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Angiogenesis, mTOR pathway, and Other Therapeutics for Kidney Cancer

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Grant/Research Support: AB Science, Janssen, Pfizer
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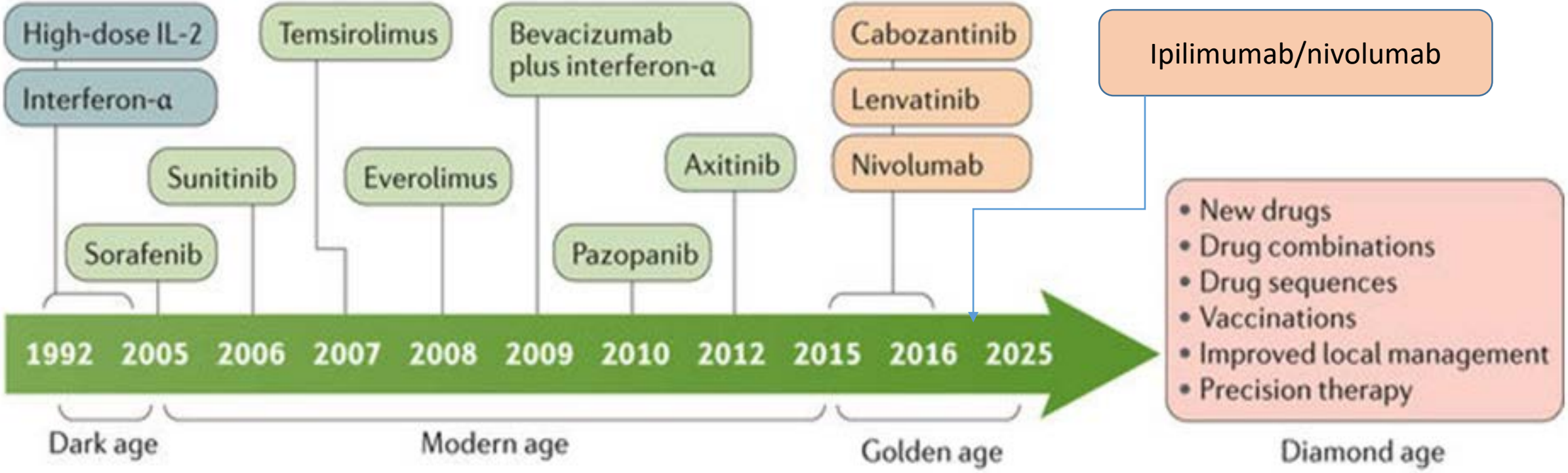
The Medical Educator Consortium

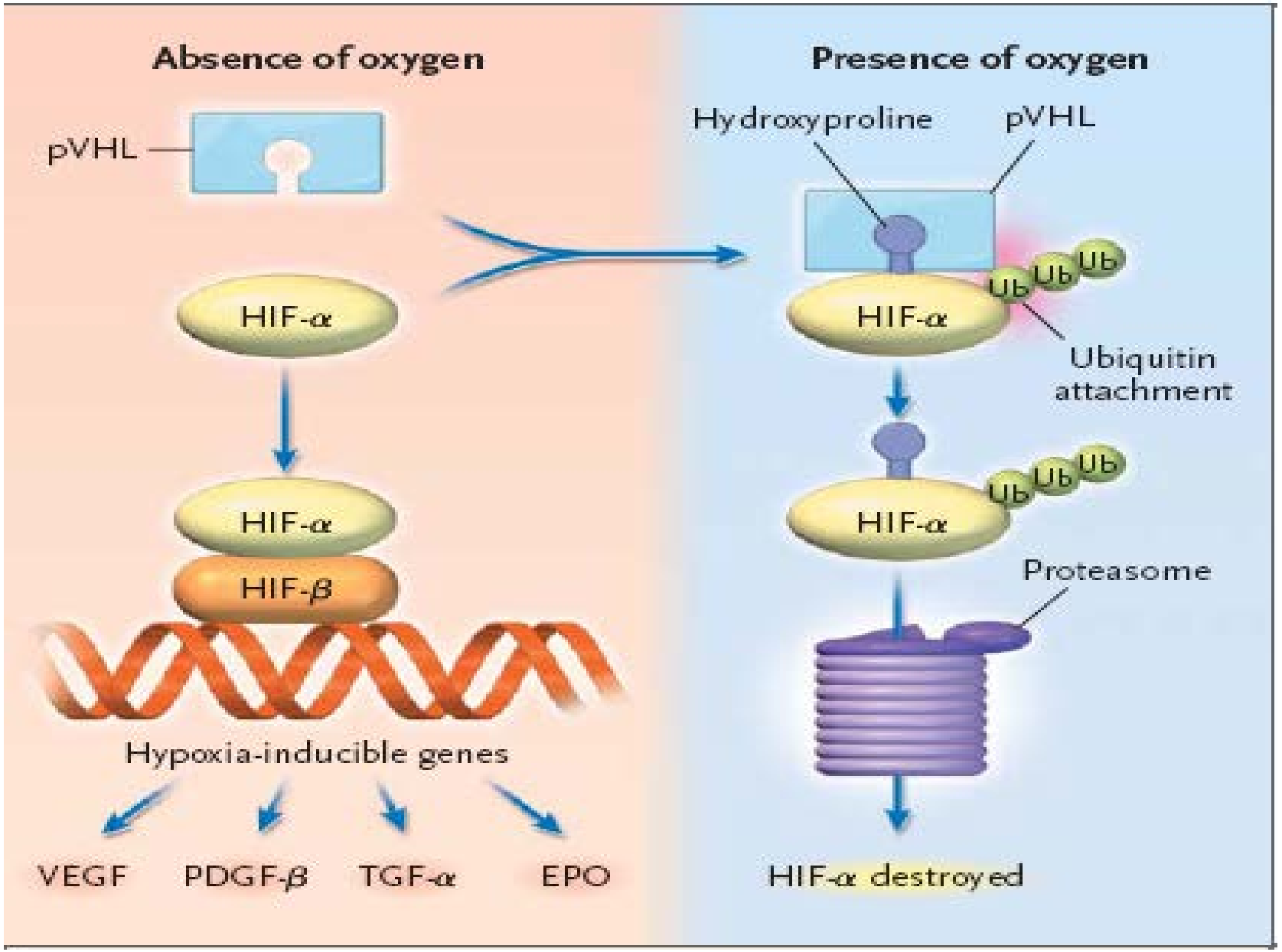
13th Annual New Orleans Summer Cancer Meeting

Objectives

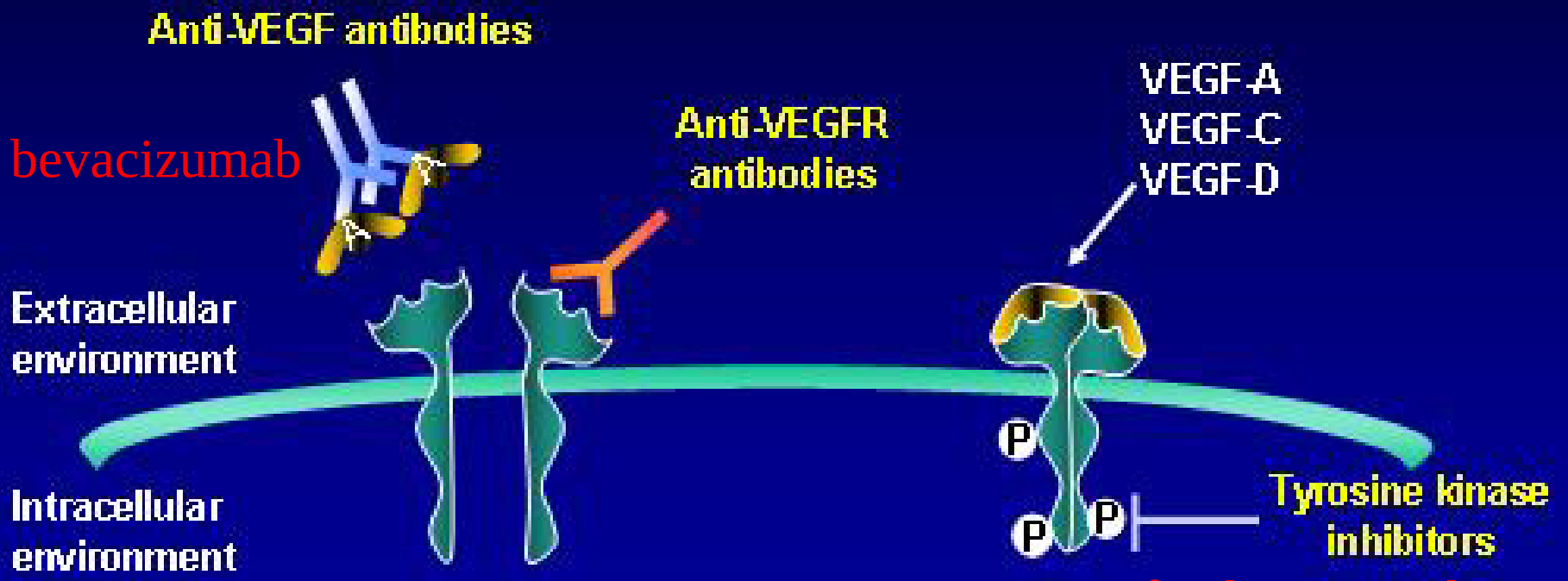
- Review registration trials for first line therapy with sunitinib, pazopanib, cabozantinib
- Review first line trials with TKI v Checkpoint inhibitor (CPI)
- Review drug sequencing algorithms
- Review biomarkers
- Review possible new targets in RCC

Targeted Agents in Treatment of RCC




Absence of oxygen
Presence of oxygen
pVHL
Hydroxyproline
pVHL
HIF-α
HIF-α
Ub
Ub
Ub
Ubiquitin attachment
HIF-α
HIF-β
HIF-α
Ub
Ub
Ub
Proteasome
Hypoxia-inducible genes
VEGF
PDGF-β
TGF-α
EPO
HIF-α destroyed

Approaches to the inhibition of VEGF signaling



sorafenib sunitinib

pazopanib, axitinib

lenvatinib, cabozantinib

Advanced Renal Cell Cancer
MSKCC Prognostic Risk

The MSKCC risk factors[1]:

- Low Karnofsky performance status (< 80%)
- High lactate dehydrogenase level (> 1.5 × ULN)
- Low serum hemoglobin level (< lower limit of normal)
- High corrected serum calcium concentration (> 10 mg/dL)
- No prior nephrectomy

MSKCC Risk	Risk Factors	Median Survival, mo	% of RCC patients
Favorable	0	19.9	25
Intermediate	1–2	10	53
Poor	? 3	3.9	22

Pre TKI era

1. Motzer. *J Clin Oncol*. 1999;17:2530-2540.

Sunitinib versus Interferon

- Randomized Phase III Trial: 750 pts
-

Variable	Sunitinib (N=375)	Interferon Alfa (N=375)
MSKCC risk factors — no. (%)†		
0 (favorable)	143 (38)	121 (34)
1–2 (intermediate)	209 (56)	212 (59)
≥3 (poor)	23 (6)	25 (7)

- Sunitinib 50 mg, 4/2
  versus IFN 9MU SQ 3x/wk
- Median PFS 11 v 5 mos.
  - HR 0.42, p < 0.001
- ORR 31% v 6% / 0 CR

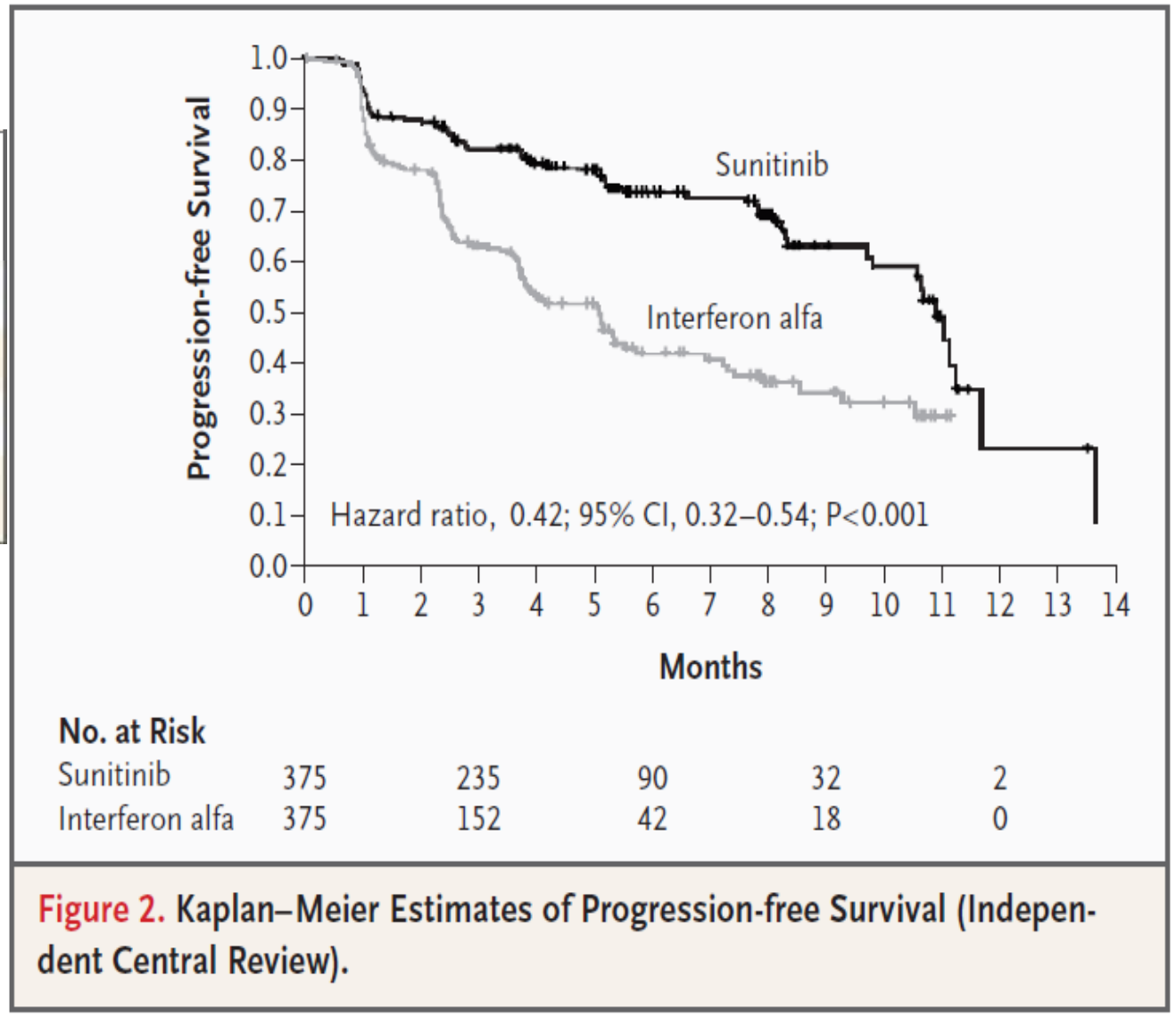


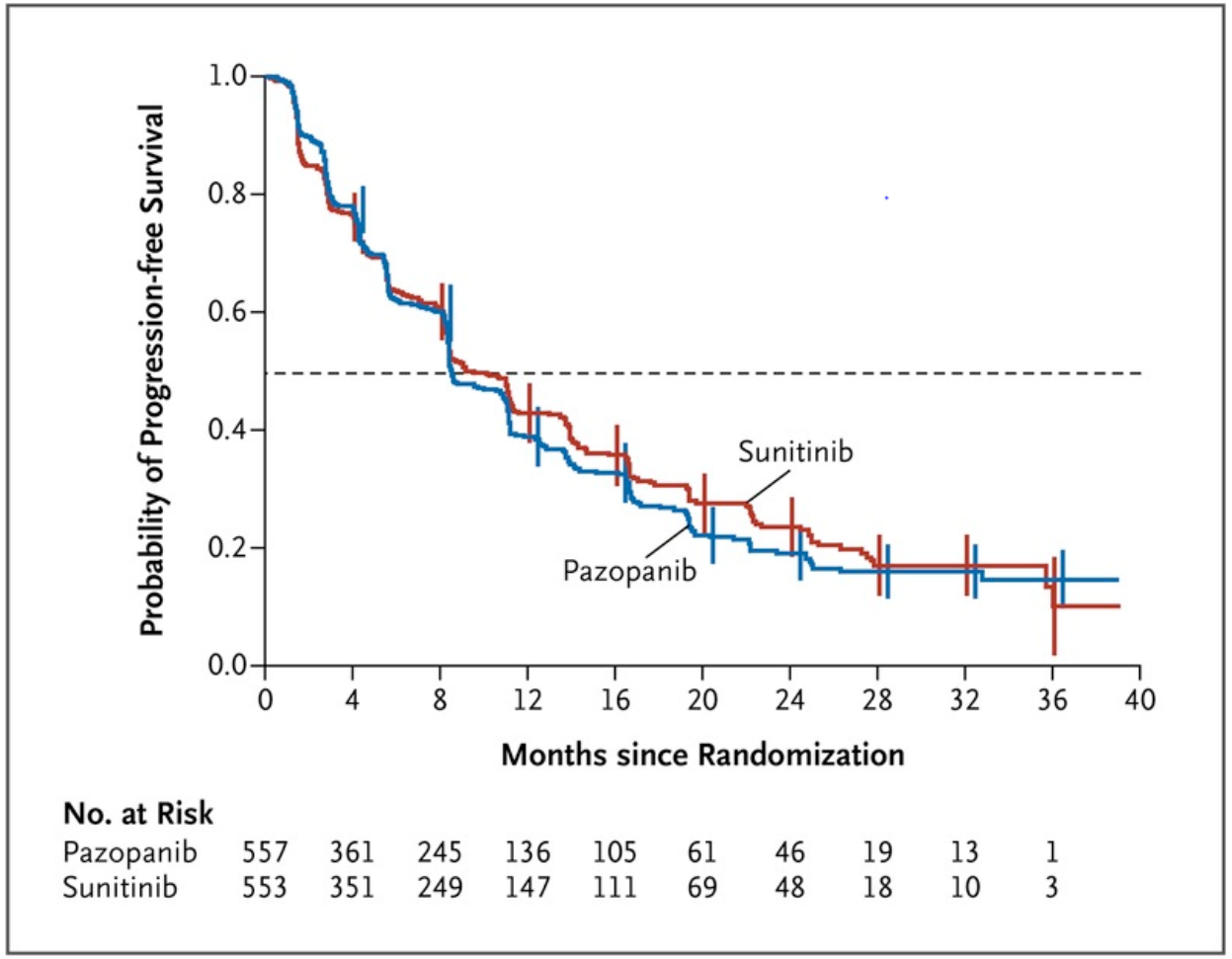
Figure 2. Kaplan–Meier Estimates of Progression-free Survival (Independent Central Review).

Motzer, et al, NEJM 356:115-124, 2007

COMPARZ TRIAL

- Sunitinib 50 mg/day 4/2
  v Pazopanib 800 mg/day
- Primary endpoint: non-inferiority PFS
- First line therapy: treatment naïve
- Stratification: KPS, LDH, Nephrectomy
- 1110 pts

MSKCC risk category,[b] n (%)		
Favorable	151 (27)	152 (27)
Intermediate	322 (58)	328 (59)
Poor	67 (12)	52 (9)
Unknown	17 (3)	21 (4)



- mPFS (mos) 8.4 (P) v 9.5 (S)
- ORR 31% (P) v 25 (S)
- Toxicity profile was similar; QOL favored P

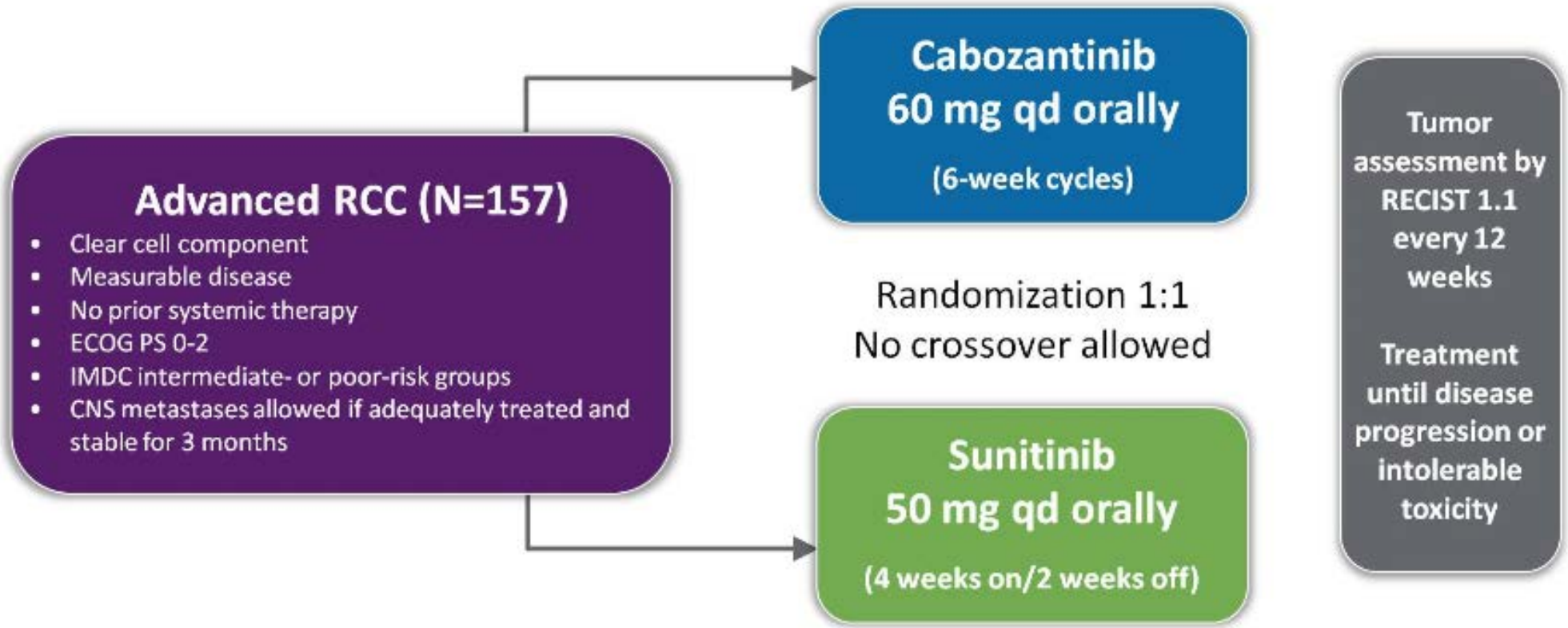
RCC Risk Classifications

IMDC		MSKCC
KPS	<80	KPS
Time from Diagnosis to Rx	< 1 year	Time from Diagnosis to Rx
Hemoglobin	< LLN	Hemoglobin
Ca		
Pl		
Ne		
Validated in TKI era		Pre-TKI

Score	Prognosis	Median Survival
≤1	Favorable	43.2 months
2	Intermediate	22.5 months
≥3	Poor	7.8 months

Favorable Risk (0), Intermediate (1-2), Poor (3-6)

Alliance A031203/CABOSUN: Randomized Phase II Trial of First-line Cabozantinib vs Sunitinib in Intermediate- or Poor-Risk Patients With mRCC[1]



Primary endpoint
- PFS by investigator assessment

Secondary endpoints
- OS, ORR, safety

Stratification
- IMDC risk group[2]: intermediate, poor
- Bone metastases: yes, no

Alliance A031203 CABOSUN Trial

- Cabozantinib: oral inhibitor of VEGF-2, MET, AXL
- Randomized Phase II trial: Cabozantinib 60 mg v Sunitinib 50 mg 4/2
- Patient Population: IMDC intermediate (81%) and poor risk (19%)
- Bone metastases: 36% in both groups
- mPFS (mos): 8.2 (C) v. 5.6 (S)
- HR = 0.66 (34% reduction in rate of progression)
- ORR 33% (C) v 12% (S)
- Grade 3/4 AEs similar 67% v 68%

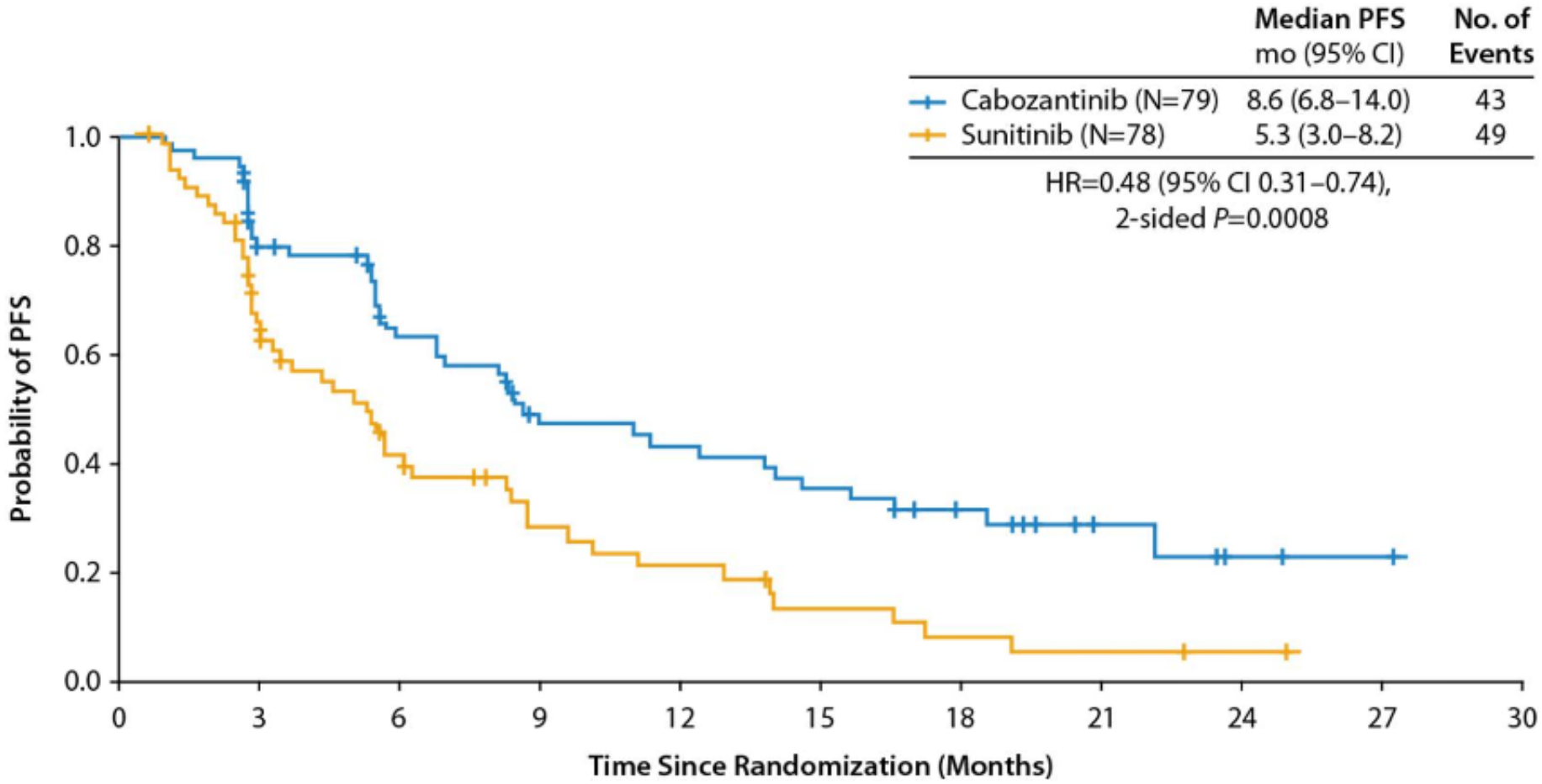
Choueri, JCO 35:591-597, 2016, data cutoff: April, 2016

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	No. (%) Cabozantinib (n = 79)	Sunitinib (n = 78)	Total (N = 157)
Age, years			
Median	63.0	64.0	63.0
Range	40.0-82.0	31.0-87.0	31.0-87.0
Sex			
Male	66 (83.5)	57 (73.1)	123 (78.3)
Female	13 (16.5)	21 (26.9)	34 (21.7)
Ethnic origin			
White	70 (88.6)	75 (96.2)	145 (92.4)
Black or African American	3 (3.8)	2 (2.6)	5 (3.2)
Native Hawaiian or Pacific Islander	1 (1.3)	0 (0.0)	1 (0.6)
Asian	1 (1.3)	0 (0.0)	1 (0.6)
American Indian or Alaska Native	1 (1.3)	0 (0.0)	1 (0.6)
Not reported	1 (1.3)	0 (0.0)	1 (0.6)
Unknown (patient unsure)	2 (2.5)	1 (1.3)	3 (1.9)
ECOG PS			
0	36 (45.6)*	36 (46.2)	72 (45.9)
1	33 (41.8)	32 (41.0)	65 (41.4)
2	10 (12.7)	10 (12.8)	20 (12.7)
IMDC risk group			
Intermediate	64 (81.0)	63 (80.8)	127 (80.9)
Poor	15 (19.0)	15 (19.2)	30 (19.1)
Bone metastases			
Yes	29 (36.7)	28 (35.9)	57 (36.3)
No	50 (63.3)	50 (64.1)	100 (63.7)
Prior nephrectomy			
Yes	57 (72.2)	60 (76.9)	117 (74.5)
No	22 (27.8)	18 (23.1)	40 (25.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PS, performance status.

Alliance A031203/CABOSUN: Kaplan-Meier Plot of Progression-Free Survival per IRC: FDA approved in advanced RCC



No. at risk											
Cabozantinib	79	51	37	24	22	18	12	5	2	1	0
Sunitinib	78	36	21	12	9	5	3	2	1	0	0

Data cutoff: September 15, 2016.

IRC=independent radiology committee.

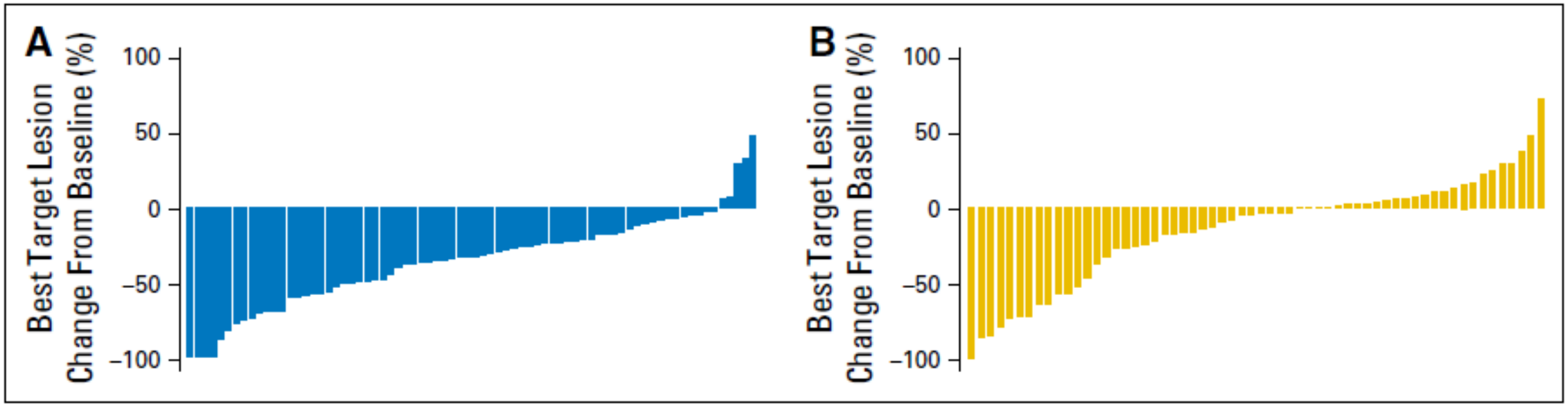


Fig 3. Best target lesion change from baseline with (A) cabozantinib and (B) sunitinib. Data are as of April 11, 2016. (A) Three patients in the cabozantinib group and (B) 16 patients in the sunitinib group were not evaluable because they had no postbaseline imaging assessments (Table 2).

Alliance A031203 CABOSUN Trial

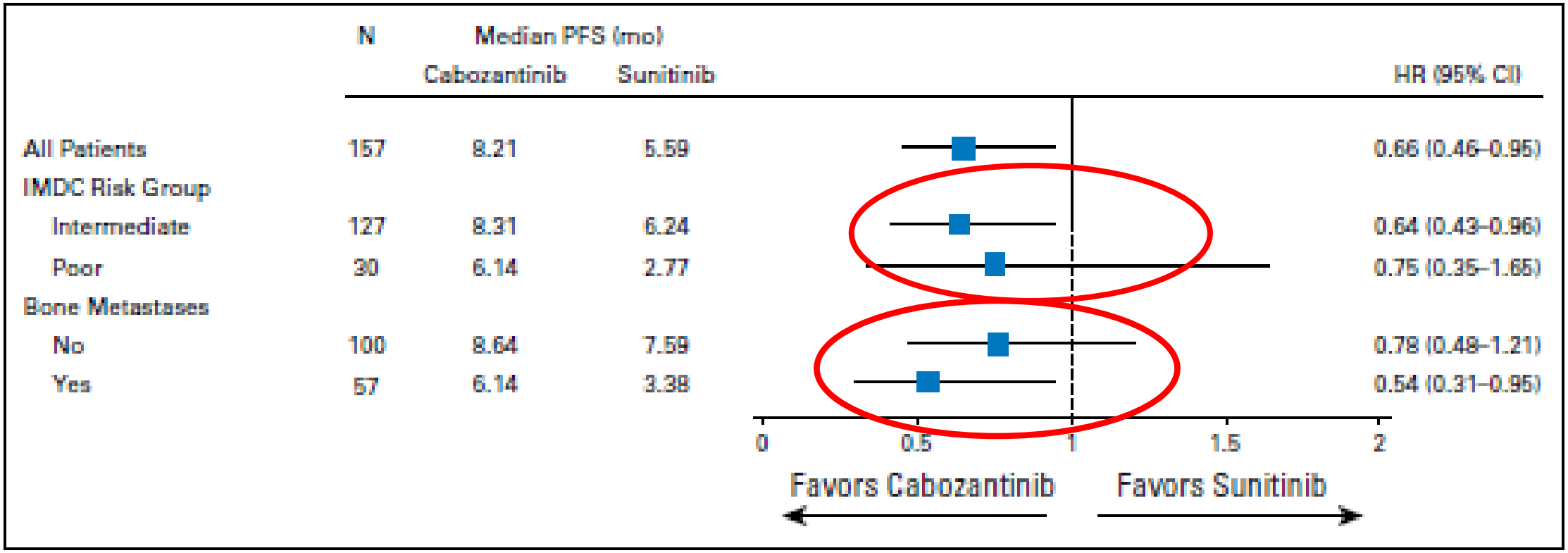
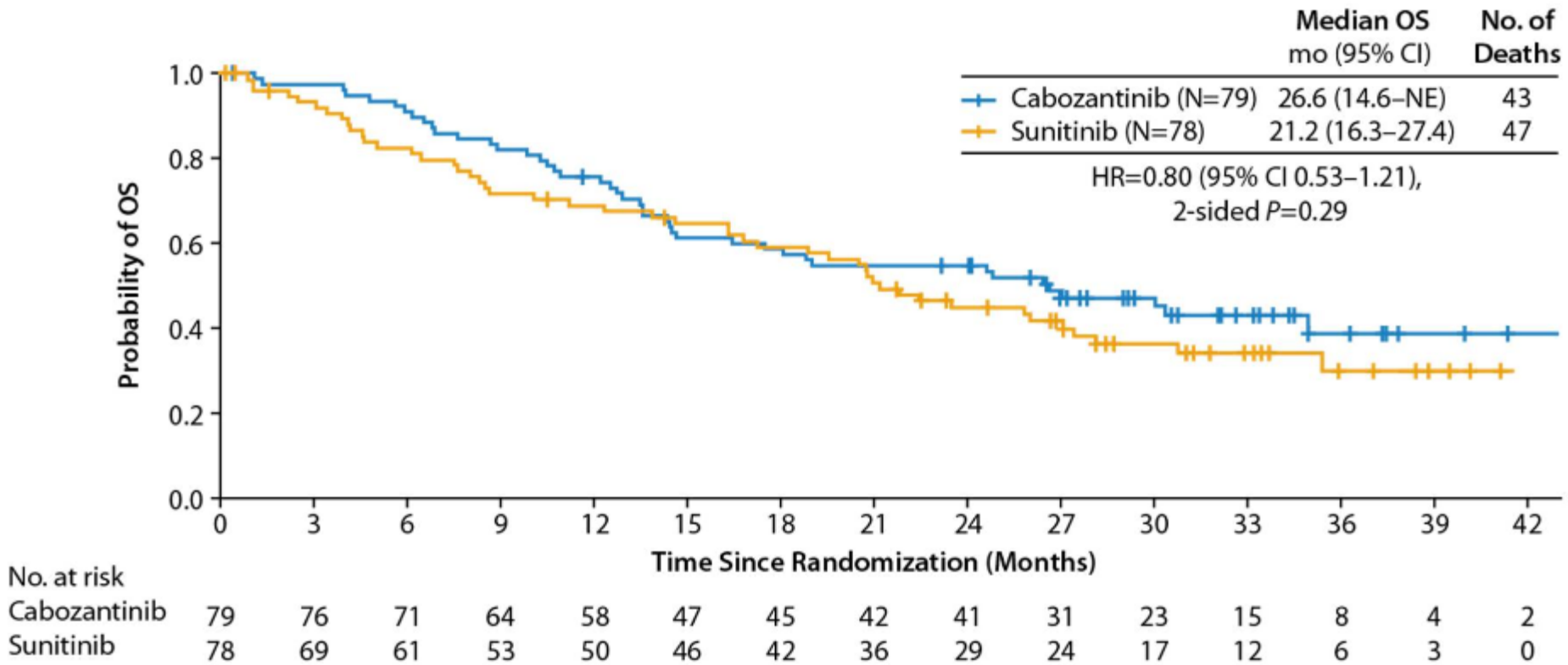


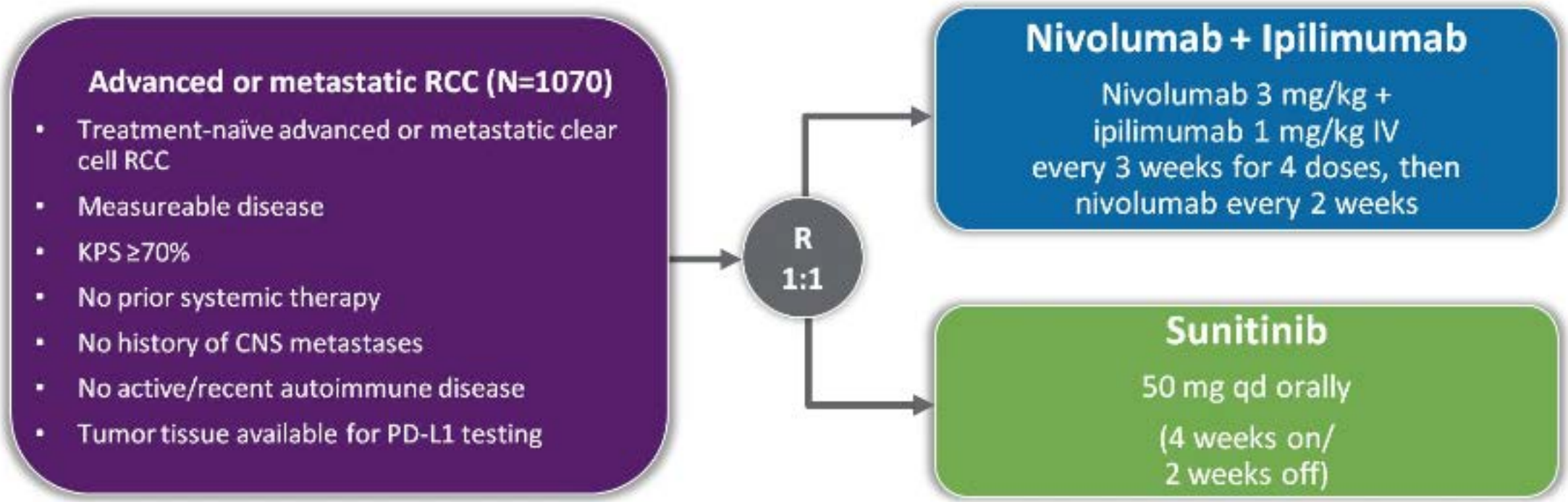
Fig A1. Forest plots of progression-free survival through April 11, 2016. All randomly assigned patients were included in the analyses. Hazard ratios (HRs) are unadjusted with the exception of that for the overall population, where stratification factors for random assignment were used. IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PFS, progression-free survival.

Alliance A031203/CABOSUN: Overall Survival



Data cutoff: July 01, 2017.
mo=months; NE=not evaluable.

CheckMate 214: Phase III Study of Nivolumab Plus Ipilimumab vs Sunitinib



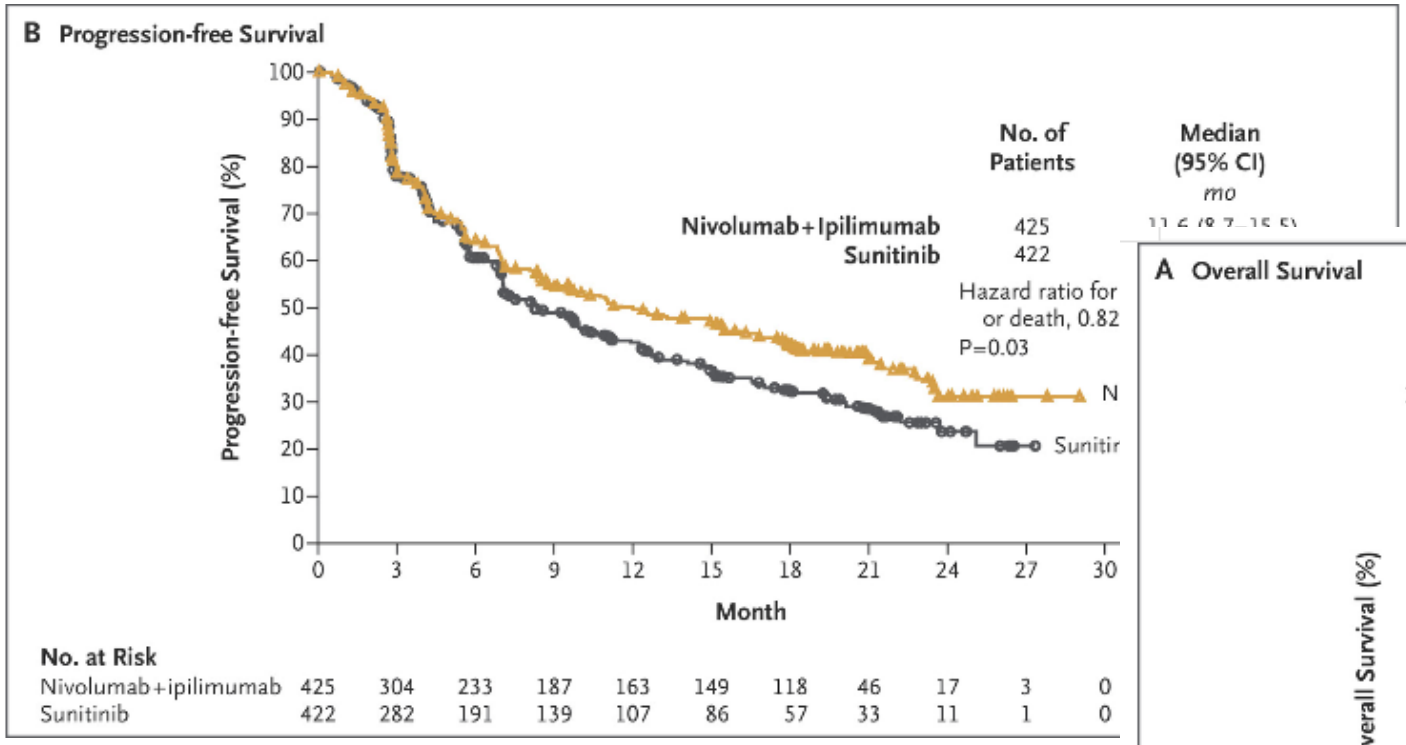
- **Stratification:** IMDC prognostic score (0 vs 1-2 vs 3-6) and region (US vs Canada/Europe vs rest of the world)
- **Co-primary endpoints:** in IMDC intermediate- and poor-risk patients
  - ORR (per IRRC), PFS (per IRRC) and OS
- **Secondary endpoints:** in ITT patients
  - ORR, PFS, OS and adverse event incidence rate (in all treated patients)

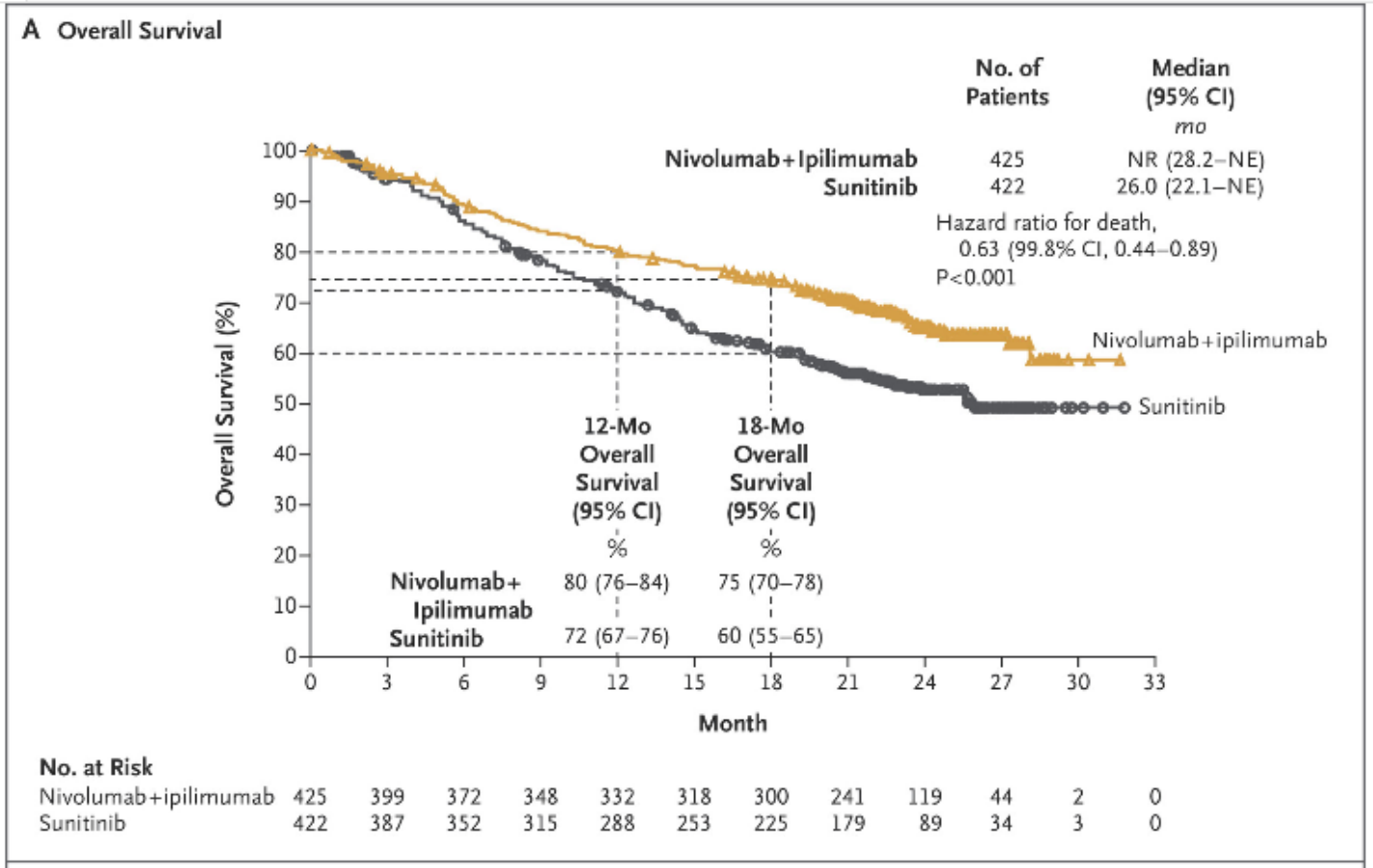
CheckMate 214

Table 1. Baseline Demographic and Clinical Characteristics of the Patients Who Underwent Randomization.*

Characteristic	IMDC Intermediate- and Poor-Risk Patients		Intention-to-Treat Population	
	Nivolumab plus Ipilimumab (N=425)	Sunitinib (N=422)	Nivolumab plus Ipilimumab (N=550)	Sunitinib (N=546)
Median age (range) — yr	62 (26–85)	61 (21–85)	62 (26–85)	62 (21–85)
Sex — no. (%)				
Male	314 (74)	301 (71)	413 (75)	395 (72)
Female	111 (26)	121 (29)	137 (25)	151 (28)
IMDC prognostic risk — no. (%)†				
Favorable	0	0	125 (23)	124 (23)
Intermediate	334 (79)	333 (79)	334 (61)	333 (61)
Poor	91 (21)	89 (21)	91 (17)	89 (16)
Geographic region — no. (%)				
United States	112 (26)	111 (26)	154 (28)	153 (28)
Canada and Europe	148 (35)	146 (35)	201 (37)	199 (36)
Rest of the world	165 (39)	165 (39)	195 (35)	194 (36)
Quantifiable tumor PD-L1 expression — no./ total no. with evaluable data (%)				
<1%	284/384 (74)	278/392 (71)	386/499 (77)	376/503 (75)
≥1%	100/384 (26)	114/392 (29)	113/499 (23)	127/503 (25)
Previous radiotherapy — no. (%)	52 (12)	52 (12)	63 (11)	70 (13)
Previous nephrectomy — no. (%)	341 (80)	319 (76)	453 (82)	437 (80)
No. of sites with target or nontarget lesions — no. (%)‡				
1	90 (21)	84 (20)	123 (22)	118 (22)
≥2	335 (79)	337 (80)	427 (78)	427 (78)
Most common sites of metastasis — no. (%)				
Lung	294 (69)	296 (70)	381 (69)	373 (68)
Lymph node	190 (45)	216 (51)	246 (45)	268 (49)
Bone§	95 (22)	97 (23)	112 (20)	119 (22)
Liver	88 (21)	89 (21)	99 (18)	107 (20)

CheckMate 214
Intermediate and Poor Risk





PFS difference did not meet prespecified threshold for significance

CheckMate 214

Table 2. Antitumor Activity in IMDC Intermediate- and Poor-Risk Patients.*

Variable	Nivolumab plus Ipilimumab (N = 425)	Sunitinib (N = 422)
Confirmed objective response rate — % (95% CI)†	42 (37–47)‡	27 (22–31)‡
Confirmed best overall response — no. (%)†		
Complete response	40 (9)‡§	5 (1)‡§
Partial response	137 (32)	107 (25)
Stable disease	133 (31)	188 (45)
Progressive disease	83 (20)	72 (17)
Unable to determine or not reported	32 (8)	50 (12)
Median time to response (range) — mo	2.8 (0.9–11.3)	3.0 (0.6–15.0)
Median duration of response (95% CI) — mo	NR (21.8–NE)	18.2 (14.8–NE)
Patients with ongoing response — no./total no. (%)	128/177 (72)	71/112 (63)

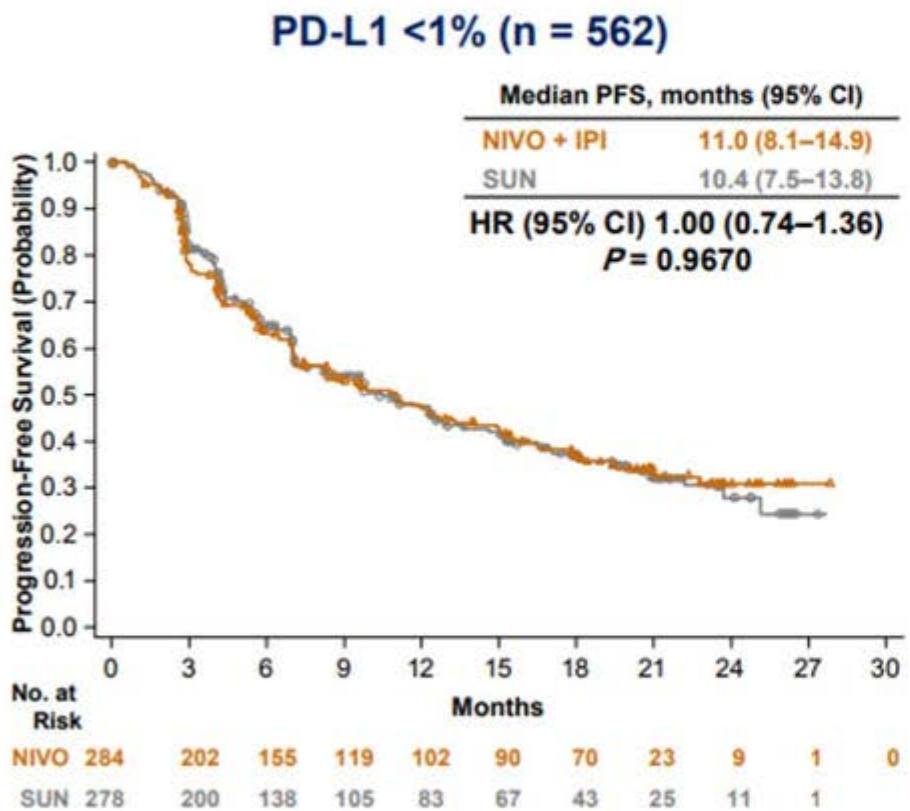
CheckMate 214

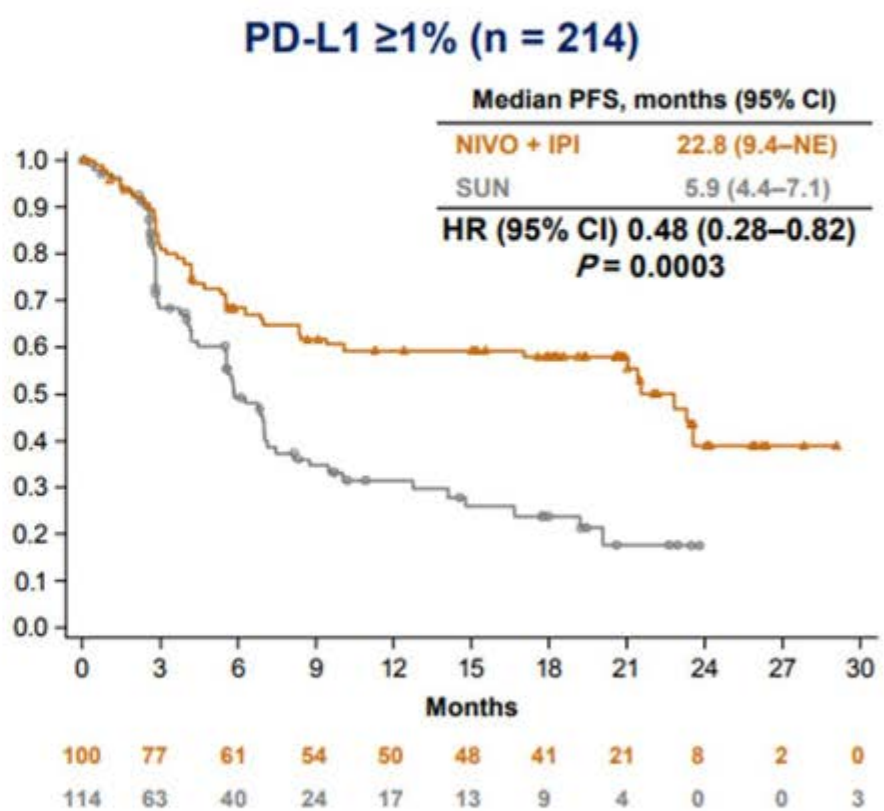
ORR and PFS: IMDC favorable risk

Outcome	N = 249[a]	
	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**	

[a]11% of patients in both arms had tumor PD-L1 expression ≥1%.
[b]IRRC-assessed by RECIST v1.1.
[c]IRRC-assessed.

CheckMate 214: PFS by PD-L1 Expression in IMDC Intermediate/ Poor-risk Patient Population *(Exploratory Endpoint)*

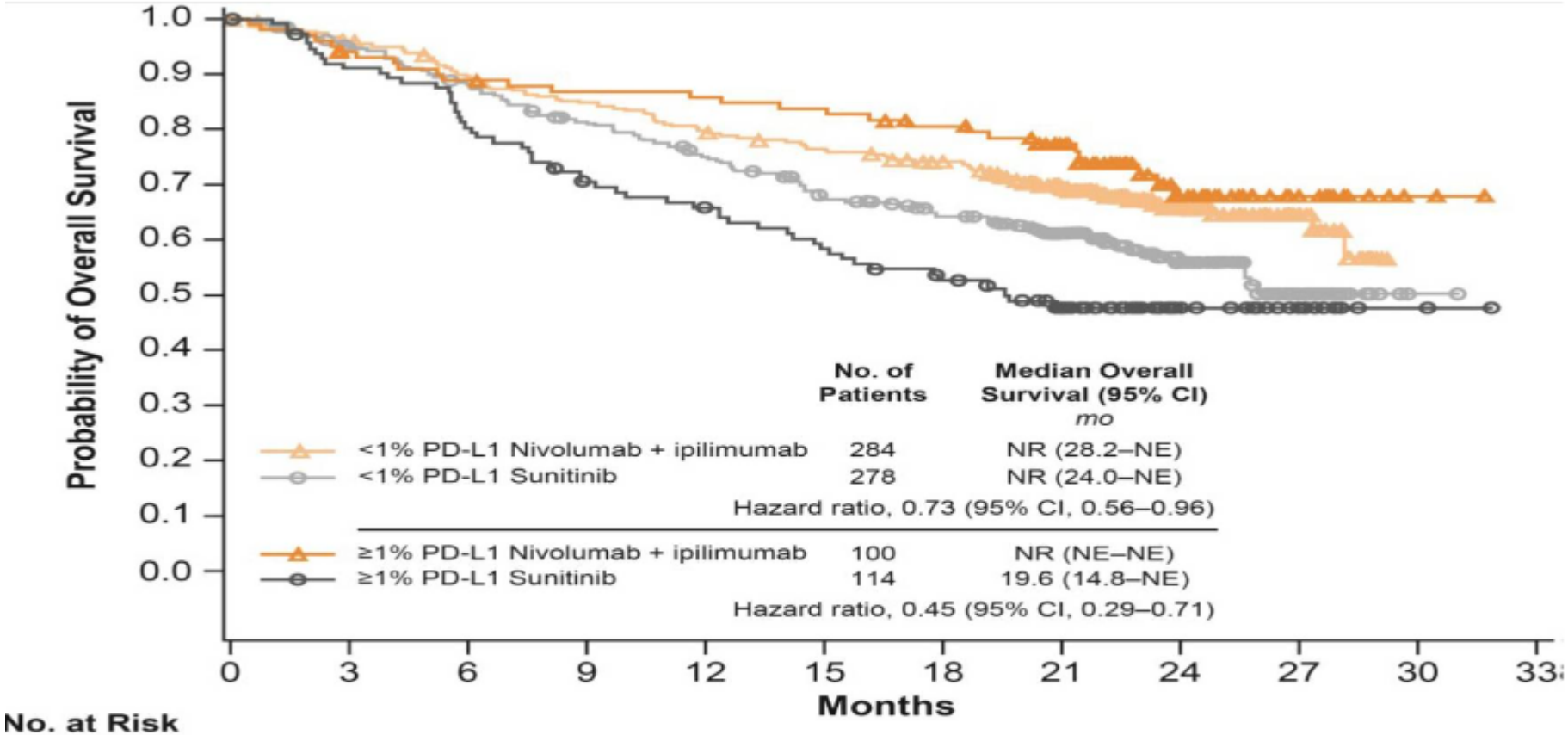




IMDC=International Metastatic Renal Cell Carcinoma Database Consortium.
Escudier B, et al. ESMO. 2017 (abstr LBA5).

CheckMate 214

OS in Int/Poor Risk by PDL-1 status

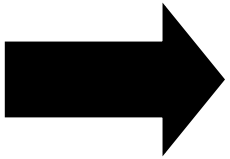


No. at Risk						
NIVO + IPI <1% PD-L1	284	251	223	200	76	0
SUN <1% PD-L1	278	239	198	157	61	1
NIVO + IPI ≥1% PD-L1	100	87	83	76	33	2
SUN ≥1% PD-L1	114	90	72	55	21	2

IMmotion 151

Patients
Eligibility Requirements:
Treatment Naïve
Clear cell and/or
Sarcomatoid component
KPS ≥ 70

Stratification
- MSKCC score
- Liver mets
- PDL1 status <1%; ≥ 1%



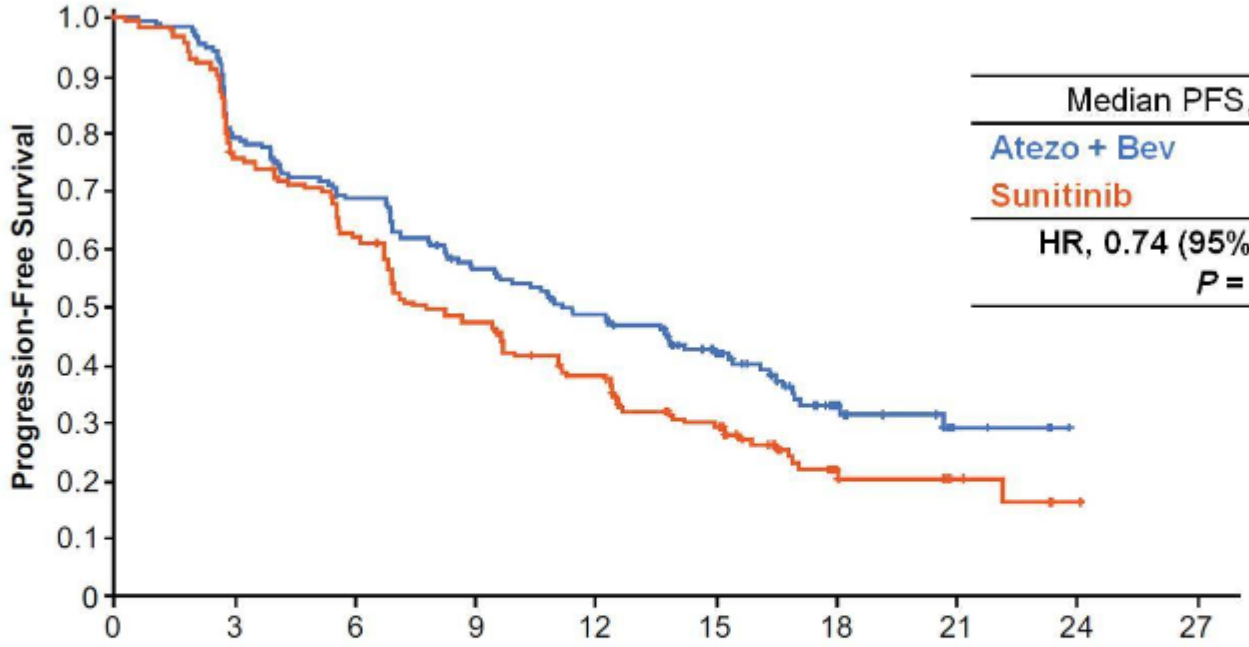
RANDOMIZE

ATEZOLIZUMAB 1200 MG +

BEVACIZUMAB 15 MG/KG Q3W

SUNITINIB 50 MG/D 4/2

Progression-Free Survival in PD-L1+



Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (8.9, 15.0)
Sunitinib	7.7 (6.8, 9.7)
HR, 0.74 (95% CI: 0.57, 0.96)	
P = 0.02	

No. at Risk									
Atezo + Bev	178	137	117	94	79	55	22	5	
Sunitinib	184	135	110	83	64	44	15	7	1

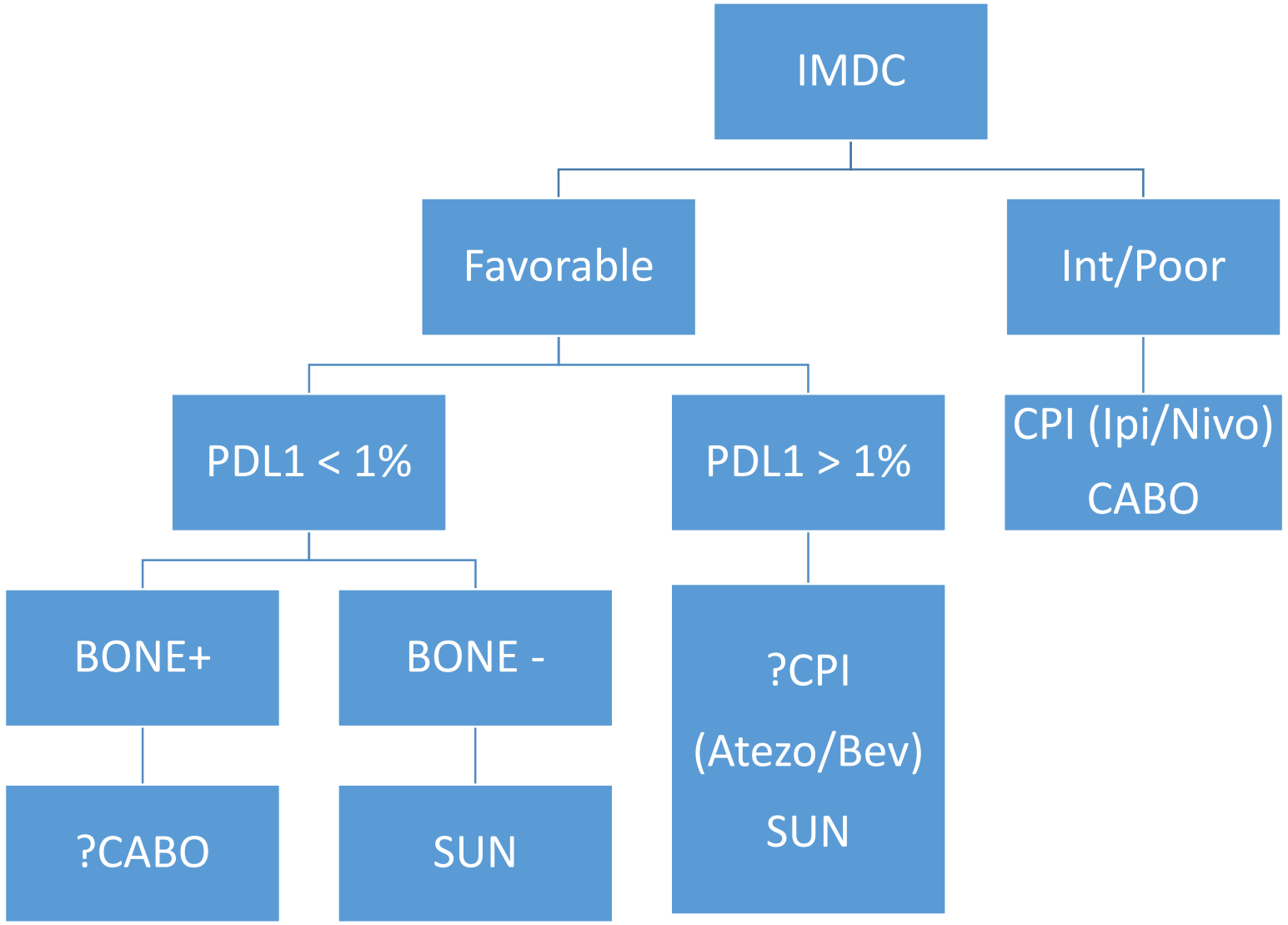
PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.
The PFS analysis passed the pre-specified *P* value boundary of alpha = 0.04.

Sunitinib arms of trials

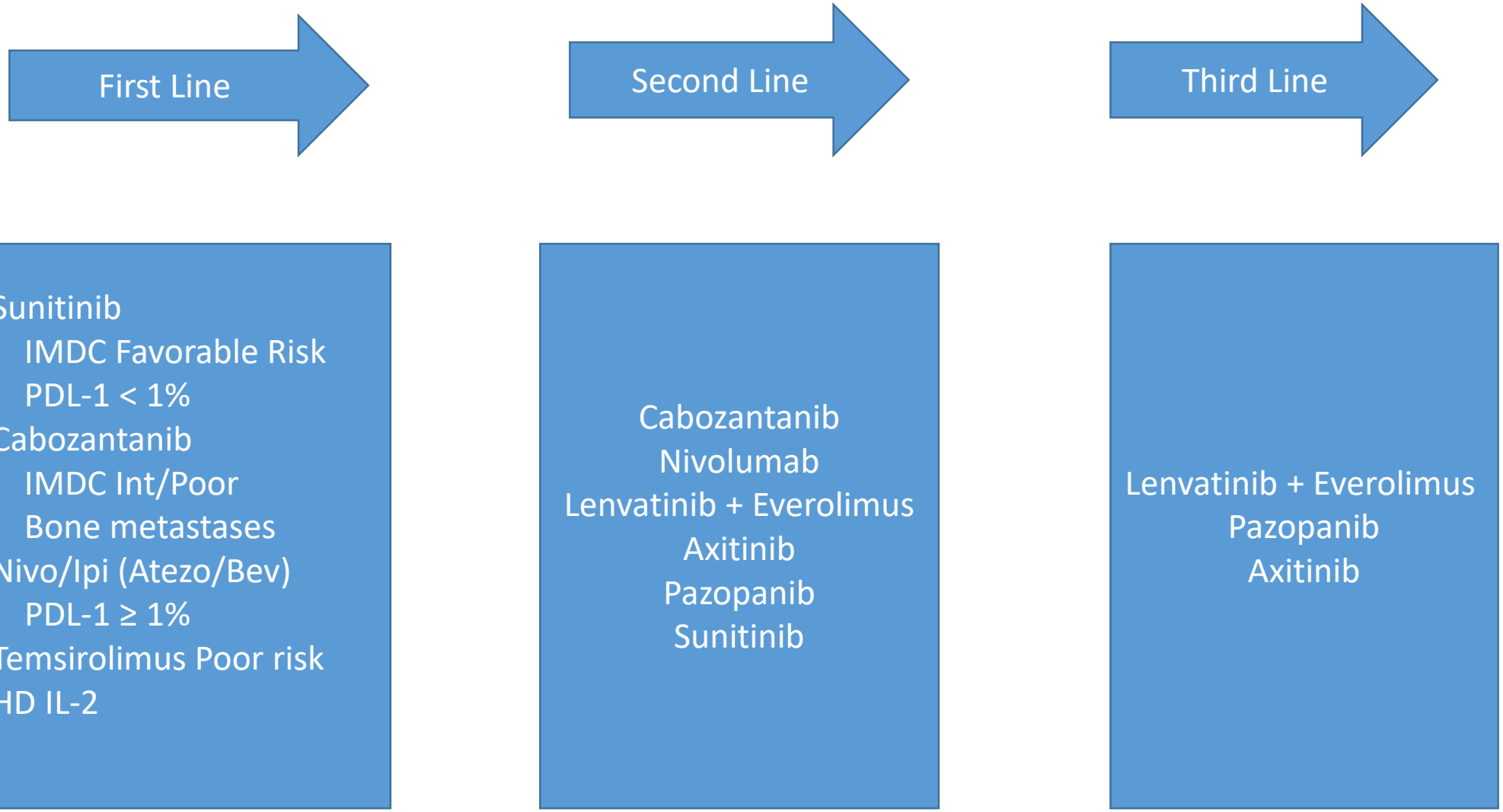
	SUN/IFN [1]	COMPARZ[2]	CABOSUN [3]	CHECKMATE 214 [4]		IMMOTION[5]
Phase	III	III	II	III		III
No pts S arm	375	553	78	422	124	461
Risk (%)	MSKCC	MSKCC	IMDC	IMDC		MSKCC
Favorable	38	27	--	--	23/(100%)	20
Intermediate	56	59	81	61		70
Poor	6	9	19	16		10
mPFS (mos)	11	8.4	5.6	8.4	25.1	8.4
ORR (%)	31	25	12	27	52	33
Results	S>IFN; PFS	S ≈ P	C > S; PFS	CPI > S ORR, OS	S > CPI ORR, PFS	PDL-1+
			OS NS	PFS NS CR (9%) > CPI		

[1] Motzer, et al, NEJM 356:115-124, 2007 [2] Motzer et al, NEJM 369(8):722-731,2013
[3] Choueri et al, JCO 35:591, 2016 [4] Motzer, et al, NEJM 378:1277,2018 [5] GU ASCO 2018

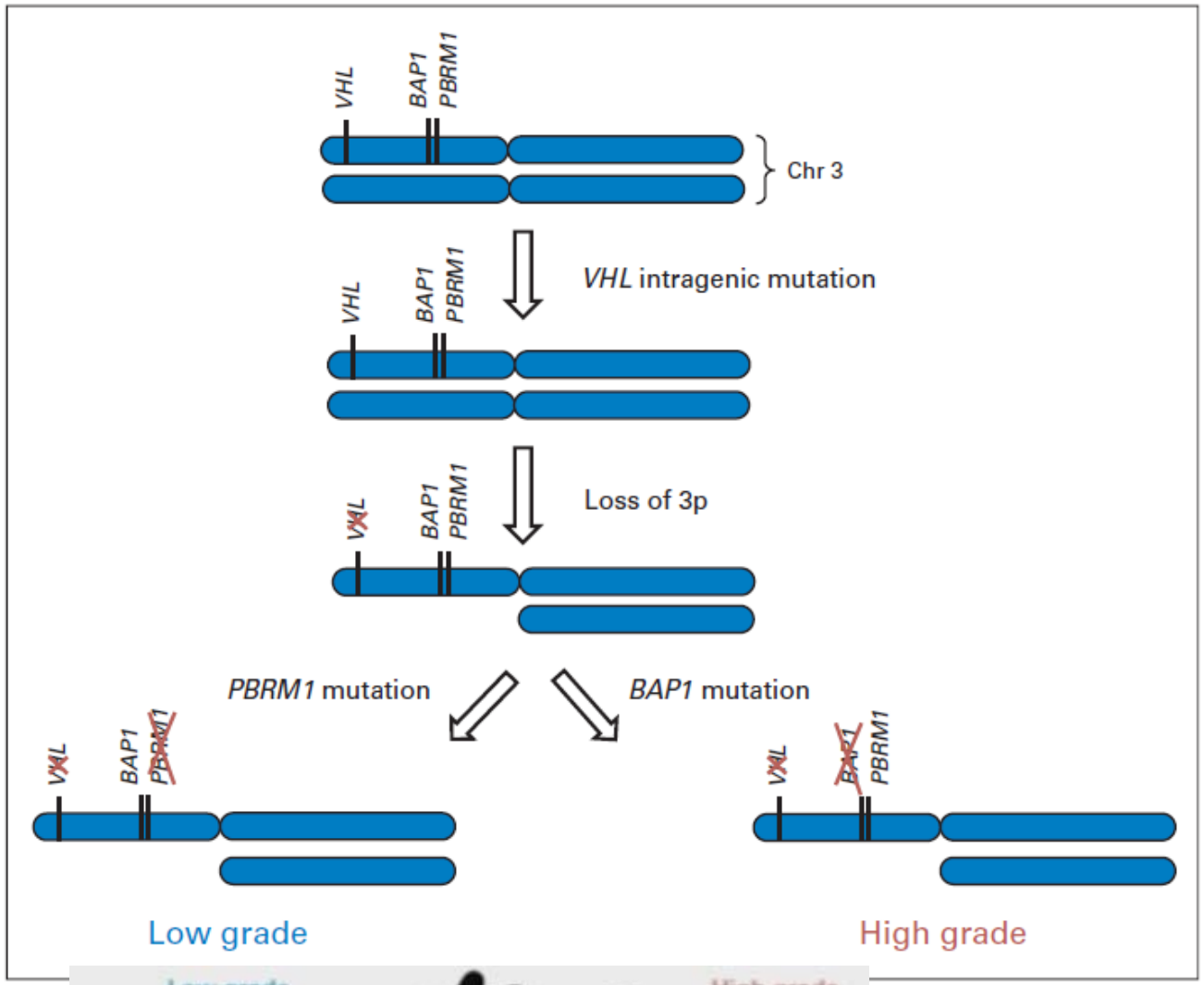
First Line Therapy for RCC

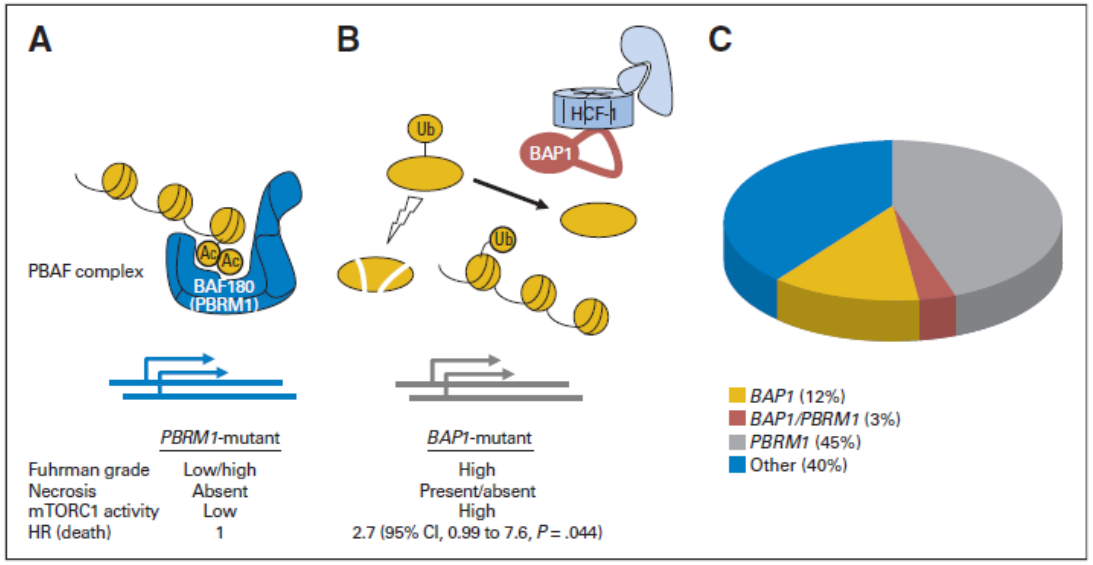


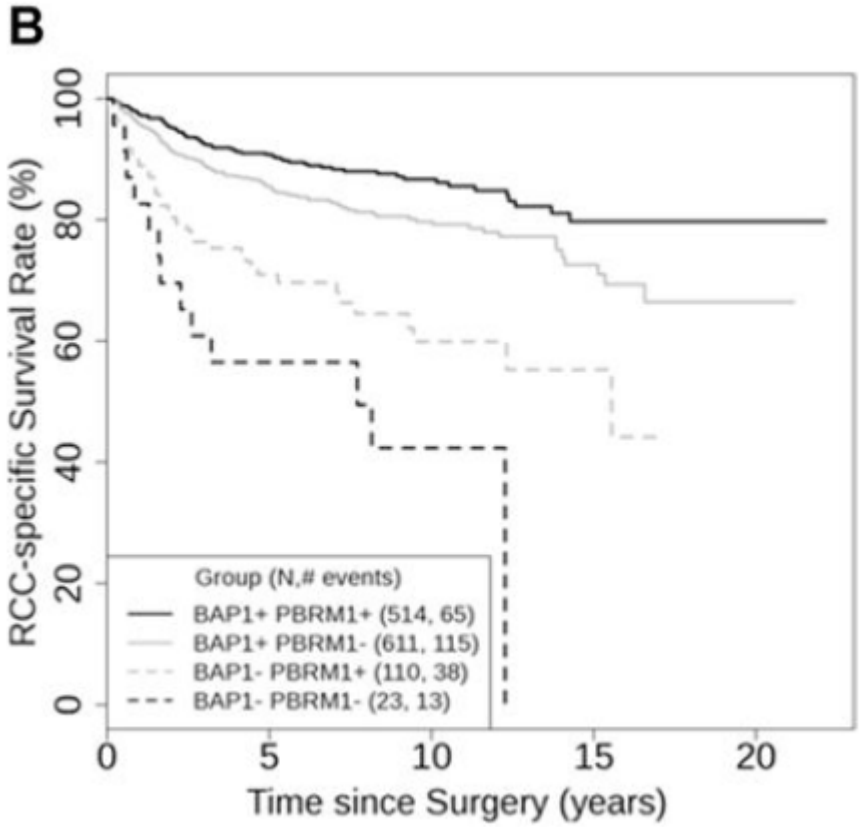
Rx Algorithm for RCC



Molecular Biology of Kidney Cancer

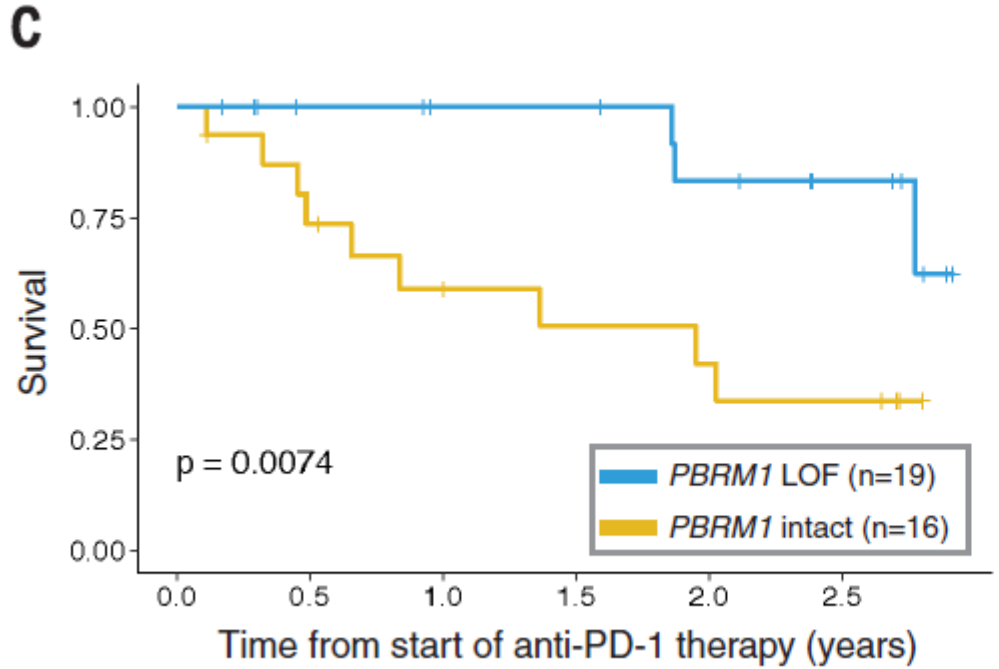


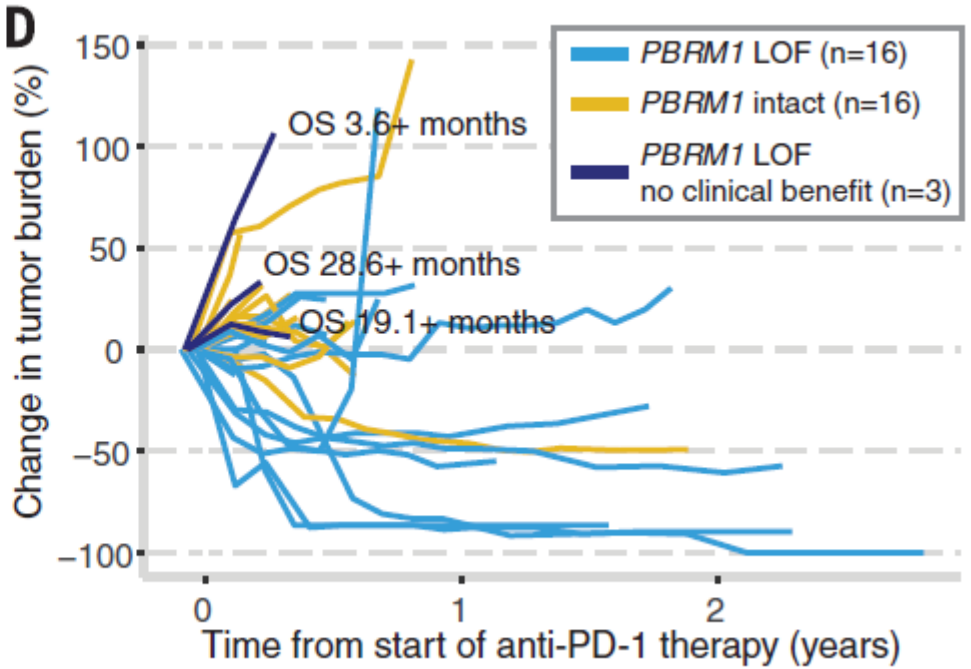




Biomarkers

- Mutations (5%) in TSC1 (LOF) or mTOR (GOF) associated with response to rapalogues (Voss, et al)
- PBRM1 mutations (45%) may predict response to IO (Miao, Science 359:801,2018)





- BAP1 loss associated with inflamed microenvironment

Future Directions

- Targeting HIF-2 downstream of pVHL
  - Small molecules to block HIF-2 transcription factor binding
  - In animal models PT2399 more potent than sunitinib
  - Phase I trial of PT2977
- CXCR4 inhibitors (X4P-001-IO) + VEGFi
  - Phase I trial (16 pts) with axitinib with ORR 29%, disease control rate 93%
- Novel immune therapy combinations

Thank You !