Systemic Therapy in RCC: Updates and New Directions

Marc R. Matrana, MD, MSc, FACP
Director, Precision Cancer Therapies Program

November 2021

Ochsner™
Healthcare With Peace Of Mind™

Outline

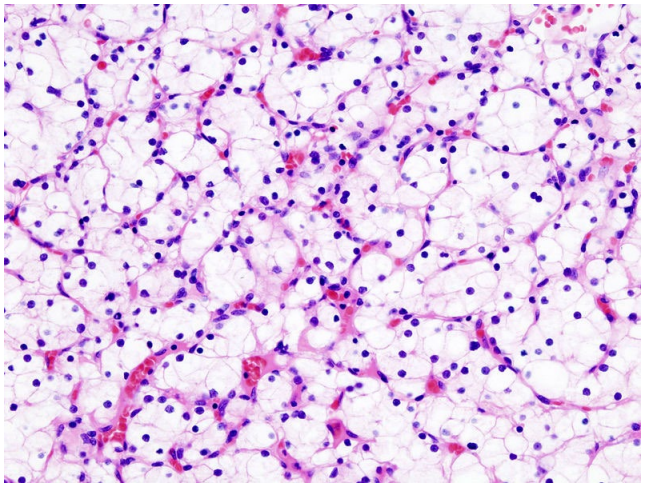
- Background and Localized RCC
- Targeted Therapies and Immunotherapies in mRCC
- Adjuvant Systemic Therapies in RCC
- Selecting a Frontline Treatment Option
- Salvage Therapy
- Future Directions
- Ochsner Trials

Disclosures

- **Speaker bureau and/or consulting for: SeaGen, Pfizer, Janssen, Astellas, AstraZeneca, Strata Oncology, Eisai, EMD Serano, Exelixis, BristolMeyersSquibb, Genentech, and Merck.**

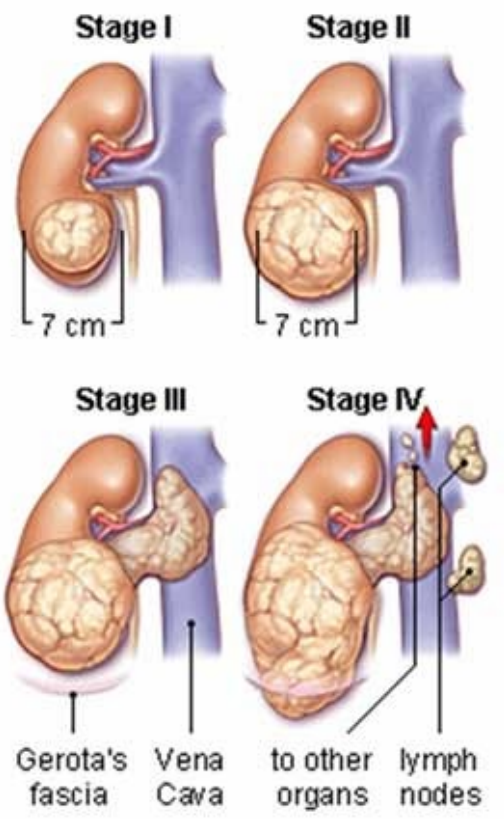
Background: Renal Cell Carcinoma

- Originate within the renal cortex
- 80,000+ new cases in the US annually
- 14,000 deaths annually
- Represent 2-3% of all cancers
- About 70% are clear cell subtype



Localized RCC

- **Localized (even advanced, but fully resectable) is best treated with surgery**



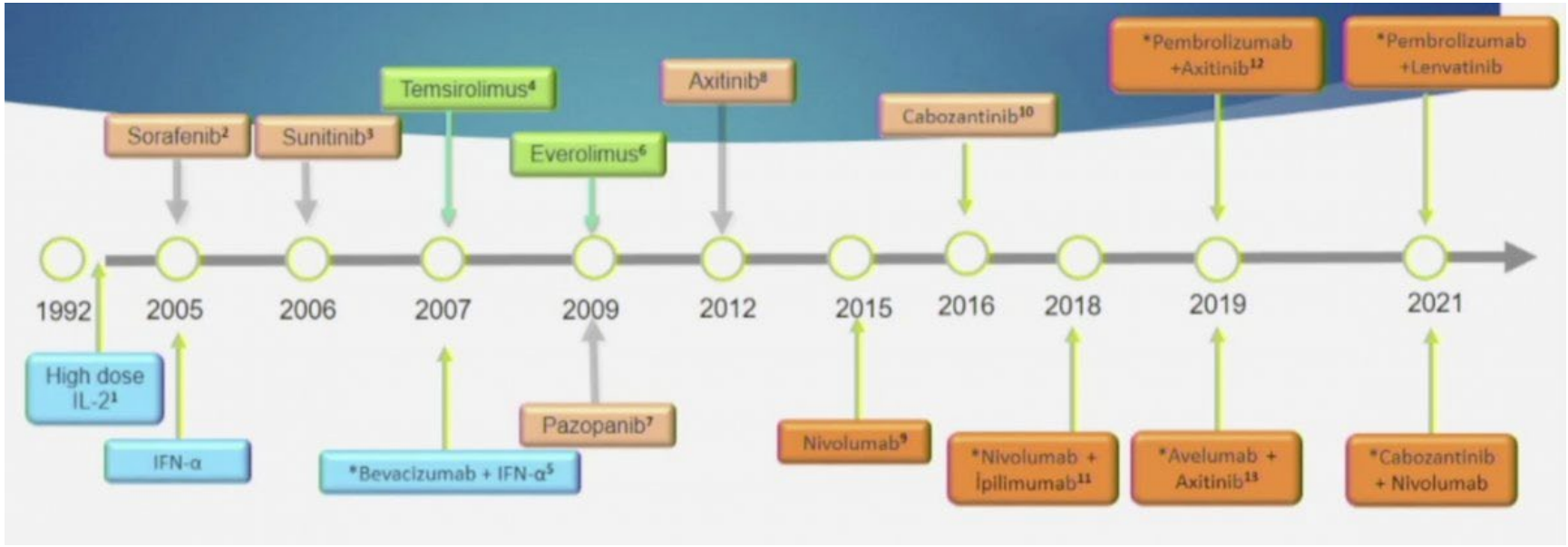
Historical Treatments for Metastatic Renal Cell Carcinoma

- IFN-a and IL-2 were previously mainstays of therapy.
- Both are toxic and associated with low response rates.
  - 10% mortality with IL-2
  - Not tolerated in patients with co-morbidities, poor PS
- IL-2 is only therapy known to lead to CR in mRCC
  - <10% PR
  - <5% durable CR

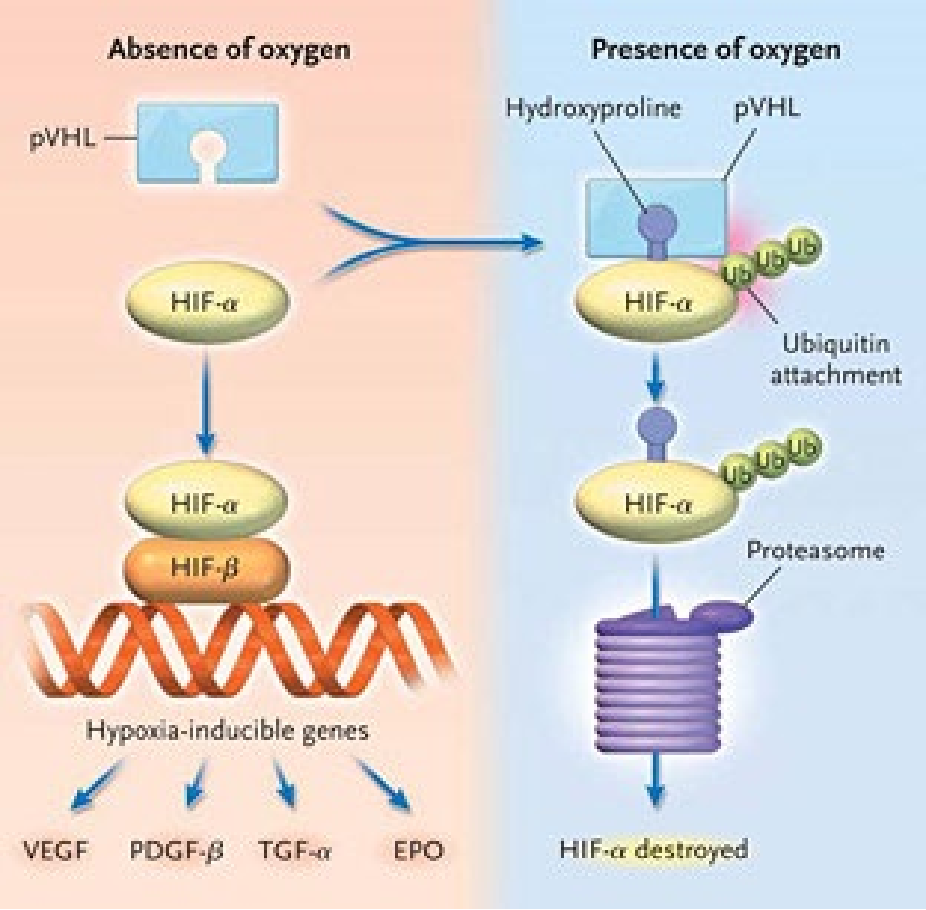
Historical Treatments for mRCC

- In the last 15 years, molecular pathways of RCC have been defined leading to new therapies.
- Since December 2005, over a dozen new agents have been approved in the USA for the treatment of advanced RCC.
- Great majority of mRCC patients now have highly efficacious therapy options.

Approvals of Systemic Therapies in RCC

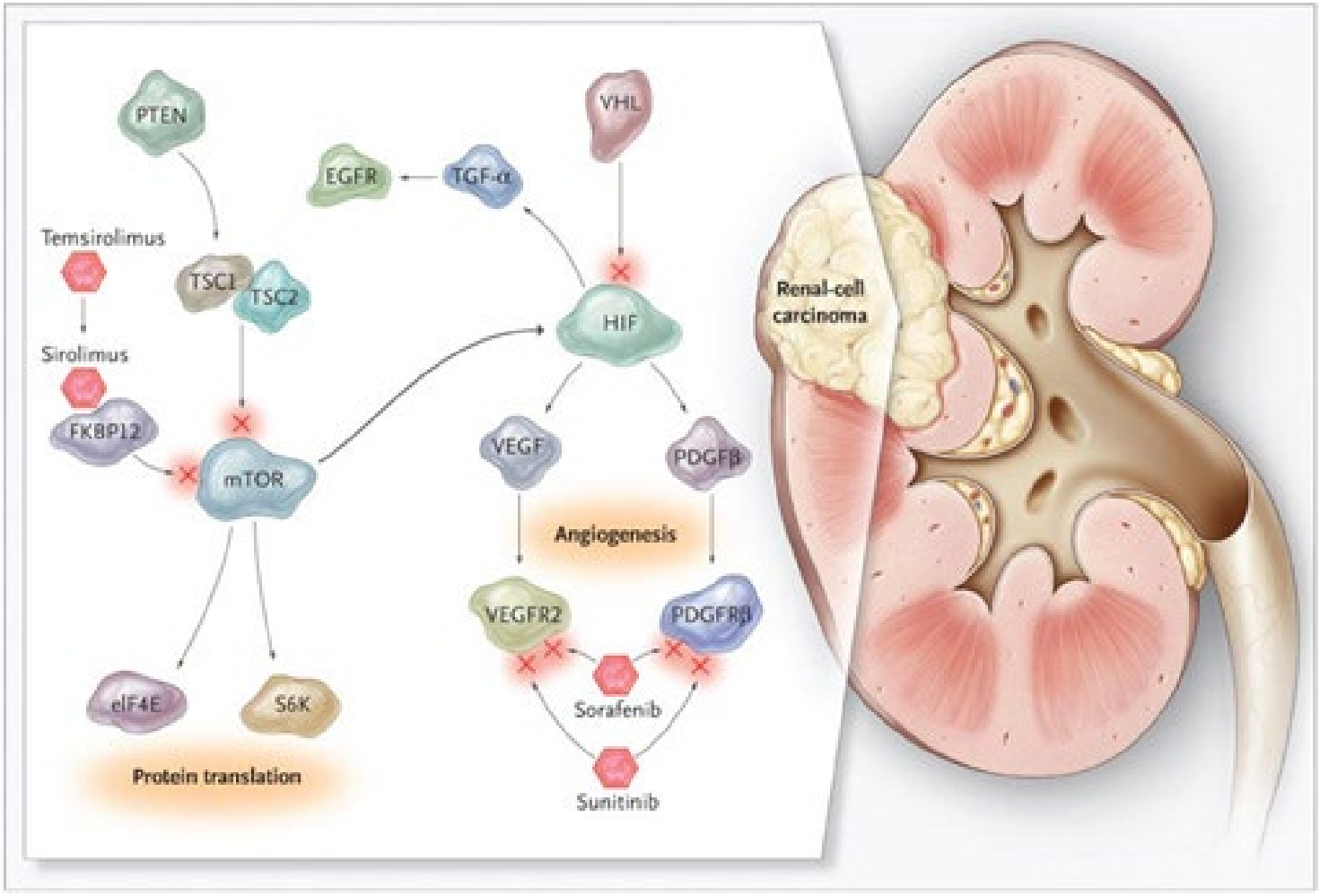


Molecular Targets

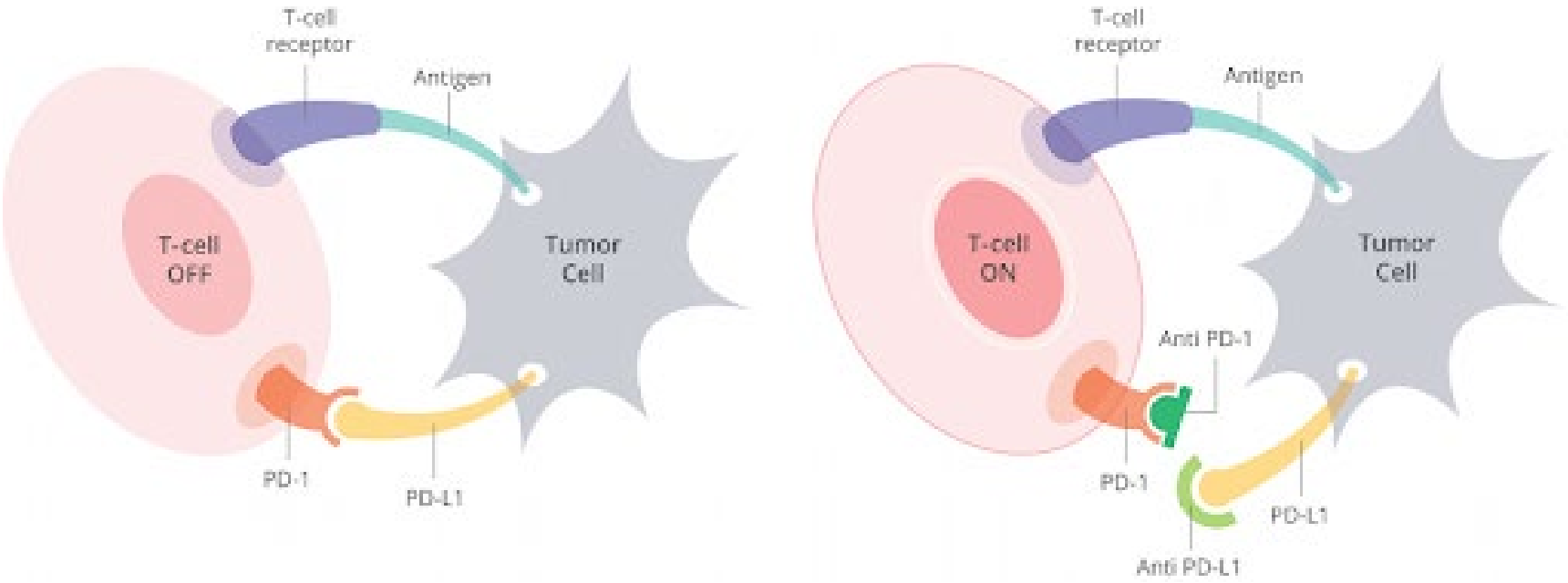


Ochsner™
Healthcare With Peace Of Mind™

Molecular Targets



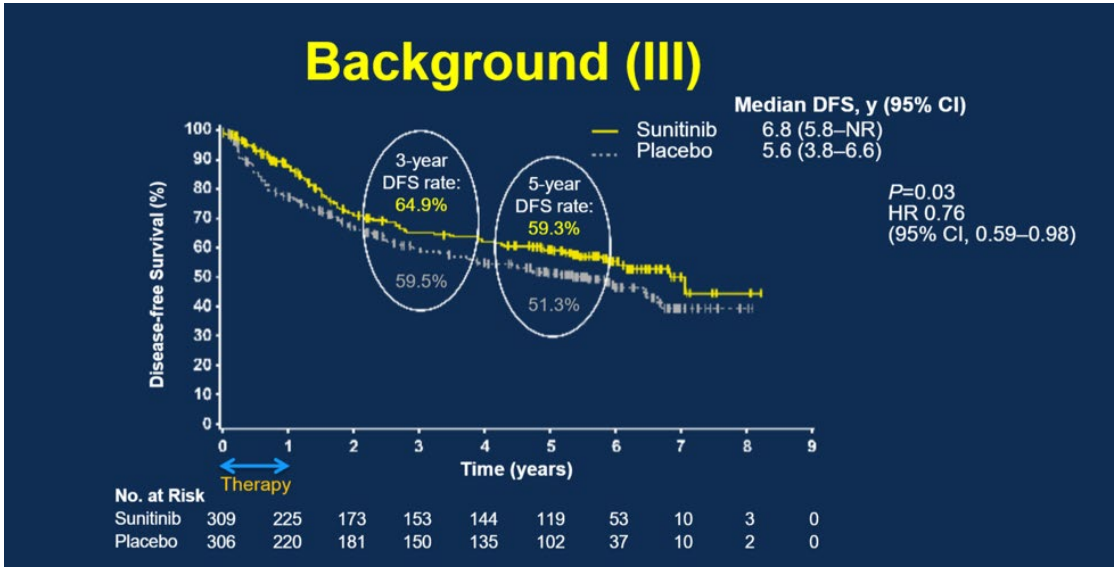
Checkpoint Inhibition



Adjuvant Therapy in RCC

- **The oral TKI sunitinib is "approved" in the adjuvant setting for localized RCC following resection.**

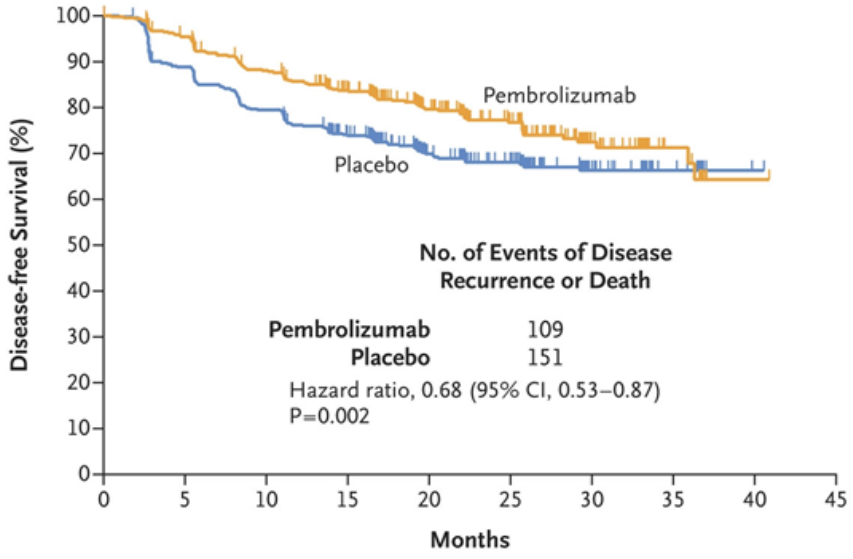
- **This approval was based on improvements in disease-free survival compared with placebo in patients with high-risk disease in the S-TRAC trial, but there was no overall survival benefit, and its use is associated with significant toxicity**



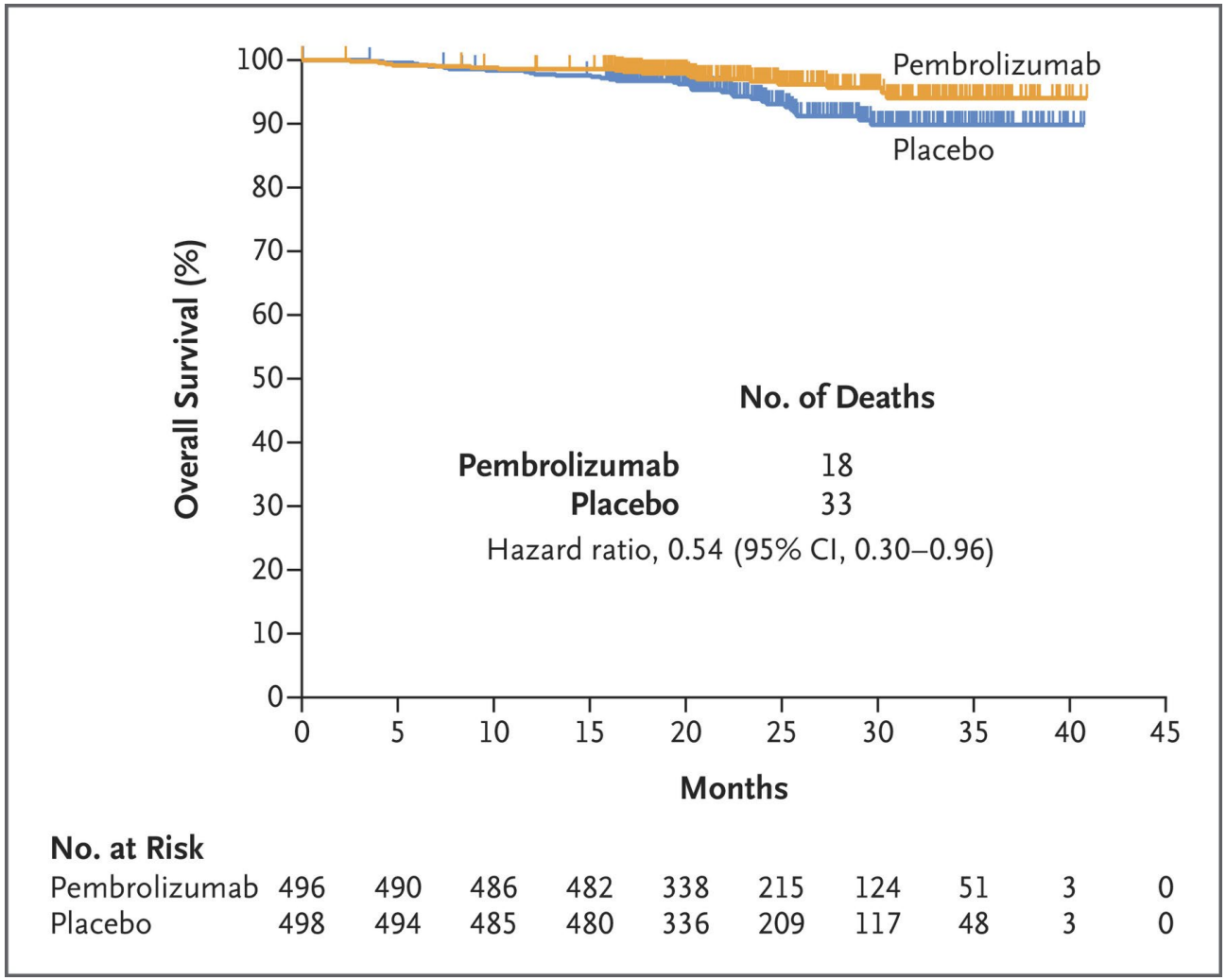
Adjuvant Therapy in RCC - KEYNOTE-564 Trial

- **Randomized patients with high risk of recurrence (i.e., tumor stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumor stage 3 or higher, regional lymph-node metastasis, or stage M1 with NED) to receive pembrolizumab or placebo for approx. 1 year following nephrectomy.**

- **DFS at 30 months, 75.2% vs. 65.5%**



Adjuvant Therapy in RCC - KEYNOTE-564 Trial

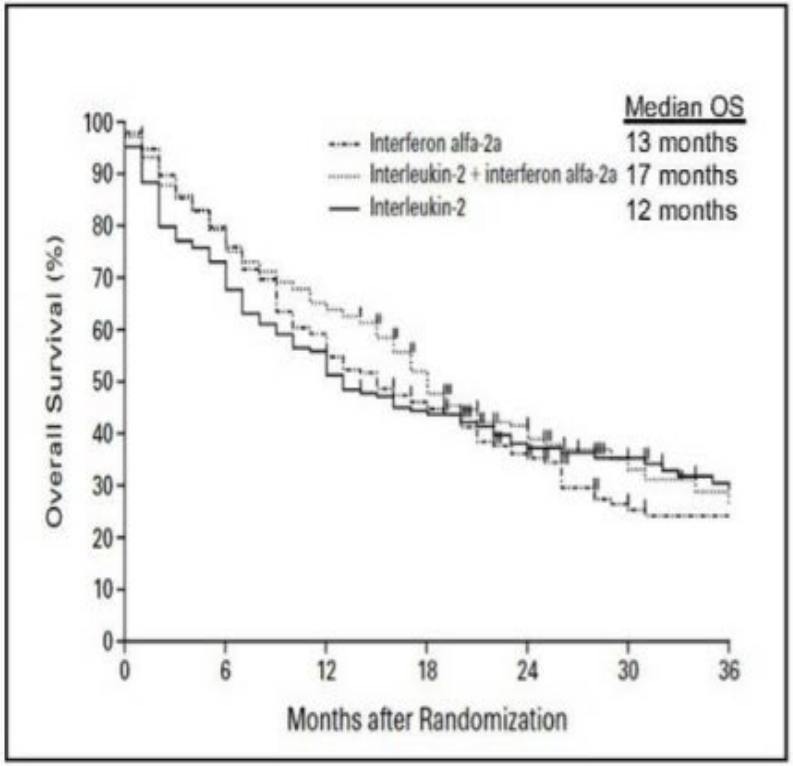


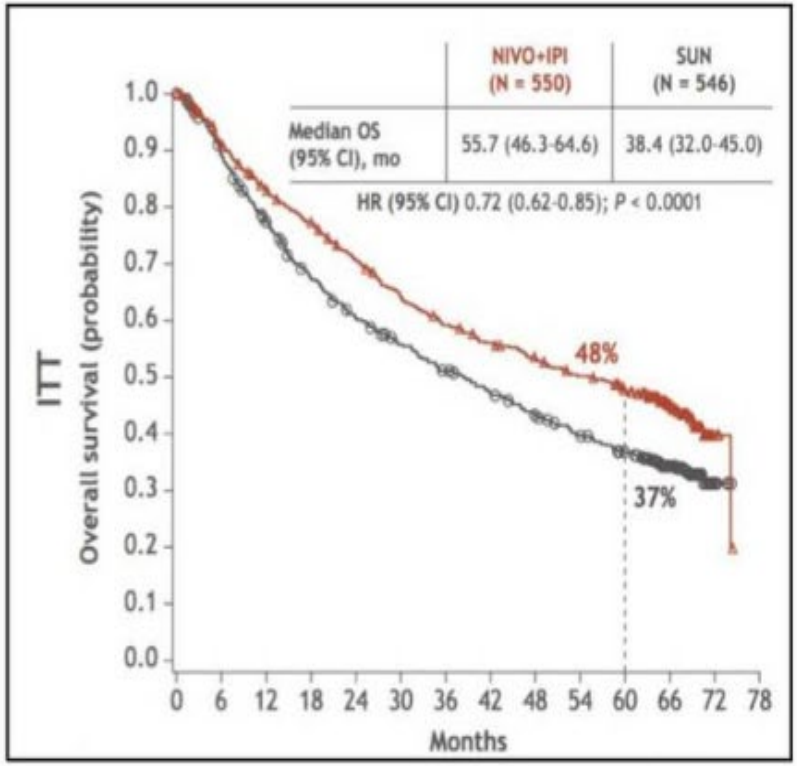
Background: Metastatic Renal Cell Carcinoma

- Approximately 25% of patients with RCC present with metastasis at the time of initial diagnosis.

- 30% of patients develop recurrent disease after treatment of localized disease and require systemic therapy.

The Good News: Progress





Negrier S *NEJM* 1998

Motzer RJ ESMO 2021

Immune checkpoint therapy in ccRCC

Front-line:

Nivolumab+ipilimumab: RR-42%; G3+ toxicities-46% (2018)

Pembrolizumab+axitinib: RR-59%; G3+ toxicities-63% (2019)

Avelumab+axitinib: RR-51%; G3+ toxicities-71% (2019)

Nivolumab+cabozantinib: RR-56%; G3+ toxicties-61% (2020)

Pembrolizumb+Lenvatinib: RR-71%; G3+ toxicities-82.4% (2021)

Second-line:

Nivolumab: RR-25%; G3+ toxicties-19% (2015)

1. NEJM 2015
2. NEJM 2018
3. NEJM 2019
4. NEJM 2019
5. NEJM 2020
6. NEJM 2021

First – Line Therapies

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)

First – Line Therapies – CHECKMATE 9ER

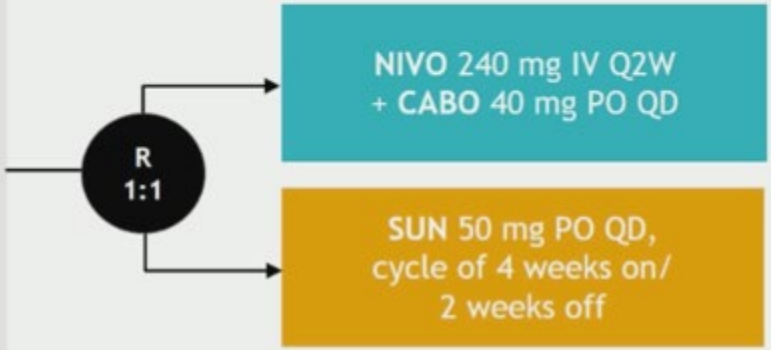
N = 651

Key inclusion criteria[1,2]

- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

Stratification factors:

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



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

Median study follow-up, 18.1 months (range, 10.6-30.6 months)

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.

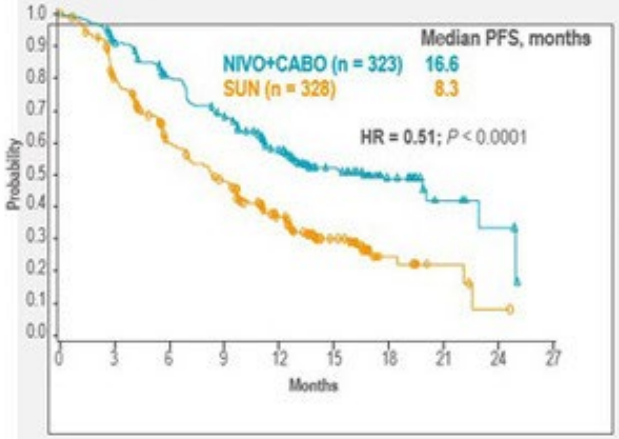
1. Clinicaltrials.gov/ct2/show/NCT03141177. Accessed June 8, 2020; 2. Choueiri TK et al. Poster presented at the American Society of Clinical Oncology Annual Meeting 2018. TPS4598.

First – Line Therapies - CHECKMATE 9ER

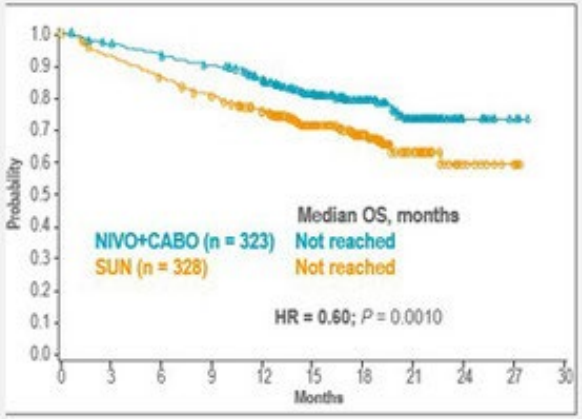
VIRTUAL 2020 ESMO congress

CheckMate 9ER efficacy: PFS, OS, and ORR

Progression-free survival (primary)



Overall survival (secondary)

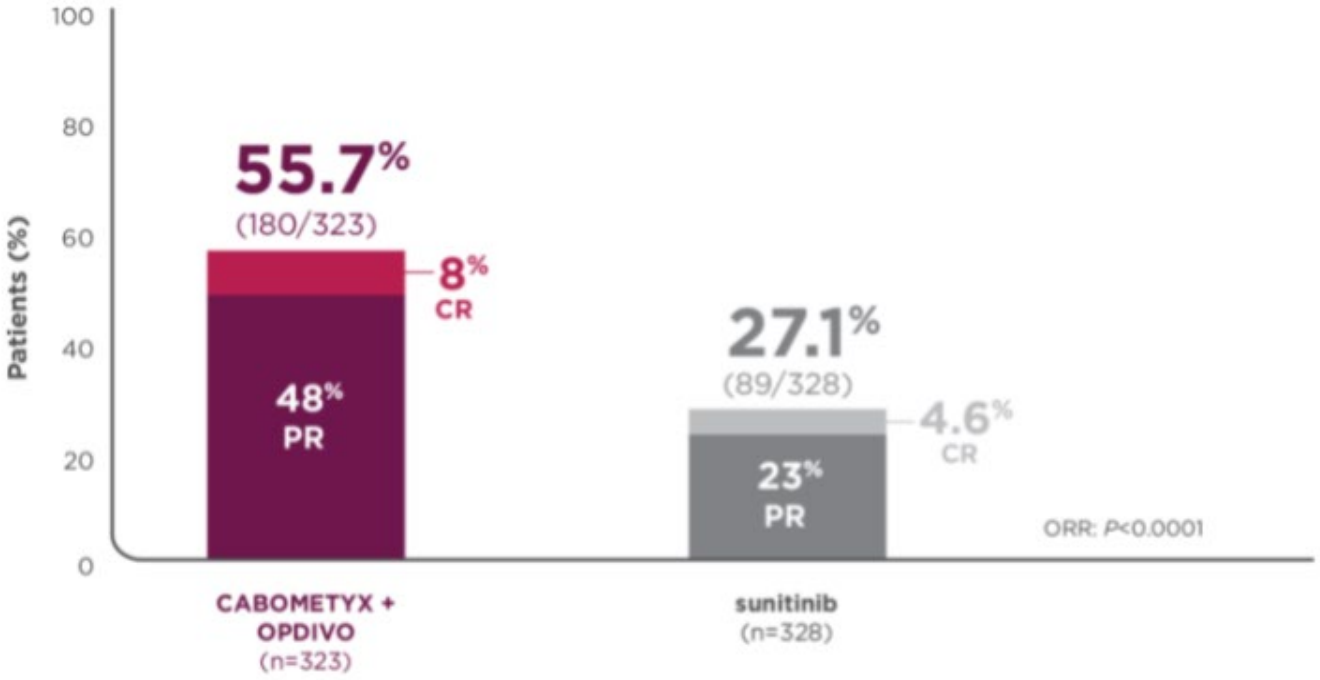


Objective response (secondary)

Outcome, %	NIVO+CABO (n = 323)	SUN (n = 328)
Confirmed ORR	55.7	27.1
	$P < 0.0001$	
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
Not evaluable/not assessed[a]	6.5	17.1

[a]Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per blinded independent central review, or other reason not reported/specified.
BOR, best overall response; ORR, objective response rate; PFS, progression-free survival.

First – Line Therapies - CHECKMATE 9ER

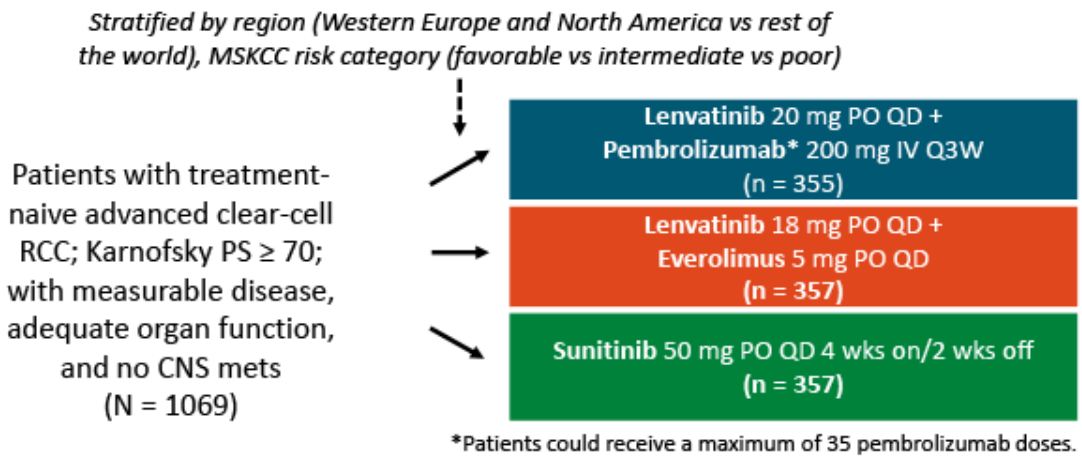


Disease control rate of nivo+cabo ~95%

First – Line Therapies – KEYNOTE-581 (CLEAR Study)

CLEAR: First-line Lenvatinib + Pembrolizumab or Everolimus vs Sunitinib in Advanced RCC

- Multicenter, randomized, open-label phase III trial



Cutoff for this final PFS and interim OS analyses: August 28, 2020

- Median follow-up: 27 mos
- Analysis at ~ 338 PFS events for 90% power and a 2-sided $\alpha = .045$

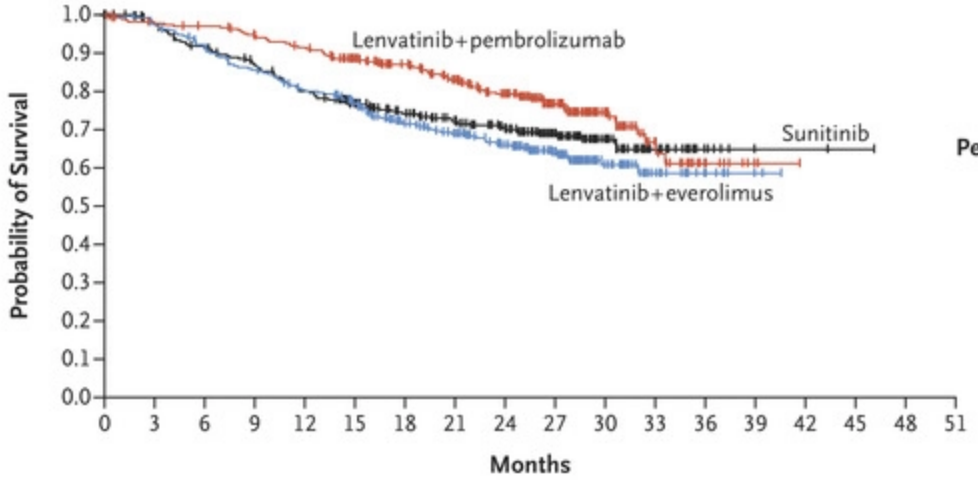
- **Primary endpoint:** PFS by IRC (per RECIST v1.1)

- **Secondary endpoints:** OS, ORR by IRC (per RECIST v1.1), safety, HRQoL
- **Key exploratory endpoints: DoR, biomarkers**

Motzer. ASCO GU 2021. Abstr 269. NCT02811861.

Slide credit: clinicaloptions.com

A Kaplan–Meier Analysis of Overall Survival



	Median Overall Survival (95% CI)
	mo
Lenvatinib+ Pembrolizumab	NR (33.6–NE)
Lenvatinib+ Everolimus	NR (NE–NE)
Sunitinib	NR (NE–NE)

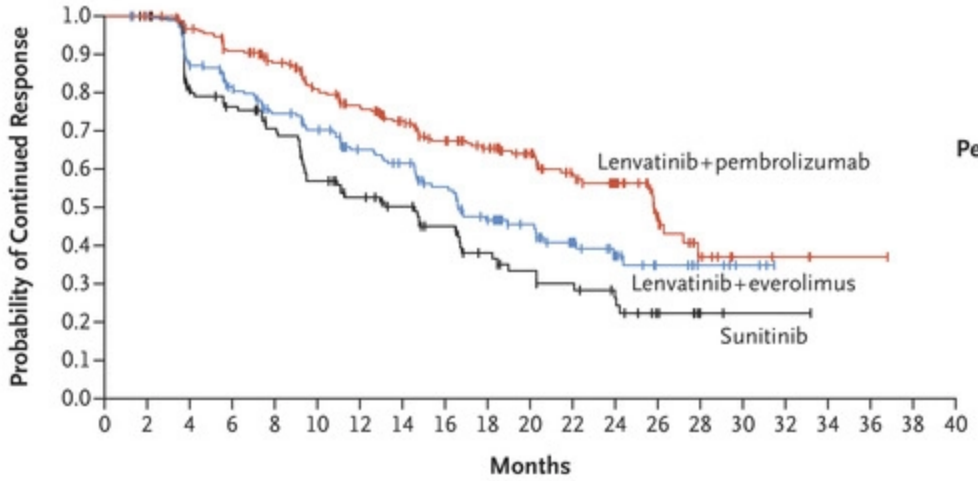
Hazard ratio for death (lenvatinib+pembrolizumab vs. sunitinib), 0.66 (95% CI, 0.49–0.88); P=0.005

Hazard ratio for death (lenvatinib+everolimus vs. sunitinib), 1.15 (95% CI, 0.88–1.50); P=0.30

No. at Risk

Lenvatinib+pembrolizumab	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0		
Lenvatinib+everolimus	357	346	321	299	277	246	205	183	154	109	46	22	8	2	0		
Sunitinib	357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

B Kaplan–Meier Analysis of Response Duration

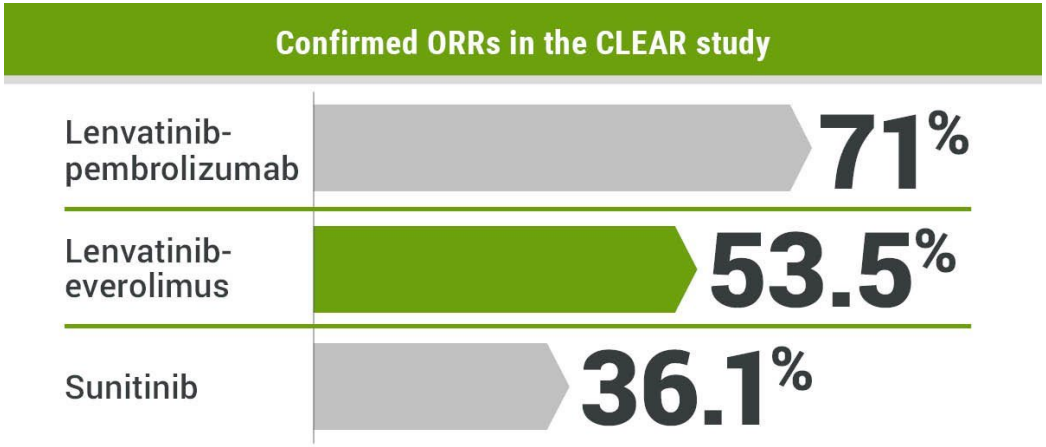


	Median Duration of Response (95% CI)
	mo
Lenvatinib+ Pembrolizumab	25.8 (22.1–27.9)
Lenvatinib+ Everolimus	16.6 (14.6–20.6)
Sunitinib	14.6 (9.4–16.7)

No. at Risk

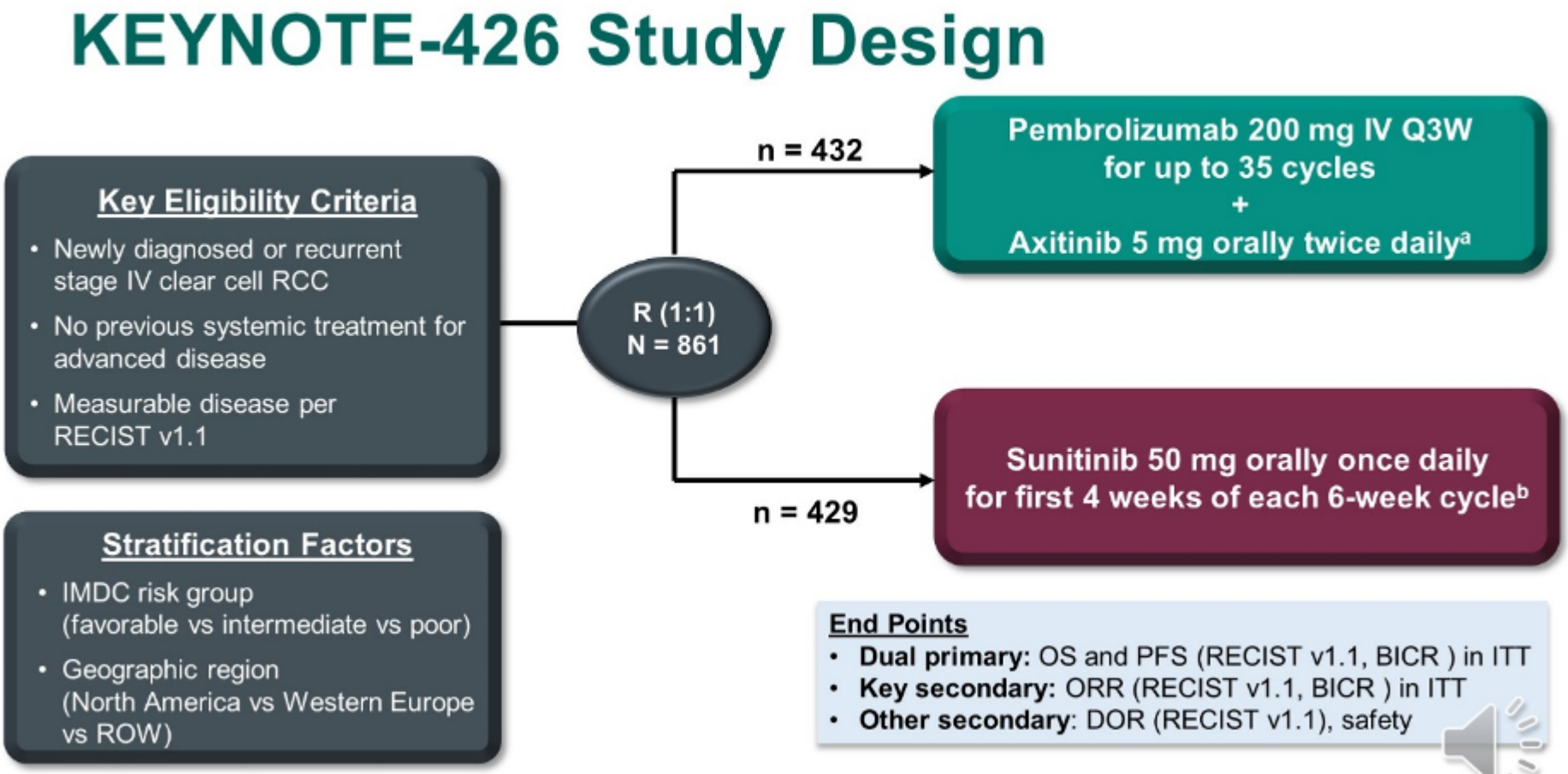
Lenvatinib+pembrolizumab	252	250	234	215	197	172	153	131	112	101	83	63	45	23	9	4	3	1	1	0
Lenvatinib+everolimus	191	186	159	142	125	113	93	83	65	50	39	27	18	11	6	3	0			
Sunitinib	129	125	91	82	73	57	47	40	33	25	20	17	13	7	2	1	1	0		

First – Line Therapies – KEYNOTE-581 (CLEAR Study)



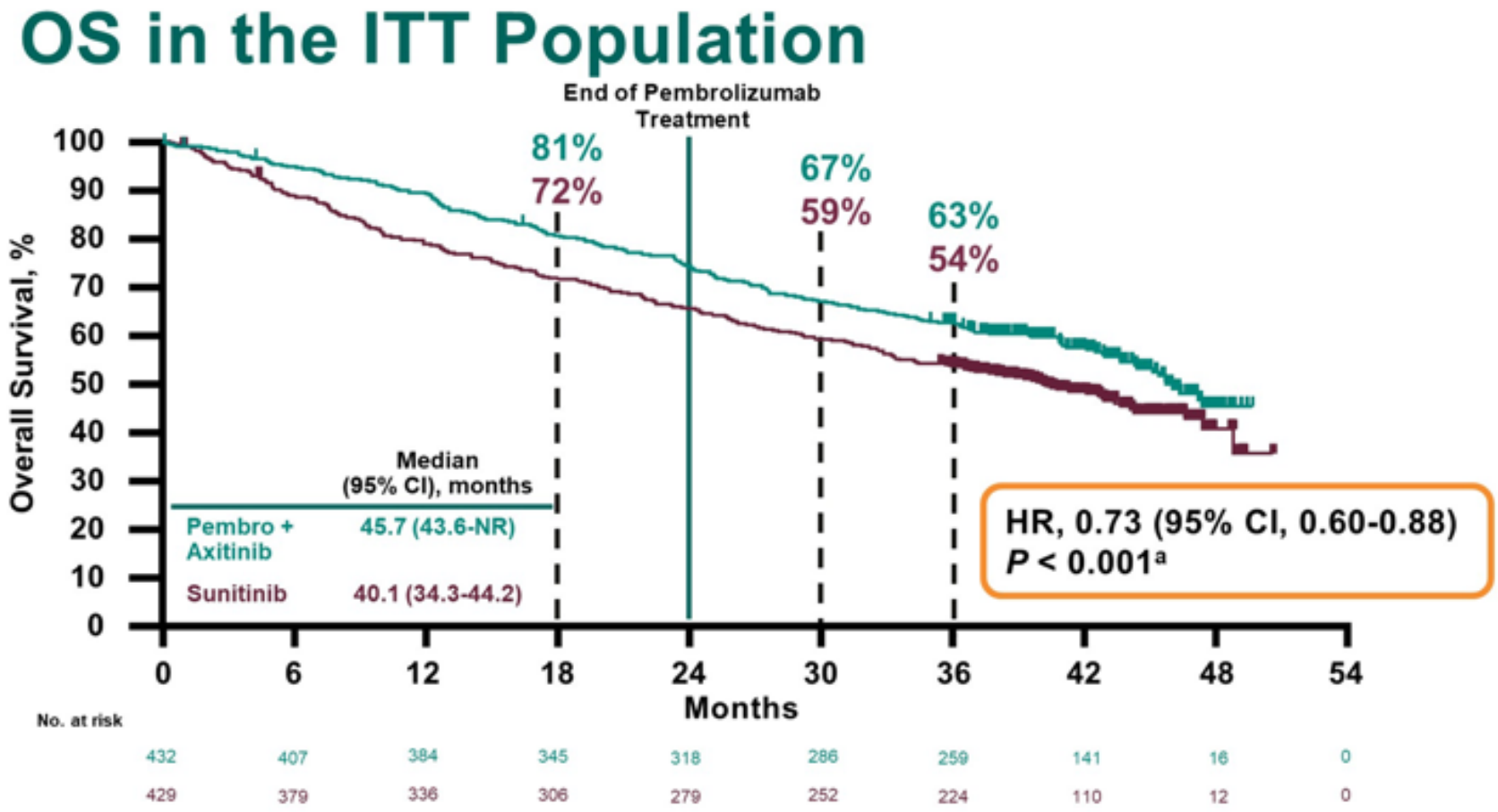
CR = 16.1 with len+pembro
mDOR=25.8
DCR ~95%

First – Line Therapies – KEYNOTE 426



[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 6, 2020.

First – Line Therapies - KEYNOTE 426

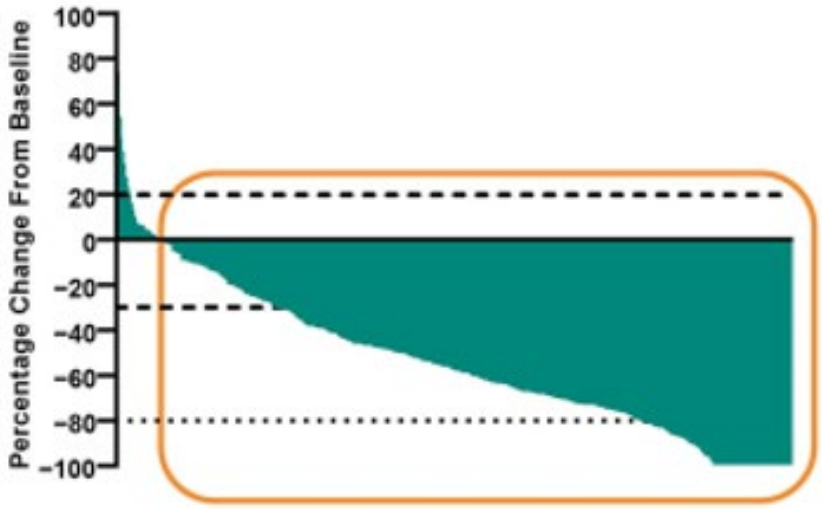


First – Line Therapies - KEYNOTE 426

Target Lesion Change From Baseline
ITT Population[a]

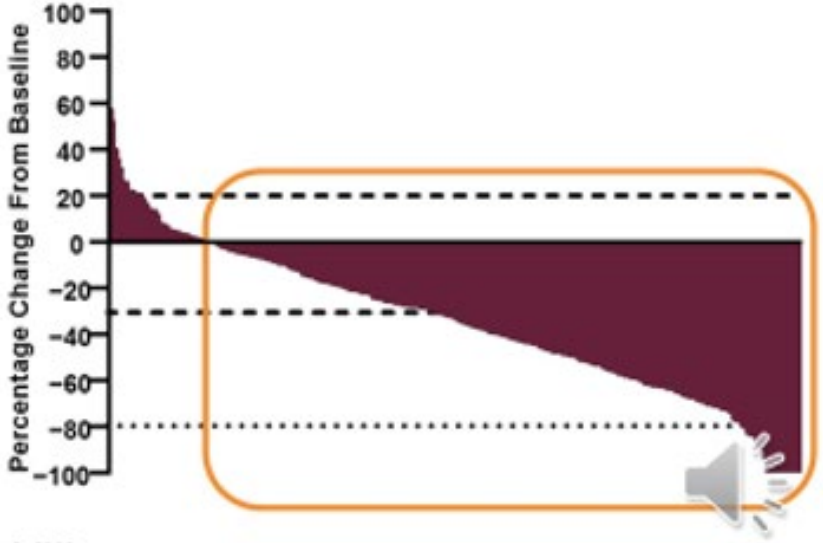
Pembrolizumab + Axitinib

- 94% of patients experienced any reduction in tumor burden



Sunitinib

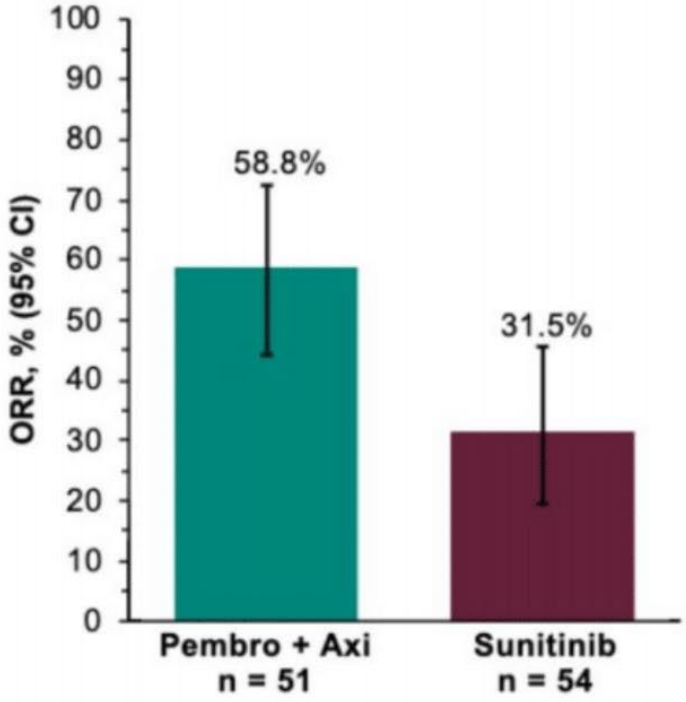
- 86% of patients experienced reduction in tumor burden

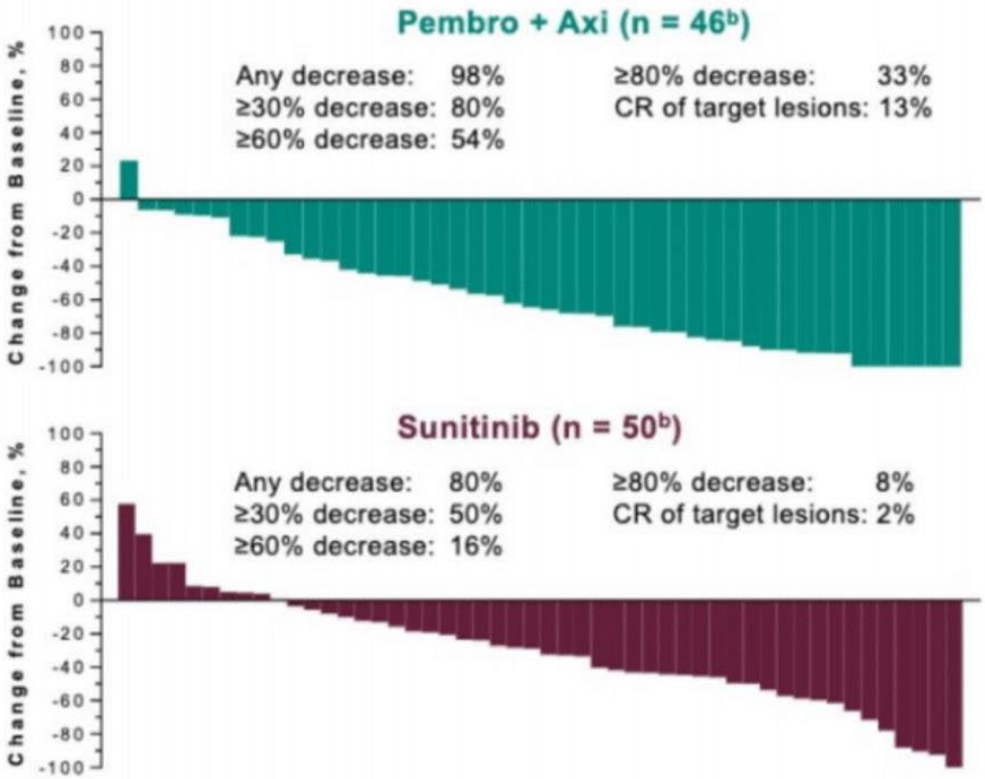


[a]Patients with measurable disease at baseline and ≥1 postbaseline measurement. Data cutoff: January 6, 2020.

First – Line Therapies - KEYNOTE 426

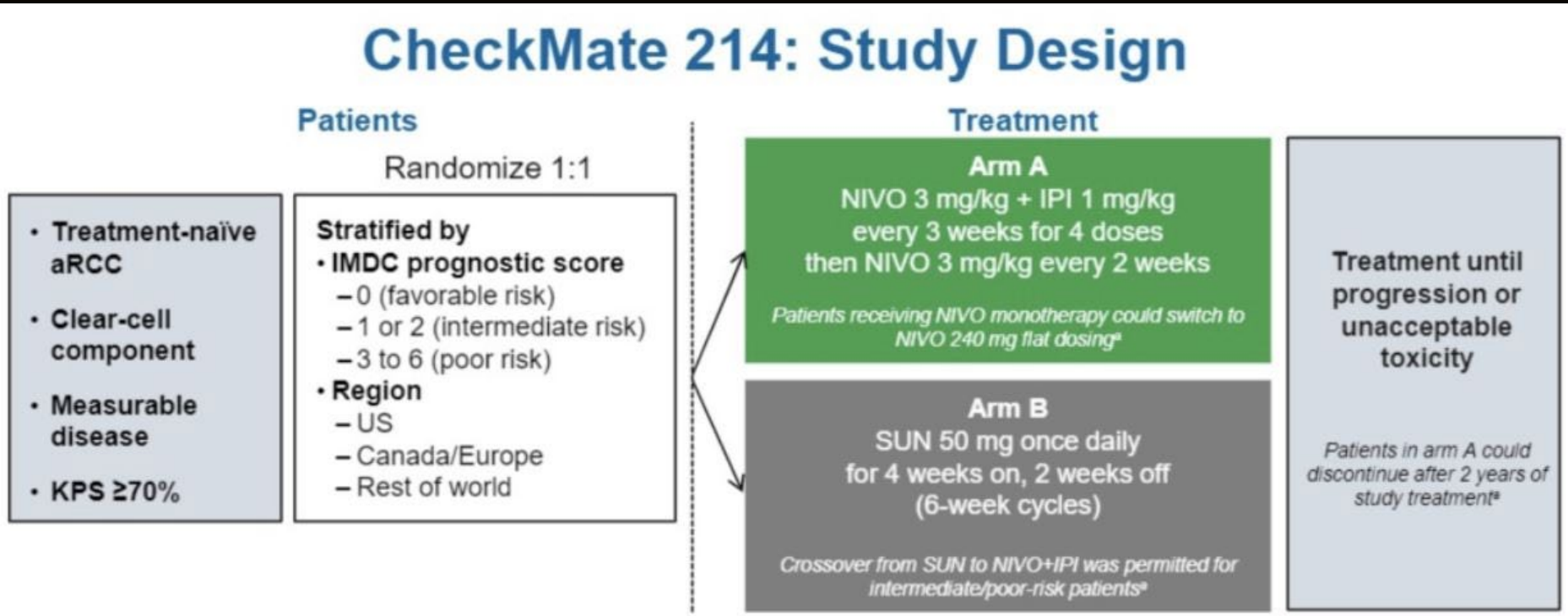
Response: Presence of Sarcomatoid Features[a]





[a]Among the 578 participants with known status assessed by local pathology review and as indicated on the eCRF. [b]Pts with ≥1 measurable lesion per RECIST v1.1 by BICR at baseline and ≥1 post-baseline imaging assessment evaluable per RECIST v1.1 by BICR. Data cutoff date: Aug 24, 2018.

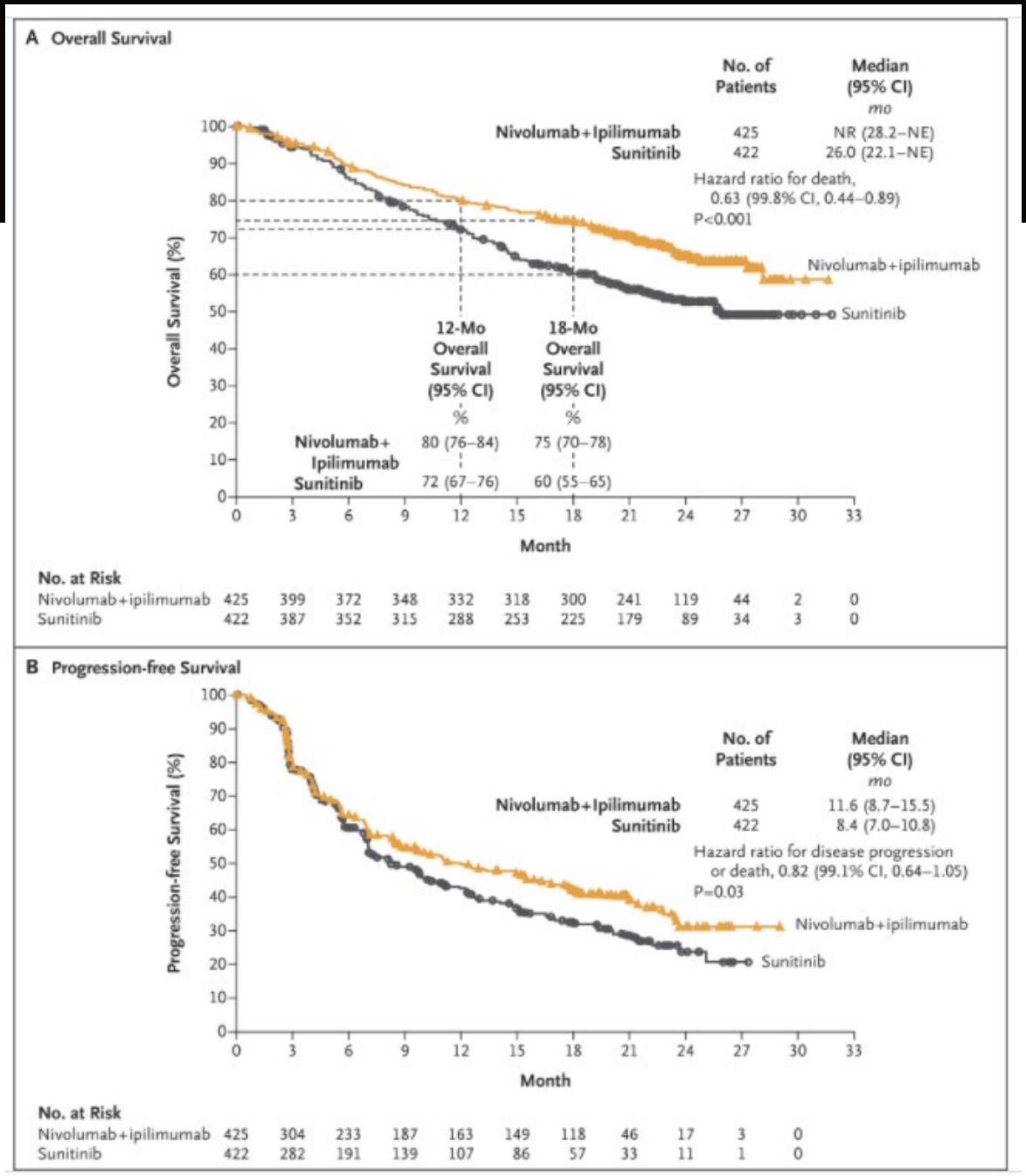
First – Line Therapies – CHECKMATE 214



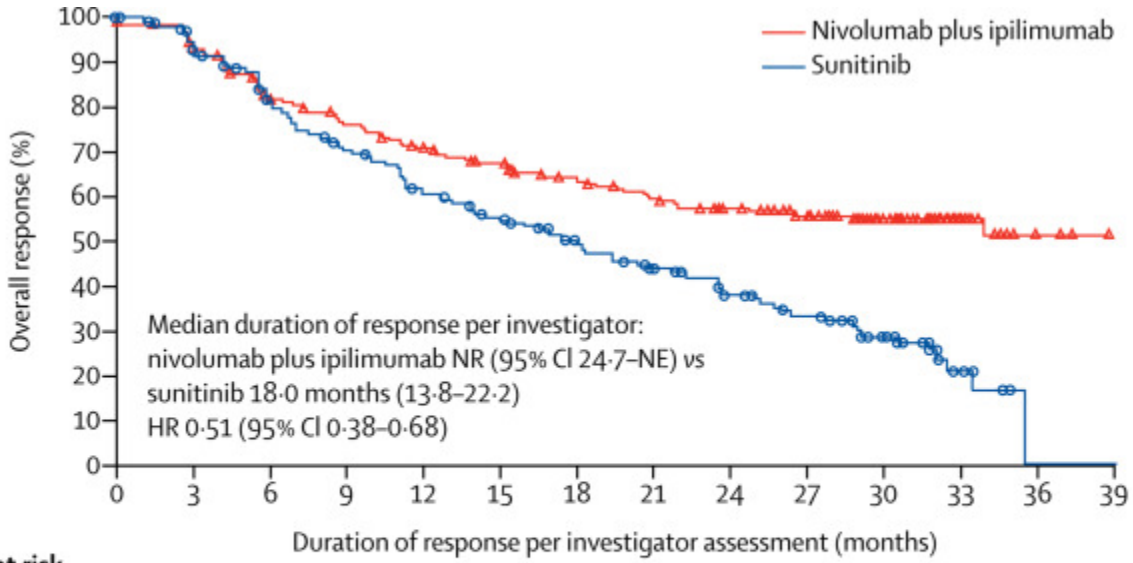
Primary endpoints: ORR, PFS (both per IRRC), and OS in IMDC intermediate- and poor-risk patients

Secondary endpoints: ORR, PFS (both per IRRC), and OS in any-risk patients (ITT); safety in all treated patients

Exploratory endpoints: ORR, PFS (both per IRRC), and OS in IMDC favorable-risk patients


A Overall Survival
No. of Patients
Median (95% CI) mo
Nivolumab+Ipilimumab 425 NR (28.2–NE)
Sunitinib 422 26.0 (22.1–NE)
Hazard ratio for death, 0.63 (99.8% CI, 0.44–0.89)
P<0.001
Nivolumab+ipilimumab
Sunitinib
Overall Survival (%)
12-Mo Overall Survival (95% CI) %
18-Mo Overall Survival (95% CI) %
Nivolumab+Ipilimumab 80 (76–84) 75 (70–78)
Sunitinib 72 (67–76) 60 (55–65)
Month
No. at Risk
Nivolumab+ipilimumab 425 399 372 348 332 318 300 241 119 44 2 0
Sunitinib 422 387 352 315 288 253 225 179 89 34 3 0
B Progression-free Survival
No. of Patients
Median (95% CI) mo
Nivolumab+Ipilimumab 425 11.6 (8.7–15.5)
Sunitinib 422 8.4 (7.0–10.8)
Hazard ratio for disease progression or death, 0.82 (99.1% CI, 0.64–1.05)
P=0.03
Nivolumab+ipilimumab
Sunitinib
Progression-free Survival (%)
Month
No. at Risk
Nivolumab+ipilimumab 425 304 233 187 163 149 118 46 17 3 0
Sunitinib 422 282 191 139 107 86 57 33 11 1 0

Checkmate 214



Number at risk (number censored)														
Nivolumab plus ipilimumab	225 (0)	205 (5)	175 (10)	160 (13)	146 (16)	136 (19)	120 (27)	111 (29)	102 (34)	90 (43)	55 (77)	20 (112)	4 (127)	0 (131)
Sunitinib	186 (0)	164 (9)	136 (17)	116 (19)	98 (21)	86 (24)	72 (30)	60 (34)	49 (37)	40 (40)	27 (48)	7 (64)	0 (69)	0 (69)

(Some) Limitations of Current IO Therapy

Good News	Less Good News
High response rates	Still see patients with primary PD
Durable responses	But patients eventually develop PD
Effective combinations	But not all patients "need" IO
IO has produced the best results in RCC	Most patients still die of RCC
IO-combinations are novel	Many "me-too" trials and limited to CPI

First – Line Therapies - THOUGHTS

Issue in first-line is too many options to choose from

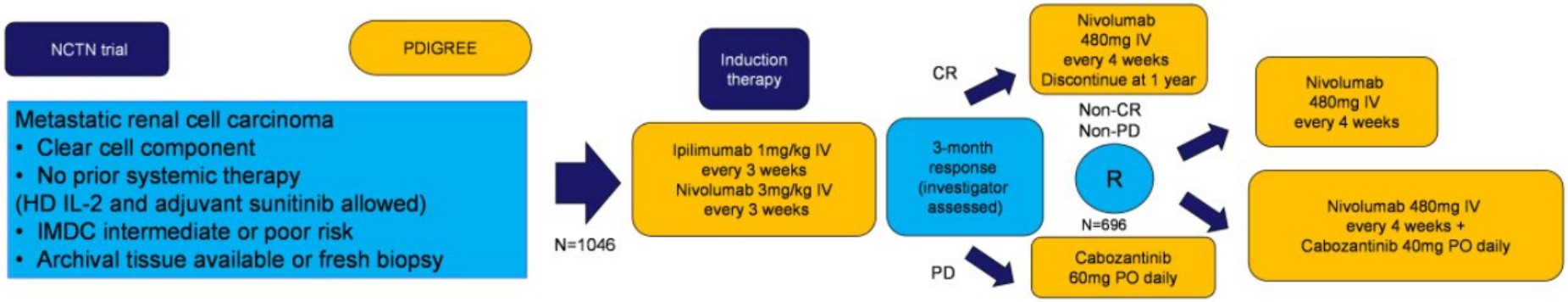
No head-to-head comparisons

No one know if sequencing IO-TKI or IO combos after combination therapy is effective.

Where will HIF-alpha inhibitors fit?

Future of first line is likely triplets+ or induction/maintenance combos based on response

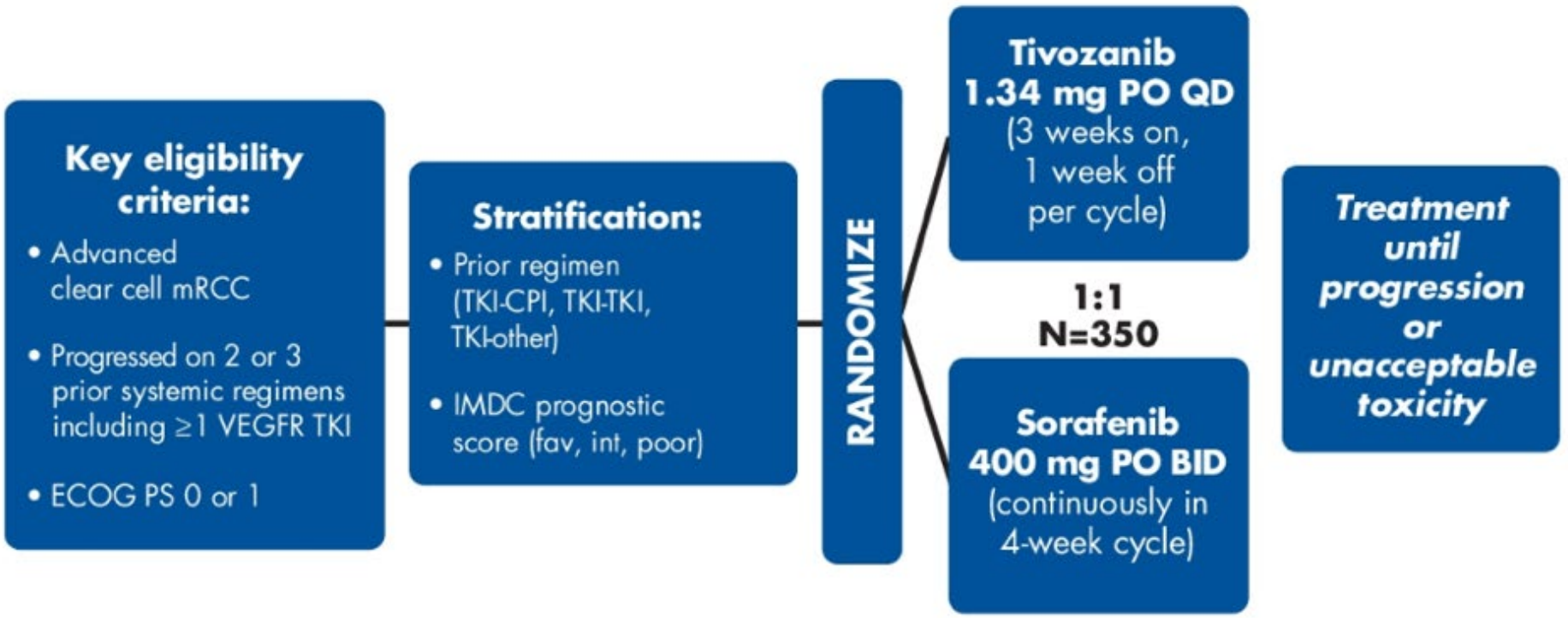
Current Ochsner Trials



Subsequent-Line Therapies

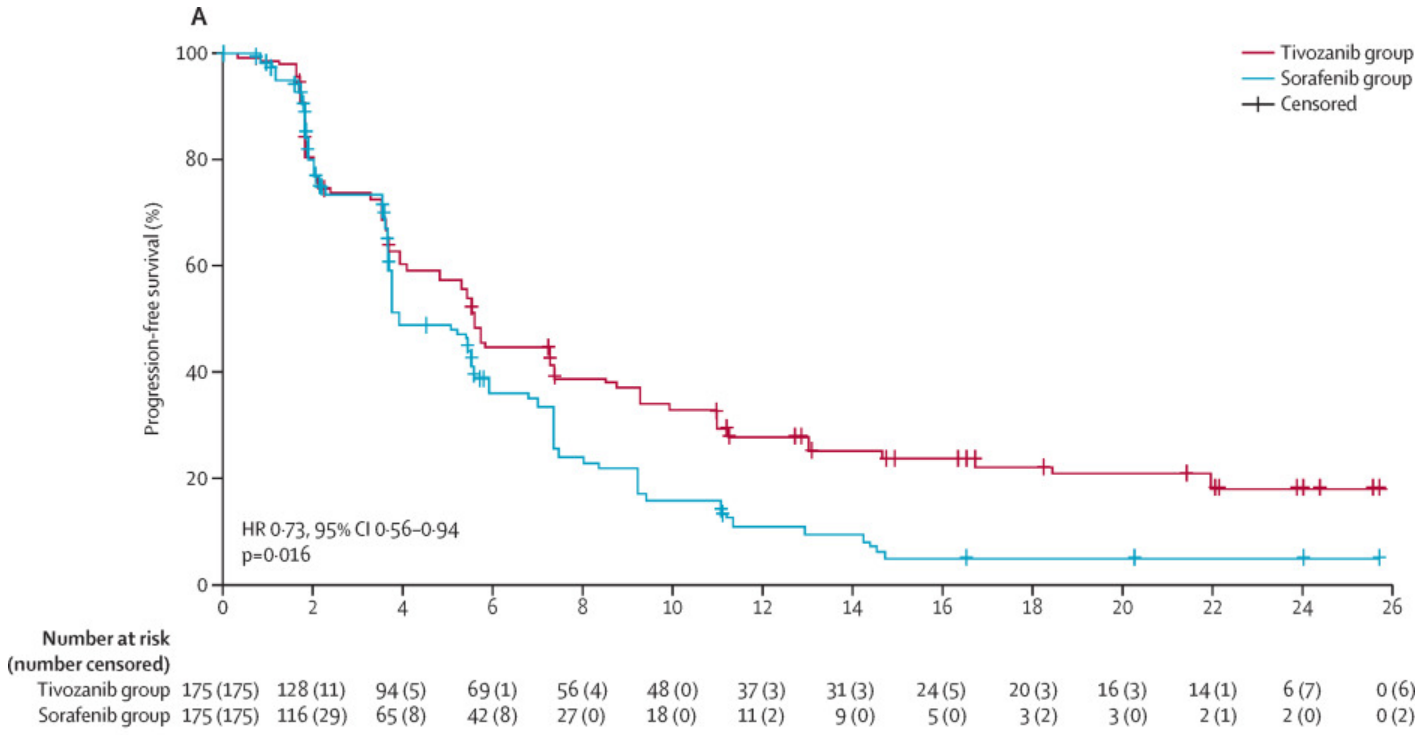
SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Cabozantinib (category 1) • Lenvatinib + everolimus • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] (category 1) • 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) • Belzutifan (category 2B)

Third-line therapy



Ochsner™
Healthcare With Peace Of Mind™

Third-line therapy

- 

28% of patients treated with tivozanib were progression free at 1 year vs 11% with sorafenib
18% of patients were progression free at 2 years vs 5% with sorafenib

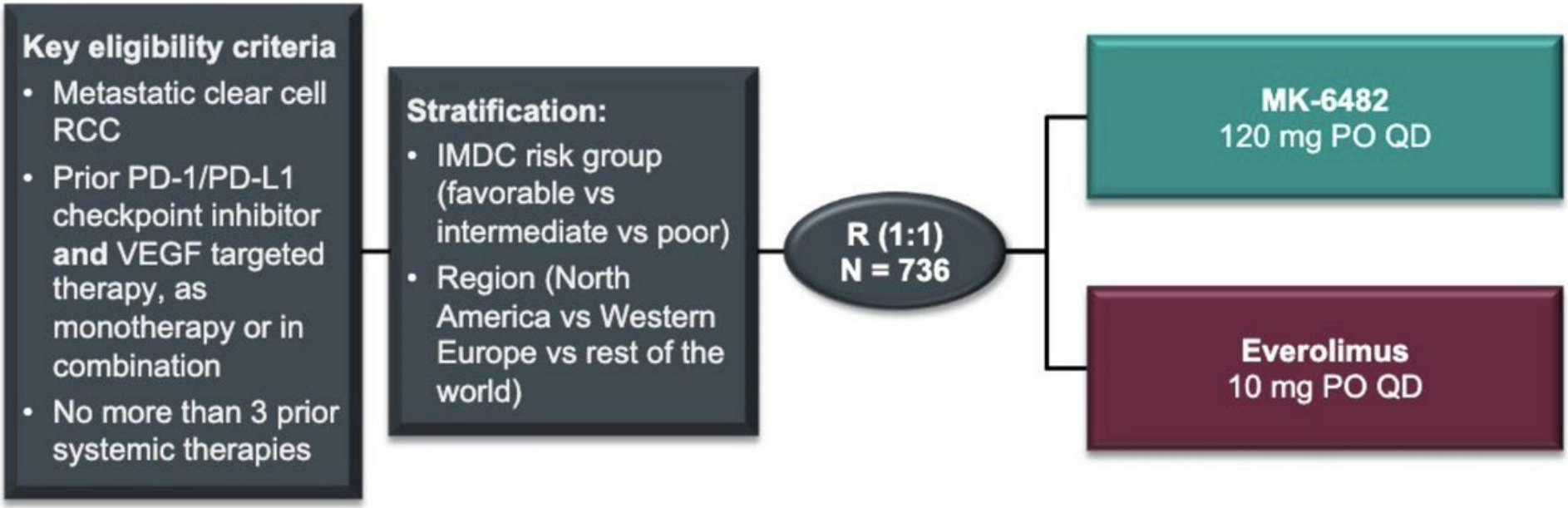
Future Directions

- **HIF2-alpha inhibitors**
  - MK-6482 WELIREG™ (belzutifan) approved for VHL DISEASE associated tumors, including RCC.
  - Is in Phase III trials for general RCC population

Ochsner™
Healthcare With Peace Of Mind™

Current Ochsner Trials

Phase 3 Study: MK-6482 Protocol 5 (NCT04195750)



Endpoints:

- **Dual primary:** PFS and OS (RECIST v1.1, BICR) in ITT
- Key secondary: ORR (RECIST v1.1, BICR) in ITT
- Other secondary: DOR (RECIST v1.1), PROs, safety

Thoughts

- Newly approved targeted therapies and immunotherapies provide an unprecedented treatment armamentarium for mRCC.
- But, precisely defining how to sequence these new drugs and how to pair them with individual patients still alludes clinicians and researchers – many additional trials are needed.
- Biomarkers of response that enable accurate selection of the right drug for each patient and indicate the need for discontinuation in the absence of efficacy must be found.

Ochsner™
Healthcare With Peace Of Mind™