First Line mRCC: Immunotherapy

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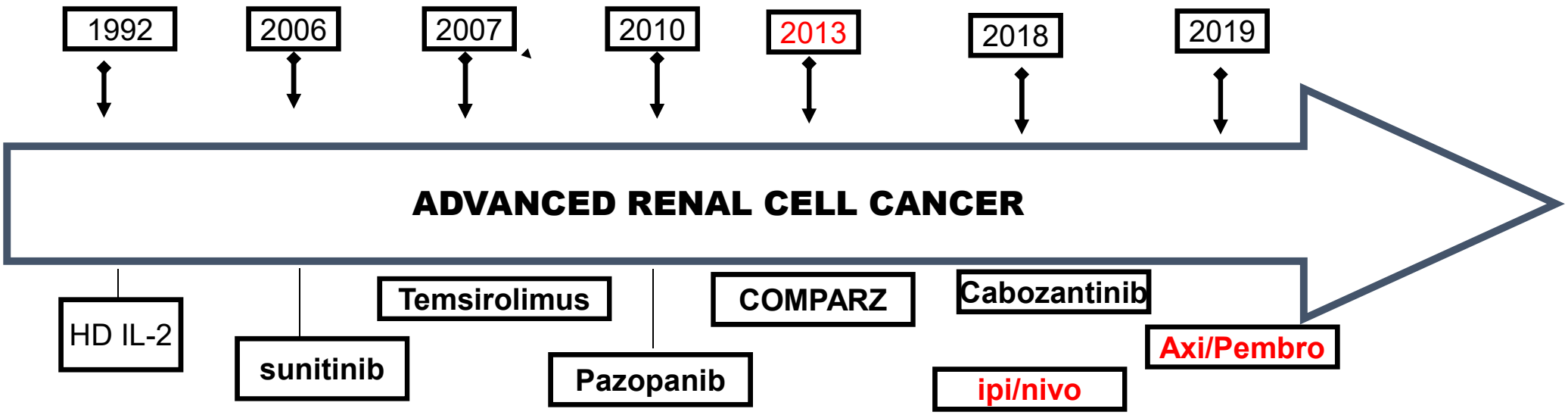
Explosion of agents in advanced disease

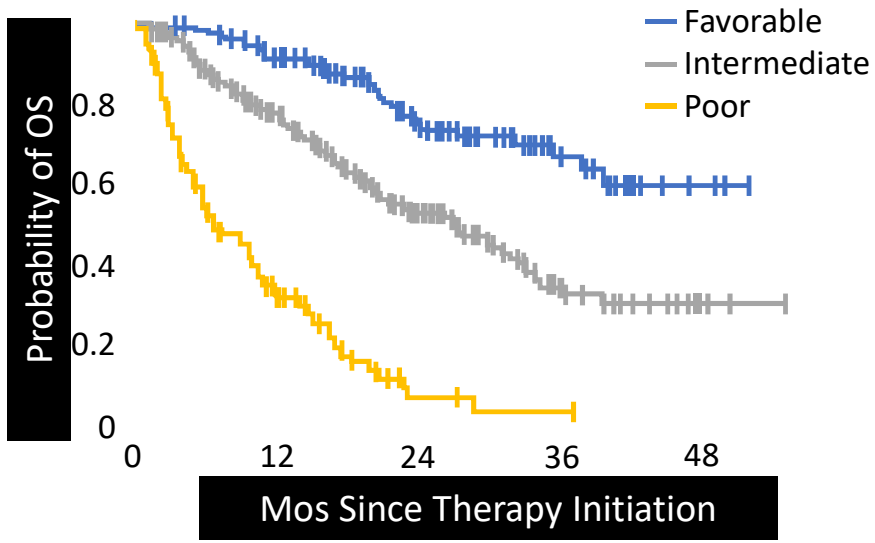


Metastatic RCC: Many choices- NCCN recommendations

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred regimens**	**Other recommended regimens**	**Useful under certain circumstances**
Favorable[a]	• Axitinib + pembrolizumab • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab	• Active surveillance[b] • Axitinib (category 2B) • High-dose IL-2[c]
Poor/ intermediate[a]	• Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (category 2B) • High-dose IL-2[c] • Temsirolimus[d]

IMDC Prognostic Criteria

- Clinical
  - KPS < 80% (*P* < .0001)
  - Time from diagnosis to tx < 1 yr (*P* = .01)
- Laboratory
  - Hemoglobin < LLN (*P* < .0001)
  - Calcium > ULN (*P* = .0006)
  - Neutrophil count > ULN (*P* < .0001)
  - Platelet count > ULN (*P* = .01)



Favorable: 0 risk factors; intermediate: 1-2 risk factors; poor: 3+ risk factors

Heng. JCO. 2009;27:5794.

CheckMate 025: First approval in Subsequent line mRCC

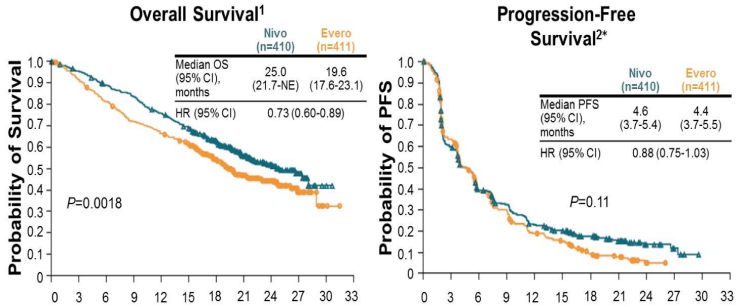
Metastatic RCC with ≤ 2 prior antiangiogenic therapies and ≤ 3 total prior systemic regimens (N = 821)

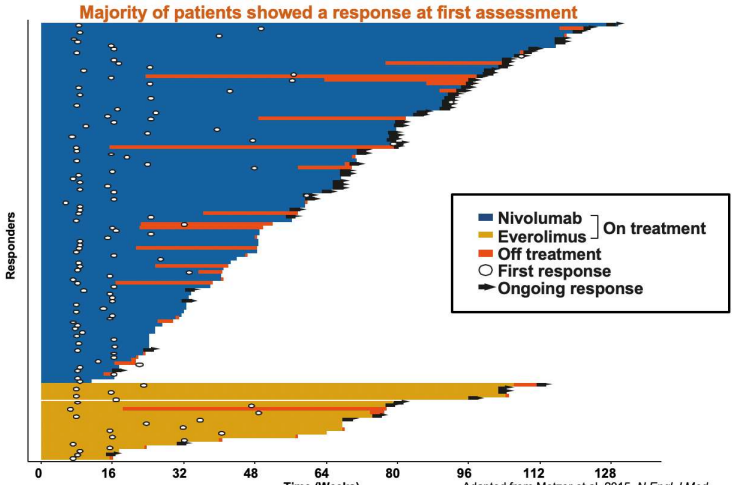
Nivolumab
3 mg/kg IV every 2 wks

Everolimus
10 mg PO daily

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, OR duration, safety

ORR: 25%

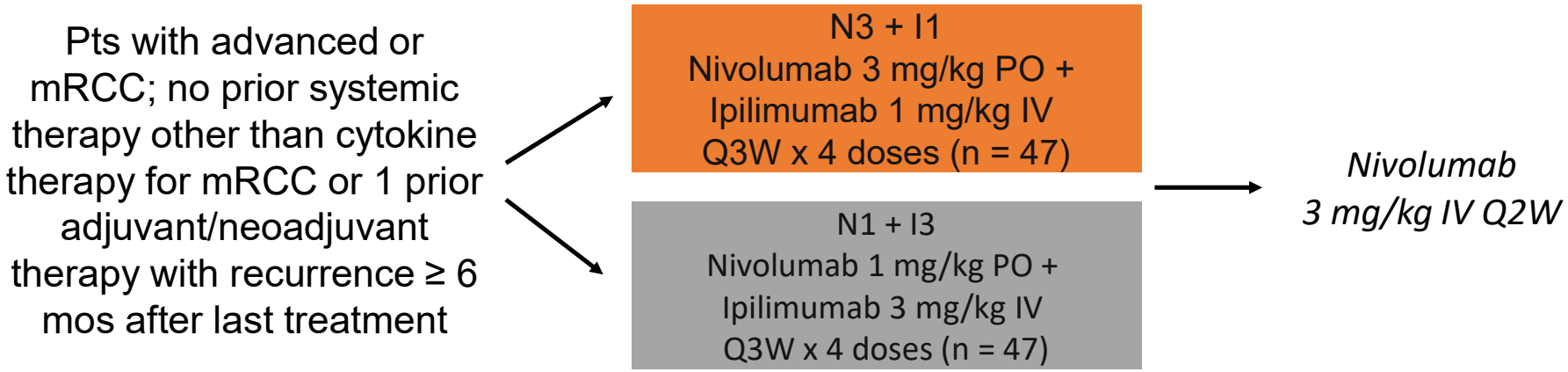




Motzer. NEJM. 2015;373:1803.

CheckMate 016: Phase I Study of Nivolumab + Ipilimumab in mRCC

- Evaluated combinations in mRCC: nivolumab + ipilimumab, sunitinib, or pazopanib
- Current analysis: nivolumab + ipilimumab cohorts



- Primary endpoint: safety/tolerability
- Secondary endpoints: ORR, DoR, PFS

Hammers H, et al. ESMO 2016. Abstract 1062P.

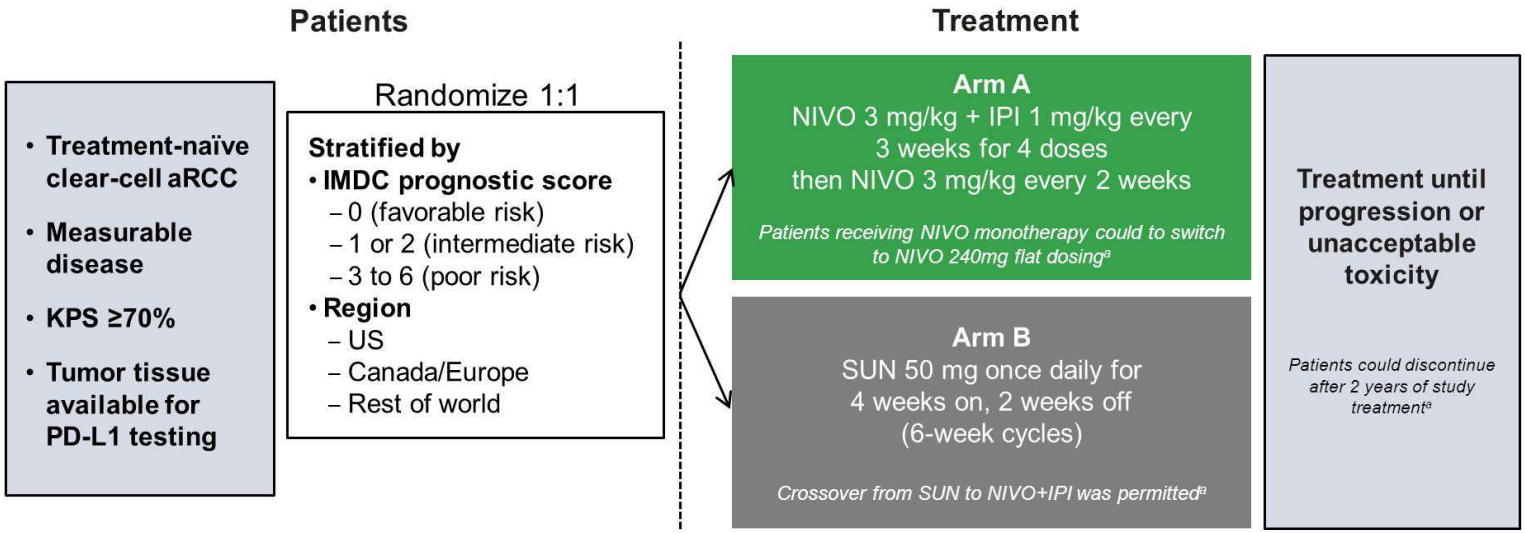
CheckMate 016: Antitumor Activity

Outcome	N3 + I1 (n = 47)	N1 + I3 (n = 47)
Confirmed ORR, % (95% CI)	40.4 (26.4-55.7)	40.4 (26.4-55.7)
Best objective response, n (%)		
▪ CR	5 (10.6)	0
▪ PR	14 (29.8)	19 (40.4)
▪ SD	19 (40.4)	17 (36.2)
▪ PD	8 (17.0)	8 (17.0)
Median DoR,* mos	20.4	19.7
24-mo OS, %	67	70
Median OS, mos	Not reached	32.6
Median PFS, mos	6.6	9.1

DoR: time between date of first response and date of disease progression or death (whichever occurs first).
Median follow-up: 22 mos

Hammers H, et al. ESMO 2016. Abstract 1062P.

CheckMate 214: Study Design

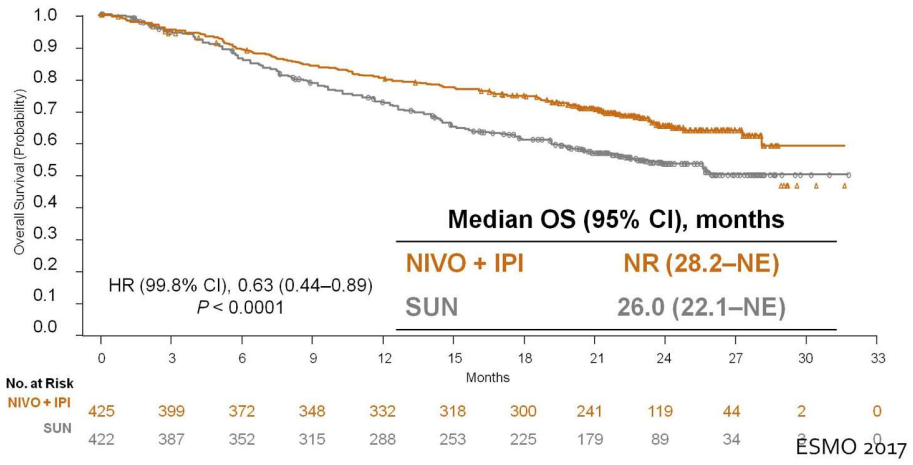


Risk criteria by IMDC
1. KPS
2. Hb
3. Thromboctyosis
4. Neutrophilia
5. Hypercalcemia
6. Time to Rx <1 yr from Dx

[a]As of a November 2017 protocol amendment.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance status; PD-L1, programmed death ligand 1.

Motzer. NEJM. 2018; 378:1277.

Checkmate 214- Nivo/Ipilumimab vs Sunitinib



	Intermediate and Poor Risk N = 847		Favorable Risk N = 249[a]	
Outcome	NIVO + IPI N = 425	SUN N = 422	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[a] % (95% CI)	42 (37–47)	27 (22–31)	29 (21–38)	52 (43–61)
	P < 0.0001		*P* = 0.0002	
Median PFS (95%)	11.6 (8.7-15.5)	8.4 (7.0-10.8)	15.3 (9.7–20.3)	25.1 (20.9–NE)
	P=0.033		*P < 0.0001*	
Median OS	Not Reached (28.2-NE)	26 (22.1-NE)	*Not reported*	

Motzer NEJM 2018

Checkmate 214- Response rates

Outcome	N = 847	
	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	**42 (37–47)**	**27 (22–31)**
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	**9[b]**	**1[b]**
Partial response	**32**	**25**
Stable disease	31	45
Progressive disease	20	17
Unable to determine/not reported	8	12

Outcome	IMDC intermediate/poor risk			
	PD-L1 <1%		PD-L1 ≥1%	
	NIVO + IPI N = 284	SUN N = 278	NIVO + IPI N = 100	SUN N = 114
ORR,[a] % (95% CI)	37 (32–43)	28 (23–34)	**58 (48–68)**	**22 (15–31)**
	P = 0.0252		*P* < 0.0001	
BOR,[a] %				
Complete response	7	1	**16**	1
Partial response	30	27	42	21

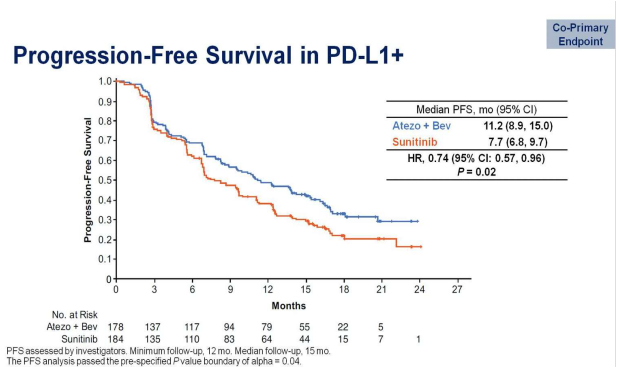
Ipilumimab/Nivolumab approved by the FDA for intermediate/poor in April 2018

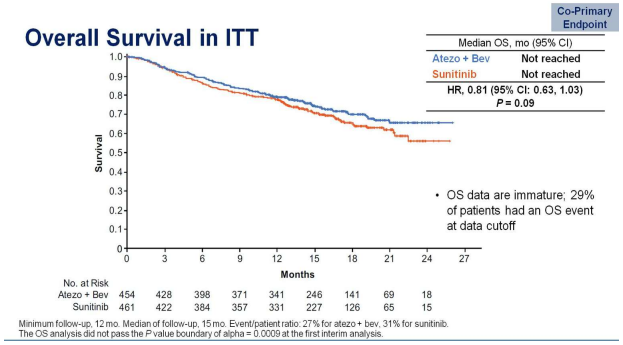
Randomized Phase III: IO/VEGF Combinations

IMmotion151	Treatment-naive advanced or metastatic RCC with clear-cell and/or sarcomatoid histology; KPS ≥ 70; tumor tissue available for PD-L1 staining (N = 915)	**Atezolizumab** 1200 mg IV + **Bevacizumab** 15 mg/kg IV Q3W **Sunitinib** 50 mg PO QD for 4 wks on, 2 wks off	1º EP: PFS in PD-L1+ pts; OS in ITT pts
JAVELIN Renal 101	Treatment-naive advanced RCC with a clear-cell component; ECOG PS 0 or 1; tumor tissue for PD-L1 staining (N = 886)	**Avelumab** 10 mg/kg IV Q2W + **Axitinib** 5 mg PO BID in 6-wk cycles **Sunitinib** 50 mg PO QD for 4 wks on, 2 wks off	1º EP: PFS and OS in PD-L1+ pts
KEYNOTE-426	Patients with treatment-naive advanced clear-cell RCC; KPS ≥ 70%; tumor tissue for PD-L1 staining (N = 861)	**Pembrolizumab** 200 mg IV Q3W + **Axitinib** 5 mg PO BID **Sunitinib** 50 mg PO QD for 4 wks on, 2 wks off	1º EP: PFS and OS in ITT

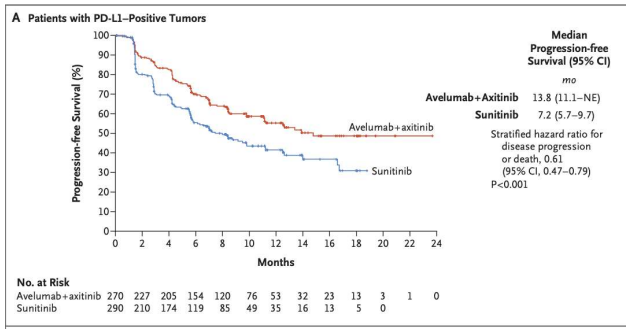
PFS/OS Results

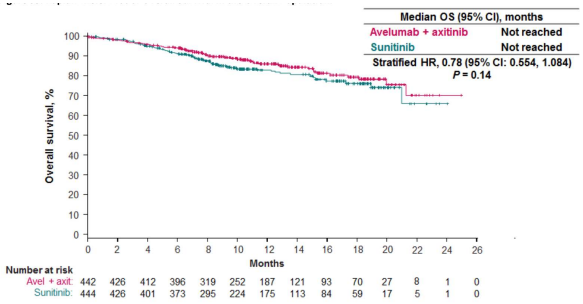
Atezo/Bev



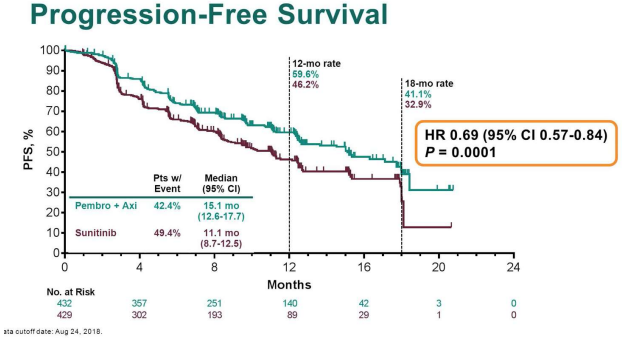


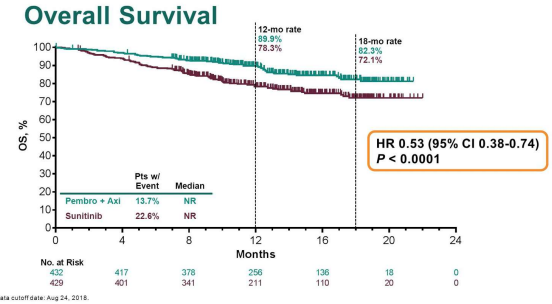
Avelumab/Axi





Pembro/Axi





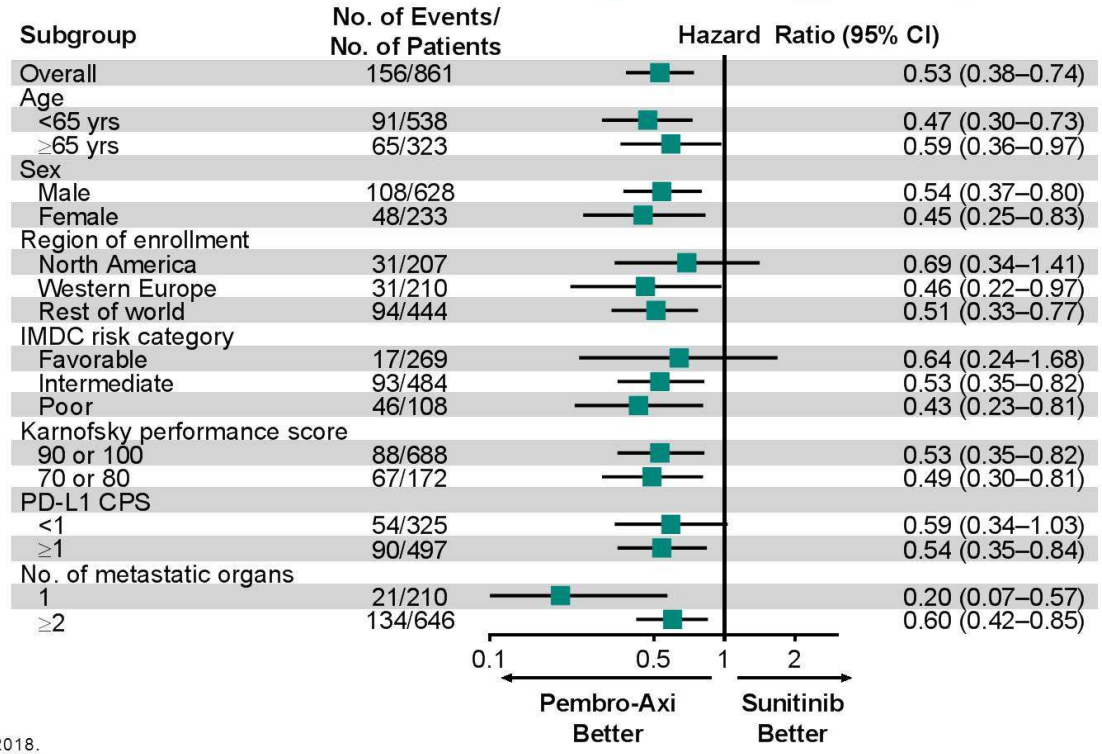
KN 426: Axitinib/Pembrolizumab in mRCC

Baseline Characteristics

	Pembrolizumab + Axitinib N = 432	Sunitinib N = 429
Age, median (range)	62 yrs (30-89)	61 yrs (26-90)
Male	308 (71.3%)	320 (74.6%)
Region of enrollment		
North America	104 (24.1%)	103 (24.0%)
Western Europe	106 (24.5%)	104 (24.2%)
Rest of world	222 (51.4%)	222 (51.7%)
IMDC risk category		
Favorable	138 (31.9%)	131 (30.5%)
Intermediate	238 (55.1%)	246 (57.3%)
Poor	56 (13.0%)	52 (12.1%)
Sarcomatoid features	51/285 (17.9%)	54/293 (18.4%)
PD-L1 CPS ≥1[a]	243/410 (59.3%)	254/412 (61.7%)
≥2 metastatic organs	315 (72.9%)	331 (77.2%)
Previous nephrectomy	357 (82.6%)	358 (83.4%)

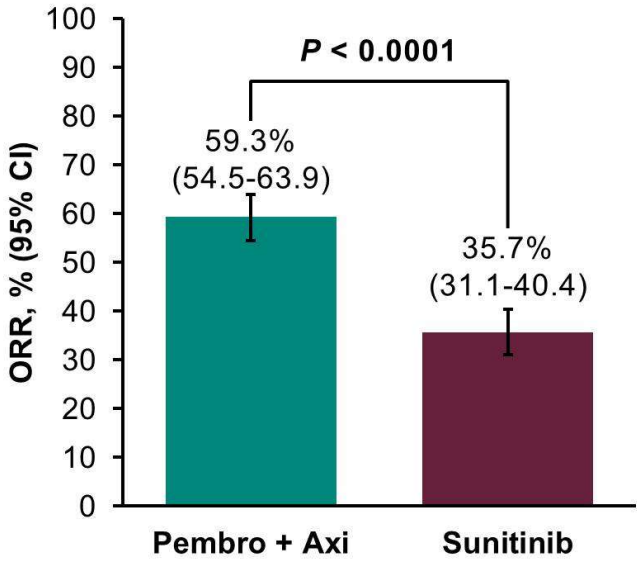
[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
Data cutoff date: Aug 24, 2018.

Overall Survival in Key Subgroups



Data cutoff date: Aug 24, 2018.

Confirmed Objective Response Rate

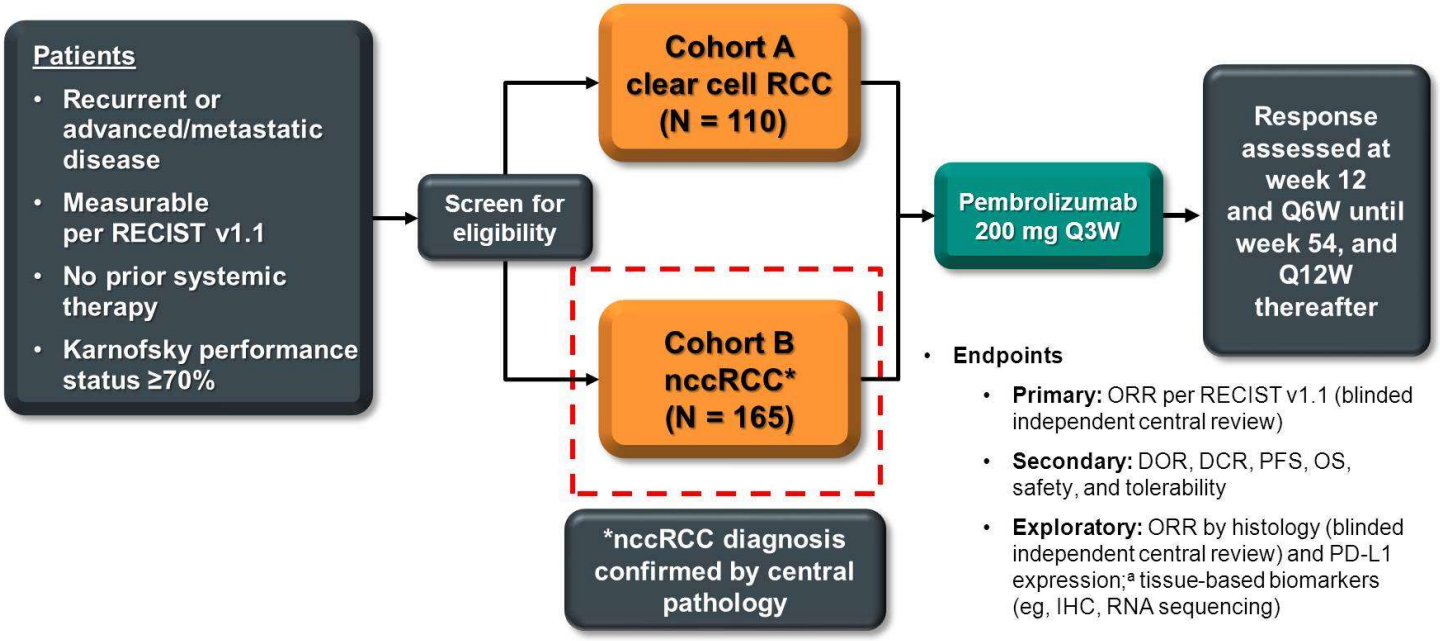


Best Response	Pembro + Axi N = 432	Sunitinib N = 429
CR	25 (5.8%)	8 (1.9%)
PR	231 (53.5%)	145 (33.8%)
SD	106 (24.5%)	169 (39.4%)
PD	47 (10.9%)	73 (17.0%)
NE[a]	8 (1.9%)	6 (1.4%)
NA[b]	15 (3.5%)	28 (6.5%)
Response Duration	**N = 256**	**N = 153**
Median (range), mo	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

[a]Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR. [b]Patients who did not have ≥1 post-baseline imaging assessment.
Data cutoff date: Aug 24, 2018.

Monotherapy in mRCC?

KEYNOTE-427: (NCT02853344)



[a]PD-L1 positive defined as combined positive score [CPS] ≥1.

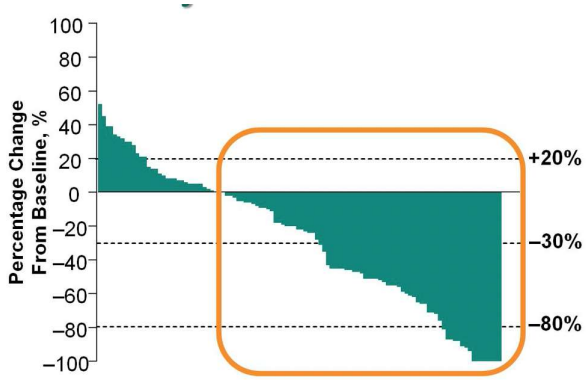
Presented By David McDermott at 2019 Genitourinary Cancers Symposium

Confirmed ORR by Blinded Independent Central Review

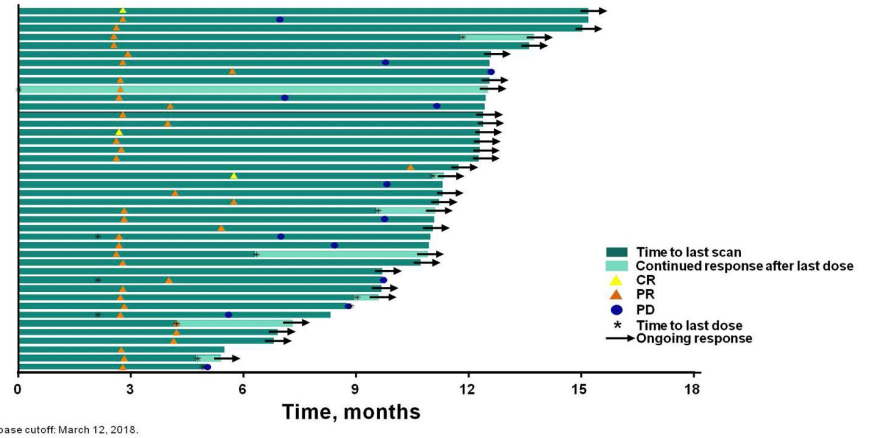
	N = 110		
	n	**%**	**95% CI**
ORR	**42**	**38.2**	**29.1-47.9**
DCR (CR + PR + SD ≥6 months)	**65**	**59.1**	**49.3-68.4**
Best overall response			
CR	3	2.7	
PR	39	35.5	
SD	35	31.8	
PD	31	28.2	
No assessment	2	1.8	

Database cutoff: March 12, 2018.

KN 427: Cohort A Results



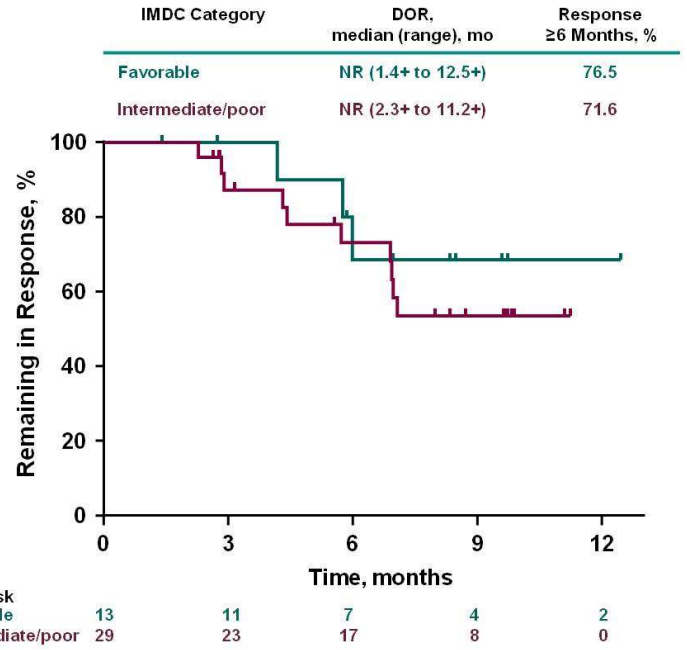
- 74 of 110 (67.3%) patients experienced a reduction in tumor burden
- 16 of 110 patients (14.5%) experienced a tumor burden reduction ≥80%
- 8 of 110 patients (7.3%) experienced 100% tumor burden reduction



tabase cutoff: March 12, 2018.

ORR and Response Duration: IMDC Categories

	Favorable n = 41	Intermediate/Poor n = 69
Confirmed ORR, % (95% CI)	**31.7 (18.1-48.1)**	**42.0 (30.2-54.5)**
DCR, % (95% CI)[a]	**65.9 (49.4-79.9)**	**55.1 (42.6-67.1)**
Confirmed BOR, %		
CR	2.4	2.9
PR	29.3	39.1
SD	51.2	20.3
PD	17.1	34.8
NA	0	2.9



BOR, best overall response; IMDC, International Metastatic RCC Database Consortium.
[a]DCR = CR + PR + SD ≥6 months.
Database cutoff: March 12, 2018.

Presented By David McDermott at 2018 ASCO Annual Meeting

Duo-IO vs VEGFI/IO

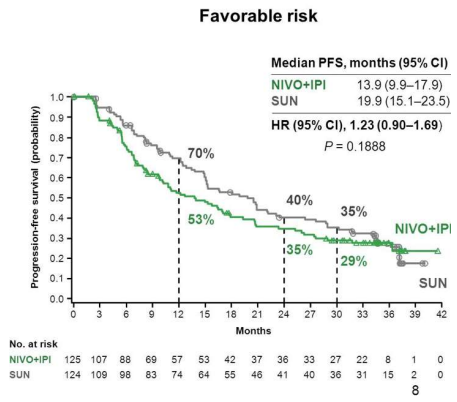
Results: CM 214

At 30 month FU

Overall Survival	NR vs 26	HR: 0.63
ORR (%)	42 vs 27	P<0.001
CR (%)	9 vs 1	P<0.001
PFS (mos)	11.6 vs 8.4	P=NS
Int/Poor Risk OS	NR vs 26	0.63
Favorable Risk OS	NR vs 32.9	2.18

	N = 249[a]	
Outcome	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS,[c] 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	

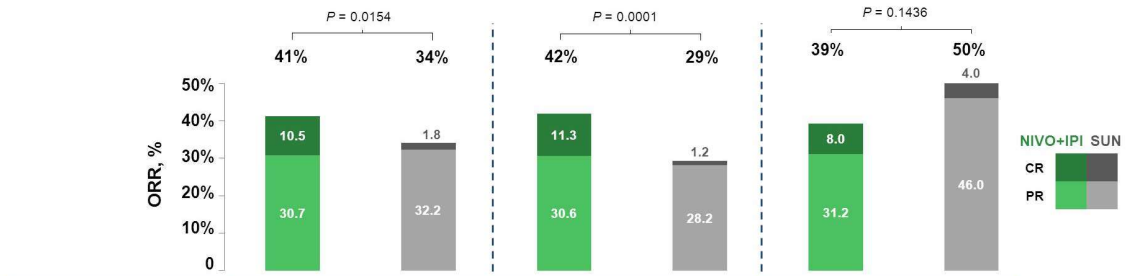
Overall Survival	NR vs 38	HR: 0.71
ORR (%)	42 vs 29	P<0001
CR (%)	11 vs 1	1
PFS (mos)	9.7 vs 9.7	HR:0.85
Int/Poor Risk OS	NR vs 27	HR: 0.66
Favorable Risk OS	NR vs NR	HR:1.22 P=NS



Motzer NEJM 2018; Tannir GU ASCO 2019

Durable/Complete Response

Investigator-Assessed Response per RECIST v1.1

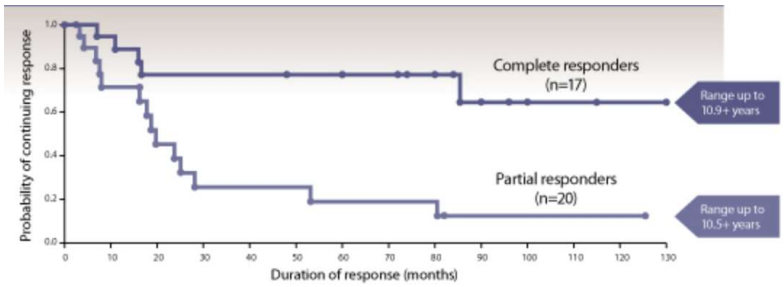


	ITT population		Intermediate/poor risk[1]		Favorable risk	
	NIVO+IPI N = 550	SUN N = 546	NIVO+IPI N = 425	SUN N = 422	NIVO+IPI N = 125	SUN N = 124
DOR ≥18 months, %	53	39	52	28	57	60
Ongoing CR, n/N (%)	51/58 (88)	6/10	42/48 (88)	4/5	9/10	2/5

- Among ITT patients, 185 (34%) versus 114 (21%) achieved ≥50% best tumor burden reduction with NIVO+IPI versus SUN

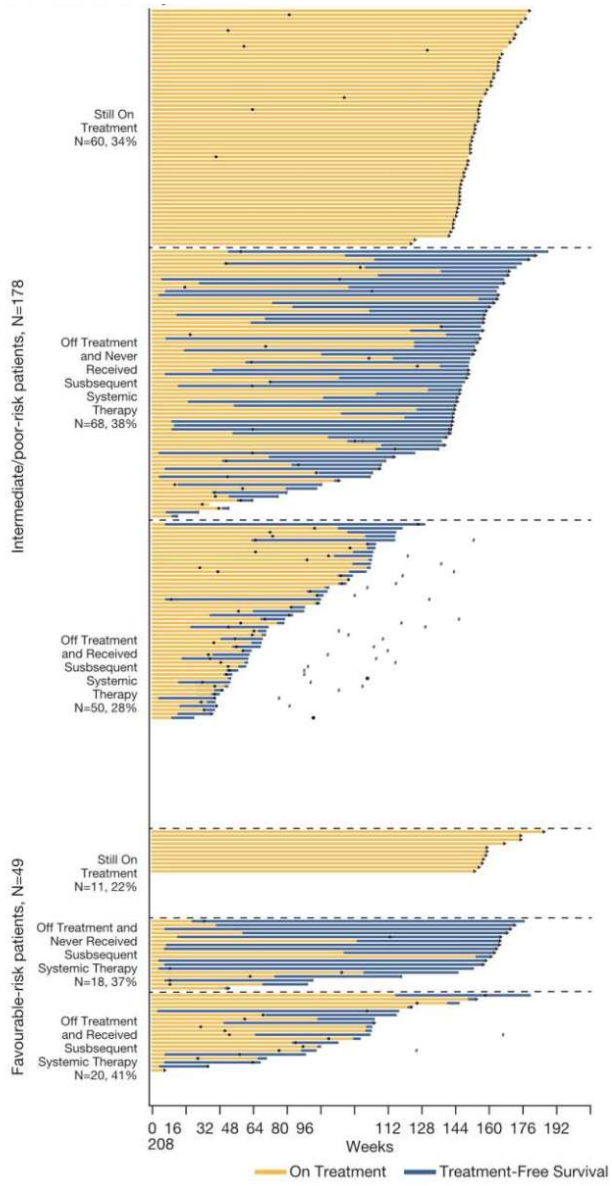
PDL1 High: CR- 16%

HD IL-2



Treatment Free Interval

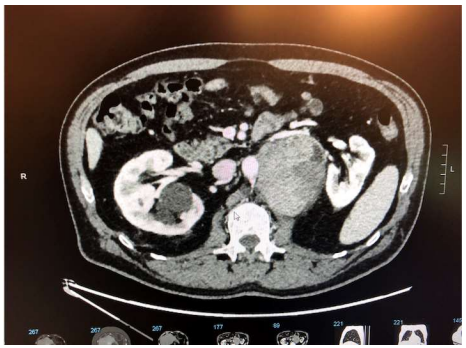
	Ipilumimab/Nivo N=425	Sunitinib N=422
TFI (Months)	15.4	8.5
% alive at 2 yrs (noRx)	42	19
D/C Rx (%)	75	85
Progression (%)	42	58
Adverse Events	23	11
@ 18 mos CR/PR9%)	48	6
SD	13	4



McDermott, Ann Oncol 2018

Adverse Events Attribution

- 70 yr old male with LUQ mass; 16 cm RP mass and a cm solid mass in Left kidney



6/10/19- Started Axitinib/Pembrolizumab
7/24/19- AST-335/ALT-325
7/29/19- AST-205/ALT-282
8/14/19- AST56 /ALT- 68----pembrolizumab
9/4/19- AST- 31/ALT-31----Axi/pembro
9/25/19- AST- 107/ALT- 153

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to 5 times upper limit of normal (ULN) if baseline less than 2 times ULN;

AST or ALT greater than 3 times baseline if baseline greater than or equal to 2 times ULN

Total bilirubin greater than 2.0 mg/dL if baseline less than 1.5 mg/dL; or

Total bilirubin greater than 3.0 mg/dL, regardless of baseline levels

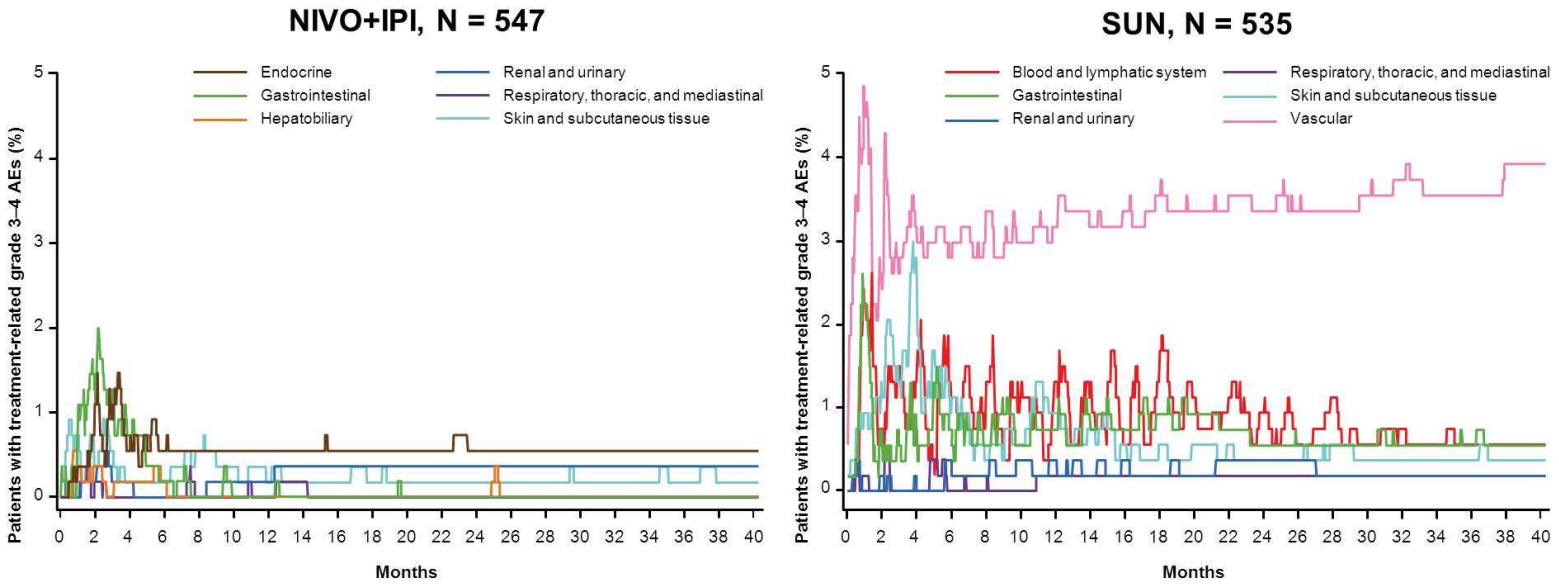
Steroid Use and Resolution of AE

	Grade ¾ (%)	Resolution Rate (%)
Skin	21	74
GI	27	91
Renal	7	82
Hepatic	8	89
Endocrine		
Thyroid	38	46
Adrenal	14	27
Pituitary	15	63
DM	6	50
Pneumonitis	6	94

Prednisone Use 40 mg =29%
Prednisone 40mg X 2 weeks= 19%
Prednisone 40mg X 30 days=10%

Motzer Lancet Oncology 2018

Treatment-Related AEs Over Time by Most Common System Organ Class (All Treated Patients)



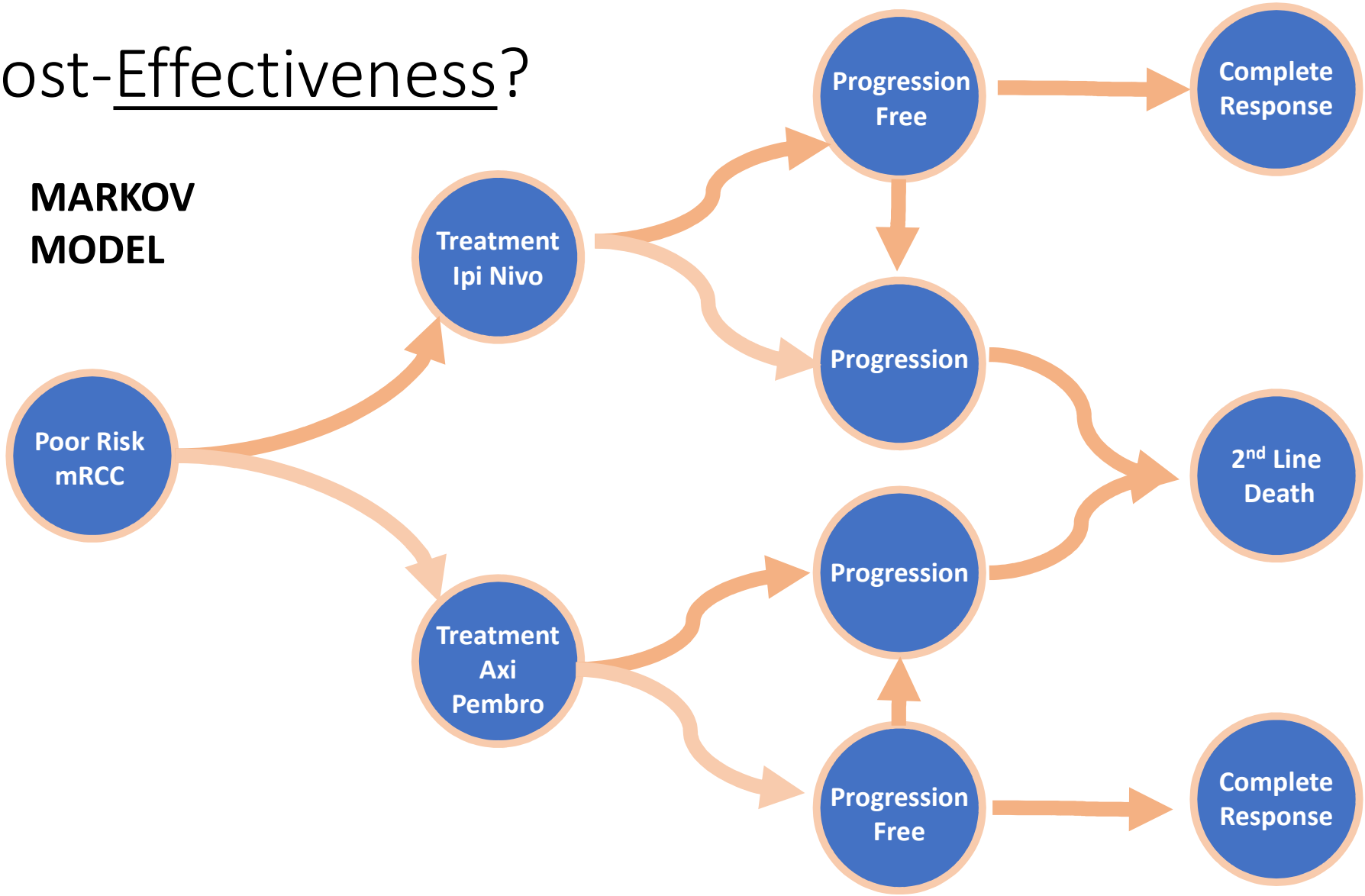
- In the NIVO+IPI arm, 35% of patients received high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent) for select treatment-related AE management
- No additional treatment-related deaths occurred

2019 Medicare Reimbursement Data

	Ipilimumab Nivolumab	Pembrolizumab Axitinib	Sutent
Months 1-3	$27,000/month	$21,000 /month	$10,733/month
Months > 4	$14,419/month	$21,000/month	$10,733/month

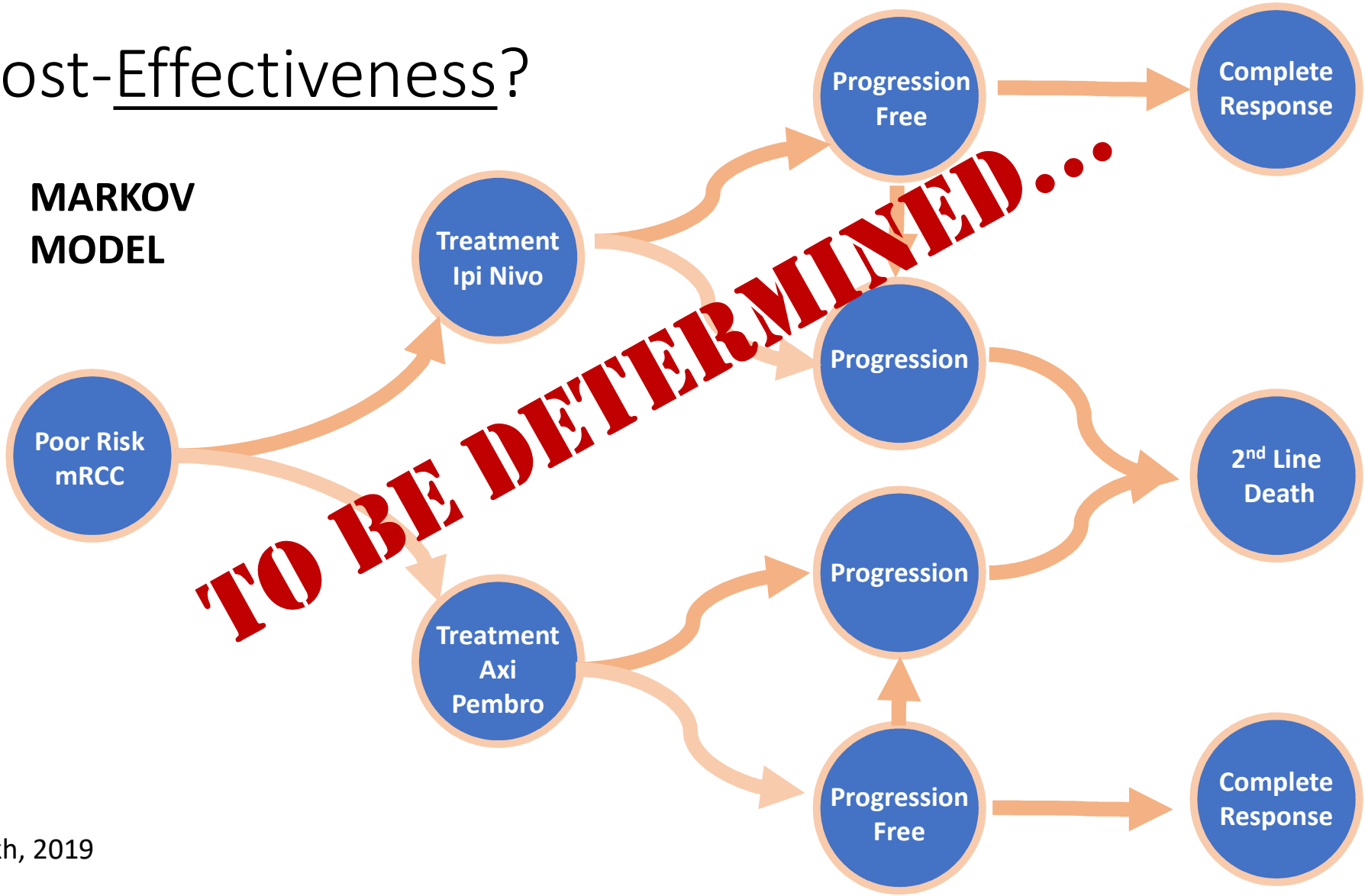
Cost-Effectiveness?

MARKOV MODEL



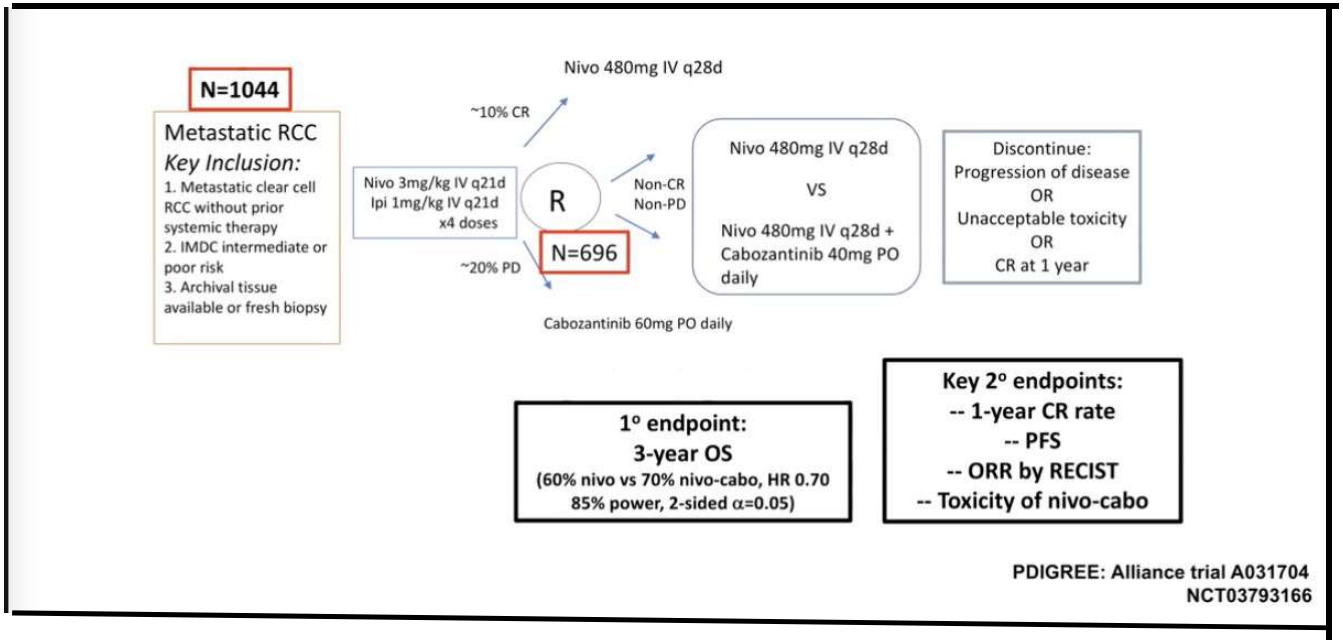
Cost-Effectiveness?

MARKOV MODEL

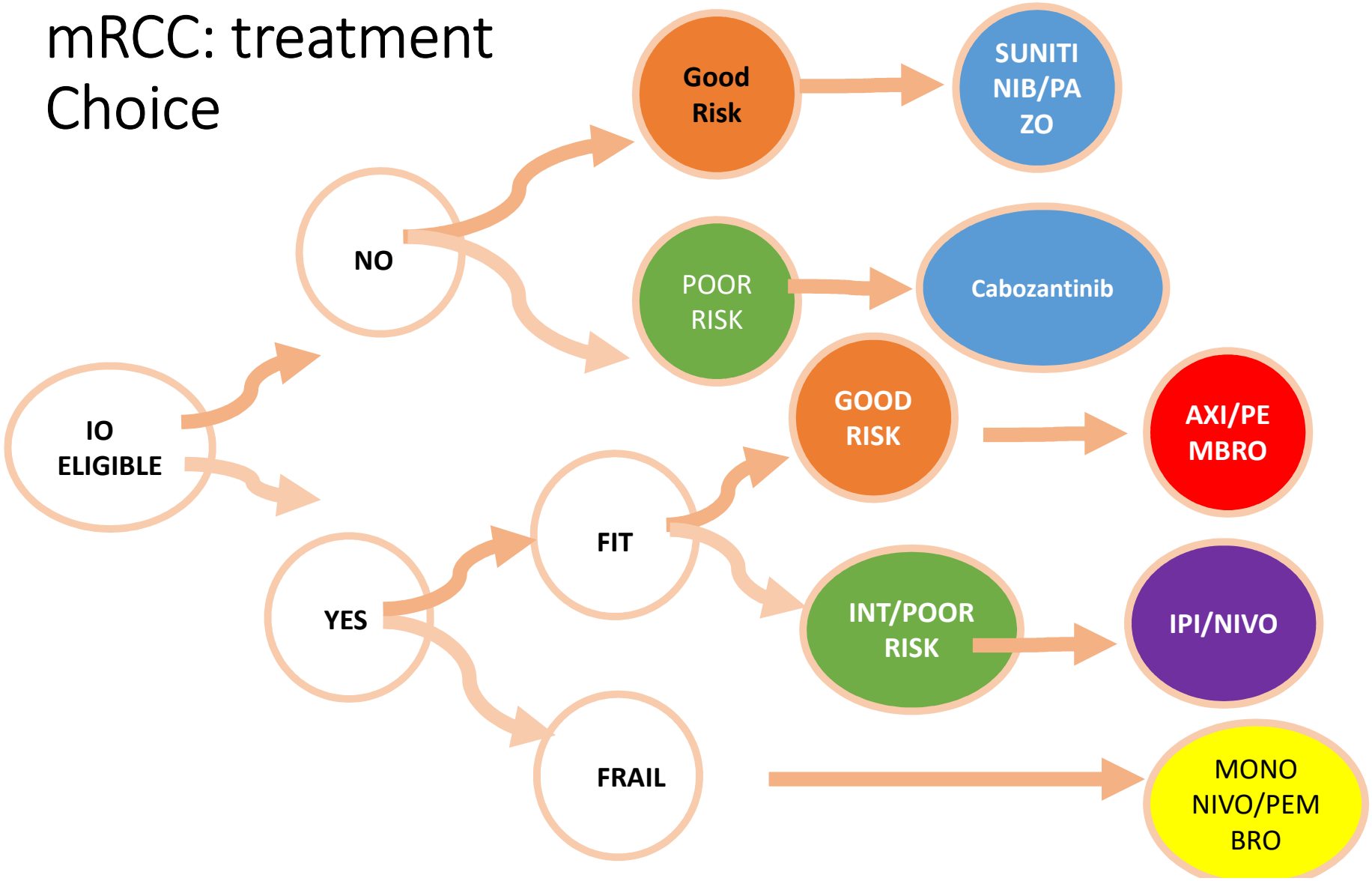


Parikh, 2019

PDIGREE: Adaptive trial



mRCC: treatment Choice



Questions? Thank You

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