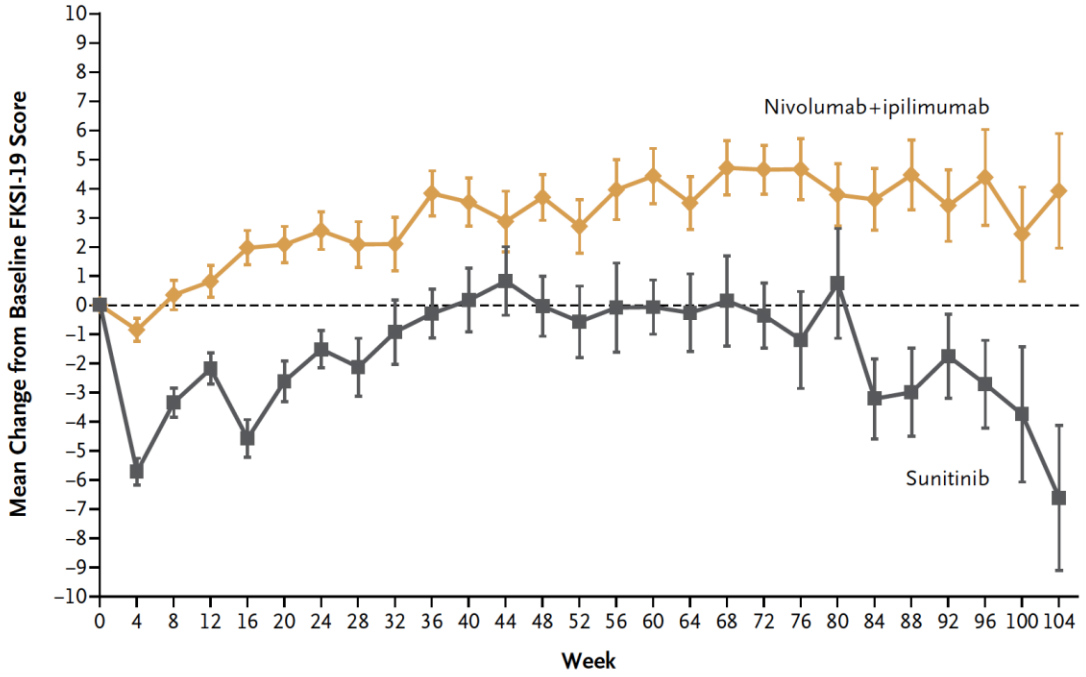
5 year PFS Rate 31%

Side Effects IO vs TKI





Quality of Life – IO/IO vs TKI



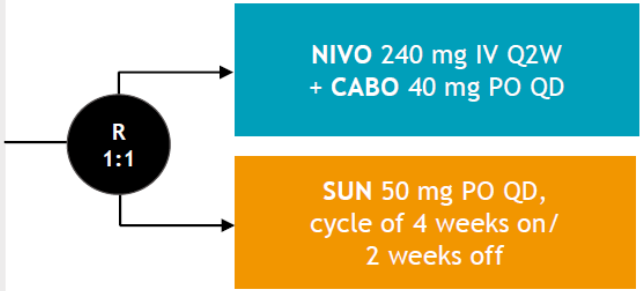
No. at Risk														
Nivolumab+ipilimumab	425	347	281	239	212	180	166	152	143	139	125	108	76	44
Sunitinib	422	371	284	221	184	147	127	113	104	93	80	64	43	26

Phase 3 CheckMate 9ER Trial: Study Design

Stratification factors:
- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region

N = 651

Key inclusion criteria[1,2]
- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group



Treat until RECIST v1.1-defined progression or unacceptable toxicity[b]

Median (range) follow-up for OS in ITT patients, 44.0 (36.5-56.5) months
Database lock, May 27, 2022

Primary endpoint: PFS
Secondary endpoints: OS, ORR, and safety

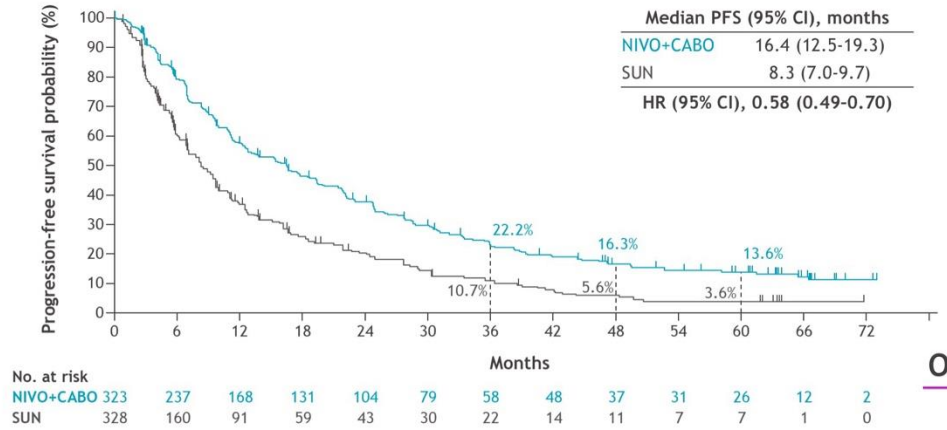
[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.
[b]NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenously; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, orally; Q2W, every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
1. Clinicaltrials.gov/ct2/show/NCT03141177. Accessed June 8, 2020; 2. Choueiri TK et al. Poster presented at the American Society of Clinical Oncology Annual Meeting 2018. TPS4598.

Burotto M, et al. *J Clin Oncol*. 2023;41(6_suppl.603):Abstract 603.
Choueiri T, et al. *N Engl J Med*. 2021;384:829-841.

Checkmate 9ER Final Analysis 2025

CheckMate 9ER

PFS per BICR in the *ITT population*



No. at risk

NIVO+CABO	323	237	168	131	104	79	58	48	37	31	26	12	2
SUN	328	160	91	59	43	30	22	14	11	7	7	1	0

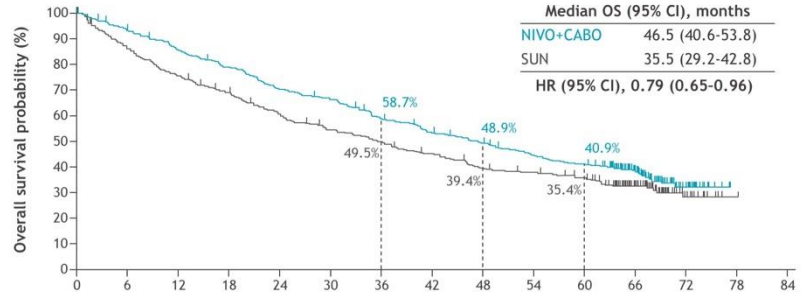
Median follow-up, 67.6 (range, 60.2-80.2) months (ITT population).
Stratified Cox proportional hazards model used for HR.

5 year PFS Rate 13.6%

OS curves converge
HRs closer to 1

CheckMate 9ER

OS in the *ITT population*



No. at risk

NIVO+CABO	323	298	272	250	222	208	183	164	149	132	122	79	18	0	0
SUN	328	277	243	218	190	169	154	138	120	113	103	59	14	1	0

Median follow-up, 67.6 (range, 60.2-80.2) months (ITT population).
Stratified Cox proportional hazards model used for HR.

Motzer et al GU ASCO 2025

IO/IO vs TKI/IO

PROS
- Durable Responses/Plateau
- Unmatched QoL
- Know what happened

> Address oligoprogression

CONS
- **Higher irAE** rate (30%)
- Lower PFS/ Response Rate
- **Primary Progression ~20%**

PROS
- High ORR
- Longer PFS
- Lower irAE rate (15%)

CONS
- **Inferior long term outcome**
- Unclear which component contributed
- Unclear when to stop therapy
- **Lower QoL, chronic TKI** toxicity

CONCLUSION

The Dust has Settled:

- IMDC not useful to select patients
- Ask: Does the patient need a TKI? (PD risk)
- For long term outcome: I prefer PD1/CTLA4 (OS curves, HR, PFS rates, TFS)
- VEGF TKIs do NOT enhance Immunotherapy

Thank you!

@HHammersMD