



Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

# Immunotherapy for Kidney Cancer

Tracy L Rose, MD MPH

Assistant Professor of Medicine, Division of Oncology

University of North Carolina

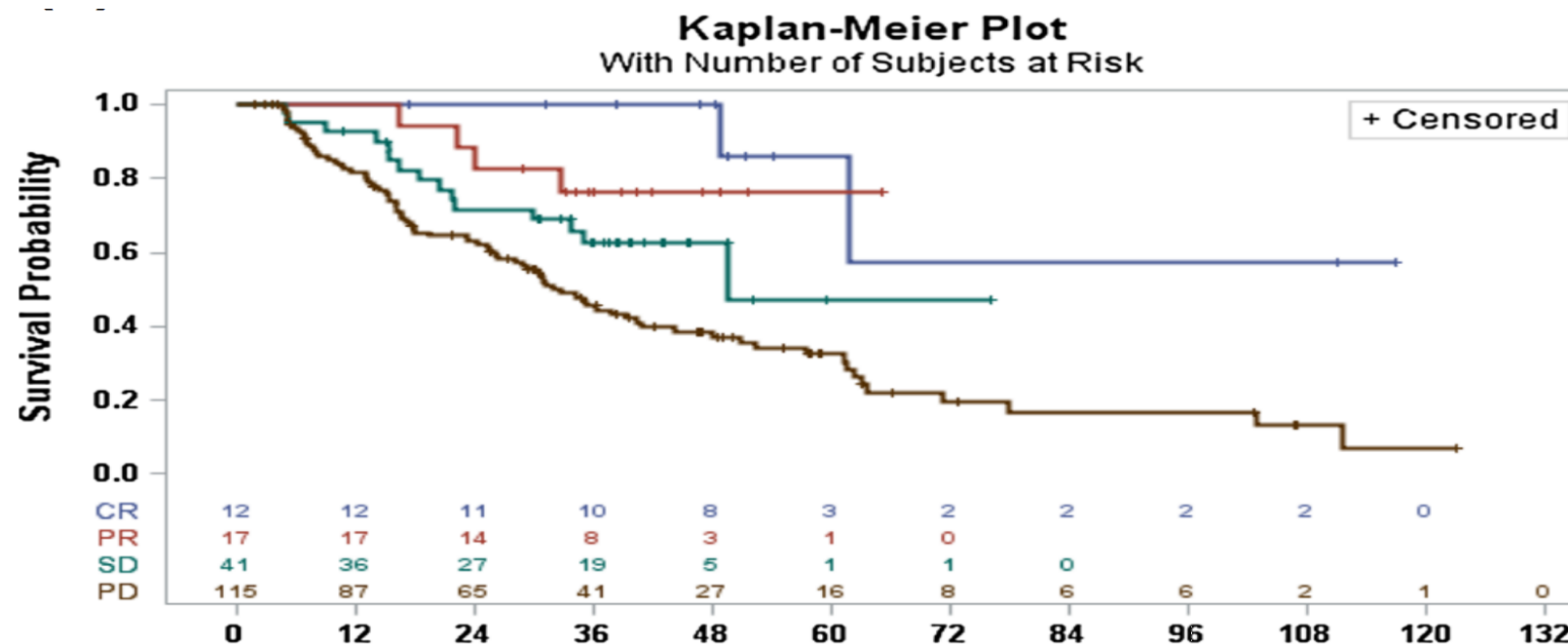
#LearnACI

# Disclosures

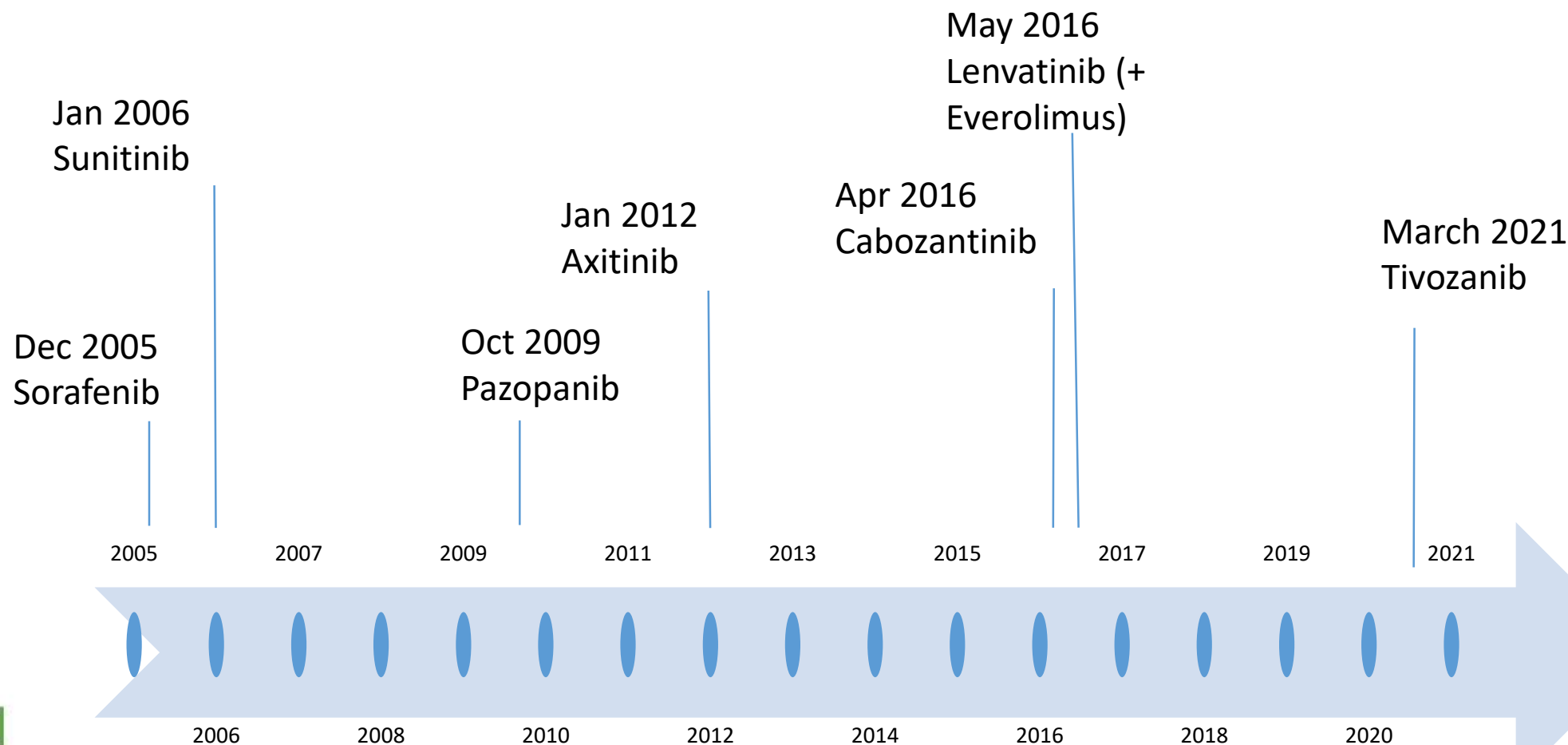
- Contracted Research: Merck, GeneCentric, Genentech, Bristol-Myers Squibb
- I will be discussing non-FDA approved indications during my presentation.

# High-dose IL-2 can achieve durable remission in a small subset of patients with RCC

PROCLAIM Registry



# But then we entered the “TKI era” with many FDA Approvals of VEGFR TKI therapy in RCC



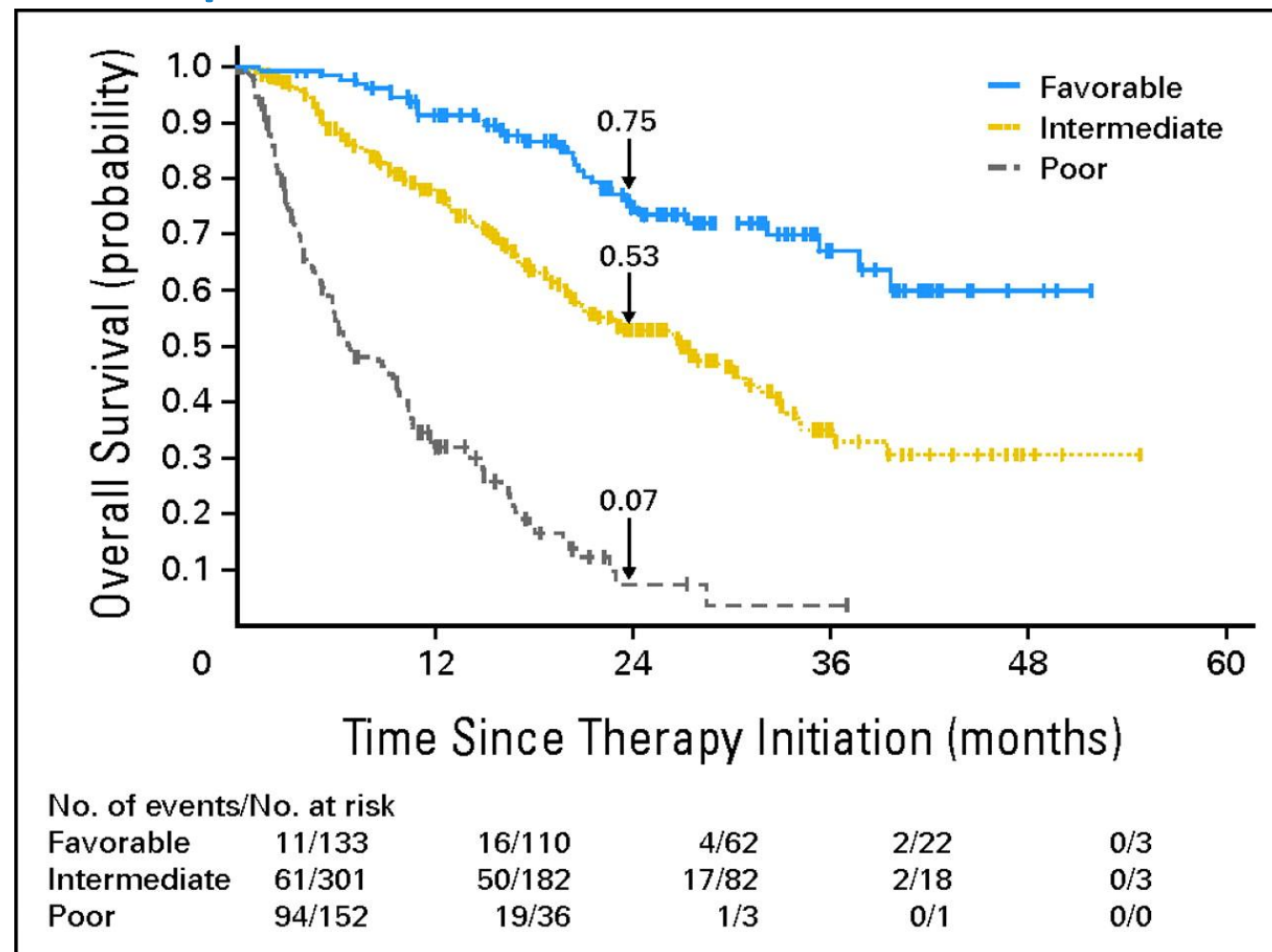
# During the TKI era, several prognostic/risk models were developed given the wide spectrum of RCC

- IMDC Criteria (International Metastatic RCC Database Consortium, “Heng” Criteria) – developed from patients that received VEGF-targeted therapy
  - Poor performance status (KPS <80%)
  - High serum calcium
  - Low hemoglobin
  - Less than 1 year interval from diagnosis to systemic treatment
  - High absolute neutrophil count
  - High platelet count

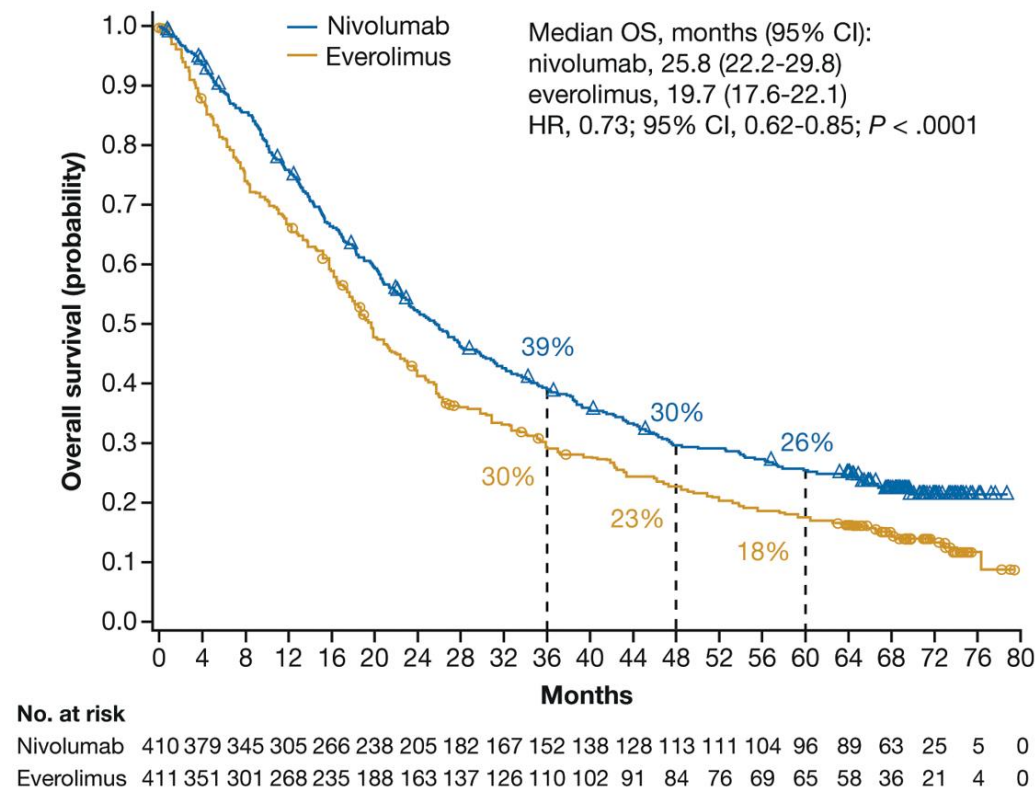
0 = favorable risk

1-2 = intermediate risk

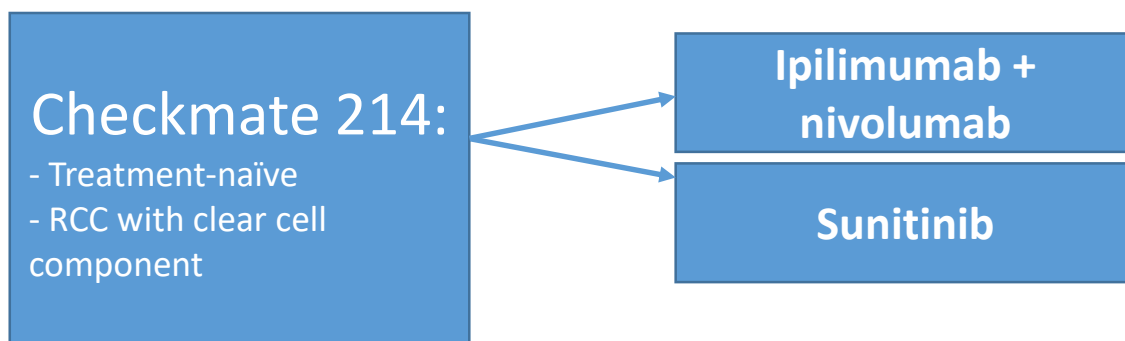
>= 3 high risk



# The first approved immune checkpoint inhibitor for RCC was nivolumab (in 2015), demonstrating improved OS compared with everolimus in pretreated RCC



# The “combination era” of RCC treatment began in 2018 with the approval of ipi/nivo for intermediate/poor risk RCC



## Dosing:

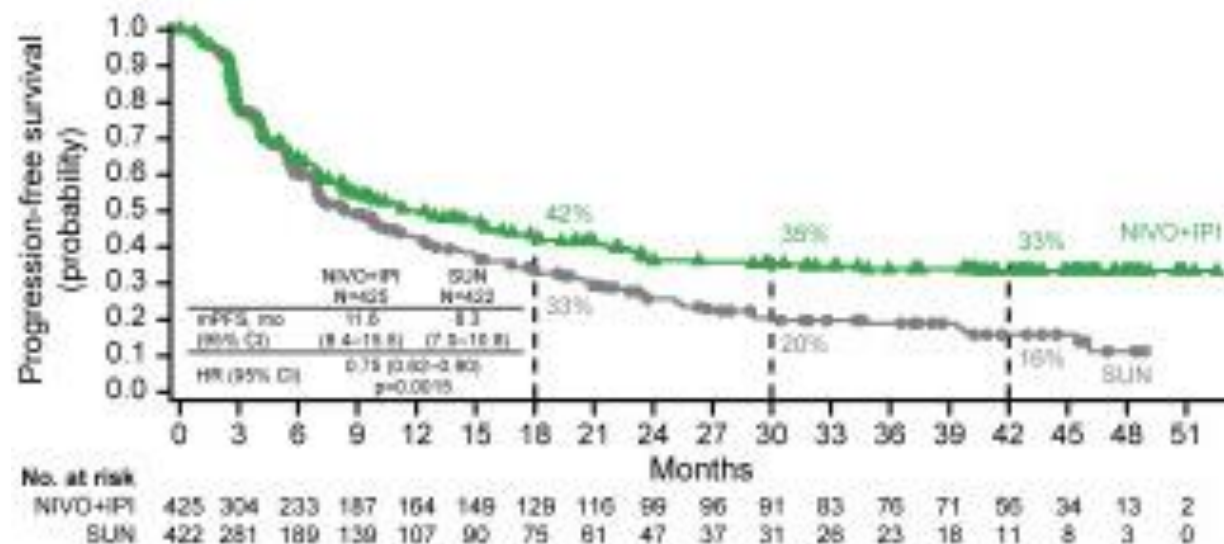
Ipilimumab 3mg/kg  
Nivolumab 1mg/kg  
Every 3 weeks x 4

Followed by  
Nivolumab 240mg IV q2w

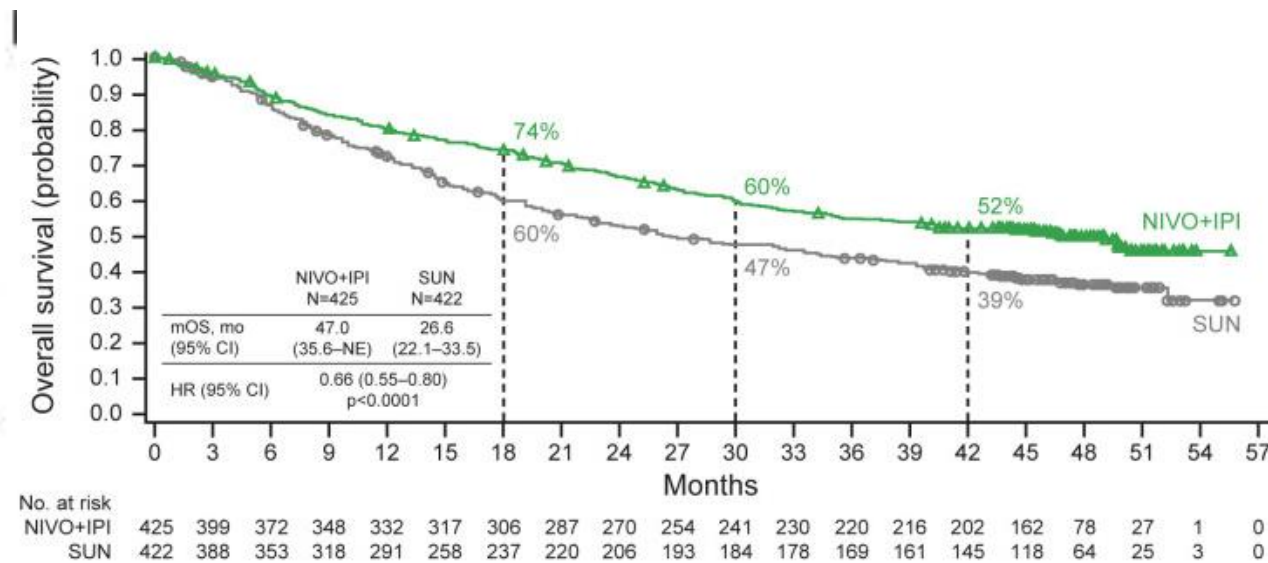


# The benefit to ipi/nivo is clear in intermediate / poor risk patients

Progression free survival



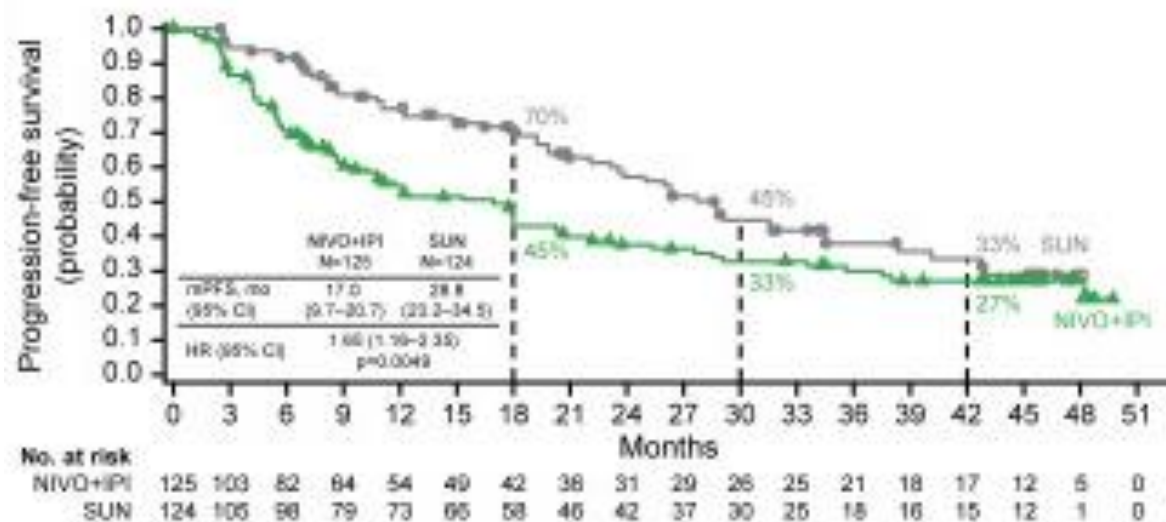
Overall survival



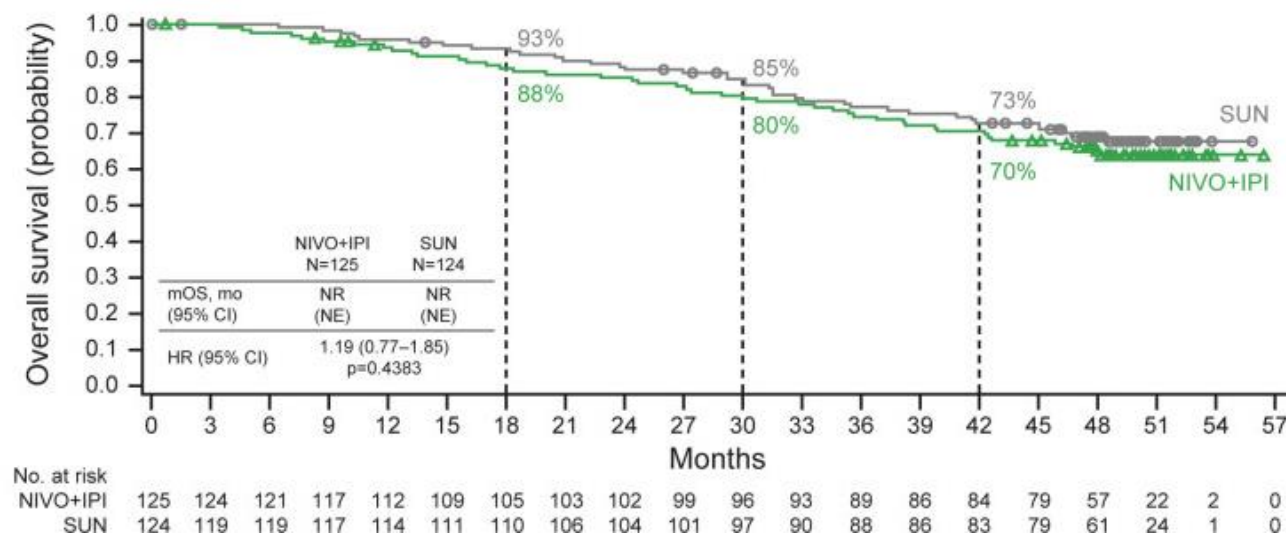


# However, patients with good risk RCC did not benefit from ipi/nivo compared to sunitinib

Progression free survival



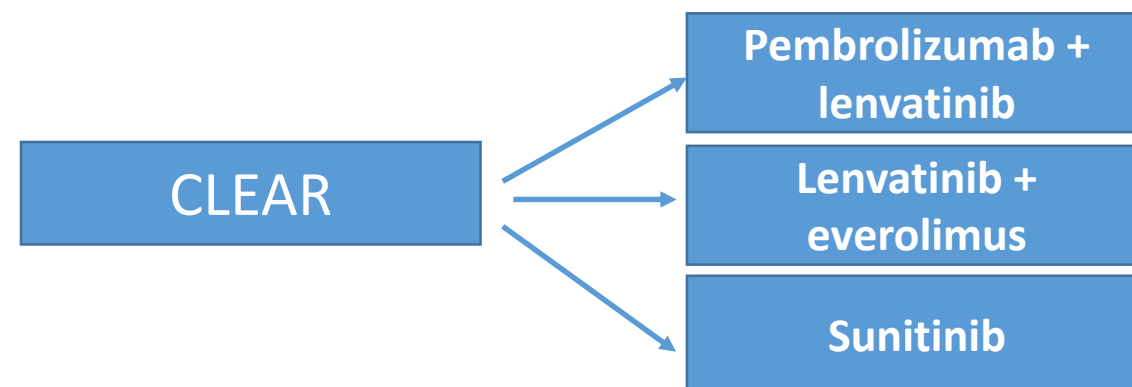
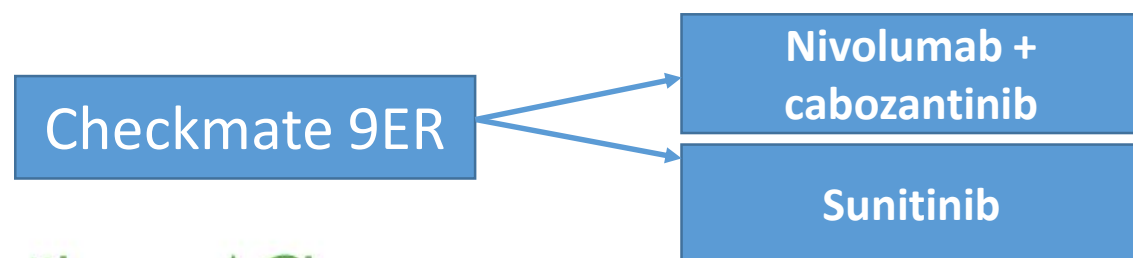
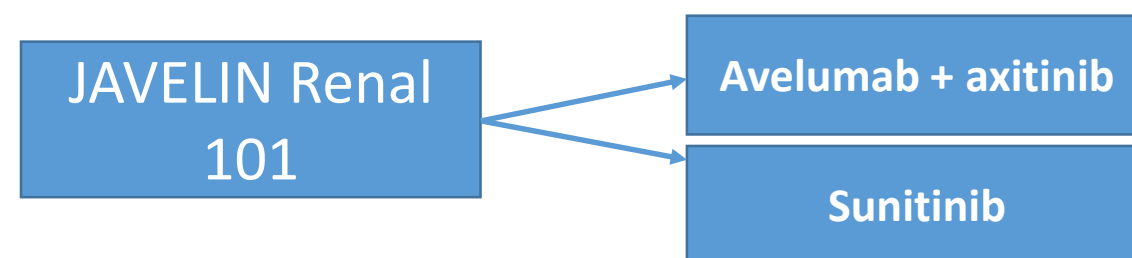
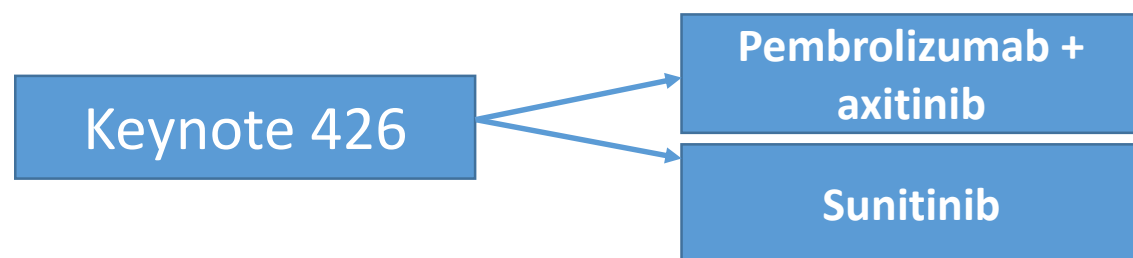
Overall survival



# If VEGF TKI therapy works, and nivolumab works – what about together?

- VEGF inhibits dendritic cell maturation and decreases antigen presentation
- VEGF inhibits T cells leading to exhaustion
- VEGF recruits myeloid derived suppressor cells (MDSCs) and Tregs
- VEGF inhibitors can reverse VEGF associated immune suppression

Based on preclinical rationale and early phase studies, 4 combinations of VEGF-targeted therapy + immune checkpoint inhibition have been studied



	Checkmate 214 Ipilimumab + Nivolumab	Keynote 426 Pembrolizumab + Axitinib	Checkmate 9ER Nivolumab + Cabozantinib	CLEAR Pembrolizumab + Lenvatinib
ORR	39%	60%	55%	71%
CR	11%	10%	9%	16%
Median follow-up	67.7 mos	43 mos	23.5 mos	27 mos
Median PFS HR	12.3 mos 0.86 (0.73-1.01)	15.7 mos 0.68 (0.58-0.8)	17 mos 0.52 (0.43-0.64)	24 mos 0.39 (0.32-0.49)
Median OS HR	56 mos 0.72 (0.62-0.85)	46 mos 0.73 (0.6-0.88)	NR 0.66 (0.50-0.87)	NR 0.66 (0.49-0.88)
>= Gr 3 TRAE	46 vs 63	68 vs 64	61 vs 51	72 vs 59

Motzer et al, ESMO 2021  
Motzer et al, NEJM 2018

Rini et al, 2020 ASCO meeting

Motzer et al, 2021 GU ASCO Meeting

Motzer et al, NEJM 2021

# IO/TKI combinations have varying schedules and pharmacologic properties.

	Keynote 426 Pembrolizumab + Axitinib	Checkmate 9ER Nivolumab + Cabozantinib	CLEAR Pembrolizumab + Lenvatinib
TKI half-life	2.5-6.1 hrs	120 hrs	28 hrs
TKI dosing interval	BID	Daily	Daily
IO dosing interval	Q3weeks (/q6w)	Q2weeks (/q4w)	Q3weeks (/q6w)
Hold TKI before surgery interval	24-48 hrs	28 days	7 days

# IO/IO (Ipi/nivo) or IO/TKI?

Ipi/Nivo	IO/TKI
Higher treatment-free survival	Higher response rate
Longer follow-up data	Chronic TKI side effects
More acute irAE – can be severe	Oral therapy financial toxicity

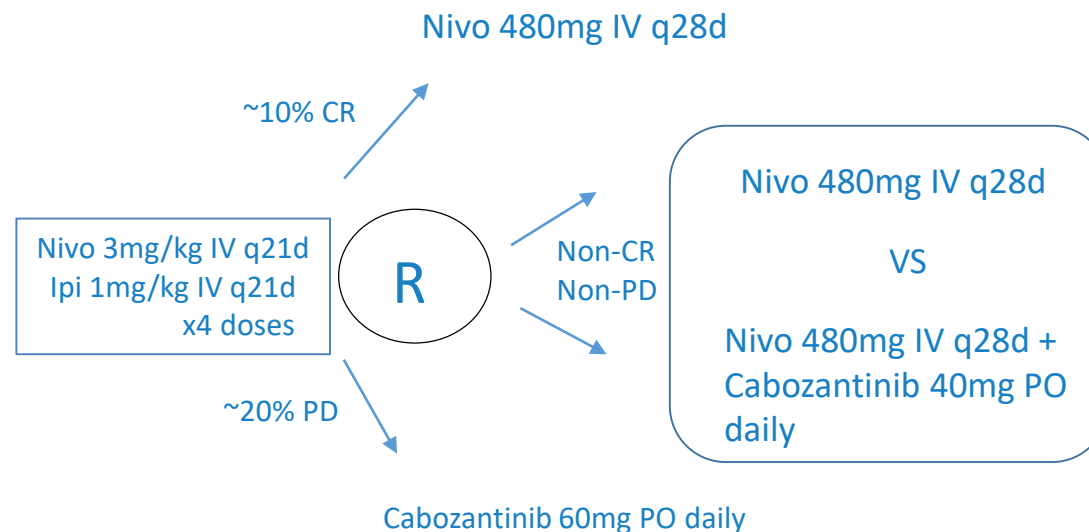


# PDIGREE – Schema

## Metastatic RCC

### Key Inclusion:

1. Metastatic clear cell RCC without prior systemic therapy
2. IMDC intermediate or poor risk
3. Archival tissue available or fresh biopsy

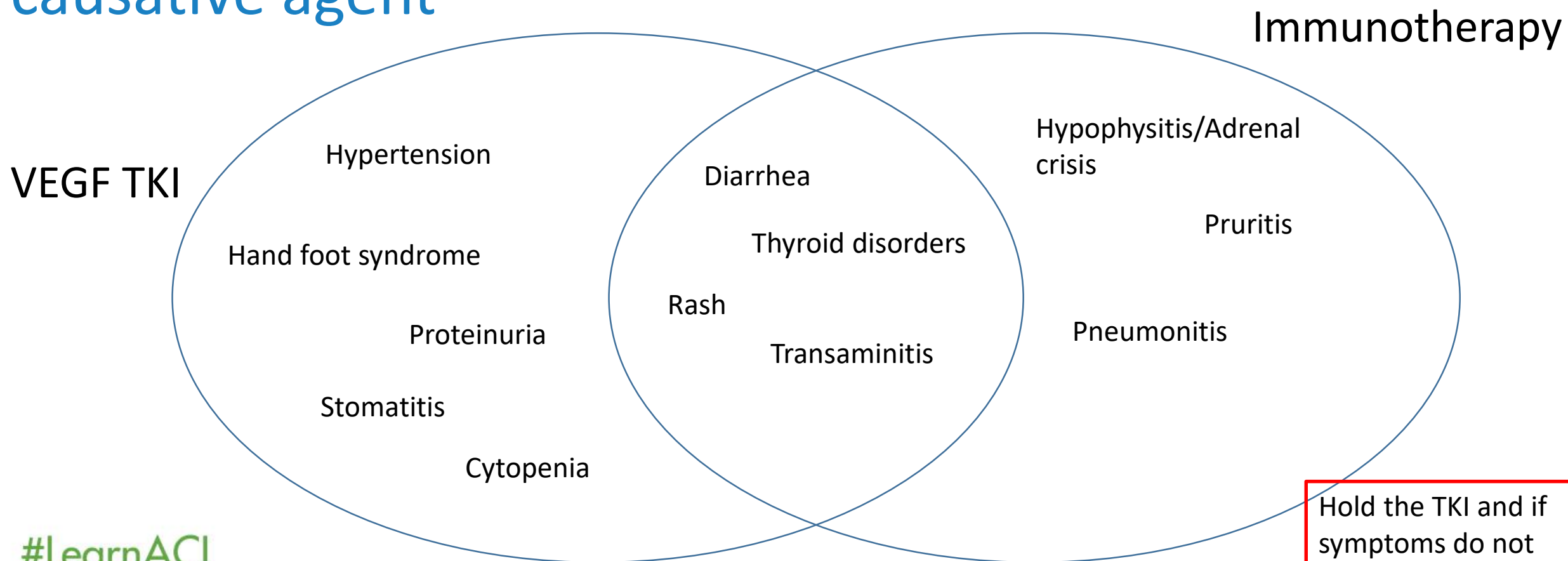


**Discontinue:**  
**Progression of**  
**disease**  
**OR**  
**Unacceptable**  
**toxicity**  
**OR**  
**CR at 1 year**

# So which patients should get which first-line combination regimens?

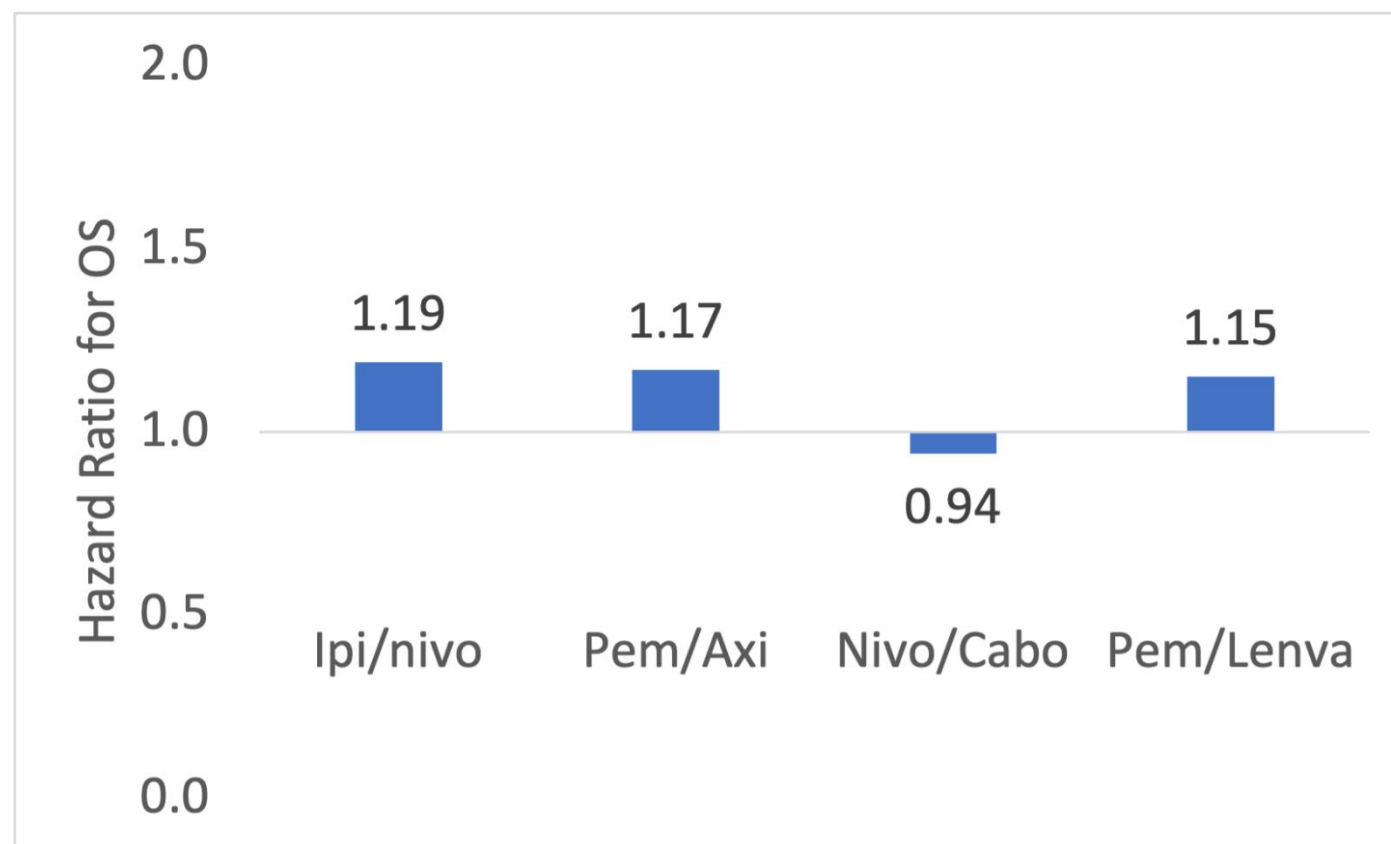
- *NEED* a tumor response -> IO/TKI
- Baseline uncontrolled HTN -> IO/IO
- Baseline autoimmune disease -> IO/TKI
- Good risk per IMDC -> ? IO/TKI (controversial)

# Immune checkpoint inhibition and VEGF TKI therapy can have overlapping toxicity –a challenge to determine causative agent



Hold the TKI and if symptoms do not improve, assume irAE

# No IO combinations have shown an overall survival benefit compared with sunitinib in good risk RCC



Motzer et al, ESMO 2021  
Motzer et al, NEJM 2018  
Rini et al, 2020 ASCO meeting  
Motzer et al, 2021 GU ASCO Meeting  
Motzer, 2021 ASCO Annual Meeting

# Immune checkpoint inhibition is especially crucial for patients with tumors with sarcomatoid differentiation

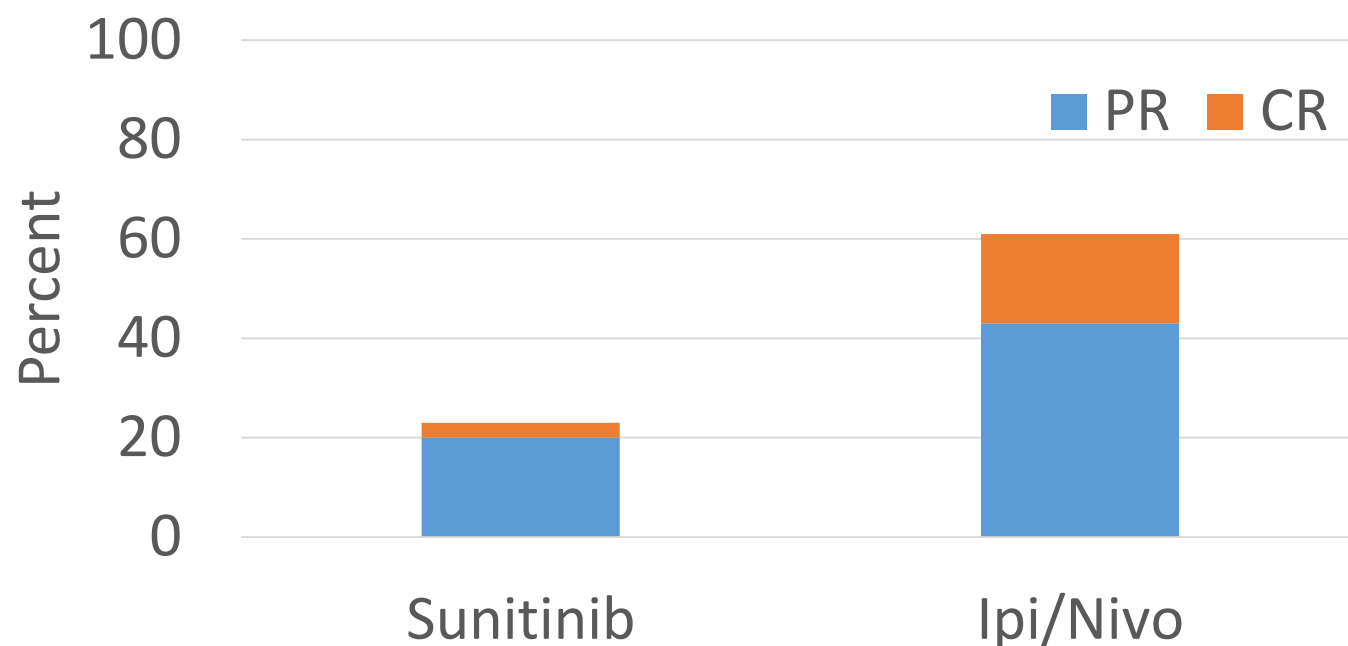
Combination	ORR	CR
Ipi/nivo	61%	18%
Pembro/axitinib	59%	12%
Nivo/cabo	56%	??
Pembro/lenvatinib	??	??

Tannir et al, *CCR* 2021; PMID: 32873572  
Rini et al, *JCO* 15\_suppl (May 20, 2019) 4500

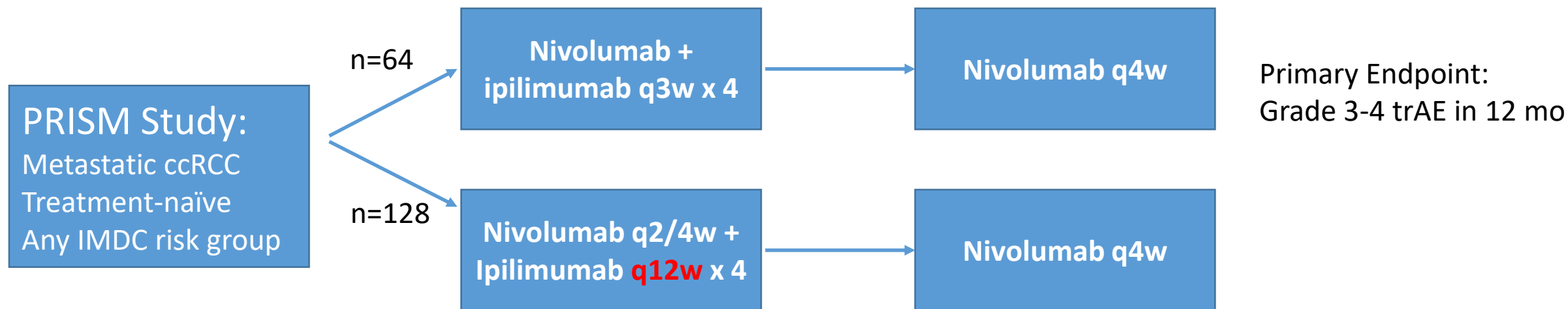
#LearnACI

© 2021–2022 Society for Immunotherapy of Cancer

Response rates for patients with sarcomatoid RCC in Checkmate-214



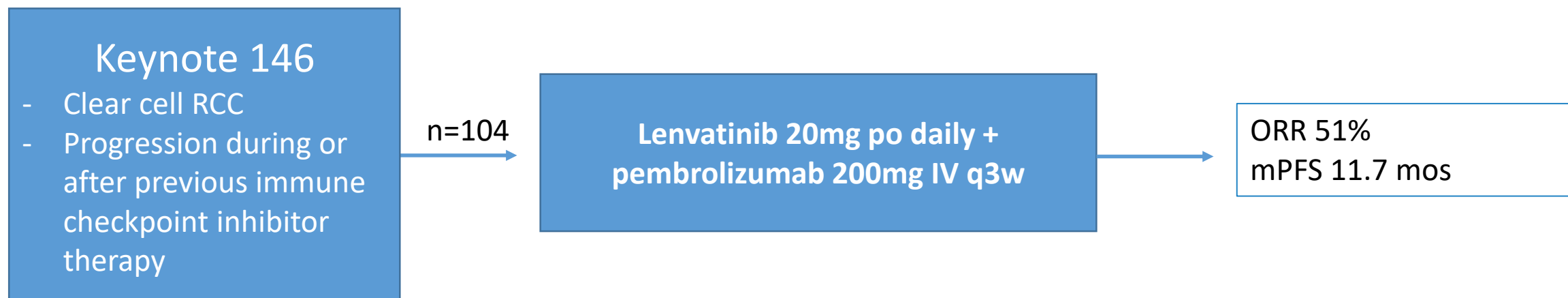
# Modification of ipilimumab dosing *may* be feasible in RCC to minimize toxicity but maintain efficacy



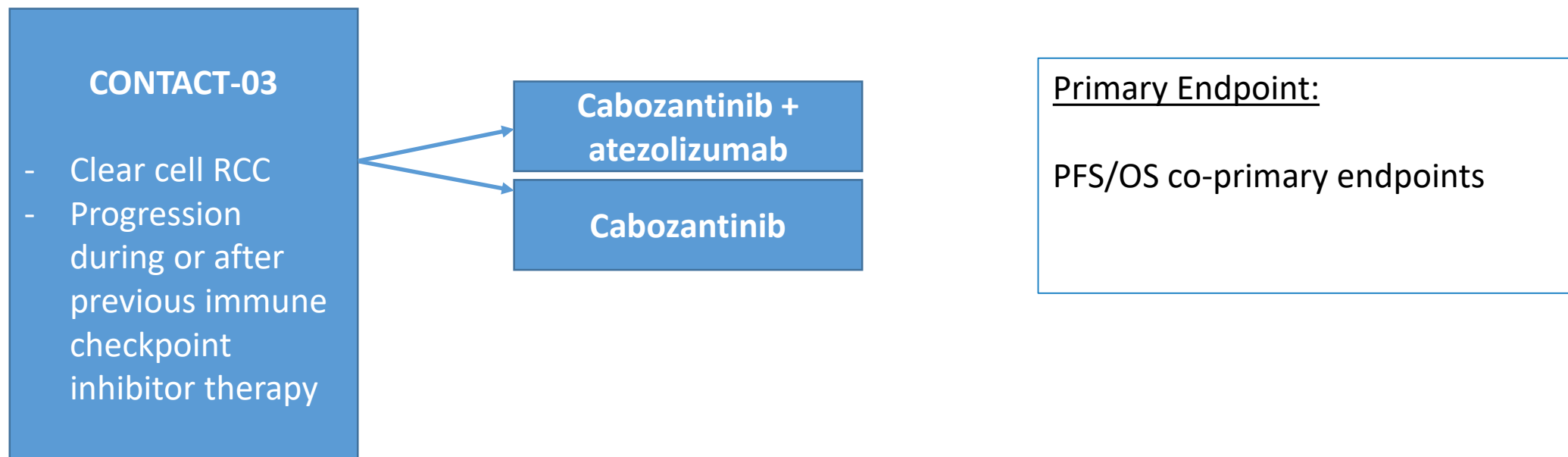
	ORR	mPFS	OS at 12 mos	Grade 3-4 trAE
Modified Ipi	45%	10.8 mos	88%	33%
Standard Ipi	36%	9.8 mos	84%	53%



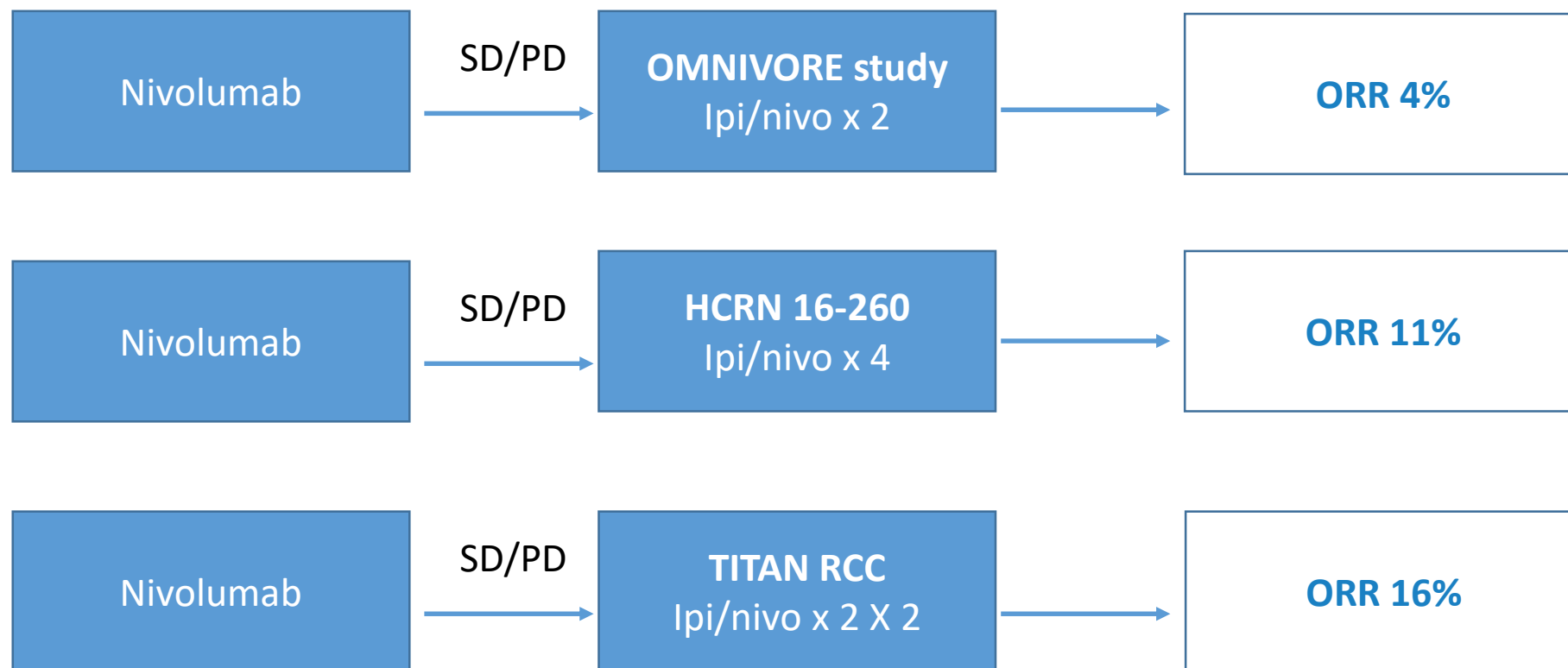
# It is unclear if there is a role for immune checkpoint inhibitor combinations after prior exposure.



# The ongoing CONTACT-03 trial may give some answers.



# Ipilimumab cannot salvage most patients who don't respond to single agent immune checkpoint inhibition



# Immune checkpoint inhibition also has activity in non-clear cell RCC

## Keynote 427 – Cohort B

Advanced RCC

Non-clear cell histology

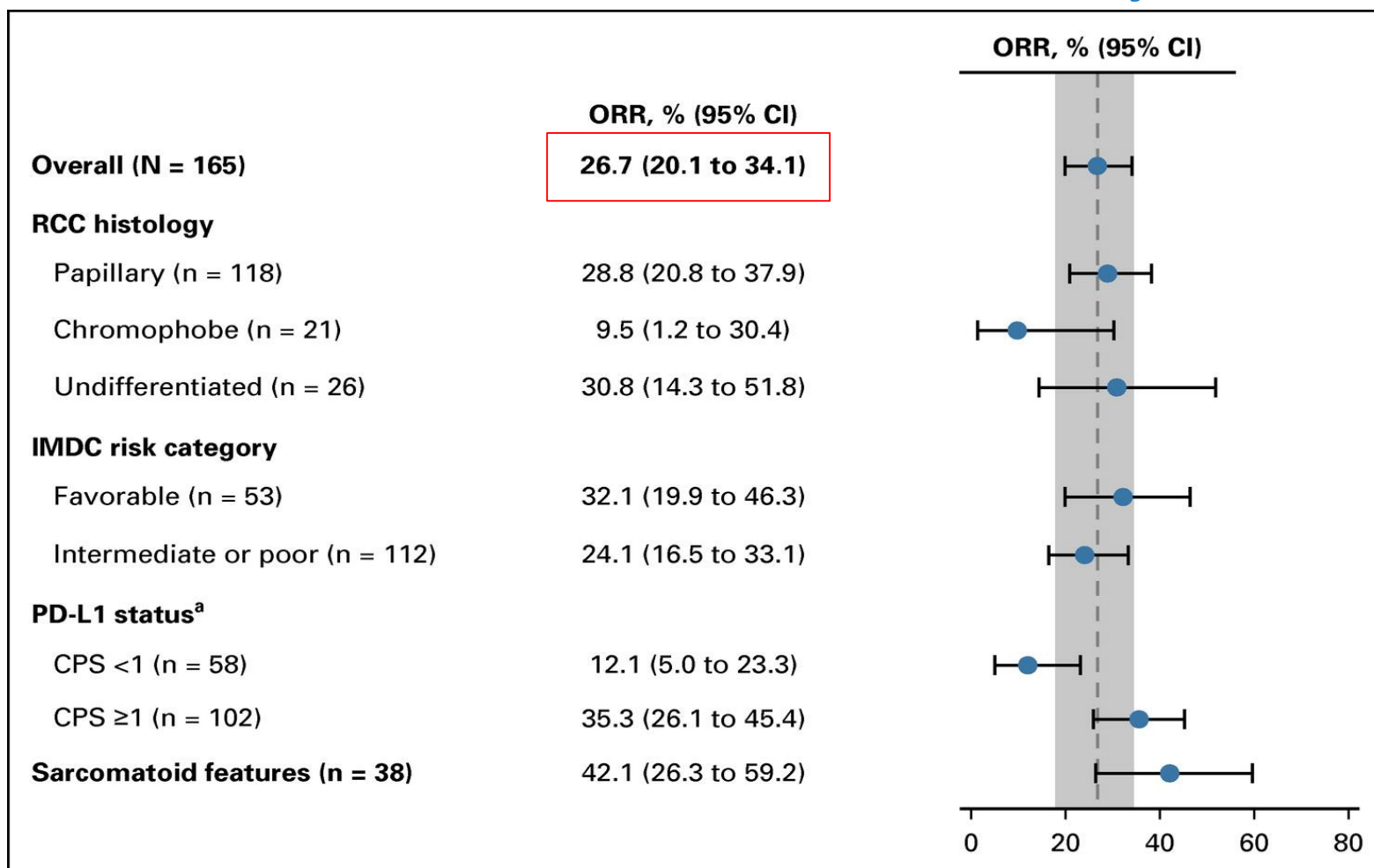
Single arm study

n = 165

Pembrolizumab monotherapy 200mg IV q3w

#LearnACI

© 2021–2022 Society for Immunotherapy of Cancer



# Combination therapy is widely used for non-clear cell RCC, but without a similar level of evidence

KEYNOTE 427 (COHORT B)

Pembrolizumab

ORR 27%



SWOG 1500 (Papillary RCC)

Cabozantinib

ORR 23%



Lee et al (ASCO 2021)

Nivolumab + Cabozantinib

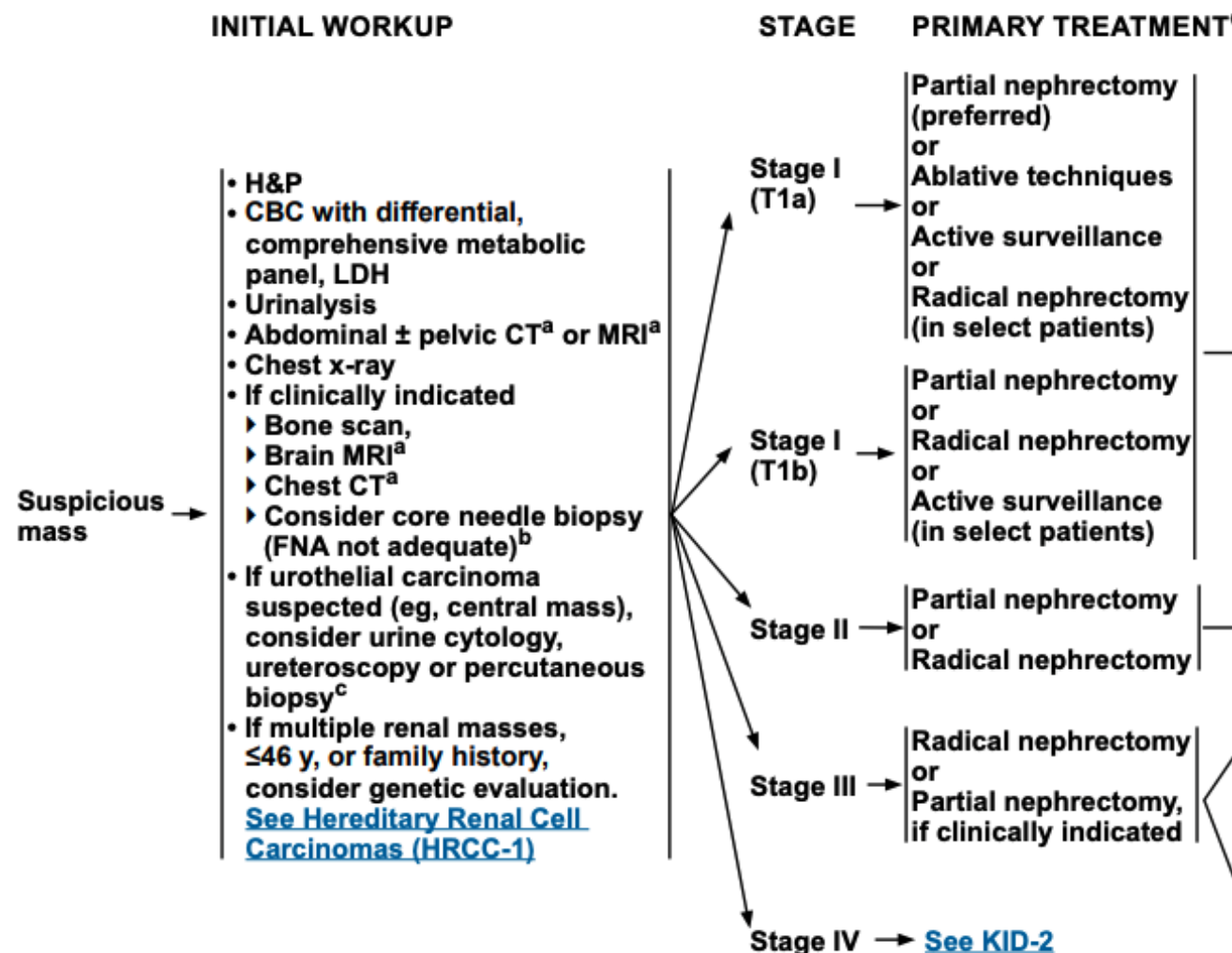
ORR 48%

Despite success of immunotherapy in advanced RCC, management of localized RCC remains upfront surgery



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 2.2022 Kidney Cancer

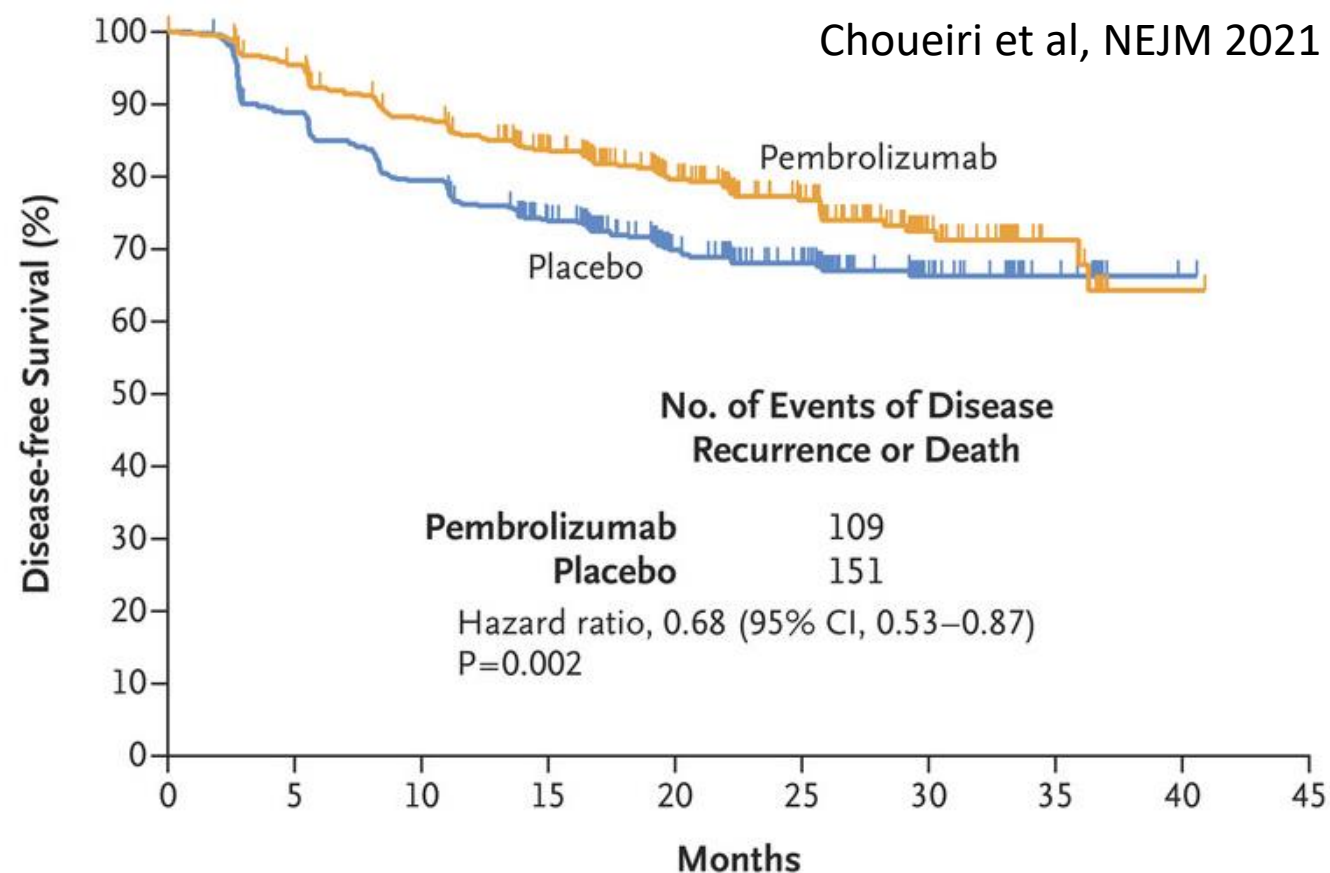




# Adjuvant pembrolizumab is associated with a benefit in DFS compared with placebo

## Keynote-564 Inclusion Criteria:

- RCC with clear cell component
- Nephrectomy within 12 weeks
- pT2 grade 4 or sarcomatoid *or* pT3-4 *or* N+ *or* M1 with NED



## No. at Risk

	0	5	10	15	20	25	30	35	40	45
Pembrolizumab	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

# On the horizon...

## NKTR-214

- Advanced or metastatic RCC with clear cell component
- Untreated

**Bempegaldesleukin (NKTR-214) + nivolumab**

**Cabozantinib or sunitinib**

NKTR-214 = CD122-preferential IL-2 pathway agonist

## HIF-2α/IO combos?

- Advanced or metastatic RCC with clear cell component
- Untreated

**Pembrolizumab + lenvatinib + belzutifan**

**MK-1308A + lenvatinib**

**Pembrolizumab + lenvatinib**

Belzutifan = HIF-2α inhibitor  
MK-1308A = Coformulation of PD1 and CTLA4 inhibitor

# On the horizon...

## CBM-588

- Advanced or metastatic RCC
- Clear cell or sarcomatoid component
- Untreated

Ipi/nivo -> nivo  
+  
CBM-588 oral BID

n=19

**ORR 58%**

Ipi/nivo -> nivo

n=10

**ORR 20%**

CBM-588 is a live bacterial product from *C. butyricum*

# Conclusions

- Immunotherapy is the cornerstone of treatment for RCC
- Single agent immune checkpoint inhibition works for some patients, although combination therapy is standard for first-line management of advanced/metastatic RCC
  - Choice of IO/IO or IO/TKI is based on comorbidities, tumor burden/need for response, and patient/provider preference
- Optimal management of good risk patients with RCC remains controversial
- Peri-operative immunotherapy in RCC appears promising