RENAL CELL CARCINOMA (RCC)

Medical management

Fazel elahi MD

Management of Renal cell carcinoma

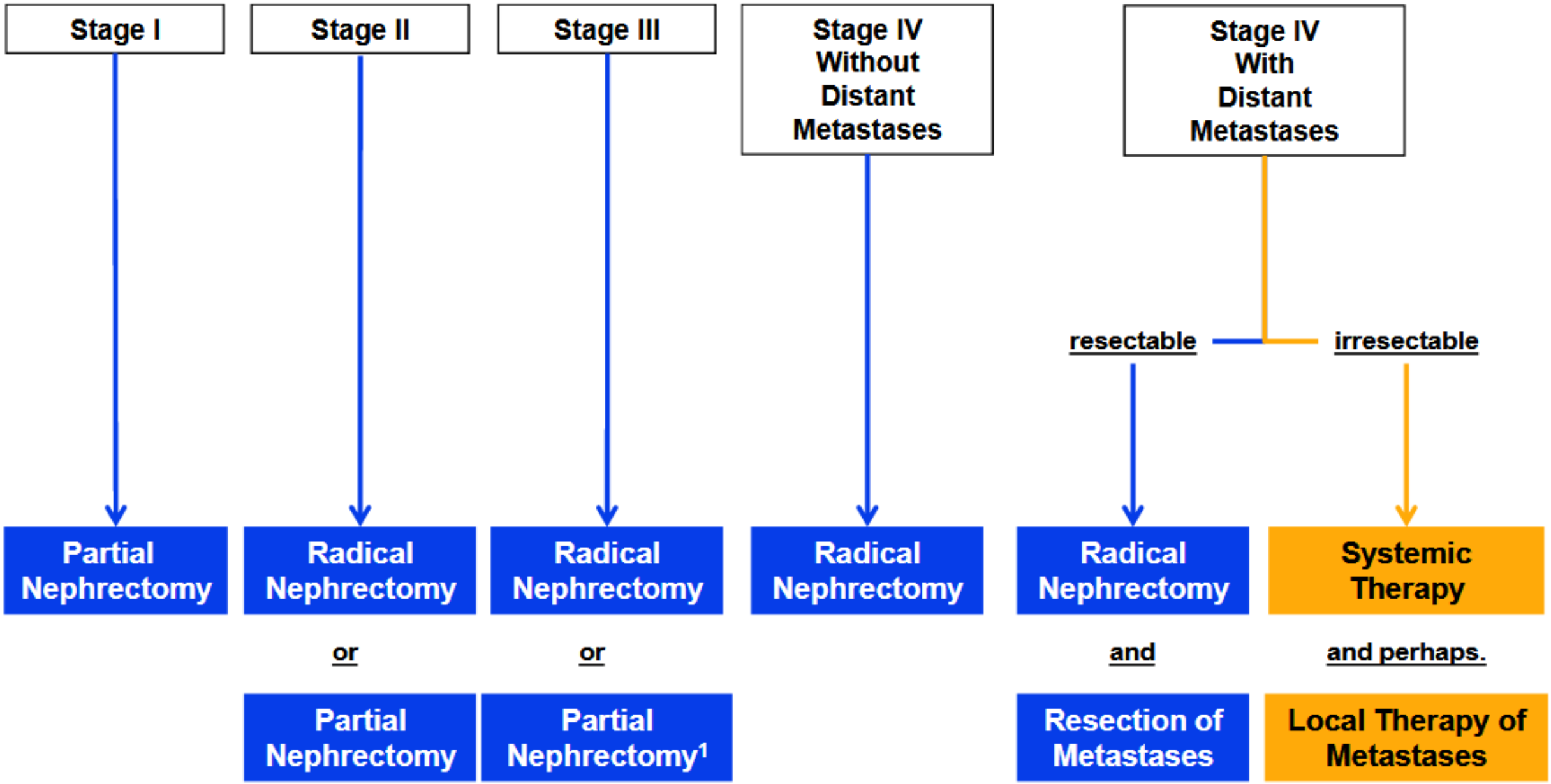
- Management of local / locoregional disease
- Management of locally advanced disease
- Management of advanced / metastatic disease

Management of Renal cell carcinoma

- Management of local / locoregional disease
- Management of locally advanced disease
- **Management of advanced / metastatic disease**

- One third with fully resected, localized disease will develop either a local or a distant recurrence, the majority of whom will succumb to distal metastases
- Patients with T3 or higher locally advanced disease have a significant risk of recurrence: 30 to 90 percent

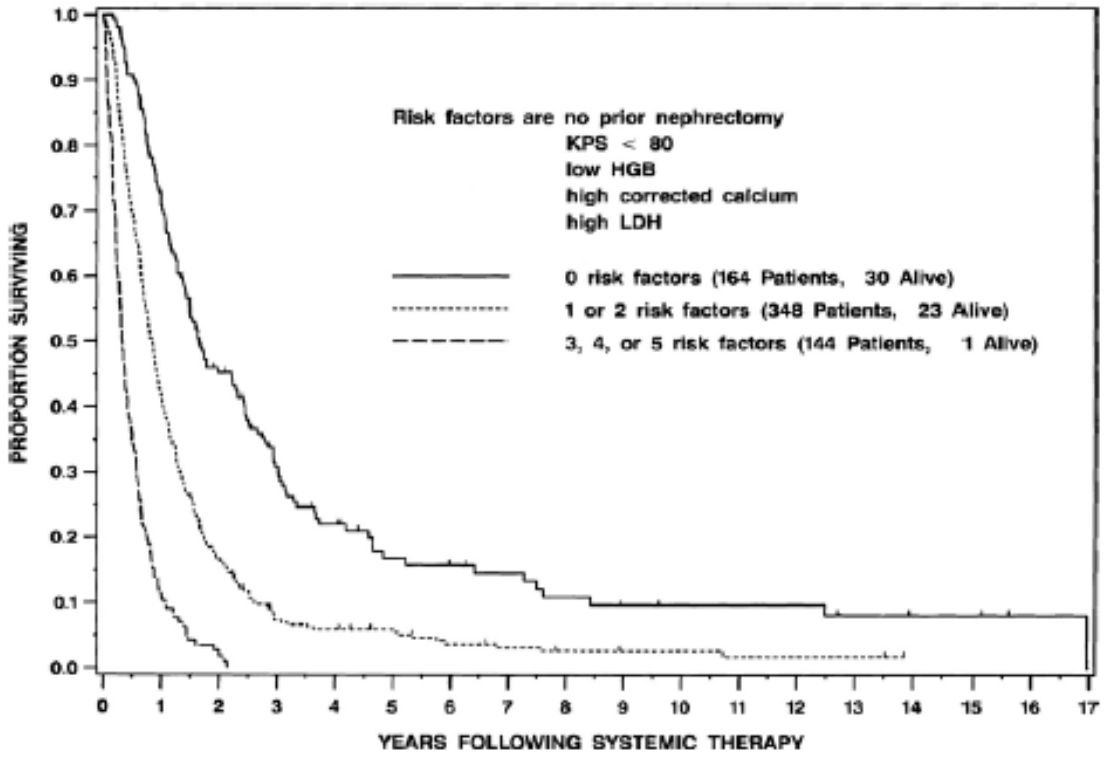
Medieval Saxon man with a large tumor of the left femur


Stage I
Stage II
Stage III
Stage IV Without Distant Metastases
Stage IV With Distant Metastases
resectable
irresectable
Partial Nephrectomy
Radical Nephrectomy
or
Partial Nephrectomy
Radical Nephrectomy
or
Partial Nephrectomy1
Radical Nephrectomy
Radical Nephrectomy
and
Resection of Metastases
Systemic Therapy
and perhaps.
Local Therapy of Metastases

What's new in kidney cancer?

- *Everything!*
- Expanded genomics.
- New ordering of VEGFR TKI
- Tumor Immunology
- Combinations!

Survival Has Improved Over the Years



1. Motzer RJ, et al. *J Clin Oncol.* 1999;17(8):2530-2540.

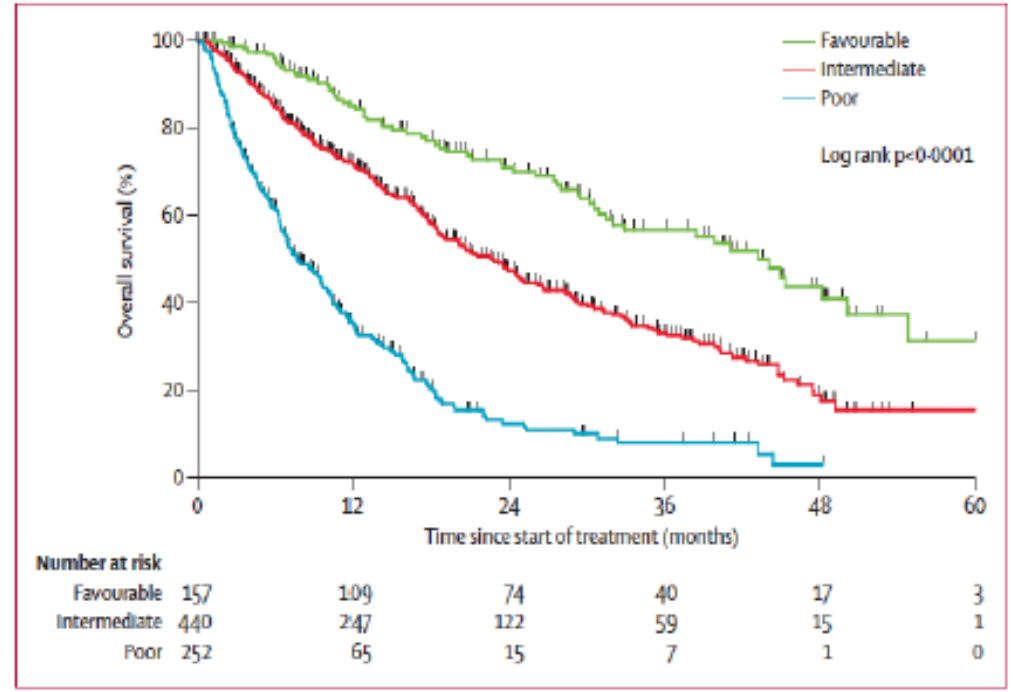


Figure 1: Results of Kaplan-Meier analysis of overall survival for the Database Consortium model

2. Heng DY, et al. *Lancet Oncol.* 2013;14(2):141-148.

	Pre–Targeted Agents Era[1]	Targeted Agents Era[2]
Median OS of good-risk patients	20 months	43.2 months (95% CI: 31.4–50.1)
Median OS of intermediate-risk patients	10 months	22.5 months (95% CI: 18.7–25.1)
Median OS of poor-risk patients	4 months	7.8 months (95% CI: 6.5–9.7)

Risk Factors in Advanced Untreated RCC

Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model[a]

Prognostic factors

- Interval from diagnosis to treatment of less than 1 year
- Karnofsky performance status less than 80%
- Serum lactate dehydrogenase (LDH) greater than 1.5 times the upper limit of normal (ULN)
- Corrected serum calcium greater than the ULN
- Serum hemoglobin less than the lower limit of normal (LLN)

Prognostic risk groups

- Low-risk group: no prognostic factors
- Intermediate-risk group: one or two prognostic factors
- Poor-risk group: three or more prognostic factors

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria[b]

Prognostic factors

1. Less than one year from time of diagnosis to systemic therapy
2. Performance status <80% (Karnofsky)
3. Hemoglobin < lower limit of normal (Normal: 120 g/L or 12 g/dL)
4. Calcium > upper limit of normal (Normal: 8.5–10.2 mg/dL)
5. Neutrophil > upper limit of normal (Normal: 2.0–7.0×10^9/L)
6. Platelets > upper limit of normal (Normal: 150,000–400,000)

Prognostic risk groups

- Favorable-risk group: no prognostic factors
- Intermediate-risk group: one or two prognostic factors
- Poor-risk group: three to six prognostic factors

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Kidney Cancer

RISK MODELS TO DIRECT TREATMENT

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Prognostic risk groups

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Poor Risk Factors in Advanced Untreated RCC: MSKCC Criteria

MSKCC Criteria	
KPS	< 80%
Time from diagnosis to treatment with IFN-α	< 12 mos
Hemoglobin	< LLN
LDH	> 1.5 x ULN
Corrected serum calcium	> 10.0 mg/dL

MSKCC or Survival After Nephrectomy and Immunotherapy (SANI) risk scores

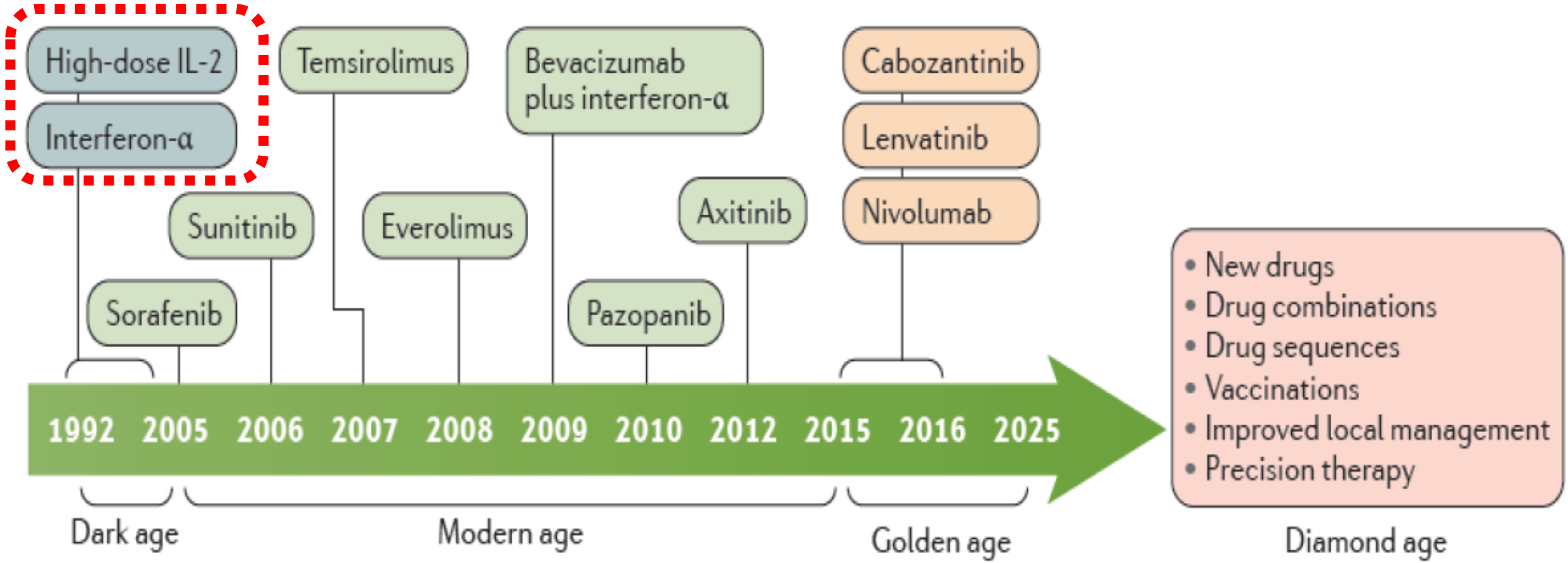
Risk Group by No. of Risk Factors	
Favorable	0
Intermediate	1 or 2
Poor	3-5

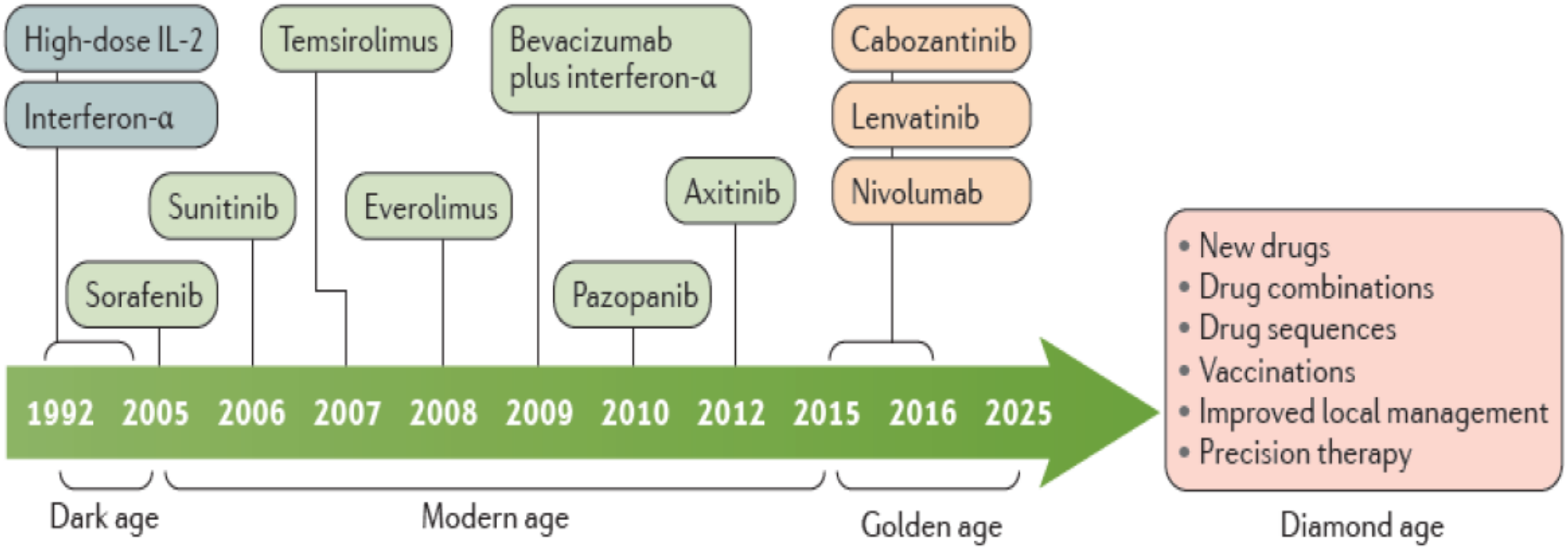
International Metastatic Database Consortium (IMDC)

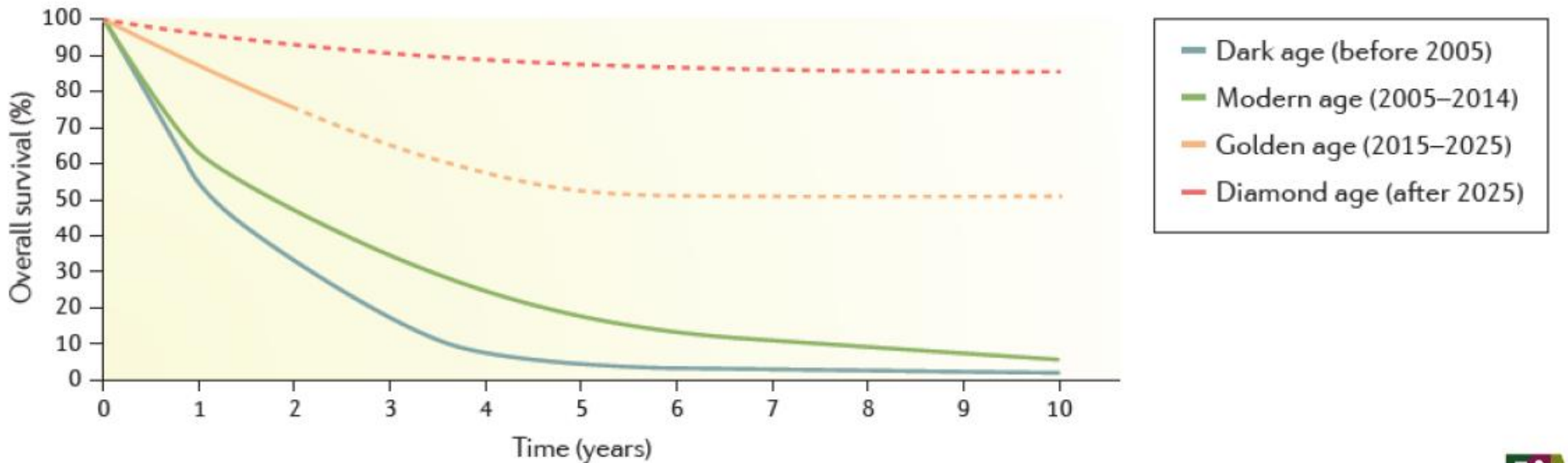
International Metastatic Renal Cell Carcinoma Database Consortium criteria

Karnofsky performance score <80
Time from original diagnosis to initiation of targeted therapy <1 year
Hemoglobin less than the lower limit of normal
Serum calcium greater than the upper limit of normal
Neutrophil count greater than the upper limit of normal
Platelet count greater than the upper limit of normal

- Good risk: None of above risk factors present.
- Intermediate risk: 1 or 2 of above risk factors present.
- Poor risk: 3 or more risk factors present.


High-dose IL-2
Interferon-α
Temsirolimus
Bevacizumab plus interferon-α
Cabozantinib
Lenvatinib
Nivolumab
Axitinib
Everolimus
Sunitinib
Sorafenib
Pazopanib
1992
2005
2006
2007
2008
2009
2010
2012
2015
2016
2025
Dark age
Modern age
Golden age
• New drugs
• Drug combinations
• Drug sequences
• Vaccinations
• Improved local management
• Precision therapy
Diamond age

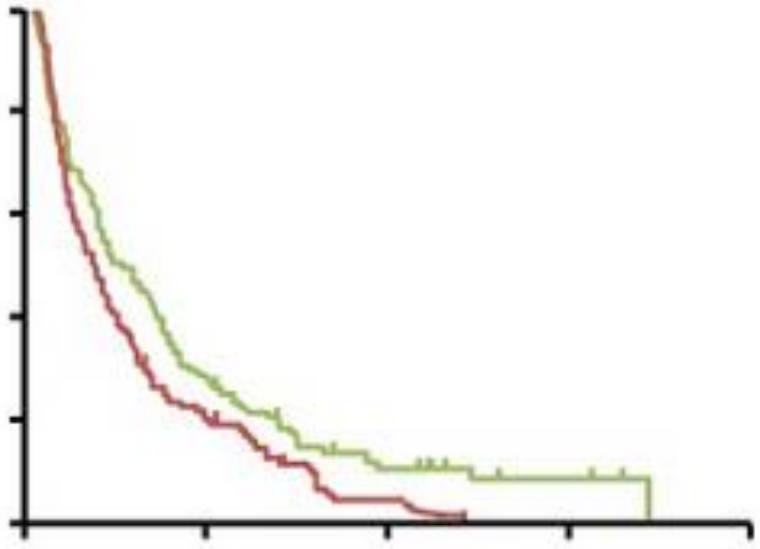




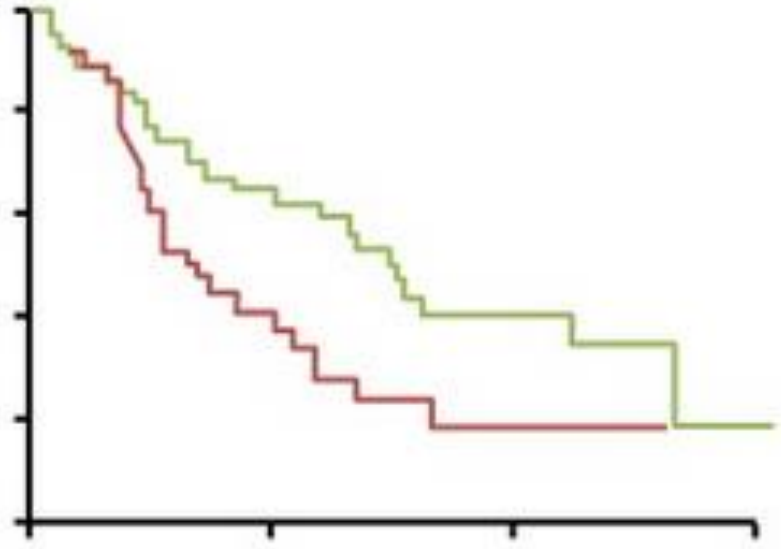
Approval	Agent	EMA and FDA Indications
1992	Intereukin-2	Metastatic
2005	Sorafenib	Advanced
2006	Sunitinib	Advanced
2007	Temsirolimus	Advanced
2009	Bevacizumab (+ IFN-α)	Metastatic
2009	Everolimus	After failure of sunitinib or sorafenib
2009	Pazopanib	Advanced
2012	Axitinib	Failure of prior systemic therapy
2015	Nivolumab	Failure of prior systemic therapy
2016	Cabozantinib	Failure of prior systemic therapy
2016	Lenvatinib plus everolimus	Failure of prior systemic therapy

Cytoreductive Nephrectomy

SWOG[1]	Median Survival, Mos
IFN-α + nephrectomy (n = 120)	11.1
IFN-α (n = 121)	8.1

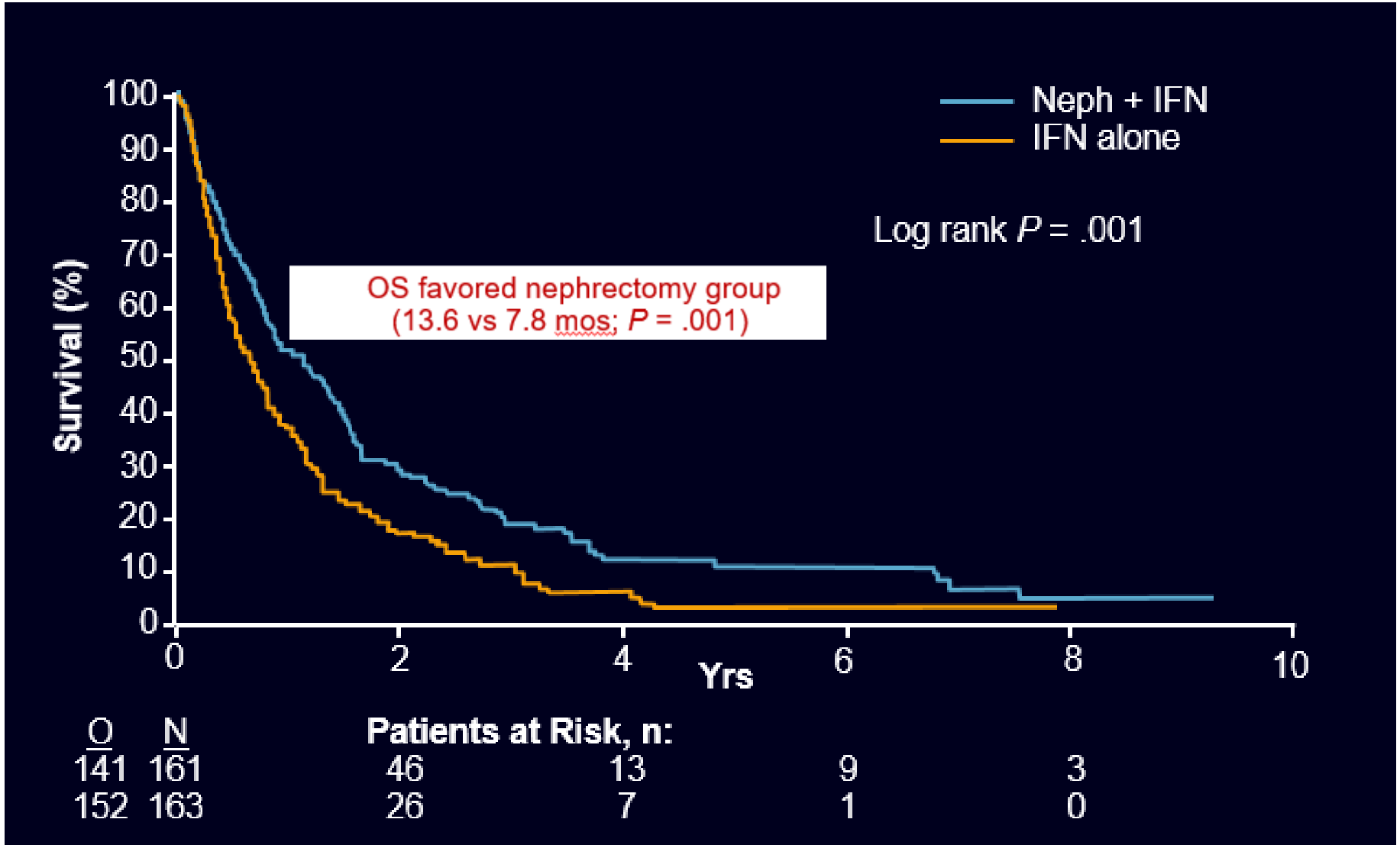


EORTC[2]	Median Survival, Mos
IFN-α + nephrectomy (n = 42)	17.0
IFN-α (n = 42)	7.0



1. Flanigan RC, et al. N Engl J Med. 2001;345:1655-1659. 2. Mickisch GH, et al. Lancet. 2001;358:966-970.

Interferon ± Cytoreductive Nephrectomy



Metastatic RCC : Cytoreductive Nephrectomy?

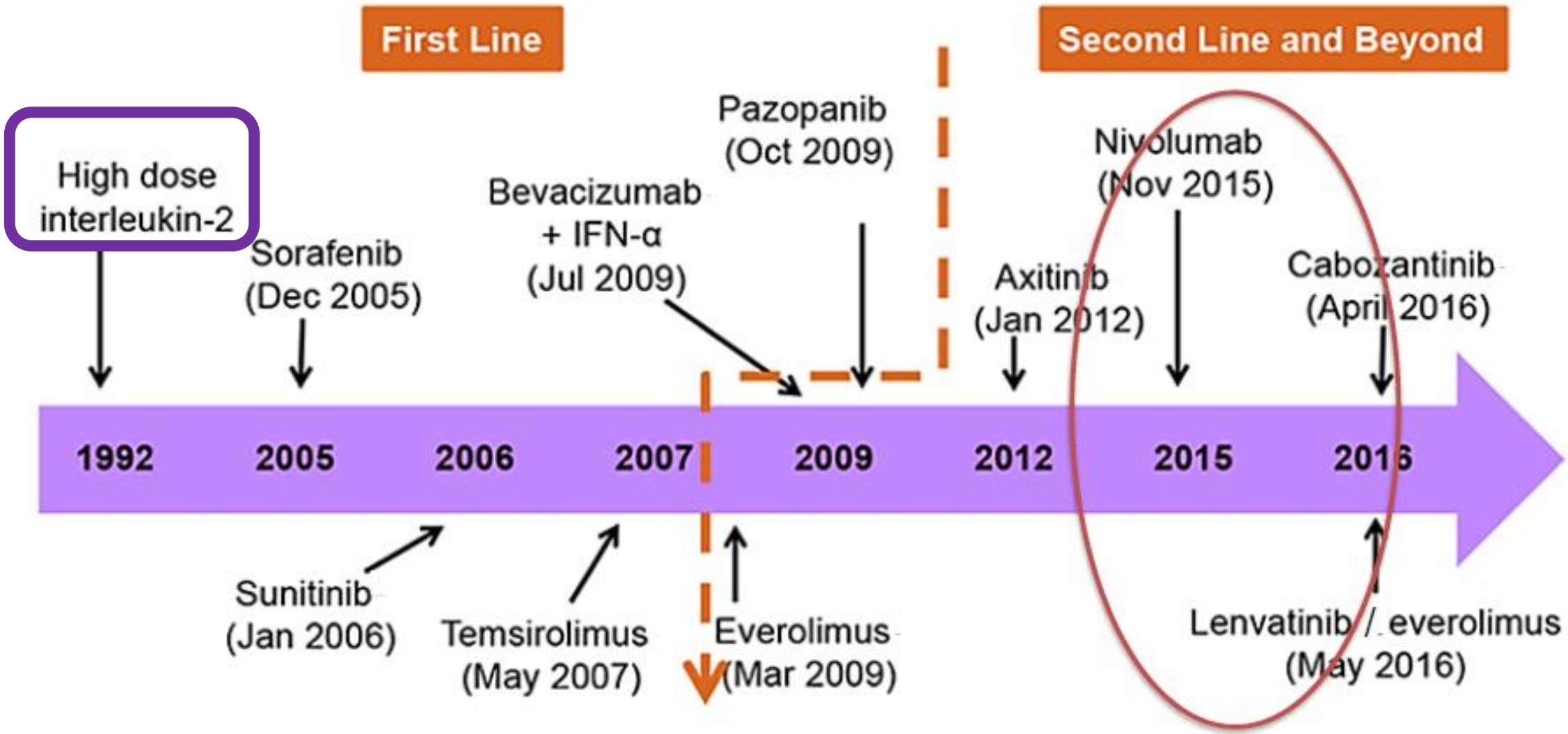
– Removal of the primary tumor (cytoreductive nephrectomy)

In retrospective studies: favorable feature?

Clinical Trials	Design	Nb pts	Resp. rates (%)	Overall survival (months)	P value
SWOG-8949[1]	N + IFNa vs IFNa alone	246	3.6 vs 3.3	11.1 vs 8.1	0.05
EORTC-30947[2]	N + IFNa vs IFNa alone	85	19 vs 12	17 vs 7	0.03
Combined analysis [3]	N + IFNa vs IFNa alone	331	6.9 vs 5.7	13.6 vs 7.8	0.002

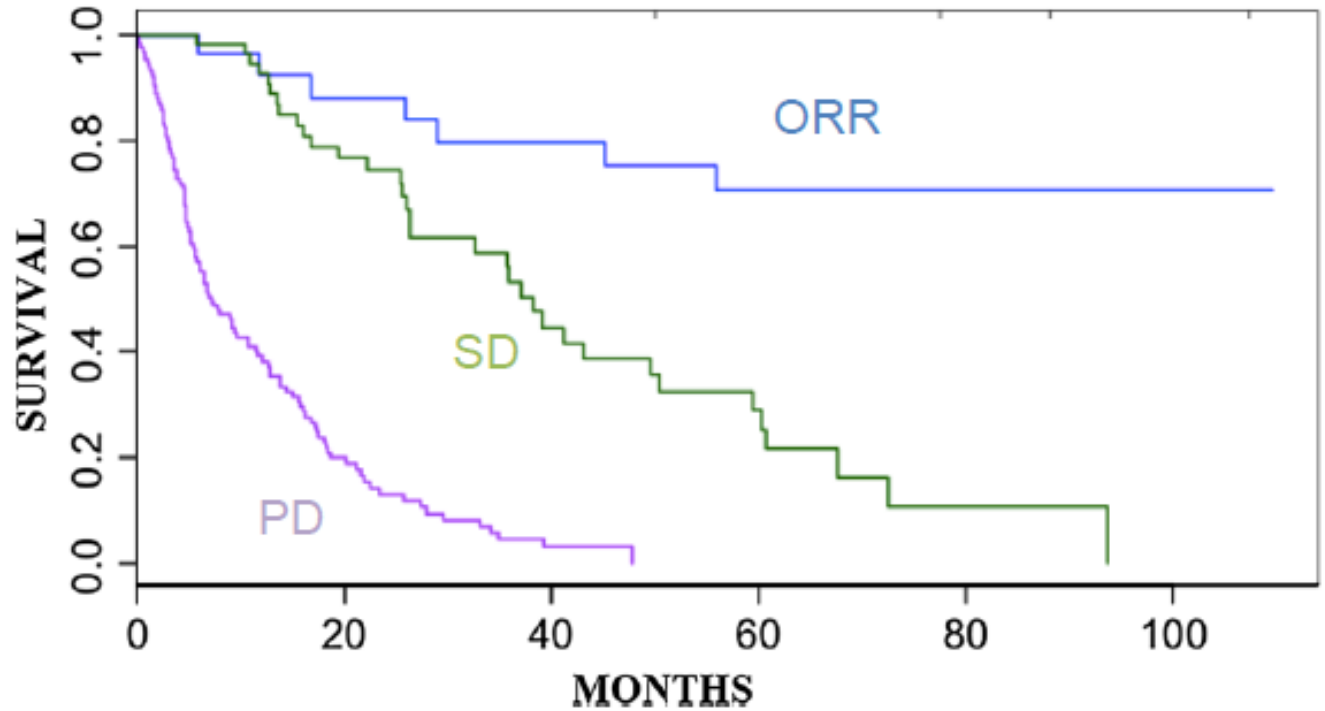
Two prospective studies evaluated impact of nephrectomy (N) on outcome

Treatment Landscape in RCC in 2016

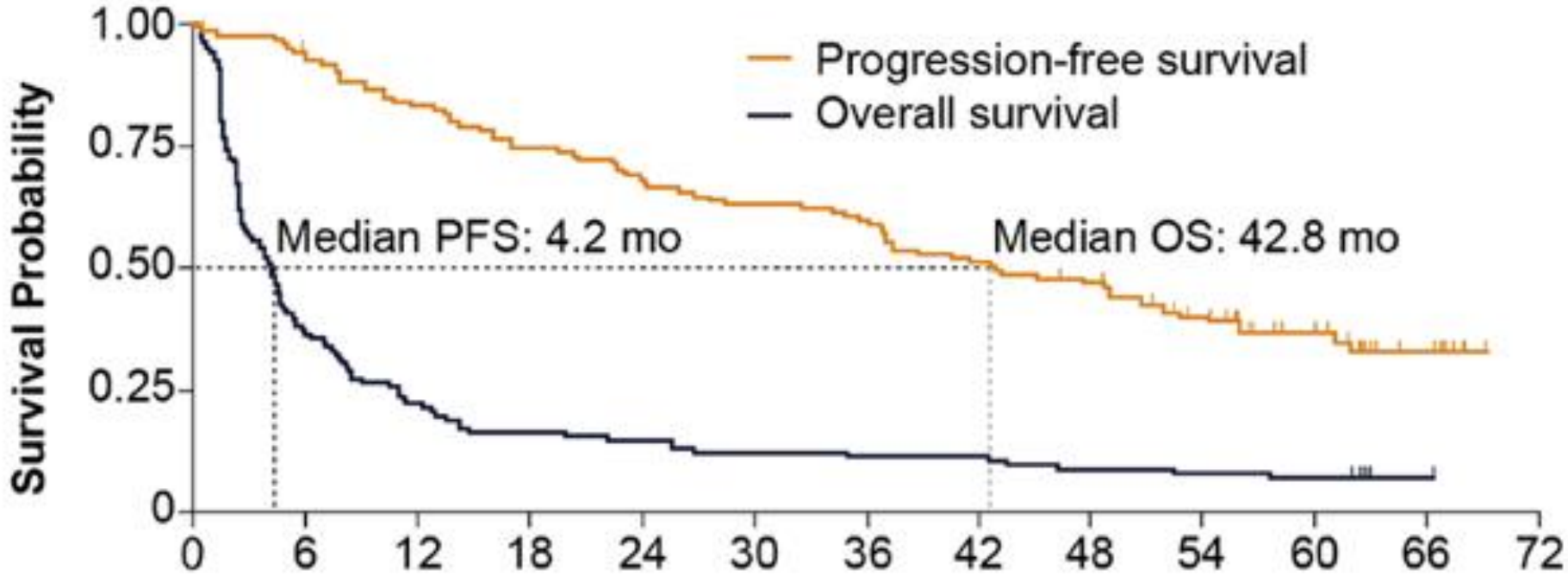


High-Dose IL-2

- Durable responses in a subgroup of patients only
- High toxicity
- High costs
- Specialized centers only



High Dose IL-2: Survival



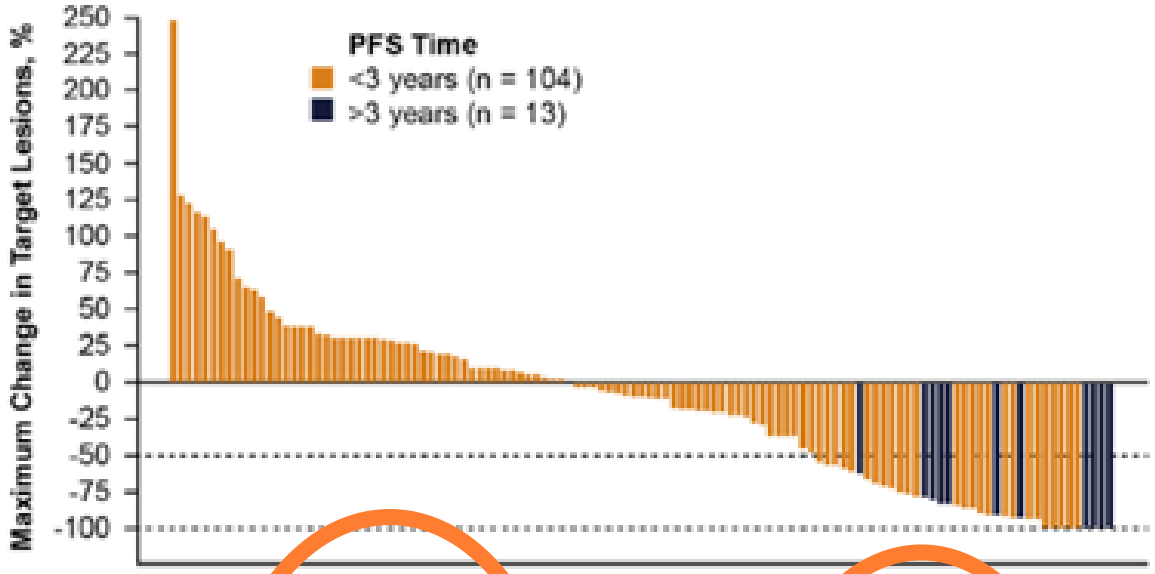
No. at Risk													
PFS	119	43	26	19	17	14	13	13	10	9	8	4	3
OS	120	110	98	88	80	74	70	60	54	42	29	15	9

1. McDermott DF et al. *Clin Cancer Res*. 2015;21:561-568. 2. Alva A et al. *Cancer Immunol Immunother*. 2016;65:1533-1544.

Immunotherapy
High Dose IL-2: Efficacy

SELECT Trial

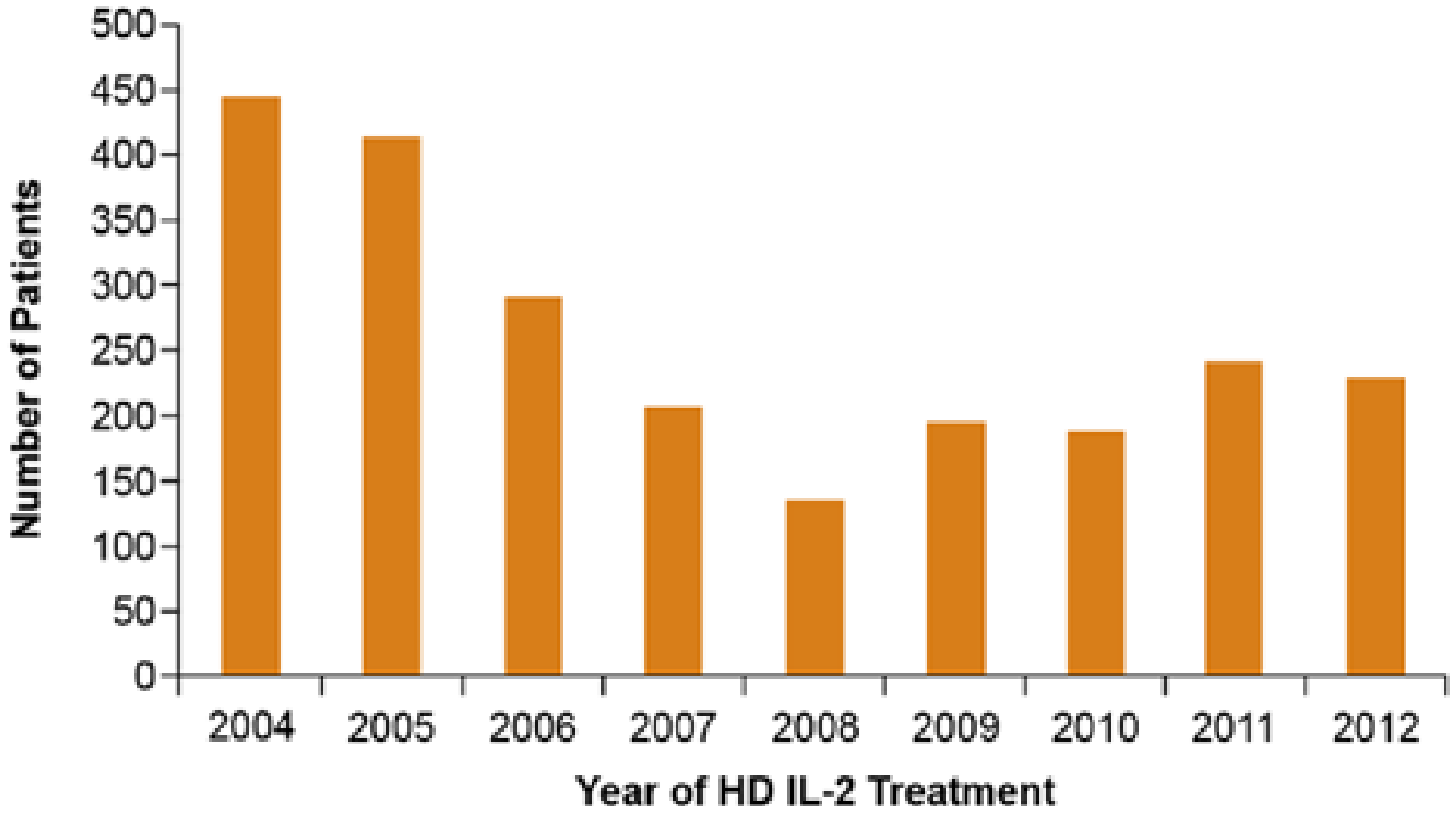
- 120 patients enrolled
- 96% clear cell histology
- MSKCC criteria
  - 70% intermediate risk
  - 11% poor risk
- CR, PR, and SD independently reviewed

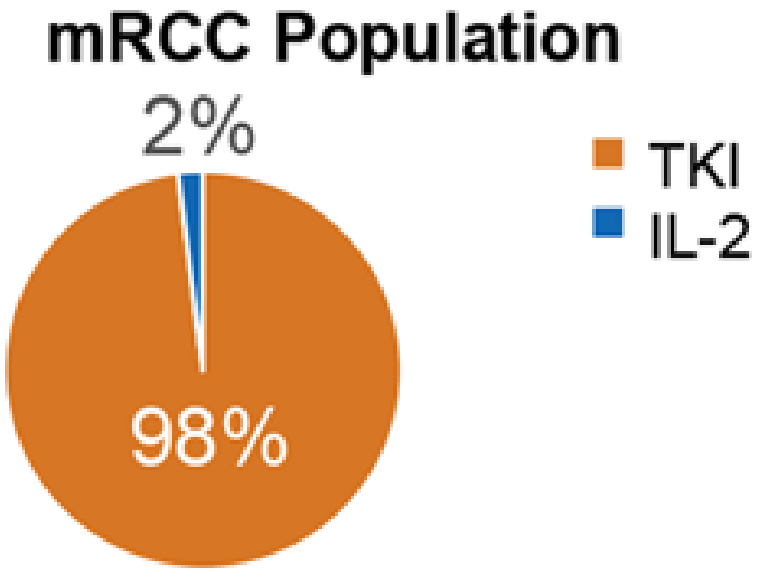


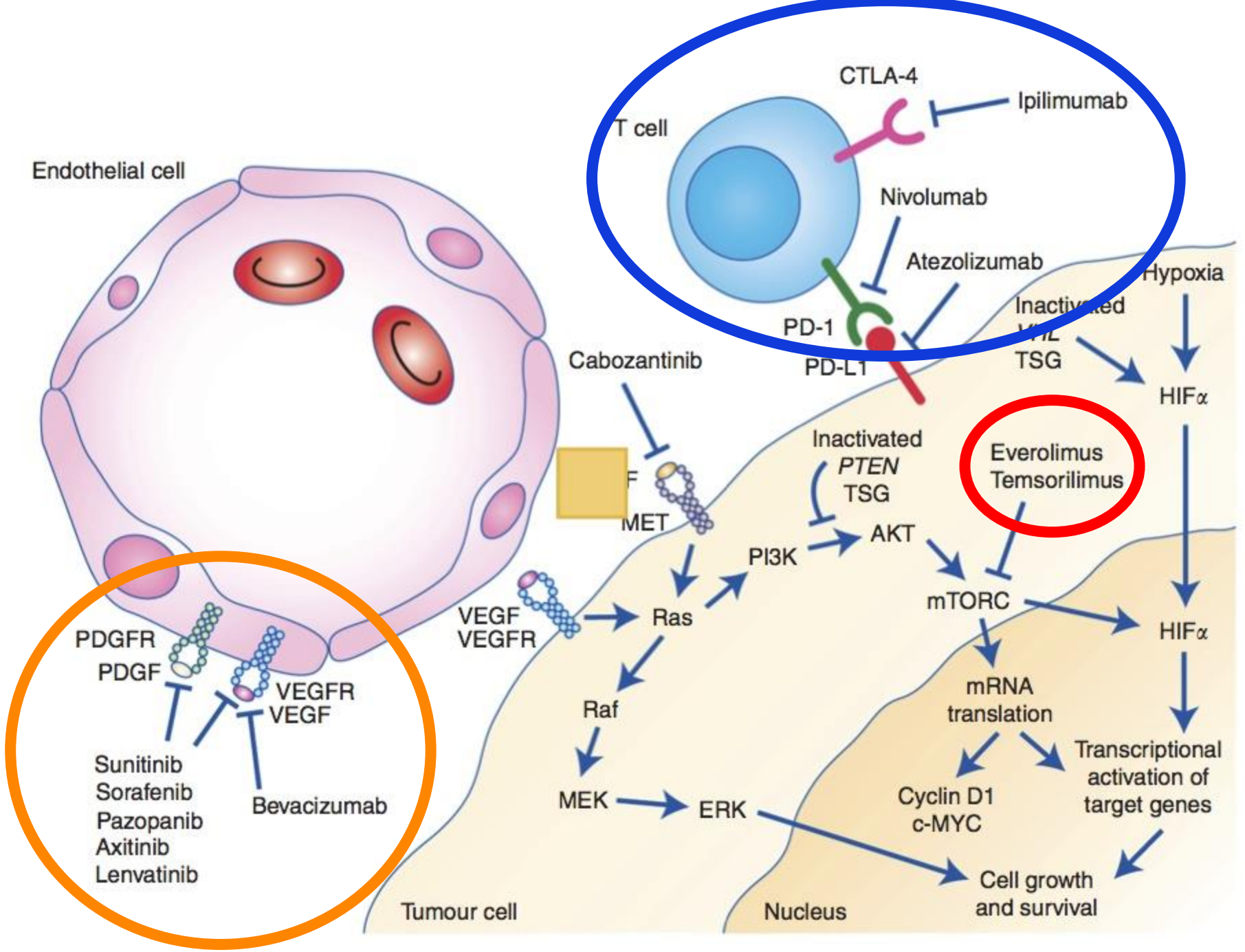
Assessment	Historical Cohort	SELECT/IL-2	Sunitinib
ORR	14%	25%	47%
CR	5%	2.5%	3%
PR	9%	22.5%	44%
SD >6 months	-	7.5%	-

1. McDermott DF et al. *Clin Cancer Res.* 2015;21:561-568. 2. Motzer RJ et al. *J Clin Oncol.* 2009;27:3584-3590. 3. Fyfe G et al. *J Clin Oncol.* 1995;13:688-696. 4. Alva A et al. *Cancer Immunol Immunother.* 2016;65:1533-1544.

IL-2 Utilization: Comparison of Impact With TKIs






CTLA-4
Ipilimumab
T cell
Nivolumab
Atezolizumab
PD-1
PD-L1
Endothelial cell
Cabozantinib
MET
Hypoxia
TSG
HIFα
Inactivated
PTEN
TSG
Everolimus
Temsorilimus
AKT
PI3K
mTORC
VEGF
VEGFR
Ras
Raf
MEK
ERK
mRNA
translation
Cyclin D1
c-MYC
Transcriptional
activation of
target genes
Cell growth
and survival
PDGFR
PDGF
VEGFR
VEGF
Sunitinib
Sorafenib
Pazopanib
Axitinib
Lenvatinib
Bevacizumab
Tumour cell
Nucleus

VEGF inhibitors

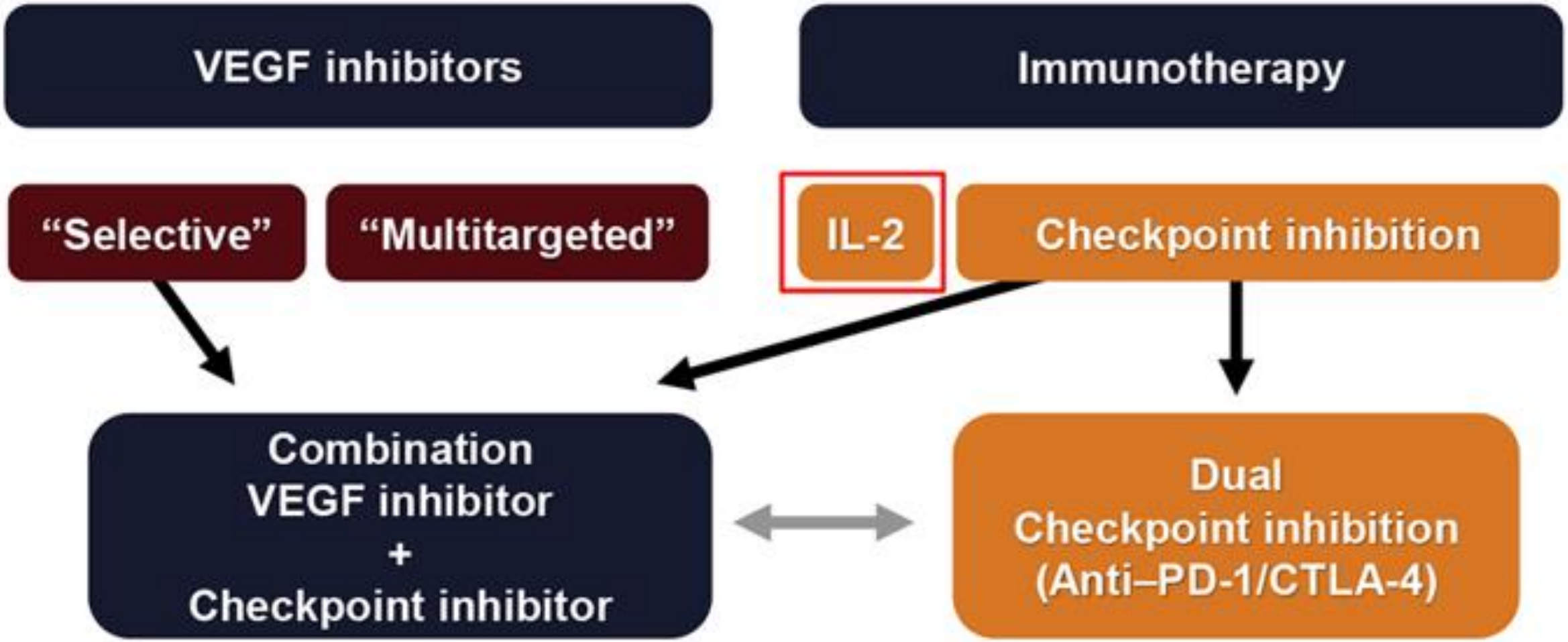
Immunotherapy

"Selective"

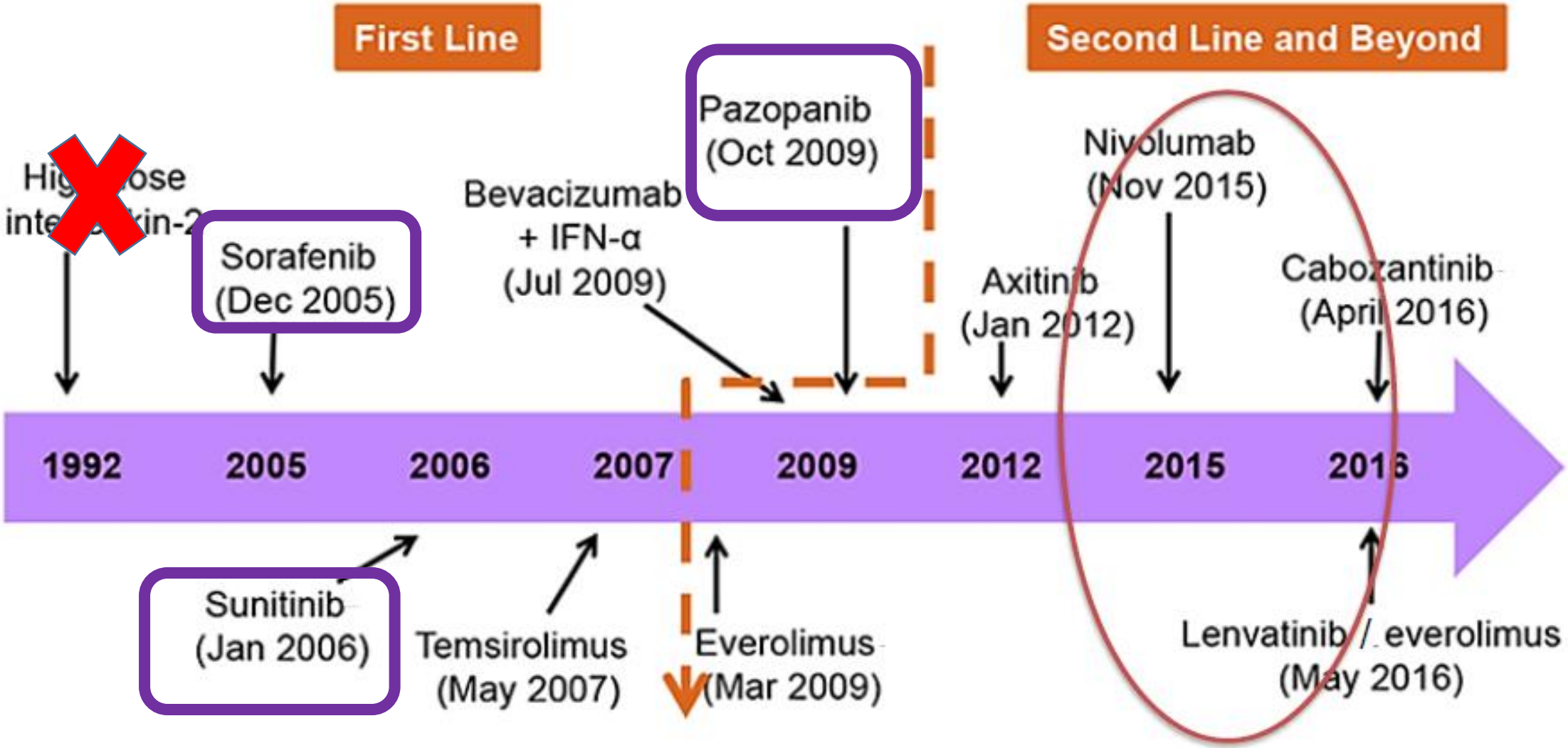
"Multitargeted"

IL-2

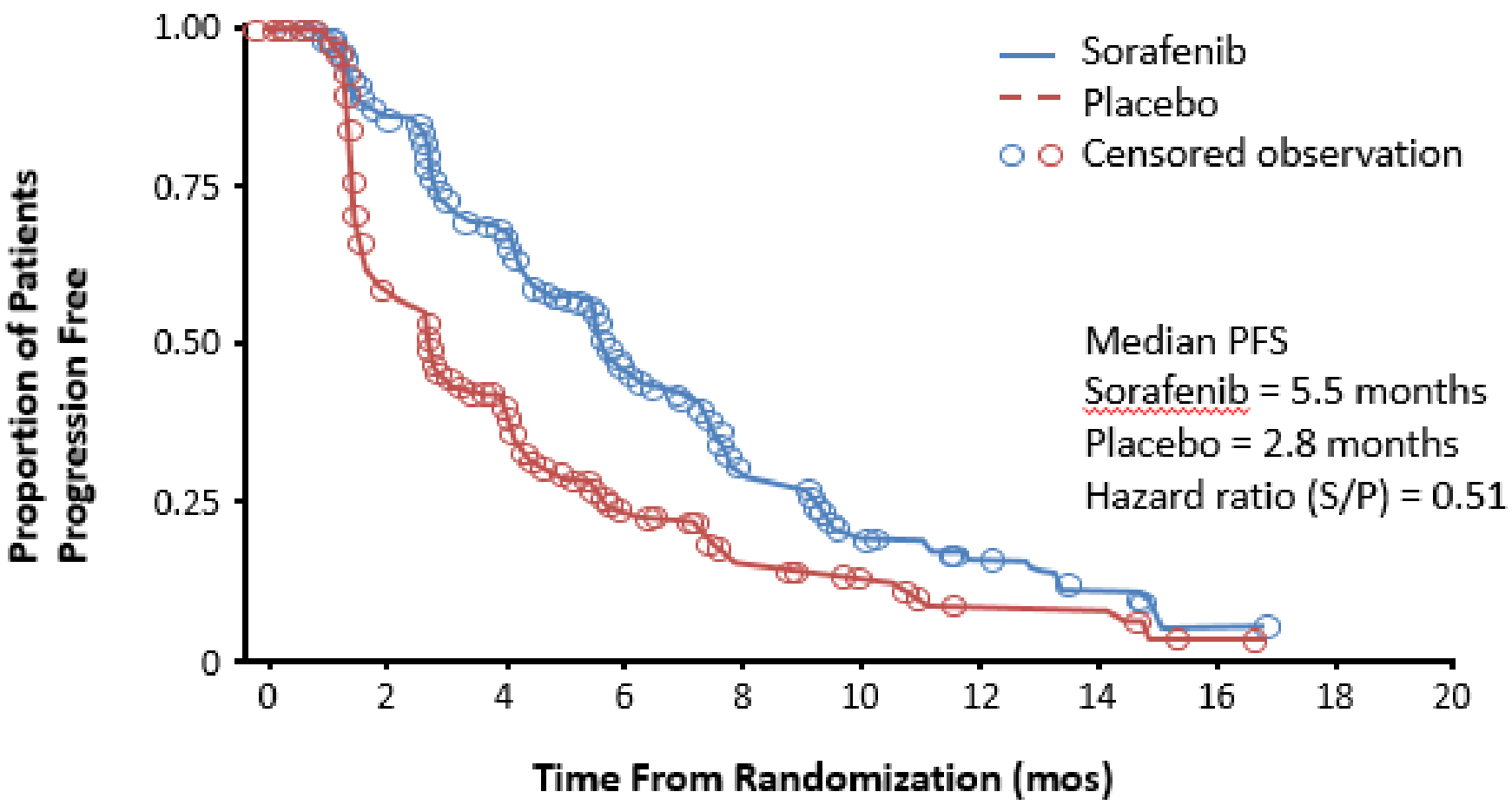
Checkpoint inhibition


VEGF inhibitors
Immunotherapy
"Selective"
"Multitargeted"
IL-2
Checkpoint inhibition
Combination
VEGF inhibitor
+
Checkpoint inhibitor
Dual
Checkpoint inhibition
(Anti–PD-1/CTLA-4)

Treatment Landscape in RCC in 2016

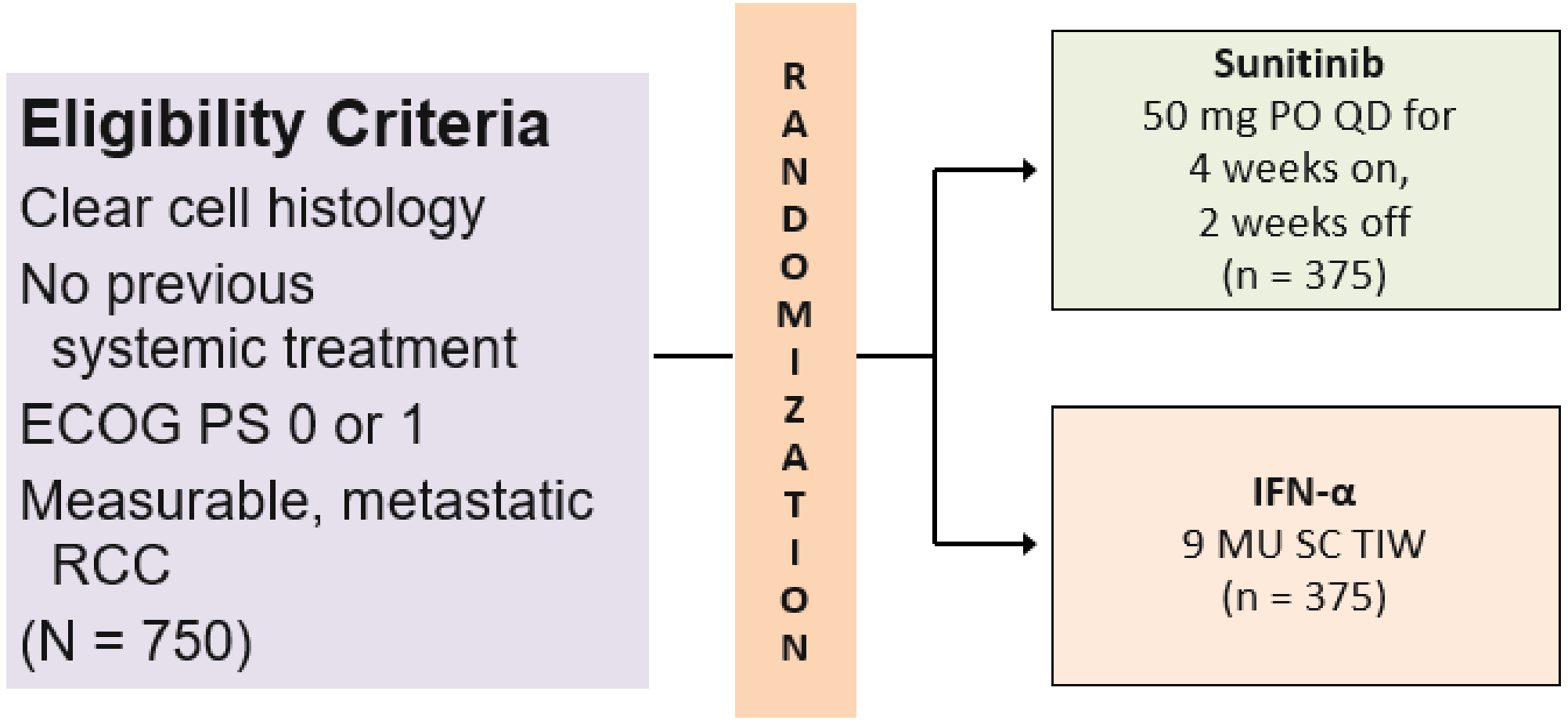


Sorafenib



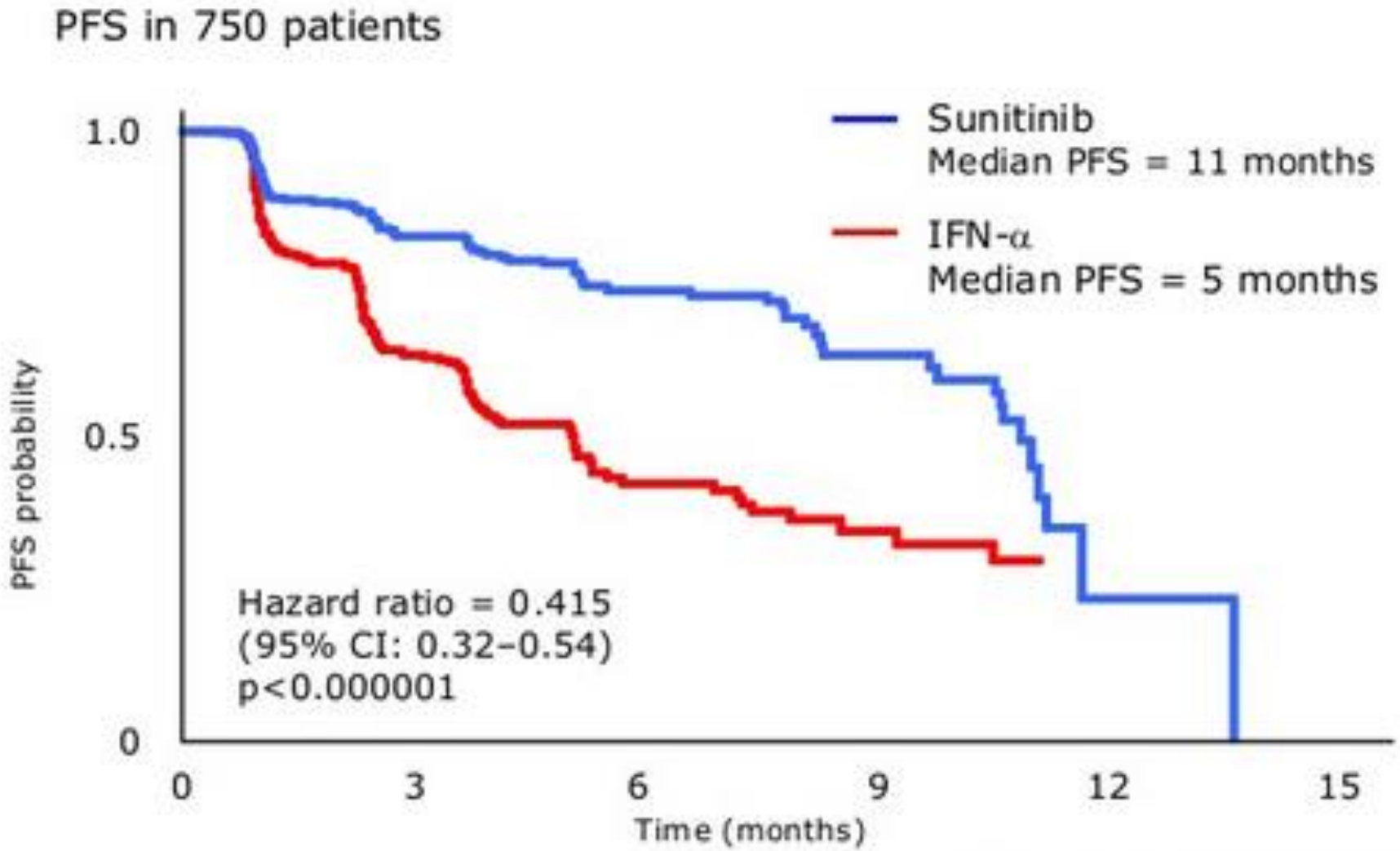
FDA approved for advanced RCC, December 2005

Sunitinib vs IFN



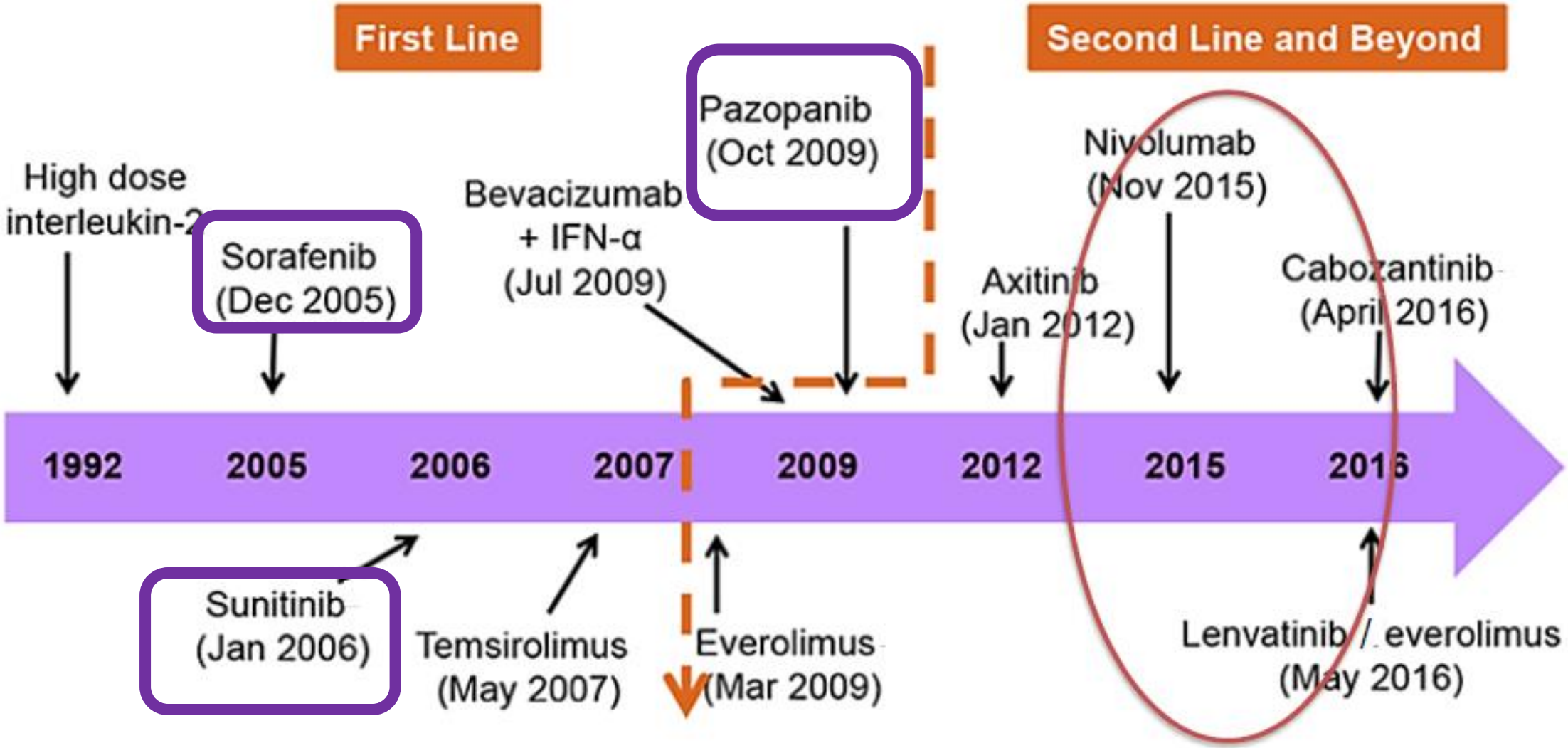
FDA approved for advanced RCC, January 2006

Sunitinib improves PFS in 1st-line mRCC

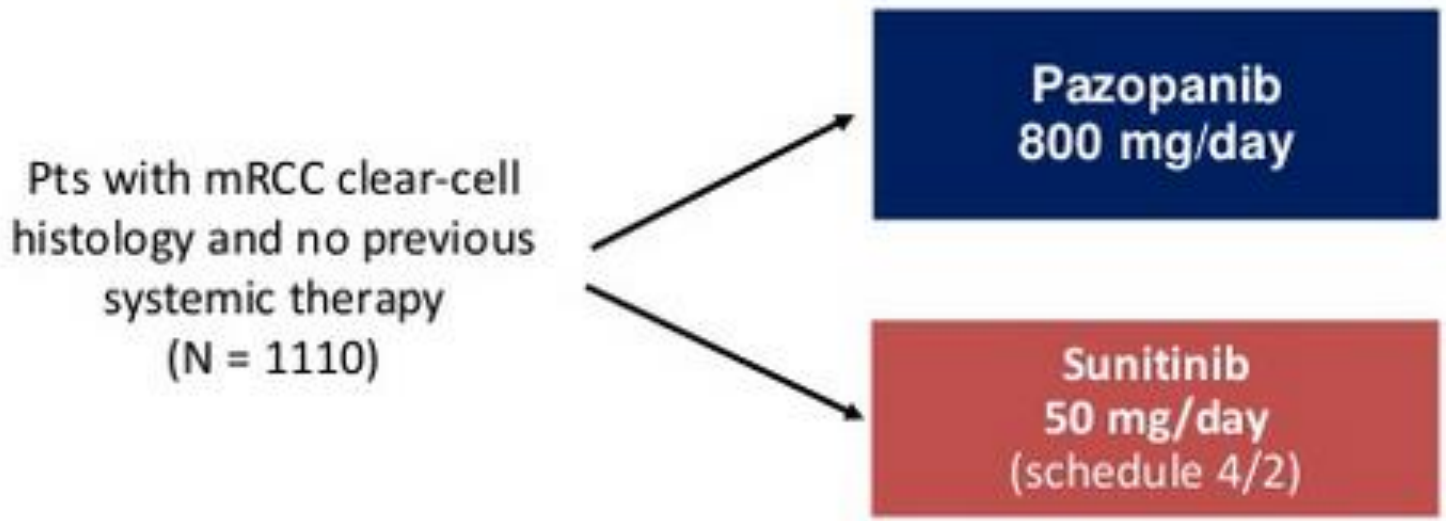


Motzer R, et al. NEJM 2007

Treatment Landscape in RCC in 2016



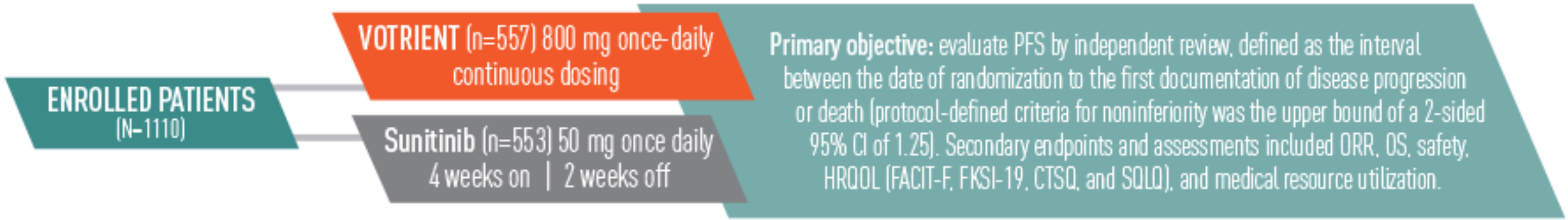
Phase III COMPARZ: First-line Pazopanib vs Sunitinib for Clear-Cell mRCC



- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, time to response, safety, QoL, medical resource utilization

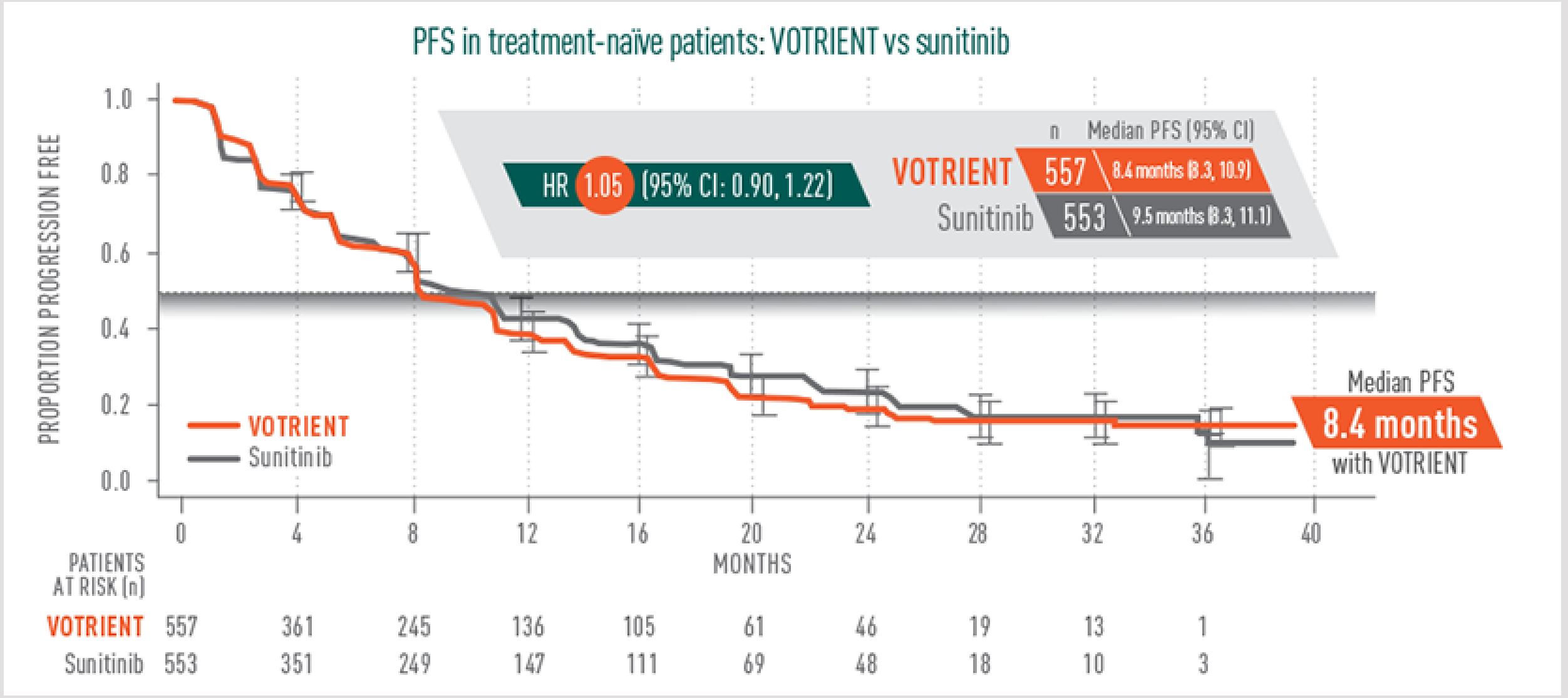
Motzer RJ, et al. N Engl J Med. 2013;369:722-731.

COMPARZ: A phase 3, head-to-head, randomized (1:1), open-label, noninferiority study comparing **VOTRIENT** with sunitinib

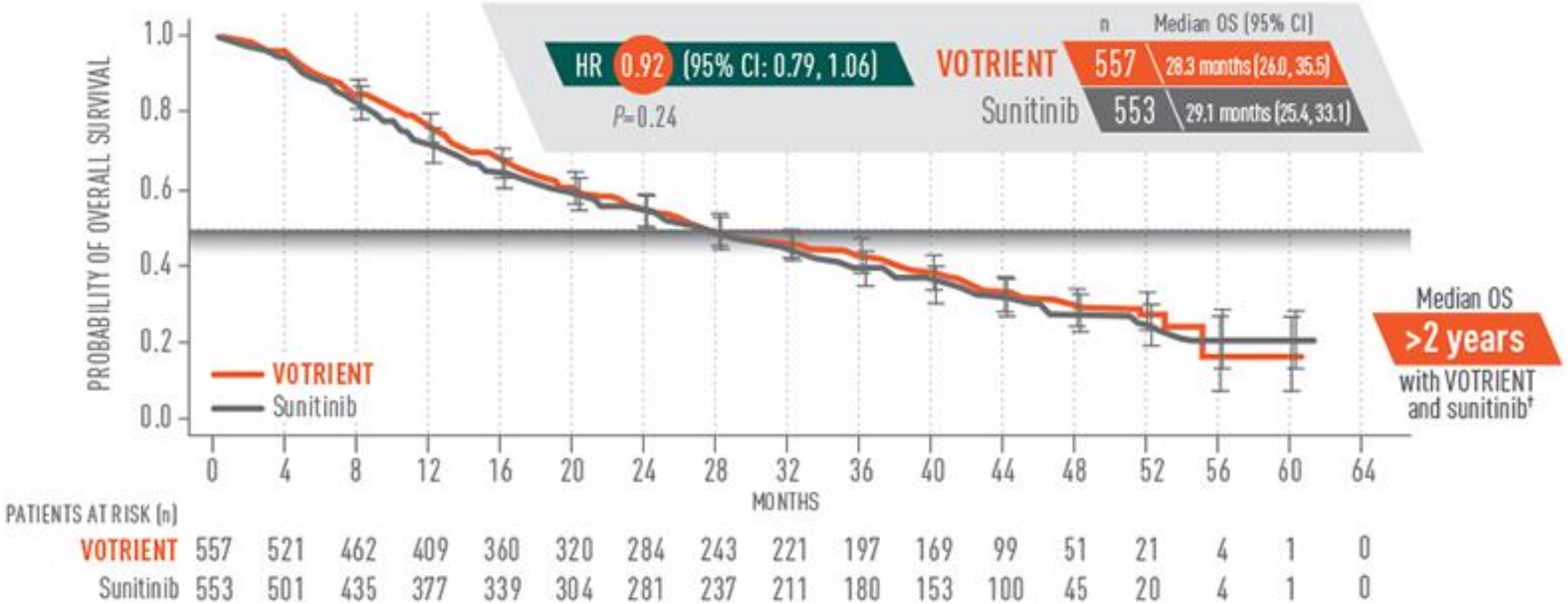


Eligibility criteria: patients aged ≥18 years with advanced RCC, clear cell histology, no prior systemic therapy, measurable disease KPS ≥70%, and adequate organ function.

Progression-free survival (PFS): noninferior[1*]



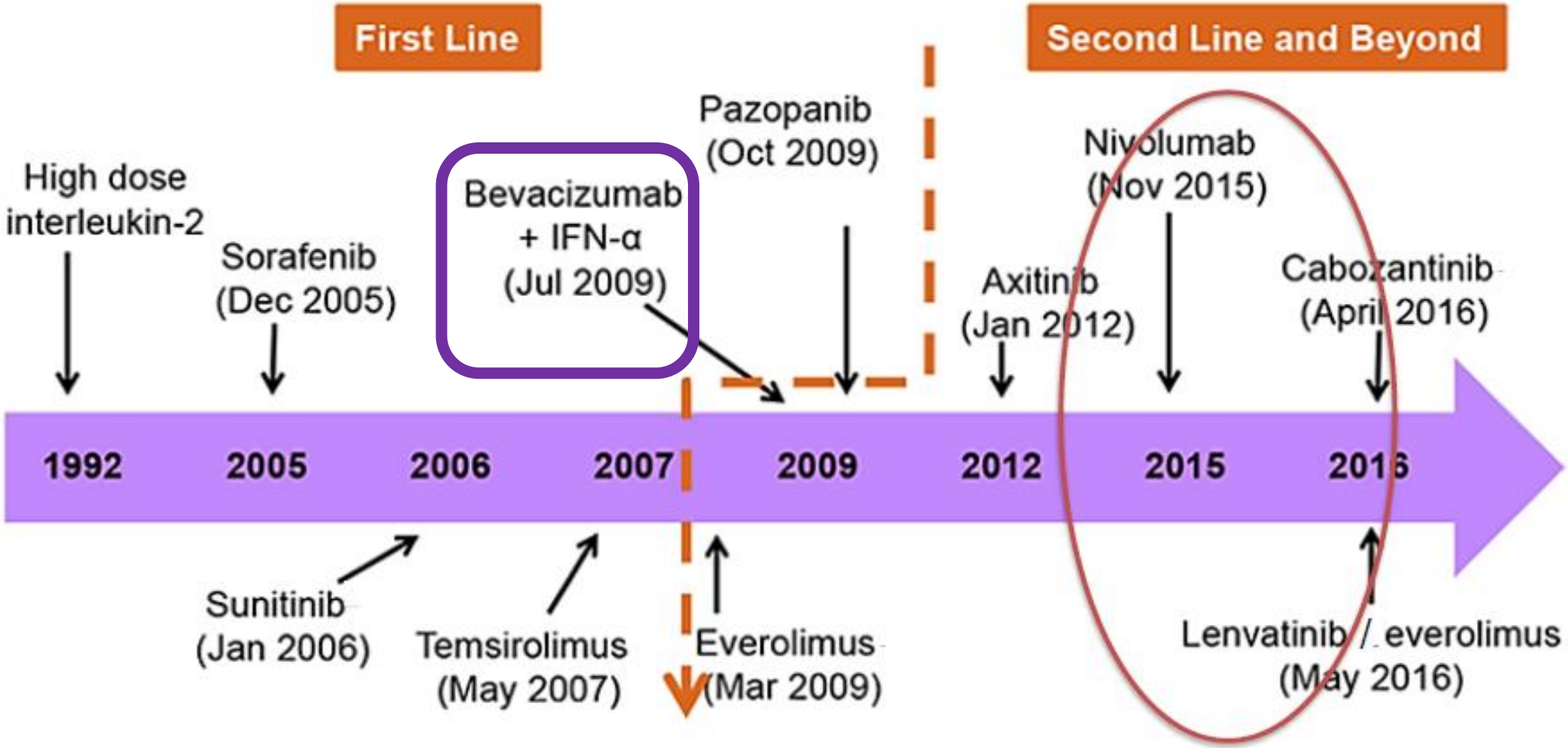
OS in treatment-naïve patients: VOTRIENT vs sunitinib



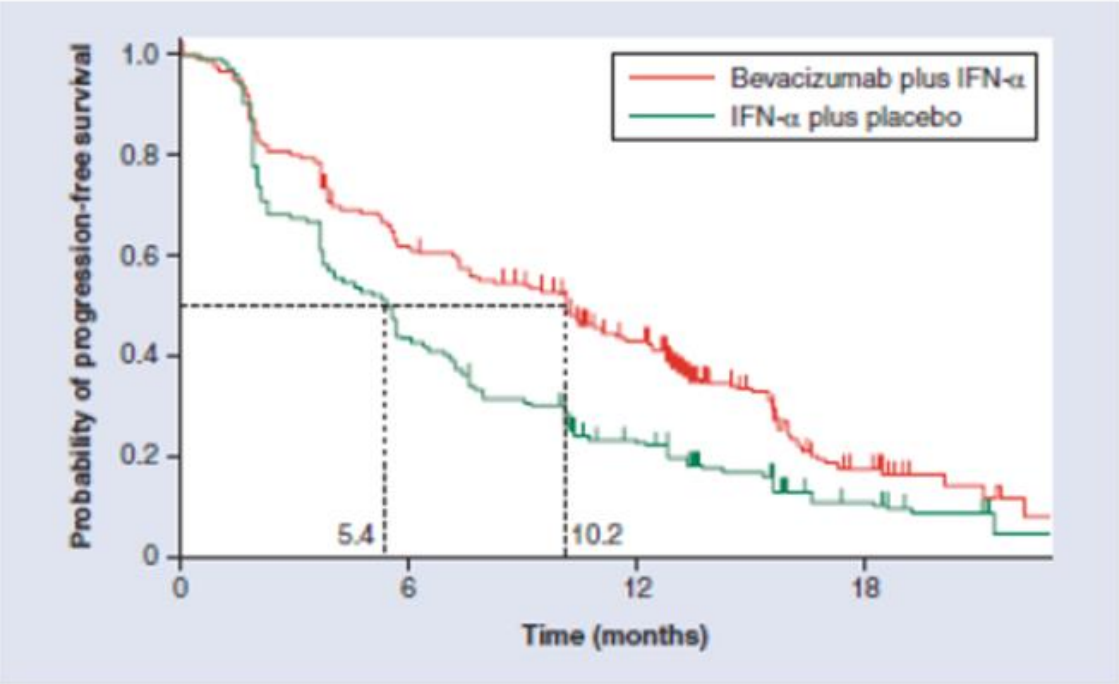
Adverse Events Relative Risk

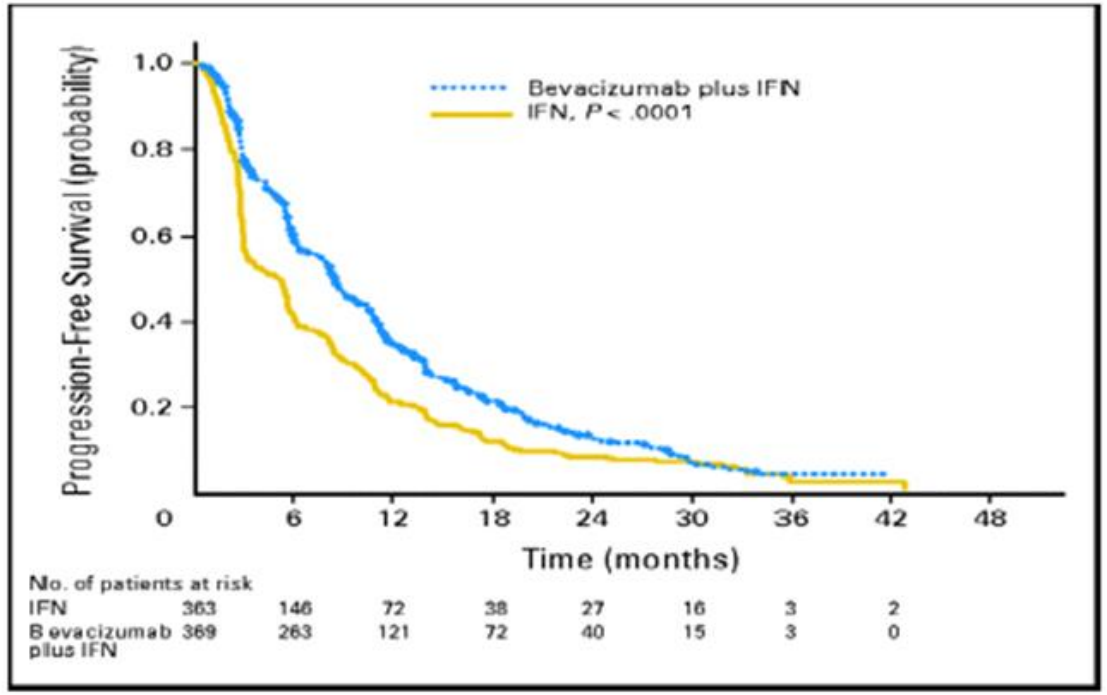
Pazopanib	Sunitinib
Hair color change	Fatigue
Weight decreased	Rash
Serum ALT increased	Pain in extremity
Alopecia	Constipation
Upper abdominal pain	Taste alteration
Serum AST increased	LDH increased
	Serum creatinine increased
	Peripheral edema
	Hand-foot syndrome
	Dyspepsia
	Pyrexia
	Leukopenia
	Hypothyroidism
	Epistaxis
	Serum TSH increased
	Mucositis
	Neutropenia
	Anemia
	Thrombocytopenia

Treatment Landscape in RCC in 2016



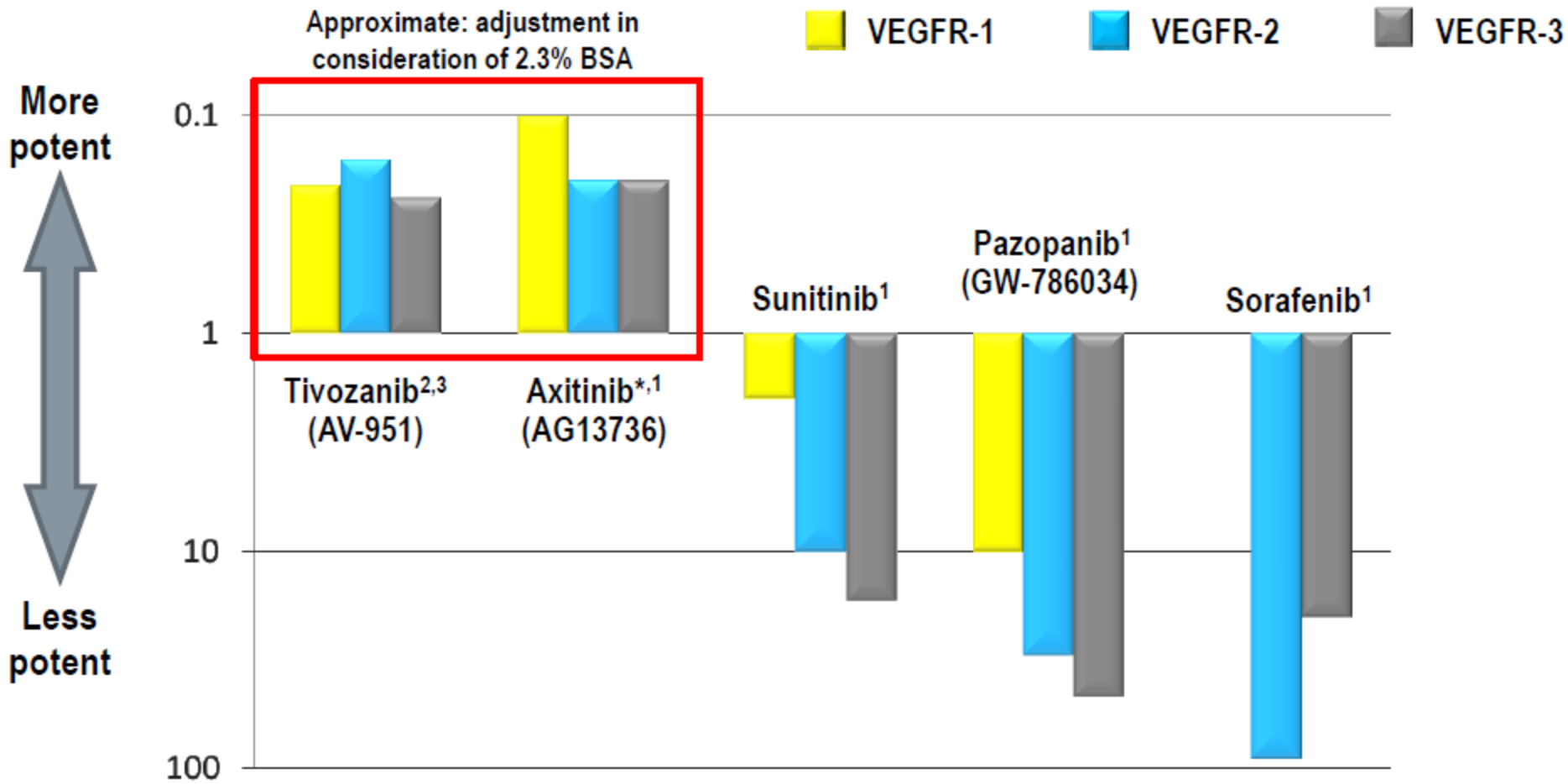
PFS in first-line randomized trials of bev + IFN





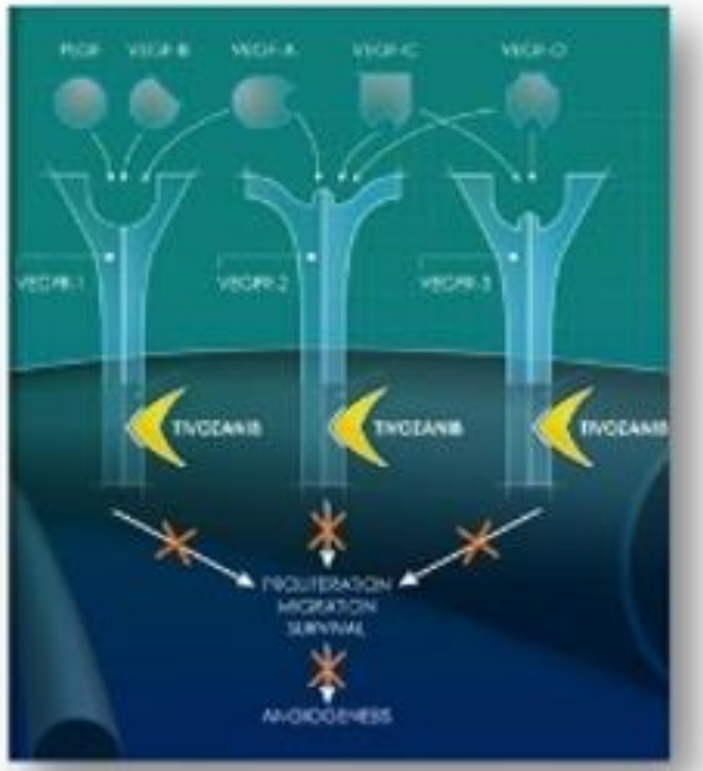
Escudier B et al. Lancet 2007, 370, 2103-2111
Rini B et al. J Clin Oncol 26, 2008, 5422-5428

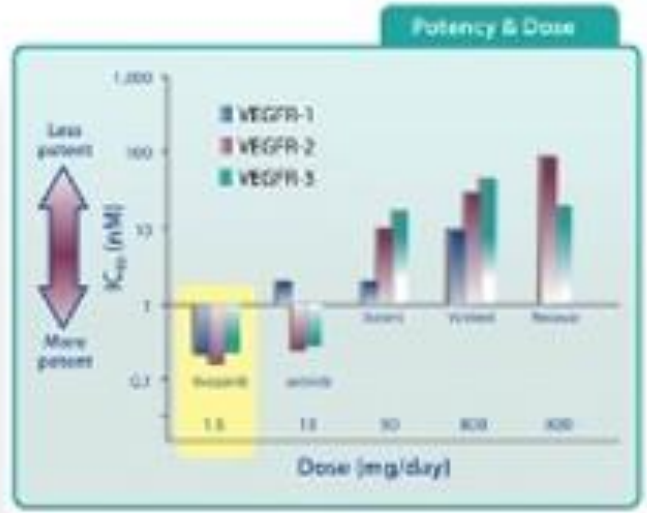
IN VITRO POTENCY OF TIVOZANIB AND AXITINIB COMPARED TO OTHER TKIs

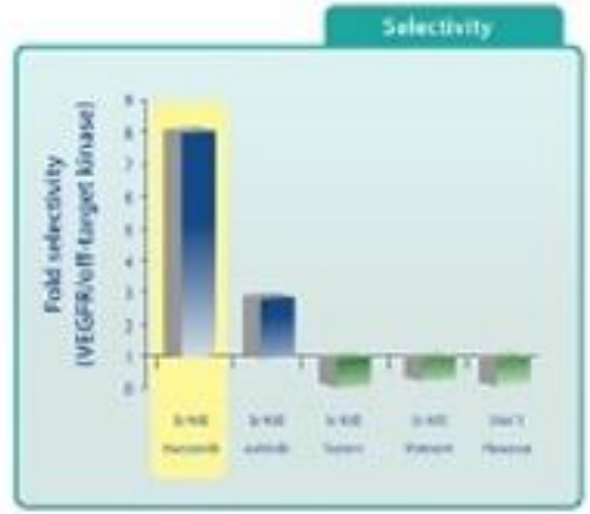


Tivozanib: VEGFR 1, 2 and 3 Tyrosine Kinase Inhibitor

Potent, selective inhibitor of VEGFRs 1, 2 and 3 with a long half-life that is designed to optimize blockade while minimizing off-target toxicities[1,2]







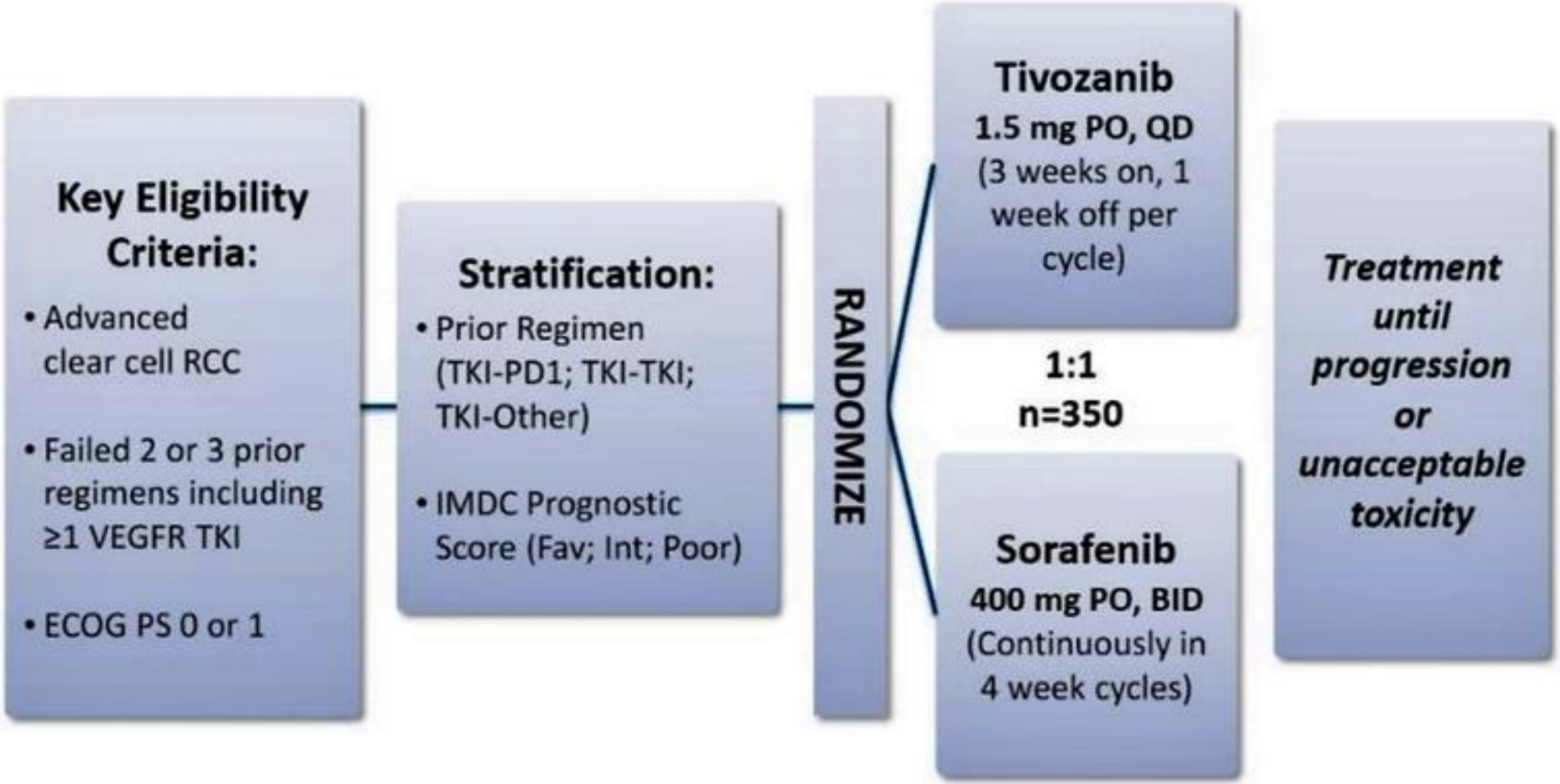
TIVO-3: Phase 3 Study Design in Recurrent/Metastatic RCC to Confirm TIVO-1

- Designed to support 1st and 3rd line indication
- Provides potential unique 3rd line dataset of patients with prior PD-1 exposure
- **Enrollment initiated 2Q 2016 On track for topline data 1Q 2018**

Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib to Sorafenib in Subjects With Refractory Advanced Renal Cell Carcinoma

ASCO GU 2019:

TIVO-3: A Phase III, Randomized, Controlled, Multicenter, Open-label Study to Compare Tivozanib to Sorafenib in Subjects with Refractory Advanced Renal Cell Carcinoma

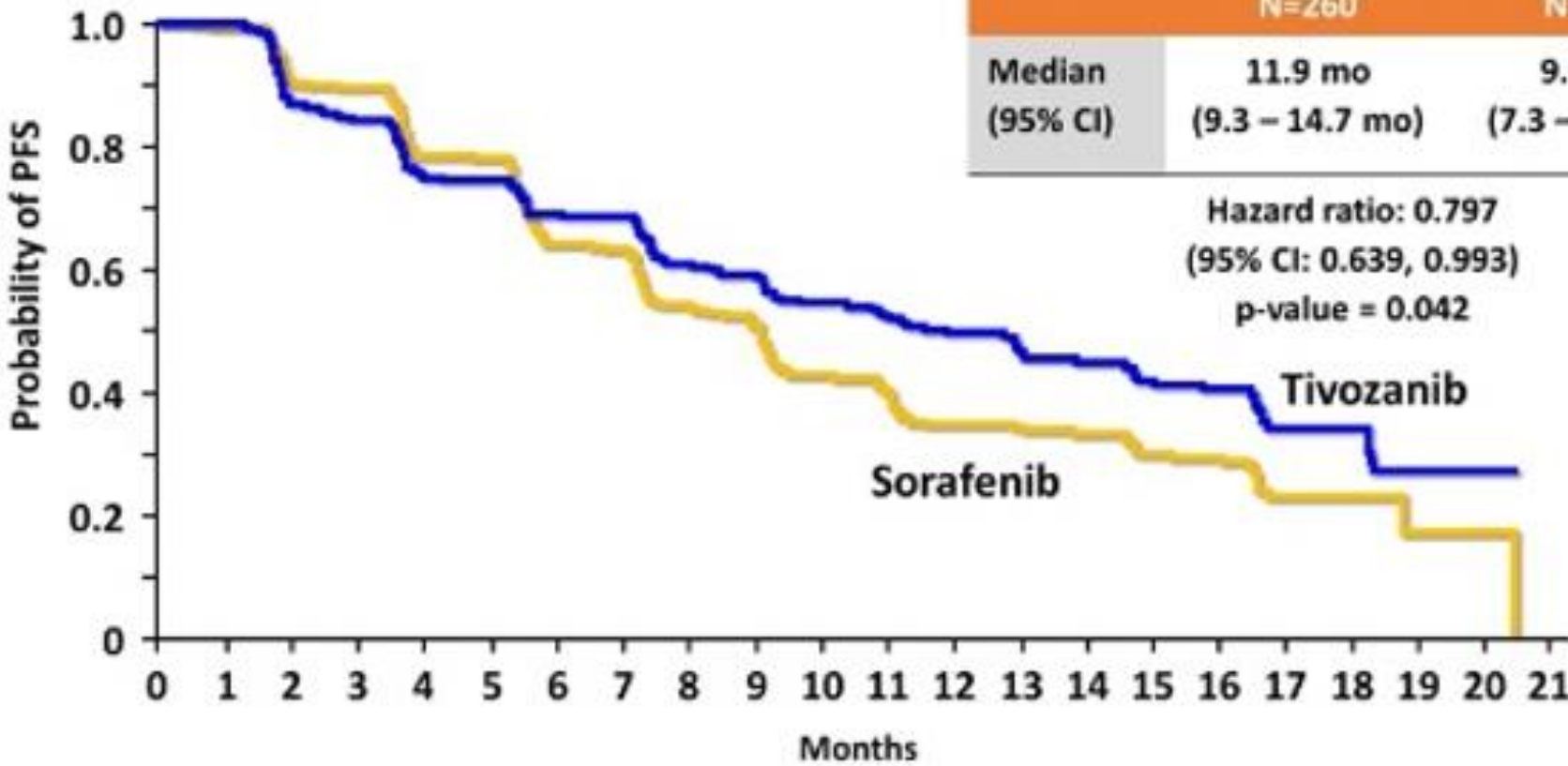


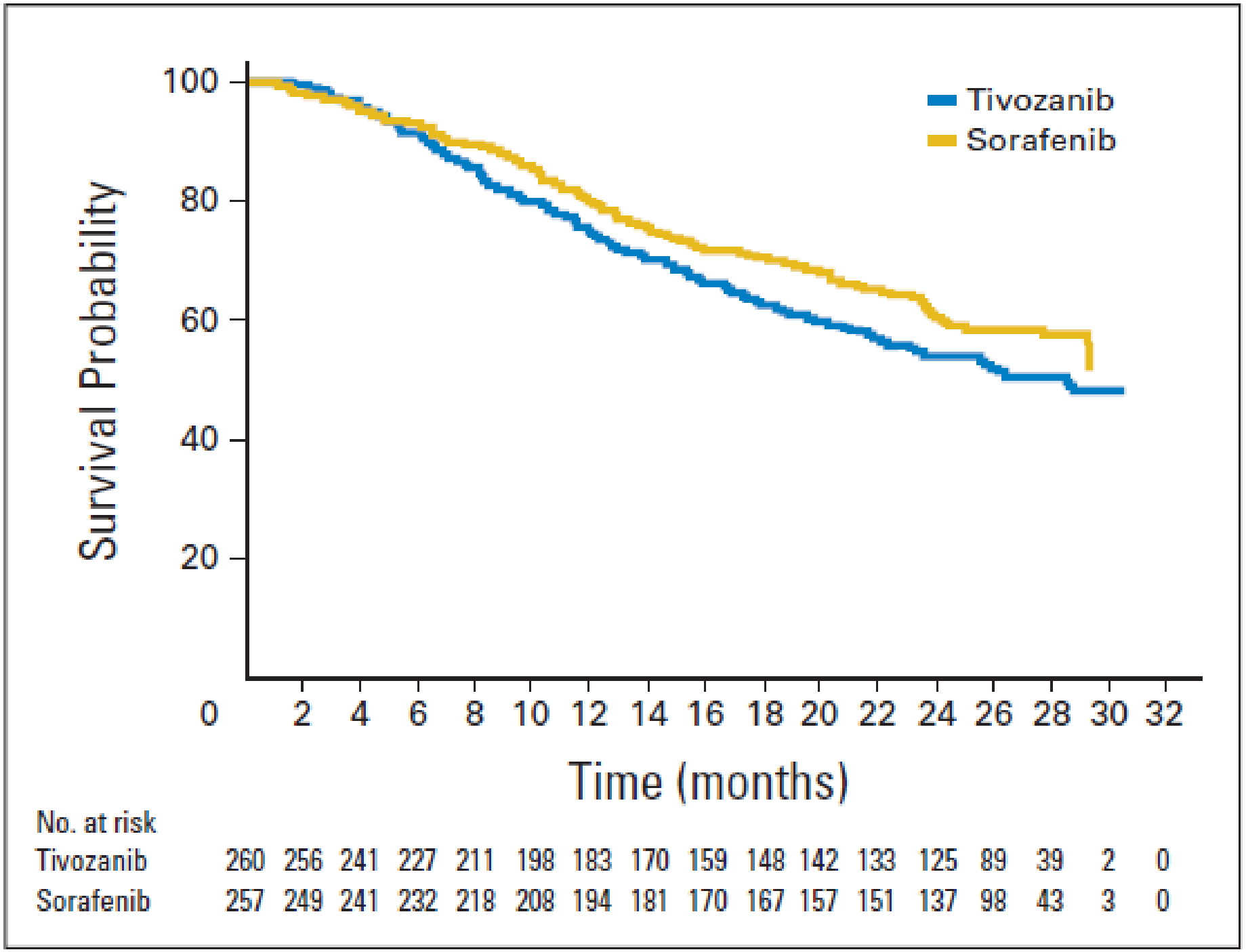
Phase 3 TIVO-1: Proven Activity in 1st line RCC

- 517 patient, global, randomized Phase 3 in 1st line RCC
- First H2H RCC pivotal to meet primary PFS endpoint of superiority vs VEGF TKI
- OS confounded by crossover; NDA not approved; FDA requested additional study
- Demonstrated favorable tolerability profile

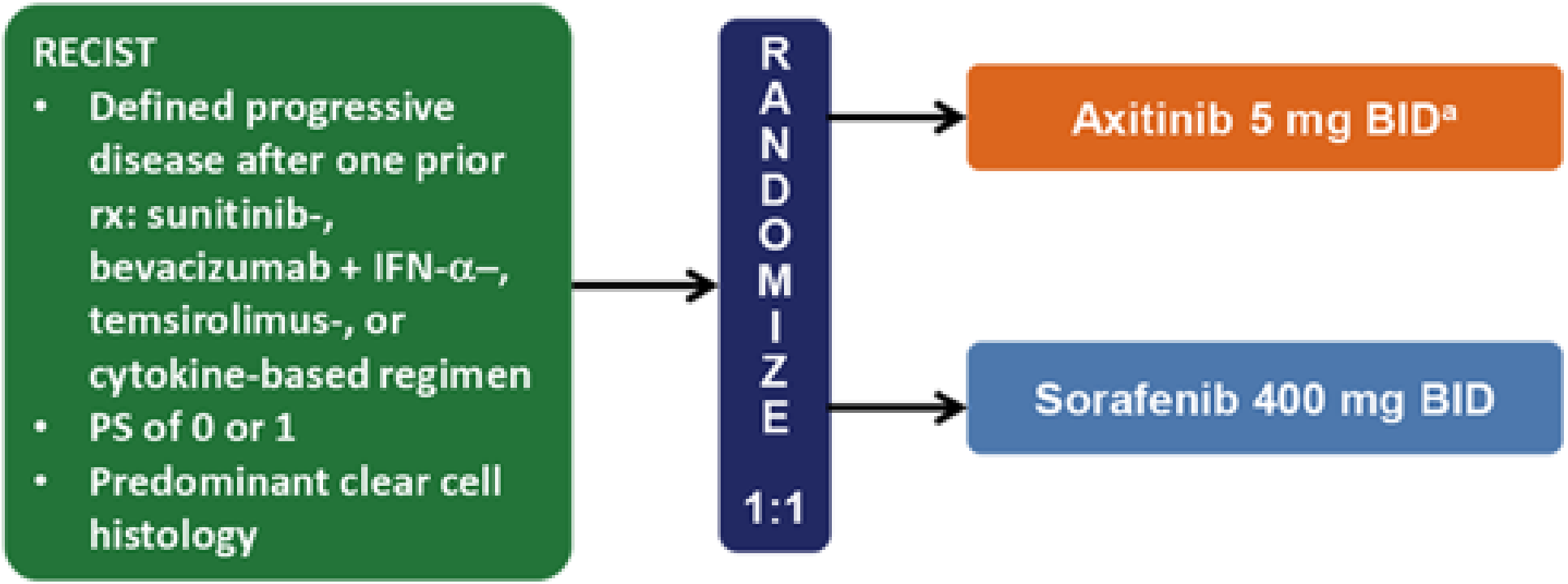
	Tivozanib N=260	Sorafenib N=257
Median (95% CI)	11.9 mo (9.3 – 14.7 mo)	9.1 mo (7.3 – 9.5 mo)

Hazard ratio: 0.797
(95% CI: 0.639, 0.993)
p-value = 0.042



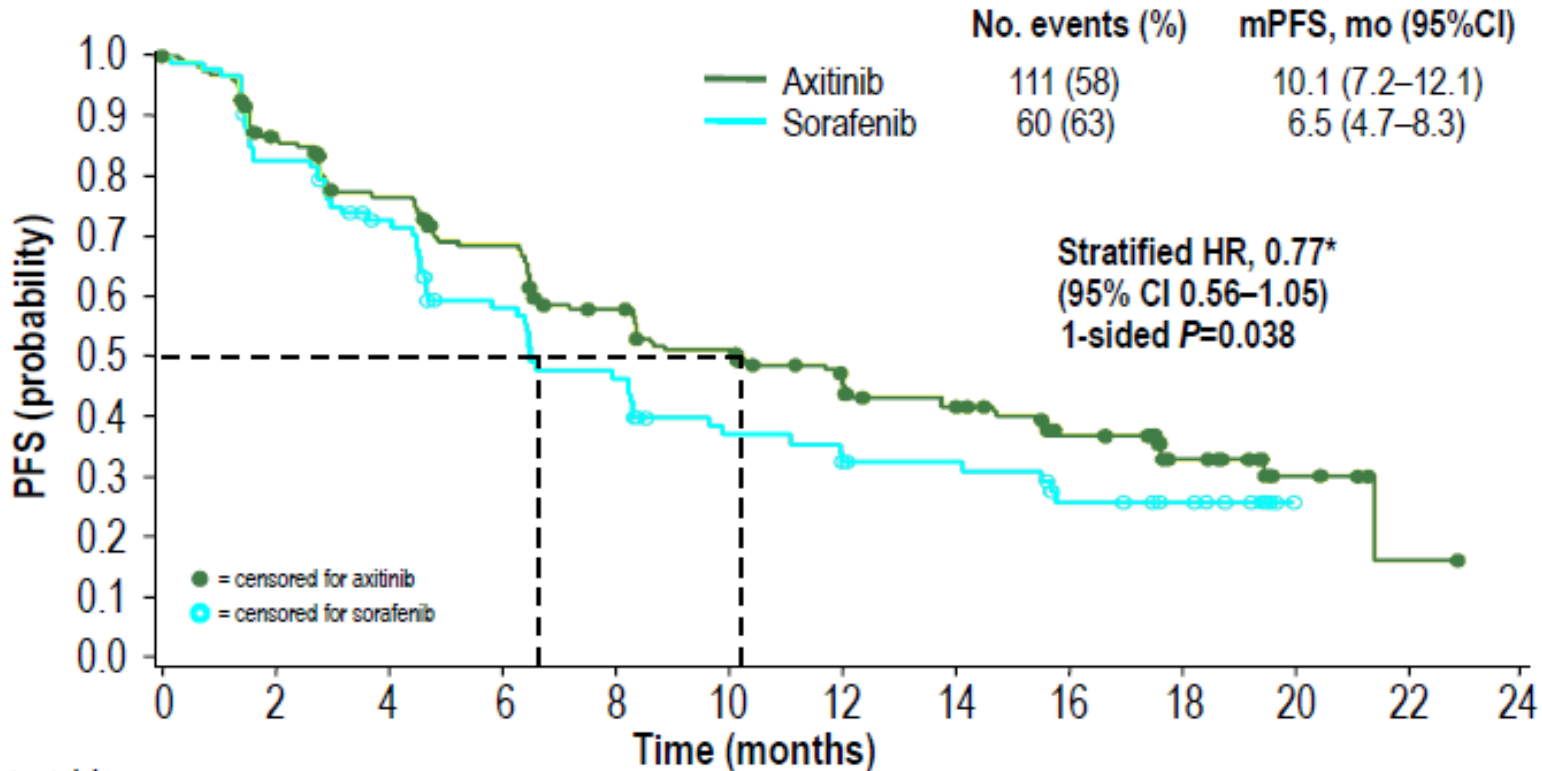

Tivozanib
Sorafenib
Survival Probability
100
80
60
40
20
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
Time (months)
No. at risk
Tivozanib 260 256 241 227 211 198 183 170 159 148 142 133 125 89 39 2 0
Sorafenib 257 249 241 232 218 208 194 181 170 167 157 151 137 98 43 3 0

AXIS: Phase 3 Study of Axitinib Versus Sorafenib[1]



- Primary endpoint: PFS
- Randomization stratified by ECOG PS and type of prior treatment

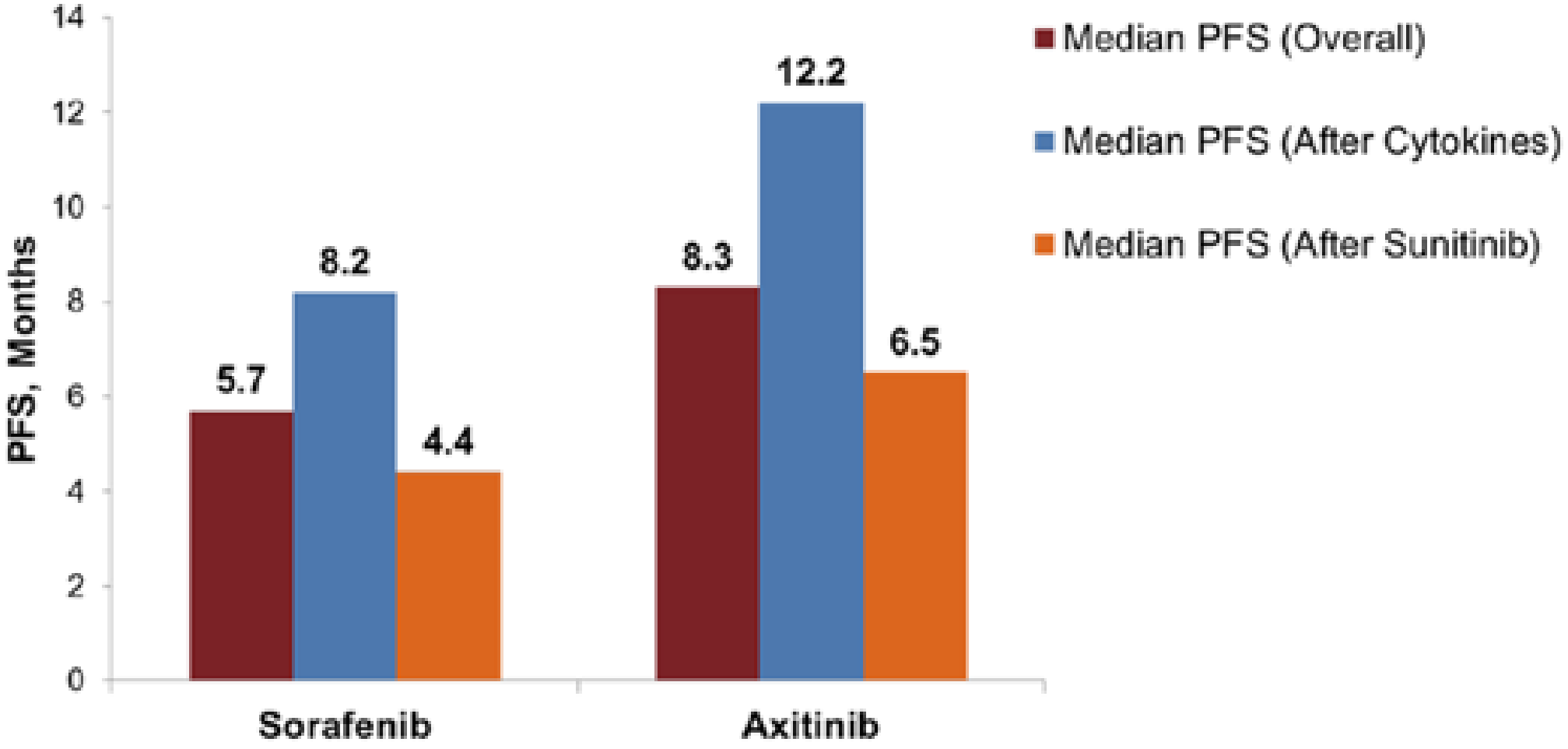
PROGRESSION-FREE SURVIVAL (IRC ASSESSMENT)



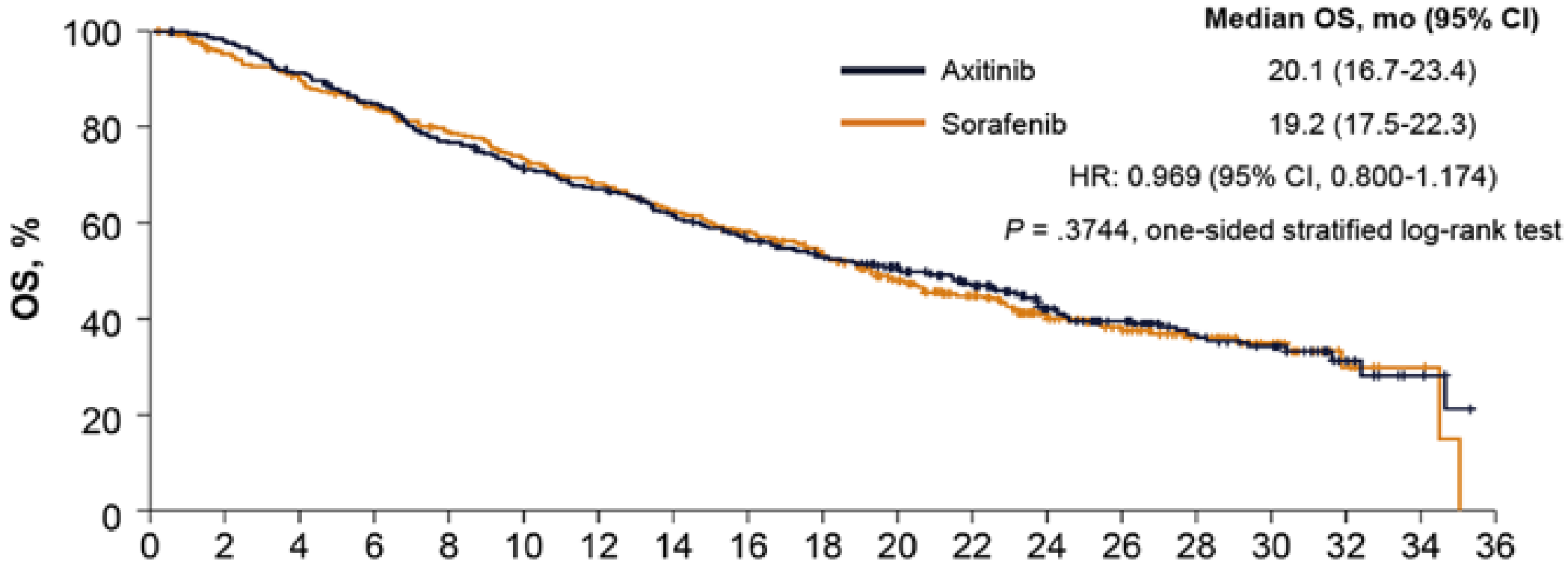
*Stratified by ECOG PS; assuming proportional hazards, HR <1 indicates a reduction in favour of axitinib and HR >1 indicates a reduction in favour of sorafenib.

IRC = independent radiology committee; mPFS = median progression-free survival

AXIS: Progression-Free Survival[1]



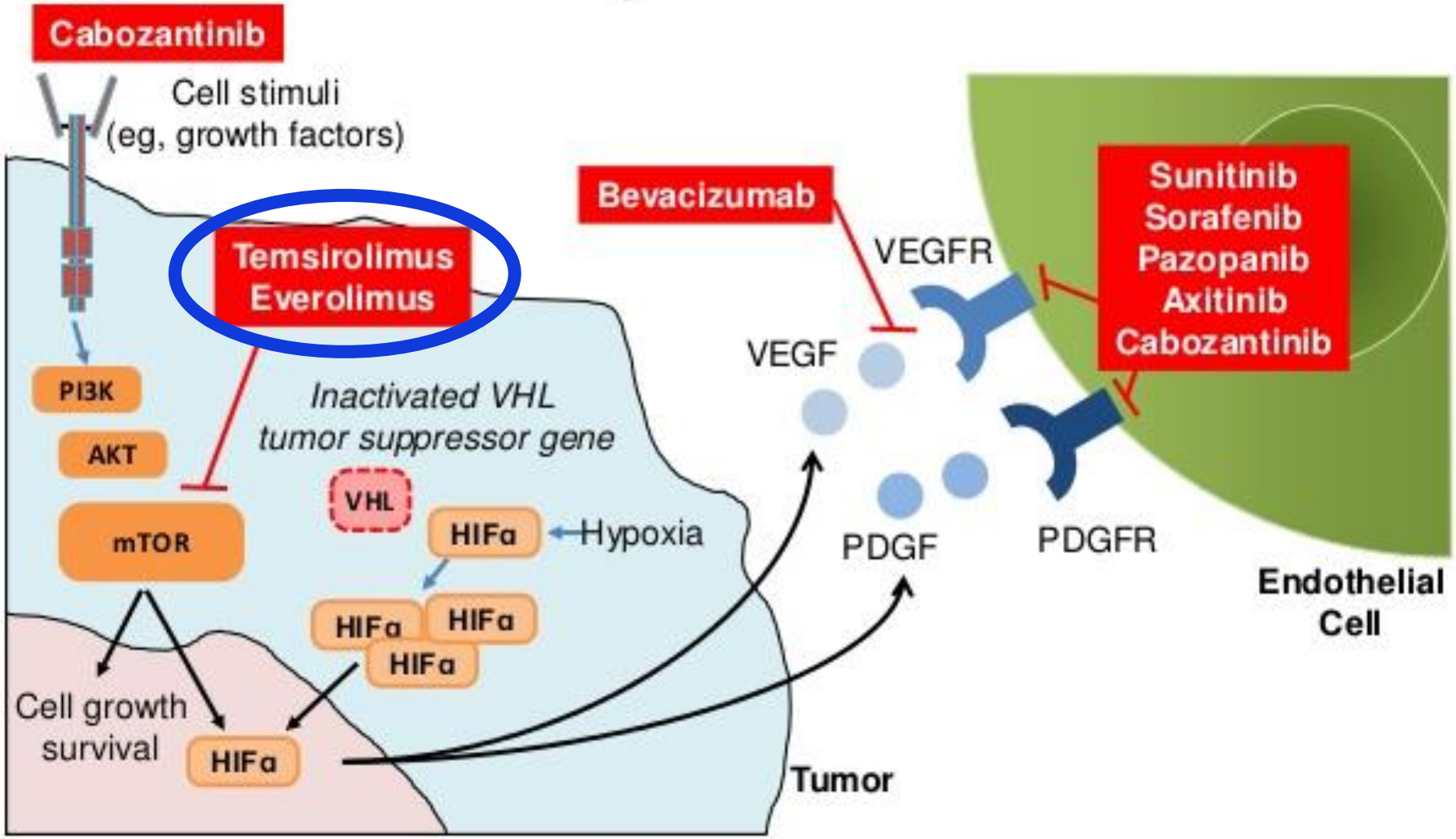
AXIS: Second-Line Axitinib Versus Sorafenib



No. at Risk

Axitinib	361	351	326	302	273	252	237	214	193	178	152	127	86	70	45	36	14	5	0
Sorafenib	362	340	318	298	278	259	240	218	202	181	145	118	88	62	41	26	9	4	0

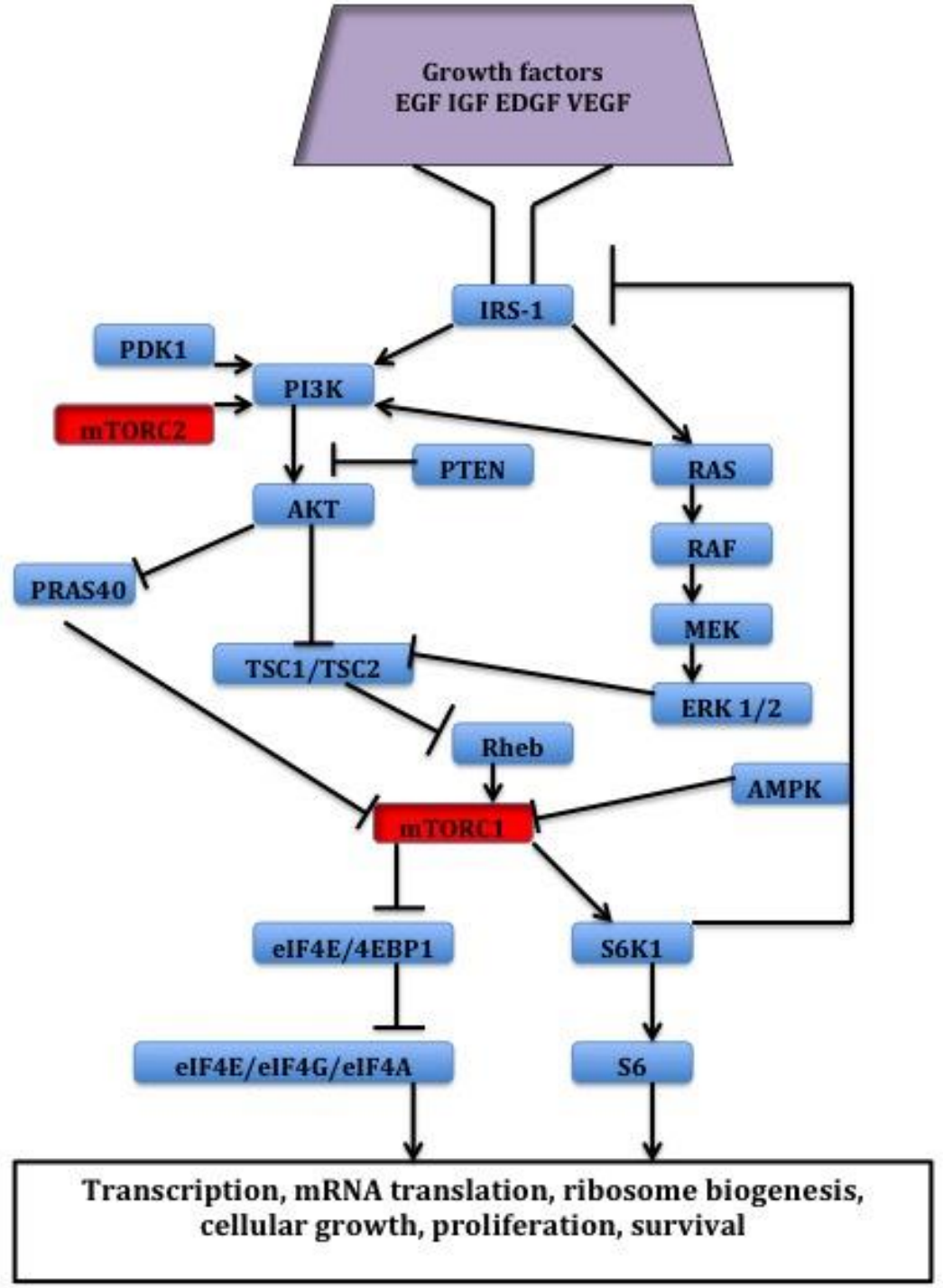
RCC Therapy: Targeting VEGF at Multiple Levels



Adapted from Rini BI, et al. Lancet. In press.

mTOR inhibitors

Temsirolimus (Sirotem)



Temsirolimus Phase III Trial in Poor-Risk RCC*: Tem ± IFN-α; OS by Treatment

3/6 Poor-Risk Features:
- LDH > 1.5 x ULN
- Hb < LLN
- Ca^{++} (corrected) > 10 mg/dL
- KPS 60-70
- Initial diag to random < 1 yr
- Multiple sites of metastases mRCC

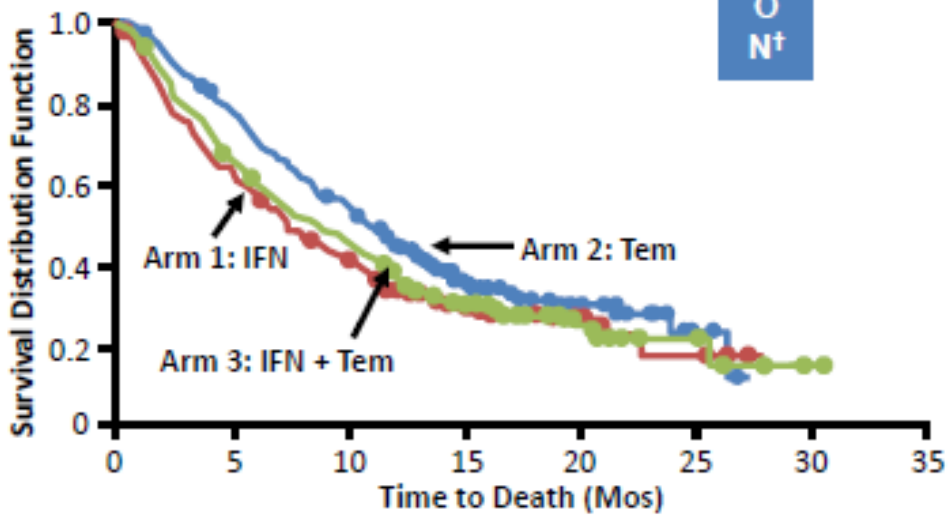
(N = 626)

RANDOMIZATION†

IFN-α 3 MU-18 MU (n = 207)
CR + PR: 4.8%
CR + PR + SD‡: 15.5%

Tem 25 mg QW (n = 209)
CR + PR: 8.6%
CR + PR + SD: 32.1%

IFN-α 3 MU-6 MU + Tem 15 mg QW (n = 210)
CR + PR: 8.1%
CR + PR + SD: 28.1%



Parameter	IFN Arm 1 (n = 207)	Tem Arm 2 (n = 209)	Tem + IFN Arm 3 (n = 210)
Median survival, Mos	7.3	10.9	8.4
Comparisons		Arm 2 to Arm 1	Arm 3 to Arm 1
Stratified log-rank P		.008	.70

*Modified MSKCC poor risk. †Stratified by country and nephrectomy status. ‡SD ≥ 24 wks.

Hudes G, et al. N Engl J Med. 2007;356:2271-2281.

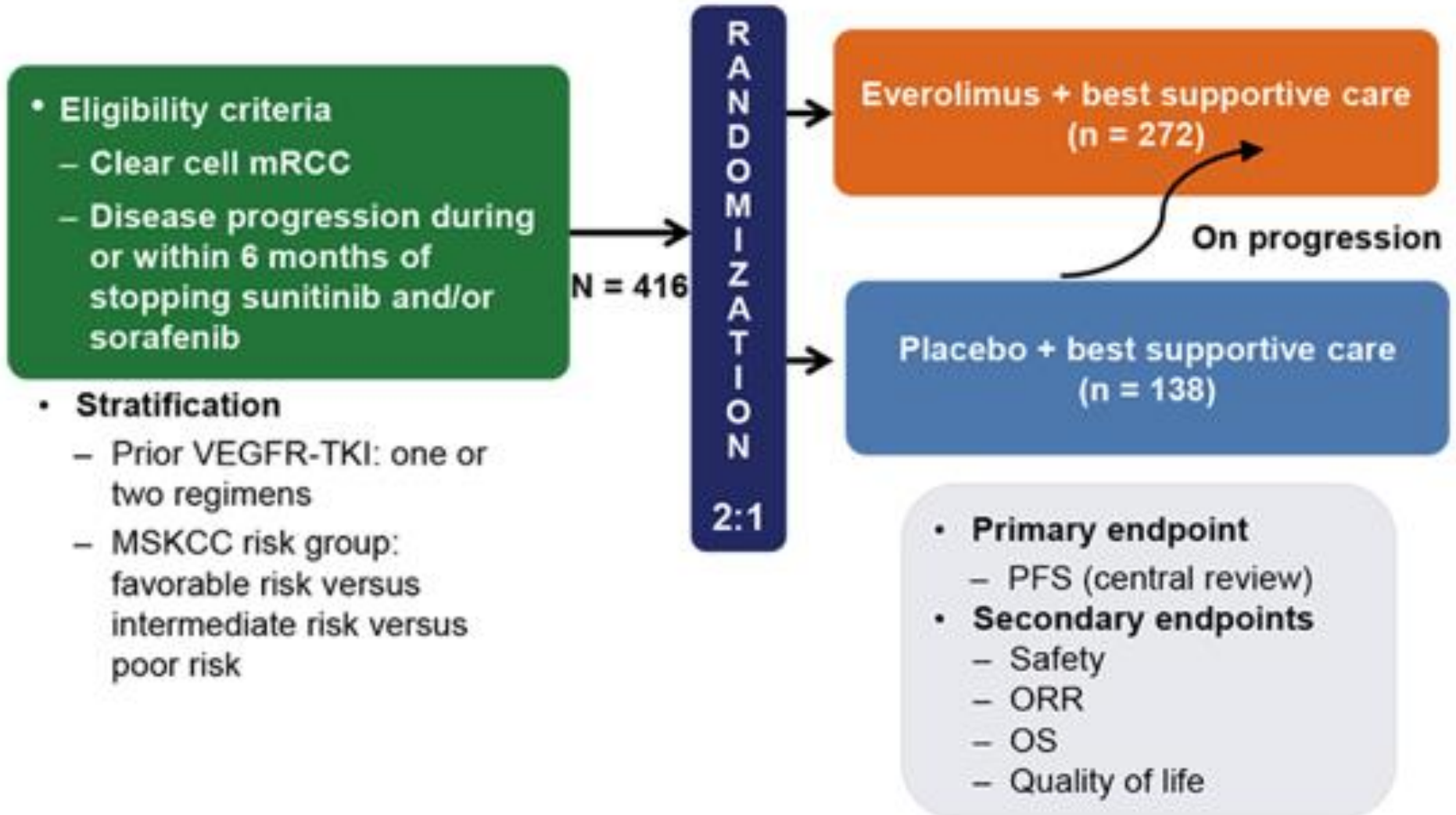
TEMSR for mRCC: Conclusion

Temsirolimus as a single agent (25 mg IV weekly) vs. IFN-α alone significantly improves OS and PFS of patients with poor-risk mRCC

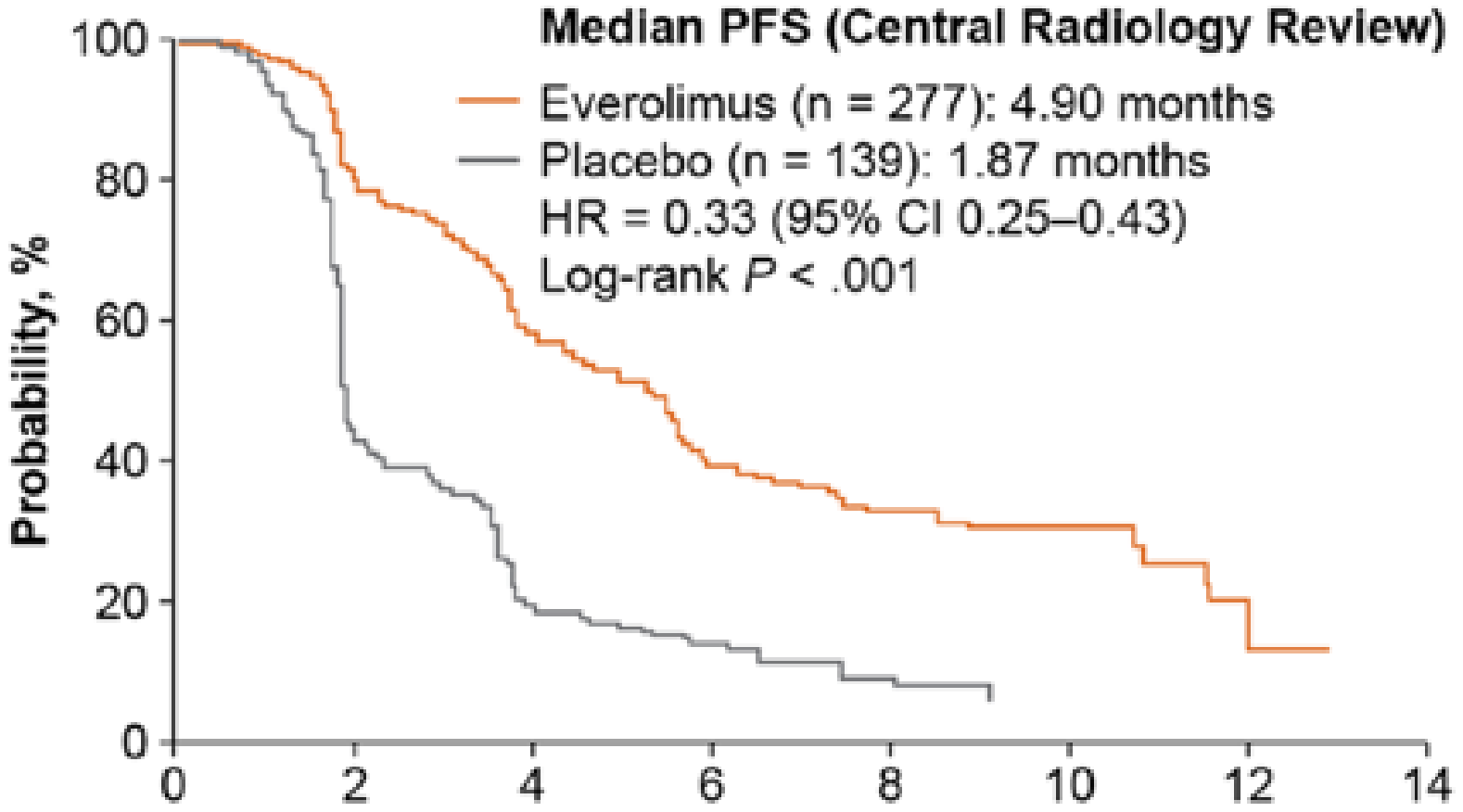
- 3.6-month (49%) improvement in median OS
- 1.8-month (95%) improvement in median PFS

The combination of temsirolimus (15 mg IV weekly) + IFN-α (6 MU 3 times weekly) did not significantly improve OS vs. IFN-α

RECORD-1: Phase 3 Study of Everolimus Versus Placebo[1,2]

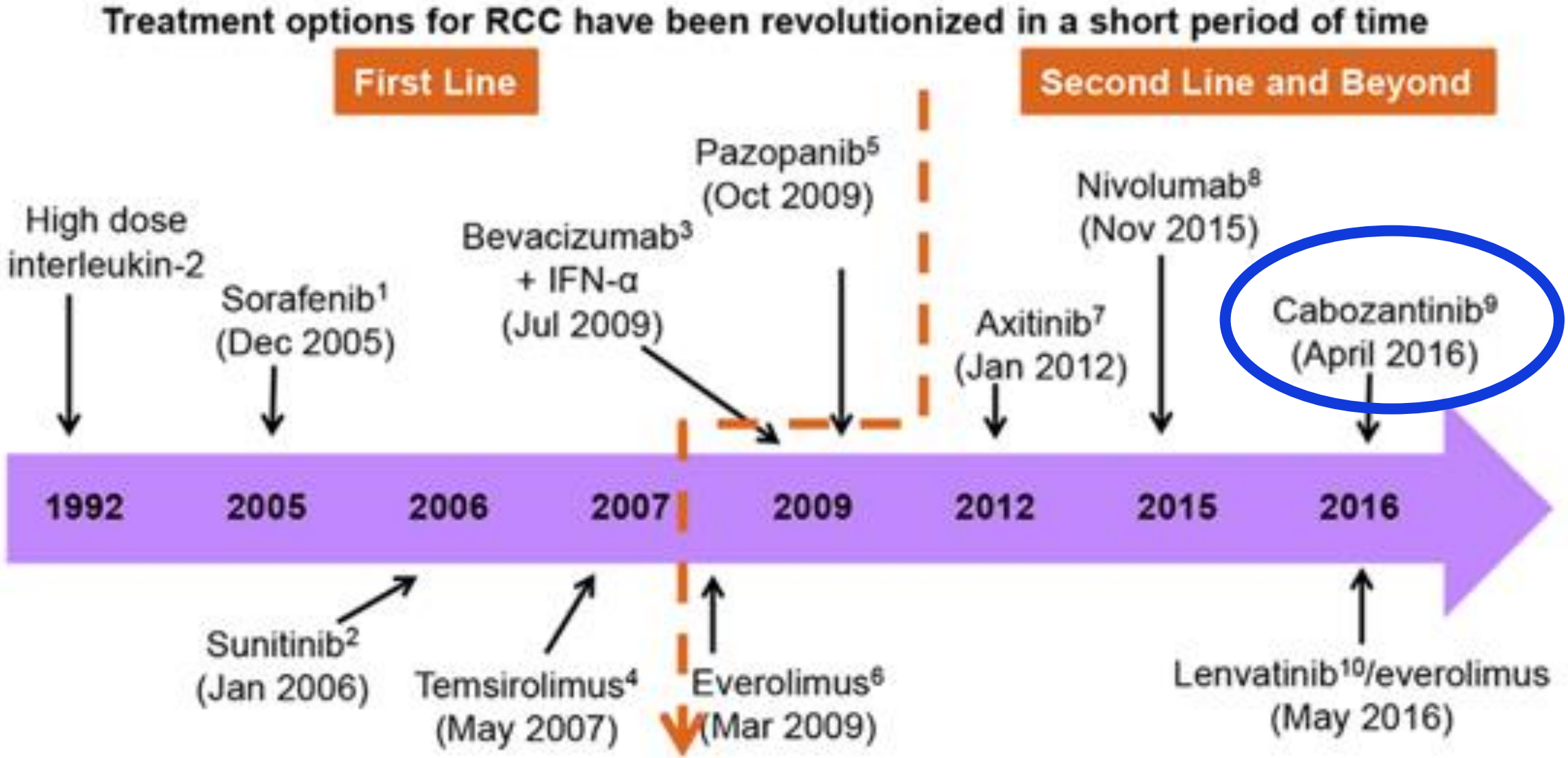


RECORD-1: Progression-Free Survival[1]



Patients at risk, n								
Everolimus	277	192	115	51	26	10	1	0
Placebo	139	47	15	6	2	0	0	0

FDA Approvals in RCC



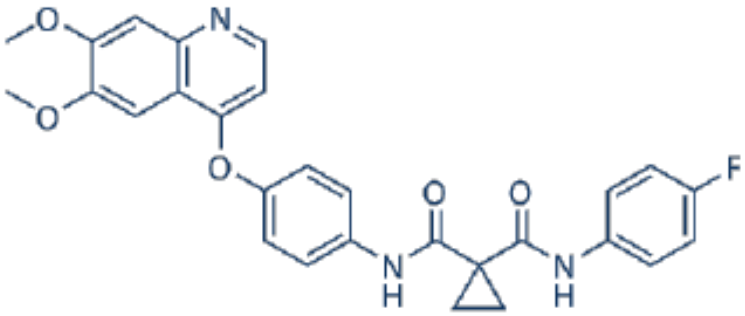
Cabozantinib: An RTKi Targeting VEGFR-2, MET, and AXL

The s-malate salt form of cabozantinib, an orally bioavailable, small-molecule RTKi, strongly binds to and inhibits several RTKs involved in tumor growth and angiogenesis

Some of them, including VEGFR-1, -2 and -3, mast/stem cell growth factor (KIT), FMS-like tyrosine kinase 3 (FLT-3), and TIE-2 (TEK tyrosine kinase, endothelial) are targeted also by many others RTKIs

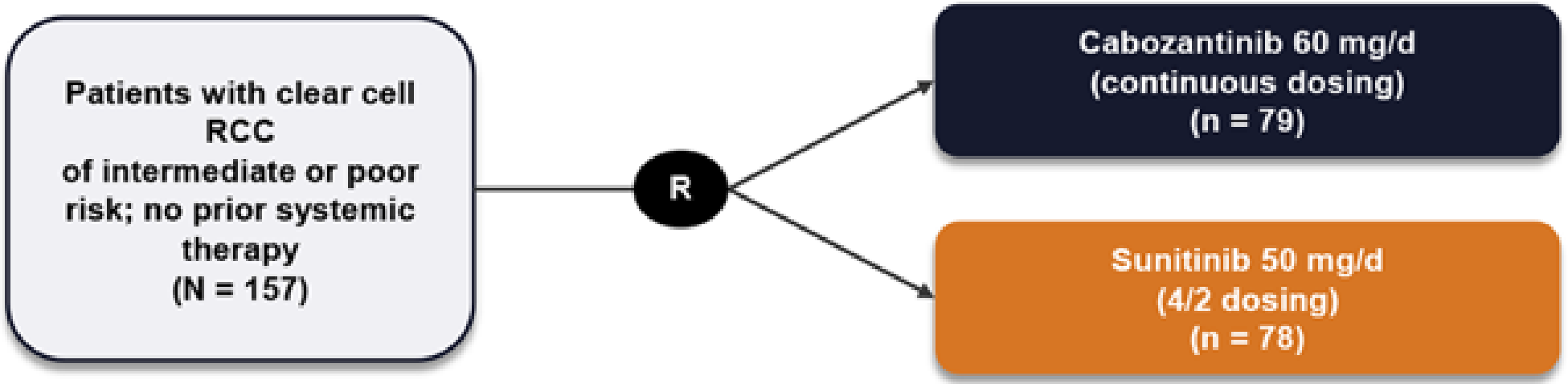
On the other hand, the hepatocyte growth factor receptor MET, AXL, RET (rearranged during transfection), and tropomyosin-related kinase B (TRKB) are specific targets of cabozantinib

As a whole, this wide spectrum of RTK inhibition results in a potent suppression of both tumor growth and angiogenesis



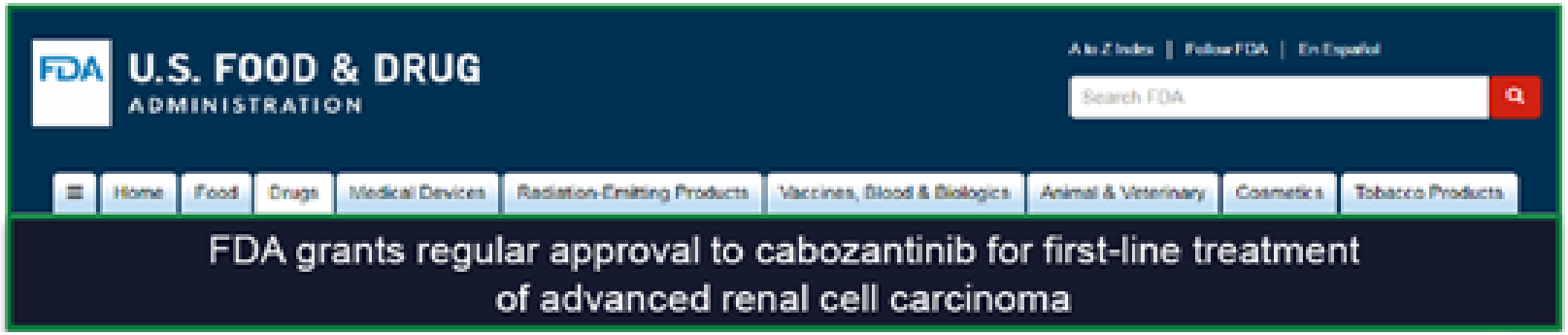
Randomized Phase 2 Assessment of Frontline Cabozantinib (CABOSUN)

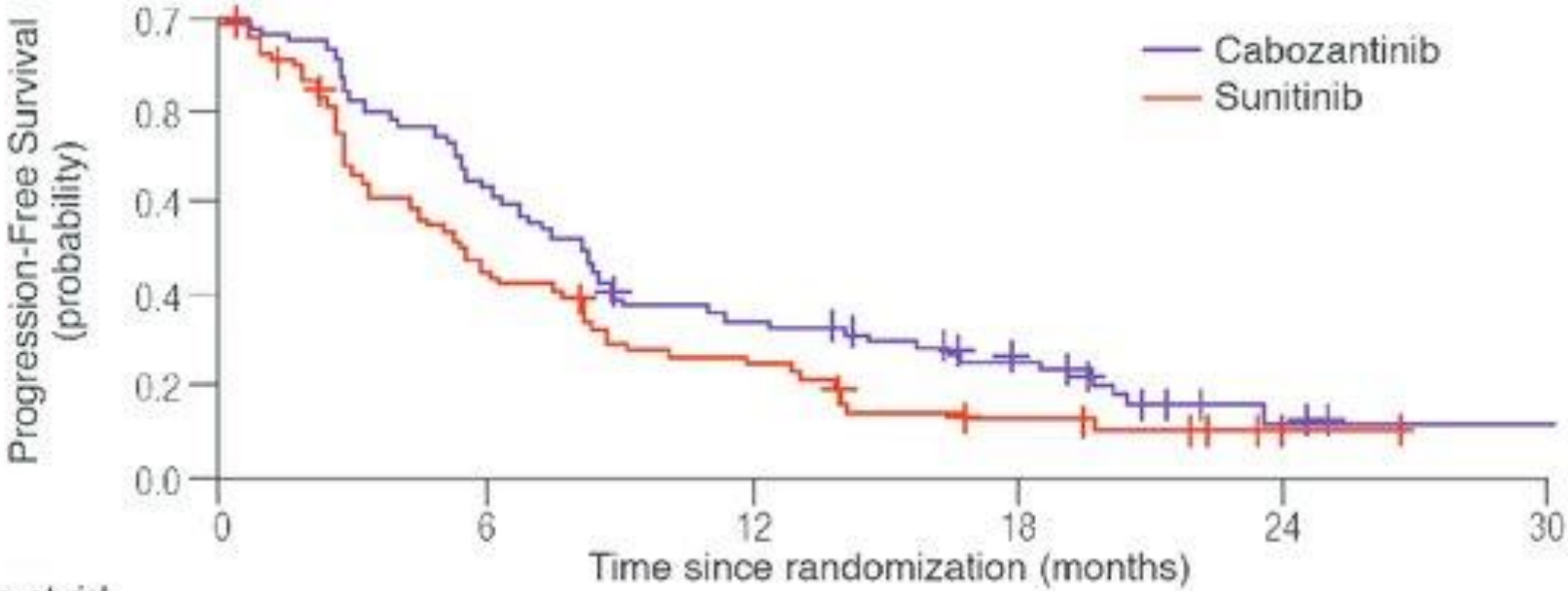
- Multicenter, randomized phase 2 study



Stratified by

- IMDC risk group (intermediate vs poor)
- Bone metastasis (yes/no)





No. at risk						
Cabozantinib	79	50	26	15	3	1
Sunitinib	78	32	17	7	1	0

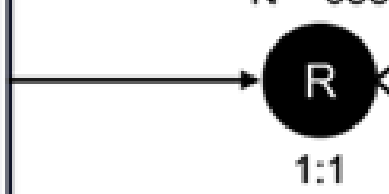
Arm	PFS Events	Median PFS (95% CI), mo	HR (95% CI)*
Cabozantinib	64	8.2 (6.2, 9.0)	0.69 (0.48-0.99)
Sunitinib	61	5.6 (3.4, 8.1)	*p*-value (one-sided) = 0.012

*Adjusted for bone metastases and IMDC risk group.

METEOR: Phase 3 Study of Cabozantinib Versus Everolimus

Eligibility criteria

- mRCC with clear cell component
- ≥1 prior VEGFR-TKI
- Progression on or after prior VEGFR-TKI within 6 mo of study enrollment
- KPS ≥70



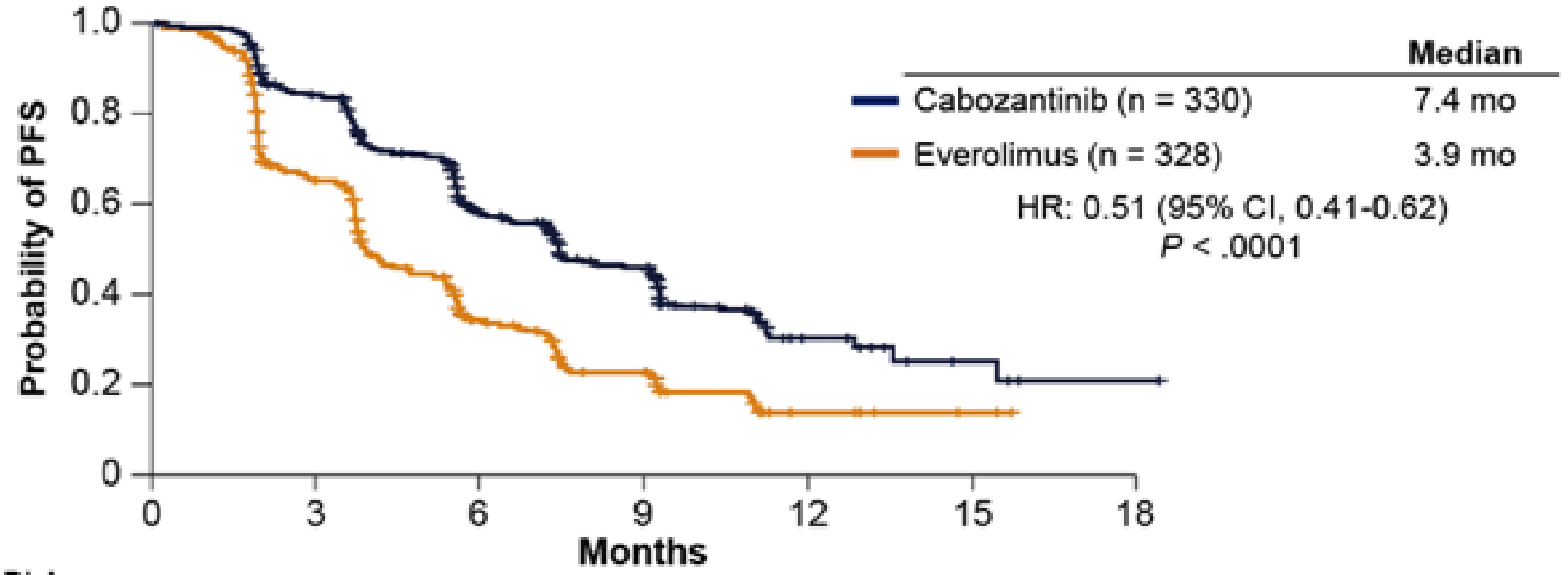
Cabozantinib
60 mg orally QD

- Treatment until loss of clinical benefit or intolerable toxicity
- Treatment beyond progression was permitted if drug was tolerable and clinical benefit was noted

Everolimus
10 mg orally QD

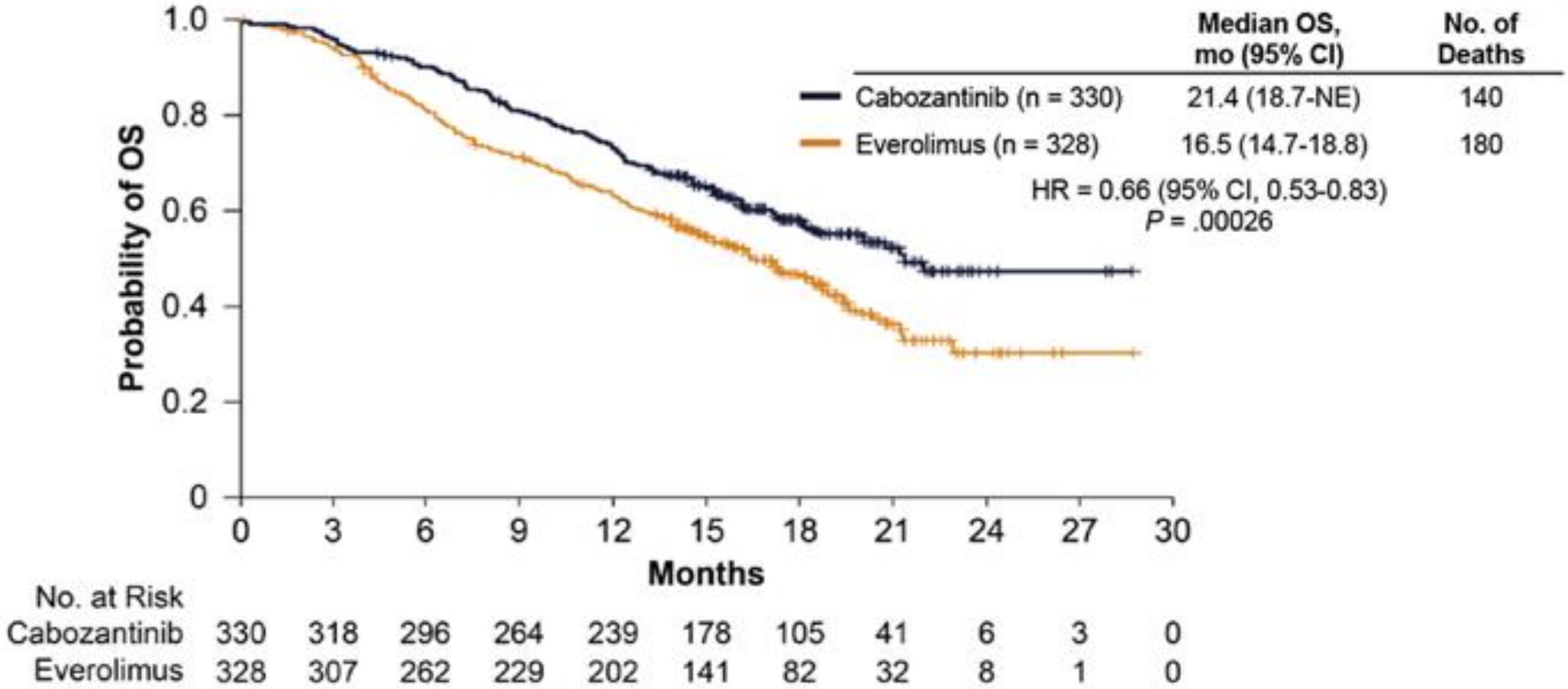
- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR
- **Exploratory endpoints:** Safety, tolerability, tumor MET status, circulating tumor cells, serum bone markers and plasma biomarkers, skeletal-related events, and HR-QoL
- **Stratification:** MSKCC risk criteria; number of prior VEGFR-TKIs

METEOR: PFS per IRC

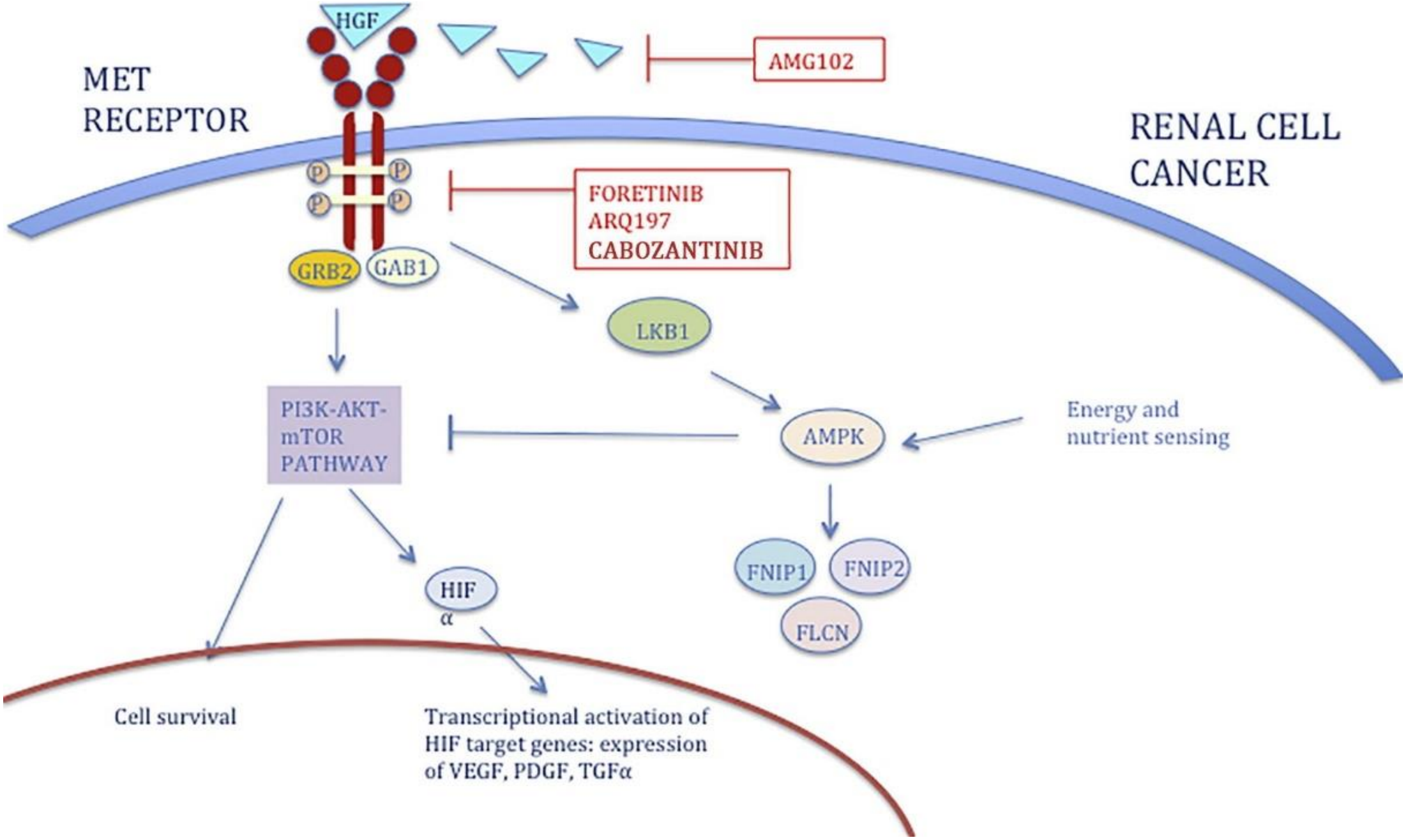


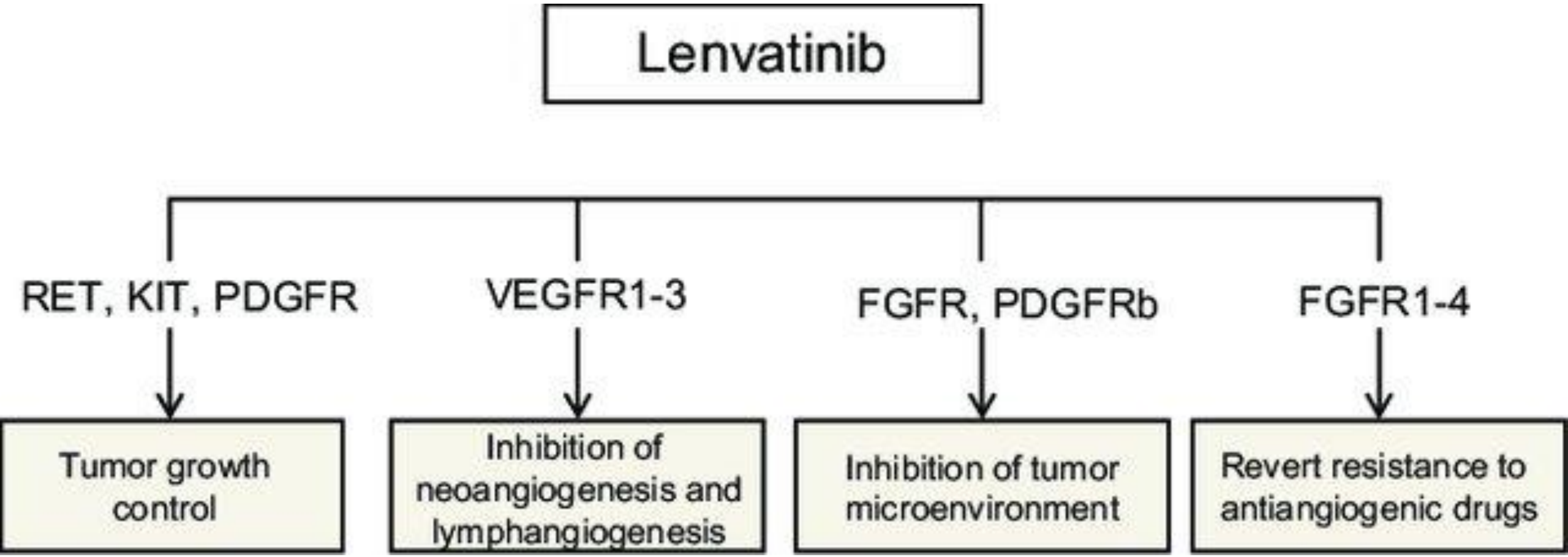
No. at Risk							
Cabozantinib	330	261	148	88	20	6	2
Everolimus	328	174	72	37	10	2	0
No. Censored							
Cabozantinib	0	17	37	32	47	12	3
Everolimus	0	51	24	13	16	8	2

METEOR: OS

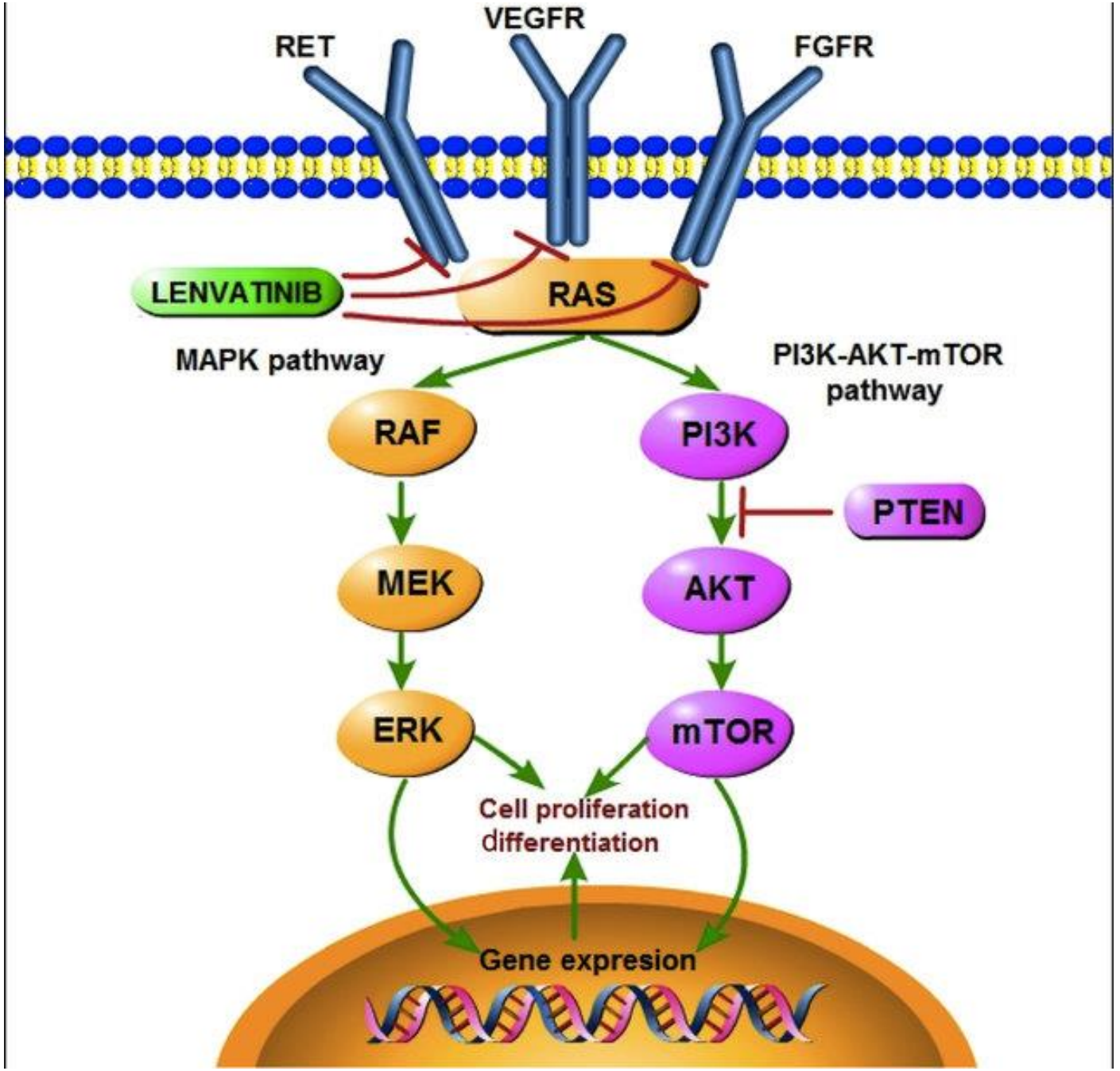

Median OS, mo (95% CI)
No. of Deaths
Cabozantinib (n = 330) 21.4 (18.7-NE) 140
Everolimus (n = 328) 16.5 (14.7-18.8) 180
HR = 0.66 (95% CI, 0.53-0.83)
P = .00026
Probability of OS
1.0
0.8
0.6
0.4
0.2
0
0 3 6 9 12 15 18 21 24 27 30
Months
No. at Risk
Cabozantinib 330 318 296 264 239 178 105 41 6 3 0
Everolimus 328 307 262 229 202 141 82 32 8 1 0

MET pathway and targeted therapies in RCC.



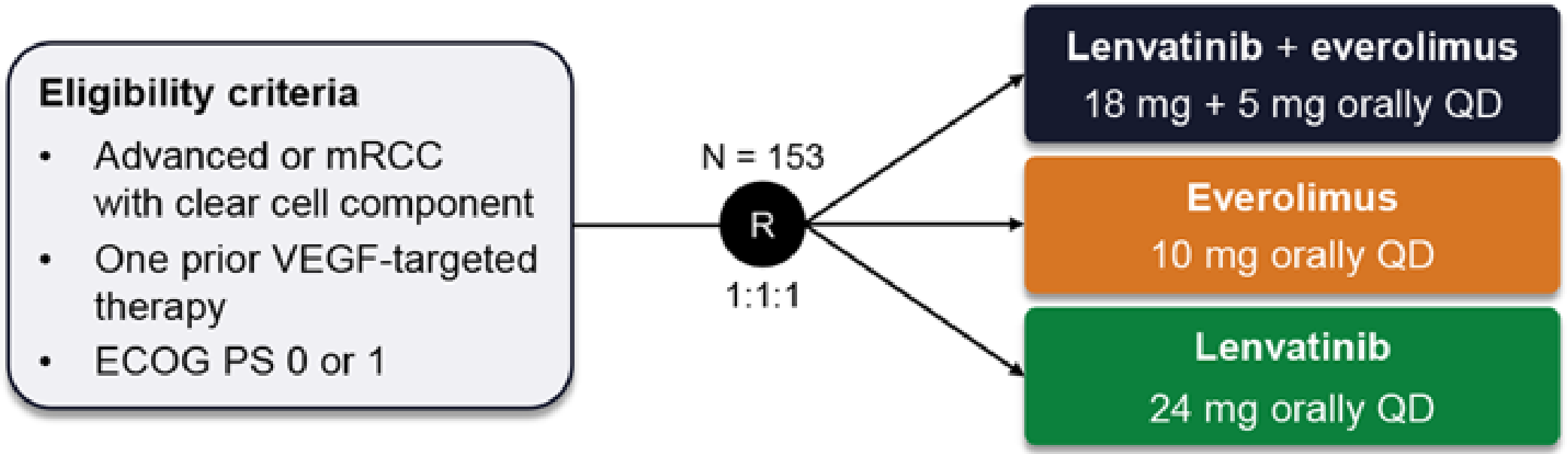

Lenvatinib
RET, KIT, PDGFR
VEGFR1-3
FGFR, PDGFRb
FGFR1-4
Tumor growth control
Inhibition of neoangiogenesis and lymphangiogenesis
Inhibition of tumor microenvironment
Revert resistance to antiangiogenic drugs

Proposed mechanism of action of lenvatinib



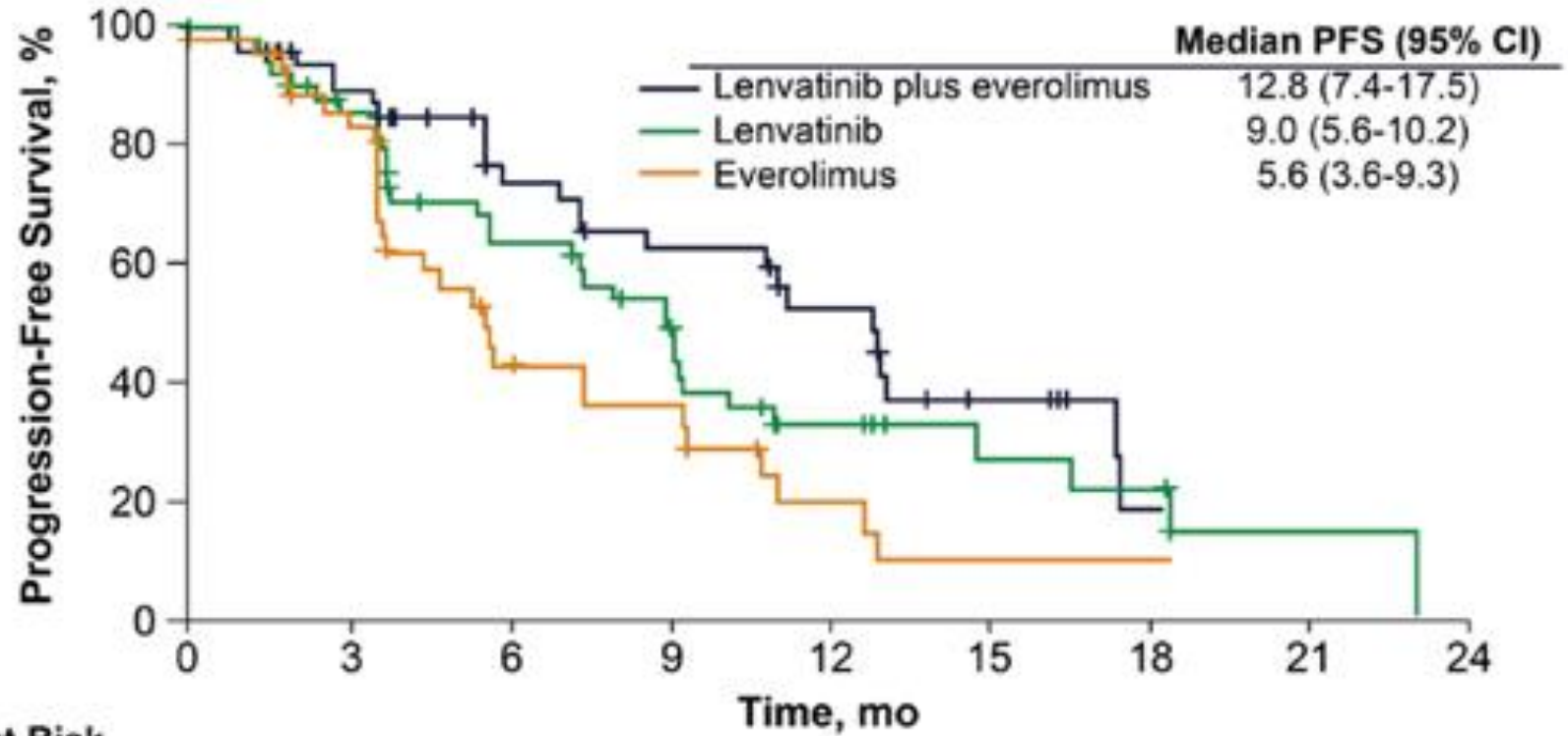
Abbreviations: ReT, rearranged during transfection tyrosine kinase receptor; VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor.

Randomized Phase 2 Trial of Lenvatinib Versus Everolimus Versus Lenvatinib Plus Everolimus



- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR, and safety

Phase 2 Lenvatinib Plus Everolimus: PFS



No. at Risk									
Lenvatinib plus everolimus	51	40	26	21	14	7	1	0	0
Lenvatinib	52	40	27	21	9	5	4	1	0
Everolimus	50	32	13	10	4	2	1	0	0

Recent Approvals

Selected Ongoing Trials

Pretreated Advanced Disease

Cabozantinib[1]
Approved April 2016
(phase 3 METEOR trial)

Nivolumab[2]
Approved November 2015 in patients who have received prior anti-angiogenic therapy
(phase 3 CheckMate 025 trial)

Lenvatinib + Everolimus[3]
Approved May 2016 in patients who have received one prior anti-angiogenic therapy
(phase 2 HOPE 205 trial)

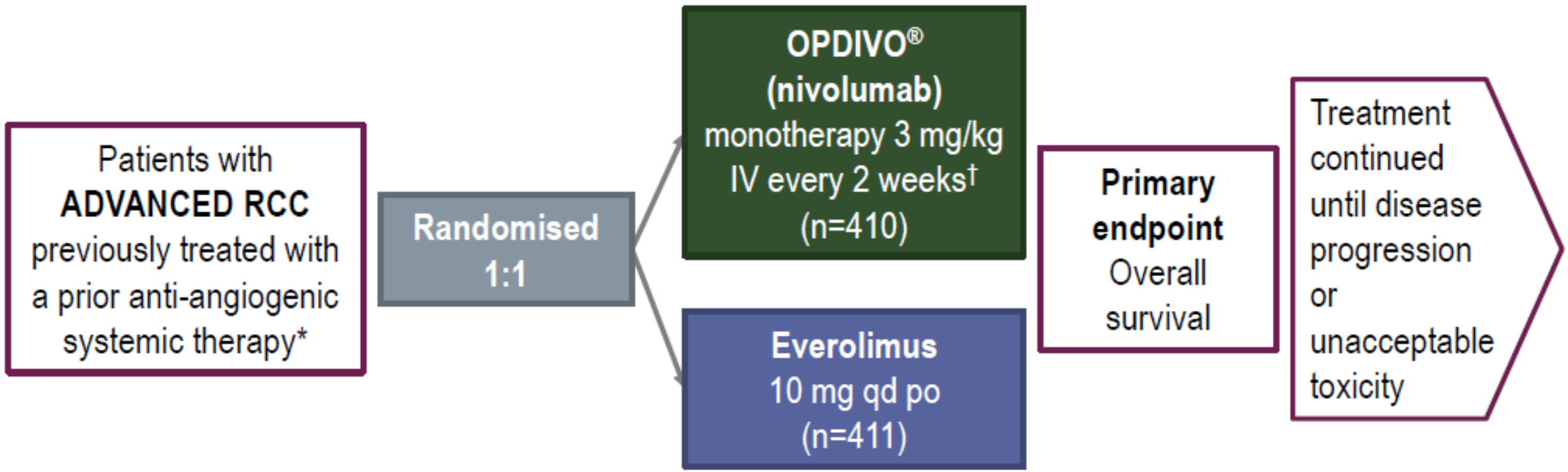
ACTIVE, NOT RECRUITING

Phase 3 TIVO-3 (NCT02627963)
Tivozanib vs sorafenib

Immunotherapy for Advanced Kidney Cancer:

CHECKMATE 025

Nivolumab *vs.* everolimus in advanced RCC



Nivolumab *vs.* everolimus in advanced RCC

CHECKMATE 025: ORR

ORR: 25% (21.5% confirmed) Nivolumab vs 5% Everolimus

Objective response rate, n (%)		
Odds ratio (95% CI)		
Best overall response, n (%)		
Complete response	4 (1)	2 (1)
Partial response	99 (24)	20 (5)
Stable disease	141 (34)	227 (55)
Progressive disease	143 (35)	114 (28)
Not evaluated	23 (6)	48 (12)
Median time to response, months (range)	3.5 (1.4–24.8)	3.7 (1.5–11.2)
Median duration of response, months (range)*	12.0 (0–27.6)	12.0 (0–22.2)

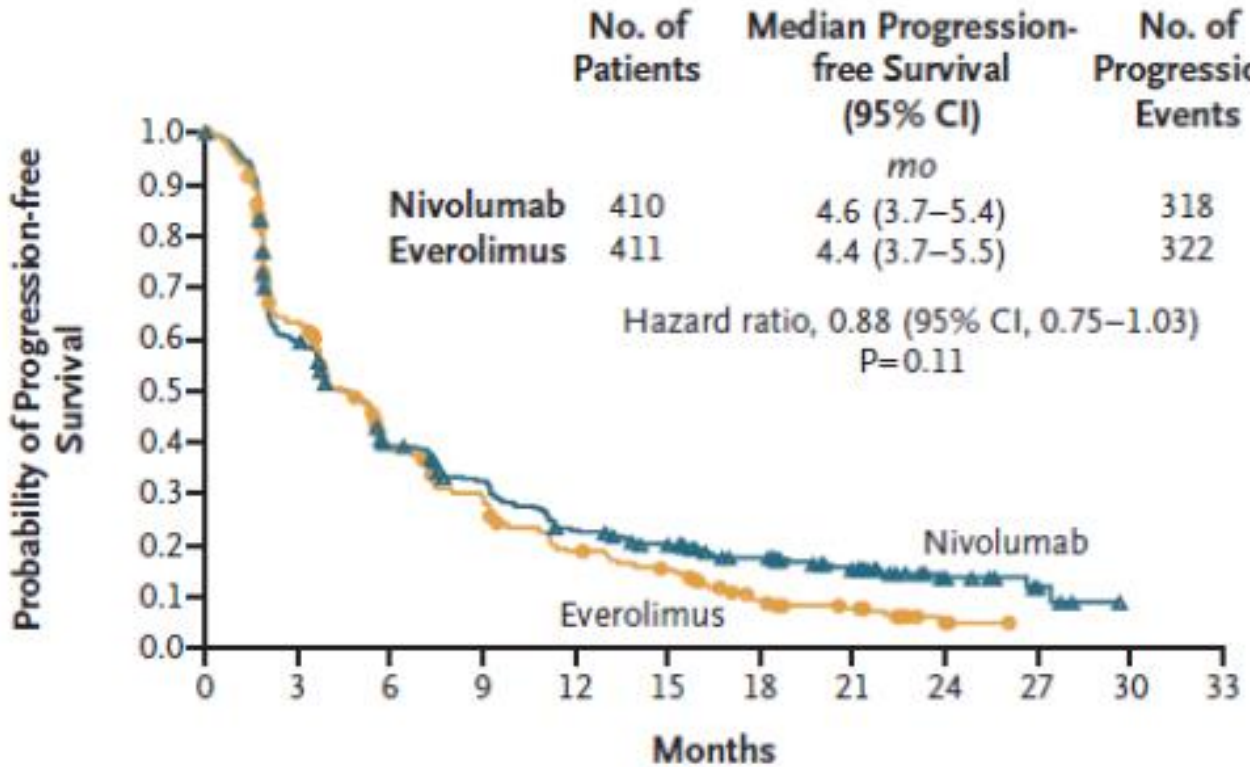
*For patients without progression or death, duration of response is defined as the time from the first response (CR/PR) date to the date of censoring.

Motzer RJ, *et al*.. N Engl J Med 2015;373(19):1803–13.

ESMO

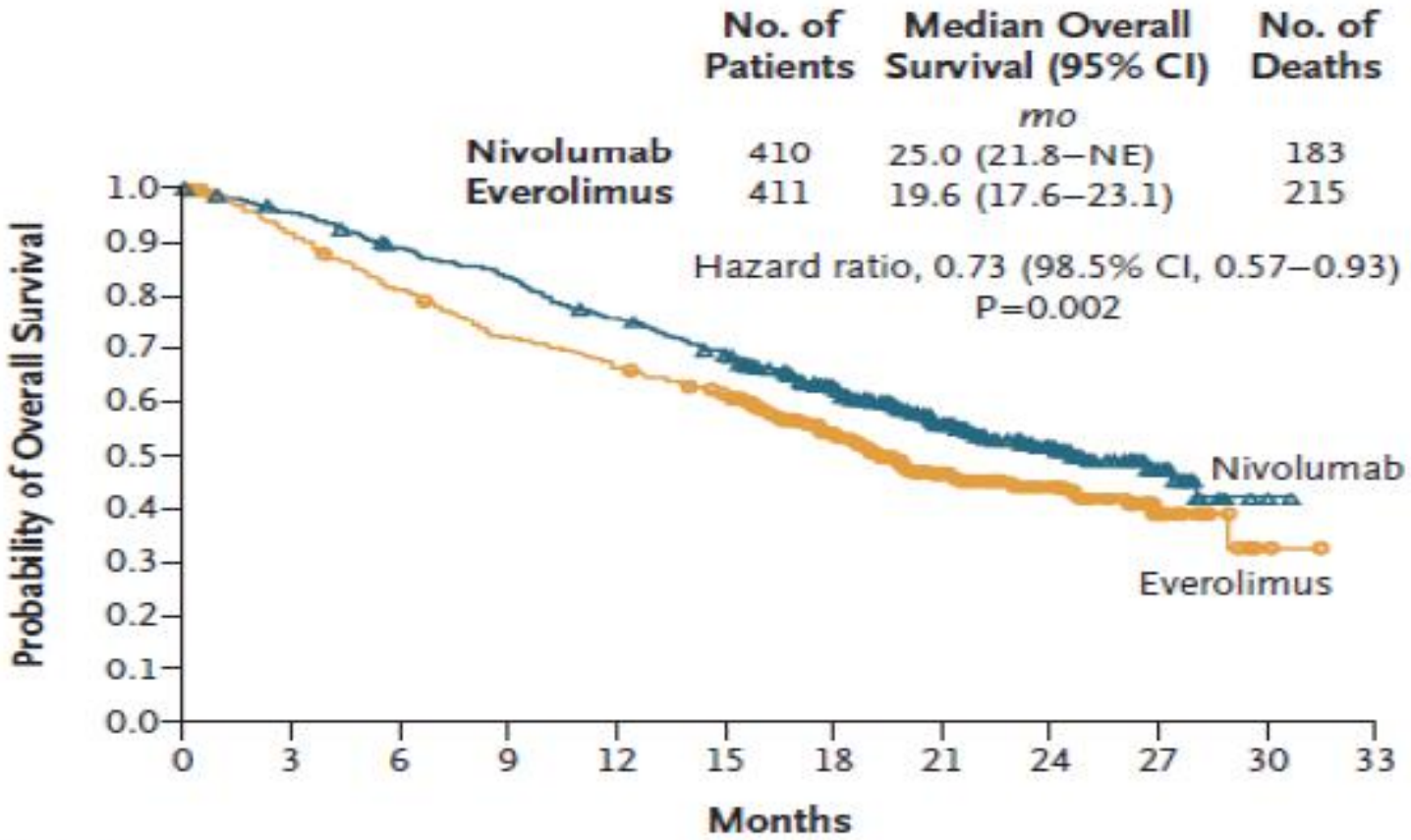
Nivolumab *vs.* everolimus in advanced RCC

CHECKMATE 025: PFS



Nivolumab *vs.* everolimus in advanced RCC

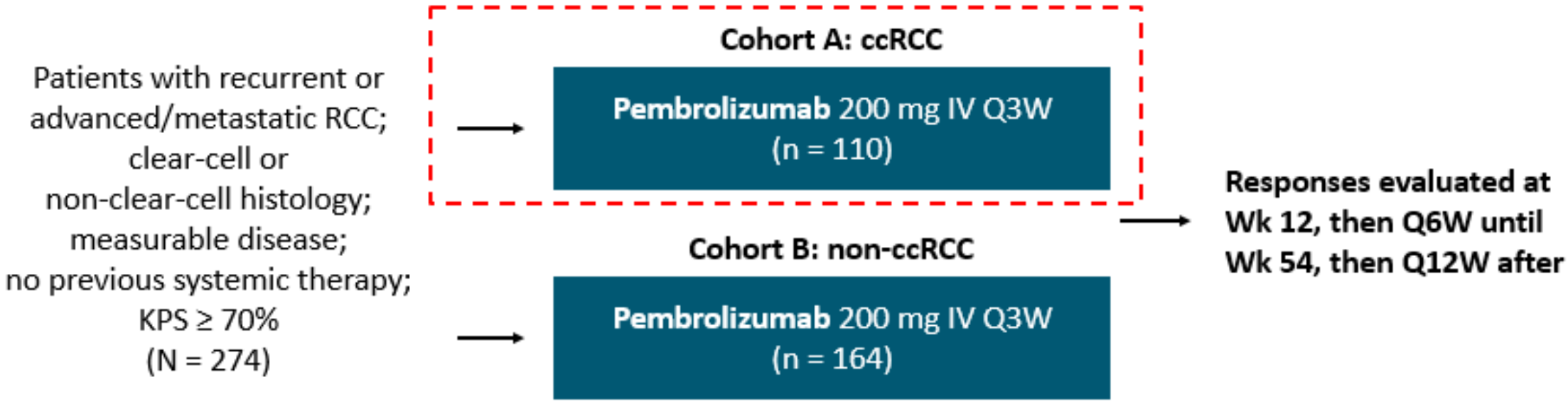
CHECKMATE 025: OS



What About First-line Anti–PD-1 Monotherapy?

KEYNOTE-427: Pembrolizumab Monotherapy in mRCC

- Single-arm, open-label, multicohort phase II trial

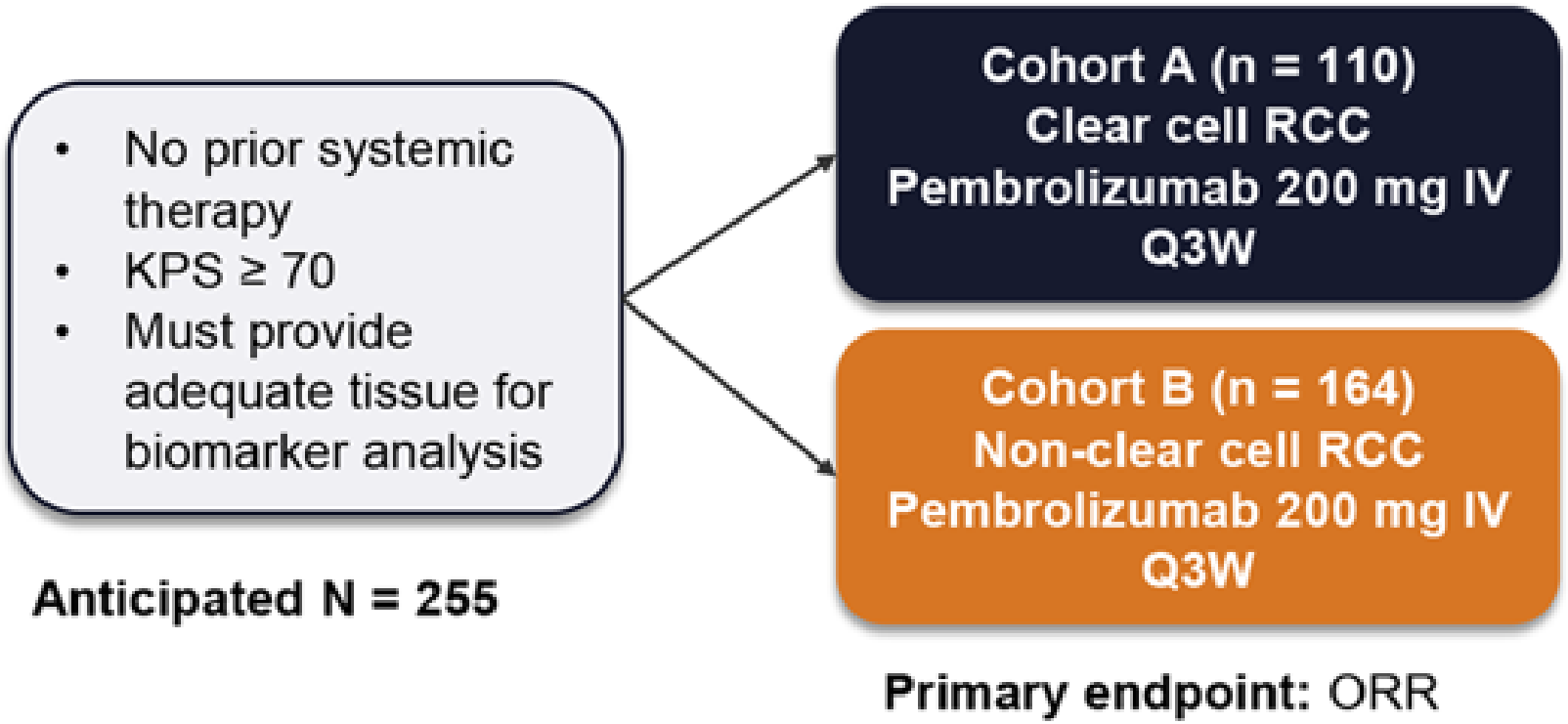


- Primary endpoint: BICR-assessed ORR per RECIST v1.1
- Secondary endpoints: DoR, DCR, PFS, OS, safety, and tolerability
- Exploratory: tissue-based biomarkers (eg, IHC, RNA sequencing)

McDermott. ASCO 2018. Abstr 4500.

KEYNOTE-427: Pembrolizumab Monotherapy in Frontline Advanced RCC

- Single-arm, nonrandomized phase 2 study[1]



Anticipated N = 255

Primary endpoint: ORR

1. McDermott D et al. ASCO 2018. Abstract 4500.

KEYNOTE-427: Pembrolizumab Monotherapy in Frontline Advanced RCC

At 12.1 mo follow-up (cohort A results)[1,2]

ORR
- Overall = 38%
- Favorable risk = 32%
- Intermediate/poor risk = 42%
- Response ≥6 mo = 75%

Median PFS 8.7 mo

Median OS NR

Safety
- Discontinuation due to TRAE = 11%
- 1 grade 5 treatment-related pneumonitis

At 11.1 mo follow-up (cohort B results)[3]

ORR
- Overall = 24.8% (CR = 5%; PR = 20%)
- Favorable risk = 28.3%
- Intermediate/poor risk = 23.2%

ORR by histology
- Papillary = 25.4%
- Chromophobe = 9.5%
- Unclassified nccRCC = 34.6%

Safety
- Discontinuation due to TRAE = 6%
- 2 grade 5 treatment-related deaths (pneumonitis and cardiac arrest)

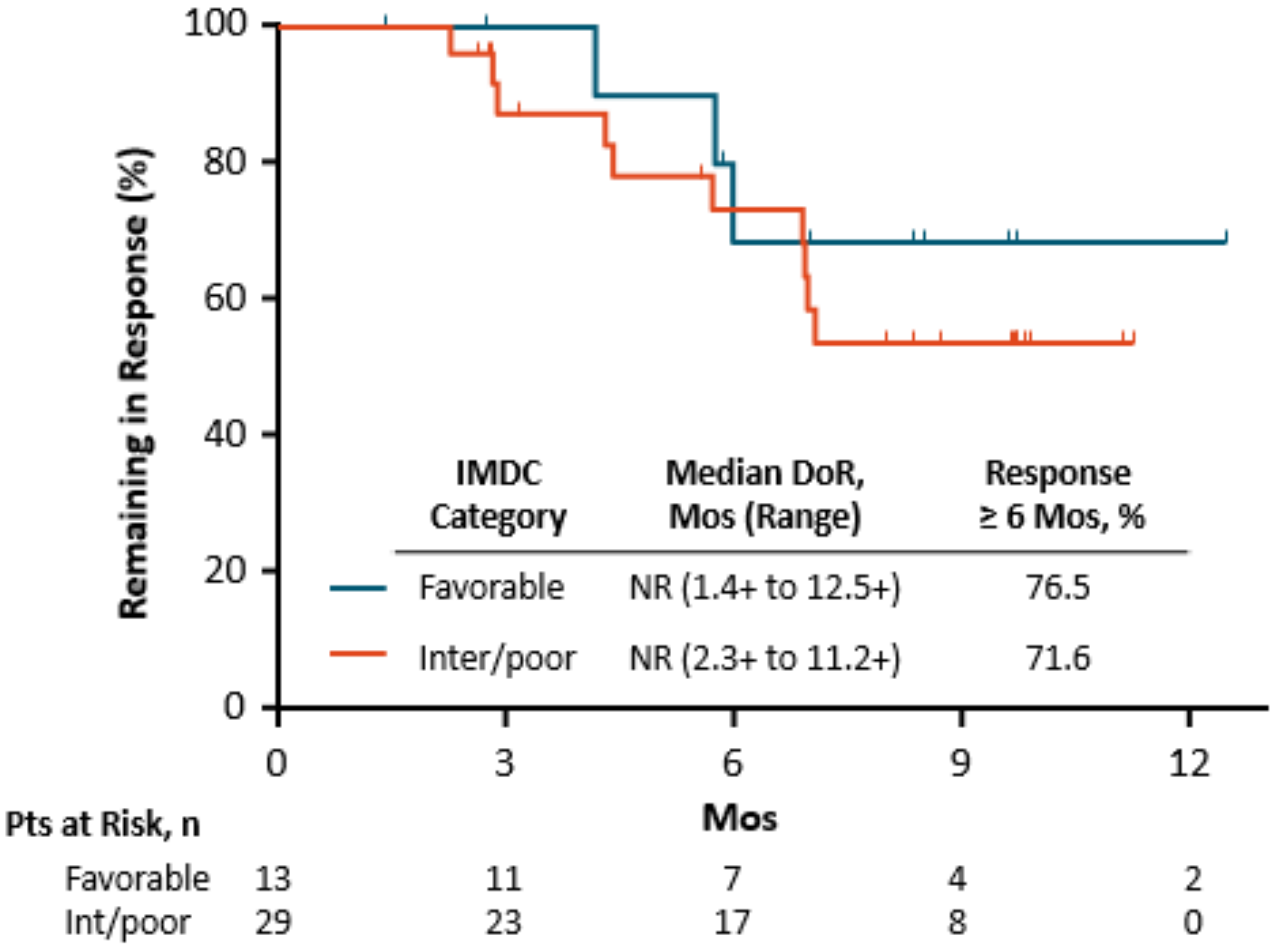
Keynote-427: Confirmed ORR by Blinded Independent Central Review

Response	Cohort A (n = 110)	
	n (%)	95% CI
ORR*	42 (38.2)	29.1-47.9
DCR (CR + PR + SD ≥ 6 mos)	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)	
Median follow-up, mos (range)	12.1 (2.5-16.8)	--

Keynote-427: ORR and Response Duration by IMDC Categories

	Favorable (n = 41)	Int/Poor (n = 69)
Confirmed ORR, % (95% CI)	31.7 (18.1-48.1)	42.0 (30.2-54.5)
DCR, % (95% CI)*	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

*DCR = CR + PR + SD ≥ 6 mos.
Database cutoff: March 12, 2018.



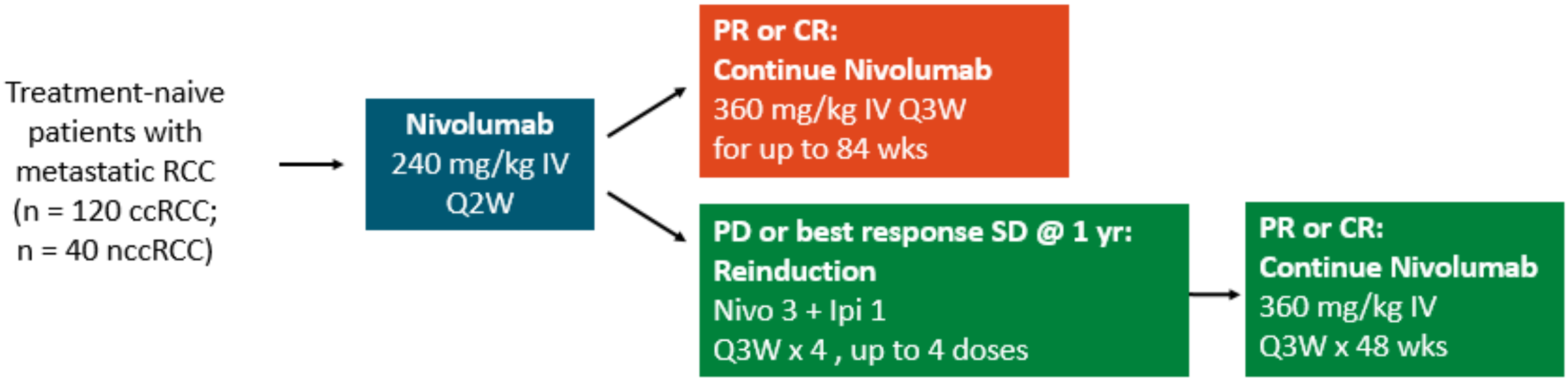
McDermott. ASCO 2018. Abstr 4500.

Keynote-427: ORR by PD-L1 Expression

	CPS ≥1 (n = 46)	CPS <1 (n = 53)	Missing (n = 11)
Confirmed ORR, % (95% CI)	**50.0 (34.9-65.1)**	**26.4 (15.3-40.3)**	**45.5 (16.7-76.6)**
DCR, % (95% CI)	**67.4 (52.0-80.5)**	**49.1 (35.1-63.2)**	**72.7 (39.0-94.0)**
Confirmed BOR, %			
CR	6.5	0	0
PR	43.5	26.4	45.5
SD	26.1	35.8	36.4
PD	23.9	34.0	18.2
NA	0	3.8	0

What About First-line Nivolumab Monotherapy?

HCRN GU16-260: Trial Schema



Extensive biomarker studies to be done in collaboration with the DFHCC Kidney Cancer SPORE Investigators
DOD Translational Partnership Grant (Atkins, Wu)

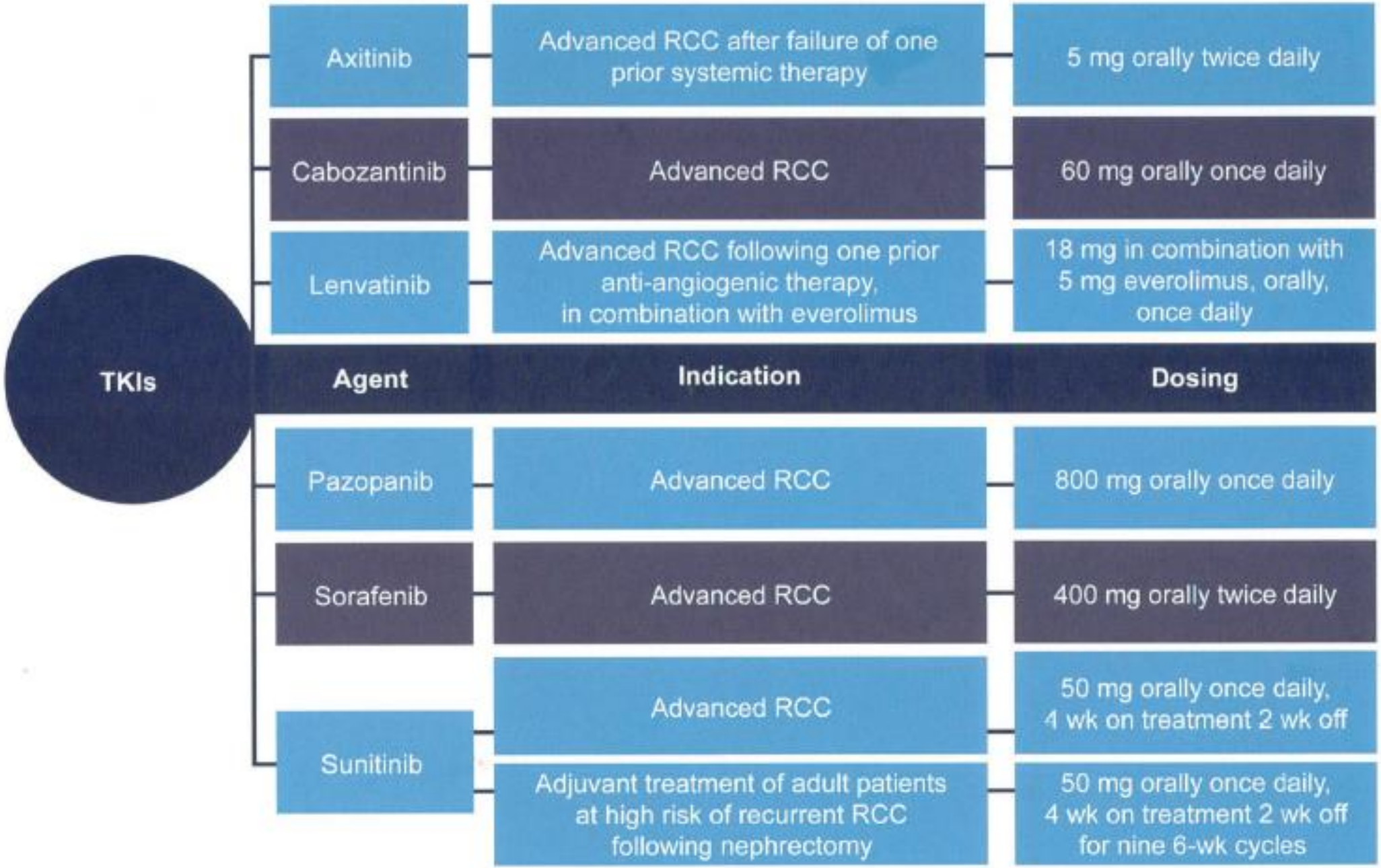
Atkins, Hammers co-leaders

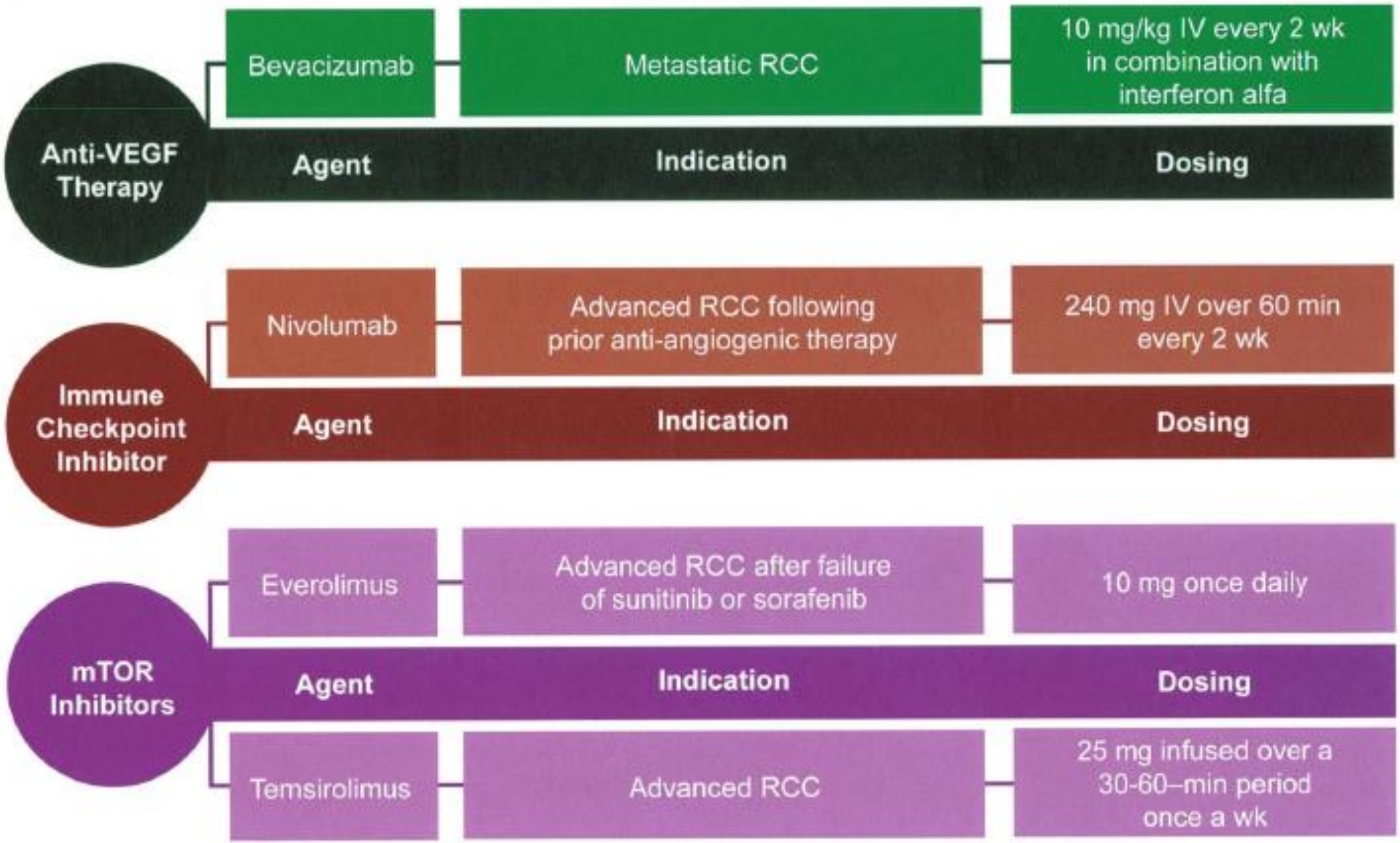
12 institutions

Drugs	Target	ORR	PFS	OS	Approval first-line treatment mRCC	Dosage
Bevacizumab (mAB)	Circulating VEGF	31% vs 13% (IFN + BV vs IFN + placebo) 25.5% vs 13% (IFN + BV vs IFN)	10.2 m vs 5.4 m, HR 0.68** (IFN + BV vs IFN + placebo) 8.5 m vs 5.2 m, HR 0.71** (IFN + BV vs IFN)	No statistically significant difference	BV + IFN (good or intermediate prognosis): FDA (Aug 2009), EMA (Nov 2007)	BV 10 mg/kg iv every 2 weeks + IFN 9 MU 3 times per week for 1 year
Sunitinib (TKI)	VEGFR 1-2-3 PDGFR, c-Kit, Fit3	39% vs 8% (SUNITINIB vs IFN)	11 m vs 5 m, HR 0.54** (SUNITINIB vs IFN)	No statistically significant difference	SUNITINIB (good or intermediate prognosis)): FDA (Jan 2006) and EMA (Feb 2007)	SUNITINIB 50 mg oral daily, 4 week ON, 2 weeks OFF
Pazopanib (TKI)	VEGFR 1-2-3 PDGFR, c-Kit.	30% vs 3% (PAZOPANIB vs placebo)	9.2 m vs 4.2 m, HR 0.46** (PAZOPANIB vs placebo)	No statistically significant difference	PAZOPANIB (good or intermediate prognosis), also in cytokine-pretreated: FDA (Feb 2007), EMA (Feb 2007)	PAZOPANIB 800 mg oral daily
Temsirolimus (mTOR inhibitor)	mTOR	8.6% vs 4.8% vs 8.1% (TEMSIROLIMUS vs IFN vs IFN + TEMSIROLIMUS)	5.5 m vs 3.1 m vs 4.7 m, (TEMSIROLIMUS vs IFN vs IFN + TEMSIROLIMUS	10.9 m vs 7.3 m vs 8.4 m(TEMSIROLIMUS vs IFN vs IFN + TEMSIROLIMUS) HR 0.73, (TEMSIROLIMUS vs IFN)	TEMSIROLIMUS (poor prognosis, non-clear cell RCC included): FDA (May 2007), EMA (Nov 2007)	TEMSIROLIMUS 25 mg iv weekly

Drugs	Target	ORR	PFS	OS	APPROVAL second-line treatment mRCC	DOSAGE
Sorafenib (TKI)	VEGFR 1-2-3, PDGFR, c-Kit, kinase Raf-1.	10% vs 2% (SORAFENIB vs placebo)	5.5 m vs 2.8 m, HR 0.44, *(SORAFENIB vs placebo)	No statistically significant difference	SORAFENIB (citokine-refractory mRCC): FDA (Dec 2005), EMA (Jul 2006)	SORAFENIB 400 mg oral twice daily
Everolimus (mTOR inhibitor)	mTOR	ORR 1.8% vs 0%, SD 63% vs 32% (EVEROLIMUS vs placebo)	PFS 4.9 m vs 1.9 m, HR 0.33** (EVEROLIMUS vs placebo)	OS no statistically significant difference	EVEROLIMUS (previously treated with VEGF targeted therapies): FDA (Mar 2009), EMA (Aug 2009)	EVEROLIMUS 10 mg oral daily
Axitinib (TKI)	VEGFR 1-2-3	ORR 19.4% vs 9.4% (AXITINIB vs SORAFENIB)	PFS 6.7 m vs 4.7 m, HR 0.67 (AXITINIB vs SORAFENIB)	No statistically significant difference	AXITINIB: FDA (Jan 2012), EMA (Sep 2007)	AXITINIB 10 mg oral twice daily
Nivolumab (mAB)	Fully human IgG4 antibody against PD1.	ORR 25% VS 5% (NIVOLUMAB vs EVEROLIMUS)	PFS 4.6 vs 4.4 mHR 0.88, 95%CI 0.75–1.03(NIVOLUMAB vs EVEROLIMUS)	OS 25 m vs 19 m, HR 0.73 p = 0.002(NIVOLUMAB vs EVEROLIMUS)	NIVOLUMAB (after progression to TKI therapy): FDA (Nov 2015)	NIVOLUMAB 3 mg/kg i.v. every 2 weeks
Cabozantinib (TKI)	MET, VEGFR2, RET	ORR 57% VS 11% (CABOZANTINIB vs EVEROLIMUS)	PFS 7.4 vs 3.9 m, HR 0·51, 95% CI 0·41-0·62	OS 21.4 vs 16.5 m, HR 0.66, 95%CI 0.53–0.83	CABOZANTINIB (after antiangiogenic therapy): FDA April 2016, EMA July 2016	CABOZANTINIB 60 mg oral daily
Lenvatinib (TKI)	VEGFR1-3, FGFR1-4, PDGFRβ, RET, KIT	ORR (LENVATINIB with EVEROLIMUS, EVEROLIMUS, LENVATINIB alone)	PFS 14.6 vs 5.5 vs 7.4 HR 0.4; 95%CI 0.24–0.68; 0.66; 95%CI 0.3–1.1 (LENVATINIB with EVEROLIMUS, EVEROLIMUS, LENVATINIB alone)	OS no statistically significant difference	LENVATINIB with EVEROLIMUS (after antiangiogenic therapy): FDA March 2016, EMA July 2016 under conditional approval	LENVATINIB: 18 mg oral daily with EVEROLIMUS 5 mg oral daily

Indications and Recommended Therapeutic Dosing of Approved Agents in Advanced/Metastatic RCC[1-10]




Anti-VEGF Therapy
Agent
Indication
Dosing
Bevacizumab
Metastatic RCC
10 mg/kg IV every 2 wk in combination with interferon alfa
Immune Checkpoint Inhibitor
Agent
Indication
Dosing
Nivolumab
Advanced RCC following prior anti-angiogenic therapy
240 mg IV over 60 min every 2 wk
mTOR Inhibitors
Agent
Indication
Dosing
Everolimus
Advanced RCC after failure of sunitinib or sorafenib
10 mg once daily
Temsirolimus
Advanced RCC
25 mg infused over a 30-60–min period once a wk

COMBINATION THERAPIES

Combinations of Immunotherapy and Targeted Therapy

Combination targeted therapy and immune checkpoint inhibitor

COMBINATION TARGETED THERAPY AND IMMUNE CHECKPOINT INHIBITOR

Rationale to combination:

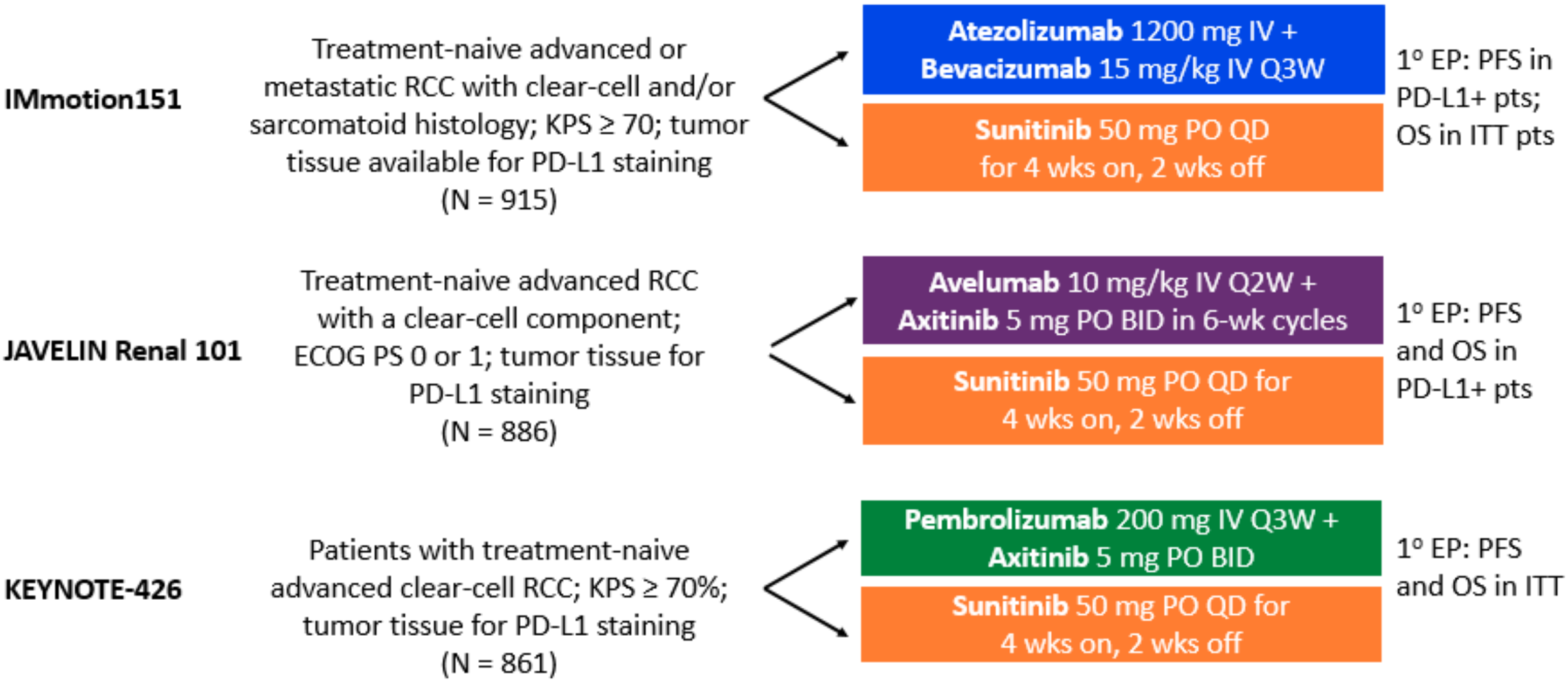
- Two drugs = better than one
- Combination takes the challenge out of choosing TKI vs IO
- TKI exposes immune system to expanded array of neoantigen

COMBINATION TARGETED THERAPY AND IMMUNE CHECKPOINT INHIBITOR

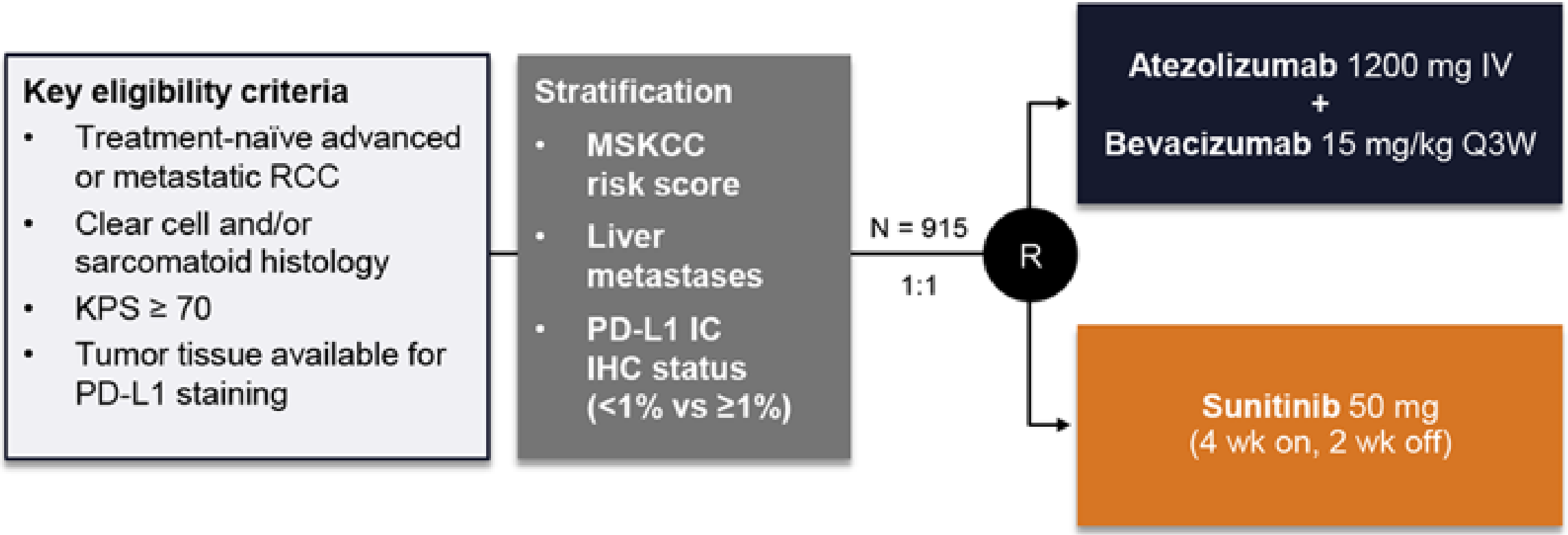
Rationale to avoid combination:

- Burns two bridges (two of potentially best tools)
- Increased toxicity

Randomized Phase III Study Designs for Combination Tx



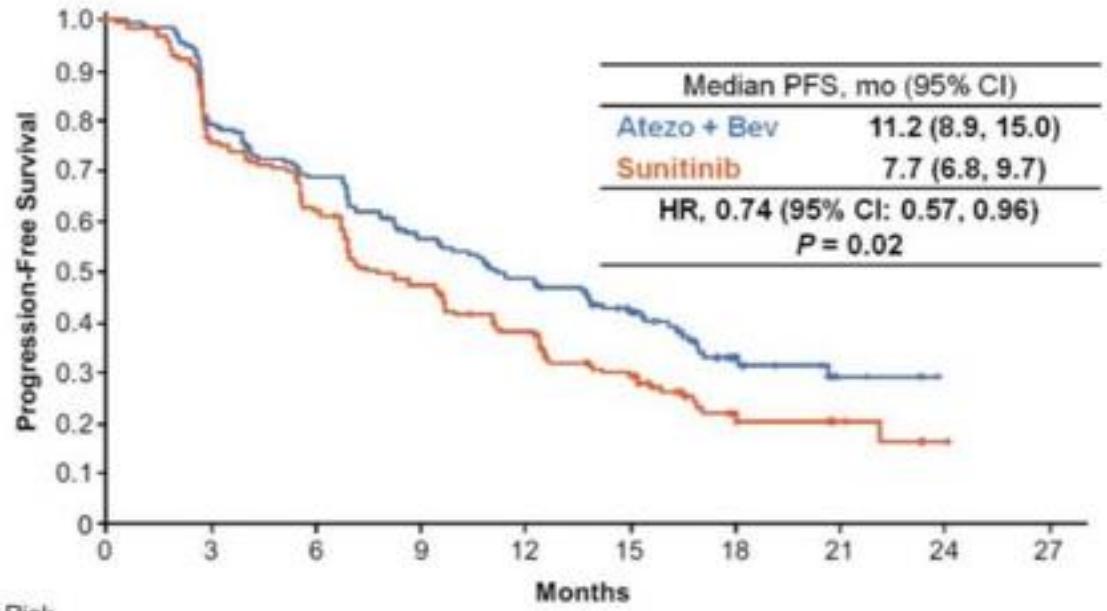
Phase 3 IMmotion151 Trial Design



- **Co-primary endpoints**: Investigator-assessed PFS in patients with PD-L1 expression ≥1 and OS in ITT population

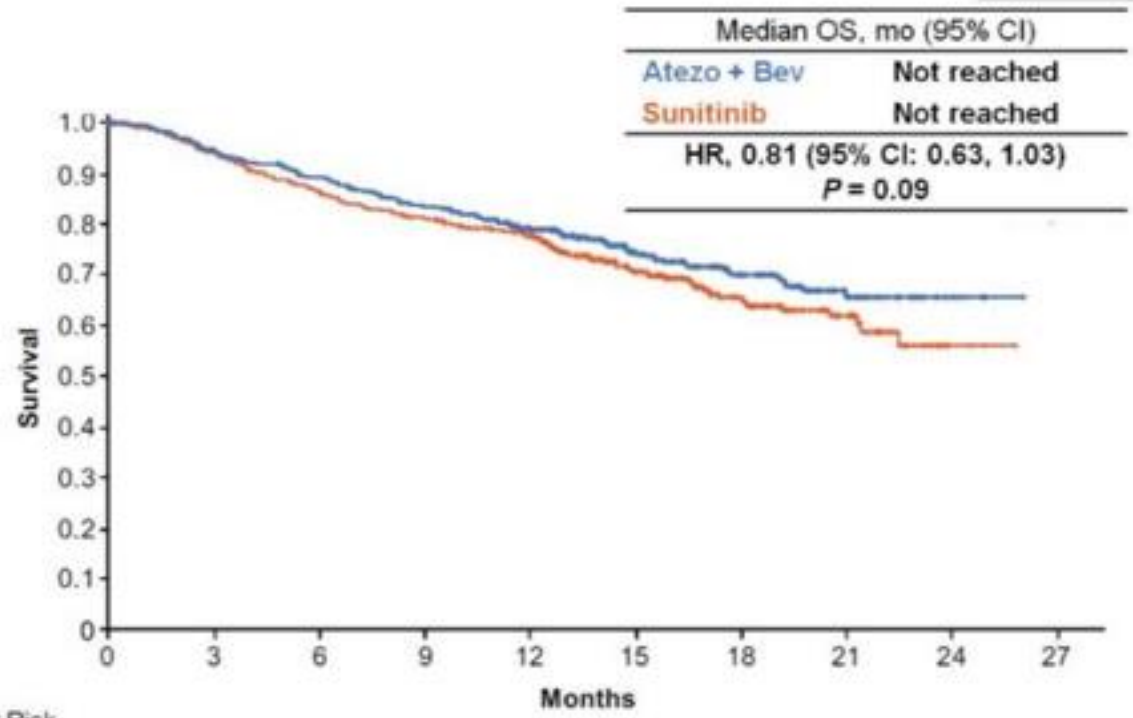
IMmotion151: Atezolizumab + Bevacizumab in Treatment-Naive Advanced RCC

PFS in PD-L1+ Cohort



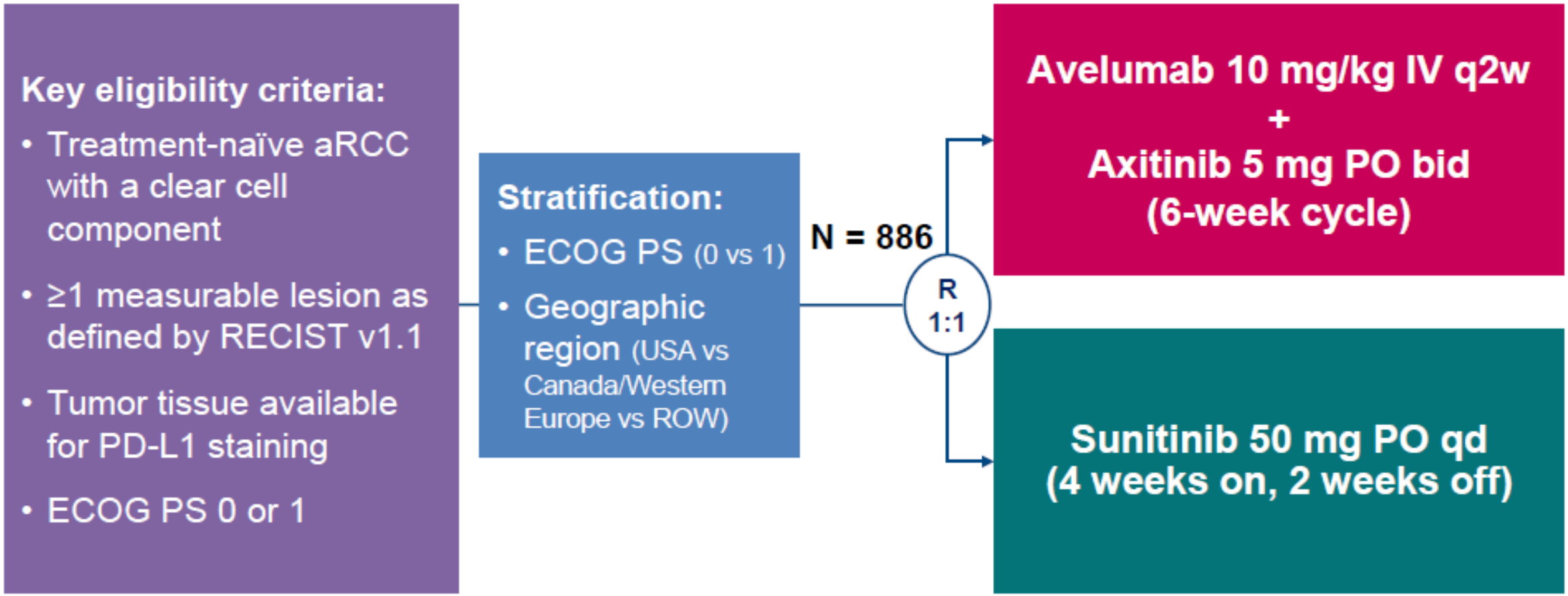
No. at Risk									
Atezo + Bev	178	137	117	94	79	55	22	5	
Sunitinib	184	135	110	83	64	44	15	7	1

OS in ITT Cohort



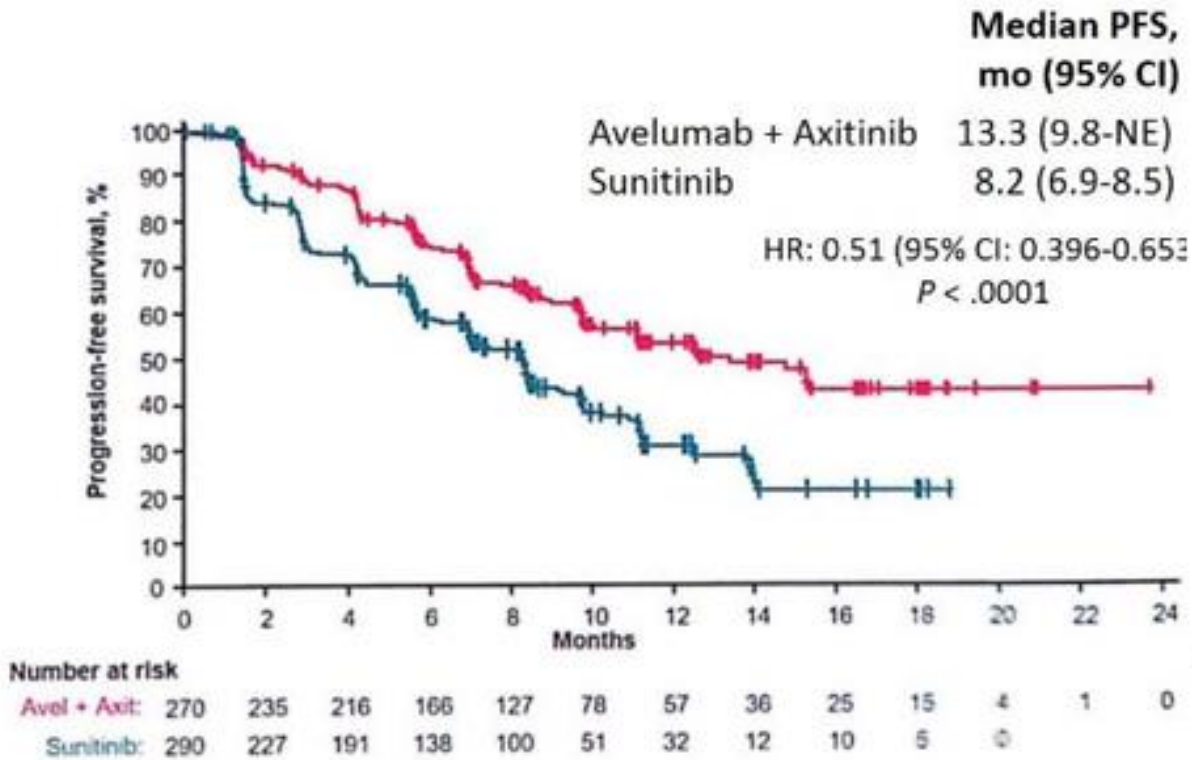
No. at Risk									
Atezo + Bev	454	428	398	371	341	246	141	69	18
Sunitinib	461	422	384	357	331	227	126	65	15

JAVELIN Renal 101: Study Design

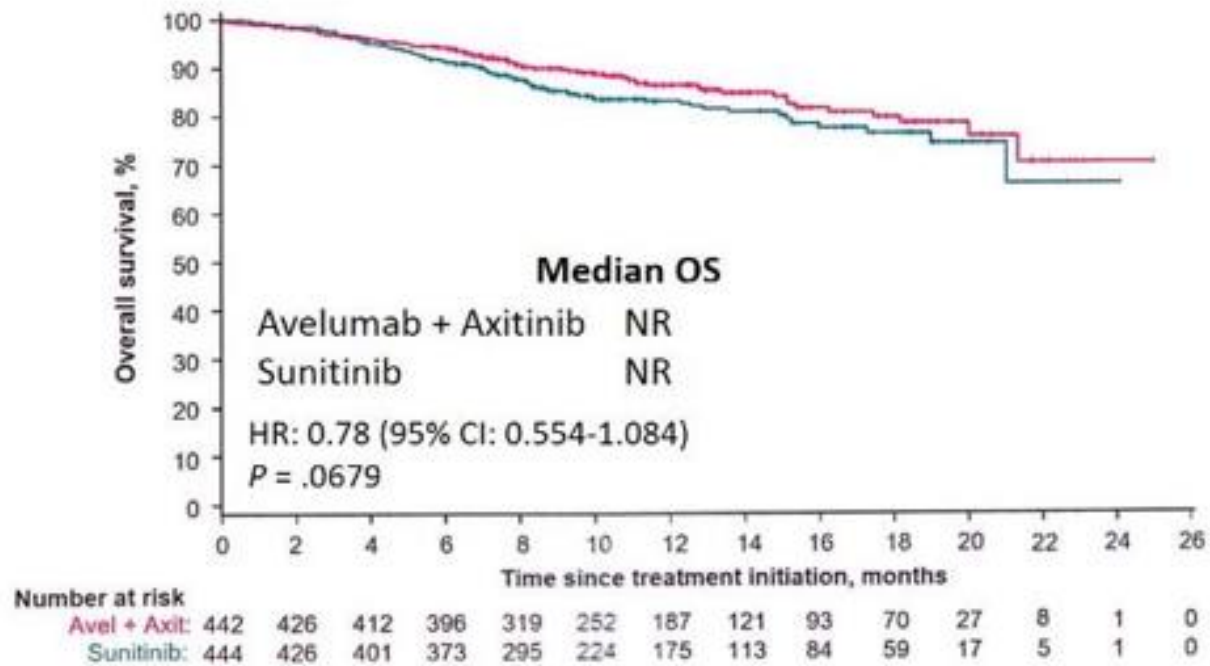


JAVELIN Renal 101: Avelumab + Axitinib in Treatment-Naive Advanced RCC

PFS in PD-L1+ Cohort



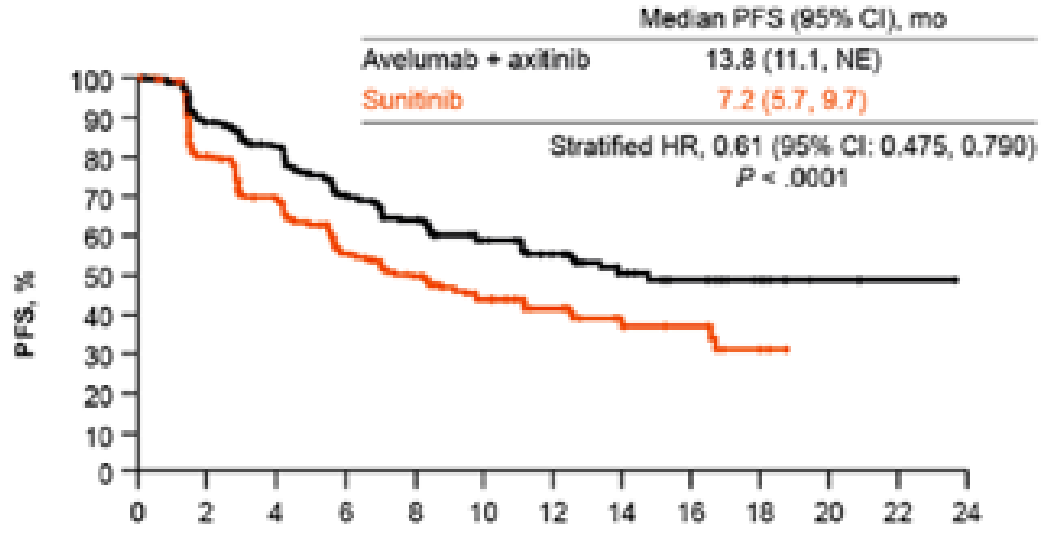
OS in ITT Cohort (Data Immature)



Phase 3 JAVELIN Renal 101: PFS Outcome

Primary Endpoint[a]

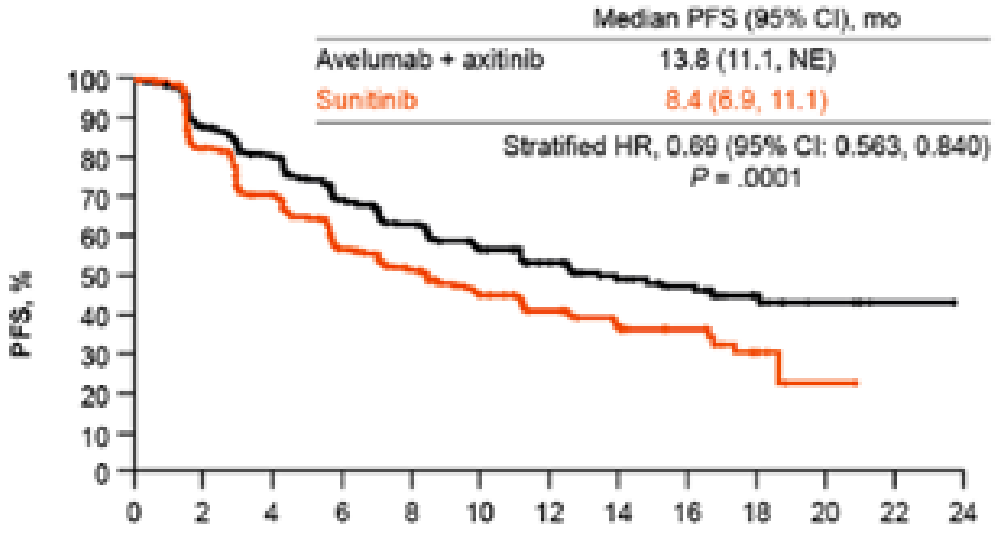
PFS per IRC in the PD-L1+ Group



No. at Risk													
Avelumab + axitinib	270	227	205	154	120	76	53	32	23	13	3	1	0
Sunitinib	290	210	174	119	85	49	35	16	13	5	0		

Secondary Endpoint[b]

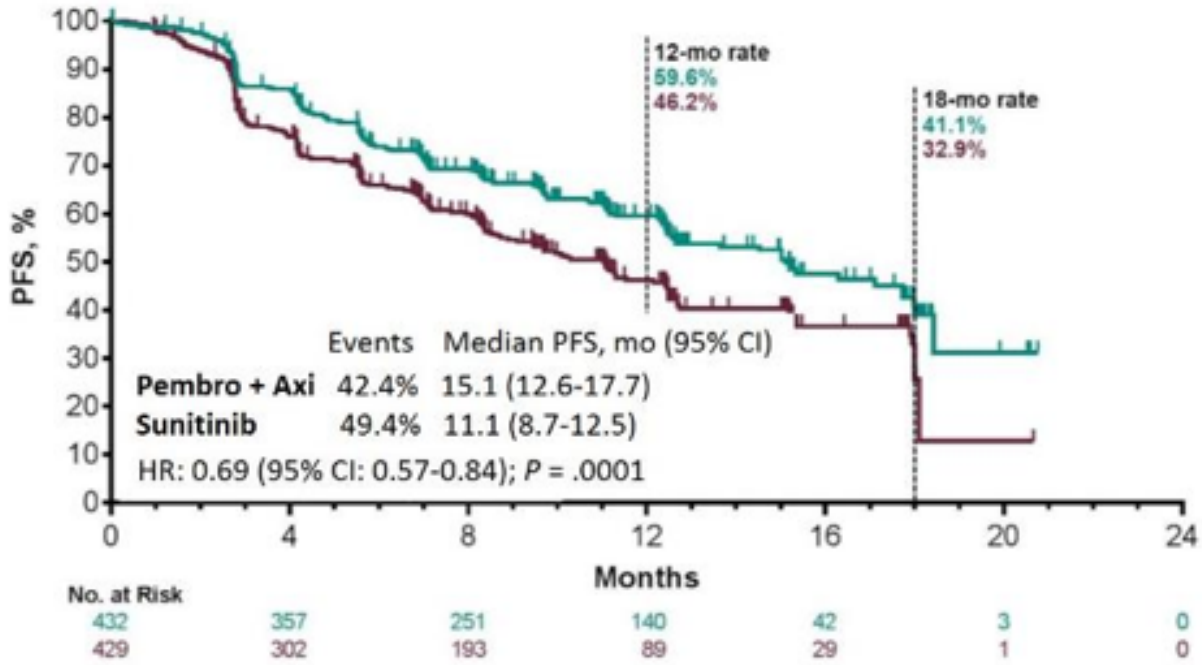
PFS per IRC in the Overall Population



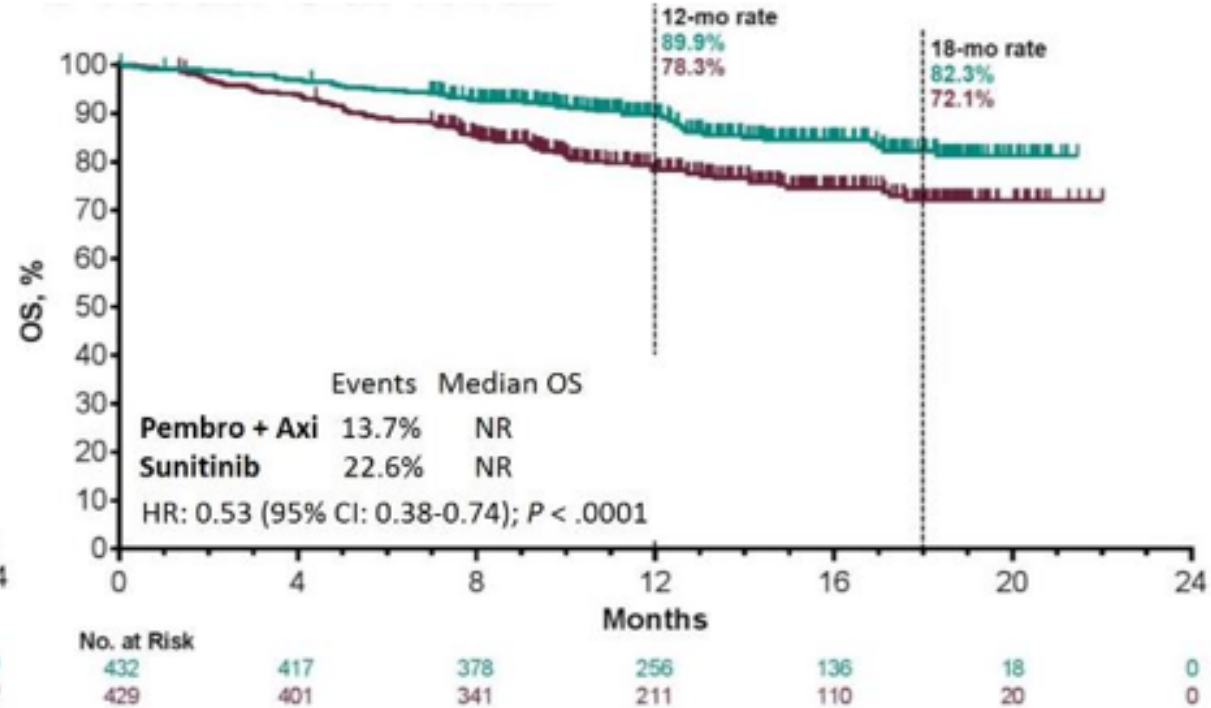
No. at Risk													
Avelumab + axitinib	442	384	321	250	193	127	94	57	42	24	8	1	0
Sunitinib	444	329	271	192	144	90	64	29	20	8	2	0	

KEYNOTE-426: Pembrolizumab + Axitinib in Treatment-Naive Advanced RCC

PFS in ITT Population



OS in ITT Population



UPDATED AT ASCO GU 2019.

Phase III IO-Based Combinations in RCC

Control	Comparator(s)	PFS (HR)	OS (HR)
Sunitinib	Nivolumab/ipilimumab	No* (0.98)	Yes (0.68)
Sunitinib	Bevacizumab + atezolizumab	Yes (0.83)	No (0.81)
Sunitinib	Axitinib + avelumab	Yes (0.69)	No (0.78)
Sunitinib	Axitinib + pembrolizumab	Yes (0.69)	Yes (0.53)
Sunitinib	Lenvatinib + everolimus *vs* lenvatinib/pembro	Pending	Pending
Sunitinib	Cabozantinib/nivolumab	Pending	Pending

Remission Rates for Major Regimens in mRCC

Regimen	Study	Efficacy Population	IRC-Assessed CR Rate	CR Rate in Selected Patients	PR Rate	Remission Rate
Nivolumab + ipilimumab	CheckMate 214	IMDC intermediate/poor risk	9.0%	PD-L1 ≥ 1%: 16% Sarcomatoid: 18%	32%	?
Atezolizumab + bevacizumab	IMmotion151	ITT	5.0%	PD-L1 ≥ 1%: 9%	31%	?
Avelumab + axitinib	JAVELIN Renal 101	ITT	3.0%	PD-L1+: 4%	48%	?
Pembrolizumab + axitinib	Phase I	All patients	7.7%	--	65.4%	?
Pembrolizumab monotherapy	KEYNOTE-427	Cohort A (ccRCC)	2.7%	PD-L1 CPS ≥ 1: 6.5%	35.5%	?
TKIs			< 5%	?	30% to 40%	~ 0

Control Disease Rates for Major Regimens in mRCC

Regimen	Study	Median PFS, Mos	Primary PD Rate, %
Nivolumab + ipilimumab	CheckMate 214 (intermediate/poor risk)	11.6	20
Atezolizumab + bevacizumab	IMmotion151 (ITT)	11.2	18
Axitinib + avelumab	JAVELIN Renal 101 (ITT)	13.8	12
Axitinib + pembrolizumab	KEYNOTE-426 (ITT)	15.1	pending
Pembrolizumab monotherapy	KEYNOTE-427	8.7	28.2
TKIs		9-12	20

First-Line Phase 3 Combinations of Anti-VEGF Agents and Immunotherapy in Advanced RCC

Experimental Arm	Primary Endpoint	Trial	ClinicalTrials.gov ID
Bevacizumab + atezolizumab	PFS and OS in PD-L1–detectable tumors	IMmotion151	NCT02420821
Axitinib + avelumab	PFS	JAVELIN Renal 101	NCT02684006
Axitinib + pembrolizumab	PFS and OS	KEYNOTE-426	NCT02853331
Nivolumab + cabozantinib	PFS in intermediate/ poor-risk patients	CheckMate 9ER	NCT03141177
Lenvatinib-pembrolizumab or lenvatinib-everolimus	PFS	CLEAR	NCT02811861

Study 111: Phase 1b/2 Trial of Lenvatinib + Pembrolizumab (RCC Cohort)

Follow-up: 9.7 mo

	ORR	Median DOR
Overall, N = 30	63%[a,b]	NR
Treatment naïve, n = 12	83%	NR
Pretreated, n = 18	50%	8.5 mo
PD-L1 negative, n = 14	71%	NR
PD-L1 positive, n = 12	58%	10.3 mo

- The most common any-grade treatment-emergent adverse events were diarrhea, fatigue, hypothyroidism, stomatitis, nausea, and hypertension

Phase 1b Cabozantinib + Atezolizumab in Urologic Cancers: Study Design

Dose-Escalation Phase

Advanced or metastatic RCC (CC, NCC) or UC

Dose level 1
Cabozantinib 40 mg QD PO + **atezolizumab** 1200 mg IV Q3W

All cohorts size, n = 30

Dose level 2
Cabozantinib 60 mg QD PO + **atezolizumab** 1200 mg IV Q3W

Dose level (-)1
Cabozantinib 20 mg QD PO + **atezolizumab** 1200 mg IV Q3W

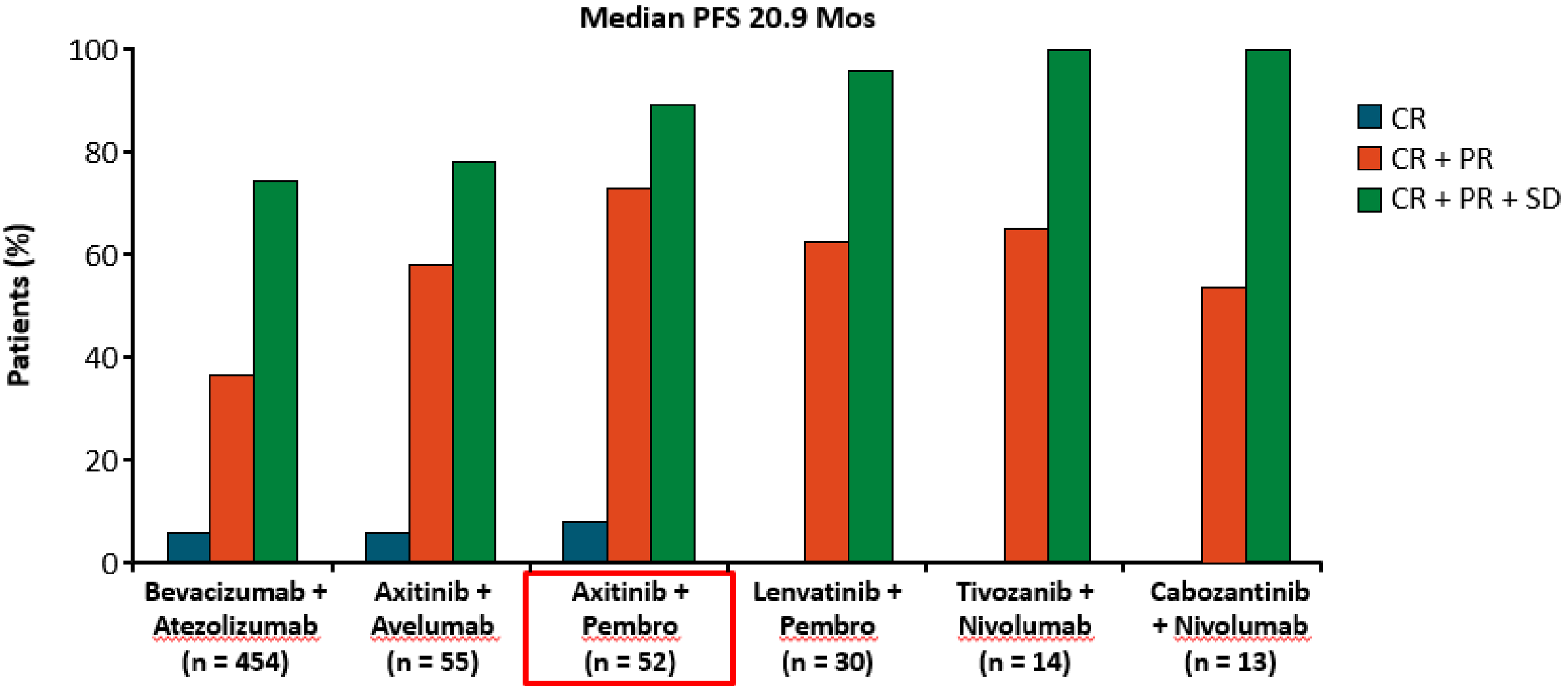
Primary endpoint: Investigator-assessed ORR

Expansion Cohorts

Cohort	Tumor Type (Histology)	Abbreviated Eligibility Description
1	RCC (clear cell)	No prior systemic anticancer therapy
2	UC (transitional cell)	Prior platinum-containing chemotherapy
3	UC (transitional cell)	Cisplatin-ineligible but no prior systemic anticancer therapy
4	UC (transitional cell)	Cisplatin-eligible but no prior systemic anticancer therapy
5	UC (transitional cell)	Prior immune checkpoint inhibitor therapy
6	CRPC (adeno)	Prior enzalutamide and/or abiraterone therapy
7	NSCLC (nonsquamous)	Prior immune checkpoint inhibitor therapy
8	NSCLC (nonsquamous)	No prior checkpoint inhibitor therapy

Cabozantinib + atezolizumab in treatment-naïve advanced RCC (COSMIC-021)[2]
N = 12;
ORR = 80%
(1 CR/7 PRs)

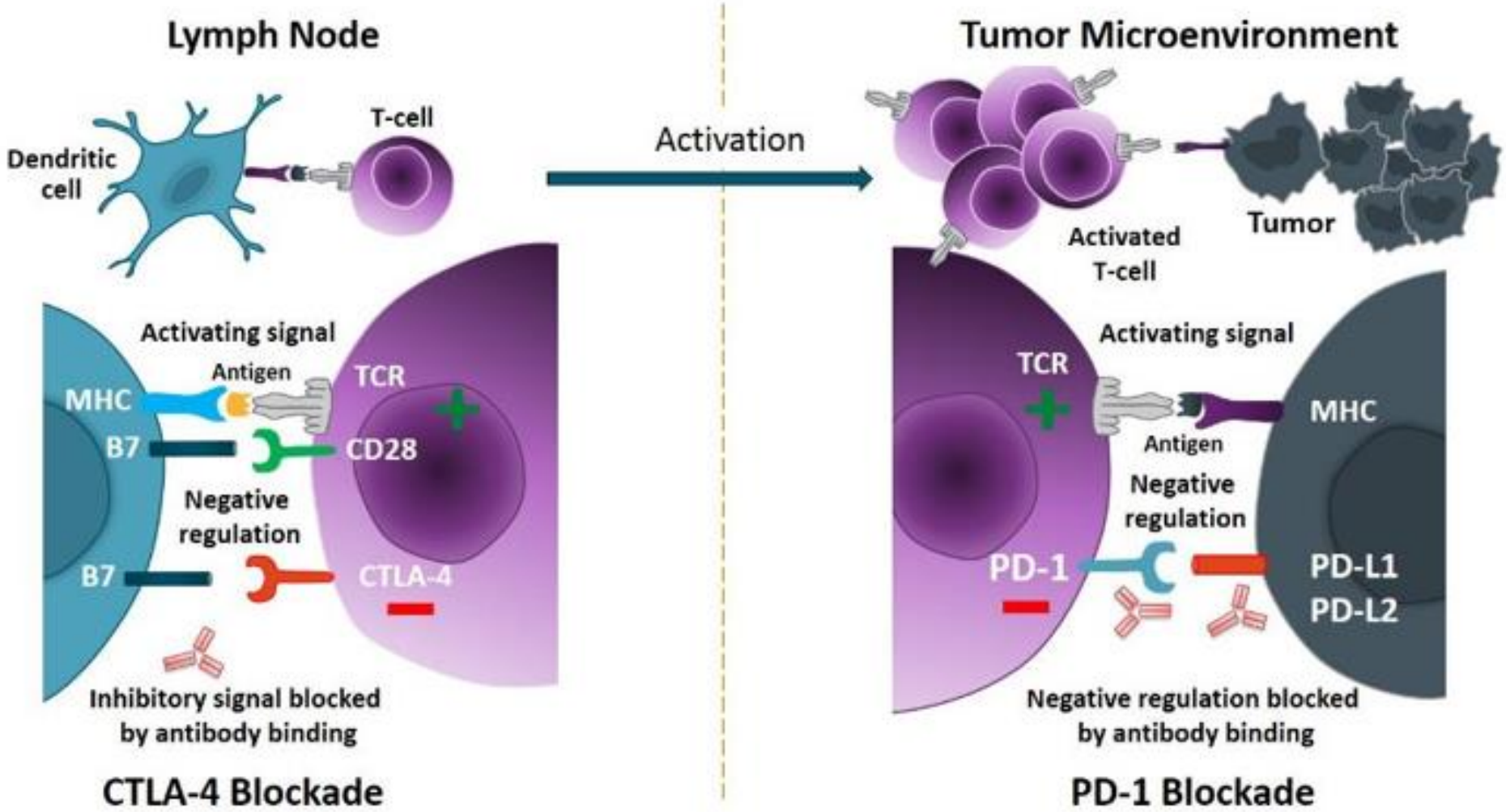
The Explosion of Anti-VEGF + CPI Trials



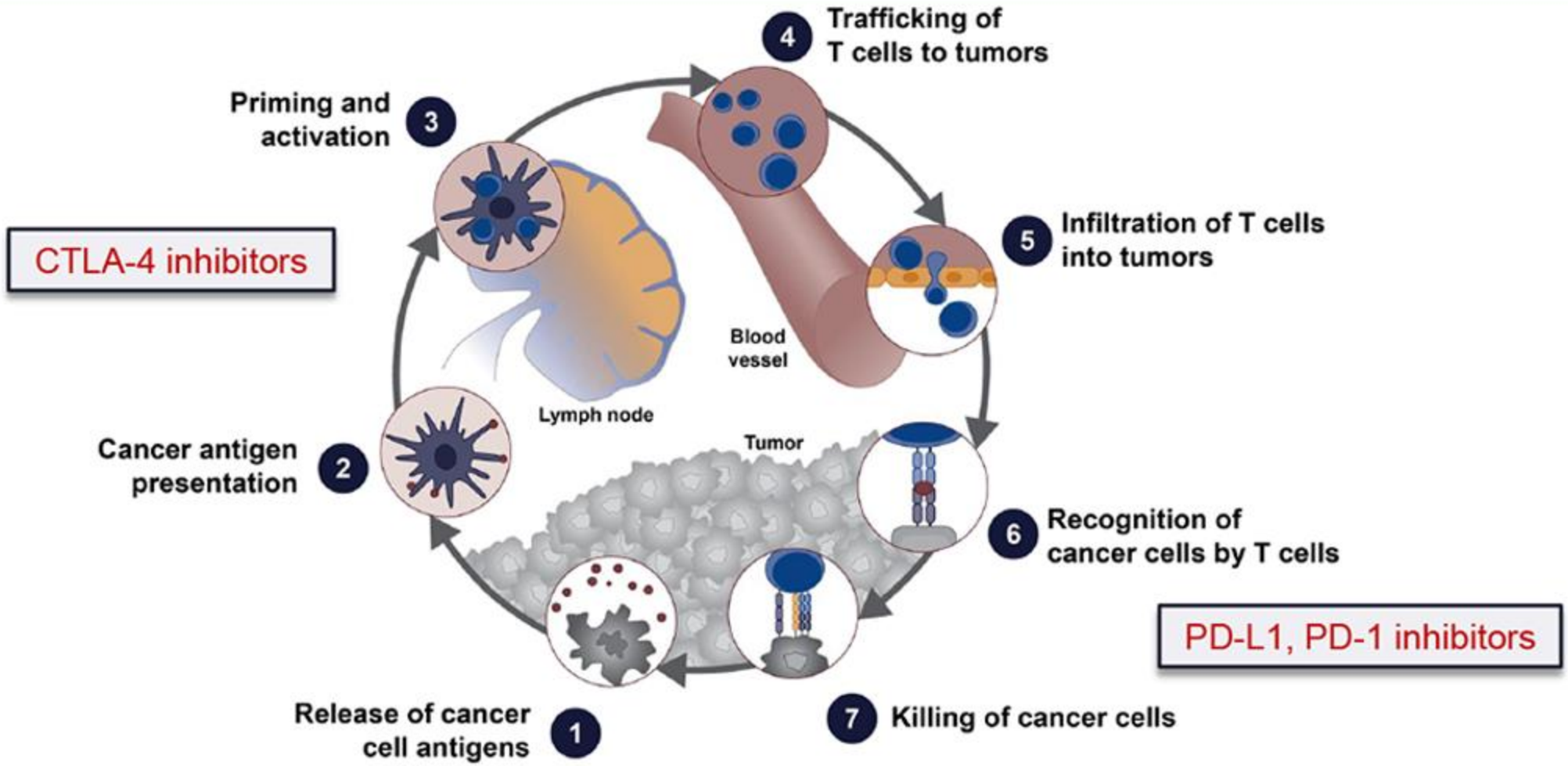
COMBINATION THERAPIES

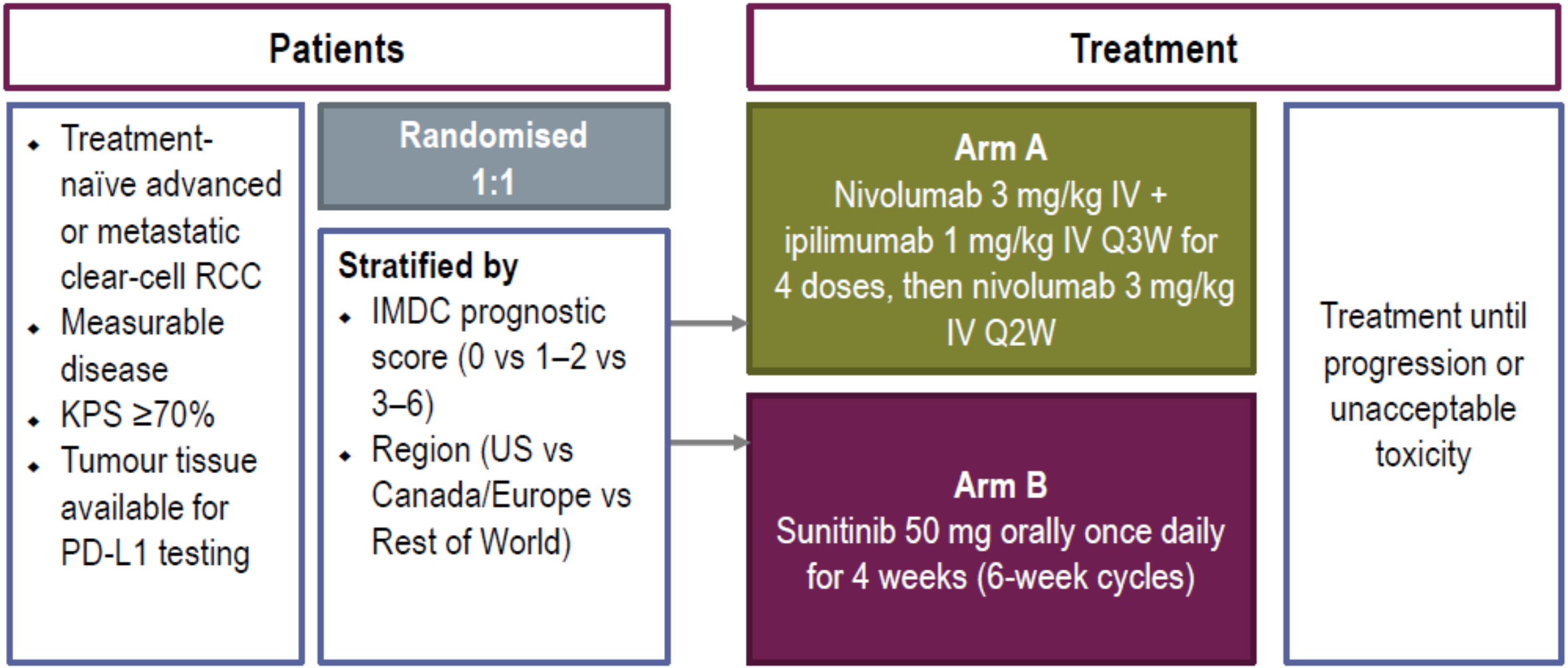
Combination of immune checkpoint inhibitors

Biologic Rationale for Combined PD-1 and CTLA-4 Blockade



Is CTLA-4 Blockade Synergistic With Anti–PD-1?[1]





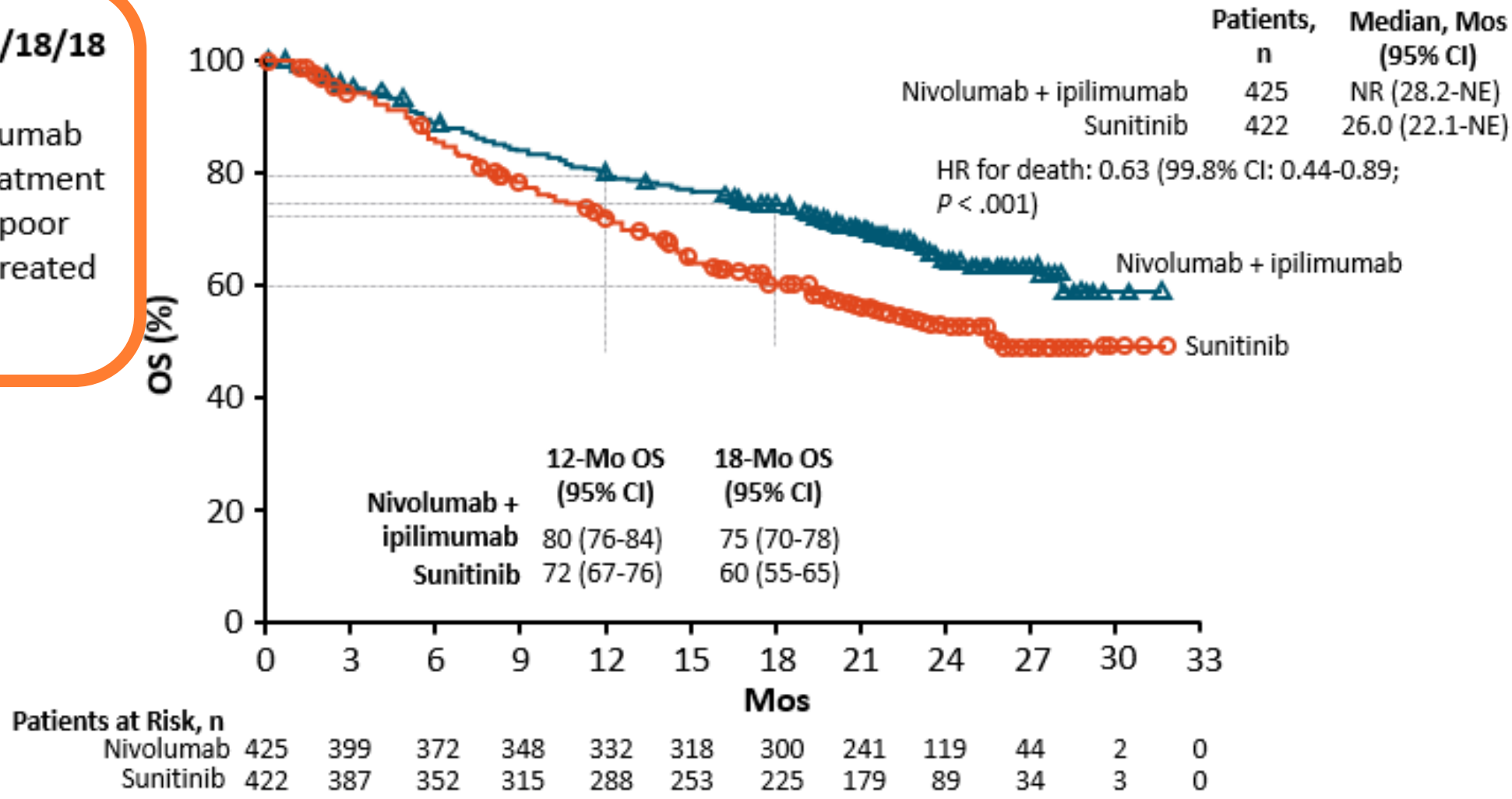
IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; Q2W, every 2 weeks; QW3, every 3 weeks.

Escudier B, *et al.*, Ann Oncol 2017;28(suppl_5): abstr. LBA5.

CheckMate 214: OS in IMDC Intermediate-/Poor-Risk Patients

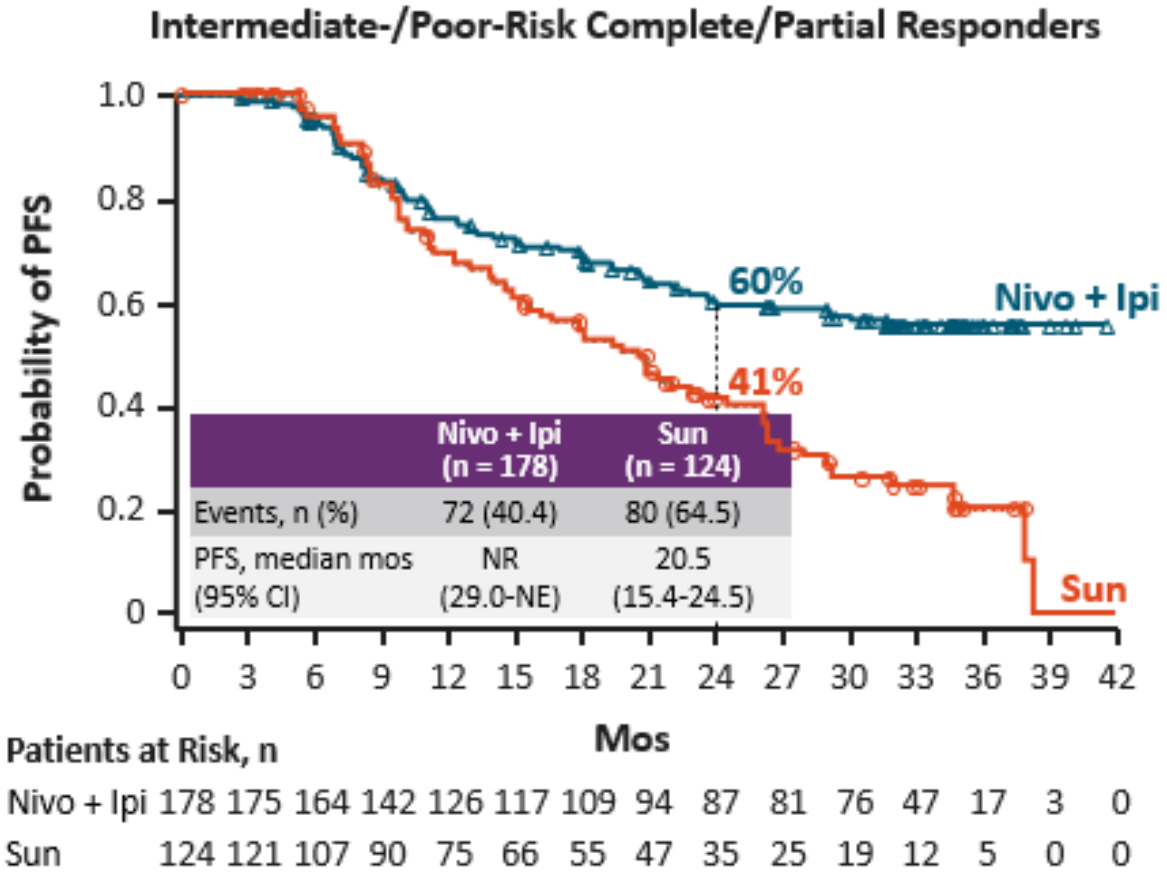
FDA Approval on 4/18/18

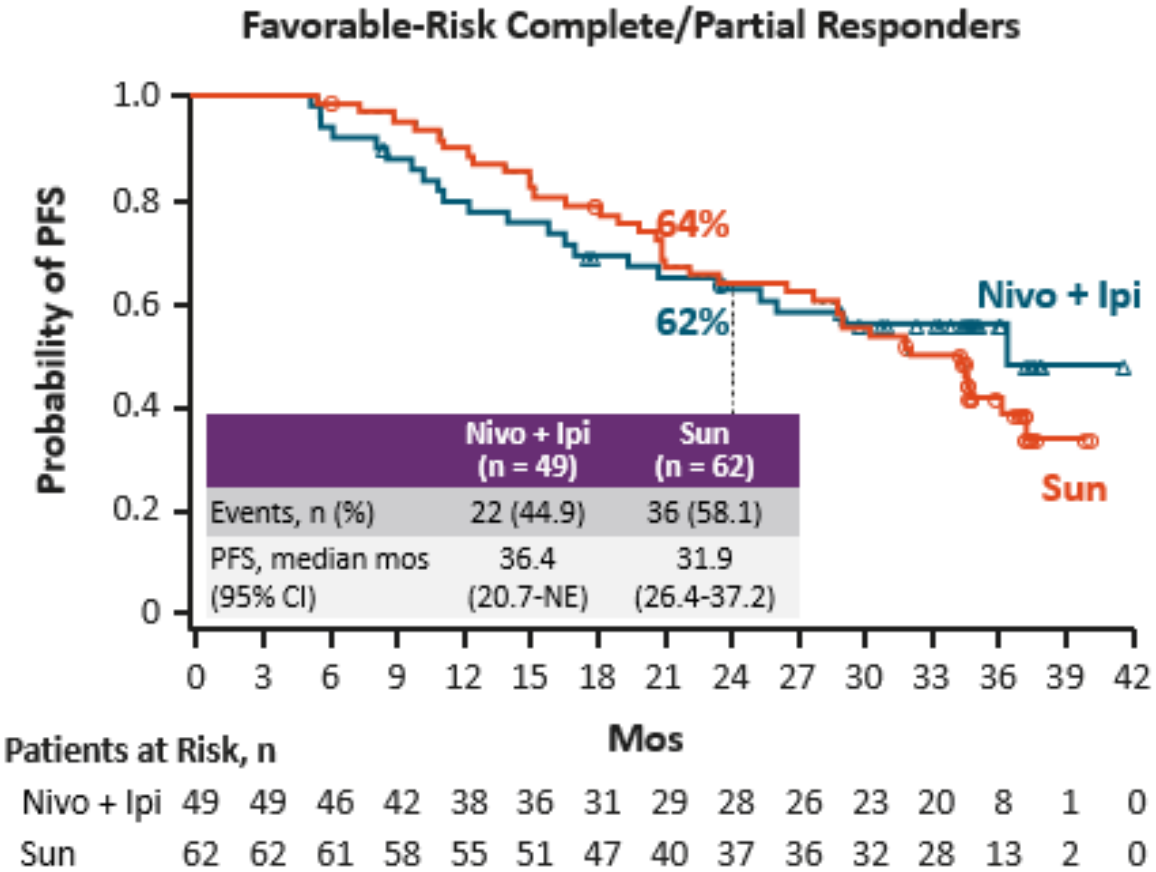
Nivolumab + ipilimumab as combination treatment of intermediate or poor risk, previously untreated RCC



Motzer. NEJM. 2018;378:1277.

CheckMate 214: Investigator-Assessed PFS in Responders





CheckMate 214: Updated Response Data at 30 Mos Minimum Follow-up

Best Overall Response According to RECIST v1.1 per Investigator	Intermediate/Poor Risk		Favorable Risk	
	Nivo + Ipi (n = 425)	Sun (n = 422)	Nivo + Ipi (n = 125)	Sun (n = 124)
ORR, % (95% CI)	41.9 (37.1-46.7)	29.4 (25.1-34.0)	39.2 (30.6-48.3)	50.0 (40.9-59.1)
P value	.0001		.1436	
Best Response, %				
CR	11.3	1.2	8.0	4.0
PR	30.6	28.2	31.2	46.0
Stable disease	25.9	41.2	44.0	38.7
Progressive disease	24.9	19.0	12.0	4.8
Unable to determine	7.3	10.4	4.8	6.5

Rini. ESMO 2018. Abstr 875P.

CheckMate 214: Nivolumab + Ipilimumab ***Inferior*** to Sunitinib in IMDC Favorable Risk[1]

Outcome	N = 249[a]	
	NIVO + IPI n = 125	Sunitinib n = 124
Confirmed ORR, % (95% CI)	29 (21-38)	52 (43-61)
	P < .001	
CR, %	11	6
PFS, median (95% CI), mo	15.3 (9.7-20.3)	25.1 (20.9-NE)
	HR (99.1% CI): 2.18 (1.29-3.68) *P* < .001	
OS, median (95% CI), mo	NR (NE-NE)	32.9 (NE-NE)
	HR (99.8% CI): 1.45 (0.51-4.12) *P* = .27	
12-mo OS rate, % (95% CI)	94 (87-97)	96 (90-98)
18-mo OS rate, % (95% CI)	88 (80-92)	93 (87-97)

HR-QoL: Significant differences in patient-reported outcomes through 2 years of follow-up[2]

[a] 11% of patients in both arms had tumor PD-L1 expression ≥1%.

1. Motzer RJ et al. *N Engl J Med*. 2018;378:1277-1290. 2. Cella D et al. ASCO 2018. Abstract 3703.

CheckMate 214: Treatment-Related Adverse Events[1] (Cont'd)

Event, %	NIVO + IPI n = 547		Sunitinib n = 535	
	Any Grade	Grades 3/4	Any Grade	Grades 3/4[a]
TRAEs in ≥15% of patients	93	46	97	63
Fatigue	37	4	49	9
Pruritus	28	<1	9	0
Diarrhea	27	4	52	5
Nausea	20	1	38	1
Hypertension	2	<1	40	16
Mucosal inflammation	2	0	28	3
PPE syndrome	<1	0	43	9
TRAEs leading to discontinuation, %	22	15	12	7
Treatment-related deaths	n = 8[b]		n = 4[c]	

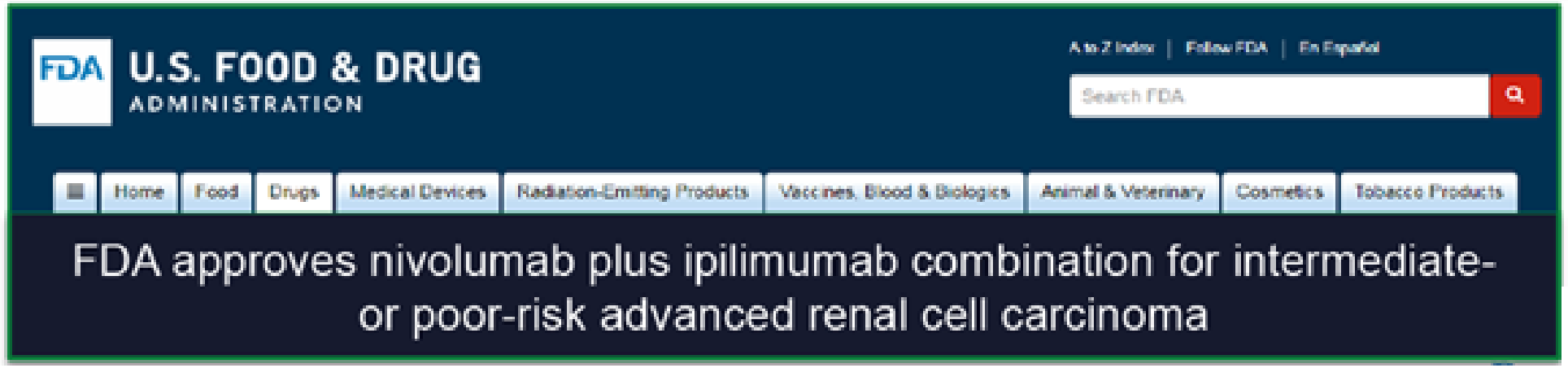
60% of patients treated with nivolumab + ipilimumab required systemic corticosteroids for an adverse event

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab Plus Ipilimumab Versus Sunitinib in Advanced Renal Cell Carcinoma

Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B; CheckMate 214 Investigators.



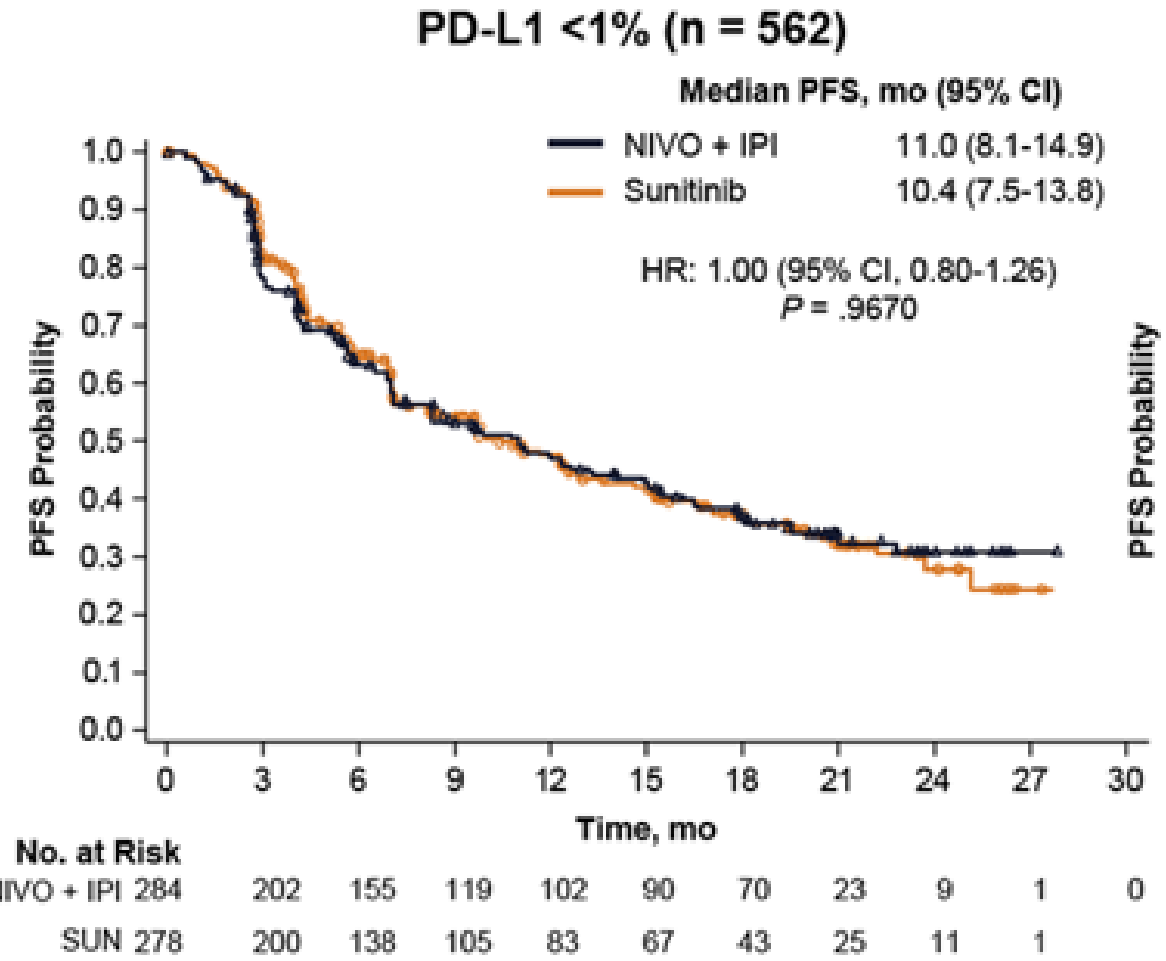
Combining Immune Checkpoint Inhibitors: Questions That Remain…

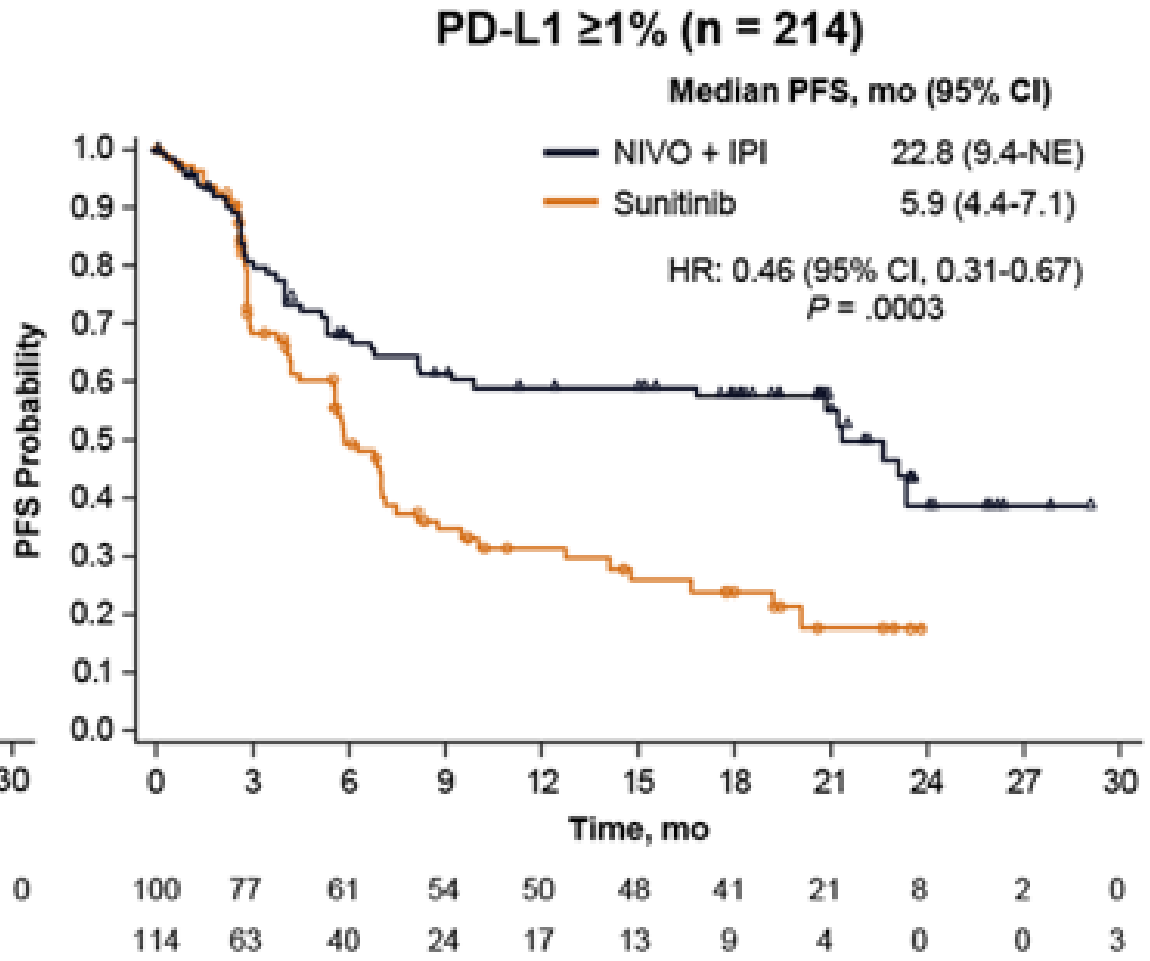
Is the toxicity of nivolumab/ipilimumab a barrier to therapy?

Is nivolumab/ipilimumab appropriate for good-risk patients?

Might PD-L1 be a useful biomarker for selecting patients?

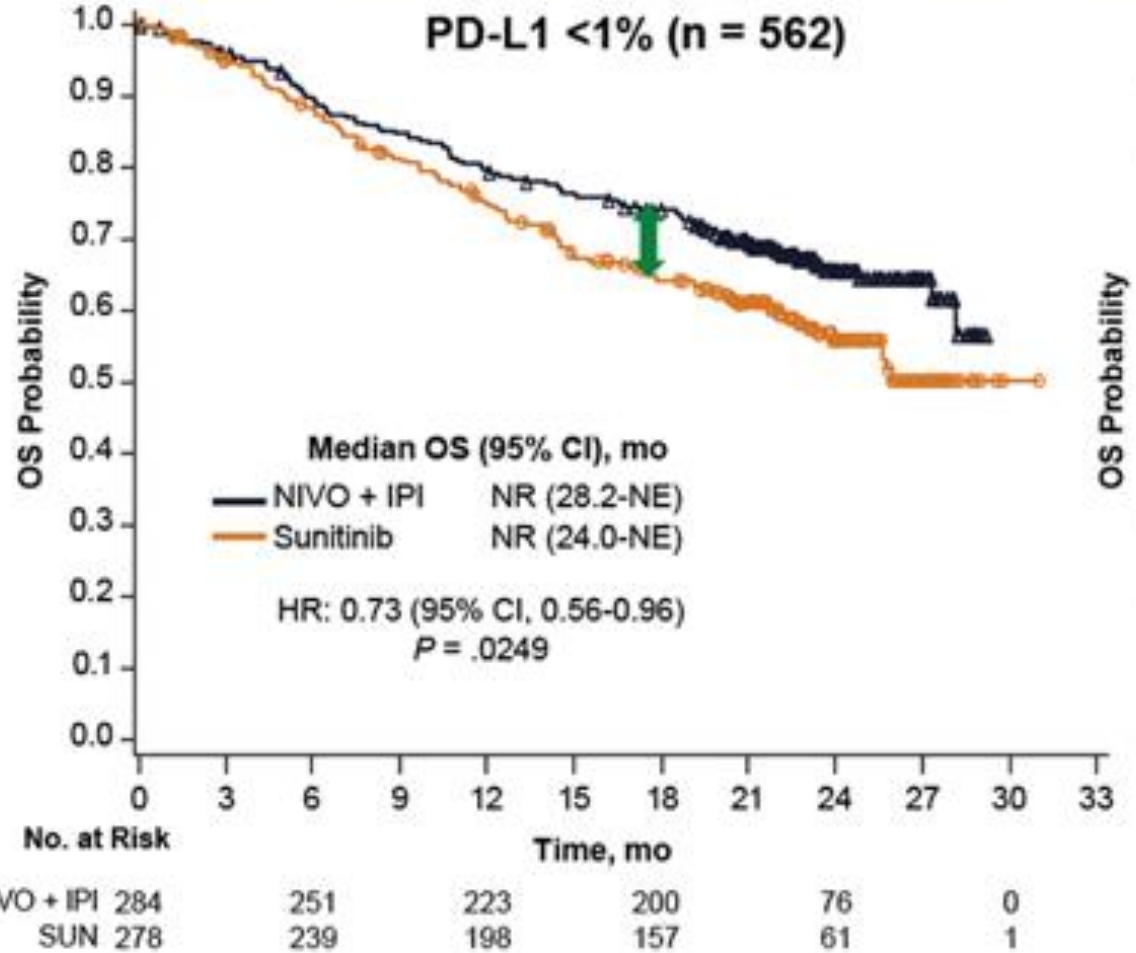
CheckMate 214: PFS by PD-L1 Expression
IMDC Intermediate-/Poor-Risk Patients

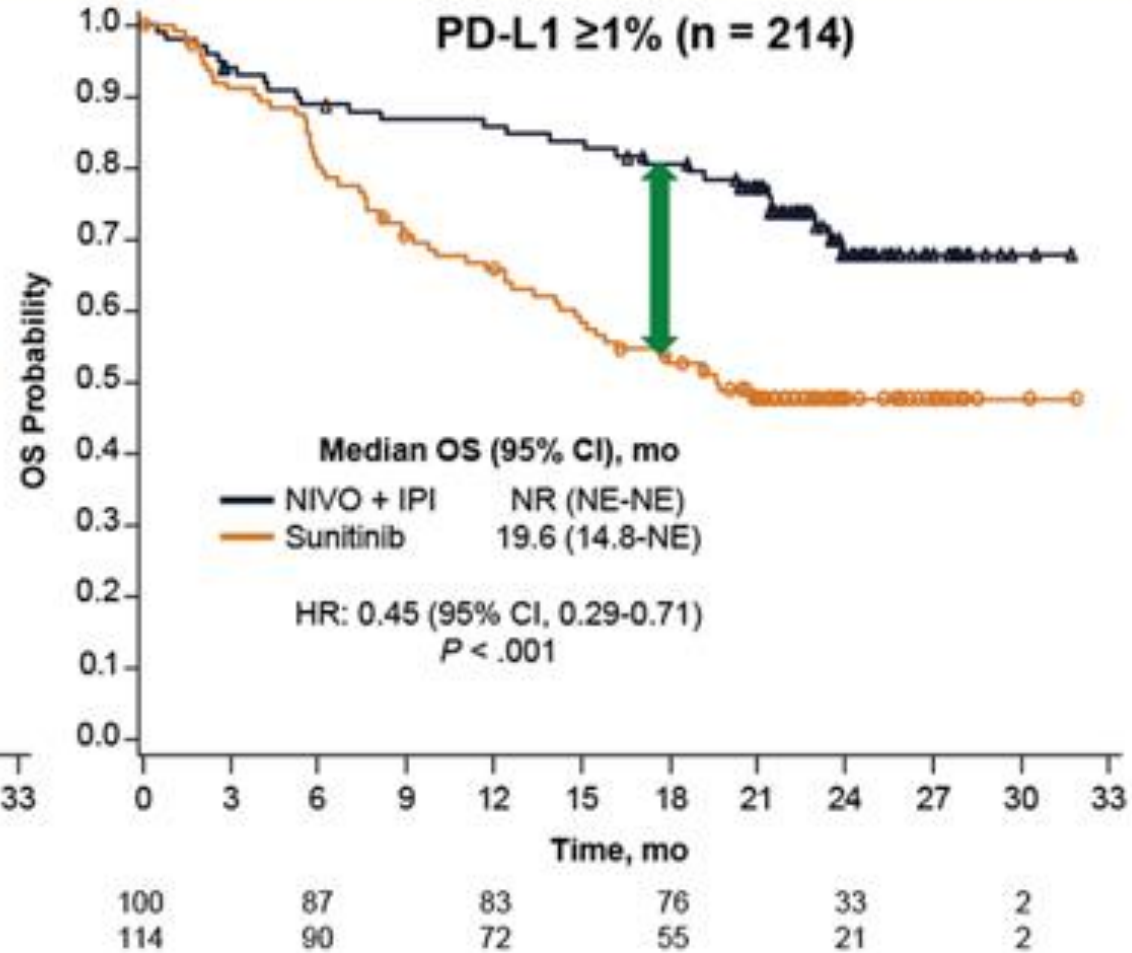




1. Motzer RJ et al. *N Engl J Med*. 2018;378:1277-1290.

CheckMate 214: OS by PD-L1 Expression
IMDC Intermediate-/Poor-Risk Patients[1]





1. Motzer RJ et al. *N Engl J Med*. 2018;378:1277-1290.

Combination Immunotherapy Development: 2 Approaches

- Use immunotherapy (PD-1/PD-L1 pathway blockers) to improve the effects of standard therapies
- **Use other agents/therapies to improve the effects of immunotherapy**

Can Nivolumab/Ipilimumab Salvage Nivolumab Nonresponders?

Recent Approvals

Frontline Advanced Disease

Cabozantinib[1]
Approved Dec 2017
(phase 2 CABOSUN trial)

Nivolumab + Ipilimumab[2]
Approved April 2018 for intermediate/poor-risk patients
(phase 3 CheckMate 214 trial)

Selected Ongoing Trials

HAS RESULTS

Phase 3 IMmotion151 (NCT02420821)
Bevacizumab + atezolizumab vs sunitinib

Phase 3 KEYNOTE-426 (NCT02853331)
Axitinib + pembrolizumab vs sunitinib

Phase 3 JAVELIN Renal 101 (NCT02684006)
Axitinib + avelumab vs sunitinib

Phase 2 KEYNOTE-427 (NCT02853344)
Pembrolizumab monotherapy

RECRUITING

Phase 3 CheckMate 9ER (NCT03141177)
Nivolumab + cabozantinib vs sunitinib

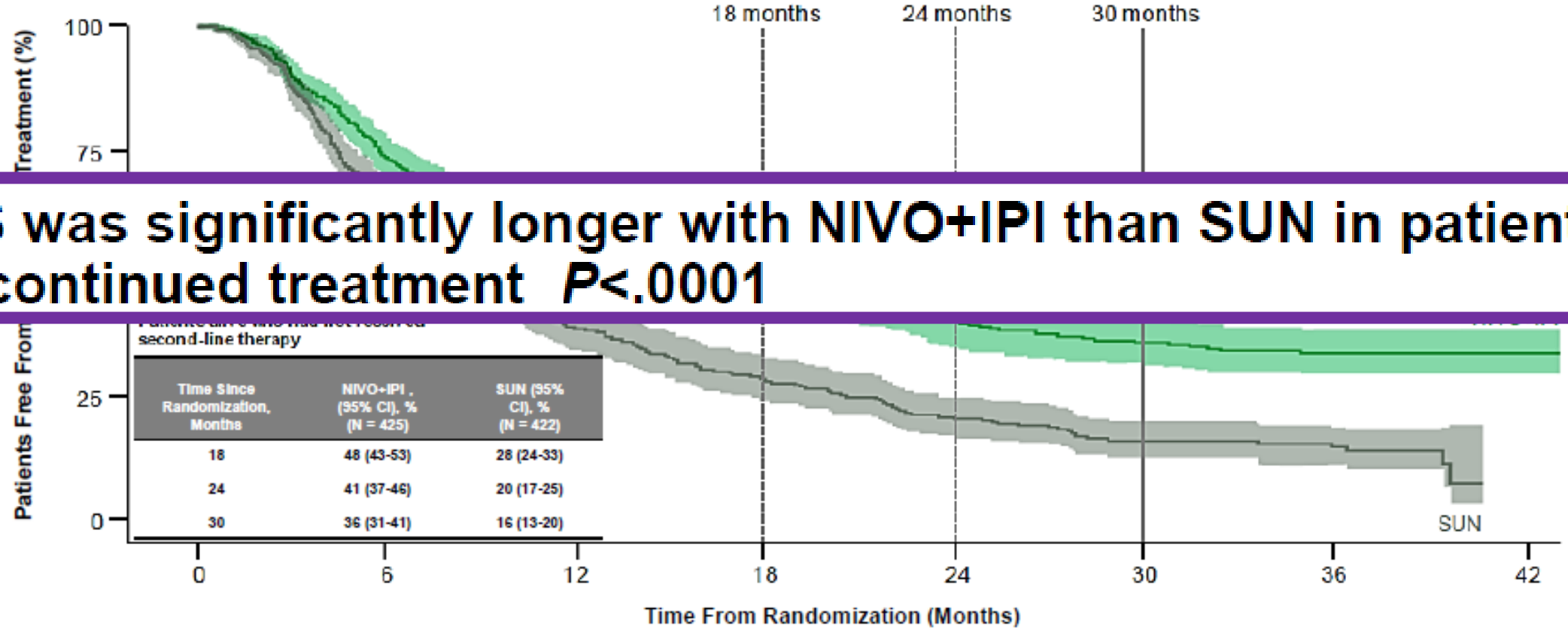
Phase 3 CLEAR (NCT02811861)
Lenvatinib + pembrolizumab or lenvatinib + everolimus vs sunitinib

NOT YET RECRUITING

Phase 3 PDIGREE (NCT03793166)
Nivolumab + ipilimumab → nivolumab vs cabozantinib vs nivolumab + cabozantinib

Treatment-Free Survival Following Discontinuation of First-Line Nivolumab Plus Ipilimumab or Sunitinib in Patients With Advanced Renal Cell Carcinoma: CheckMate 214 Analysis

Time From Randomization to Second-Line Treatment Initiation or Death in All Patients Classified as IMDC Intermediate/Poor-Risk



TFS was significantly longer with NIVO+IPI than SUN in patients who discontinued treatment *P*<.0001

No. at risk								
NIVO+IPI	425	305	225	197	167	140	53	1
SUN	422	260	157	112	82	58	27	0

Shaded area around curves represents 95% CI

Systemic treatment for mRCC

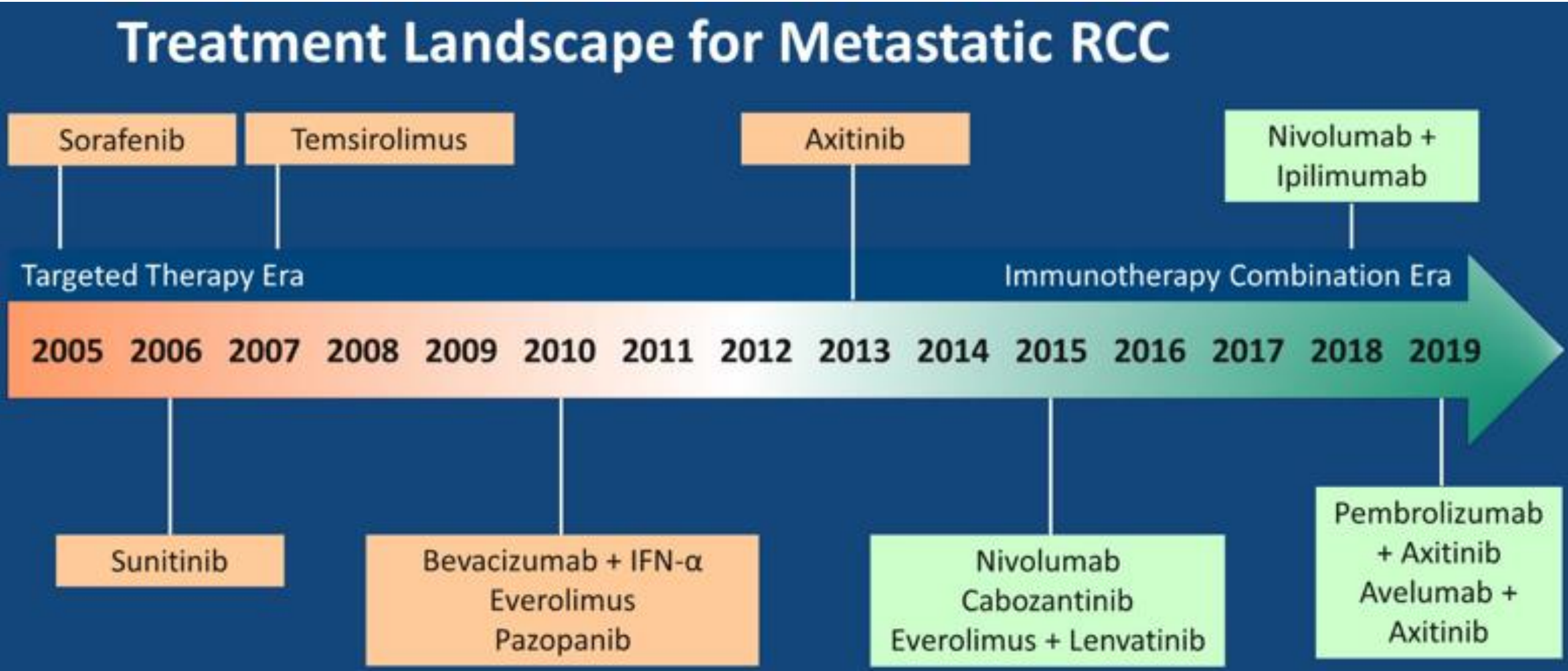
ASCO 2019:

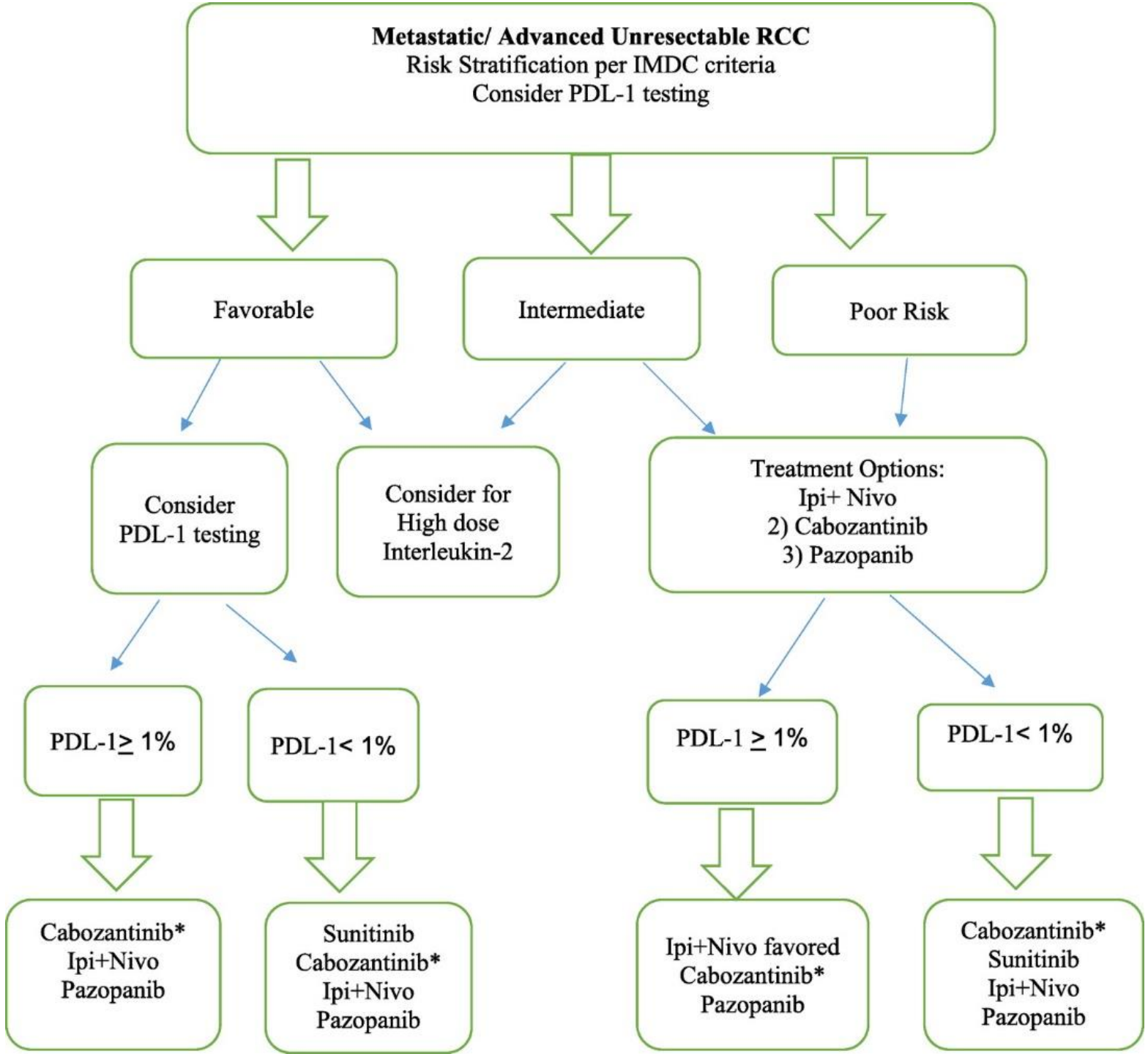
Evolving Front-Line Therapy in Metastatic RCC

Currently, we have three combination therapy regimens approved in the first-line setting:

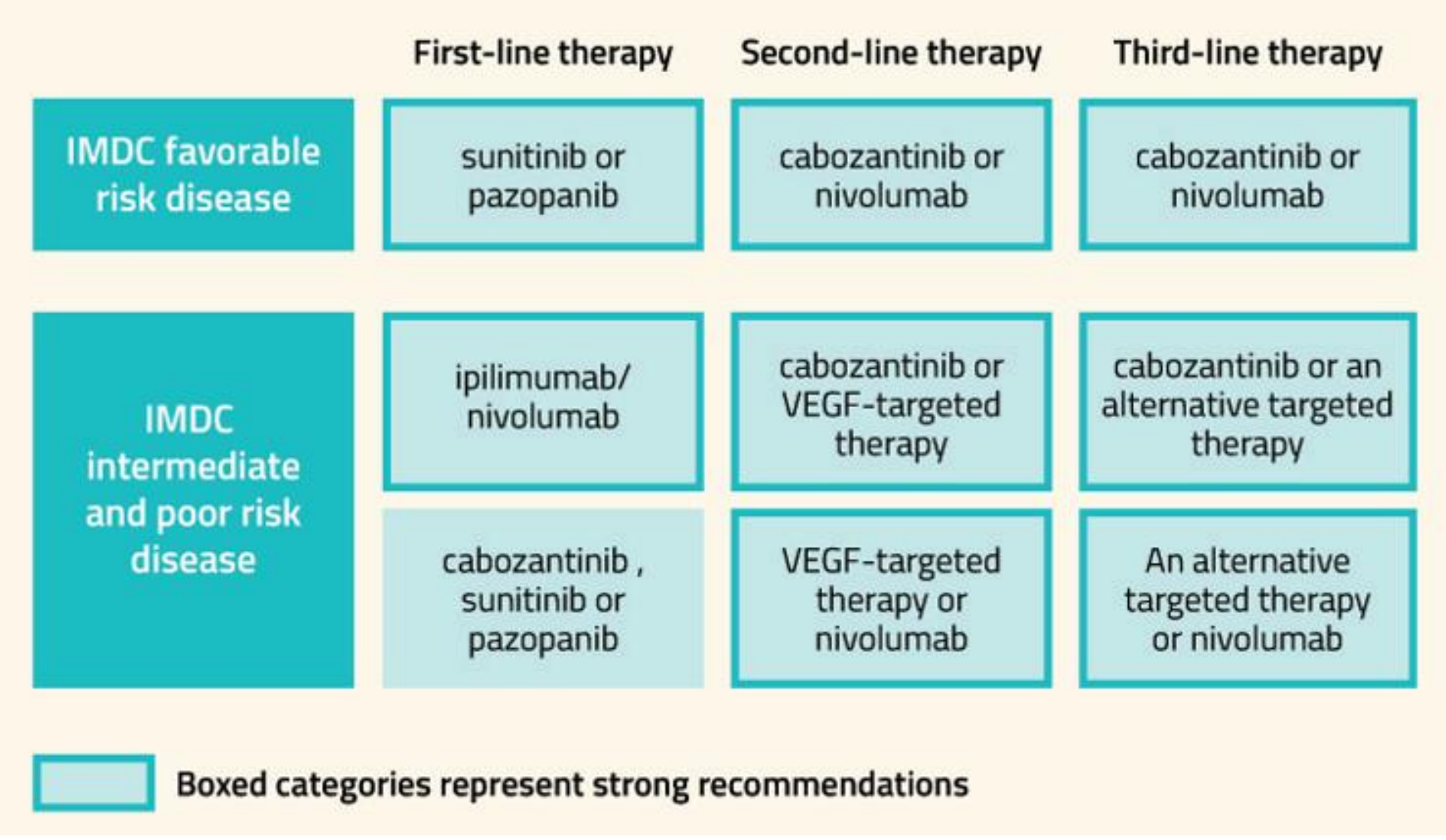
- Nivolumab + ipilimumab (CheckMate 214)[1]; OS HR 0.68 (99.8% CI 0.49-0.95)
- Pembrolizumab + axitinib (KEYNOTE-426) [2]; OS HR 0.53 (95% CI 0.38-0.74)
- Avelumab + axitinib (JAVELIN Renal 101) [3]; OS HR 0.78 (95% CI 0.55-1.08)

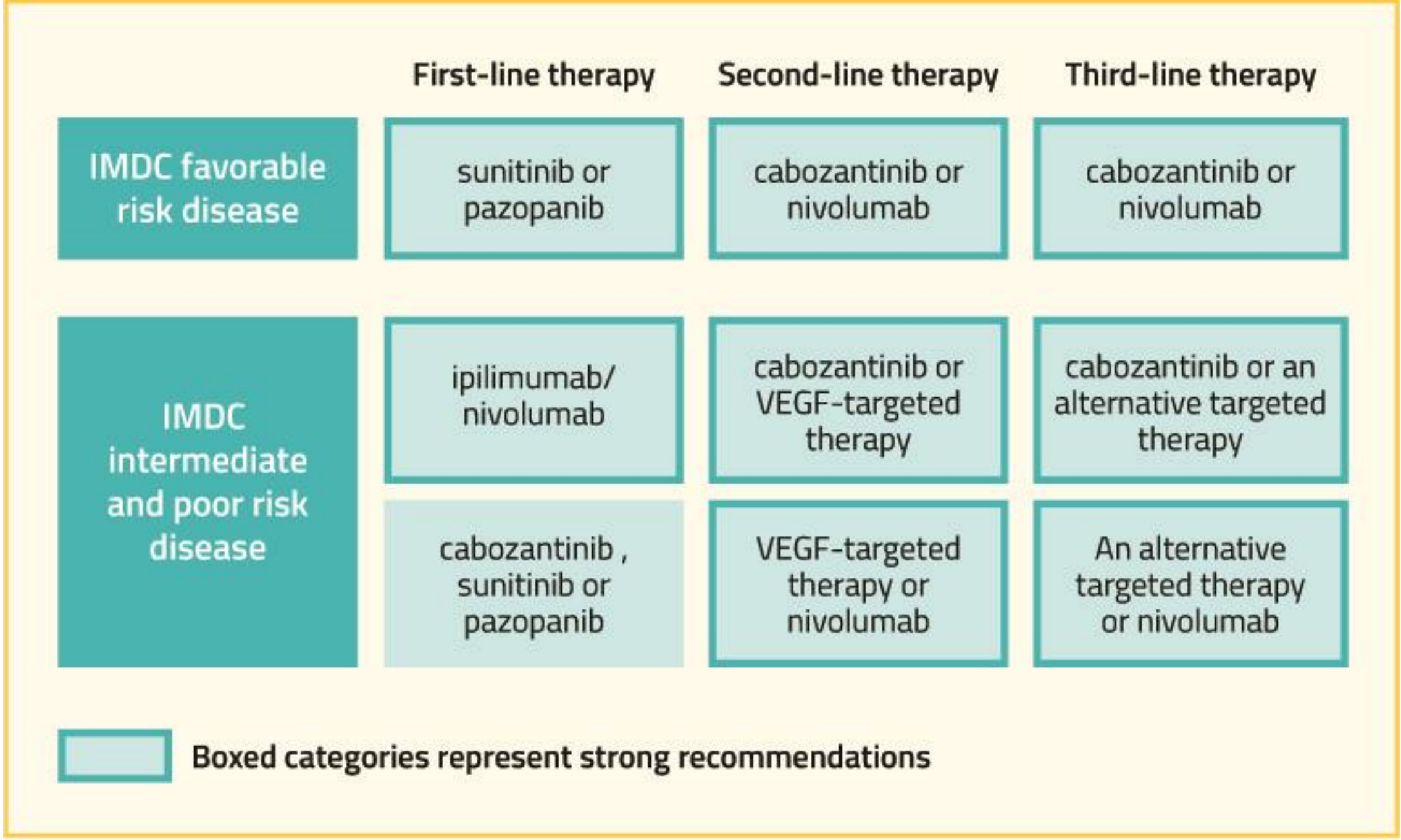
ASCO 2019:
Evolving Front-Line Therapy in Metastatic Renal Cell Carcinoma



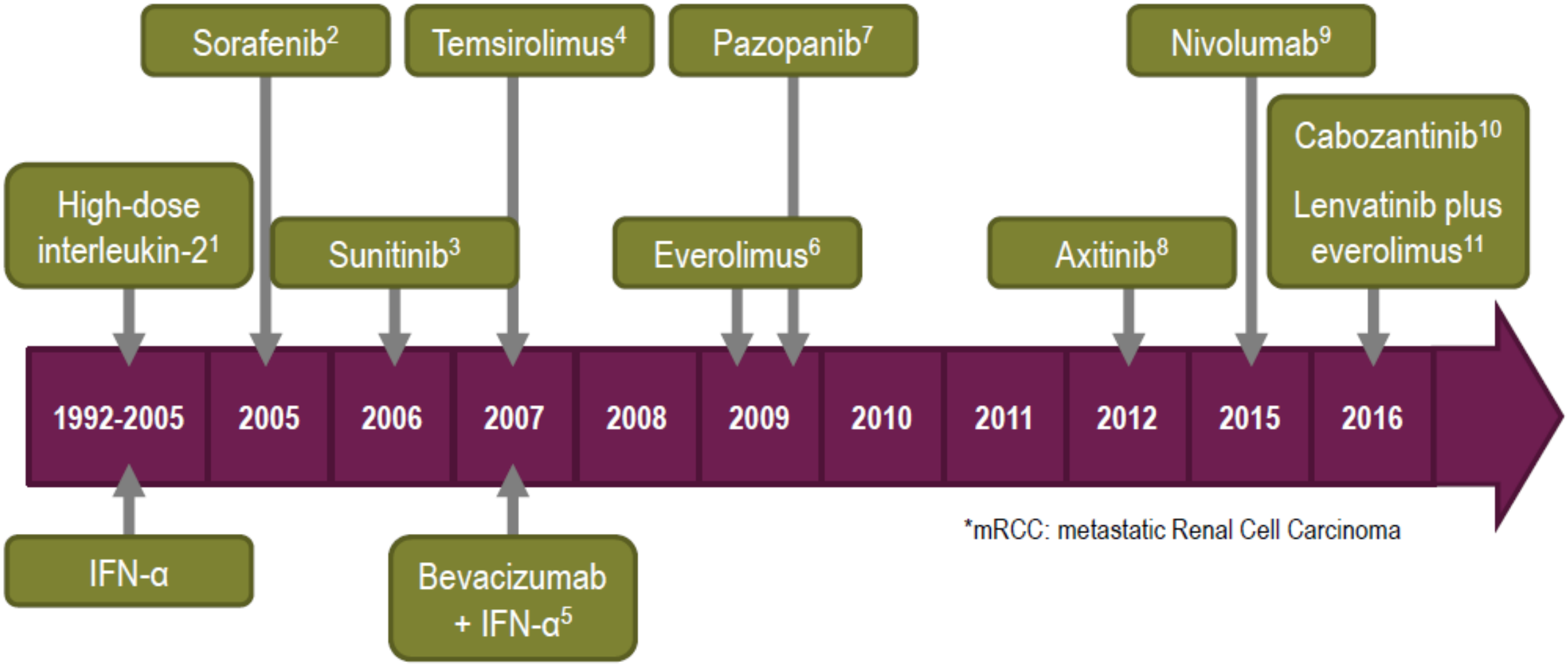

Metastatic/ Advanced Unresectable RCC
Risk Stratification per IMDC criteria
Consider PDL-1 testing
Favorable
Intermediate
Poor Risk
Consider PDL-1 testing
Consider for High dose Interleukin-2
Treatment Options:
Ipi+ Nivo
2) Cabozantinib
3) Pazopanib
PDL-1≥ 1%
PDL-1< 1%
PDL-1 ≥ 1%
PDL-1< 1%
Cabozantinib*
Ipi+Nivo
Pazopanib
Sunitinib
Cabozantinib*
Ipi+Nivo
Pazopanib
Ipi+Nivo favored
Cabozantinib*
Pazopanib
Cabozantinib*
Sunitinib
Ipi+Nivo
Pazopanib

Updated European Association of Urology Guidelines recommendations for the treatment of first-line ccRCC 2018



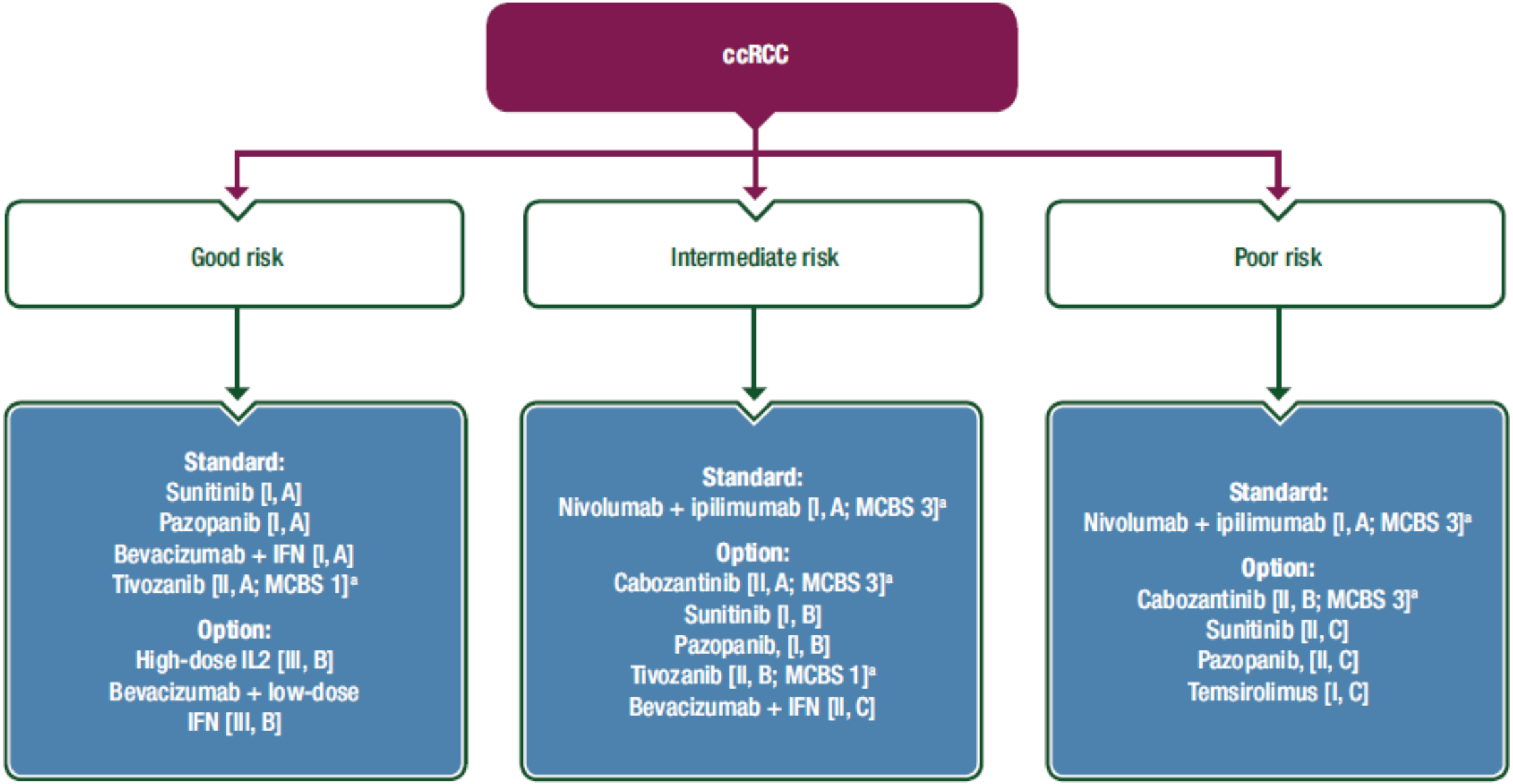


GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

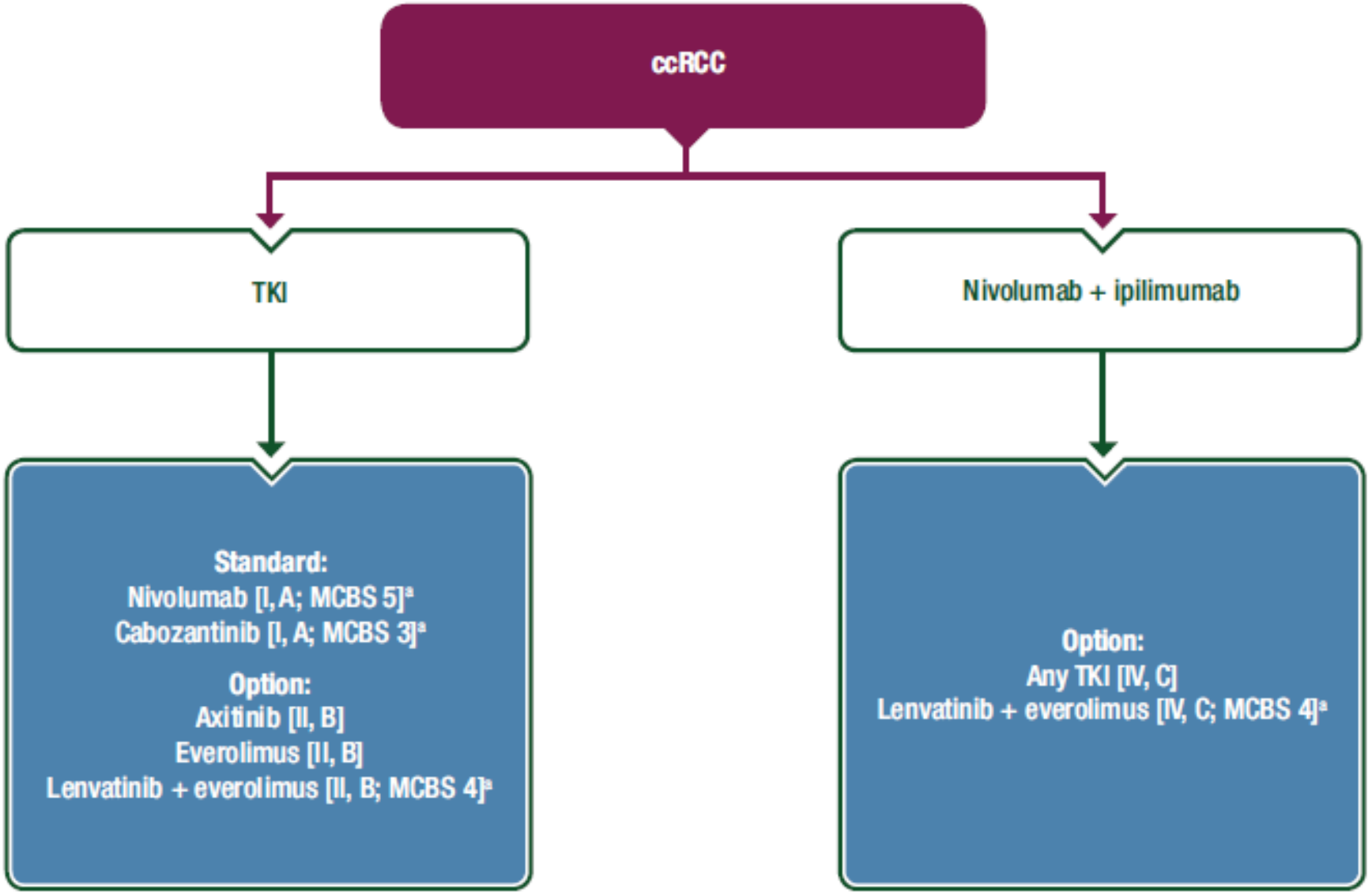


*mRCC: metastatic Renal Cell Carcinoma

Systemic first-line treatment of ccRCC.

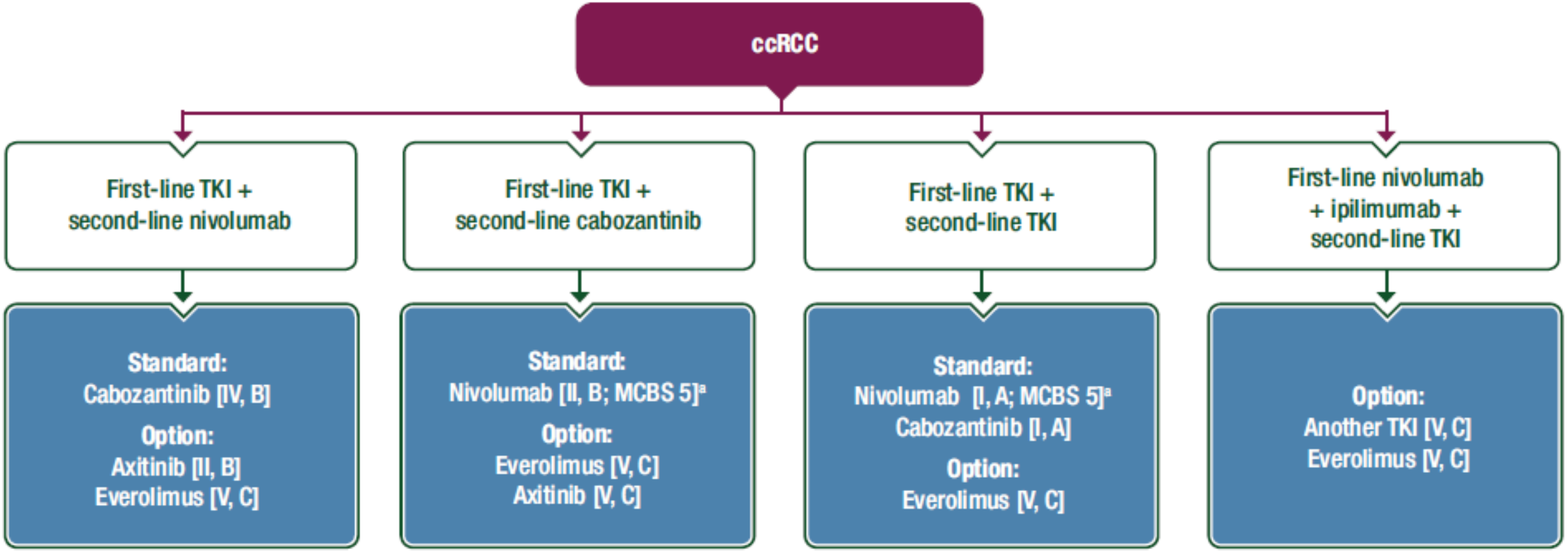


Second-line treatment of ccRCC.



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Third-line treatment of ccRCC.



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Kidney Cancer

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred regimens	**Other recommended regimens**	**Useful under certain circumstances**
• Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab (category 3)	• Bevacizumab or biosimilar[e] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[c] (category 2B) • Temsirolimus[d] (category 2B)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Kidney Cancer

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

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]

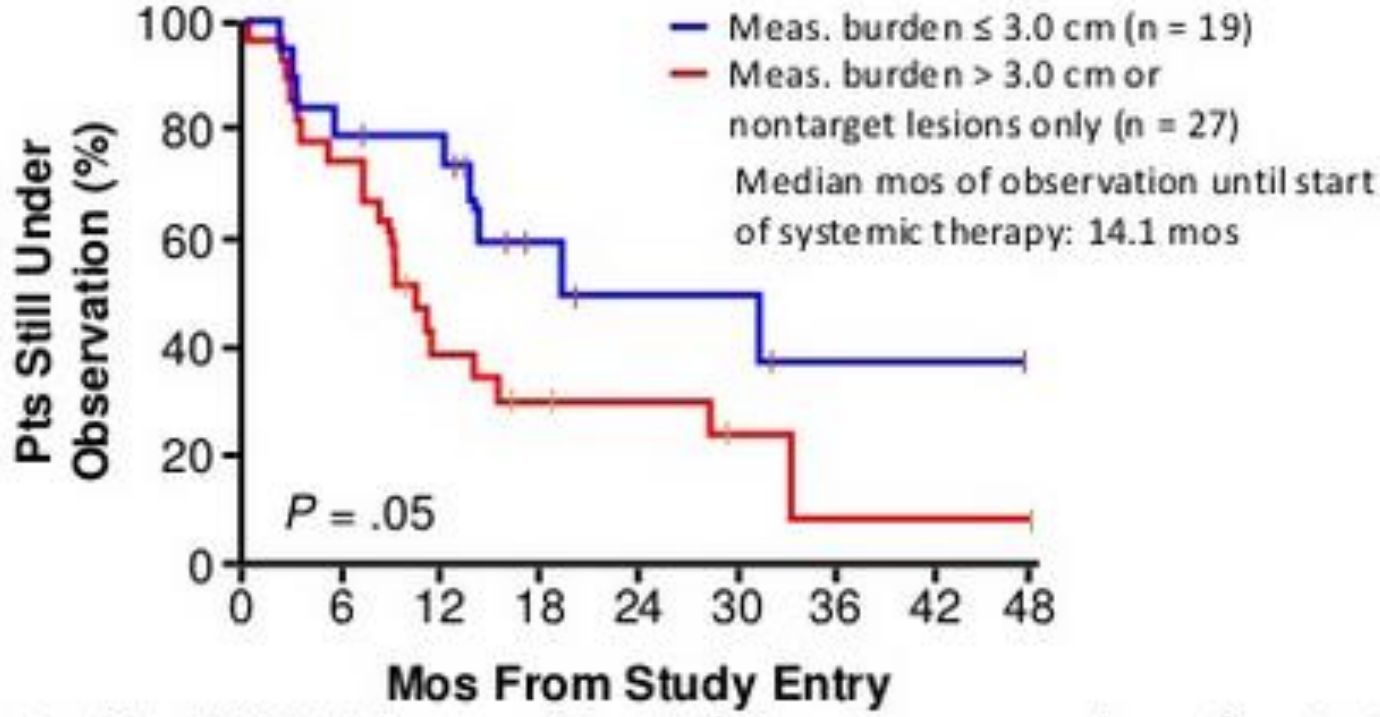
Dilemma :

What is the “best” initial systemic therapy for mRCC?

1. Who to treat ?
2. When to start treatment ?
3. When to stop a treatment ?
4. How best to use what is available ?

Observation Before Systemic Therapy Safe for a Subset of Pts With mRCC

- Phase II study of pts with mRCC and no previous systemic therapy
  - Observation with periodic CT assessment; initiation of systemic treatment per discretion of physician and pt



  - Unaffected by IMDC risk group (P = .57), location or number of metastases

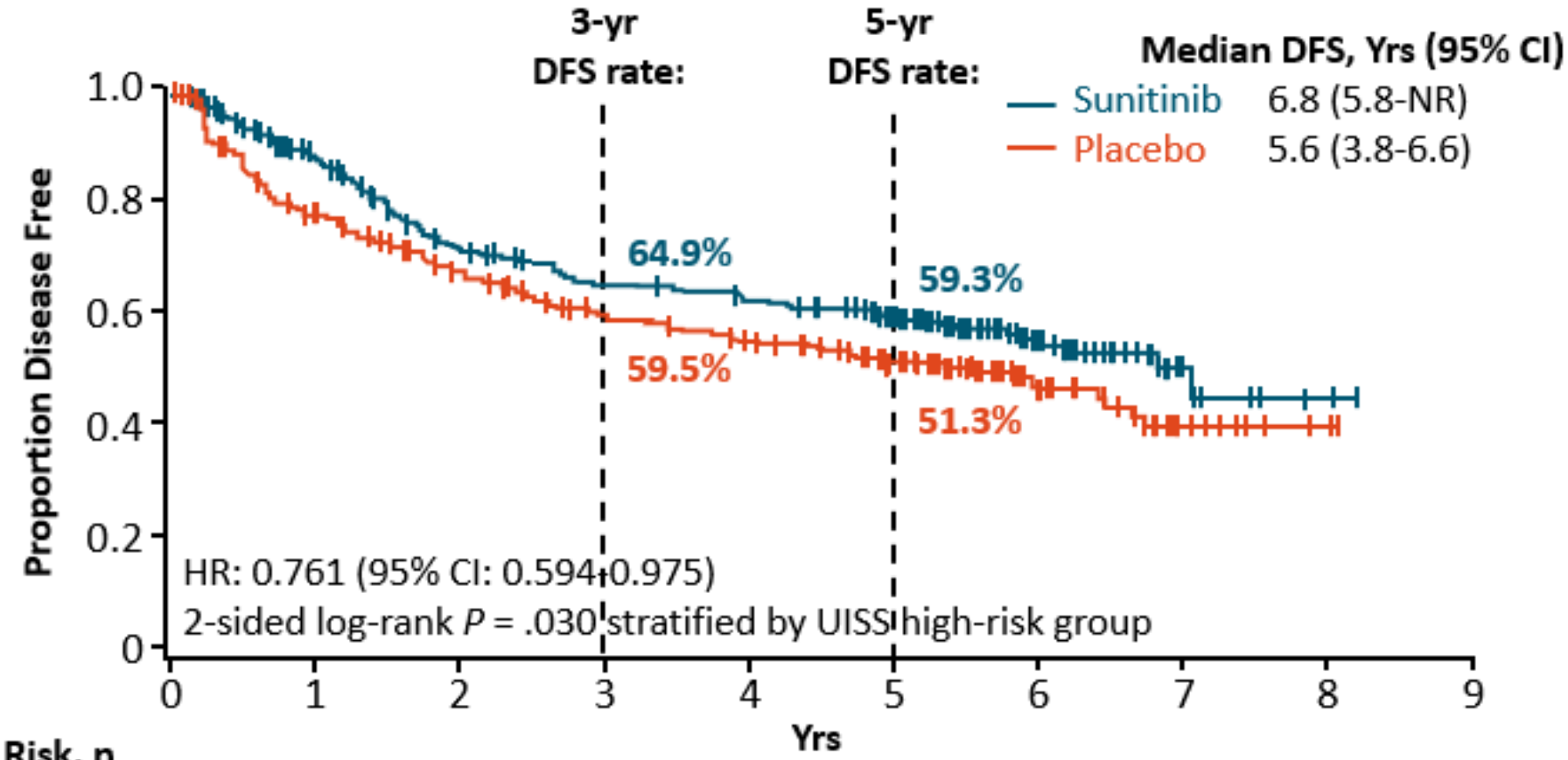
Adjuvant therapy ?

- Up to 40% of patients with renal cell carcinoma (RCC) will develop metastatic disease
- 60% recurrence rate over a 5-year period for high-risk patients
- Adjuvant therapy for RCC is an unmet medical need for high-risk patients
- Surveillance remains the standard of care for adjuvant treatment of RCC

Adjuvant therapy ?

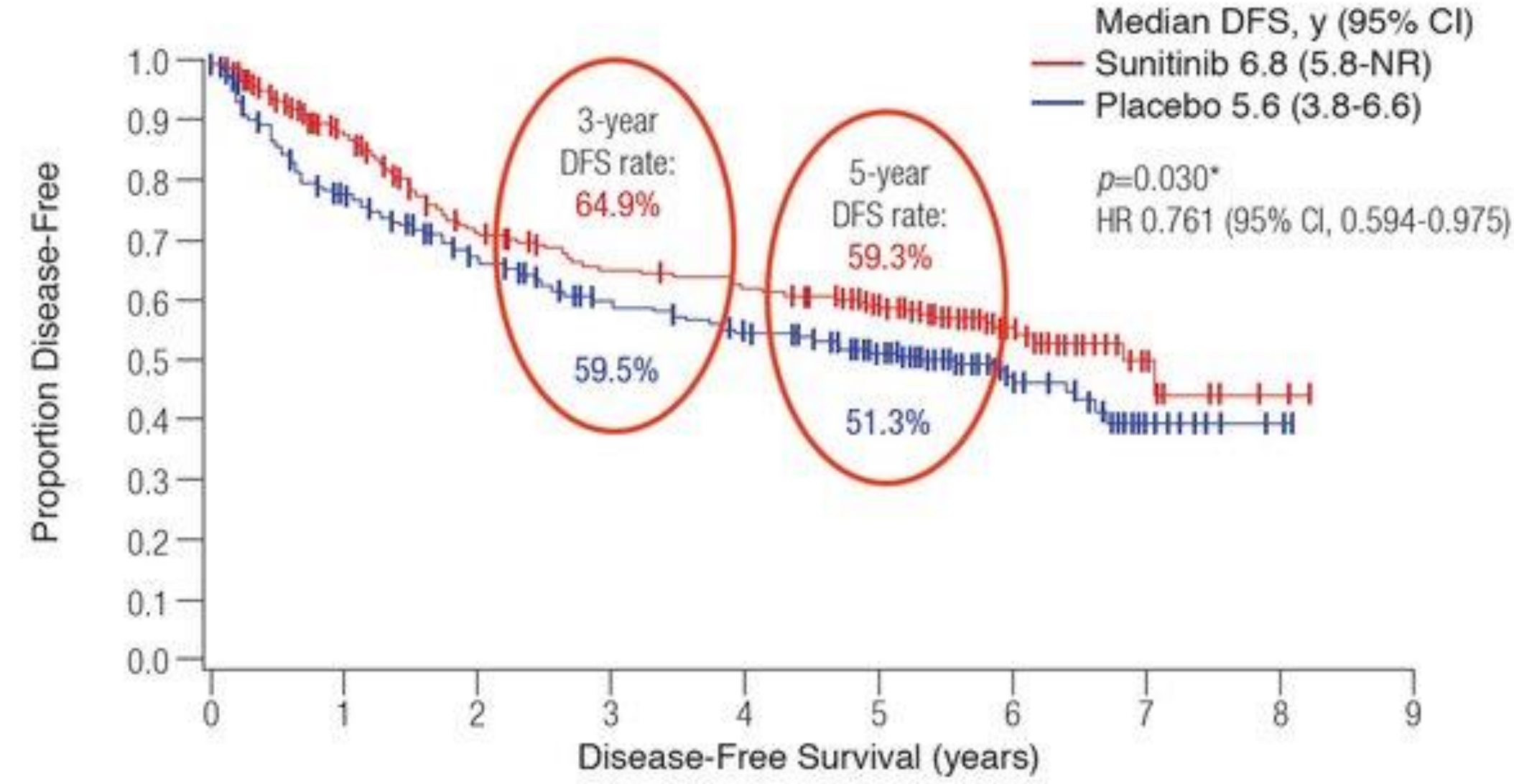
Sunitinib vs Placebo in Patients With Locoregional, High-Risk ccRCC

S-TRAC Phase III Trial: DFS With Sunitinib vs Placebo in Patients With Locoregional, High-Risk ccRCC



Patients at Risk, n

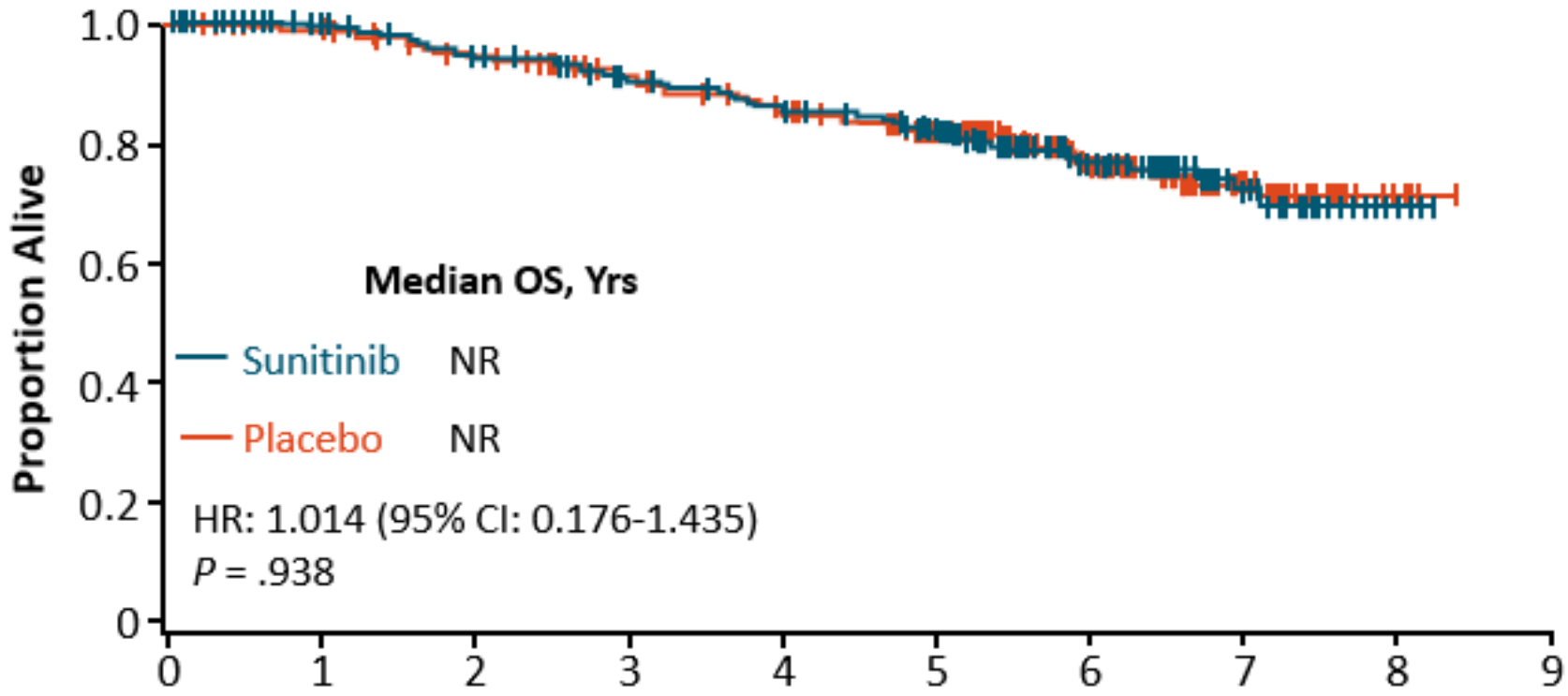
Sunitinib	309	225	173	153	144	119	53	10	3	0
Placebo	306	220	181	150	135	102	37	10	2	0



No. at risk	309	225	173	153	144	119	53	10	3	0
Placebo	306	220	181	150	135	102	37	10	2	0

*Two-sided *p* value from log-rank test stratified by UISS high-risk group.

S-TRAC Phase III Trial: OS With Sunitinib vs Placebo in Patients With Locoregional, High-Risk ccRCC



Patients at Risk, n									
Sunitinib	309	278	258	236	222	196	98	31	4	0
Placebo	306	289	269	250	231	197	96	40	4	0

FDA Approves Sunitinib for Adjuvant Treatment of RCC

By Natasha Persaud November 16, 2017

At 5 years, 59.3% of patients treated with sunitinib were free from recurrence versus 51.3% who received placebo.

- **Sunitinib, a multi-targeted tyrosine kinase inhibitor, is FDA approved for the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy[4] (≥T3, any Fuhrman grade and/or nodal involvement)**

Recent Approvals

Selected Ongoing Trials

Adjuvant Therapy

Sunitinib[4]
Approved November 2017 in patients at high risk of recurrent disease following nephrectomy (phase 3 S-TRAC trial)

RECRUITING

Phase 3 IMmotion010 (NCT03024996)
Atezolizumab vs placebo

Phase 3 KEYNOTE-564 (NCT03142334)
Pembrolizumab vs placebo

Phase 3 PROSPER (NCT03055013)
Nivolumab + nephrectomy vs nephrectomy

Phase 3 CheckMate 914 (NCT03138512)
Nivolumab + ipilimumab vs placebo

Phase 3 RAMPART (NCT03288532)
Durvalumab + tremelimumab vs durvalumab vs active surveillance

Axitinib vs Placebo in Patients at High Risk of Recurrent Renal Cell Carcinoma: ATLAS Trial Results

- Clear-cell RCC (>50%) (≥pT2 and/or N+), any Fuhrman grade
- Prior nephrectomy
- Systemic treatment-naïve
- No evidence of macroscopic residual or metastatic disease (confirmed by IRC)

Stratified by AJCC TNM risk groups and country

RANDOMIZATION (1:1)*

Arm A: Oral axitinib 5 mg BID

Arm B: Oral placebo BID

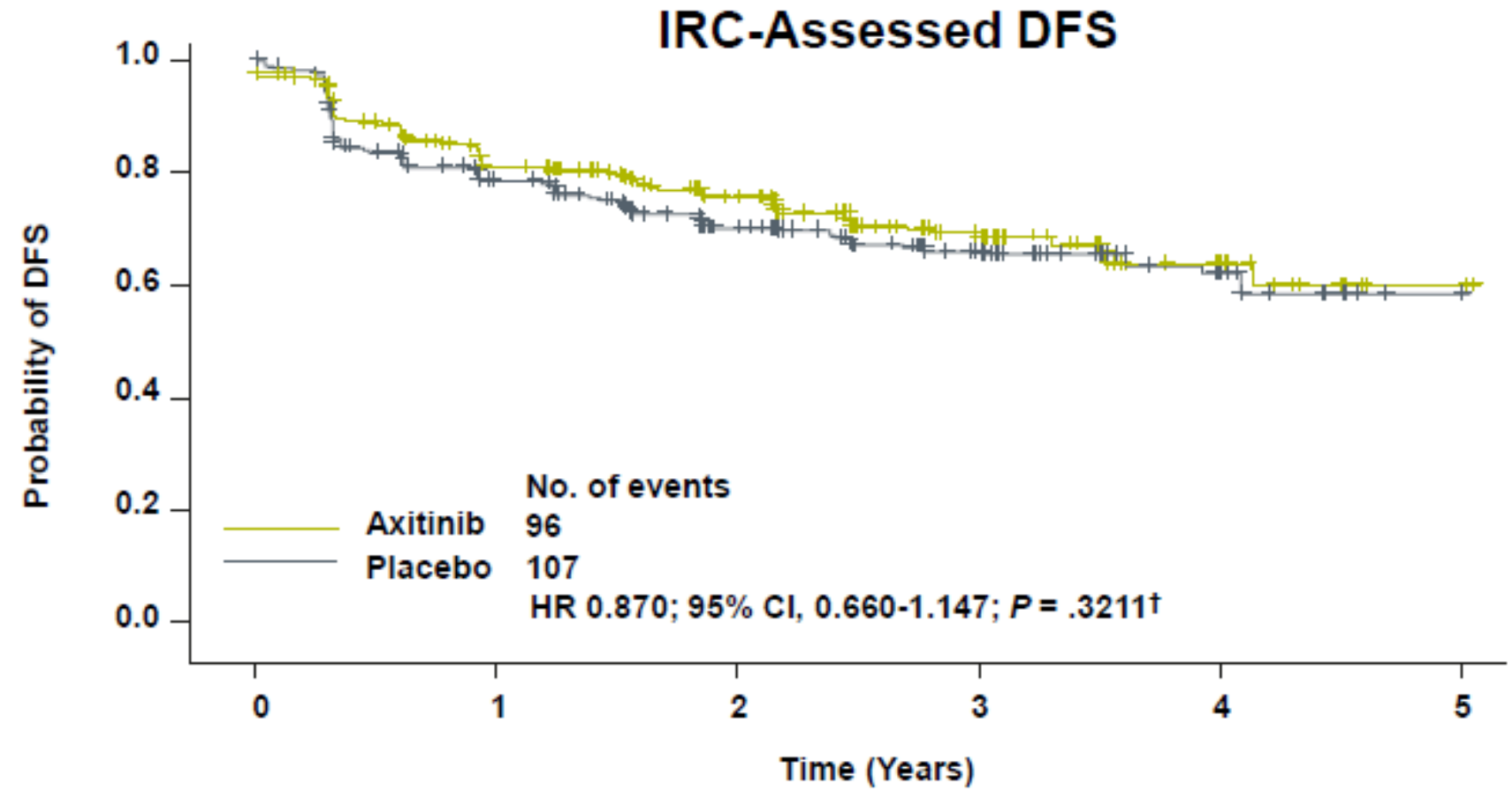
Patients were treated for a minimum of 1 year and up to 3 years unless recurrence, occurrence of a second primary malignancy, significant toxicity, or withdrawal of consent

N = 700 (planned)
N = 724 (accrued)

*Randomized **4-12** weeks after nephrectomy

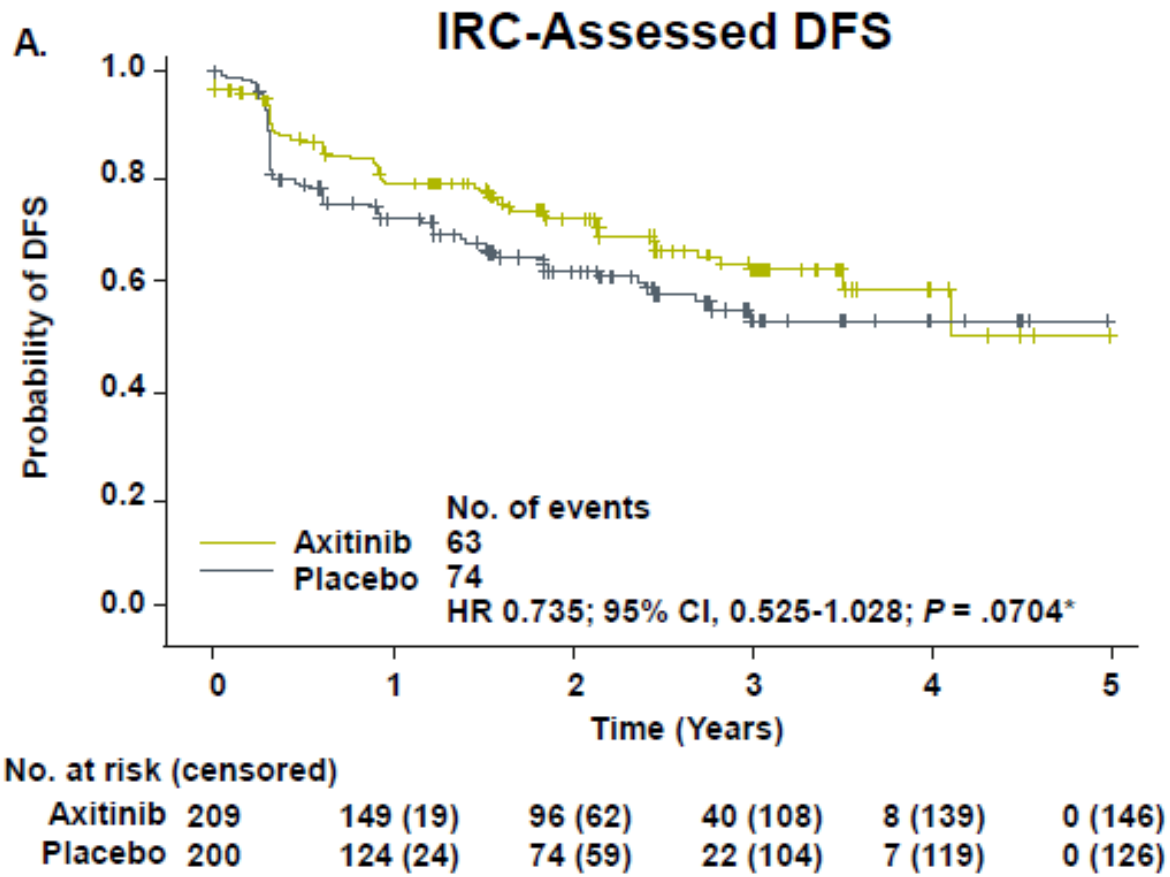
- Dose interruptions and stepwise reductions to a minimum of **1 mg** BID were allowed
- Stepwise dose increases up to **10 mg** BID were allowed

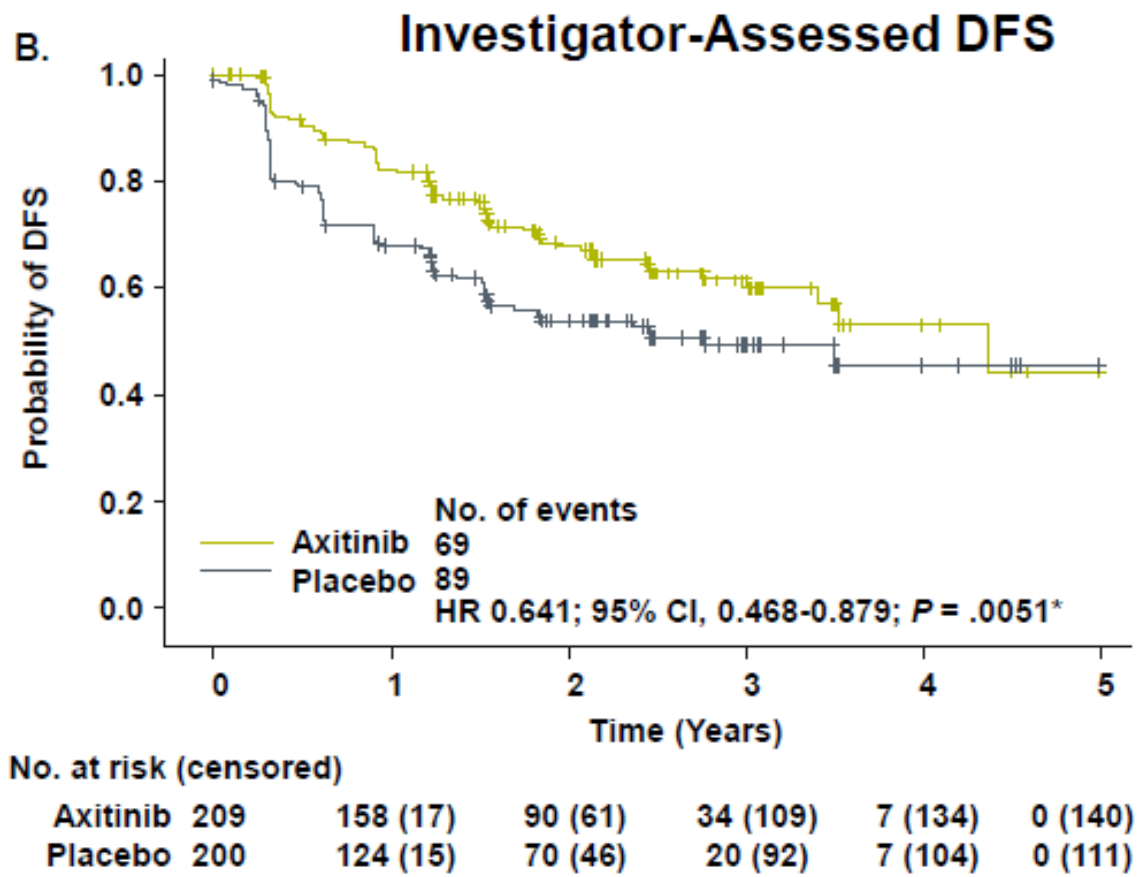
Disease-Free Survival — ITT Population*



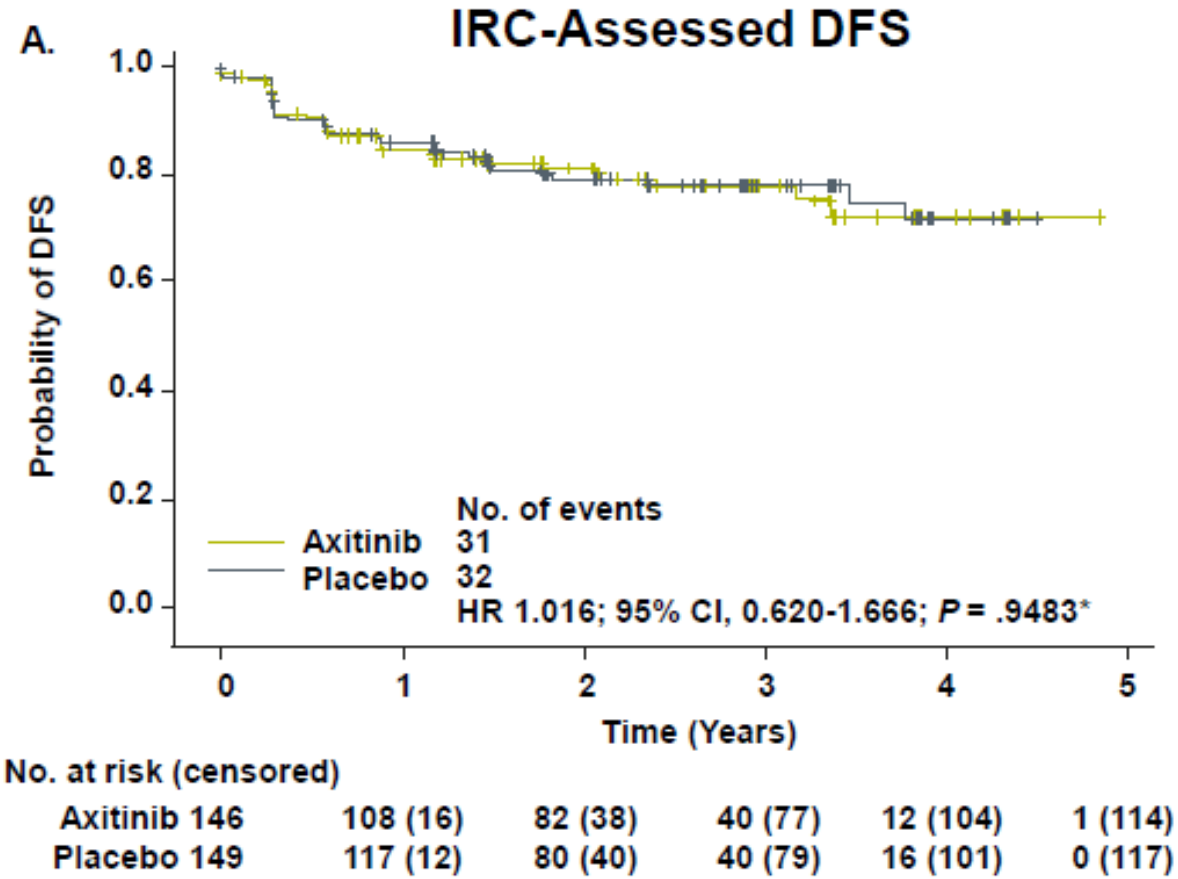
No. at risk (censored)						
Axitinib	363	264 (35)	182 (102)	81 (190)	20 (249)	1 (266)
Placebo	361	252 (37)	164 (101)	72 (185)	26 (229)	0 (254)

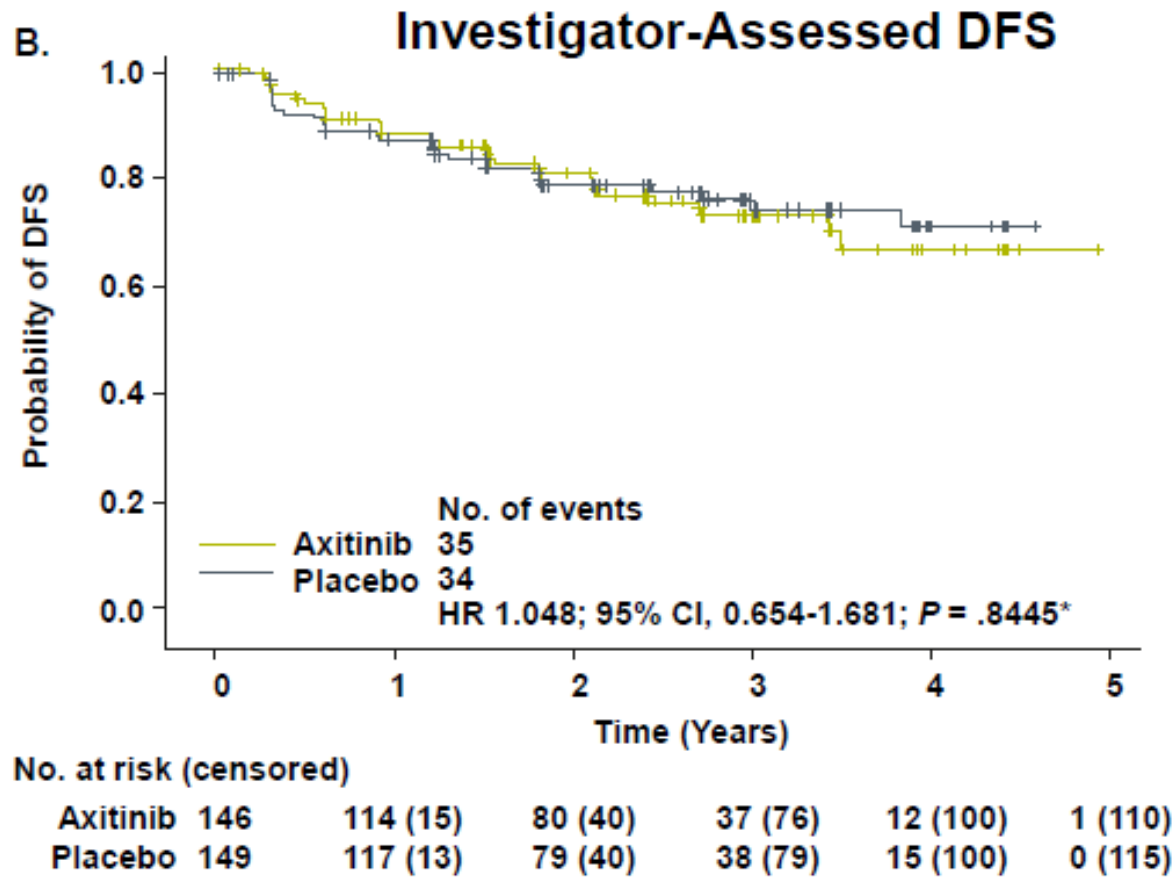
Subgroup Analysis: DFS—Highest-Risk Subpopulation





Subgroup Analysis: DFS—Lower-Risk Subpopulation





Overall Survival: ITT Population

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 00: 1–9, 2018
doi:10.1093/annonc/mdy454

ORIGINAL ARTICLE

Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial

Published Tyrosine Kinase Inhibitor Adjuvant Trials

Trial	Therapy	N	Histology	Stage	Starting Dose	Minimum Dose	DFS	OS
ASSURE	Sunitinib Sorafenib Placebo	1943	**79% ccRCC**	> pT1b, G3-4, or N+	50 or 37.5 mg (Su)/ 400 mg (So)	25 mg (Su)/40 mg (So)	No	No
S-TRAC	Sunitinib Placebo	615	ccRCC	> pT3b or N+	**50 mg**	**37.5 mg**	Yes	No
PROTECT	Pazopanib Placebo	1538	ccRCC or mostly ccRCC	pT2 (G3-4), ≥ pT3, or N+	600 mg	400 mg	No	No

Ongoing Phase III Adjuvant Trials: Immunotherapy vs Placebo

Parameter	IMmotion010 (NCT03024996)	PROSPER (NCT03055013)	KEYNOTE-564 (NCT03142334)	CheckMate 914 (NCT03138512)
Drug	Atezolizumab	Nivolumab	Pembrolizumab	Nivolumab + ipilimumab
Histology	Clear-cell ± sarcomatoid histology	RCC of any histology	Clear-cell ± sarcomatoid features	Clear-cell ± sarcomatoid features
Dose duration	1 yr	2 doses prior to surgery and adjuvant nivolumab for 9 mos	1 yr	6 mos
Risk classification	T2 grade 4, T3a grade 3/4, T3b/c any grade, T4 any grade, or TxN+ any grade	Clinical stage ≥ T2 or any N+	pT2, grade 4; pT3/4, any grade; N+ M0; M1 NED	pT2aN0, grade 3-4; pT2b-T4; N+
Primary endpoint	DFS	RFS at 5 yrs	DFS	DFS
BICR	Yes	Yes	Yes	Yes
Status	Active, recruiting	Active, recruiting	Active, recruiting	Active, recruiting

ASCO 2019:
Evolving Front-Line Therapy in Metastatic Renal Cell Carcinoma

Summary of Reported Adjuvant TKI Studies

	ASSURE (n=1943)	STRAC (n=615)	PROTECT (n=1538)	ATLAS* (n=724)
Arms	Sunitinib vs. Sorafenib vs. Placebo x 1 year	Sunitinib vs. Placebo x 1 year	Pazopanib vs. Placebo x 1 year	Axitinib vs. Placebo x 3 years
Start Dose Reduction	Yes	No	Yes	No
Non-Clear Cell	Yes	No	No	No
Eligibility	pT1bG3-4N0, pT2-4GxN0, TxGxN+	pT3-4GxN0-x, TxGxN1-2	pT2G3-4N0M0, pT3-4N0M0, pTxN1M0	pT2-4N0M0, pTxN1M0
Median DFS (years)	5.8 vs. 6.1 vs. 6.6	6.8 vs. 5.6	NR vs. NR	NR vs. NR
Hazard Ratio (CI)	Sunitinib – 1.02 (97.5% CI 0.85-1.23) Sorafenib – 0.97 (97.5% CI 0·80-1.17)	0.76 (95% CI 0.59-0.98)	0.94 (95% CI 0.77-1.14)	0.87 (95% CI 0.660-1.147)

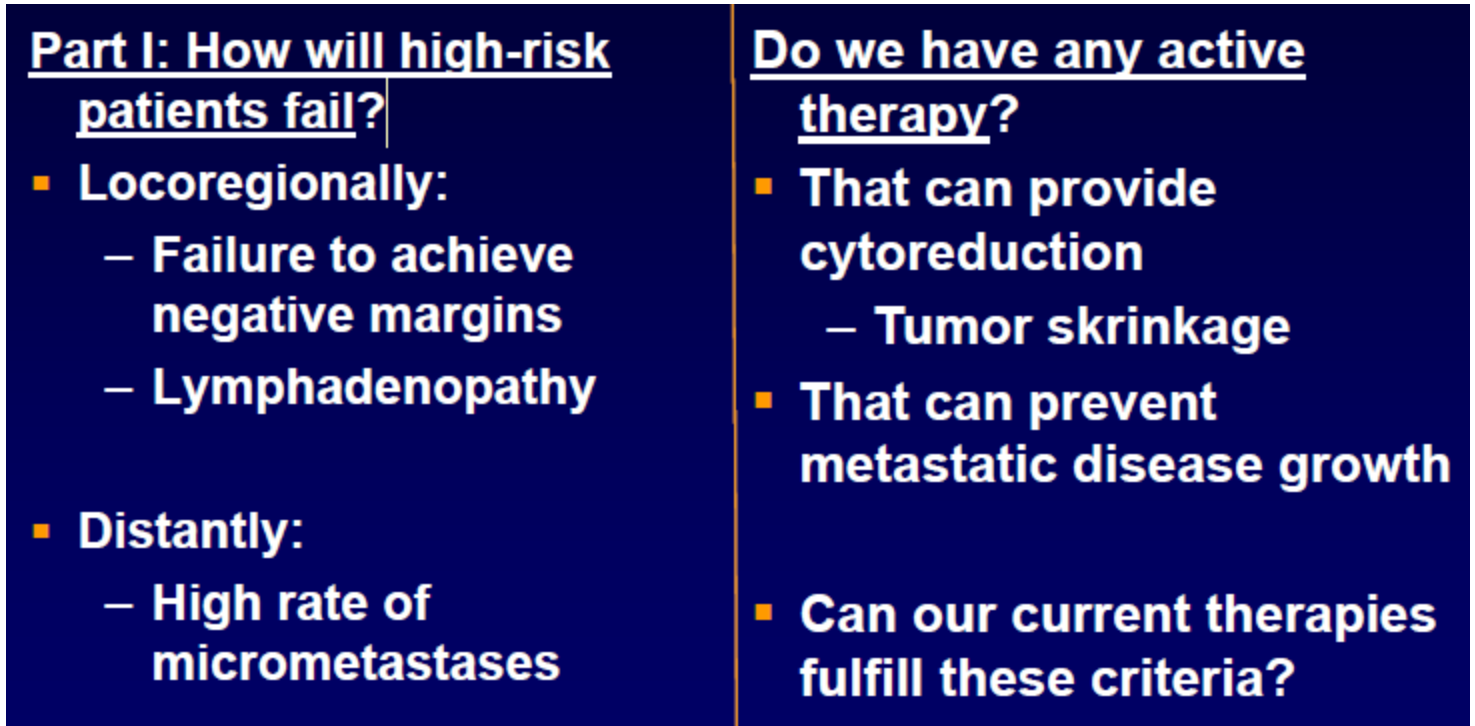
Definition of high-risk patients

- **Mayo Clinic stage (SSIGN)**

  TNM stage, Size, grade and necrosis system

- **University of California-Los Angeles** (UCLA) system (**UISS**)

  PS, Fuhrman grade and TNM stage



Prognostic factors affecting outcome of patients with renal cell carcinoma		
Anatomic prognostic factors	Tumor size Tumor extension Adrenal involvement	Venous involvement Lymph node incolvement Distant metastases
Histologic prognostic factors	Tumor grade Histologic subtype Sarcomatoid features	Necrosis Collecting system invasion
Clinical prognostic factors	Performance status Localized symptoms	Cachexia Platelet count

Comparison of the clinical stage, size, grade, and necrosis (SSIGN) score and the University of California-Los Angeles integrated staging system (UISS)

Model	*Parameters*	*Histology validation*	*External (n)*	*Patients*	*Limitations*
SSIGN	TNM stage, size, grade, necrosis	CCRCC	Yes	2656	Reliance upon subjective variable of necrosis
UISS	ECOG-PS, Fuhrman grade, TNM stage	RCC	Yes	8249	Reduced predictive power in nonmetastatic patients

TNM=tumor size, metastasis, and nodal involvement staging system; CCRCC=clear-cell renal cell carcinoma; ECOG-PS=Eastern Cooperative Oncology performance status' RCC=renal cell carcinoma

In Which Situation Could Neoadjuvant treatment Be Performed in RCC?

- **Two situations of interest:**
  - Nonmetastatic RCC:
    - Locally advanced disease (unresectable primary tumors)
      - Bulky regional lymph node metastases
      - Caval thrombi
    - Hereditary forms of RCC (Von Hippel-Lindau disease)
    - Anatomical or functional solitary kidney
  - Metastatic clear cell carcinoma:
    - But talk in term of “presurgical therapy”

Advantages Using Neoadjuvant

- **Disease down-staging**
  - Allowing less radical surgical approaches with possible benefits in terms of surgical morbidity and/or functionality
    - Radical nephrectomy → nephron-sparing surgery
- **Destroy tumor vasculature**
  - Might induced reduction mortality and the ability to treat high-risk surgical candidates

- **Evaluation of tumor sensitivity to treatment**
  - Interesting in patients selected for adjuvant therapy
    - Responders: maintenance of the same drug
    - Nonresponders: alternative therapy
- **Identification of molecular markers and imaging parameters of response**
  - Measurement of parameters prior to and after nephrectomy

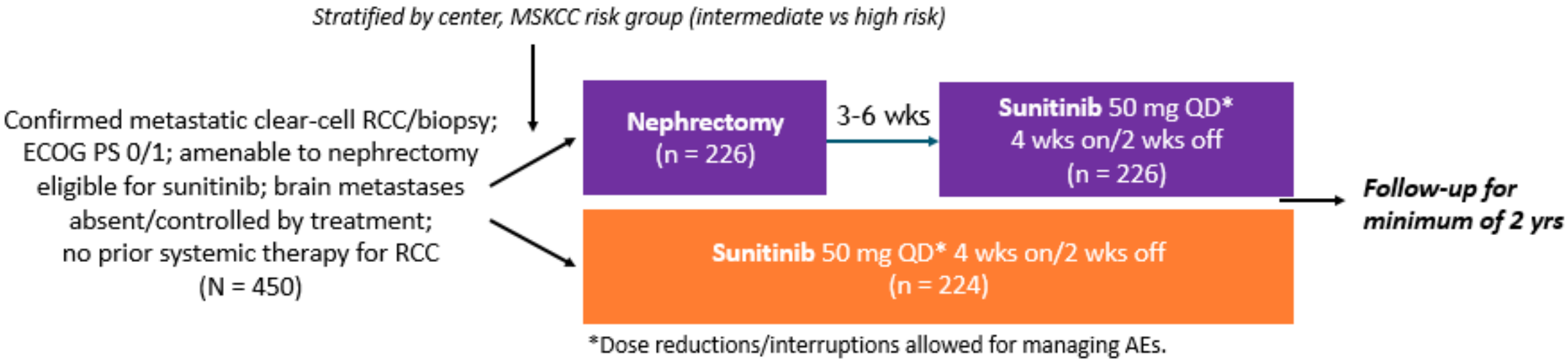
Does nephrectomy increase the likelihood of benefit from tyrosine kinase inhibitors (TKIs)?

- **Yes, definitely**
- **No, definitely**
- **Maybe, but I'm not sure**

In the era of anti vascular therapy, is cyto reductive nephrectomy a necessity?

CARMENA: Prospective, Multicenter, Open-Label, Randomized Phase III Noninferiority Study

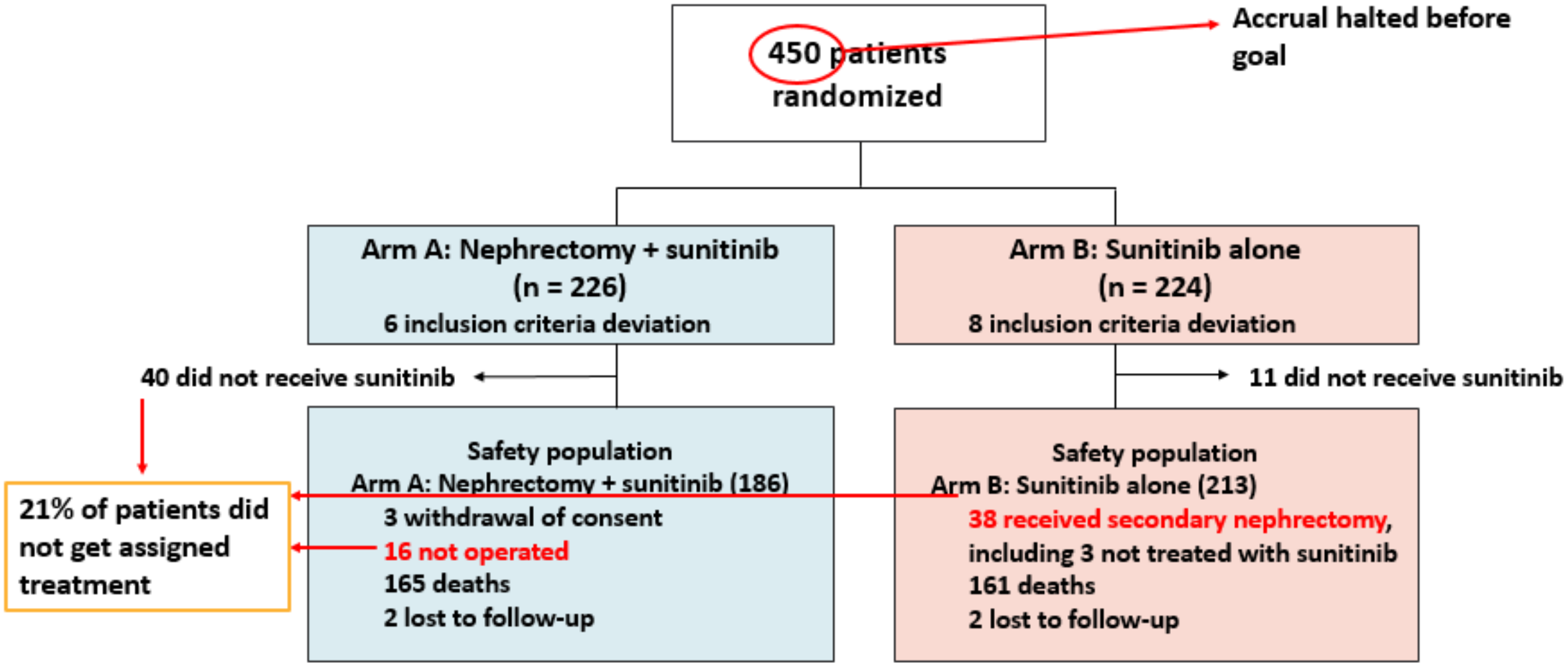
- Multicenter, randomized, open-label noninferiority phase III trial



- Primary endpoint: OS
- Secondary endpoints: PFS, ORR (RECIST v1.1), clinical benefit, safety

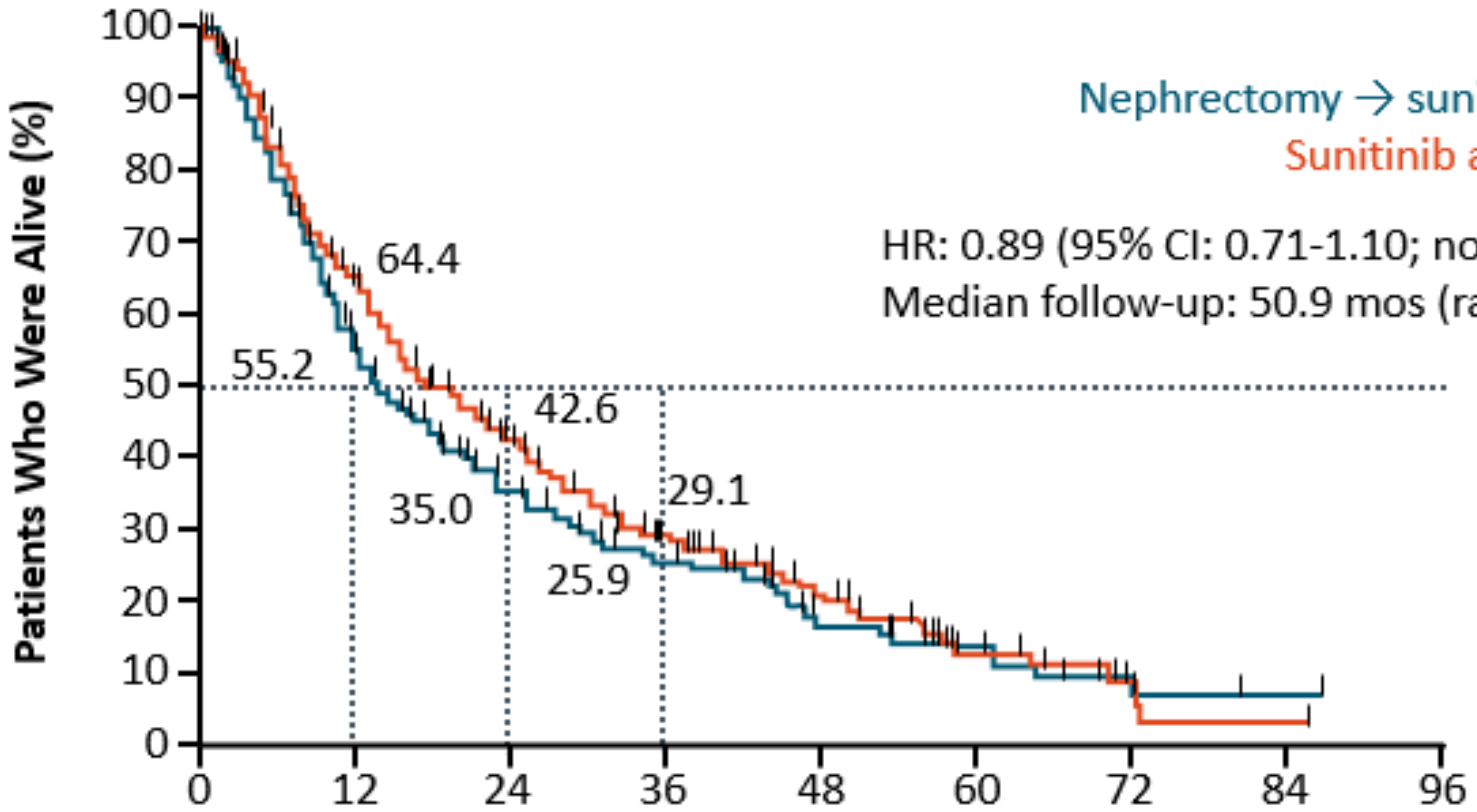
Méjean. ASCO 2018.

CARMENA: Patient Disposition



Méjean. ASCO 2018. Abstr LBA3.

CARMENA: Overall Survival (ITT)

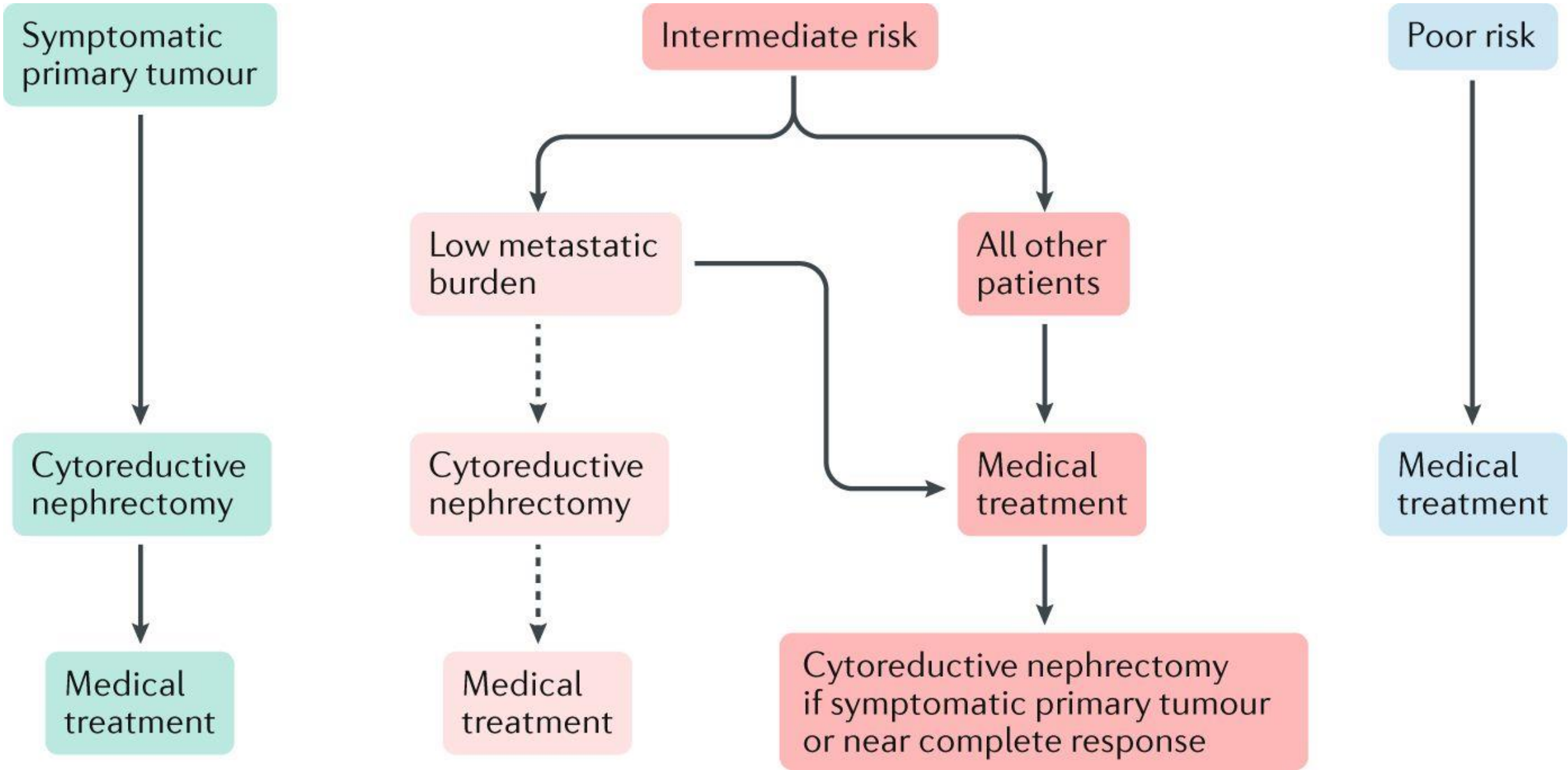


mOS, Mos	
Nephrectomy → sunitinib	13.9
Sunitinib alone	18.4

HR: 0.89 (95% CI: 0.71-1.10; noninferiority ≤ 1.20)
Median follow-up: 50.9 mos (range: 0-86.6)

Patients at Risk, n									
Nephrectomy→ sunitinib	226	110	61	40	19	11	4	1	0
Sunitinib alone	224	128	76	44	26	8	3	1	0

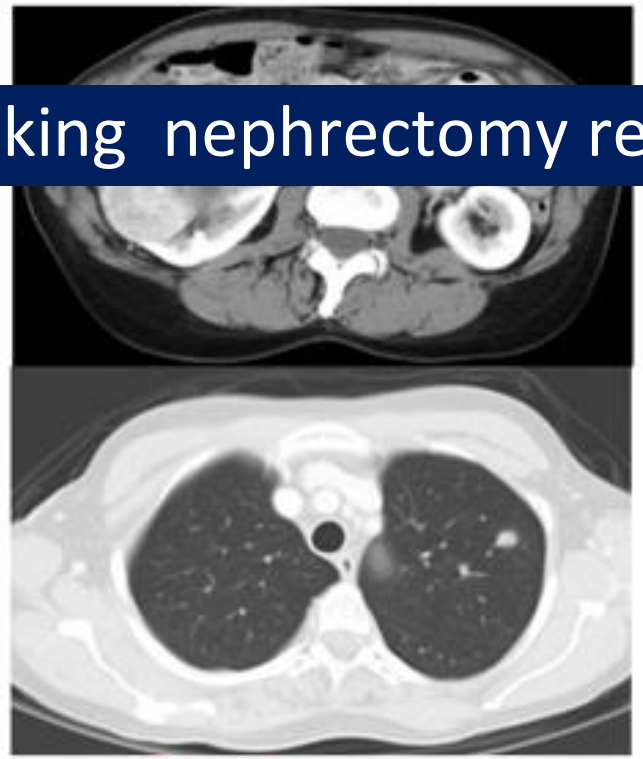
Méjean. ASCO 2018. Abstr LBA3.


Symptomatic primary tumour
Cytoreductive nephrectomy
Medical treatment
Intermediate risk
Low metastatic burden
All other patients
Cytoreductive nephrectomy
Medical treatment
Medical treatment
Cytoreductive nephrectomy if symptomatic primary tumour or near complete response
Poor risk
Medical treatment

Considerations for Nephrectomy

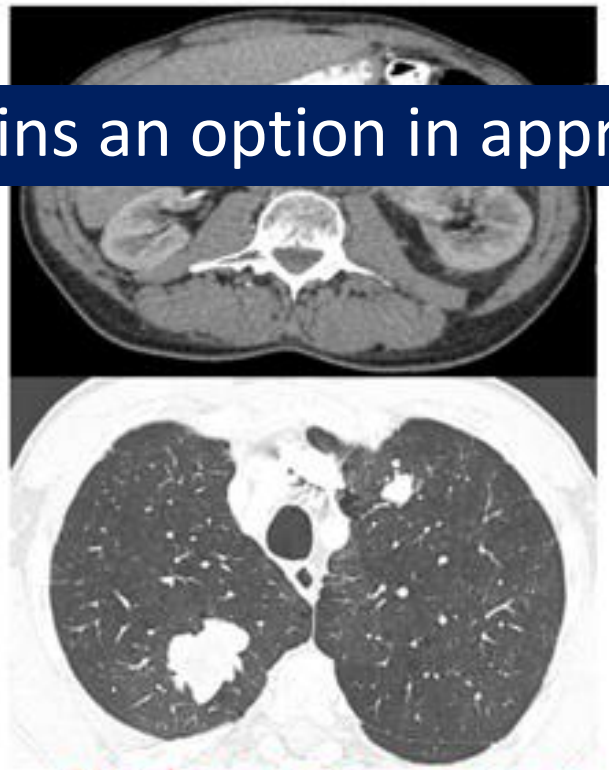
- Debulking nephrectomy remains an option in appropriately selected patients

PS 0
Minimal extrarenal disease



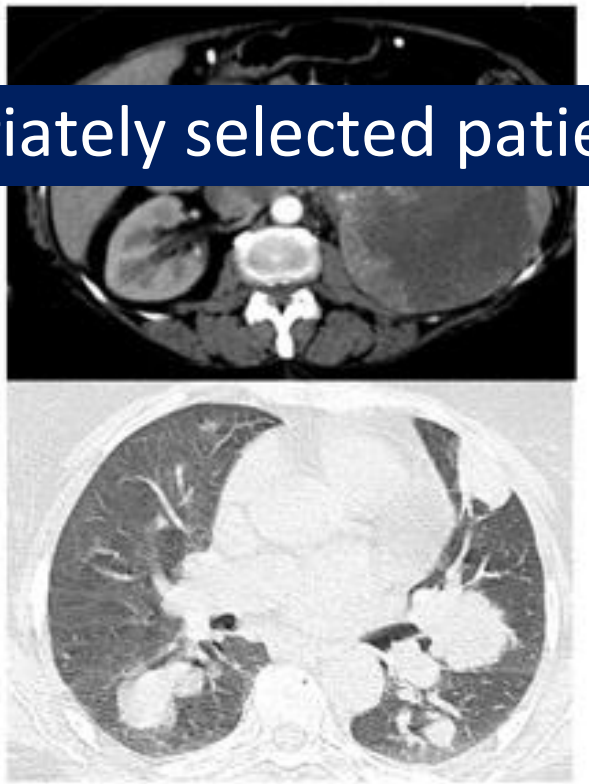
Nephrectomy makes sense

PS 0/1
Intermediate risk
Moderate extrarenal disease

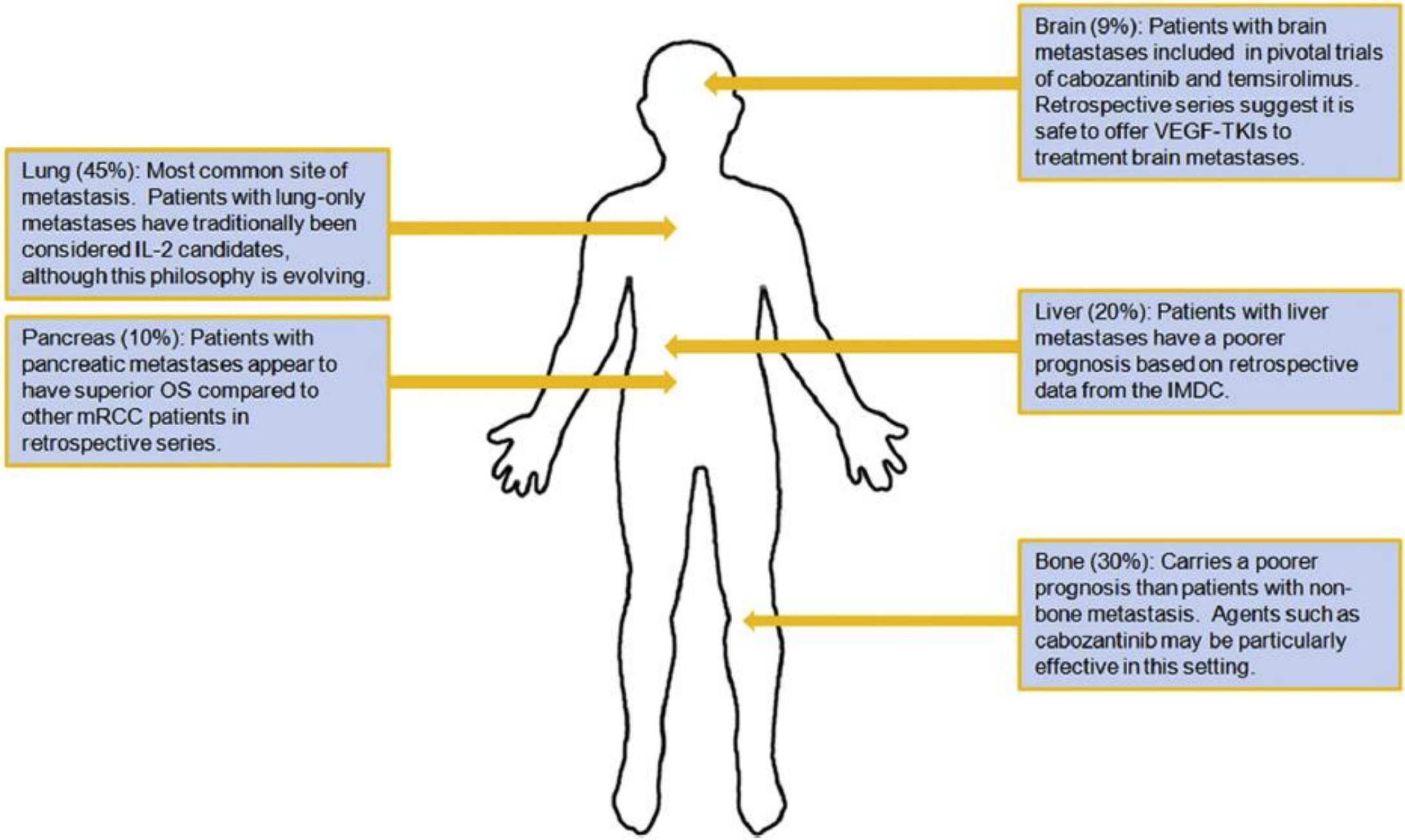


Nephrectomy may or may not be indicated

Poor PS, poor risk
Large primary
Extensive extrarenal disease



Nephrectomy does not make sense


Brain (9%): Patients with brain metastases included in pivotal trials of cabozantinib and temsirolimus. Retrospective series suggest it is safe to offer VEGF-TKIs to treatment brain metastases.
Lung (45%): Most common site of metastasis. Patients with lung-only metastases have traditionally been considered IL-2 candidates, although this philosophy is evolving.
Liver (20%): Patients with liver metastases have a poorer prognosis based on retrospective data from the IMDC.
Pancreas (10%): Patients with pancreatic metastases appear to have superior OS compared to other mRCC patients in retrospective series.
Bone (30%): Carries a poorer prognosis than patients with non-bone metastasis. Agents such as cabozantinib may be particularly effective in this setting.

Metastasectomy by Anatomic Site

- **Rare Metastatic Sites in mRCC : A Different Disease?**

	
Lung	Brain
Bone	Liver 
Adrenals	

Nasopharynx	3 (8.11)
Vagina	2 (5.40)
Omentum	1 (2.70)
Spleen	1 (2.70)
Stomach	1 (2.70)
Breast	1 (2.70)
Total	37 (100)

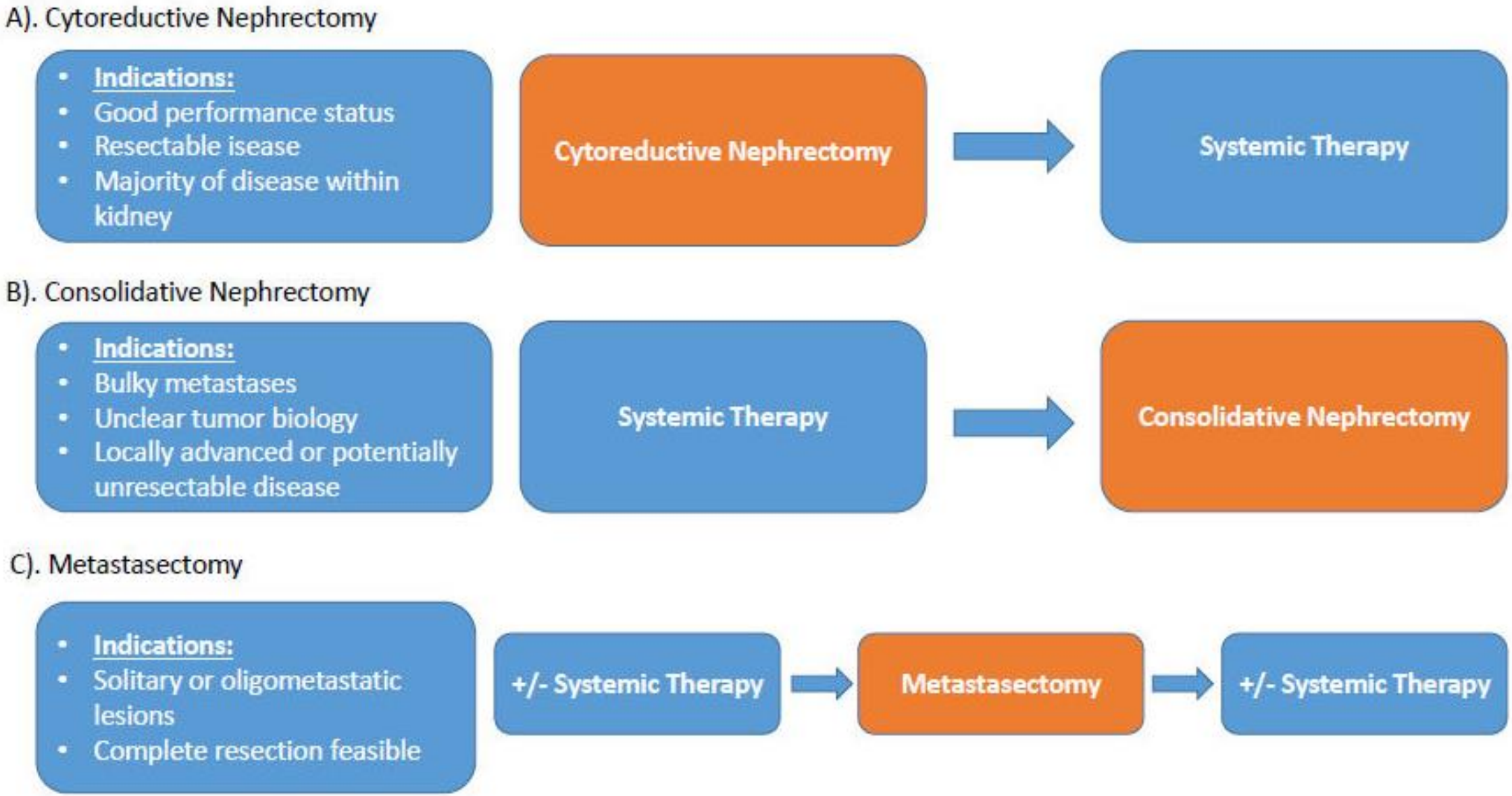
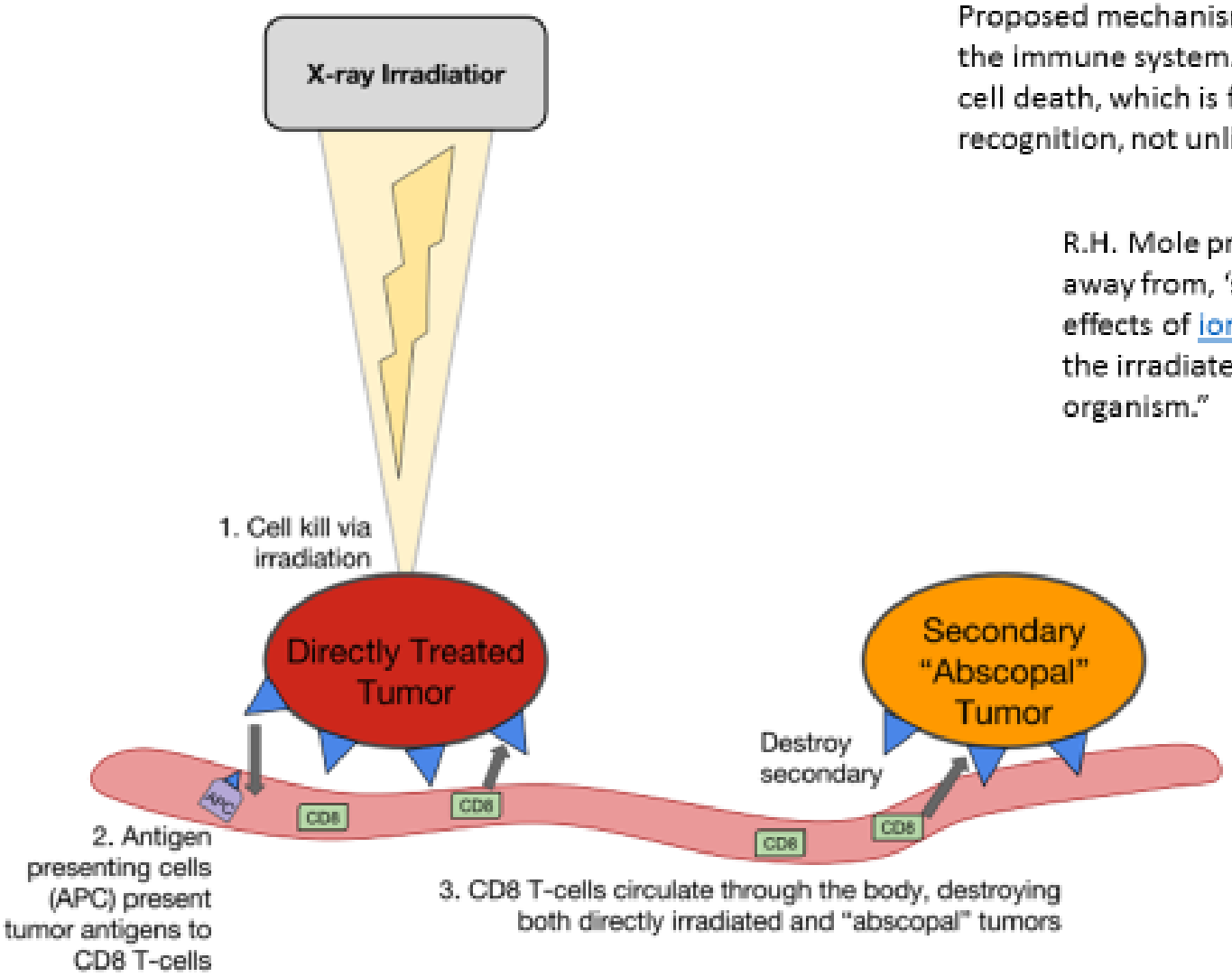


Figure 1. Timing of surgery and systemic therapy in metastatic renal cell carcinoma. Cytoreductive nephrectomy (A) refers to nephrectomy prior to systemic therapy, while consolidative nephrectomy (B) refers to systemic therapy prior to nephrectomy. (C) Metastasectomy refers to resection of metastatic lesions.

Thank you for your attention

? Questions ?

The Abscopal Effect:
A Reemerging Field of Interest



Proposed mechanism of the abscopal effect, mediated by the immune system. Here, local radiation causes tumor cell death, which is followed by adaptive immune system recognition, not unlike a vaccine.

R.H. Mole proposed the term "abscopal" ('ab' - away from, 'scopus' - target) in 1953 to refer to effects of ionizing radiation "at a distance from the irradiated volume but within the same organism."