Metastatic Renal Cell Cancer: Navigating a Maze of Choices

UCDAVIS COMPREHENSIVE CANCER CENTER

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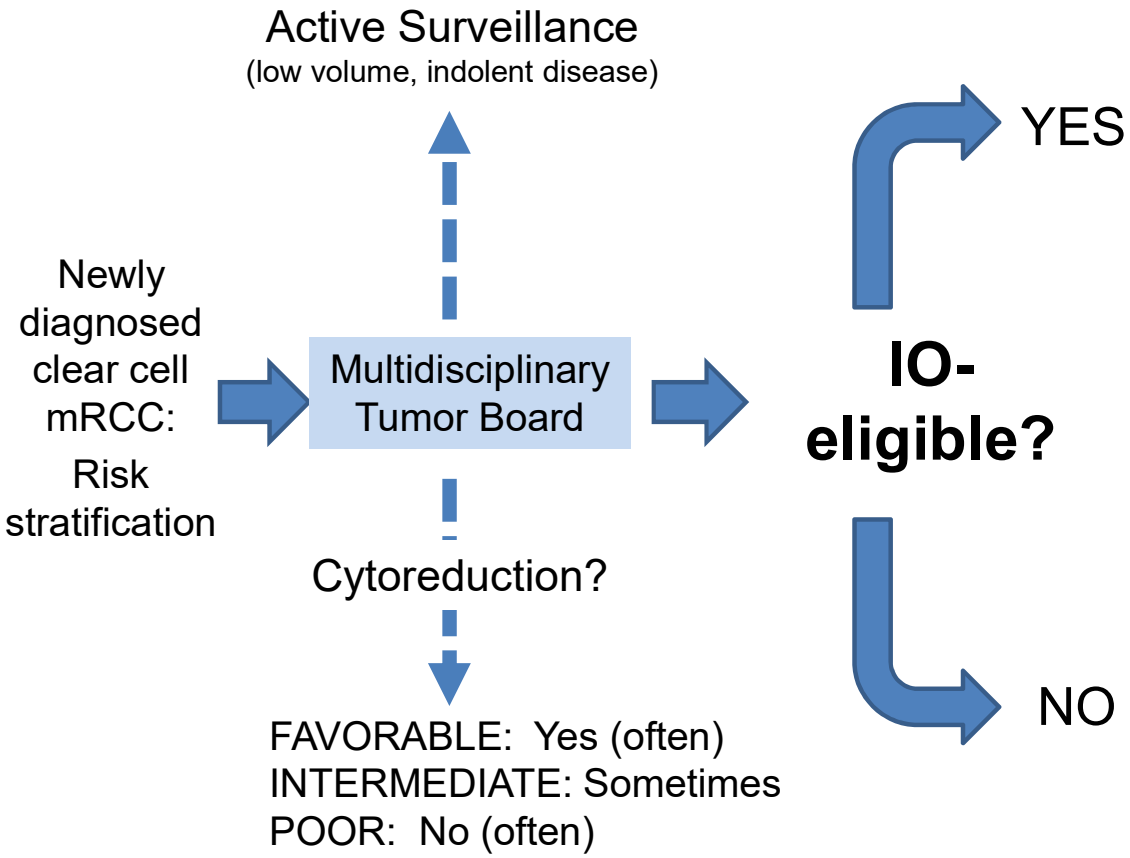
NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

mRCC Treatment Principles

1. Goal is CURE
   - … or prolongation of life
2. Immunotherapy offers best chance for cure
   - With rare exceptions, combination IO-based therapy is frontline standard of care (SOC)
3. Angiogenesis is active throughout ccRCC natural history
   - Allows for within-class sequential therapy

mRCC Decision Tree



IO-Based Combo

ALL RISK GROUPS:
Pembrolizumab-Axitinib
(Avelumab-Axitinib)

INTERMEDIATE or POOR:
Nivolumab-Ipilimumab

Single agent IO

SELECTED PATIENTS:
Pembrolizumab
Nivolumab

Cost, convenience, physician experience, and patient preference apply

TKI

FAVORABLE:
Sunitinib, Pazopanib

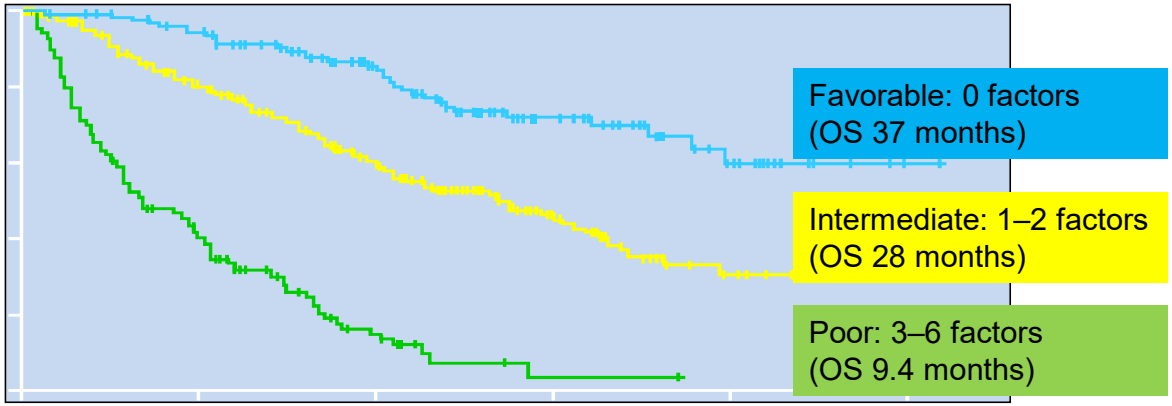
INTERMEDIATE or POOR:
Cabozantinib

Risk Stratification in mRCC

- **N = 645 patients with mRCC treated with VEGF-targeted therapy**
  - Sunitinib (61%); Sorafenib (31%); Bevacizumab (8%)

- **Predictors for OS:**
  - Time from diagnosis to treatment*
  - Hemoglobin*
  - Calcium*
  - Performance status*
  - Neutrophil count
  - Platelet count

* Components of MSKCC prognostic criteria

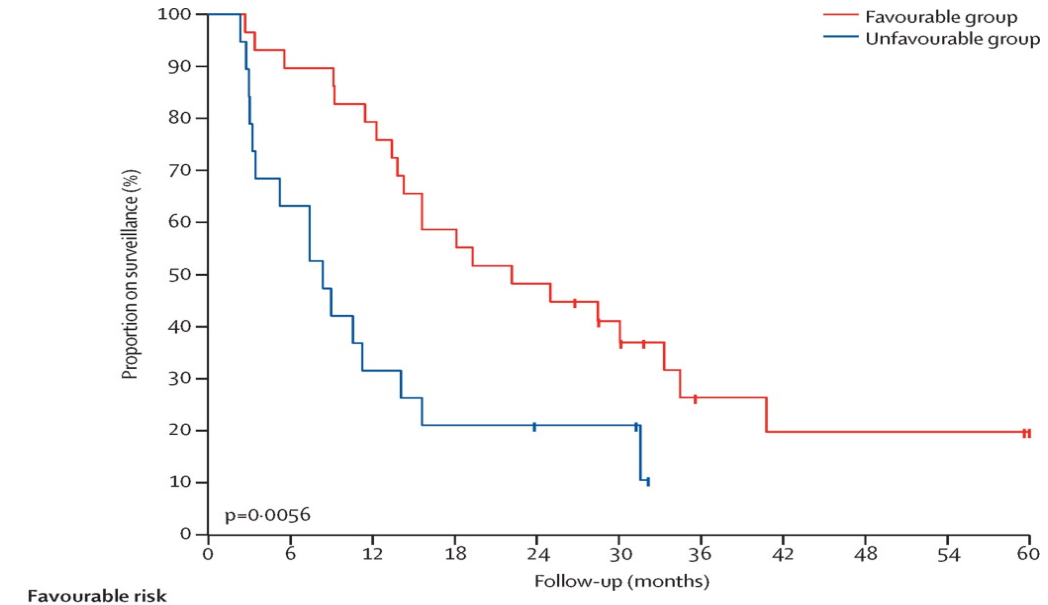


Risk Group	Number of Risk Factors	Median Survival Time
Favorable Risk (n=133)	0	37 months
Intermediate Risk (n=292)	1-2	28.5 months
Poor Risk (n=139)	>2	9.4 months

Heng DY, et al. J Clin Oncol 2009

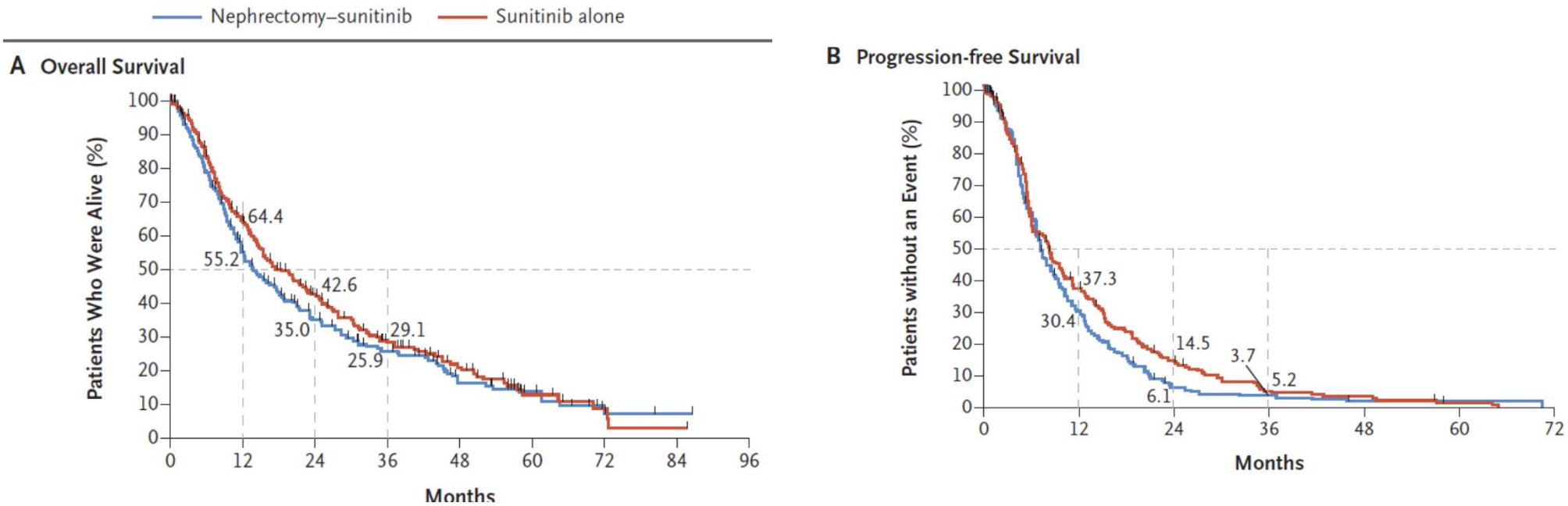
Who are candidates for active surveillance?

- Asymptomatic, low volume
- Phase II trial (n=22_
- Radiographic assessments:
  - Baseline, q3 months in year 1; q4 months in year 2; q6 months thereafter
- Median time-to-treatment initiation (TTI) for symptomatic disease was 14.9 months
  - Poor risk group expectedly had shorter TTI
- Median OS = 38.6 months



Rini B et al. Lancet Oncology 2017

Who should undergo cytoreductive nephrectomy (CN) in mRCC?: Phase III trial of sunitinib with or without CN

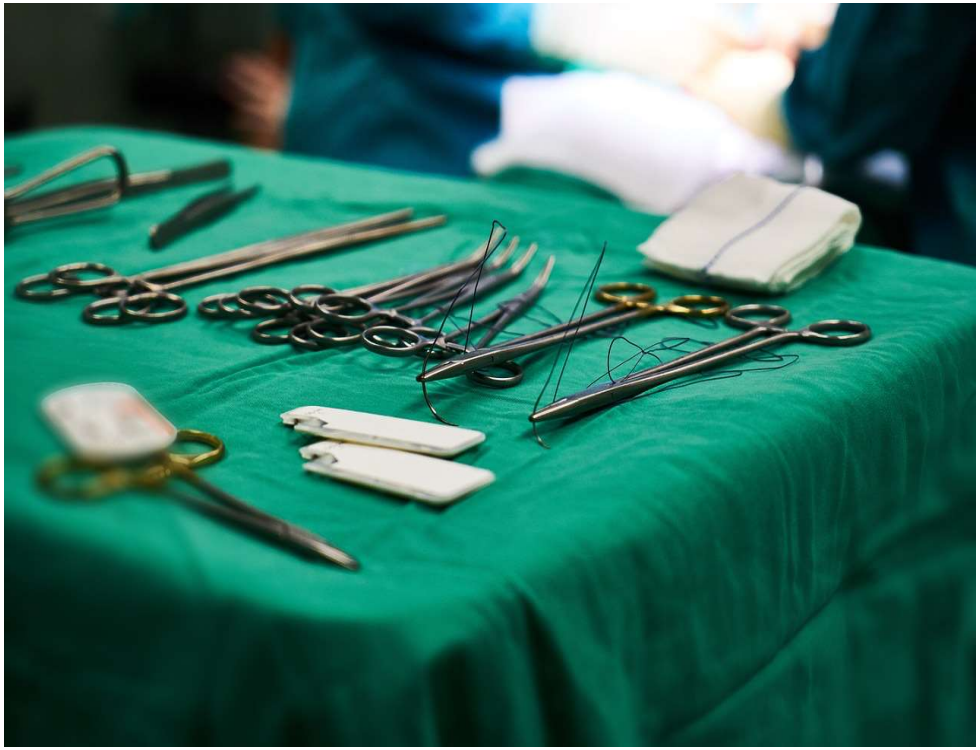


"Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were classified as having intermediate risk or poor-risk disease."

Mejean, et al NEJM 2018

Who should undergo cytoreductive nephrectomy?

- Decision must be individualized according to risk
  - Avoid reflexive decisions
  - Seek multidisciplinary input
  - Most favorable risk and some intermediate risk patients remain candidates
    - Large and/or symptomatic primary tumors, low volume metastatic disease
  - Many intermediate and nearly all poor risk patients start systemic therapy first



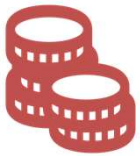
Lara and Evans, JAMA Oncol 2019

Who should undergo metastasectomy in mRCC?

- Highly selected patients
- Quality of evidence limited to retrospective studies
- Clinical features associated with benefit:
  - Good performance status
  - Isolated/oligometastatic disease
  - Disease-free interval post-nephrectomy >2 years
  - Absence of lymph node involvement
  - Lung-only disease

Ouzaid, et al. Eur Urol Oncol. 2019

If systemic therapy is indicated, why choose monotherapy?



Lower cost

Simplicity

Tolerability

Reduced drug-drug interactions

Adherence

mRCC used to be dominated by monotherapy

Single-agent Angiogenesis Inhibitors	Single-agent mTOR Inhibitors	Single-agent Immunotherapy	Combinations
• Sunitinib • Pazopanib • Cabozantinib • Axitinib • Sorafenib • Bevacizumab	• Everolimus • Temsirolimus	• HD IL2 • Nivolumab	• Bevacizumab + IFN

FDA-approved agents in mRCC

mRCC used to be dominated by monotherapy

Single-agent Angiogenesis Inhibitors	Single-agent mTOR Inhibitors	Single-agent Immunotherapy	Combinations
• Sunitinib • Pazopanib • Cabozantinib • Axitinib • Sorafenib • Bevacizumab	• Everolimus • Temsirolimus	• HD IL2 • Nivolumab	• Bevacizumab + IFN • Nivolumab + Ipilimumab • Pembrolizumab + Axitinib • Avelumab + Axitinib • Lenvantinib + Everolimus • (Cabozantinib + Nivolumab)*

*not FDA approved

… but many combinations are now established (or emerging) as SOC options

Fate of mRCC Monotherapy Control Arms

Interferon

Everolimus

Sunitinib

Scorecard: Randomized Frontline mRCC Trials

Pivotal Trial	N	Response Rate (%)	Median PFS (months)	Median OS (months)
Sunitinib vs. IFN-α[1]	750	47 vs. 12	11 vs. 5	26.4 vs. 21.8
Bevacizumab + IFN-α vs. IFN-α[2]	649	31 vs. 12	10.4 vs. 5.5	23.3 vs. 21.3
	732	25.5 vs. 13.1	8.4 vs. 4.9	18.3 vs. 17.4
Pazopanib vs. Placebo[3]	233	30 vs. 3	11.1 vs. 2.8	22.9 vs. 20.5
Pazopanib vs. Sunitinib[4]	1,110	31 vs. 25	8.4 vs. 9.5	28.4 vs. 29.3
Cabozantinib vs. Sunitinib (int/poor risk)*[5]	157	46 vs. 18	8.2 vs. 5.6	30 vs. 21.8
Temsirolimus vs. IFN-α (poor risk)[6]	626	8.6 vs. 4.8	5.5 vs. 3.1	10.9 vs. 7.3
Nivo/Ipi vs. Sunitinib (int/poor risk)[7]	1,070	41.6 vs. 26.5	11.5 vs. 8.4	NR vs 26
Avelumab/Axitinib vs. Sunitinib[8]	886	55 vs 25.5	13.8 vs 8.4	NR
Pembrolizumab/Axitinib vs. Sunitinib[9]	840	60.2 vs 39.9	15.4 vs 11.1	NR vs. 35.7
Nivolumab/Cabozantinib vs. Sunitinib[10]	651	55.7 vs. 27.1	16.6 vs. 8.3	NR (HR 0.6)

* Phase II trial

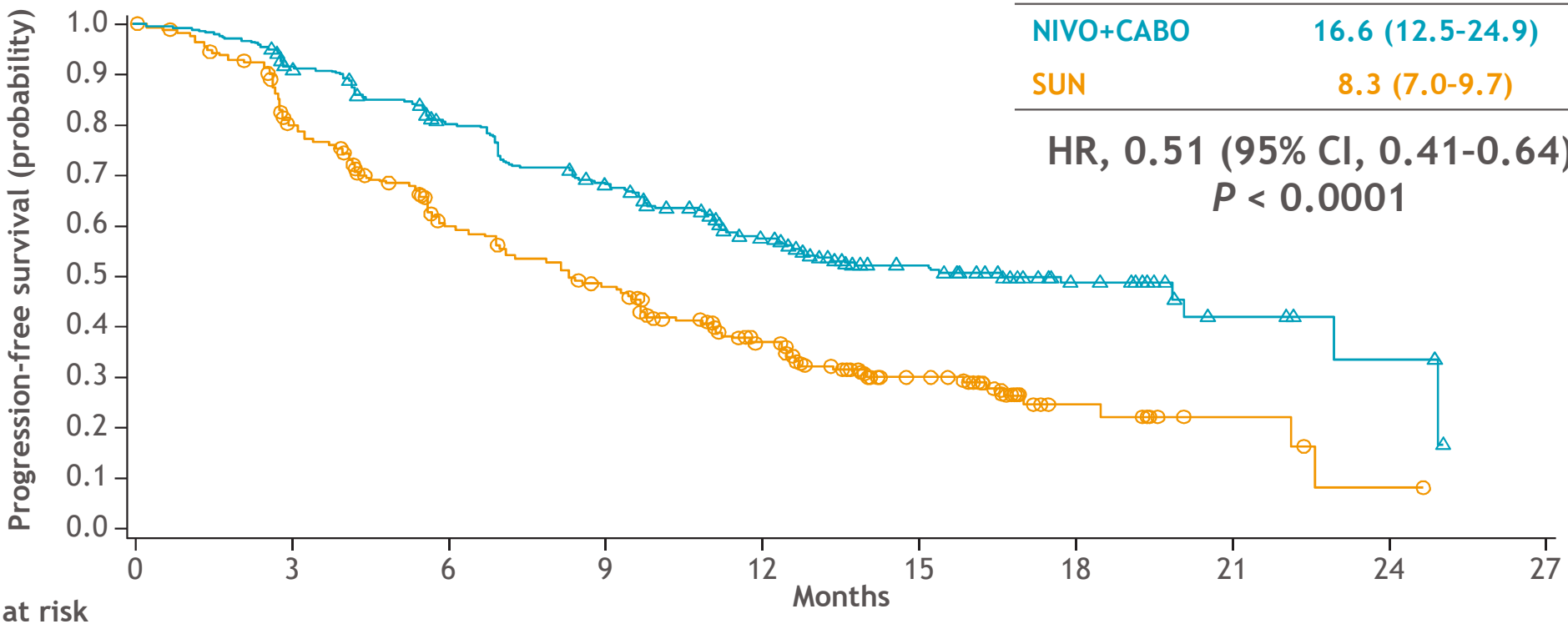
Angiogenesis inhibition | mTOR inhibition | IO-based therapy

1) Motzer NEJM 2007,2) Escudier Lancet 2007, 3) Stemberg JCO 2010, 4) Motzer NEJM 2013, 5) Choueiri JCO 2017,6) Hudes NEJM 2007, 7) Motzer NEJM 2018; 8) Motzer NEJM 2019; 9) Rini, NEJM 2019; 10) Choueiri, ESMO 2020

Systemic Frontline mRCC Therapy: Standard-of-Care 2020

- Immunotherapy-based combination therapy is SOC
  - Most mRCC patients should be considered for combination therapy
  - Immunotherapy-TKI combinations
    - Pembrolizumab-Axitinib: all risk groups
    - Avelumab-Axitinib: all risk groups
    - Nivolumab-Cabozantinib (FDA approval pending)
  - All-immunotherapy doublet
    - Nivolumab-Ipilimumab: intermediate/poor risk groups

Checkmate 9ER Phase III: Progression-free survival per BICR

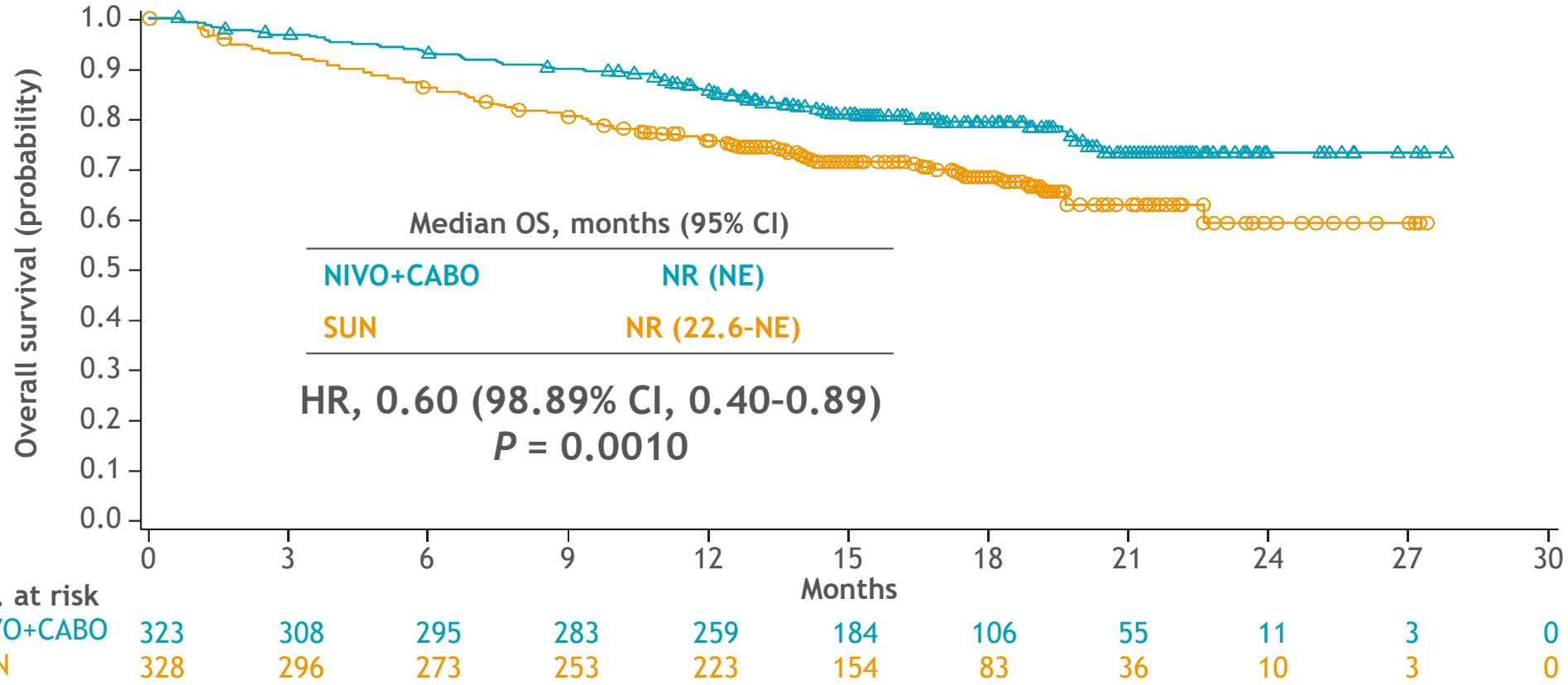


No. at risk										
NIVO+CABO	323	279	234	196	144	77	35	11	4	0
SUN	328	228	159	122	79	31	10	4	1	0

Minimum study follow-up, 10.6 months.

Choueiri, ESMO 2020

Checkmate 9ER: Overall survival



Minimum study follow-up, 10.6 months.
NE, not estimable; NR, not reached.

Choueiri, ESMO 2020

Who is NOT eligible for immunotherapy?

- Active autoimmune disease
- History of solid organ transplantation
- Supraphysiologic corticosteroids
- Chronic immunosuppressive therapy
- Personal preference (e.g., refuses IV therapy)

Frontline mRCC:
Who deserves checkpoint inhibitor monotherapy?

Answer: A few patients…

- Ineligible for (or refuse) VEGFR-TKI containing combination
- Averse to ipilimumab

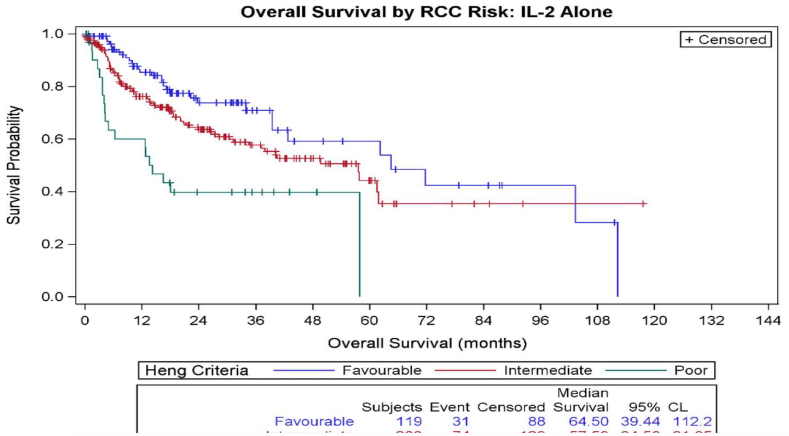
	Number of ccRCC patients	ORR (95% CI)	PFS, months(95% CI)
Pembrolizumab	110	33.6% (24.8–43.4)	6.9 (5.1–NR)
Nivolumab	123	36.4% (27.4-46.1)	8.3 (5.5-10.9)

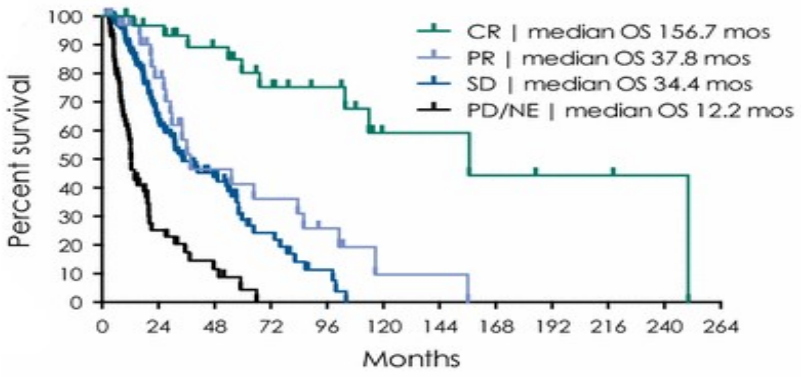
*Tykodi, ASCO 2019 (Keynote 427A); Donskov, ESMO 2018 (KN427A); Atkins, ASCO 2020 (*HCRN GU16-260)

Frontline mRCC:
Who deserves HD-IL2 monotherapy?

Answer: Almost no one

- HD IL2 still listed as monotherapy option in some guidelines
  - Reserved for robust patients with excellent PS and normal end-organ function
  - Long term survival observed, particularly those with favorable/int risk and/or CR
- Requirement for inpatient care and high toxicity limits routine use of HD IL2





Fishman, JITC 2019; Stenehjem, Cancer Immunol Immunother 2016

Frontline mRCC:
Who deserves mTORi monotherapy?

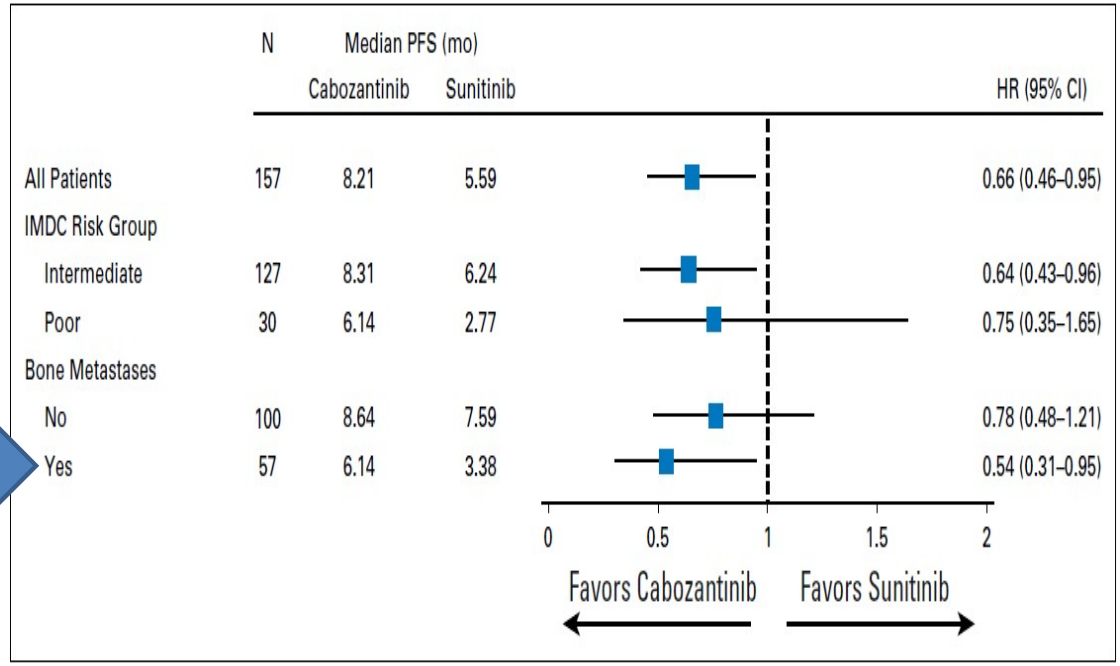
Answer: No one

- Temsirolimus monotherapy is FDA approved for frontline mRCC
- Original registration trial was in a “poor risk” subset (composite criteria)
- In era of more active, life-prolonging therapies…

There is little justification for routine Temsirolimus use

Frontline mRCC:
Who deserves VEGFR-TKI monotherapy?

1. Ineligible for IO
2. Refuses IO
3. Intolerant of IO
4. Selected patient subsets
   - Bone-only metastases? (Cabozantinib)
   - Non-clear cell histology
   - Some favorable risk patients?

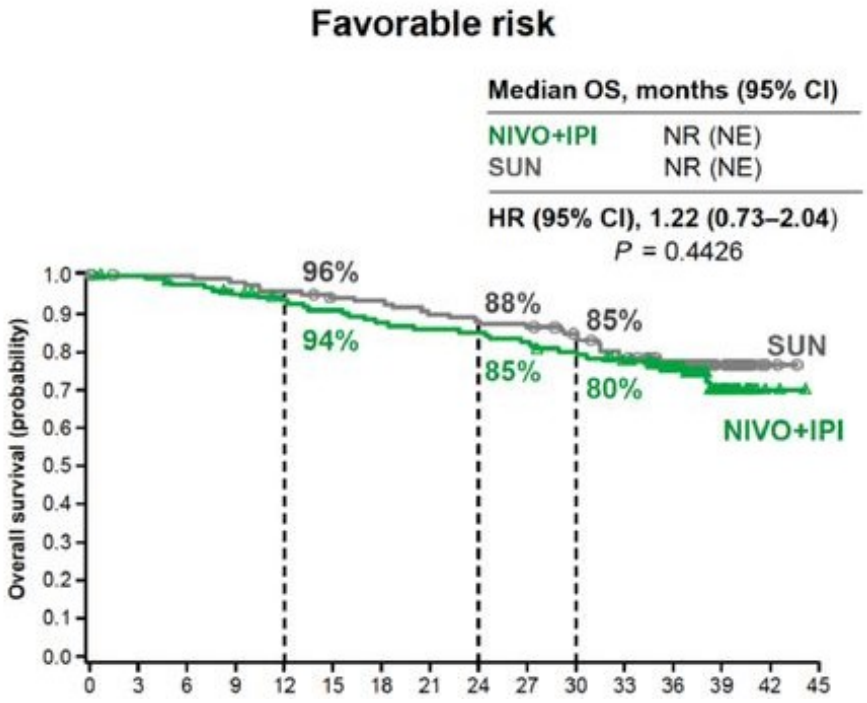


Choueiri, JCO 2017

Checkmate 214: Nivo/Ipi vs. Sunitinib

<u>Favorable risk subset:</u> Higher RR and PFS with sunitinib; no OS difference

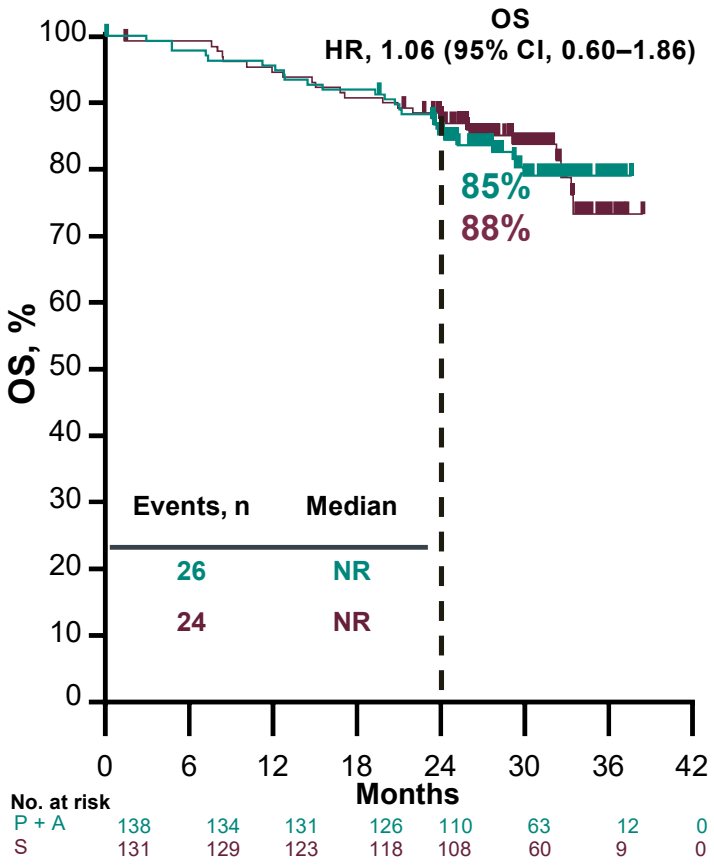
Outcome	N = 249	
	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR, % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS, median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68)	
	P < 0.0001	

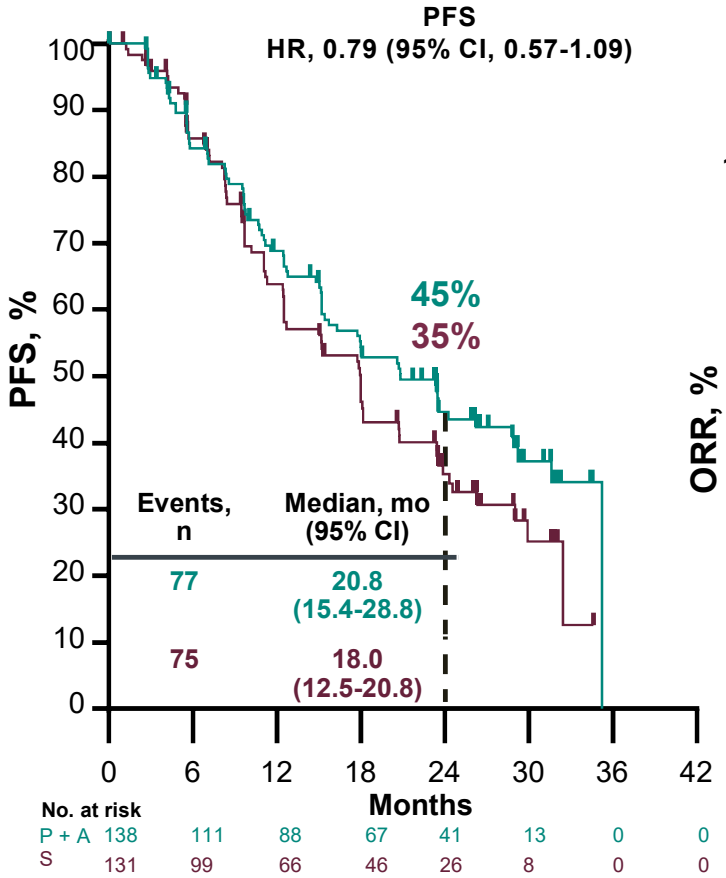


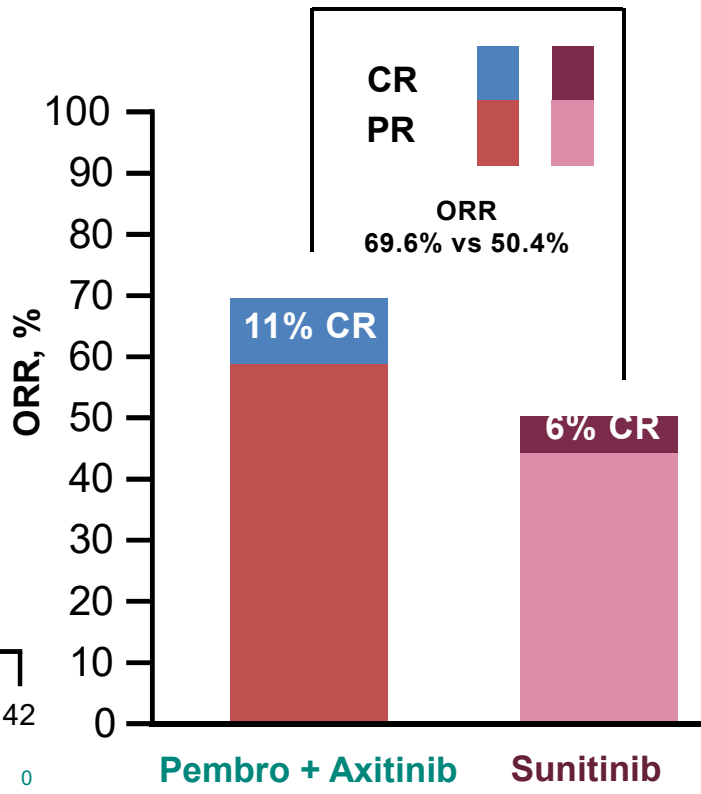
Tannir, ASCO GU 2019 Escudier et al ESMO 2017

Keynote 426: Pembro/Axitinib vs. Sunitinib

No OS or PFS Benefit with Pembro/Axi in Favorable Risk







Plimack, ASCO 2020

Summary: Frontline mRCC Therapy

- Key steps for the practicing clinician:
  - Risk stratify
  - Seek multidisciplinary input
  - Consider active surveillance and cytoreduction
  - Assess for immunotherapy eligibility
- Combination immunotherapy-based therapy is SOC for most
- Monotherapy is limited to a small (and diminishing) subset
- Clinical trial participation, where appropriate