Where are we today?
Evidence Based Medicine and the evolving treatment paradigm in mRCC

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Outline

- Introduction
- Clear cell RCC
  - Adjuvant treatment
  - mRCC
    - 1st line
    - 2nd line
    - Further line

RAMATHIBODI CANCER REPORT

2015

Table 3.2 Ten leading sites of cancer in male.

Site	ICD-O	Number of cases	%
1. PROSTATE GLAND	C61	204	14.3
2. LIVER AND INTRAHEPATIC BILE DUCTS	C22	194	13.6
3. LUNG AND BRONCHUS	C34	132	9.2
4. COLON	C18	122	8.5
5. HEMATOPOIETIC AND RETICULOENDOTHELIAL SYSTEMS	C42	88	6.1
6. RECTUM	C20	77	5.4
7. LYMPH NODES	C77	61	4.3
8. URINARY BLADDER	C67	60	4.2
9. SKIN	C44	58	4.0
10. KIDNEY	C64	45	3.1
11. Other		390	27.3
Total		**1,431**	**100.0**

Figure 3.2 Ten leading sites of cancer in male.

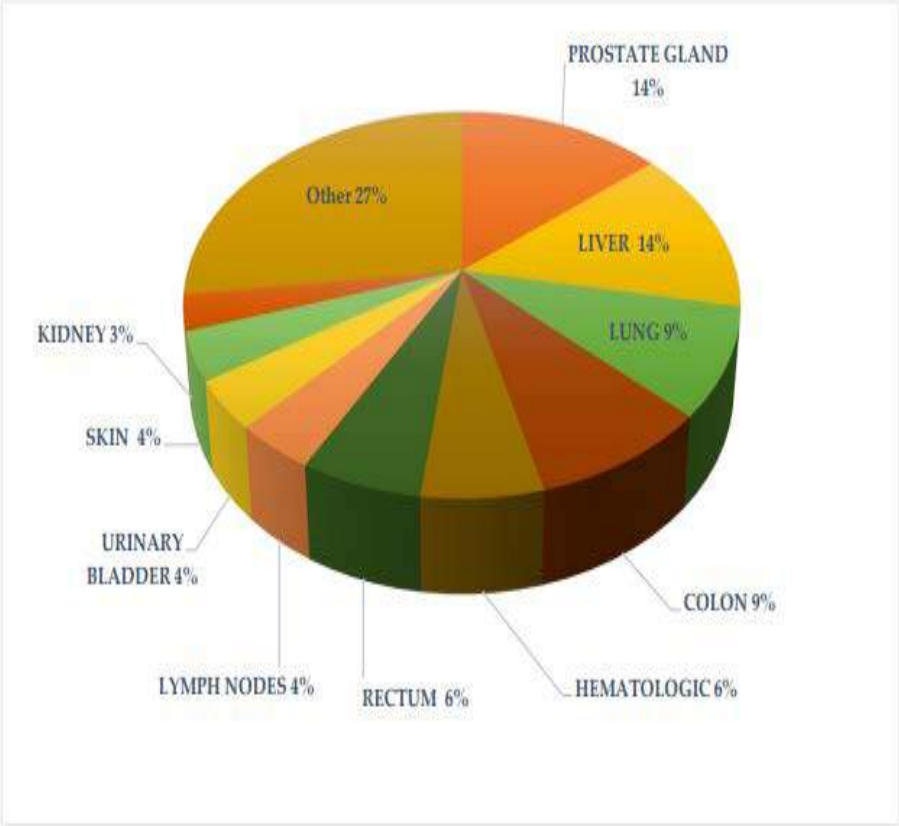


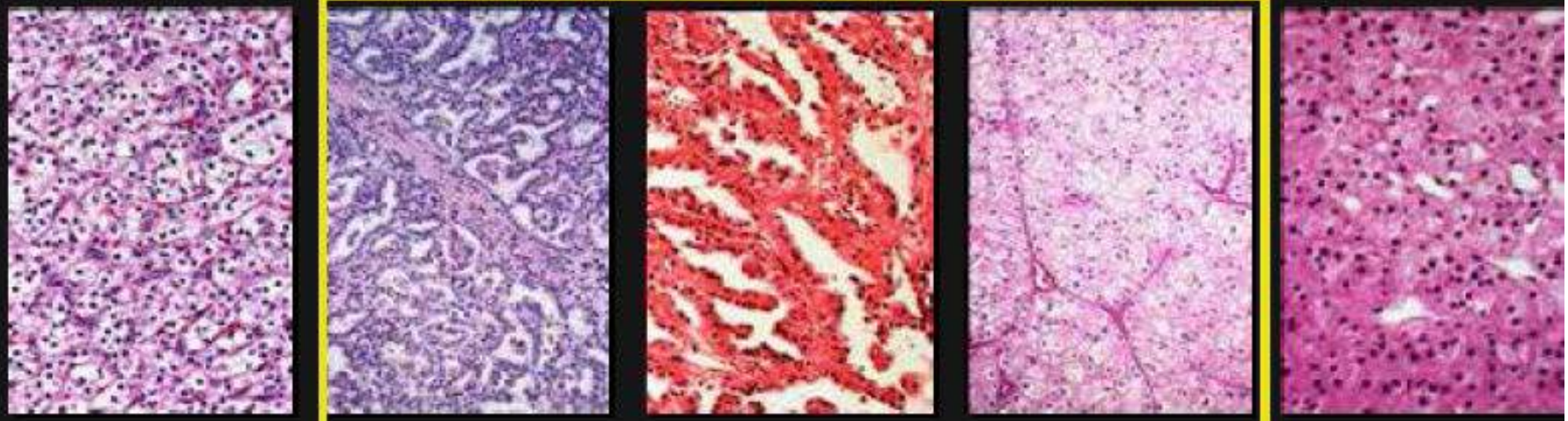
Table 4.1 Annual reports

Site	Male		Female		Total		ICD O
	N	(%)	N	(%)	N	(%)	
Bladder	60	4.2	21	1.1	81	2.4	C67
Kidney etc	51	3.6	26	1.4	77	2.3	C64-C66,C68
Penis	11	0.7	0	0.0	11	0.3	C60
Prostate	204	14.3	0	0.0	204	6.1	C61
Testis	8	0.5	0	0.0	8	0.2	C62
Thyroid	30	2.1	126	6.6	156	4.6	C73
Adrenal gland	4	0.3	1	0.1	5	0.2	C74
Other endocrine gland	4	0.3	2	0.1	6	0.2	C75
Other and ill-defined site	1	0.1	0	0.0	1	0.1	C76
Lymphnodes	61	4.3	70	3.6	131	3.9	C77
Unknown primary site	7	0.5	6	0.3	13	0.4	C80
All sites	1431	100	1906	100	3337	100	ALL

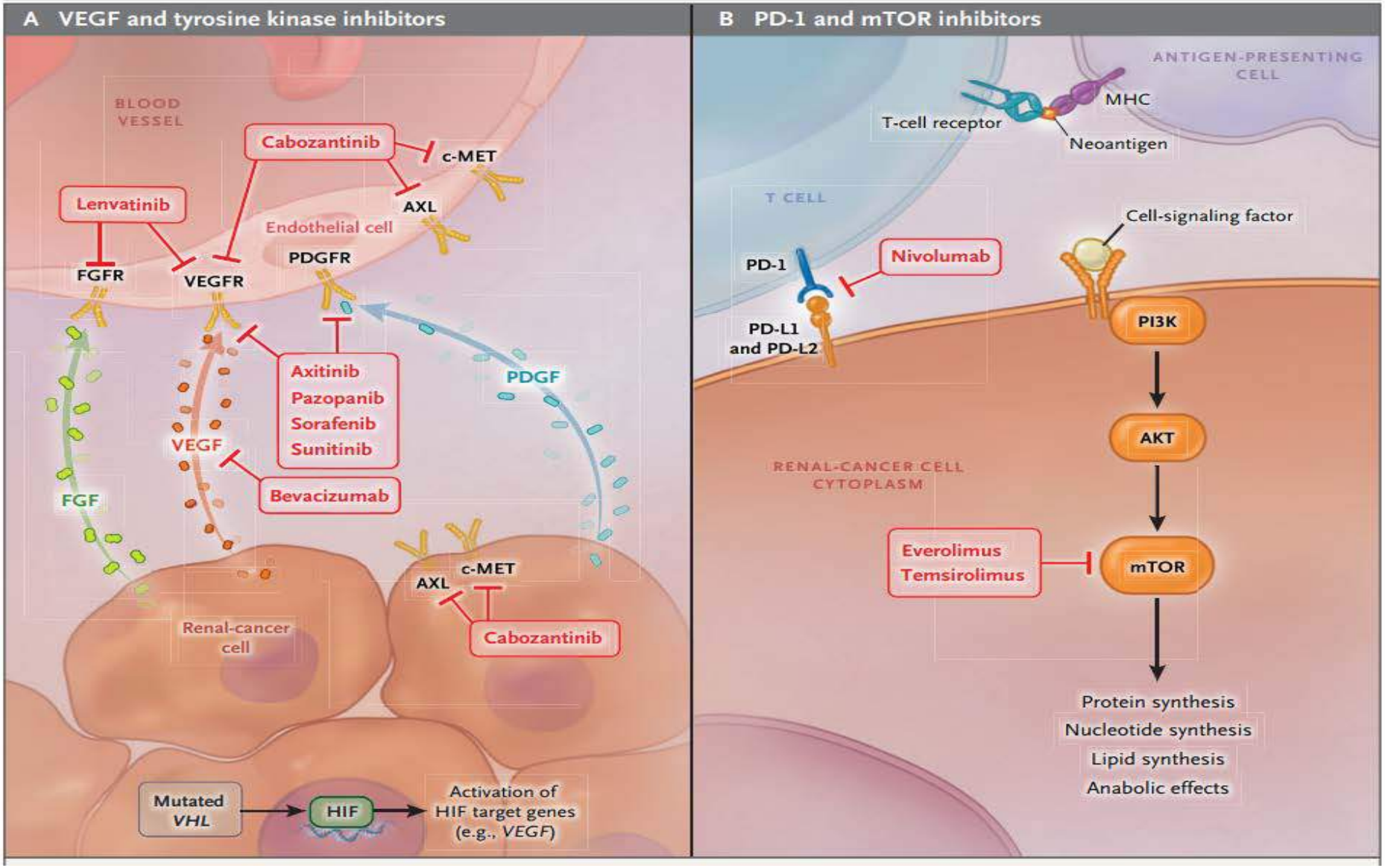
HOSPITAL-BASED CANCER REGISTRY 2015

	Bladder	RCC	Prostate	testis	penis
Case/yr	81	77	204	8	11

Pathology and gene expression



Clear Cell	Papillary Type 1	Papillary Type 2	Chromophobe	Oncocytoma
75%	5%	10%	5%	5%
VHL BAP1 PBRM1	cMET	FH cMYC	BHD	



Pathway and current drugs in mRCC

N Engl J Med 2017; 376:354-366

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

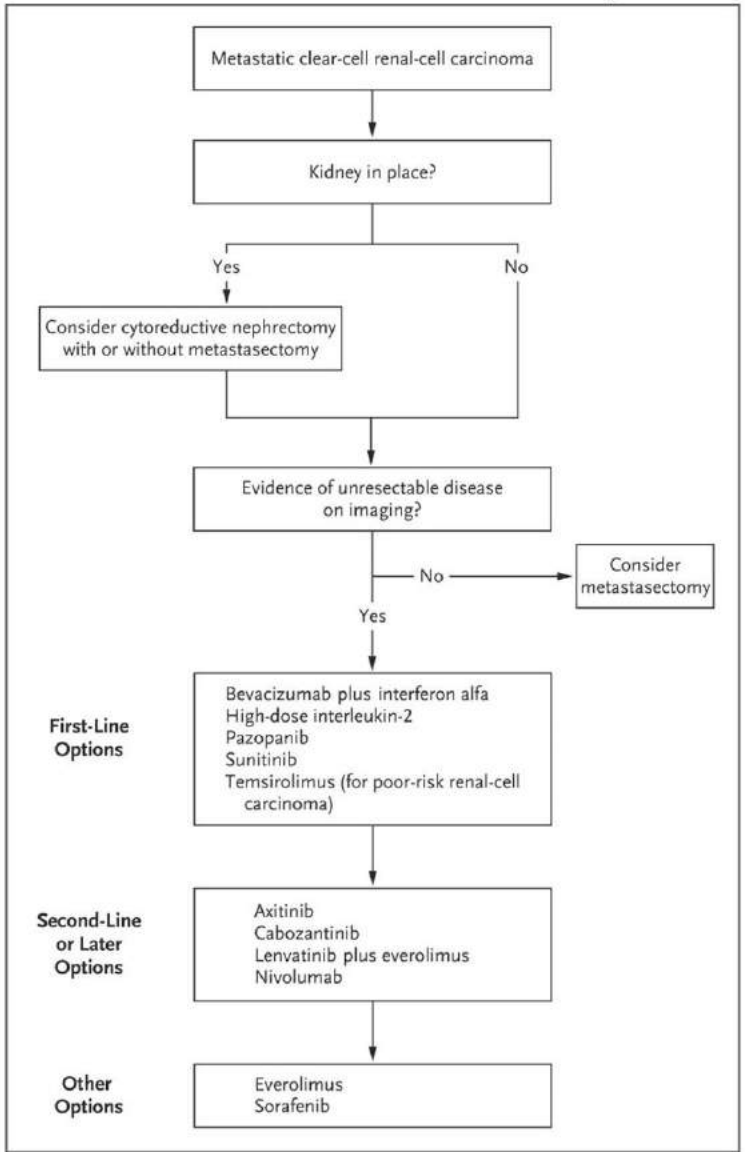
Systemic Therapy for Metastatic Renal-Cell Carcinoma

Toni K. Choueiri, M.D., and Robert J. Motzer, M.D.

N Engl J Med 2017; 376:354-366

RCC Decision making

Chouieri T, Motzer R. New Engl J Med 2017



- Surgical resection if feasible
- Consider high dose IL-2 in the appropriate patient
- Common front line therapies are sunitinib and pazopanib

Presented By Ulka Vaishampayan at 2017 Genitourinary Cancers Symposium

The Impact on Cytoreductive Nephrectomy on OS in the Era of TKI's

- No prospective data yet
- The majority of patients in the phase III trials had previously undergone nephrectomy
- CARMENA trial[1]: nephrectomy followed by sunitinib vs sunitinib alone, primary EP: OS
- Retrospective data[2,3] strongly show **benefits of surgery**

1.NCT00930033; PI: Arnaud Mejean; estimated completion date: May 2013
2.Choueiri T et al., J Urol 2011; 3. Abern *et al. Anticancer Res* 2014

Risk assessment: metastatic disease (Heng criteria)

- **Six risk factors:**
  - **Karnofsky performance status < 80%**
  - **Haemoglobin < lower limit of normal**
  - **Time from diagnosis to treatment < 1 year**
  - **Corrected calcium > upper limit of normal**
  - **Platelets > upper limit of normal**
  - **Neutrophils > upper limit of normal**

Frontline therapy in mRCC

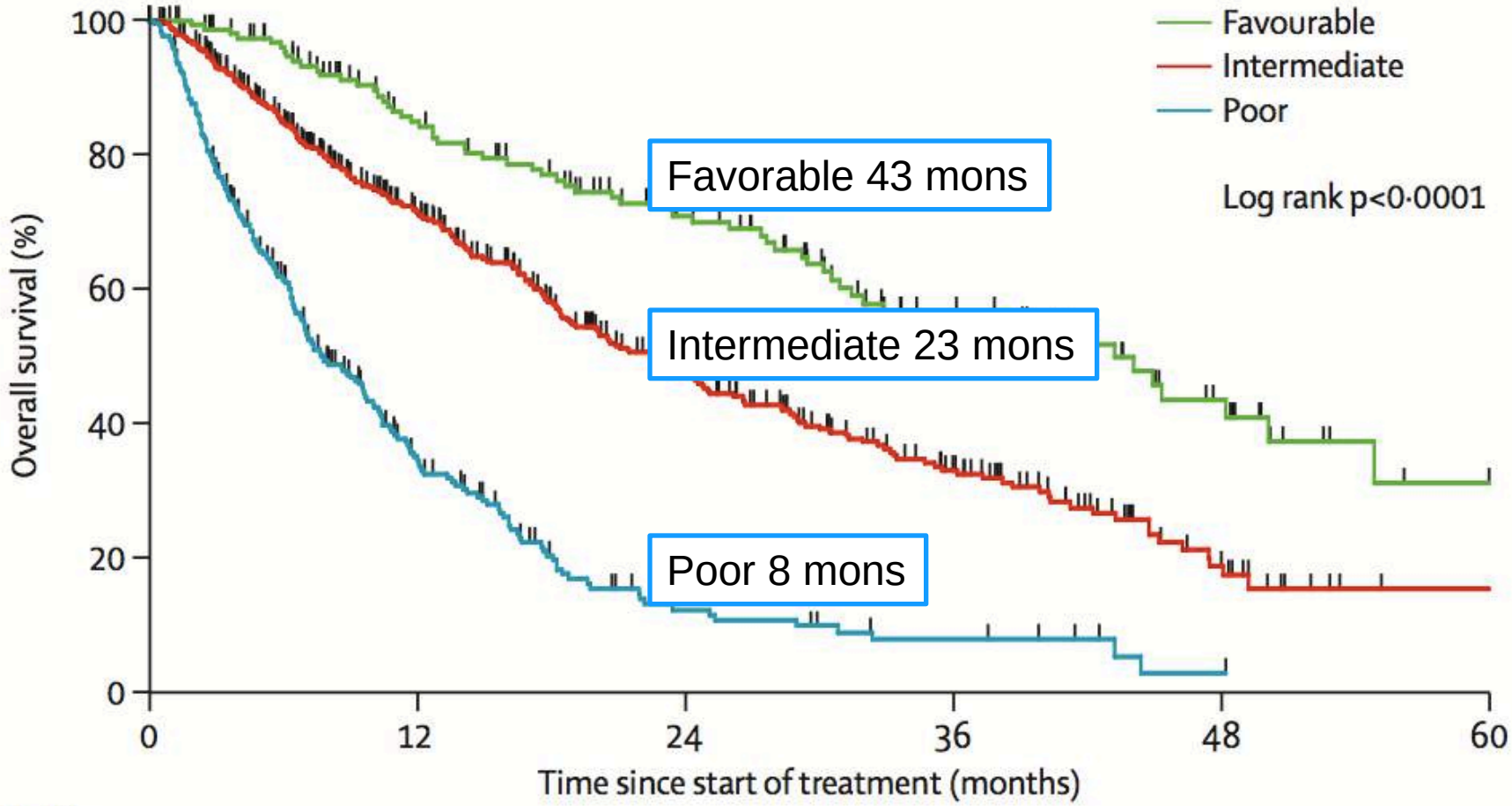
First-line treatment of good/intermediate mRCC: Current options

Study	ORR, %	Median PFS, mo*	Median OS, mo*
Sunitinib vs IFN-α[1]	47 vs. 12	11 vs. 5 *P* < 0.001	26.4 vs 21.8 *P* = 0.051
Bevacizumab + IFN-α vs IFN-α[2]	31 vs. 13	10.2 vs. 5.4 *P* = 0.0001	23.3 vs. 21.3 *P* = 0.91
Bevacizumab + IFN-α vs IFN-α[3]	25.5 vs. 13.1	8.5 vs. 5.2 *P* = 0.0001	18.3 vs. 17.4 *P* = 0.097
Pazopanib vs placebo[6]	32 vs. 4	9.2 vs. 4.2 *P* = 0.0001	22.9 vs. 20.5 *P* = 0.224
Pazopanib vs Sunitinib[7]	31 vs. 24	8.4 vs. 9.4 noninferior	28.4 vs 29.3 noninferior

*Intent to treat analysis

1. Motzer RJ et al. *J Clin Oncol*, 2009; 2. Escudier B et al. *Lancet* 2007. 3. Rini B et al. *J Clin Oncol*, 2008; 4. Escudier B et al. *J Clin Oncol*, 2009; 5. Hudes G et al. *N Engl J Med*. 2007. 6. Sternberg C et al. *J Clin Oncol*, 2010; Motzer et al NEJM 2013

IMDC Prognostic Factors



Number at risk

Favourable	157	109	74	40	17	3
Intermediate	440	247	122	59	15	1
Poor	252	65	15	7	1	0

Heng et al Lancet Oncology 2013

Benchmarks from IMDC

Population (Data from IMDC)	PFS (mon) (95% CI)	OS (mon) (95%CI)
1st line therapy (all pts)	7.2 (6.7-7.7) n=2659	20.9 (19.6-22.5) n=2705
1st line therapy in intermediate/poor risk patients & diagnosis to treatment interval < 1 year *(similar to ADAPT (AGS003) pts)*	5.6 (5.3-6.1) n=1174	14.7 (13.3-16.5) n=1189
1st line therapy in patients with prior nephrectomy *(similar to TIVO-1 (Tivozanib) pt)*	8.2 (7.8-8.6) n=2080	24.8 (23.1-27.3) n=2117
2nd line therapy *(similar to INTORSECT patients)*	3.9 (3.6-4.3) n=1151	13.0 (12.2-14.7) n=1157
3rd line therapy (all pts)	4.0 (3.4-4.5) n=425	12.1 (10.7-13.9) n=455
3rd line therapy in patients with 1 prior VEGF and 1 prior mTOR inhibitor *(similar to GOLD (dovitinib) pts)*	4.4 (3.3-5.2) n=140	18.0 (11.8-24.0) n=147

Ko et al BJC 2014

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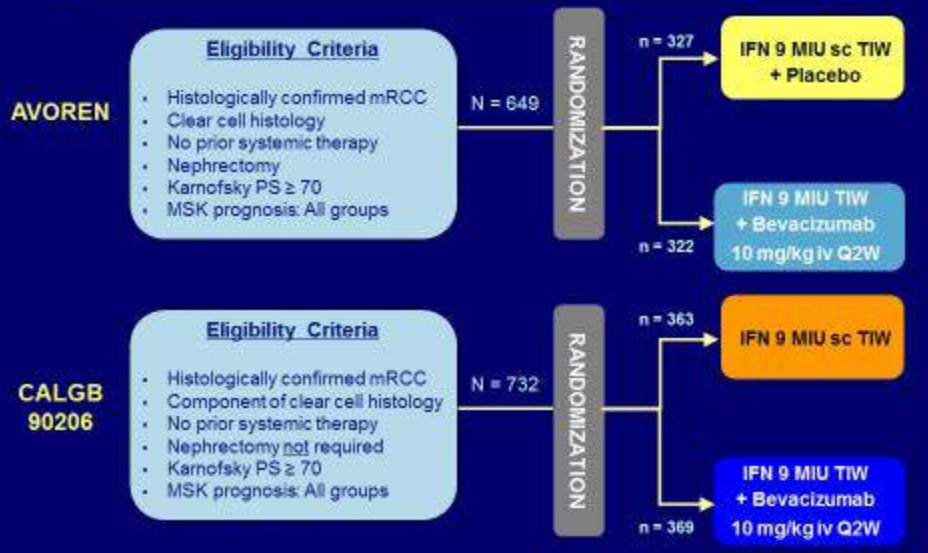
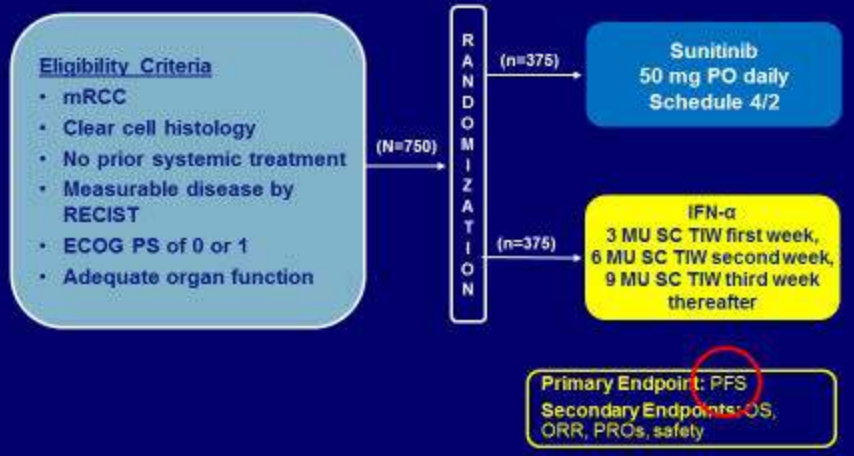
Ko et al BJC 2014

Bevacizumab and interferon-α



Escudier B, Koralewski P, Pluzanska A, et al. *J Clin Oncol*. 2007;25(suppl 18
Rini BI, et al. *J Clin Oncol*. 2009;27(Suppl 18s):LBA5015 (Abstra

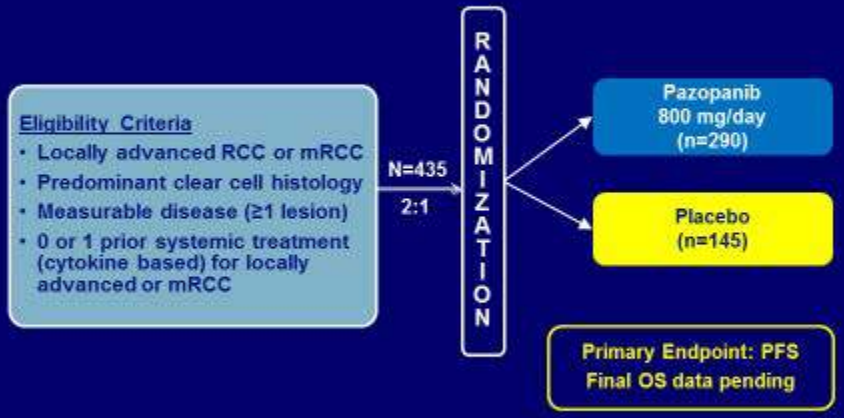
Pivotal phase 3 study of first-line sunitinib in mRCC



ECOG PS = Eastern Cooperative Oncology Group Performance Status; PO = by mouth; Schedule 4/2 = 4 weeks on treatment, 2 weeks off; SC = subcutaneously; TWI = three times weekly

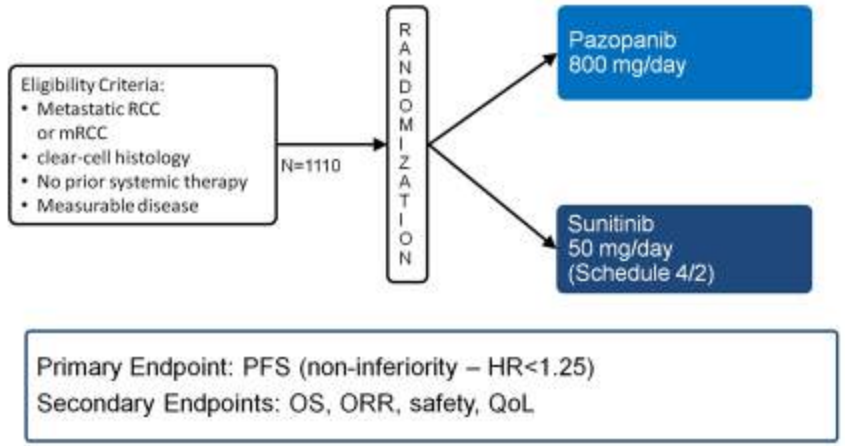
Motzer RJ, et al. *N Engl J Med* 2007;356:115–124

Pazopanib vs. placebo for first- and second-line mRCC treatment



Sternberg C, et al. *J Clin Oncol*. 2010

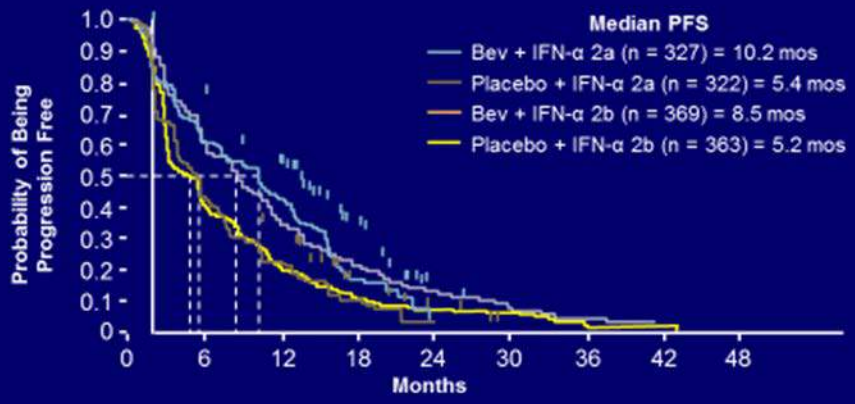
Pazopanib vs Sunitinib in 1st line mRCC (COMPARZ)



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

Presented By Ulka Vaishampayan at 2017 Genitourinary Cancers Symposium

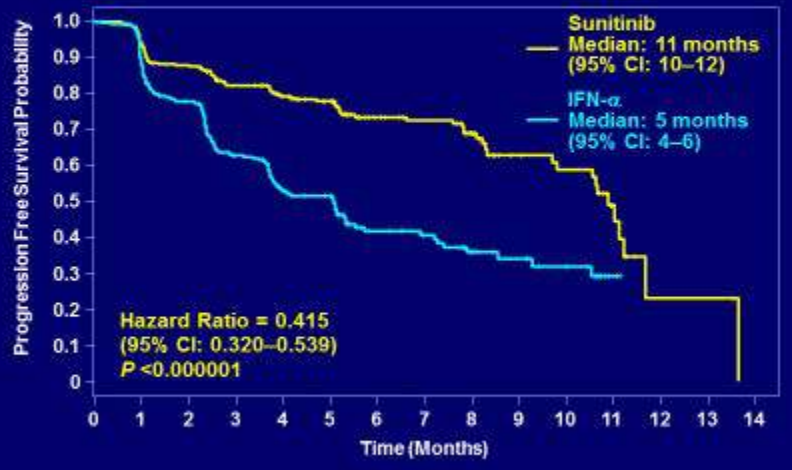
AVOREN[1] and CALGB 90206[2]: PFS* in evaluable patients



*AVOREN: primary endpoint, OS: Bev + IFN = NR; IFN + placebo = 19.8 mos (HR: 0.75; $P < .0267$) at interim analysis.[3] CALGB 90206: primary endpoint, OS: NR.[2]

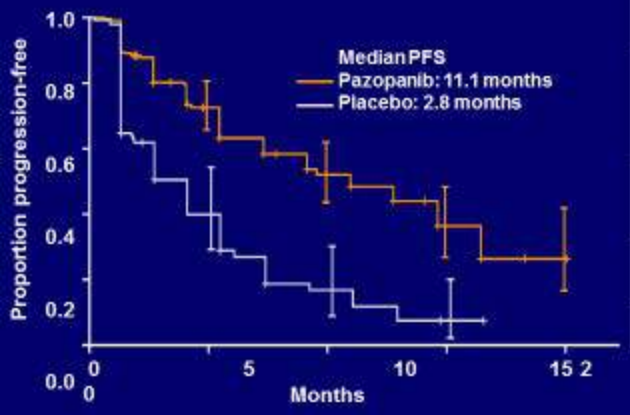
1. Escudier B, et al. Lancet. 2007;370:2103-2111.
2. Rini, BI, et al. J Clin Oncol. 2008;26:5422-5428.
3. Escudier B, et al. ASCO 2009. Abstract 5025.

Phase 3 study of first-line sunitinib in mRCC Progression-free survival



Motzer NEJM 2007
Figlin ASCO 2008
Motzer JCO 2009

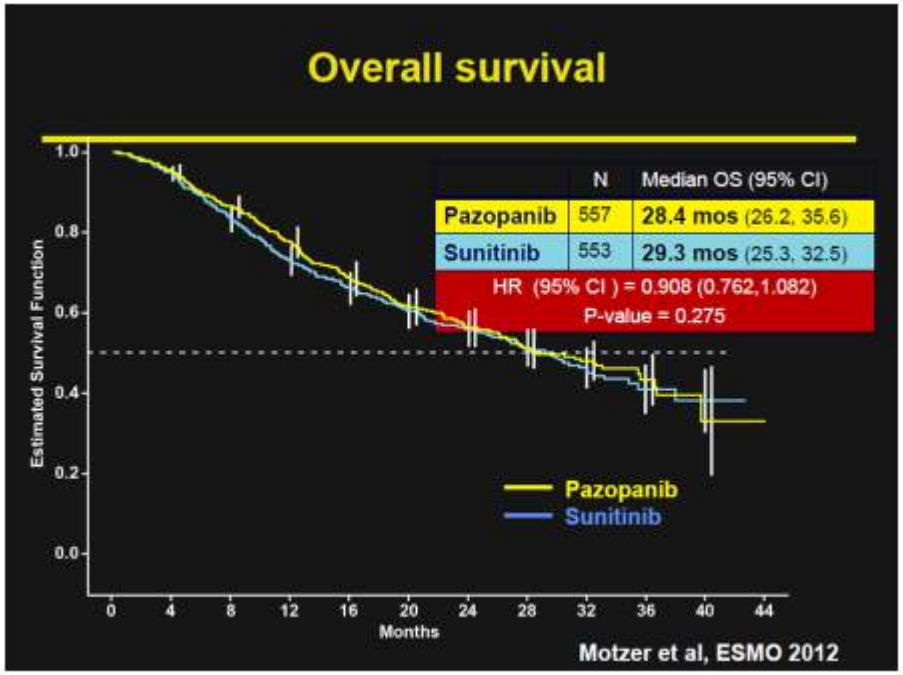
PFS / RR in treatment-naïve subpopulation



	Pazopanib (n=290)
ORR (CR + PR), %	
Overall population	30
Treatment-naïve	32
Cytokines	29
Duration of response, weeks	59
% of placebo pts crossing over at PD	48%
Preliminary Med OS	21 months

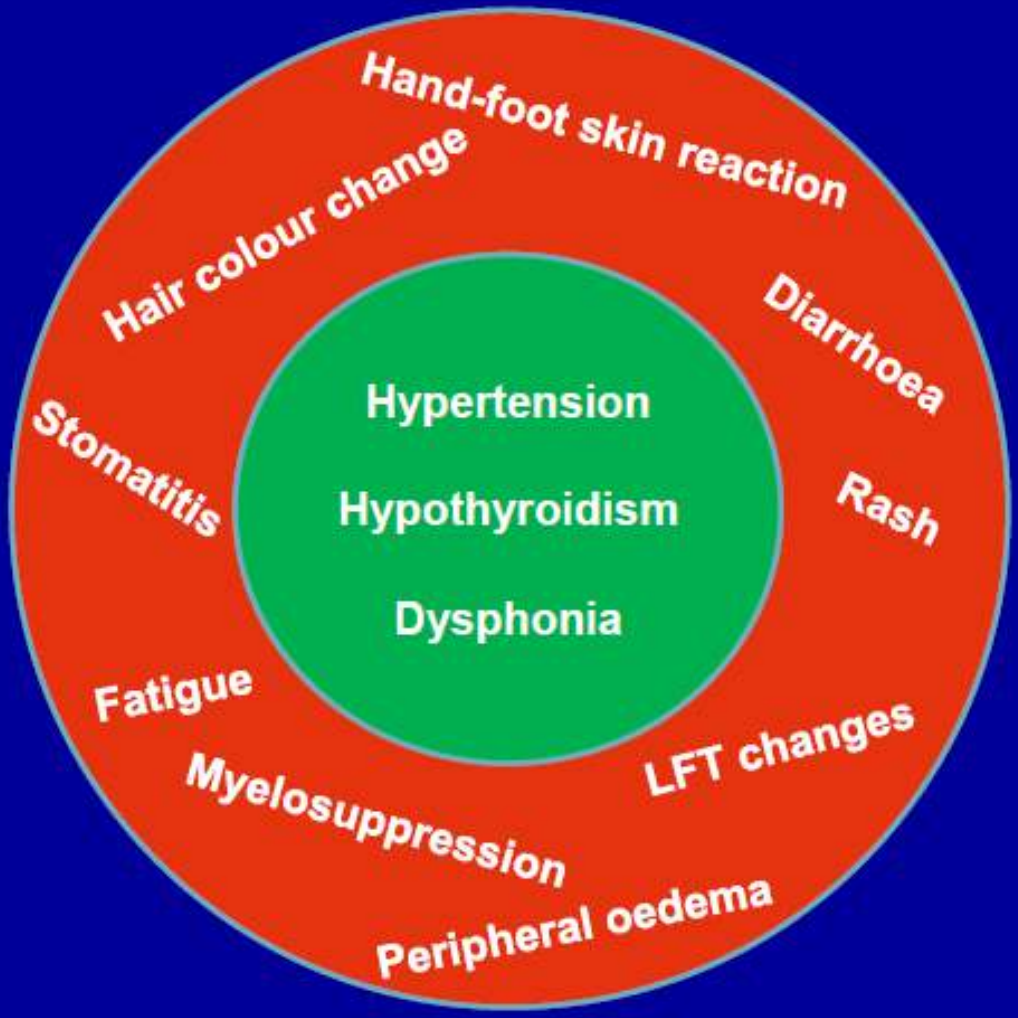
Sternberg CN, et al. J Clin Oncol. 2009;27(Suppl 15s):5021 (Abstract)

Overall survival

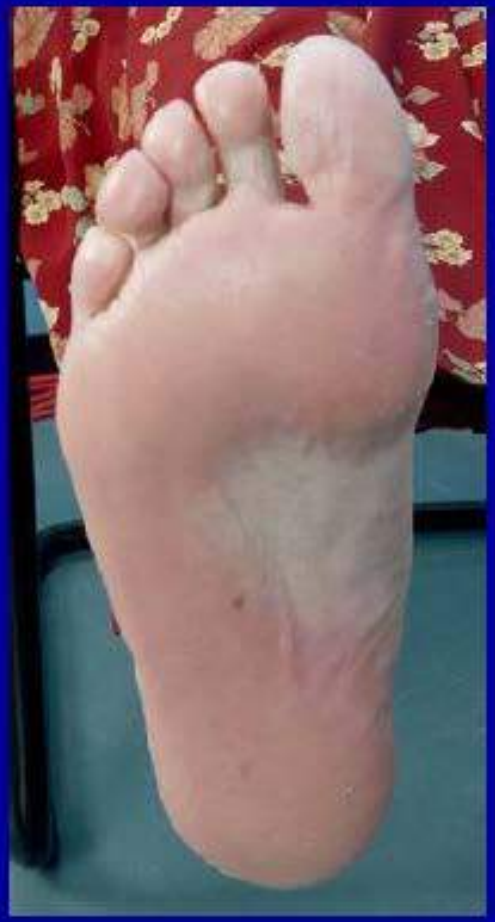


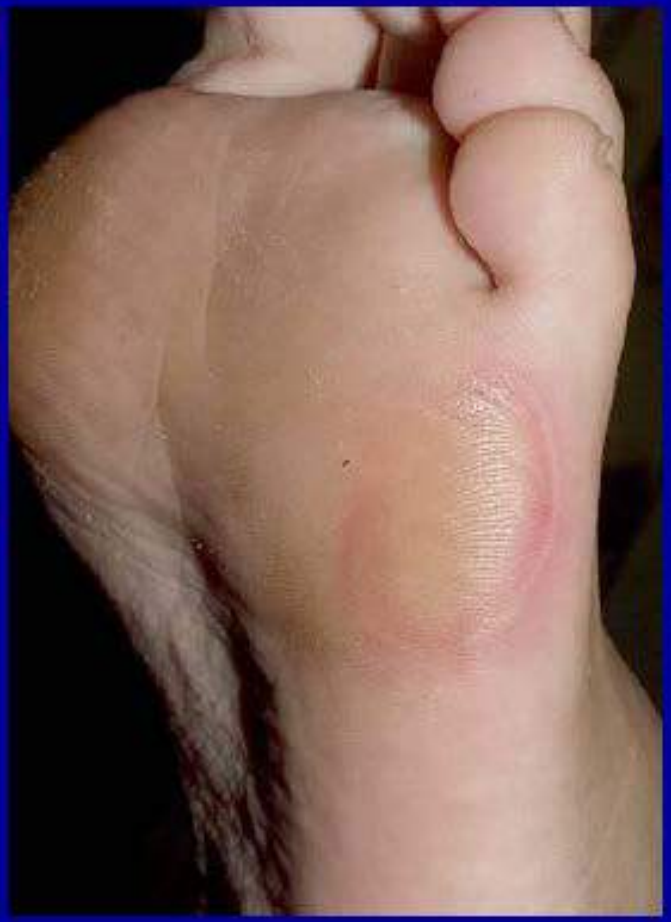
Motzer et al, ESMO 2012

On-Target V Off-Target Side Effects



Hand-Foot Skin Reaction





Common Adverse Events

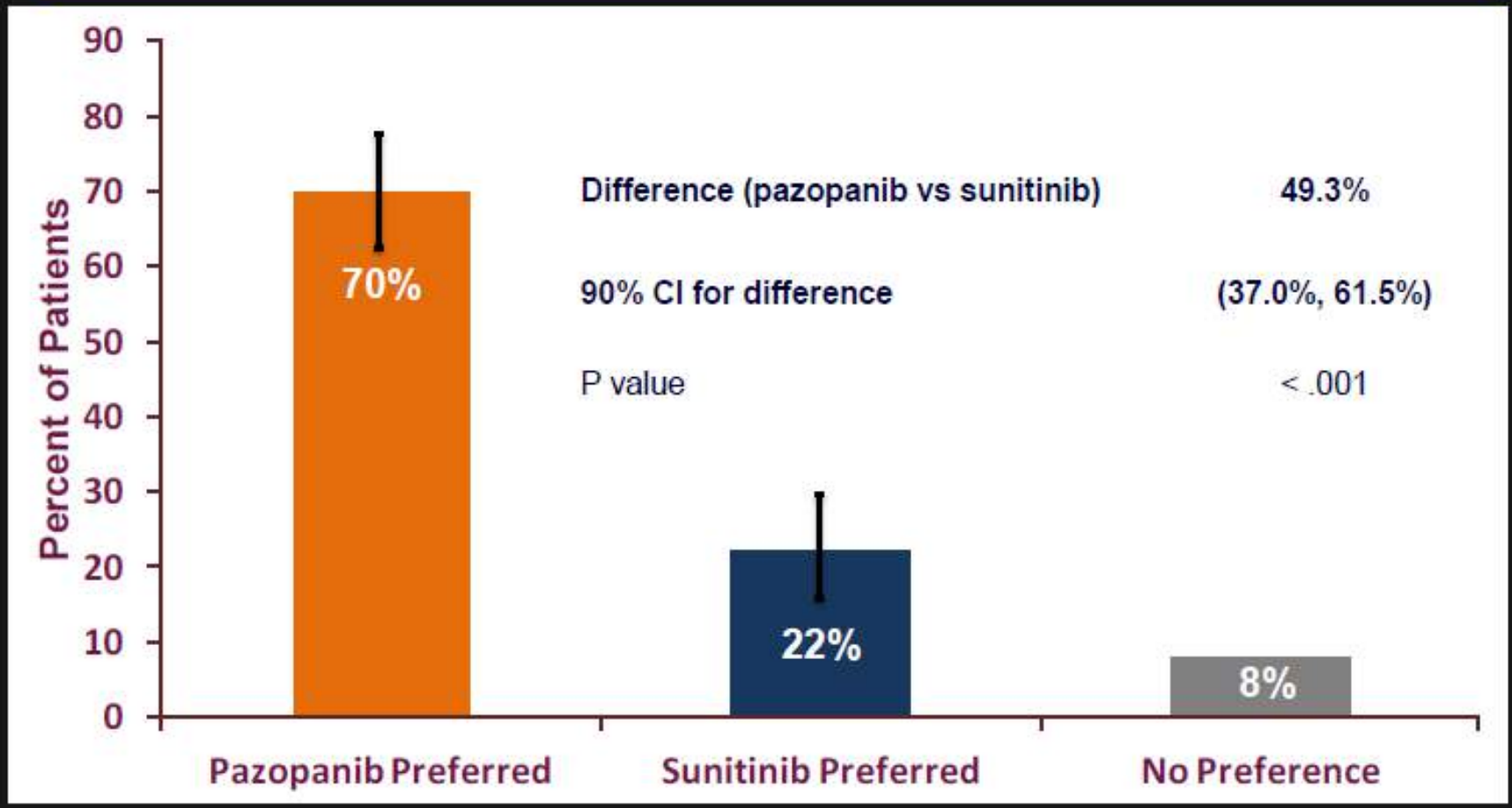
	Pazopanib (n = 554), %	Sunitinib (n = 548),%
Chemistry labs (≥35%)	**All Grades**	**All Grades**
ALT	60	43
Hypoalbuminemia	33	42
Bilirubin	36	27
Creatinine	32	46
Hypophosphatemia	36	52
Leukopenia	43	78
Neutropenia	37	68
Thrombocytopenia	41	78
Lymphopenia	38	55
Anemia	31	60

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

Table 1. Adverse Events and Laboratory Abnormalities during Treatment for Which the Relative Risk Differed Significantly between Groups.*

Event	Pazopanib (N = 554)			Sunitinib (N = 548)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse events						
Increased risk with sunitinib — no. of patients (%)†						
Fatigue‡	302 (55)	58 (10)	1 (<1)	344 (63)	92 (17)	2 (<1)
Hand–foot syndrome‡	163 (29)	32 (6)	0	275 (50)	62 (11)	2 (<1)
Dysgeusia	143 (26)	1 (<1)	0	198 (36)	0	0
Rash	97 (18)	4 (1)	0	125 (23)	4 (1)	0
Constipation	94 (17)	4 (1)	0	130 (24)	5 (1)	0
Dyspepsia	78 (14)	0	0	133 (24)	3 (1)	0
Stomatitis	77 (14)	4 (1)	0	150 (27)	8 (1)	0
Hypothyroidism	67 (12)	0	0	133 (24)	2 (<1)	0
Pain in a limb	67 (12)	2 (<1)	0	91 (17)	6 (1)	0
Mucosal inflammation‡	61 (11)	3 (1)	0	141 (26)	16 (3)	0
Peripheral edema	59 (11)	1 (<1)	0	91 (17)	2 (<1)	0
Epistaxis	48 (9)	1 (<1)	0	97 (18)	6 (1)	0
Pyrexia	48 (9)	2 (<1)	0	88 (16)	6 (1)	0
Increased blood LDH	39 (7)	2 (<1)	0	58 (11)	3 (1)	0
Increased blood thyrotropin	31 (6)	0	0	66 (12)	0	0
Gastroesophageal reflux disease	19 (3)	1 (<1)	0	56 (10)	2 (<1)	0
Yellow skin	4 (1)	0	0	83 (15)	0	0
Increased risk with pazopanib — no. of patients (%)§						
Changes in hair color	168 (30)	0	0	53 (10)	1 (<1)	0
Weight loss	84 (15)	5 (1)	0	33 (6)	1 (<1)	0
Alopecia	75 (14)	0	0	45 (8)	0	0
Hematologic and other laboratory abnormalities						
Increased risk with sunitinib — no. of patients/total no. (%)¶						
Leukopenia‡	237/548 (43)	8/548 (1)	0/548	423/542 (78)	34/542 (6)	0/542
Thrombocytopenia‡	227/548 (41)	17/548 (3)	3/548 (1)	421/542 (78)	95/542 (18)	22/542 (4)
Lymphocytopenia‡	208/548 (38)	29/548 (5)	0/548	300/542 (55)	76/542 (14)	1/542 (<1)
Neutropenia‡	203/548 (37)	20/548 (4)	5/548 (1)	370/542 (68)	103/542 (19)	6/542 (1)
Anemia‡	171/548 (31)	7/548 (1)	5/548 (1)	326/542 (60)	34/542 (6)	6/542 (1)
Hypophosphatemia‡	193/539 (36)	24/539 (4)	0/539	279/533 (52)	44/533 (8)	5/533 (1)
Hypoalbuminemia	179/544 (33)	4/544 (1)	0/544	225/539 (42)	9/539 (2)	0/539
Increased creatinine	177/548 (32)	4/548 (1)	0/548	250/542 (46)	5/542 (1)	3/542 (1)
Hypomagnesemia‡	125/539 (23)	1/539 (<1)	0/539	128/535 (24)	6/535 (1)	1/535 (<1)
Hypermagnesemia‡	62/539 (12)	13/539 (2)	0/539	97/535 (18)	25/535 (5)	0/535
Increased risk with pazopanib — no. of patients/total no. (%)						
Increased AST‖	333/547 (61)	62/547 (11)	7/547 (1)	323/541 (60)	15/541 (3)	0/541
Increased ALT§‖	326/547 (60)	84/547 (15)	12/547 (2)	234/540 (43)	19/540 (4)	2/540 (<1)
Increased total bilirubin§	199/546 (36)	16/546 (3)	2/546 (<1)	144/541 (27)	11/541 (2)	2/541 (<1)
Increased alkaline phosphatase‖	154/547 (28)	17/547 (3)	0/547	131/540 (24)	5/540 (1)	0/540
Hypoglycemia§	83/548 (15)	2/548 (<1)	0/548	57/541 (11)	3/541 (1)	0/541

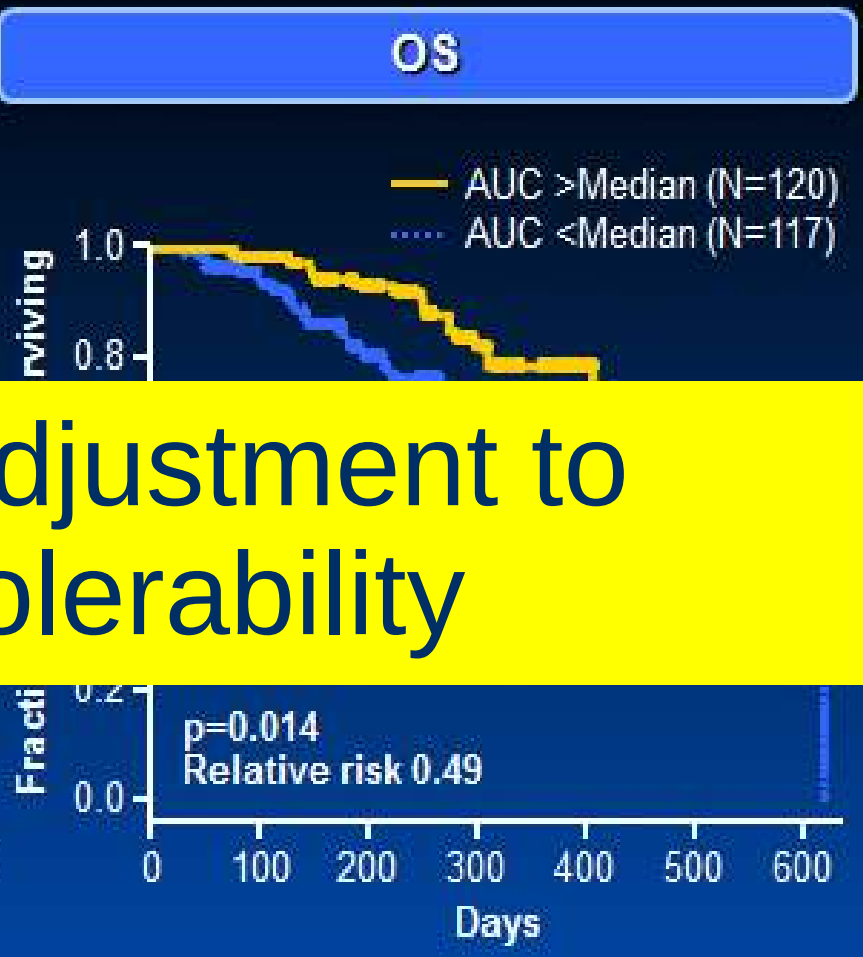
Primary Endpoint: Patient Preference
Primary Analysis Population



Escudier ASCO 2012

Abbreviation: CI, confidence interval.

Higher Exposure to Sunitinib Is Associated with Longer Time to Progression and OS



Need dose adjustment to improve tolerability

Source: Houk BE, et al. Cancer Chemother Pharmacol 2010, 66:357-371

First-line treatment of good/intermediate mRCC: Current options

Study	ORR, %	Median PFS, mo*	Median OS, mo*
Sunitinib vs IFN-α[1]	47 vs. 12	11 vs. 5 *P* < 0.001	26.4 vs 21.8 *P* = 0.051
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Trials leading to FDA Approval for agents in mRCC

Drug	Line of therapy	FDA Approval	Patients	Control Arm	PFS (months) vs. control	OS (months) vs. control
Interleukin-2[1]	First	1992	255	None	15% ORR	
Temsirolimus[14]	First#	2007	626	Interferon	5.5 vs. 3.1	10.9 vs 7.3*
Sunitinib[9,56]	First	2006	750	Interferon	11.0 vs. 5.0	26.4 vs 21.8
Bevacizumab + interferon[10,57]	First	2009	649	Interferon	10.2 vs. 5.4	23.3 vs 21.3^
Pazopanib[11]	First/Second[C]	2009	435	Placebo	9.2 vs. 4.2	22.9 vs. 20.5^
Sorafenib[6]	Second[C]	2005	903	Placebo	5.5 vs. 2.8	19.3 vs. 15.9 ^
Everolimus[23,58]	Second[TKI]	2009	410	Placebo	4.9 vs. 1.9	14.8 vs. 14.4^
Axitinib[24,25]	Second[S]	2012	723	Sorafenib	6.7 vs. 4.7	20.1 vs. 19.2^
Nivolumab[27]	Second[AA]	2015	821	Everolimus	4.6 vs. 4.4^	25.0 vs. 19.6*
Cabozantinib[28,59]	Second[AA]	2016	658	Everolimus	7.4 vs 3.8	21.4 vs. 16.5
Lenvatinib + Everolimus[29,60]	Second[AA]	2016	153	Everolimus	14.6 vs. 5.5	25.5 vs. 15.4

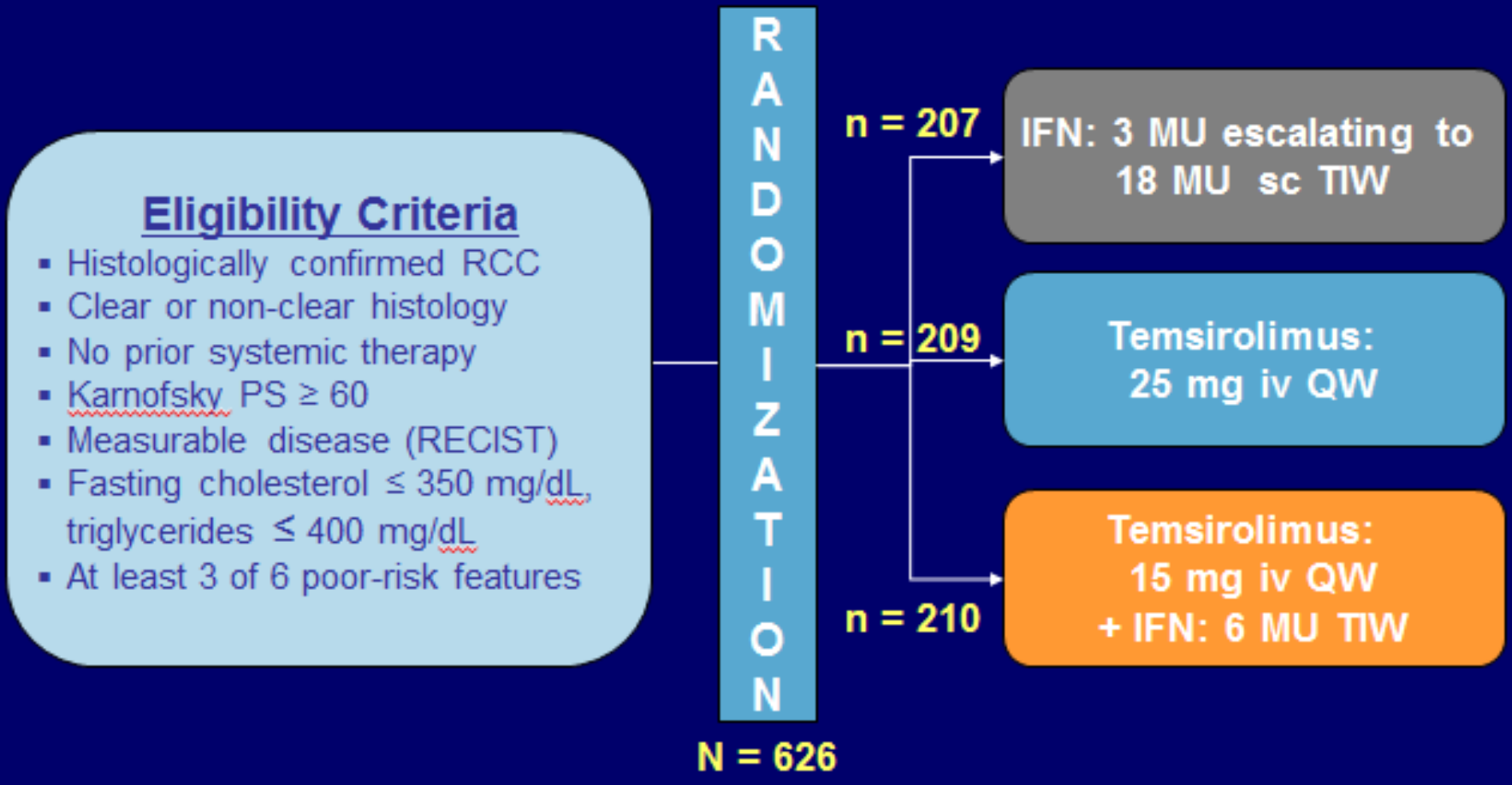
#At least 3 poor prognostic factors
*OS primary outcome
^Did not reach statistical significance

Previous Treatment: C=cytokines, TKI = sorafenib or sunitinib, S = systemic, AA = anti-angiogenic
PFS = progression free survival, OS = overall survival, ORR = overall response rate

Presented By Ulka Vaishampayan at 2017 Genitourinary Cancers Symposium

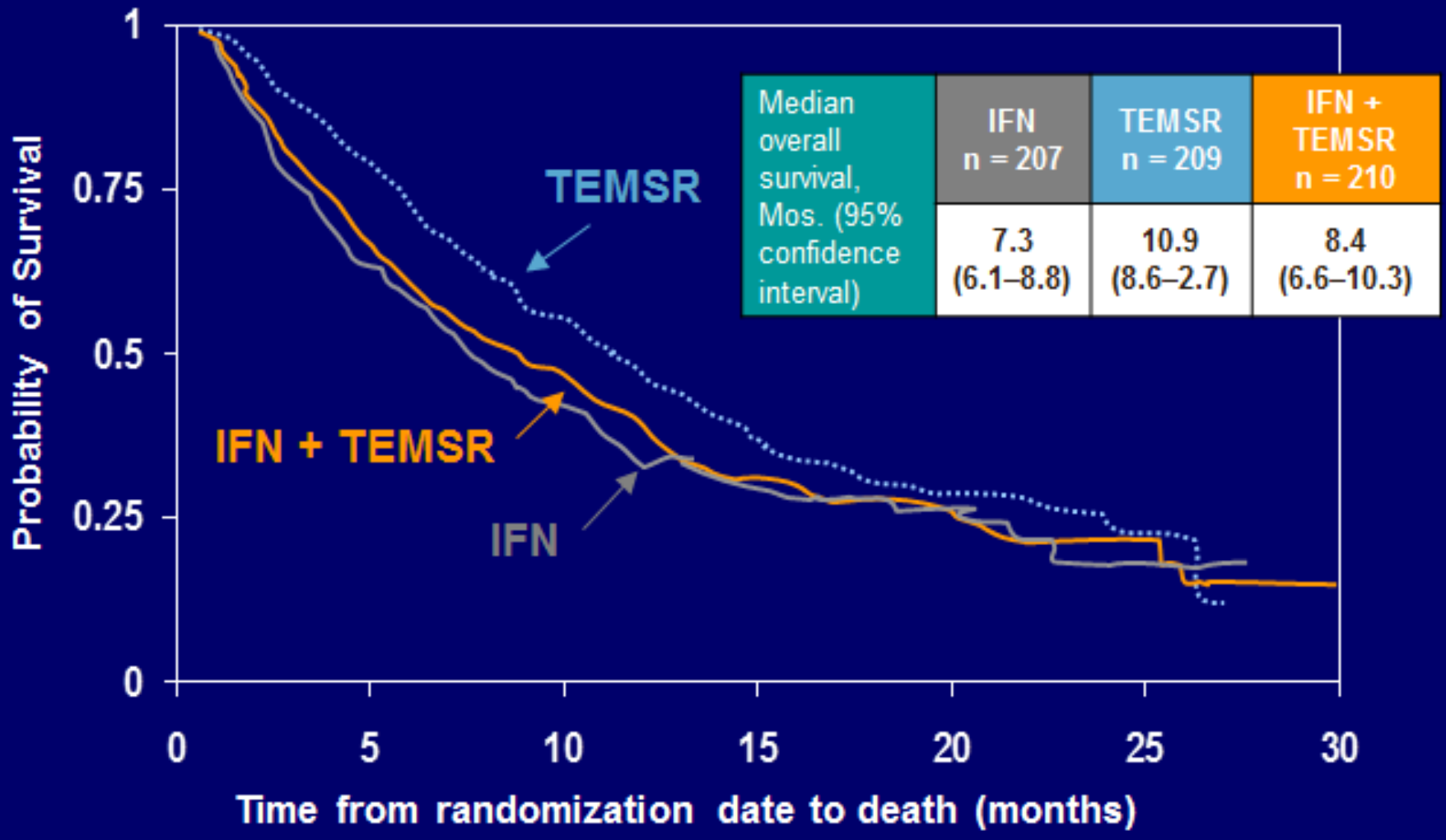
Poor risk group mRCC

Phase 3 study of temsirolimus and IFN in advanced RCC (ARCC trial)



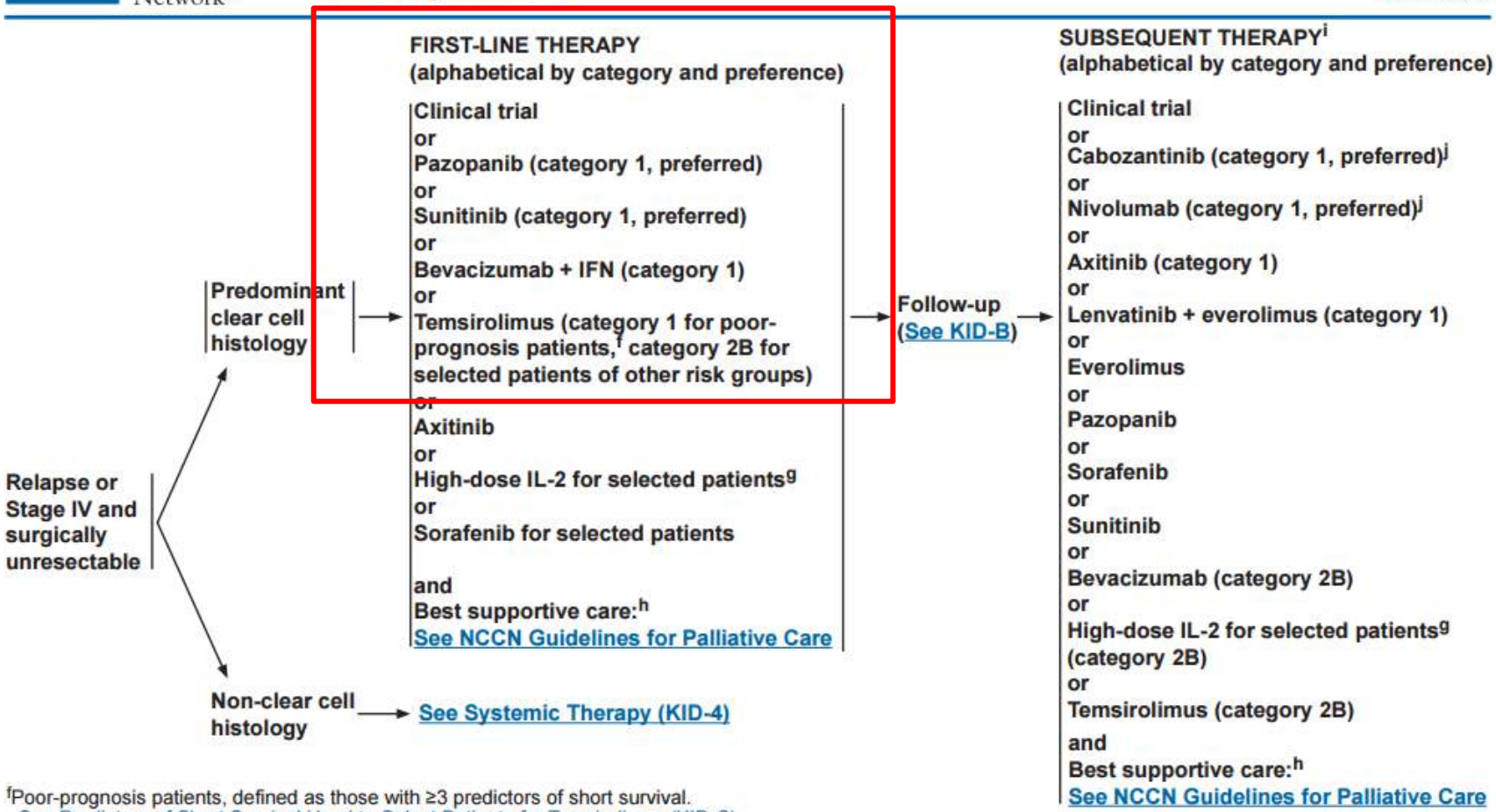
Hudes G *et al. N Engl J Med.* 2007;356:2271-2281.

Overall survival was superior with temsirolimus versus interferon



Median overall survival, Mos. (95% confidence interval)	IFN n = 207	TEMSR n = 209	IFN + TEMSR n = 210
	7.3 (6.1–8.8)	10.9 (8.6–2.7)	8.4 (6.6–10.3)

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



[f]Poor-prognosis patients, defined as those with ≥3 predictors of short survival.
See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-C).

[g]Patients with excellent performance status and normal organ function.

[h]Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.

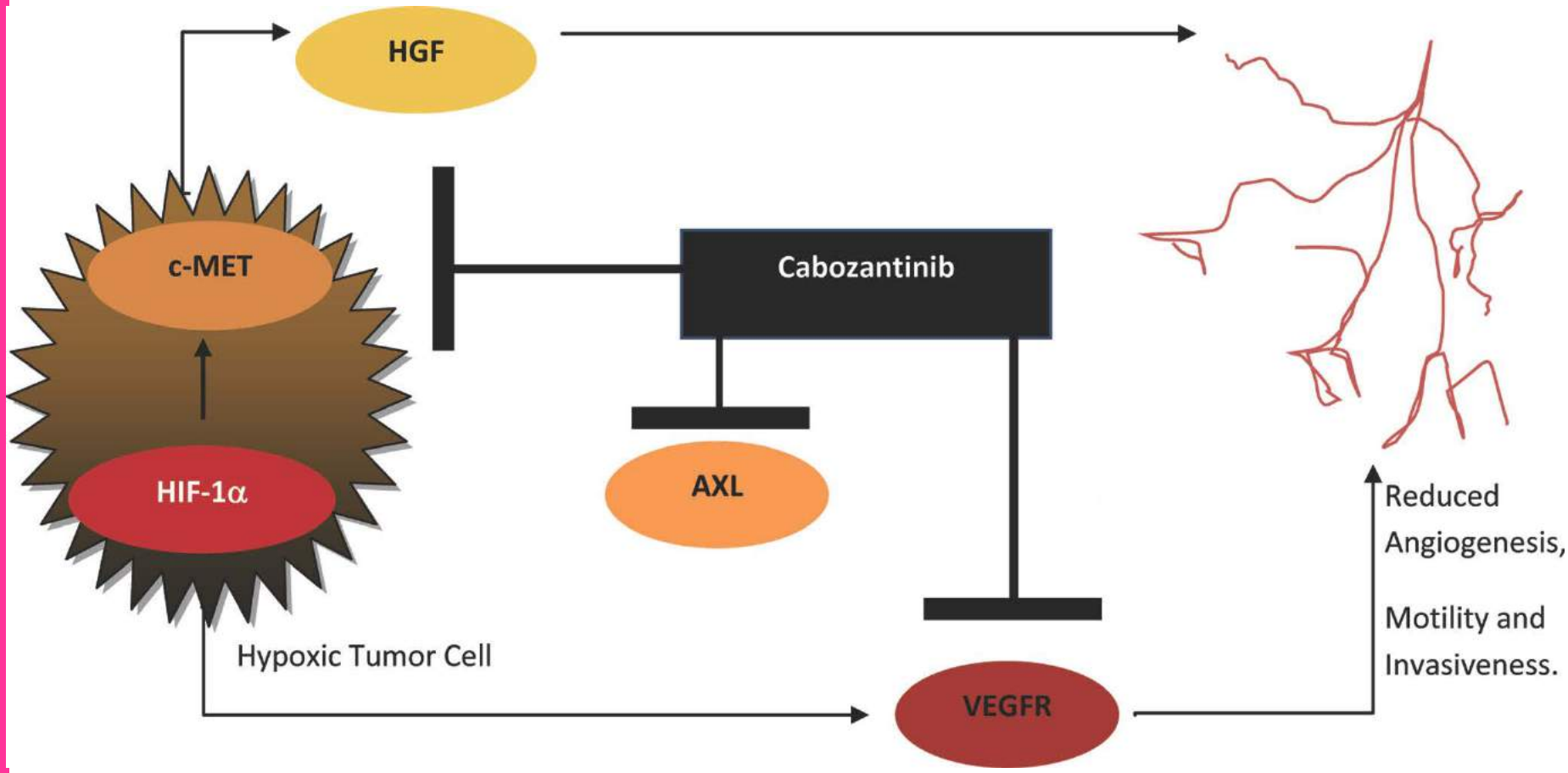
[i]In clear cell and non-clear cell RCC with predominant sarcomatoid features, gemcitabine + doxorubicin (category 2B) and gemcitabine + sunitinib (category 2B) have shown benefit.

[j]Based on the results of phase III trials, eligible patients should preferentially receive this agent over everolimus. See Discussion.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

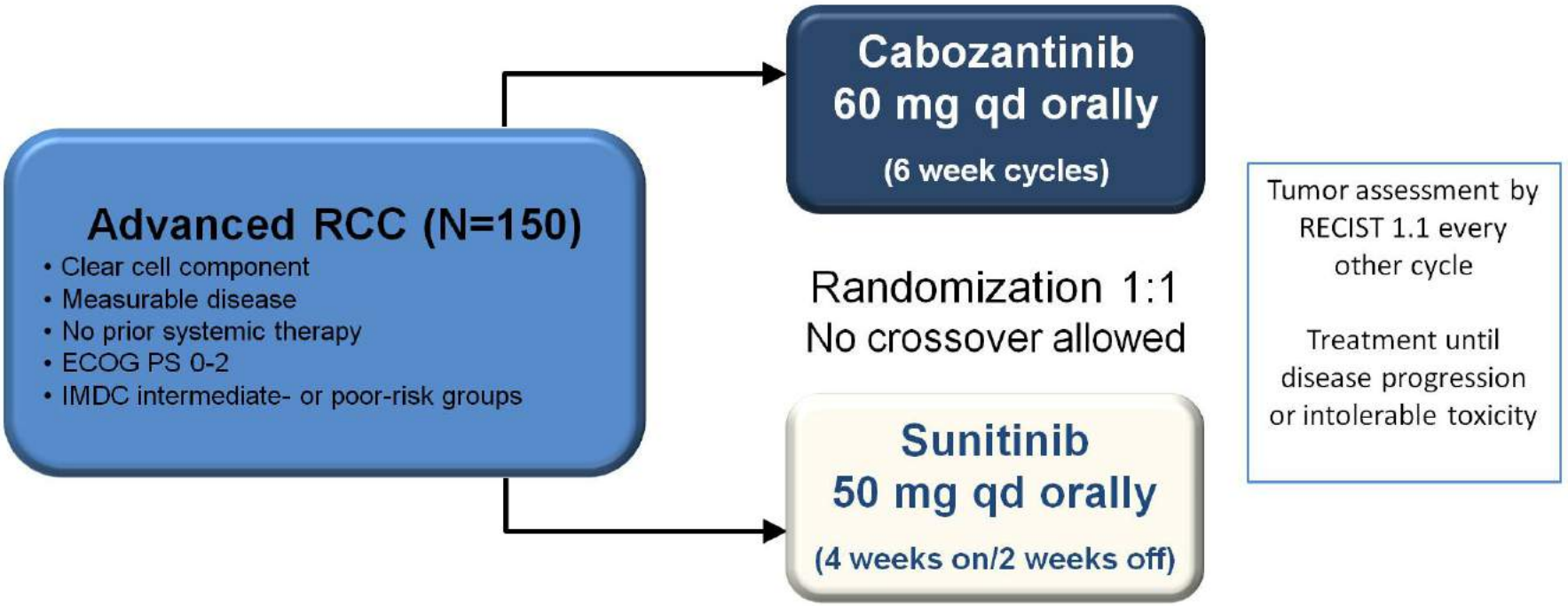
New treatment in First line MRCC

Cabozantinib



Igor Stukalin

CABOSUN: Study Design



Primary endpoint
- PFS by investigator assessment

Secondary endpoints
- OS, ORR, safety

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

1. Choueiri TK, et al. Presented at: ESMO. 2016 (abstr LBA30). 2. Heng DY, et al. *J Clin Oncol*. 2009;27:5794-9.

CABOSUN: Baseline Characteristics

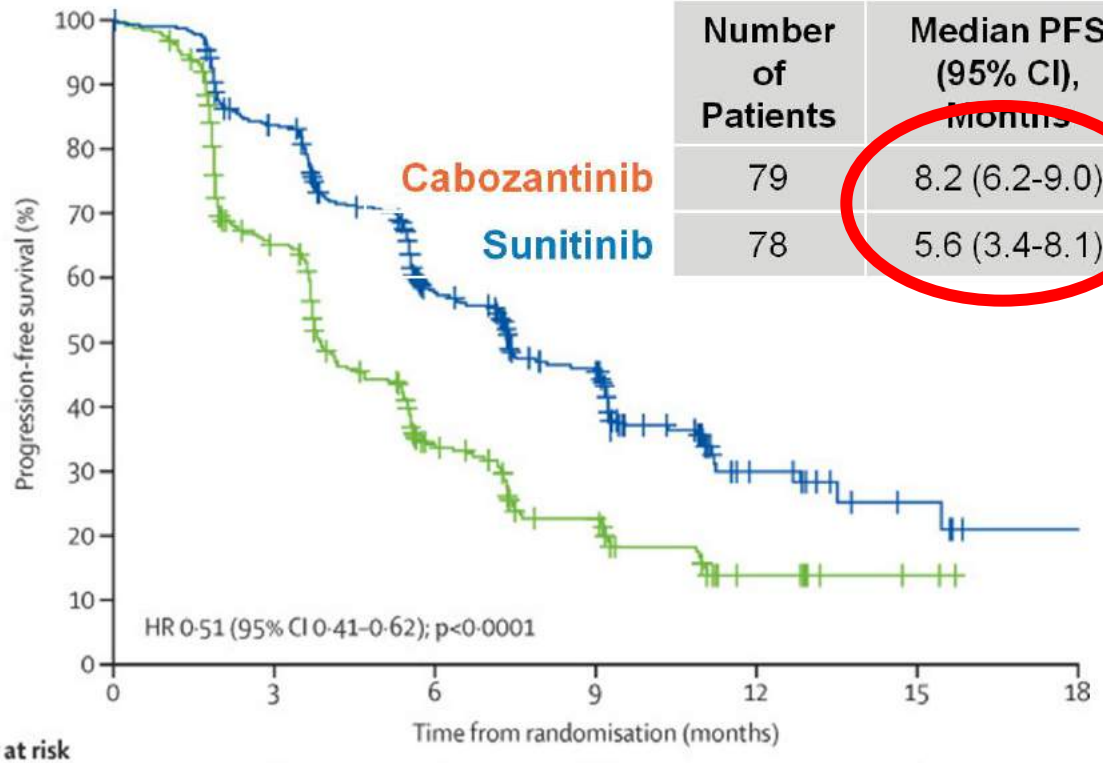
Characteristic	CABOSUN (N=157)	
	Cabozantinib (n=79)	Sunitinib (n=78)
Median age (range), years	63 (40-82)	64 (31-87)
Male, %	84	73
ECOG performance status, %		
0	46	46
1	42	41
2	13	13
IMDC risk group[2,*], %		
Intermediate	81	81
Poor	19	19
Prior nephrectomy, %	72	77
Bone metastases, %	37	36

*Adverse risk factors: Hemoglobin <LLN, corrected serum calcium >ULN, Karnofsky performance score <80%, neutrophils >ULN, time from diagnosis to therapy <1 year, platelets >ULN. Intermediate-risk group: 1-2 risk factors. Poor-risk group: 3 or more risk factors.

1. Choueiri TK, et al. Presented at: ESMO. 2016 (abstr LBA30). 2. Heng DY, et al. *J Clin Oncol.* 2009;27:5794-9.

CABOSUN : Progression Free Survival

Choueiri T et al. Lancet Oncol 2016

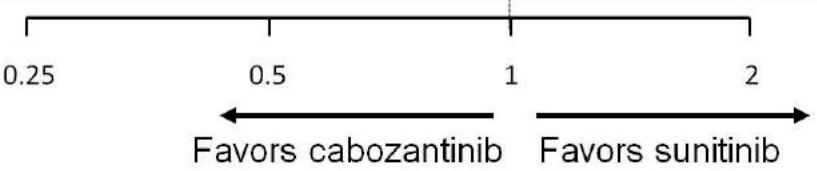


Number of Patients	Median PFS (95% CI), Months	Number of Events
79	8.2 (6.2-9.0)	64
78	5.6 (3.4-8.1)	61

Presented By Ulka Vaishampayan at 2017 Genitourinary Cancers Symposium

CABOSUN: PFS Subgroup Analysis*

	N	Median PFS, mos: Cabozantinib	Median PFS, mos: Sunitinib	HR (95% CI)
All patients	157	8.2	5.6	0.69 (0.48-0.99)
IMDC risk group				
Intermediate	127	8.4	6.2	0.68 (0.45-1.01)
Poor	30	6.3	2.8	0.75 (0.34-1.66)
Bone metastases				
No	100	8.7	7.6	0.80 (0.51-1.26)
Yes	57	6.3	3.4	0.51 (0.29-0.90)



*Content is not FDA-approved and is beyond the scope of the CABOMETYX™ label.
Choueiri TK, et al. Presented at: ESMO. 2016 (abstr LBA30).

CABOSUN: Tumor Response – Investigator Assessment*

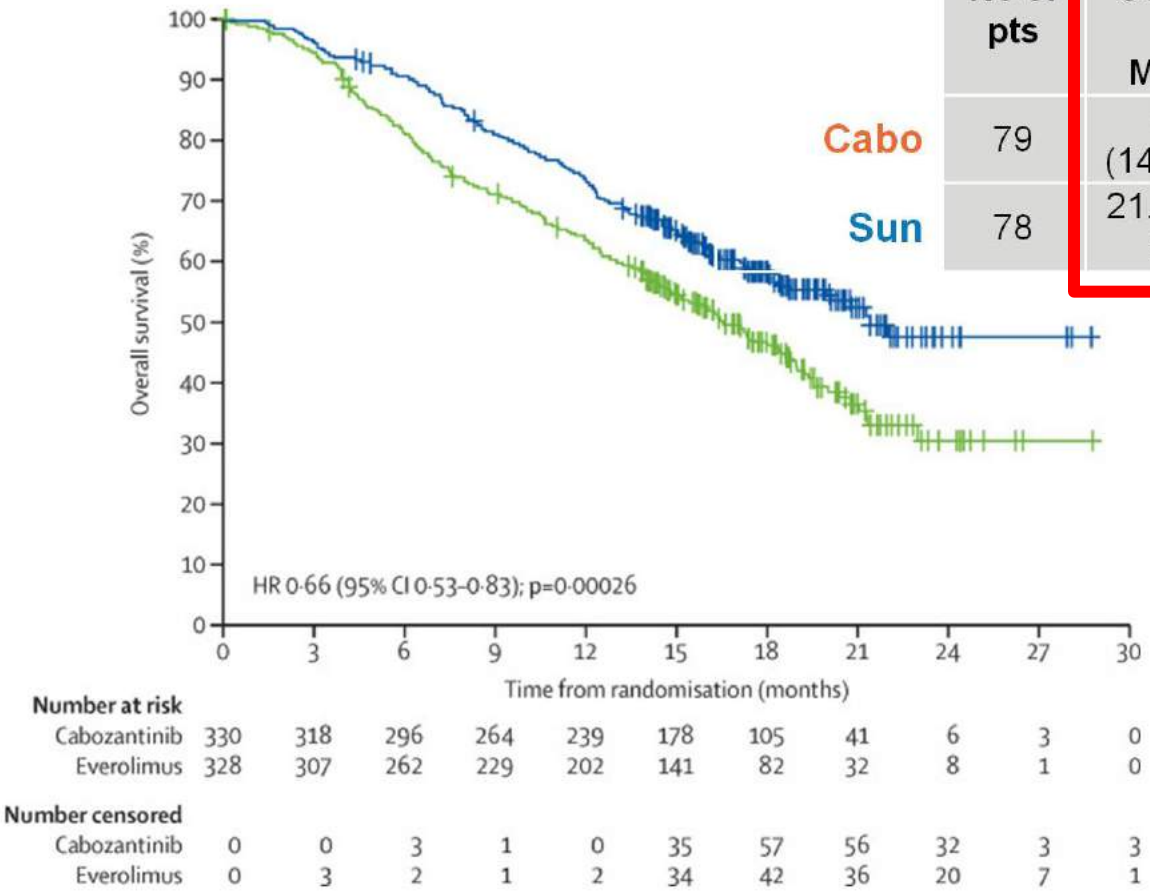
	Cabozantinib (n=79)	Sunitinib (n=78)
Objective response rate (95% CI), %	46% (34-57)	18% (10-28)
Best overall response, n		
Complete response	1	1
Partial response	35	13
Stable disease	26	28
Progressive disease	14	20
Not evaluable or missing†	3	16

†No post-baseline imaging performed for the following reasons:
Cabozantinib: clinical progression (1), withdrew consent (1), initiation of alternative therapy (1).
Sunitinib: clinical progression (2), withdrew consent (7), adverse event (4), death (2), initiation of alternative therapy (1).

*Content is not FDA-approved and is beyond the scope of the CABOMETYX™ label.
Choueiri TK, et al. Presented at: ESMO. 2016 (abstr LBA30).

CABOSUN: Overall Survival

Choueiri T et al. Lancet Oncol 2016



	No of pts	Median OS (95% CI), Months	Number of Events
Cabo	79	30.3 (14.6-35.0)	37
Sun	78	21.8 (16.3-27.0)	41

Presented By Ulka Vaishampayan at 2017 Genitourinary Cancers Symposium

CABOSUN: All-Causality High-Grade Adverse Events*

Grade	Cabozantinib (n=78)	Sunitinib (n=72)
Grade 3, %	58	60
Grade 4, %	8	8
Grade 5, % Possibly, probably, or definitely related, n	5%† 3§	4%‡ 2‖

*Content is not FDA-approved and is beyond the scope of the CABOMETYX™ label.
†Cause of death not specified; ‡Respiratory failure; §Acute kidney injury, sepsis, jejunal perforation; ‖Sepsis, vascular disorders.

Choueiri TK, et al. Presented at: ESMO. 2016 (abstr LBA30).

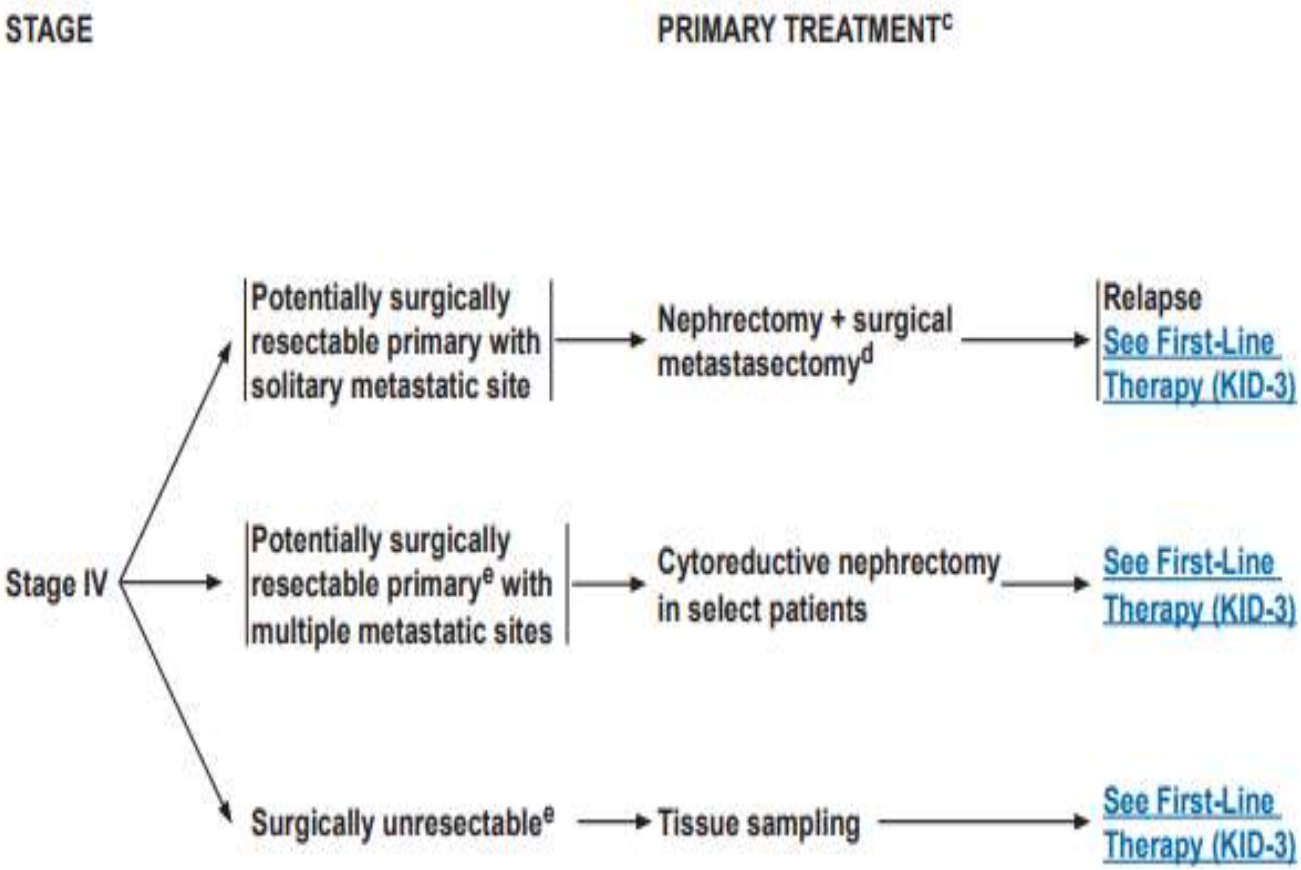
CABOSUN Results Review

- First time an agent (Cabo) demonstrated consistently superior efficacy in RR, PFS and OS as compared to sunitinib, in the front line setting.
- The study was conducted only in intermediate and high risk RCC patients
- Small sample size, phase II randomized trial, however lenvatinib+everolimus was approved by FDA based on an even smaller sample size.
- Results of independent review for response and progression are awaited.
- If sunitinib is used in adjuvant setting based on S-TRAC results, then the metastatic disease therapy paradigm will change.

Presented By Ulka Vaishampayan at 2017 Genitourinary Cancers Symposium

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Kidney Cancer



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Kidney Cancer

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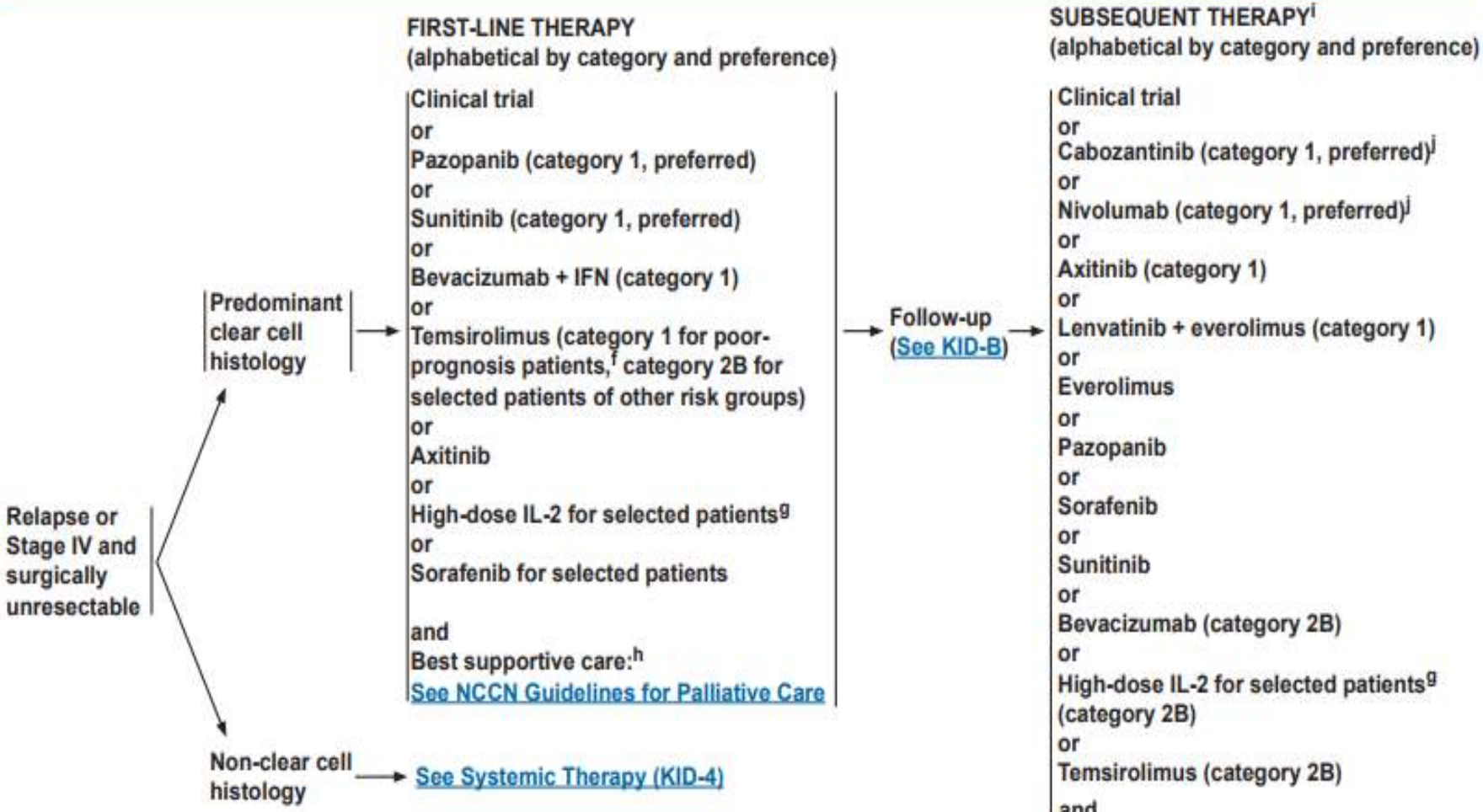

[f]Poor-prognosis patients, defined as those with ≥3 predictors of short survival.
See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-C).

[g]Patients with excellent performance status and normal organ function.

[h]Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Kidney Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
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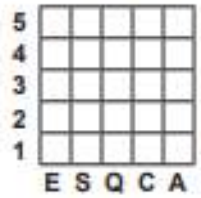
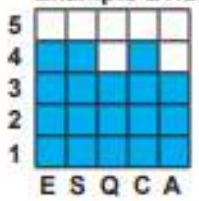
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Often provides long-term survival advantage or has curative potential
4	**Very effective:** Sometimes provides long-term survival advantage or has curative potential
3	**Moderately effective:** Modest, no, or unknown impact on survival but often provides control of disease
2	**Minimally effective:** Modest, no, or unknown impact on survival and sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs is common
2	**Moderately toxic:** Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
1	**Highly toxic:** Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** Several well-designed randomized trials
3	**Average quality:** Low quality randomized trials or well-designed non-randomized trials
2	**Low quality:** Case reports or clinical experience only
1	**Poor quality:** Little or no evidence

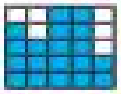
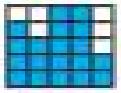
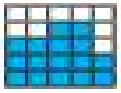
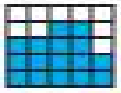
Consistency of Evidence

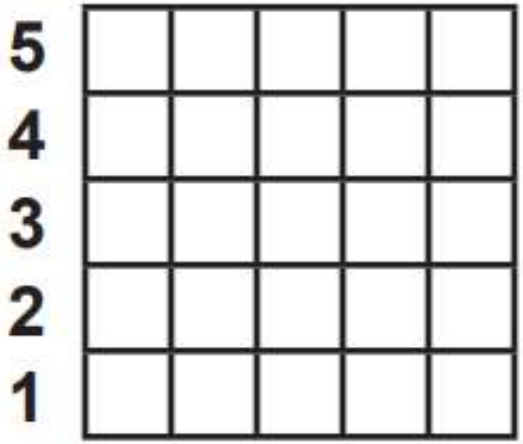
5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients; lower quality trials whether randomized or not
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

First-line Therapy for Clear Cell Carcinoma

Pazopanib	
Sunitinib	
Bevacizumab + IFN	
Temsirolimus for poor risk group	



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

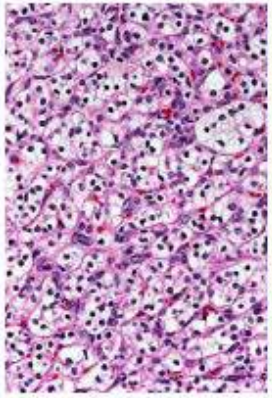
European Society for Medical Oncology

RCC: key biological features

mutated

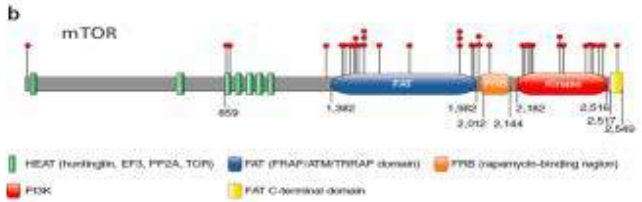
Increased tumor cell survival and resistance to apoptosis

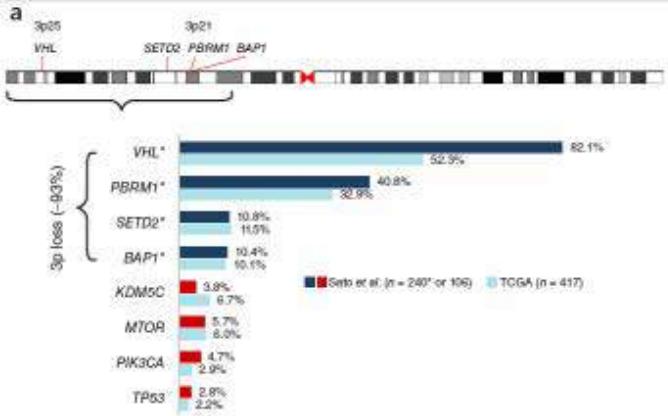
mTOR

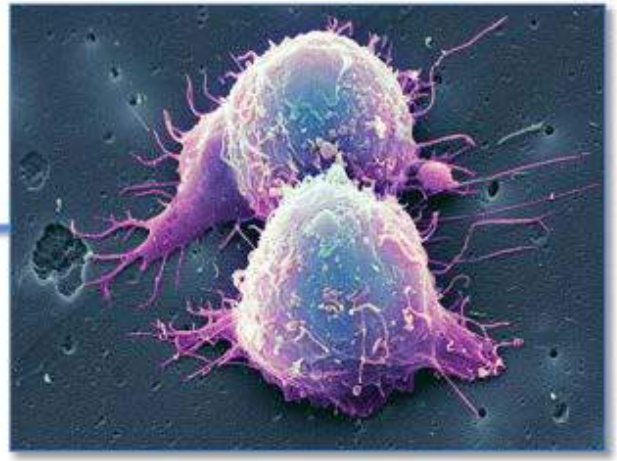


clear cell RCC (75-85%)

VHL





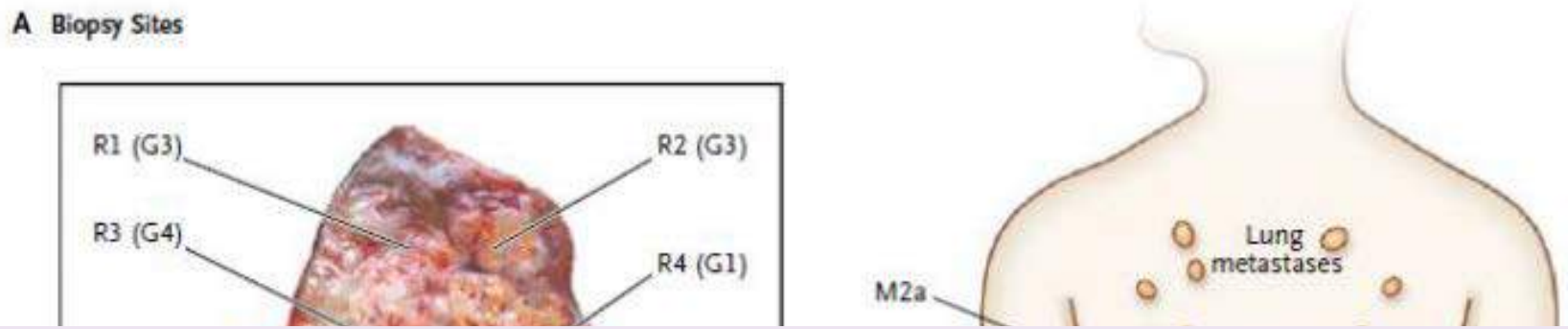


Immunogenicity

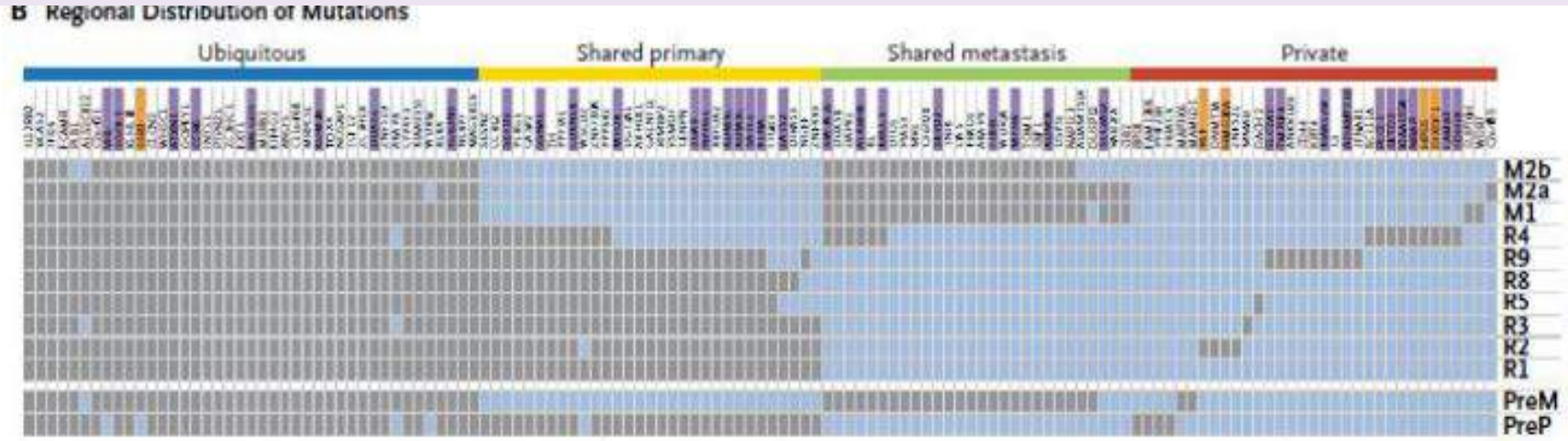
mutated, deleted or hyper-methylated

Hyperproduction of VEGF and other pro-angiogenic cytokines

Exasperated angiogenesis



Heterogeneity
Only targeted therapy may be the final answer



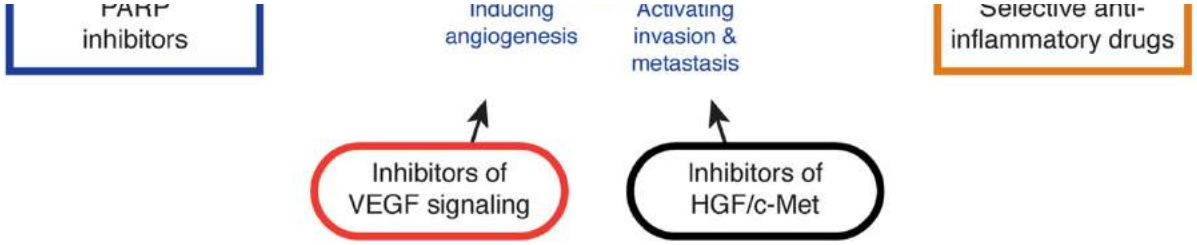
Gerlinger NEJM 2012

Cell

Leading Edge
Review

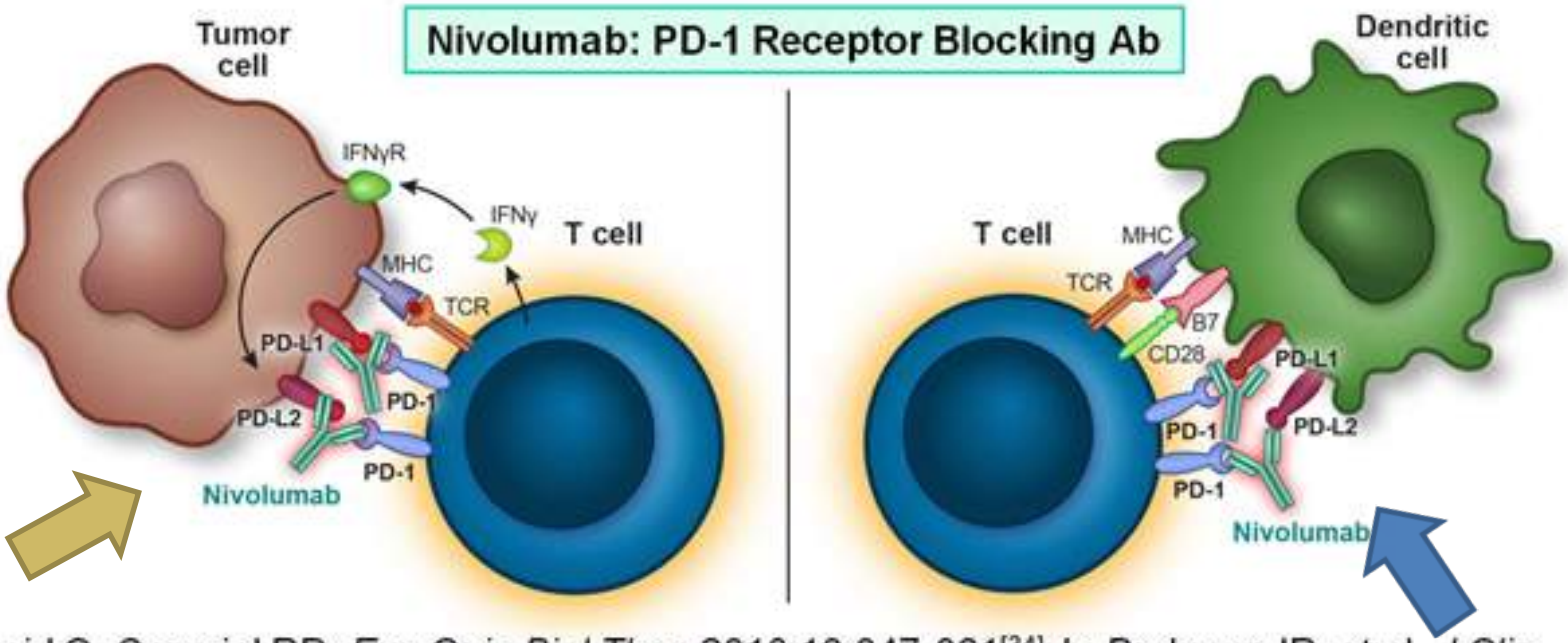
Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
DOI 10.1016/j.cell.2011.02.013



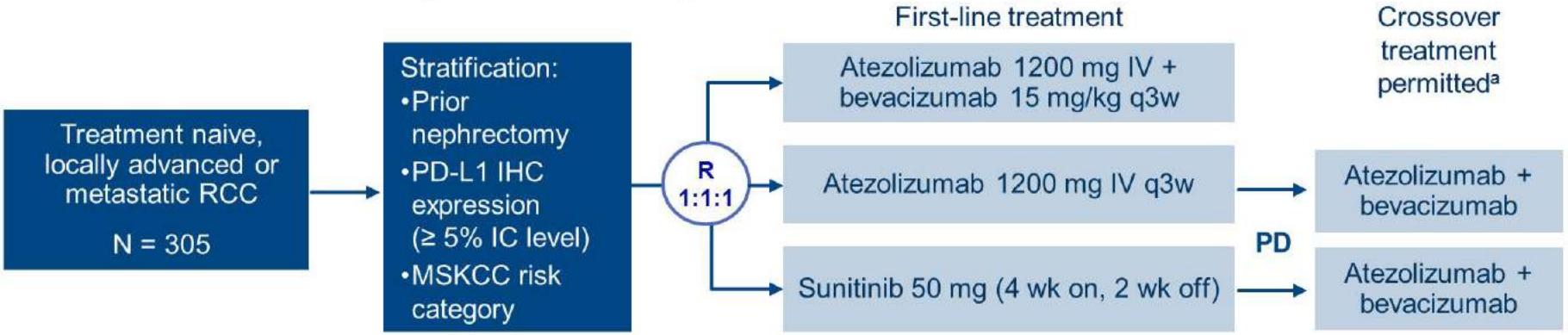
Nivolumab
Mechanism of Action

- Binding of PD-1 to its ligands PD-L1 and PD-L2 leads to downregulation of the antitumor immune response[a]
- Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor
- Nivolumab selectively blocks the PD-1 and PD-L1/PD-L2 interaction, restoring antitumor T-cell function[a-d]



a. Hamid O, Carvajal RD. *Exp Opin Biol Ther.* 2013;13:847-861[34]; b. Brahmer JR, et al. *J Clin Oncol.* 2010;28:3167-3175 [41]; c. Nurieva RI, et al. *Immunol Rev.* 2011;241:133-144[42]; d. Hamanishi J, et al. *Proc Natl Acad Sci USA.* 2007;104:3360-3365.[43]

IMmotion150 (Phase II) Trial Design

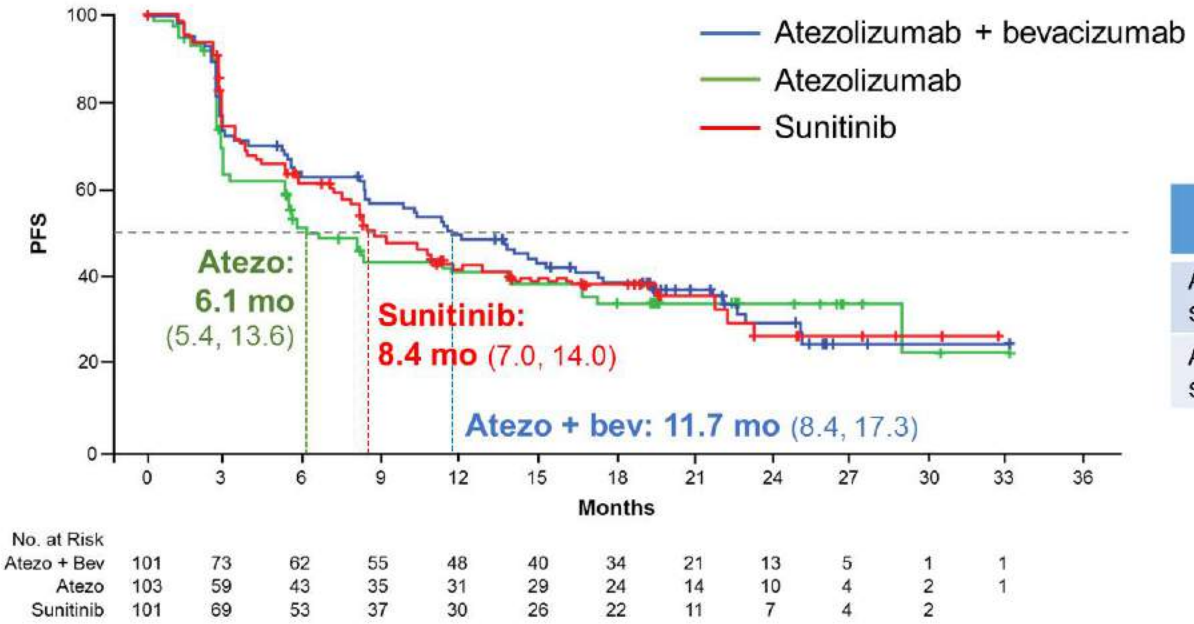


- The coprimary endpoints are PFS (RECIST v1.1 by IRF) in ITT and PD-L1+ patients
- IMmotion150 was designed to be hypothesis generating and inform the trial design of the Phase III study IMmotion151
- Amendments included:
  - Based on Phase 1a data, the definition of PD-L1 positivity was revised from ≥ 5% to ≥ 1% of IC expressing PD-L1[1]
  - In addition to ITT patients, PD-L1+ patients were included in the coprimary endpoint of IRF-assessed PFS, after interim analyses

IC, tumor-infiltrating immune cells; IRF, independent review facility. 1. McDermott *JCO* 2016. [a] Crossover from atezolizumab monotherapy not allowed in Europe.

IRF-Assessed PFS

ITT

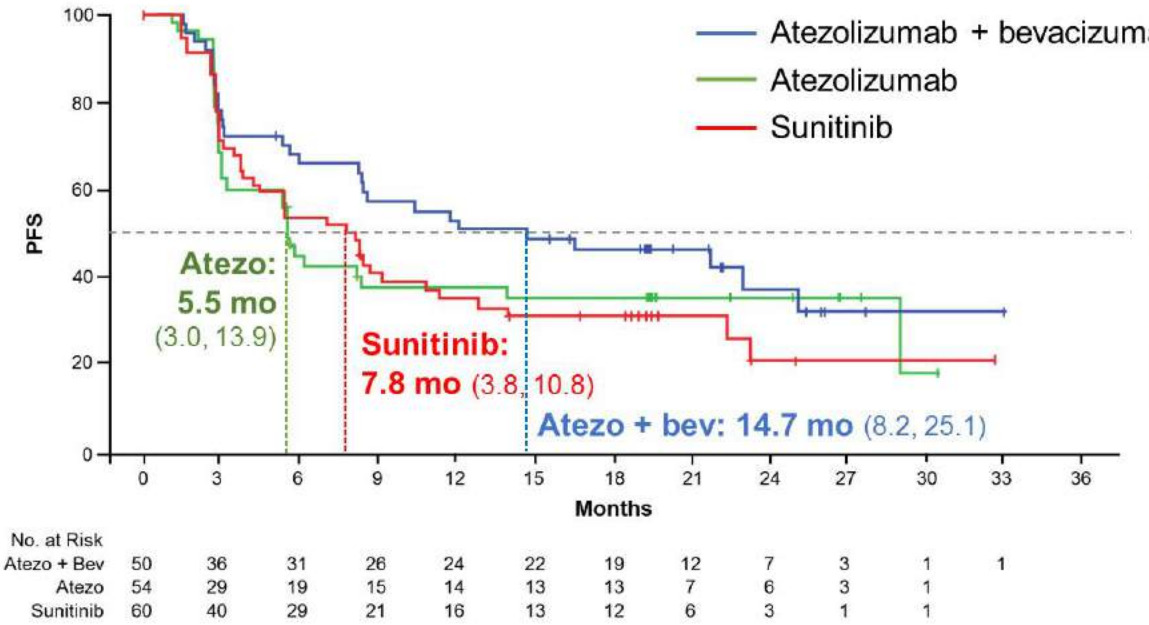


	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	**1.00 (0.69, 1.45)**	0.982
Atezo vs sunitinib	**1.19 (0.82, 1.71)**	0.358

[a] *P* values are for descriptive purposes only and not adjusted for multiple comparisons.

IRF-Assessed PFS

≥ 1% of IC Expressing PD-L1



	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	**0.64 (0.38, 1.08)**	0.095
Atezo vs sunitinib	**1.03 (0.63, 1.67)**	0.917

[a] *P* values are for descriptive purposes only and not adjusted for multiple comparisons.

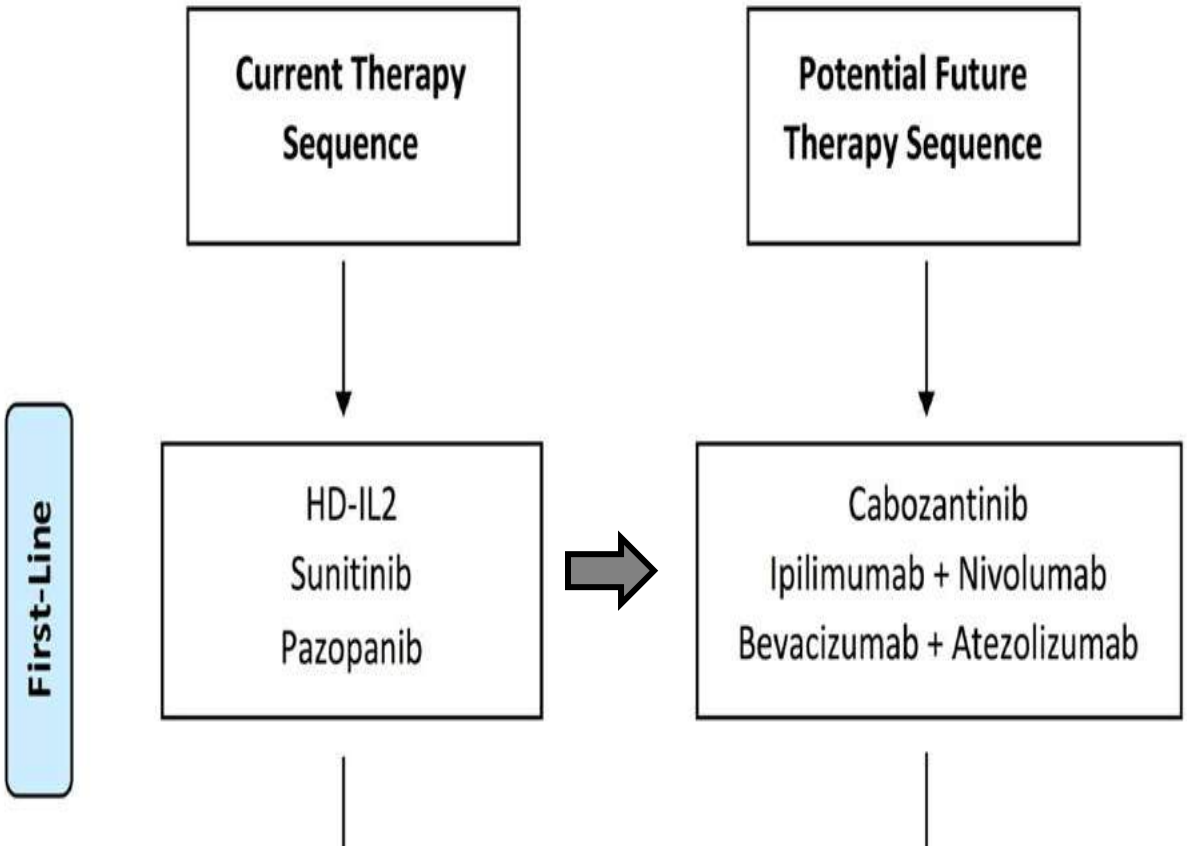
Presented By Thomas Powles at 2017 Genitourinary Cancers Symposium

Combination studies of PD-1 and PD-L1 inhibitors in RCC: phase I trials

Line	Treatment	n	ORR (%)	PFS	OS	Adverse events (all grades)
1L	Atezolizumab + bevacizumab (15 mg/kg Q3W)[1]	10	40	NA	NA	Fatigue (70%) Arthralgia, hypertension, productive cough, Pyrexia, nausea decreased appetite (40%)
1L	Pembrolizumab + axitinib[2]	52	67	NA	NA	Six pts discontinued secondary to AEs
IL	Avelumab + axitinib	6	100	NA	NA	1 pt with grade 3 protienuria

1. Sznol et al. ASCO GU 2015;
2. Atkins et al ESMO 2016
3. Larkin et al ESMO 2016

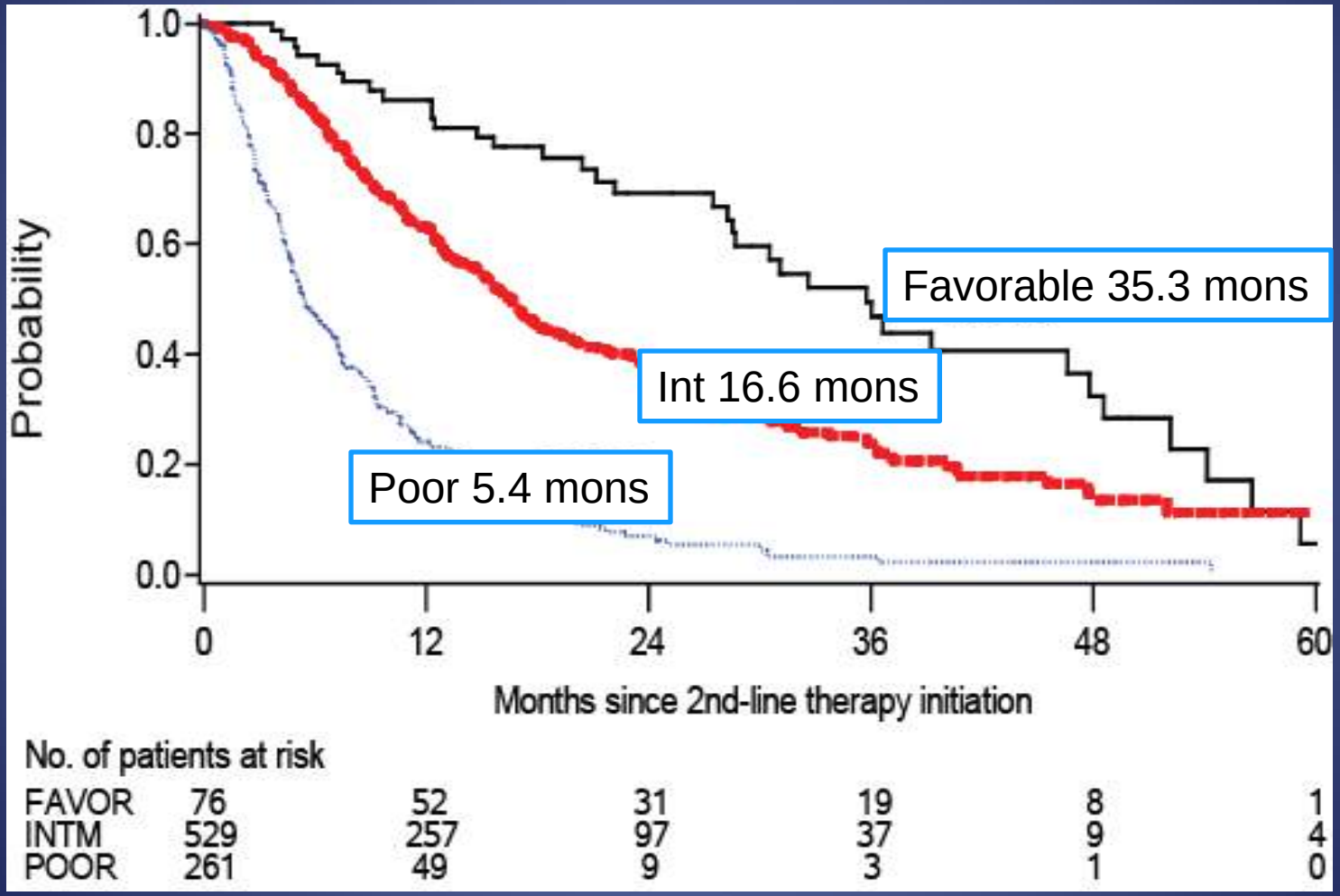
Figure 3 – Sequencing paradigm of mRCC



Second line options

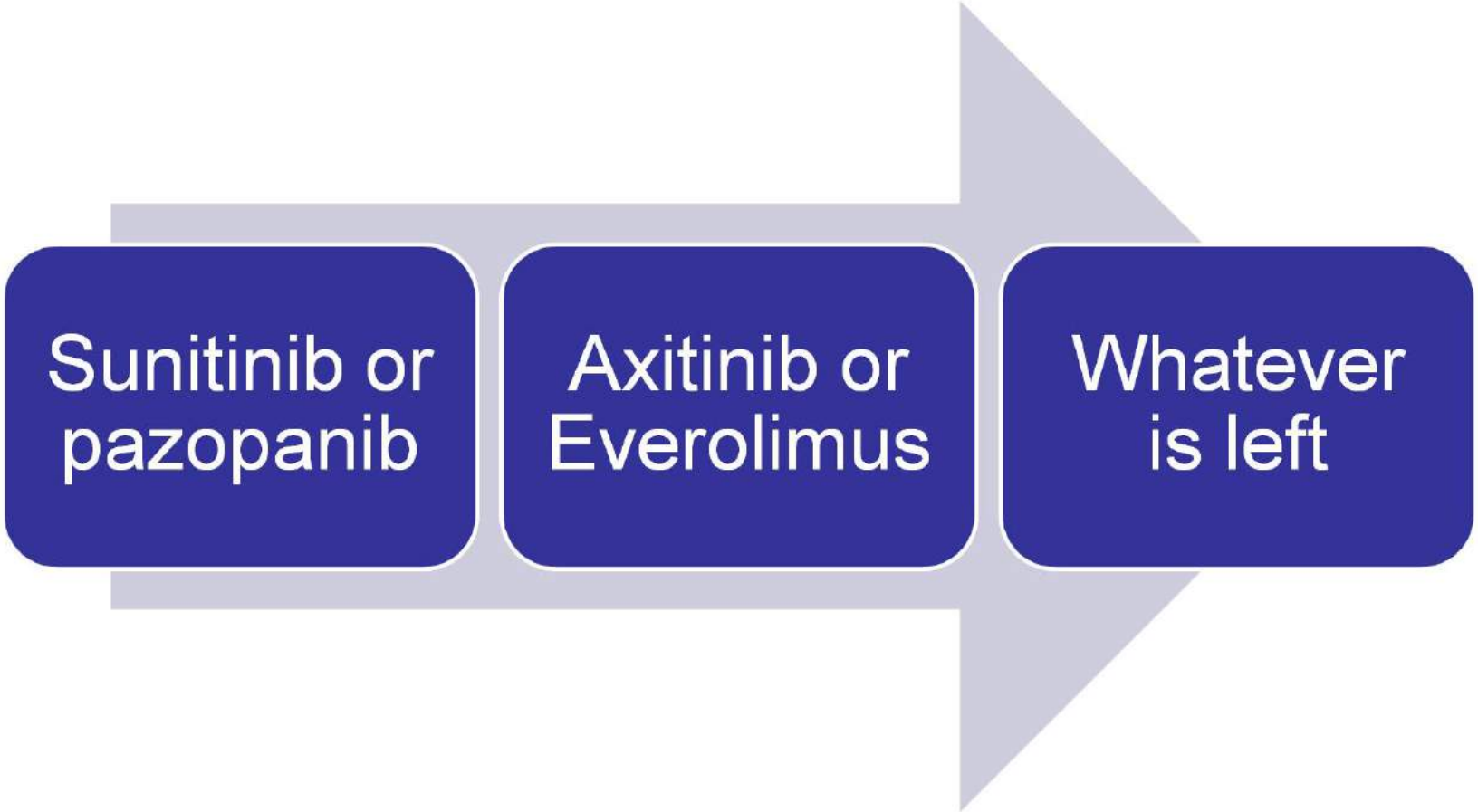
No direct comparison

IMDC in 2nd-line targeted therapy



Ko et al GU Cancers Symposium 2014

The landscape



The current paradigm of therapy in mRCC is an empiric sequence of monotherapies

Everolimus in RCC: RECORD 1

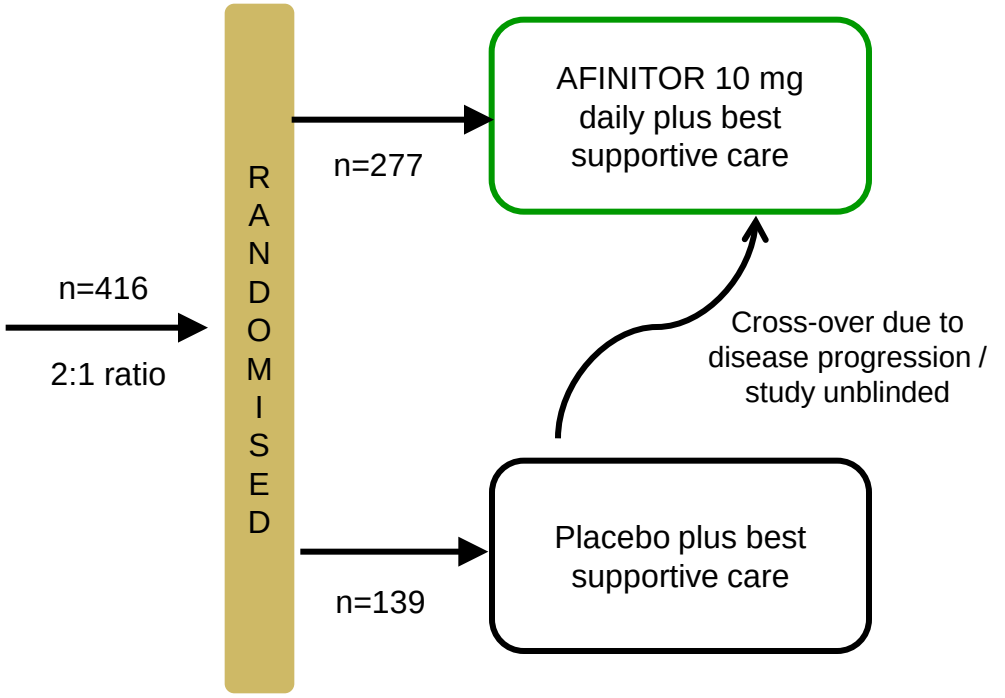
Eligibility criteria

- Metastatic RCC with clear-cell component
- RCC had progressed on or within 6 months of stopping therapy with sunitinib, sorafenib or both
- Presence of measurable disease (RECIST)
- Karnofsky performance score ≥70%
- Adequate bone marrow, renal and hepatic function
- No prior mTOR inhibitor therapy

  Prior therapy with bevacizumab and interferon-α was permitted

Stratification

- MSKCC prognostic score
- Previous anticancer therapy : 1 previous VEGFR TKI / 2 previous VEGFR TKIs



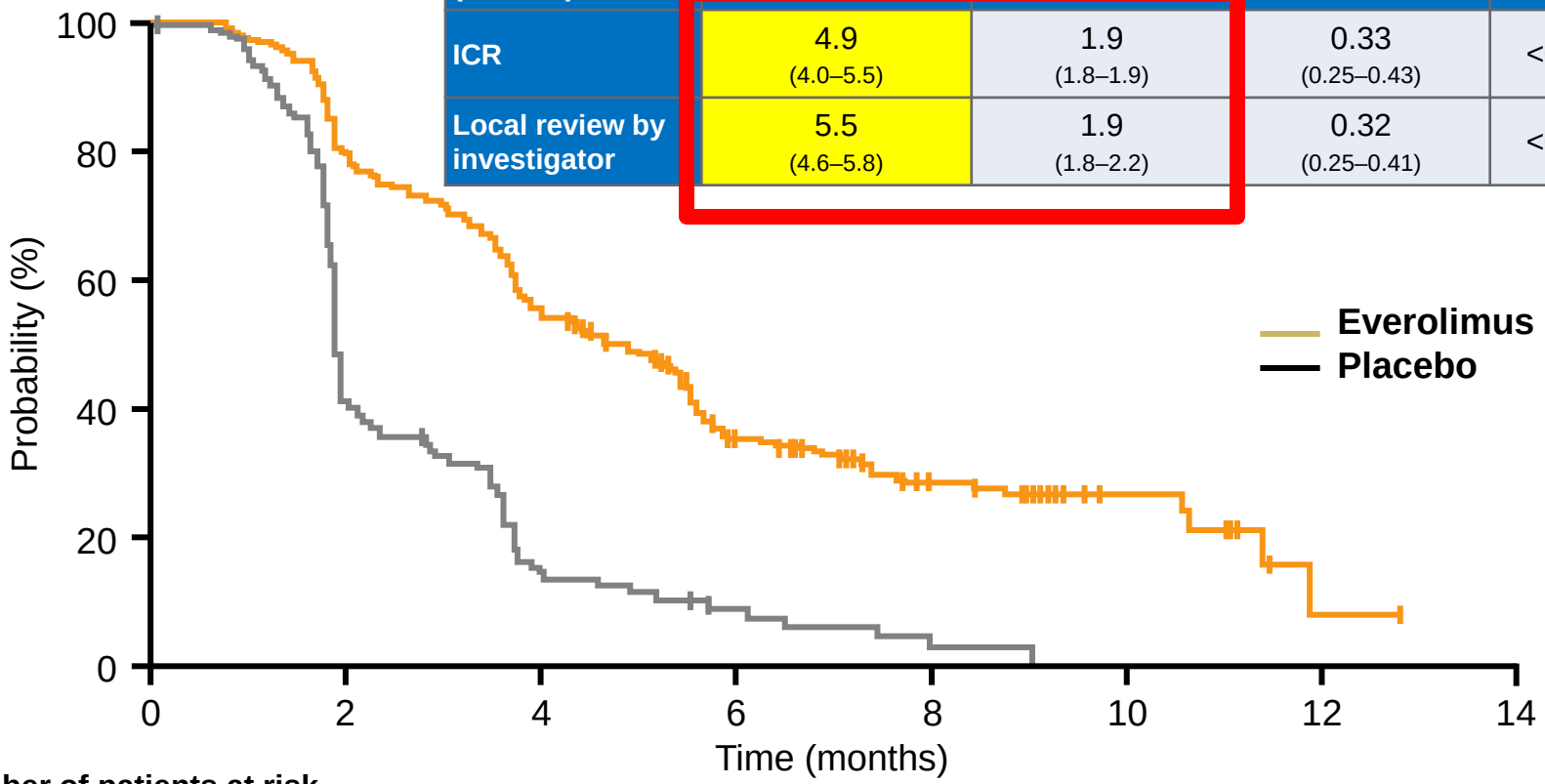
- **Primary endpoint: PFS**
  Secondary endpoints: Safety, ORR, OS, disease-related symptoms, quality of life

MSKCC = Memorial Sloan-Kettering Cancer Center; ORR = objective response rate; OS = overall survival; PFS = progression-free survival
RECIST = Response Evaluation Criteria in Solid Tumours; VEGF TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor

Motzer et al. Lancet 2008; Motzer et al. Cancer 2010

RECORD-1 Primary Endpoint: PFS Longer with Everolimus than with Placebo

Median PFS (months) (95% CI)	AFINITOR (n=277)	Placebo (n=139)	HR (95% CI)	P value
ICR	4.9 (4.0–5.5)	1.9 (1.8–1.9)	0.33 (0.25–0.43)	<0.0001
Local review by investigator	5.5 (4.6–5.8)	1.9 (1.8–2.2)	0.32 (0.25–0.41)	<0.0001



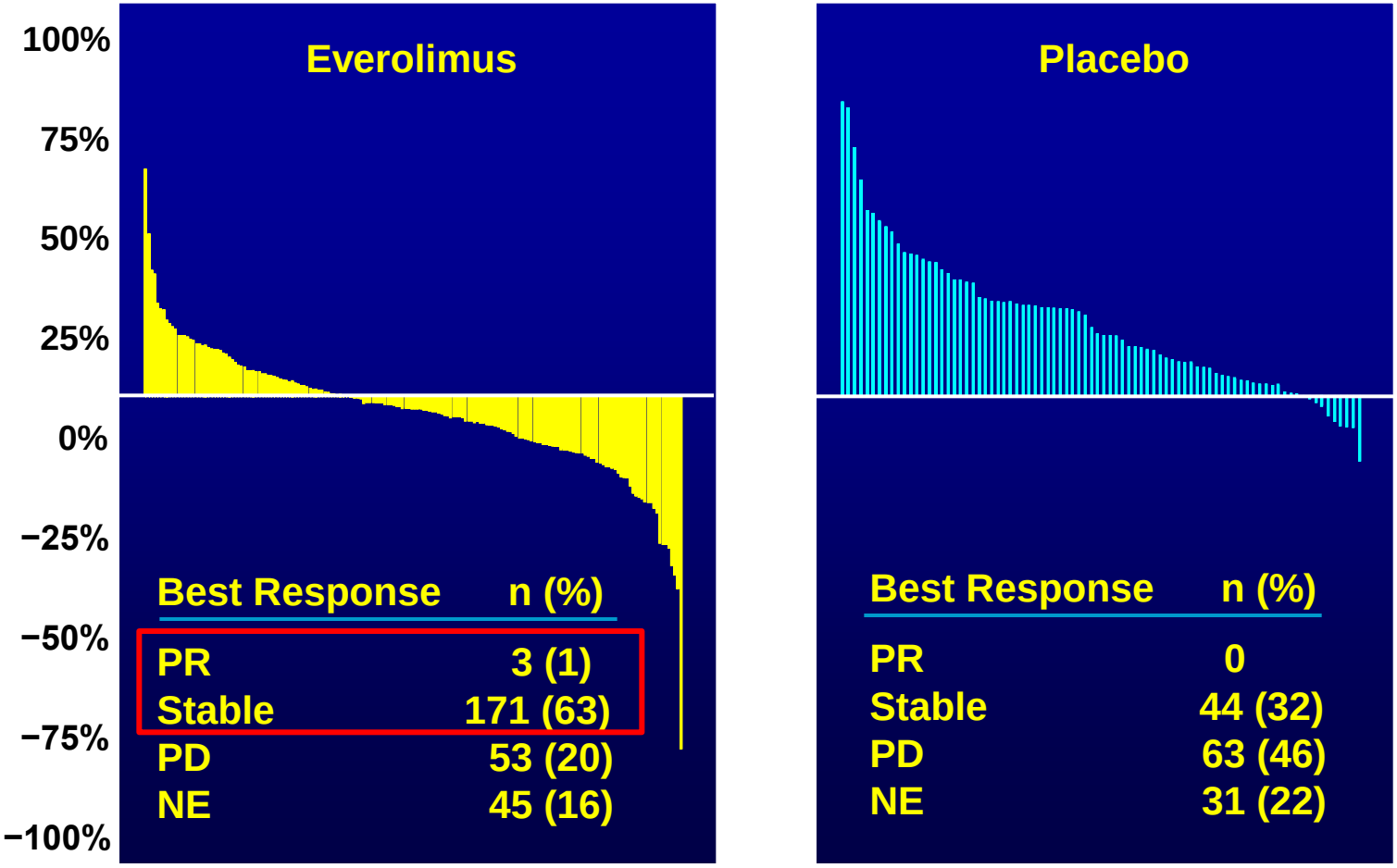
Number of patients at risk

Everolimus	277	192	115	51	26	10	1	0
Placebo	139	47	15	6	2	0	0	0

CI = confidence interval ; BICR = Blinded independent central review

Motzer et al. *Lancet* 2008; Motzer et al. *Cancer* 2010; AFINITOR SmPC

Maximum % of Change in Tumor load



NE = not evaluable

*** Central Radiology Review**

Motzer et al. *J Clin Oncol.* 2004;22:454-463.

Axitinib is a highly selective and more potent VEGFR-TKI than other approved agents

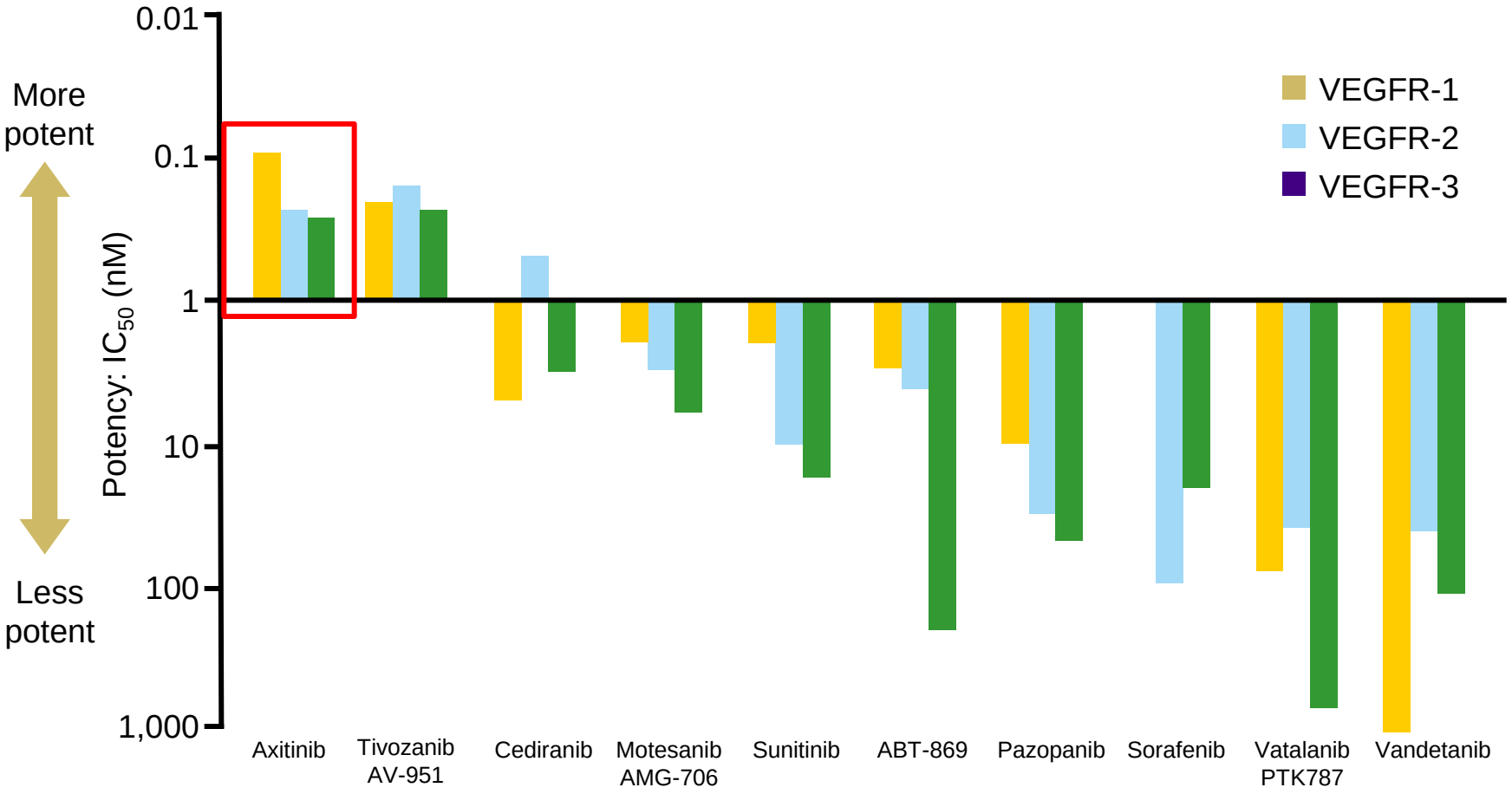
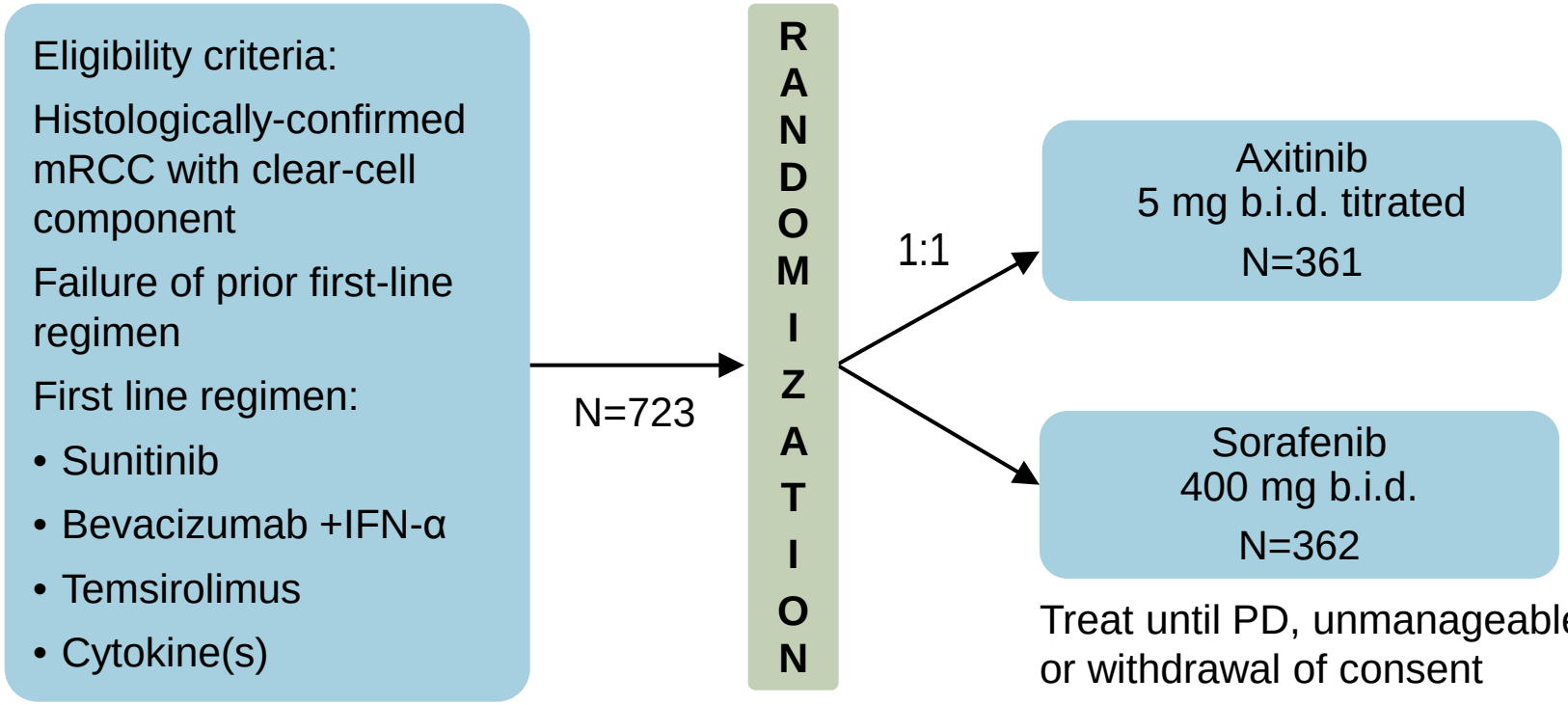


Figure modified using data from Chow LQM & Eckhardt SG. *J Clin Oncol* 2007; Eskens FALM, et al. AACR 2008:Abstract LB-201; Hu-Lowe DD. *Clin Cancer Res* 2008

Phase III Study of Axitinib vs Sorafenib as Second-line Therapy for mRCC (AXIS)



Treat until PD, unmanageable AE or withdrawal of consent

Stratification:

- Prior regimen
- ECOG PS (0 vs 1)

- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, duration of response, safety, QoL (FKSI and EQ-5D)

Rini BI et al. *Lancet* 2011; 378: 1931–39

Best Response by RECIST
(IRC Assessment)

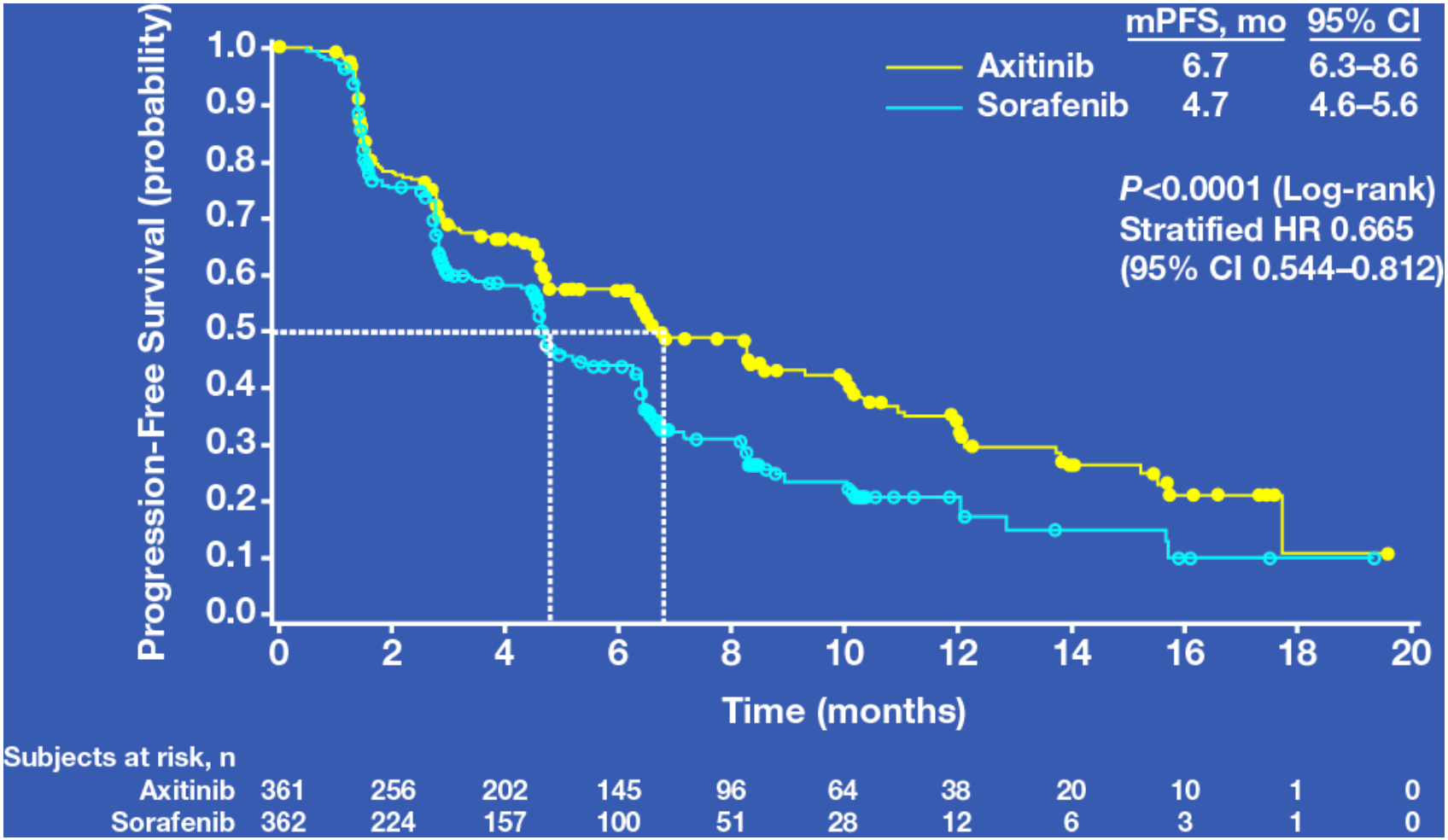
Best overall response, %	Axitinib	Sorafenib
Complete response	0	0
Partial response	19.4	9.4
Stable disease	49.9	54.4
Progressive disease	21.6	21.0
Indeterminate	6.1	11.6
Objective Response Rate	19%	9%
95% CI	15.4-23.9	6.6-12.9
P value	0.0001	

Median duration of response was 11 months (95% CI 7.4–not estimable) for axitinib and 10.6 months (8.8–11.5) for sorafenib

Rini BI et al. *Lancet* 2011; 378: 1931–39

Progression-Free Survival (IRC Assessment)

43% improvement in median PFS



Rini BI et al. *Lancet* 2011; 378: 1931–39

PFS by Prior Regimen

Prior treatment regimen	Axitinib (n=361)	Sorafenib (n=362)	HR	P value*
Cytokines (n=251)				
IRC	12.1	6.5	0.464	<0.0001
Investigator	12.0	8.3	0.636	0.005
Sunitinib (n=389)				
IRC	4.8	3.4	0.741	0.011
Investigator	6.5	4.5	0.636	0.0002
Temsirolimus (n=24)				
IRC	10.1	5.3	0.511	0.142
Investigator	2.6	5.7	1.210	0.634
Bevacizumab (n=59)				
IRC	4.2	4.7	1.147	0.637
Investigator	6.5	4.5	0.753	0.213

***One-sided log-rank test stratified by ECOG PS.**

Rini BI et al. *Lancet* 2011; 378: 1931–39

Table 2. Selected Toxic Effects from Approved Systemic Therapies in Advanced Renal-Cell Carcinoma.

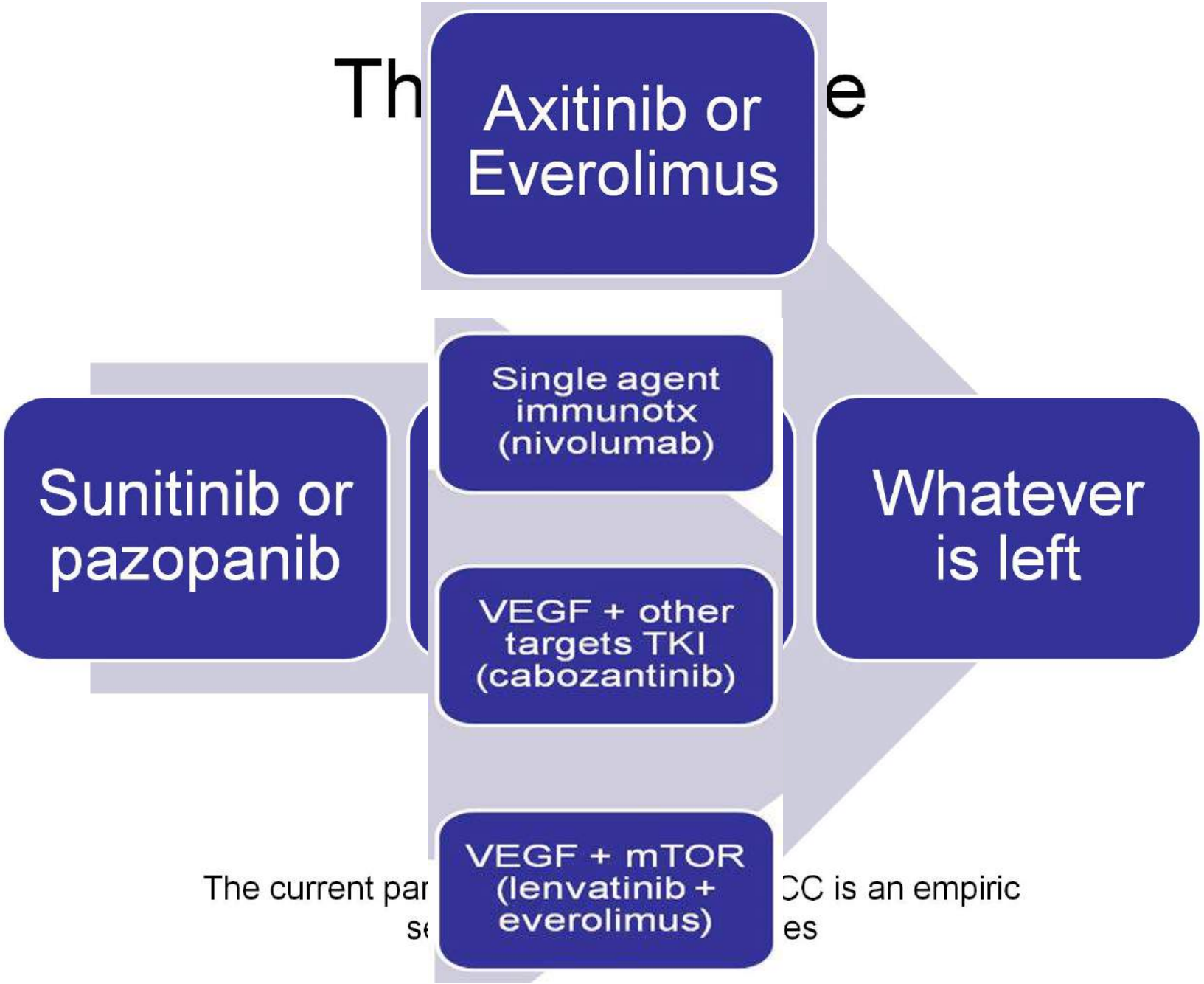
Class and Drug*	Toxic Effects
VEGF ligand antibody: bevacizumab	Hypertension, proteinuria, impaired wound healing, gastrointestinal perforation
Tyrosine kinase inhibitor: axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib	Fatigue, hypertension, oral and gastrointestinal side effects (mucositis, dysphonia, nausea, vomiting, stomatitis, dysgeusia, diarrhea), skin problems (rash, hand–foot skin reactions), hair loss and changes in hair color, weight loss, cytopenias, hypothyroidism, elevated liver-function values
Mechanistic target of rapamycin inhibitor: everolimus, temsirolimus	Fatigue, nausea, rash, pulmonary side effects (cough, dyspnea, pneumonitis), diarrhea, infections, peripheral edema, anemia, hyperlipidemia, hyperglycemia
Programmed death-1 inhibitor: nivolumab	Fatigue, nausea, diarrhea,† skin problems (pruritus, rash),† hypothyroidism,† pulmonary side effects (cough, dyspnea, pneumonitis),† elevated liver-function values,† other uncommon immune-related events

Suggestions for Switching Therapy to a

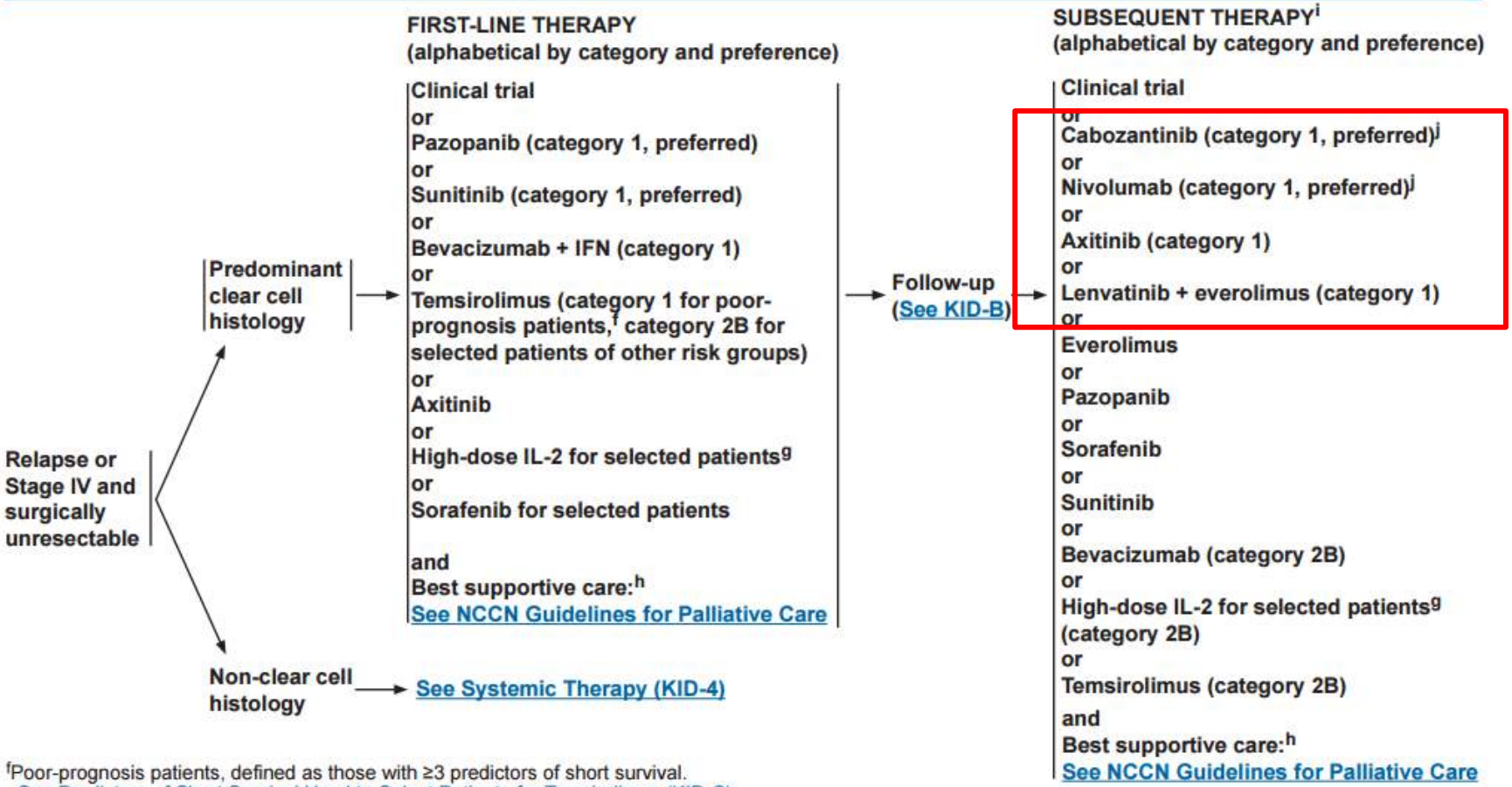
Mixed response to therapy (eg, SD in 1 lesion and PD in another)	Also consider the possibility of treatments that target isolated progressing lesions (for example, surgery, radiosurgery, radiotherapy) while continuing ongoing systemic treatment (any targeted therapy)
Discovery of new disease site	Switch immediately to another targeted agent if lesion is significant and a newly confirmed lesion, rather than being previously undetected
Unacceptable toxicity	Any treatment strategy should aim to reduce as much as possible the number of patients with unacceptable toxicity. Toxicity is often higher with the second-line tyrosine kinase inhibitor compared with first-line therapy, and since many adverse events (for example, hypertension, diarrhea, stomatitis) can be managed effectively, there is no reason to switch immediately

hypertension, diarrhea, stomatitis) can be managed effectively, there is no reason to switch immediately

Th e



The current par CC is an empiric
s es



[f]Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-C).
[g]Patients with excellent performance status and normal organ function.
[h]Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.
[i]In clear cell and non-clear cell RCC with predominant sarcomatoid features, gemcitabine + doxorubicin (category 2B) and gemcitabine + sunitinib (category 2B) have shown benefit.
[j]Based on the results of phase III trials, eligible patients should preferentially receive this agent over everolimus. See Discussion.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

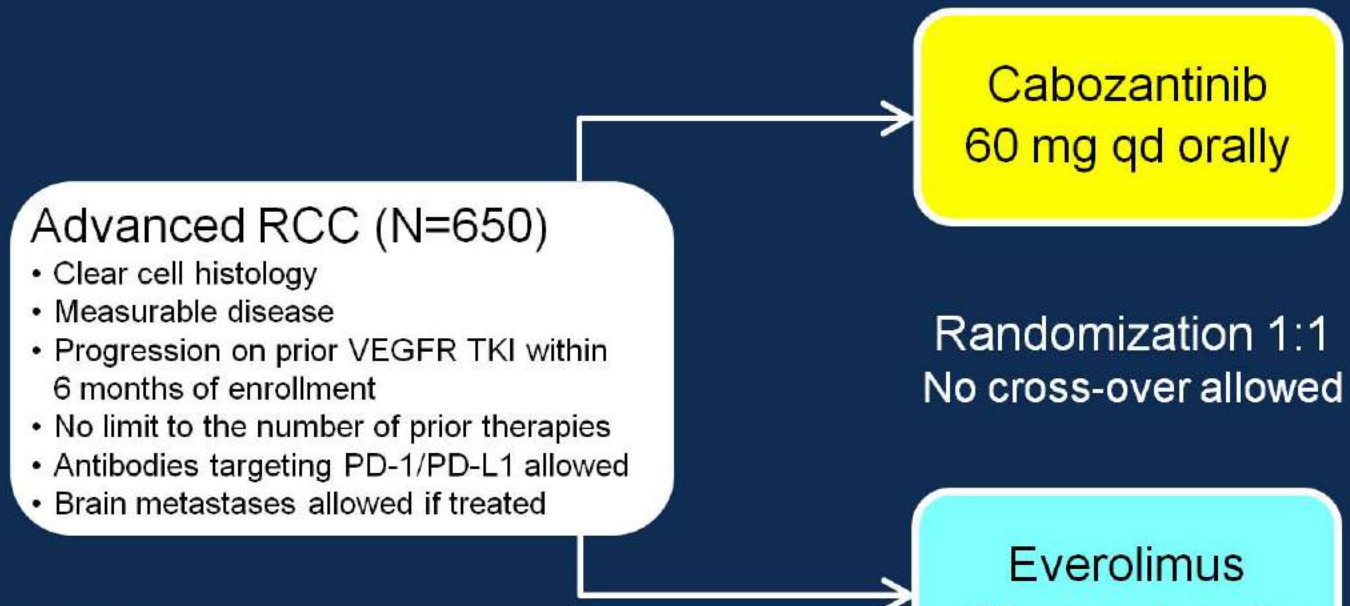
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*

METEOR Study Design



Tumor assessment by RECIST 1.1 every 8 weeks

Treatment until loss of clinical benefit or intolerable toxicity

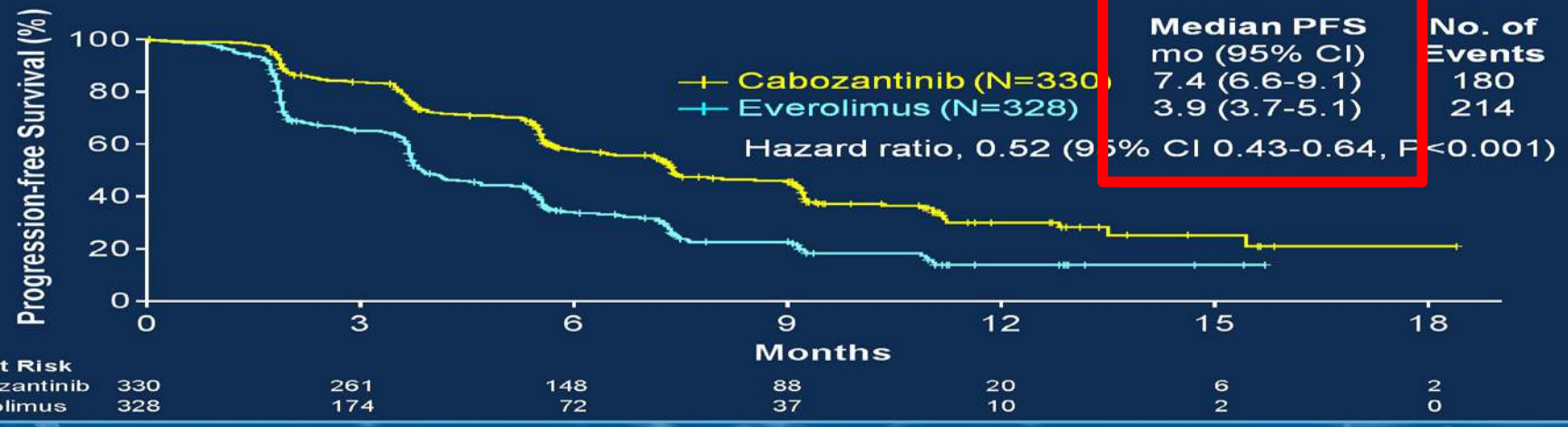
Stratification:

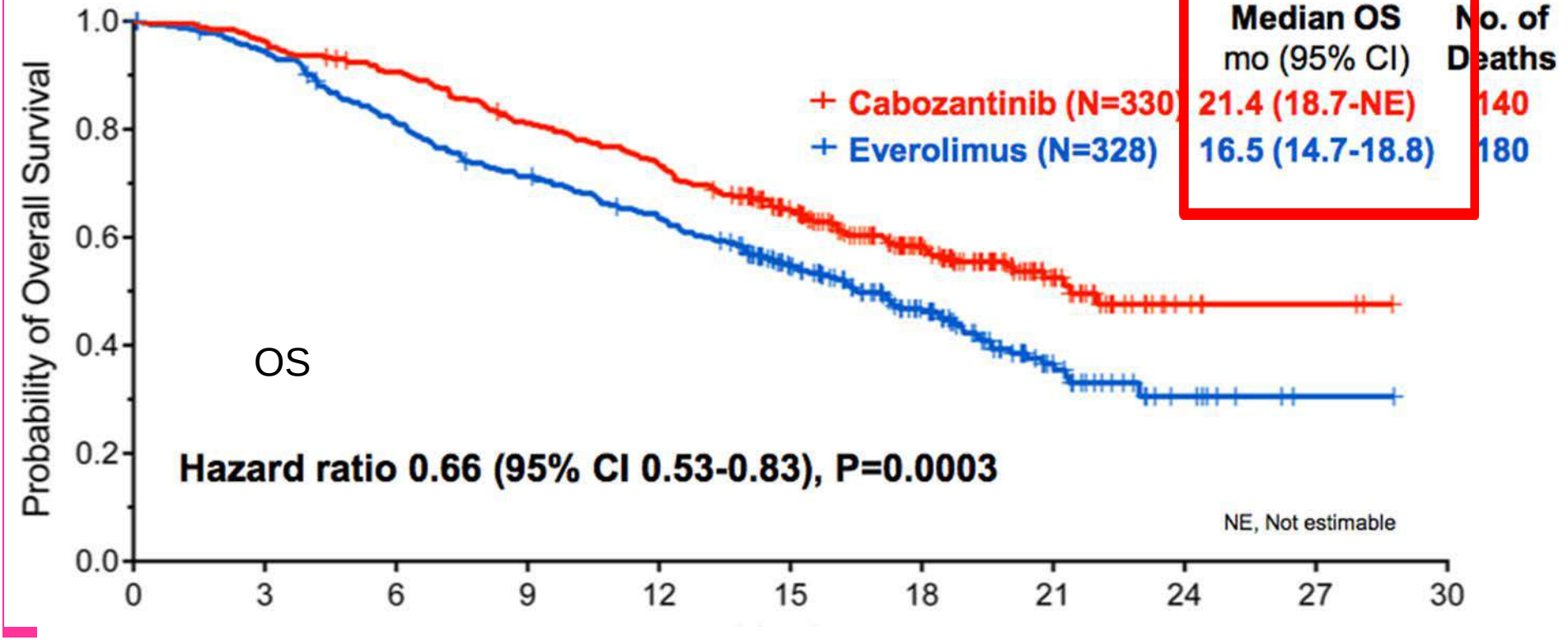
- MSKCC[1] risk groups: favorable, intermediate, poor
- Number prior VEGFR-TKIs: 1, 2 or more

[1] Motzer R. et al., J Clin Oncol, 2004

Presented By Bernard Escudier at Genitourinary Cancers Symposium 2016

PFS by IRC: All 658 Enrolled Patients

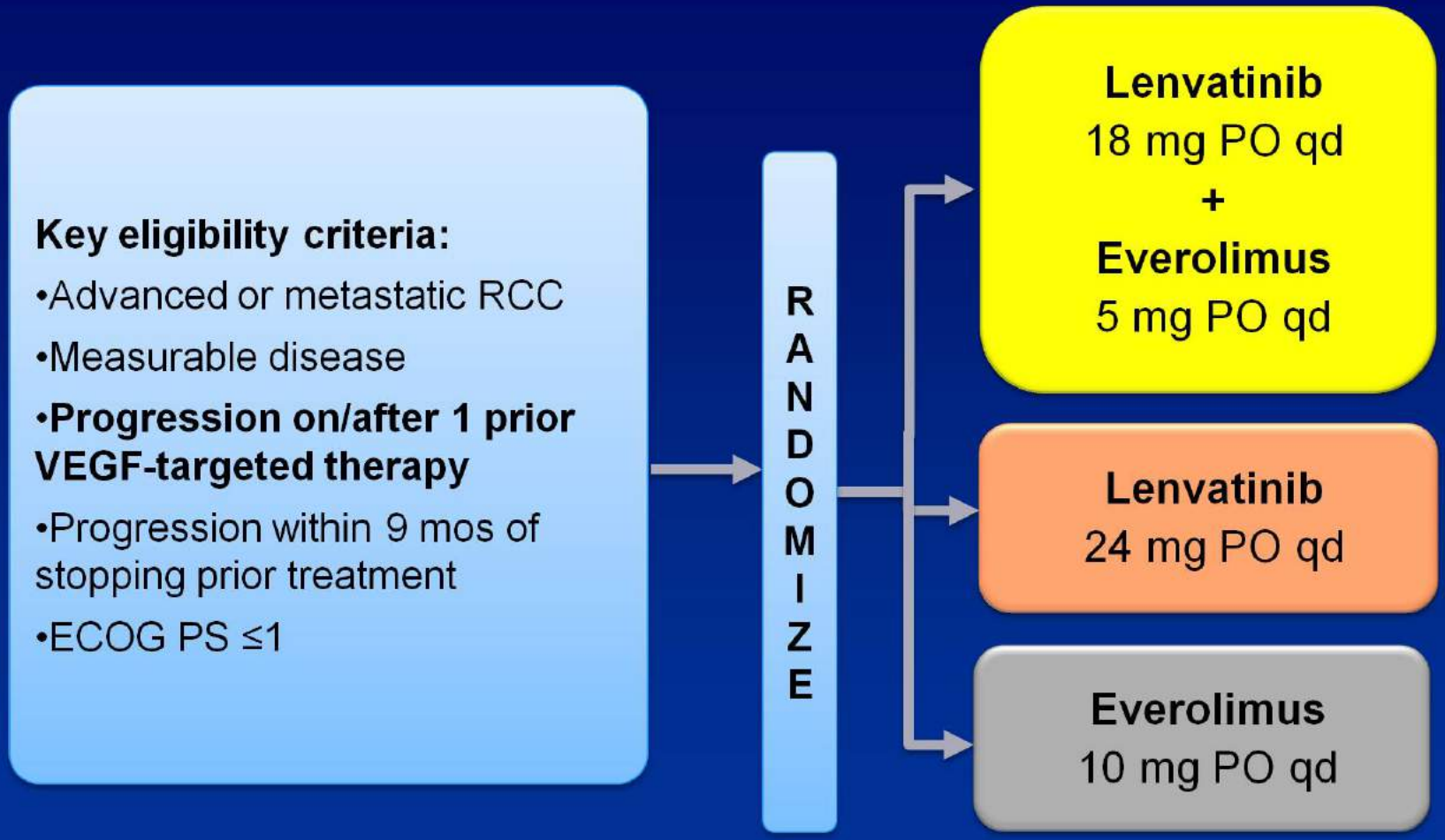




Lenvatinib

- **Lenvatinib (Eisai) is an oral molecular targeted agent that selectively inhibits the kinase activities of**
  - **vascular endothelial growth factor (VEGF) receptors (VEGFR1 (FLT1), VEGFR2 (KDR) and VEGFR3, (FLT4))**
  - **pro-angiogenic and oncogenic pathway-related RTKs including**
  - **fibroblast growth factor (FGF) receptors FGFR1, 2, 3 and 4**
  - **the platelet-derived growth factor (PDGF) receptor PDGFRα**
  - **KIT**
  - **RET**

Lenvatinib+Everolimus rPII Study Design



Phase 2: Lenvatinib vs Lenvatinib + Everolimus vs Everolimus - Efficacy

	Lenvatinib/Everolimus (n = 51)	Lenvatinib (n = 52)	Everolimus (n = 50)
PFS			
Median, months	14.6	7.4	5.5
95% CI	5.9-20.1	5.6-10.2	3.5-7.1
Benefit vs everolimus	*P* < 0.001	*P* = 0.048	NA
ORR, %	43	27	6
95% CI	29-58	16-41	1-17
Benefit vs everolimus	*P* < 0.001	*P* = 0.007	NA
OS (updated)			
Median, months	25.5	19.1	15.4
95% CI	16.4-NE	13.6-26.2	11.8-19.6
Benefit vs everolimus	*P* = 0.024	*P* = 0.118	NA

NA, not applicable; NE, not estimable; ORR, objective response rate.

Motzer RJ et al. *Lancet Oncol.* 2015;16(15):1473-82

The NEW ENGLAND JOURNAL of MEDICINE

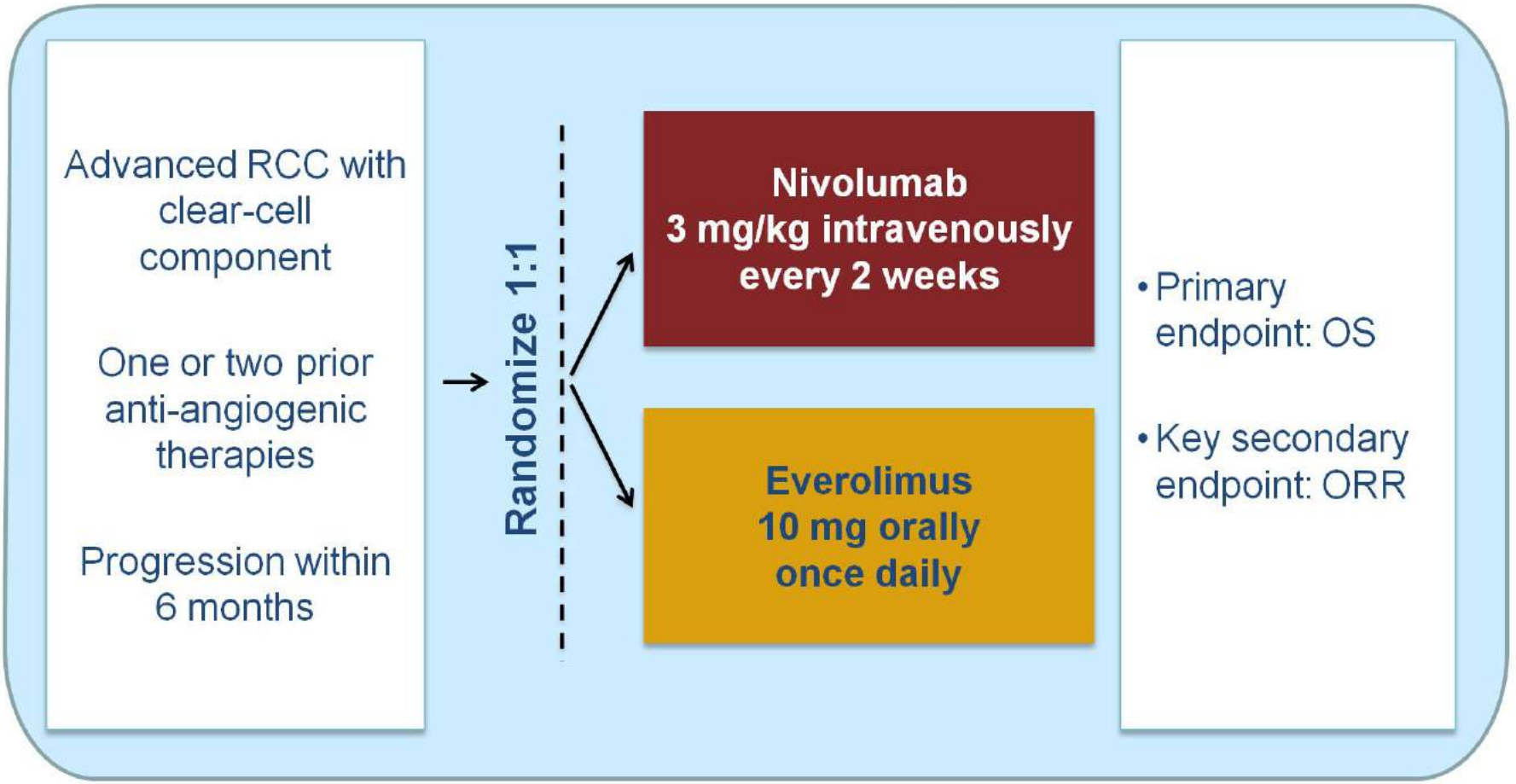
ORIGINAL ARTICLE

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas,
. Castellano, T.K. Choueiri,
uler, T. Ueda, Y. Tomita,
ud, J.S. Simon, L.-A. Xu,
e 025 Investigators*

CheckMate 025: A randomized, open-label, phase III study of nivolumab versus everolimus in advanced renal cell carcinoma

Phase III Study Design



- 821 patients randomized from October 2012 through March 2014
- Study halted July 2015 at preplanned interim analysis of OS

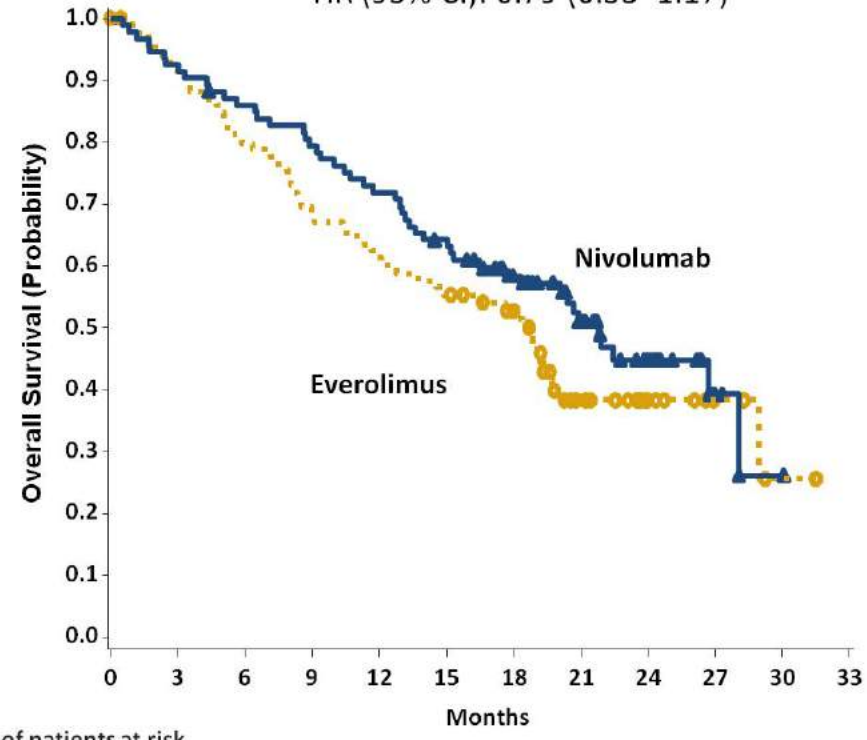
Sharma et al. NEJM

Overall survival by PD-L1 expression

PD-L1 ≥1% (n = 24%)

Median OS, months (95% CI)	
Nivolumab	21.8 (16.5–28.1)
Everolimus	18.8 (11.9–19.9)

HR (95% CI): 0.79 (0.53–1.17)



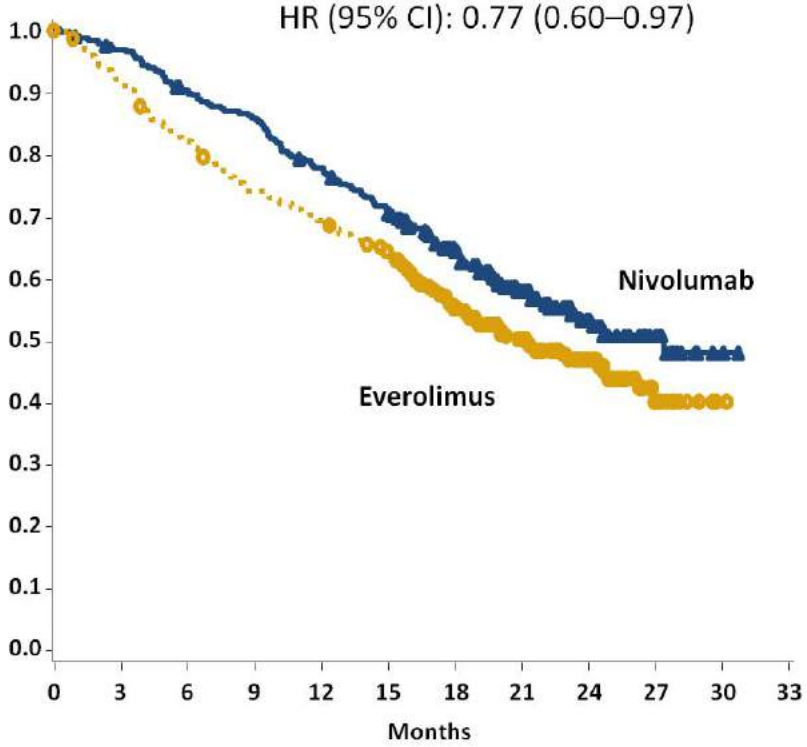
No. of patients at risk

Nivolumab	94	86	79	73	66	58	45	31	18	4	1	0
Everolimus	87	77	68	59	52	47	40	19	9	4	1	0

PD-L1 <1% (n = 76%)

Median OS, months (95% CI)	
Nivolumab	27.4 (21.4–NE)
Everolimus	21.2 (17.7–26.2)

HR (95% CI): 0.77 (0.60–0.97)



	276	265	245	233	210	189	145	94	48	22	2	0
	299	267	238	214	200	182	137	92	51	16	1	0

Antitumor activity*

	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	21.5	3.9
P value	<0.0001	
Best overall response, %		
CR/PR	21.5	3.9
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12
Median time to response, months (range)	3.0 (1.4–13.0)	3.7 (1.5–11.2)
Median duration of response, months (range)*	23.0 (12-NE)	13.7 (8.3–21.9)

* Information from PI

Survival by subgroups in phase III CheckMate 025 study

	Median overall survival, months (95% CI)	
	Nivolumab N = 410	Everolimus N = 411
Overall median OS, months (95%CI)[1]	25.0 (21.8–NE)	19.6 (17.6–23.1)
Median OS by MSKCC risk group, months (95%CI)[1]		
Favorable	NR	29.0 (26.9–NE)
Intermediate	21.8 (18.3–NE)	18.4 (16.1–23.1)
Poor	15.3 (9.6–22.4)	7.9 (5.4–9.7)
Median OS by KPS, months (95%CI)[1]		
90 or 100	NR (26.7–NE)	29.0 (24.3–NE)
≤70[a] or 80	18.1 (14.3–22.2)	10.1 (7.9–12.8)
Median OS by response, months (95%CI)[2,b]		
CR/PR	NR (24.1–NE)	NR (12.4–NE)
SD	NR (22.7–NE)	25.0 (22.9–NE)
PD	14.0 (11.3–16.9)	9.8 (6.1–12.2)

[a]All patients had a KPS of 70 at time of study entry but this may have decreased at randomization.
[b]All treated patients evaluable for best overall response by 4 months.
1. Motzer, RJ, et al. *J Clin Oncol* 2016;34(suppl 2S):abstr 498. 2. Motzer, RJ, et al. ASCO 2016 Abstract 4552.

- Minimum follow-up was 14.0 months

Presented By Daniel George at 2016 ASCO Annual Meeting

Safety Summary

	Nivolumab N = 406		Everolimus N = 397	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related AEs, %	79	19	88	37
Treatment-related AEs leading to discontinuation, %	8	5	13	7
Treatment-related deaths, n	0		2[a]	

- 44% of patients in the nivolumab arm and 46% of patients in the everolimus arm were treated beyond progression

[a] Septic shock (1), bowel ischemia (1).

Abstract #4507

Long-term overall survival (OS) with nivolumab in previously treated patients with advanced renal cell carcinoma (aRCC) from phase I and phase II studies

David McDermott,[1] Robert Motzer,[2] Michael Atkins,[3] Elizabeth Plimack,[4] Mario Sznol,[5] Saby George,[6] Charles Drake,[7] Brian Rini,[8] Toni Choueiri,[9] Timothy Kuzel,[10] Jeffrey Sosman,[11] David Smith,[12] Ulka Vaishampayan,[13] John Powderly,[14] Suzanne Topalian,[7] Huanyu Zhao,[15] Ian Waxman,[15] Hans Hammers[7]

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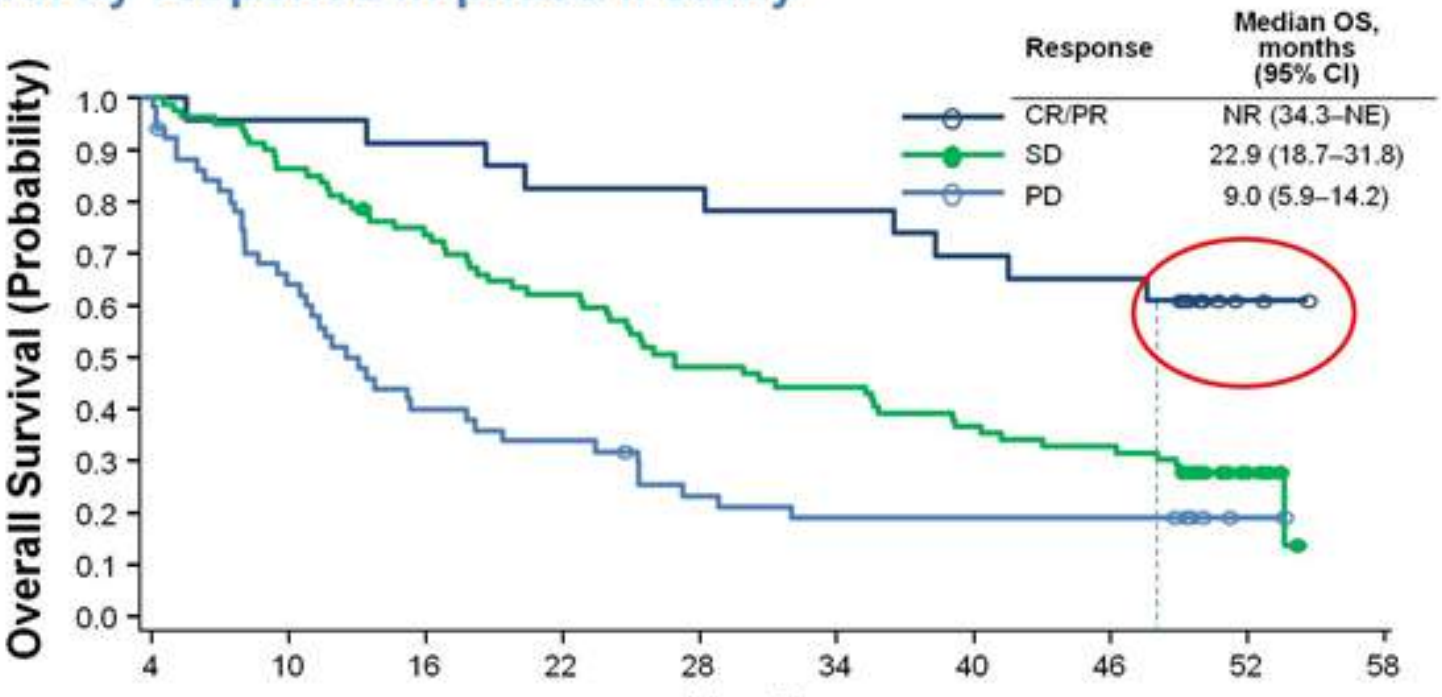
PRESENTED AT: ASCO ANNUAL MEETING '16

Survival by response in phase II study



Number at risk[a]

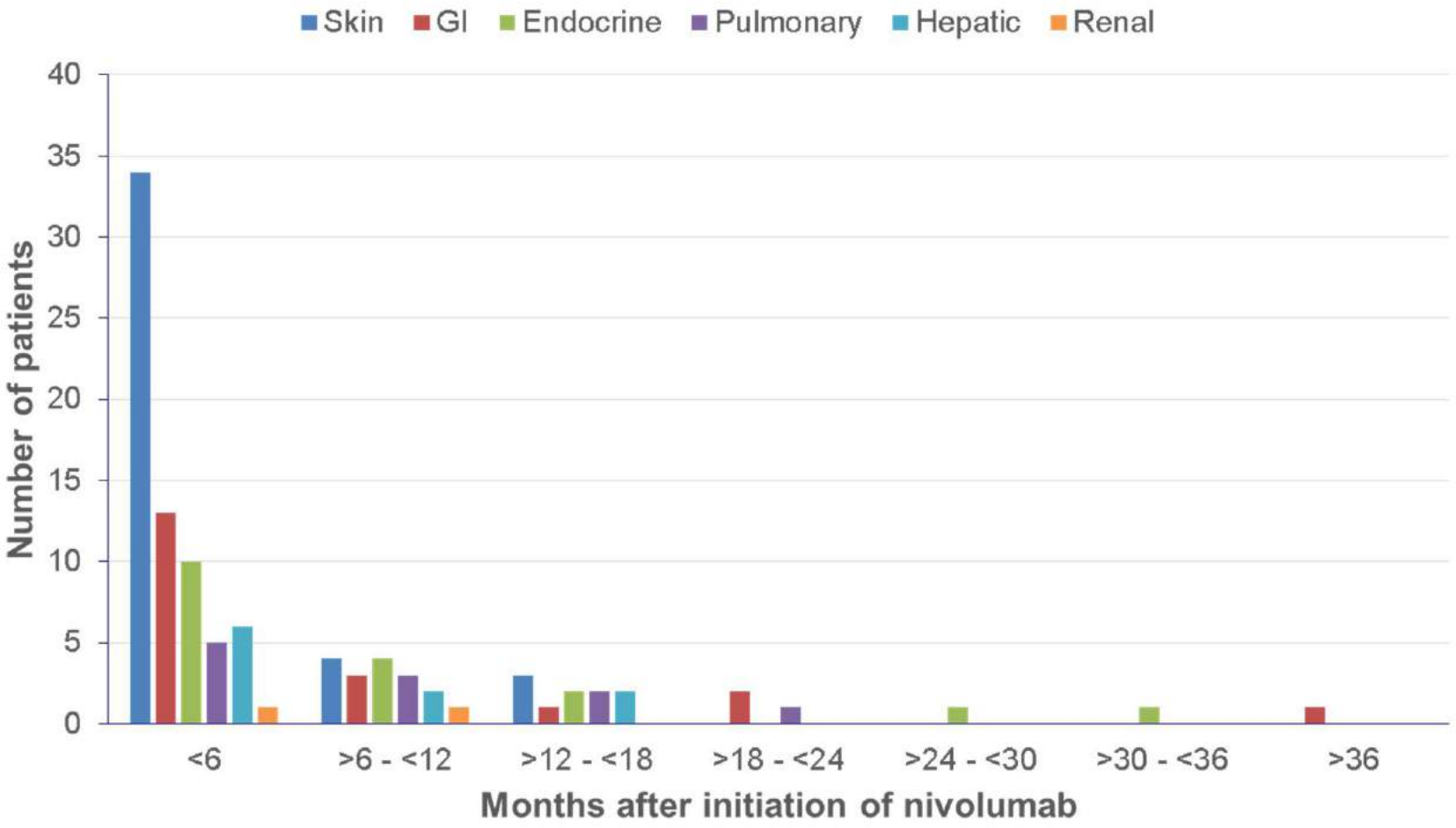
CR/PR	23	22	21	19	19	18	16	15	2	0
SD	80	69	58	49	38	35	29	26	9	0
PD	51	32	20	17	11	9	9	9	1	0

[a] All treated patients evaluable for best overall response by 4 months.

Presented By Daniel Geynisman at 2016 ASCO Annual Meeting

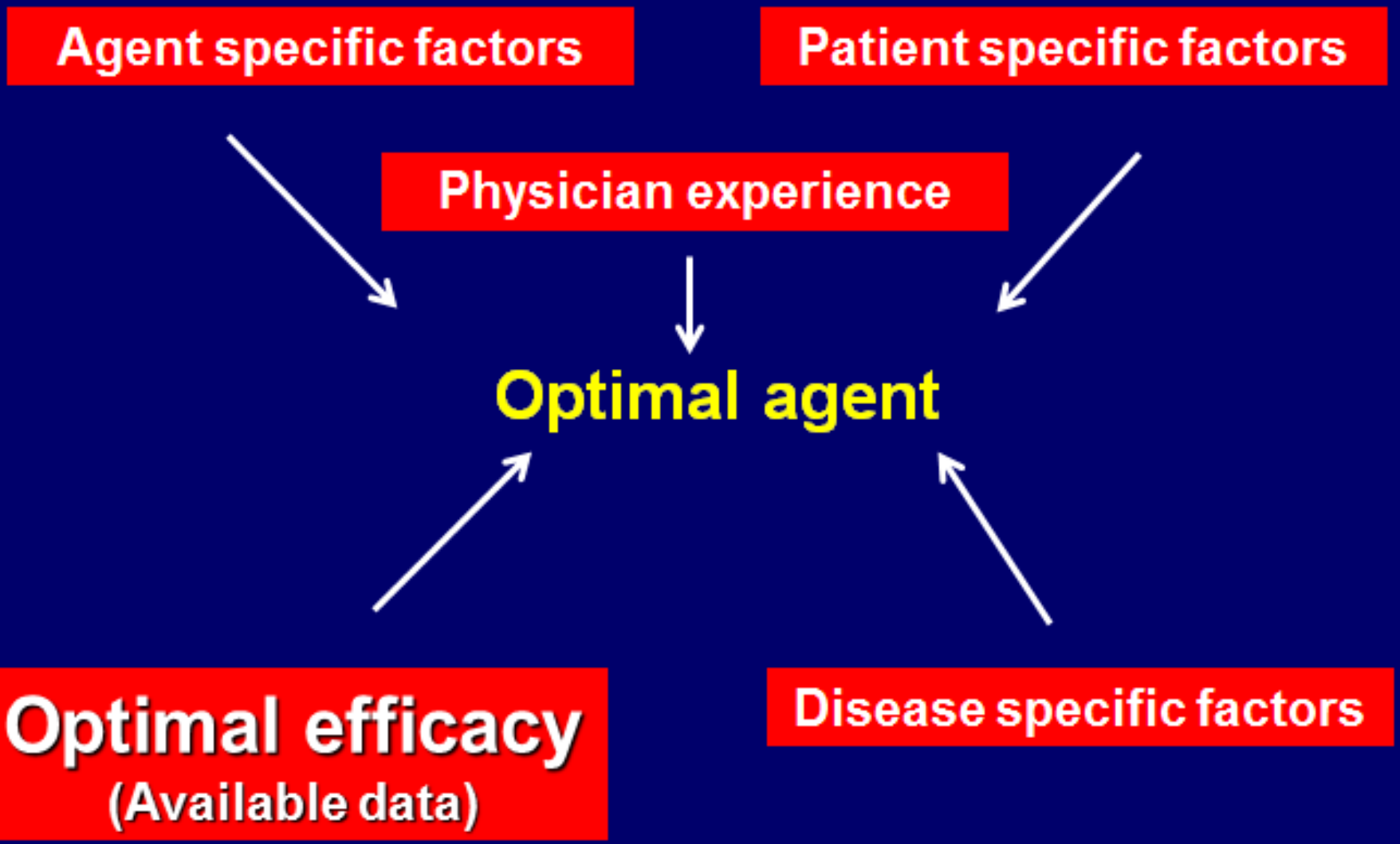
Emerging select TRAEs over time in Phase II studies

Treatment related Adverse events



TRAEs, treatment-related adverse events

Optimal therapy selection for metastatic RCC



Second-Line Systemic Therapy for Metastatic Renal Cell Carcinoma

	Axitinib[1]	Nivolumab[2]	Cabozantinib[3]	Lenvatinib/eve (RP2)[4]
Patient Population	2nd Line	TKI refractory (72% 1 prior)	TKI refractory (71% 1 prior)	TKI refractory (100% 1 prior)
MSKCC risk good/int/poor risk groups	2nd	2nd -3rd	Any line + Post check point inh	2nd
Comparator	Post cytokine Post VEGF INH	Post anti angiogenic		Everolimus
ORR, %			17%	Post VEGF inh
PFS, months		4.6		
OS, months		BENEFIT IN ALL RISK GROUP		25.5
Dose reductions			12% of cases experienced PD as best response with cabozantinib as compared with 35% with nivolumab.	
D/C due to AE				
Toxicity		1% G4 (tx-related)		

PR

PD

Axitinib
0
19.4
49.9
21.6
6.1

+ QoL

Best response, %	
CR	2
PR	41
SD	41
PD	4
Not evaluated	12

PRESENTED AT ASCO ANNUAL

Presented By Robert Figlin at 2016 ASCO Annual Meeting

Second-Line Systemic Therapy for Metastatic Renal Cell Carcinoma

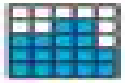
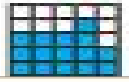
	Axitinib[1]	Nivolumab[2]	Cabozantinib[3]	Lenvatinib/eve (RP2)[4]
Patient Population	2nd Line	TKI refractory (72% 1 prior)	TKI refractory (71% 1 prior)	TKI refractory (100% 1 prior)
MSKCC risk good/int/poor risk groups	28 / 37 / 33	35 / 49 / 16	45 / 42 / 12	24 / 37 / 39
Comparator	Sorafenib	Everolimus	Everolimus	Everolimus
ORR, %	19%	22%	17%	35%
PFS, months				12.8
OS, months				25.5
Dose reductions				71%
D/C due to AE				29%
Toxicity				57% G3
				14% G4

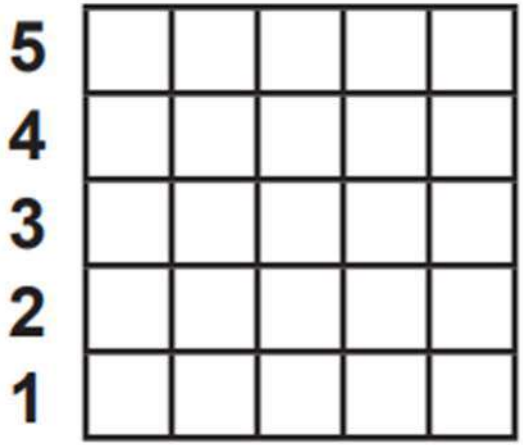
3:1814; 4. Motzer et al. *Lancet Oncol* 2015;16:1473

PRESENTED AT: ASCO ANNUAL MI

Presented By Robert Figlin at 2016 ASCO Annual Meeting

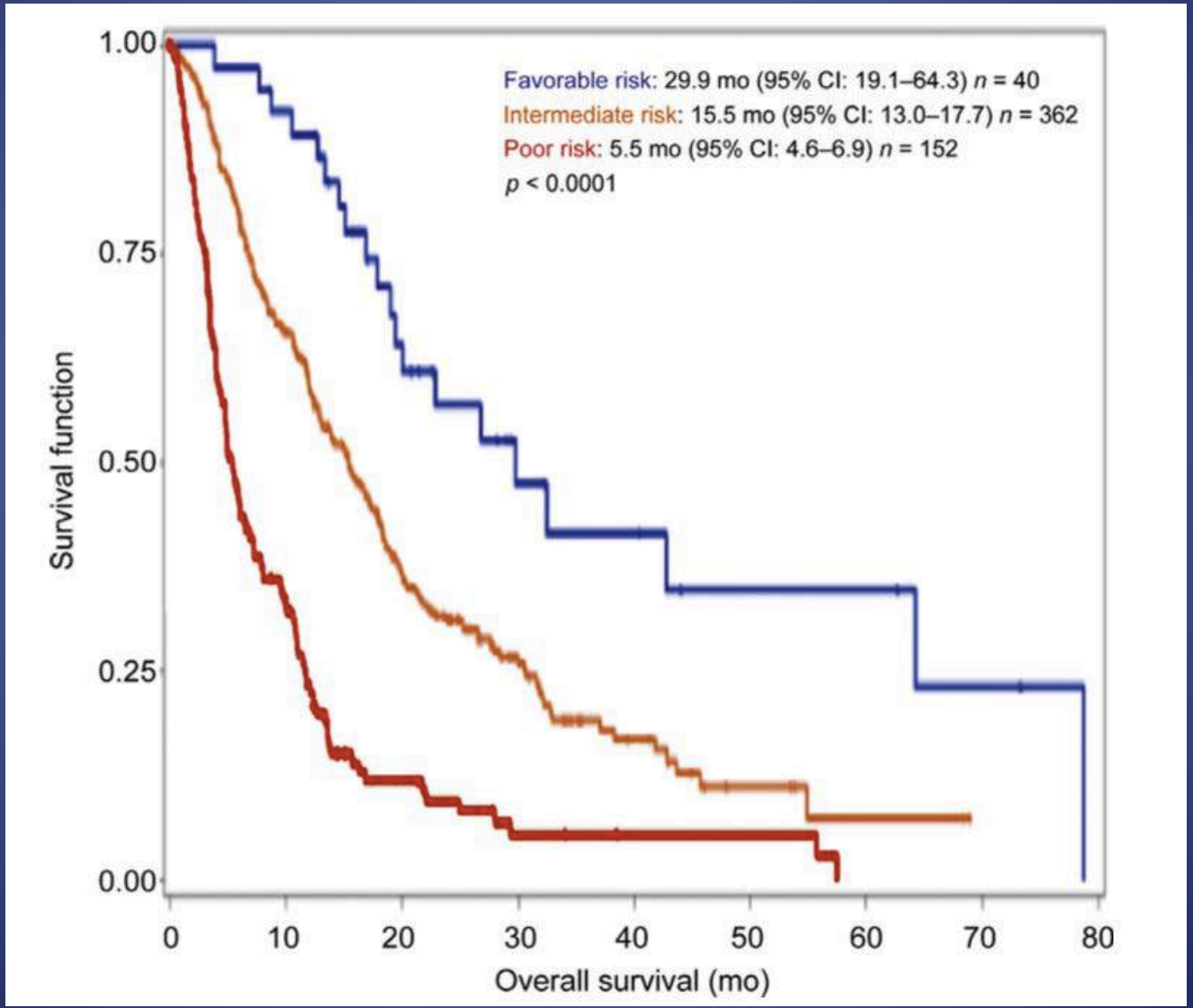
Subsequent Therapy for Clear Cell Carcinoma

Cabozantinib	
Nivolumab	
Axitinib	
Lenvitinib + everolimus	
Everolimus	
Pazopanib	



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

IMDC in 3nd-line targeted therapy



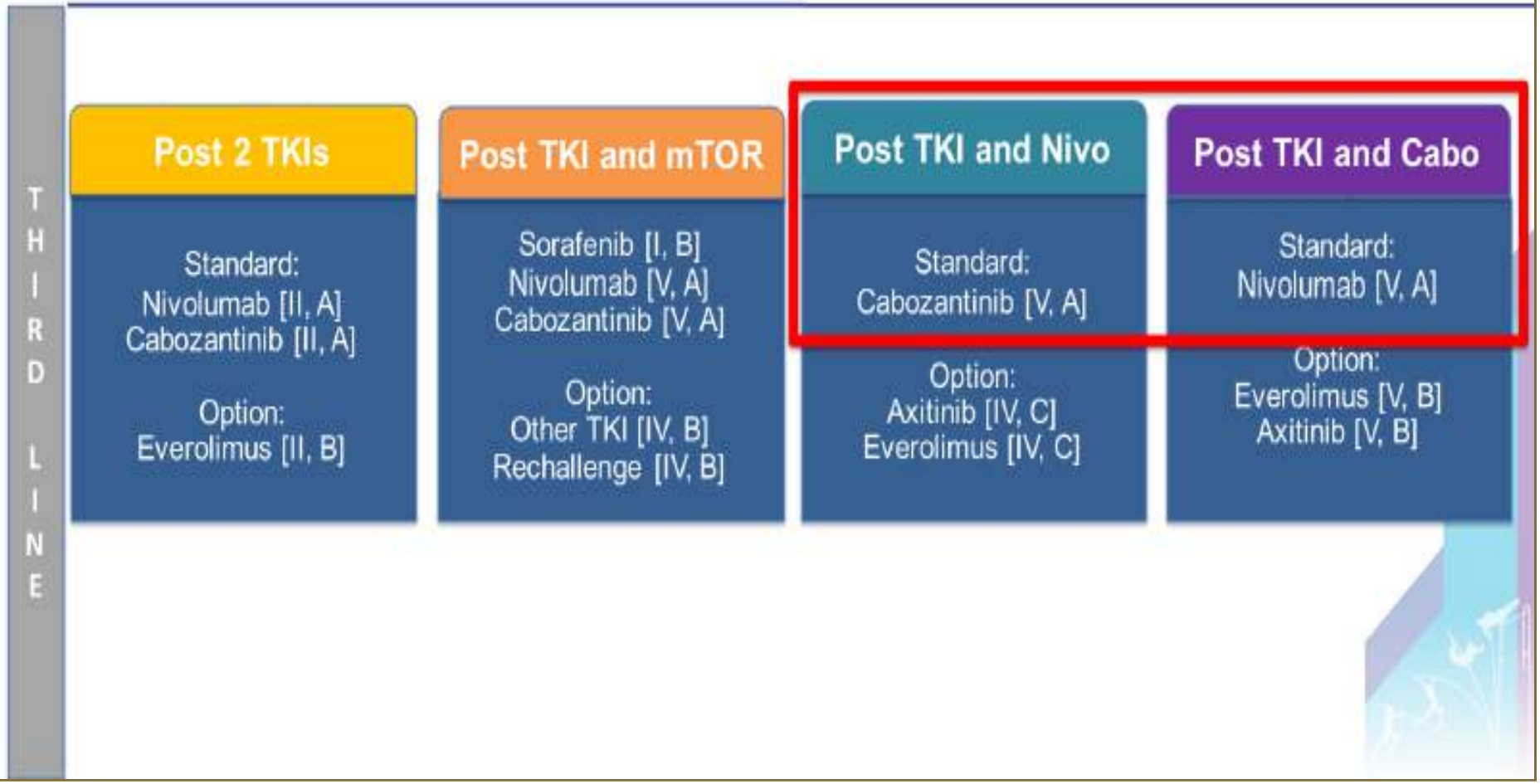
Wells JC European Urol 2016

Patients eligible for third line

- **IGR experience: 18.7%**
- **Italian experience (Iacovelli et al, EJC 2013): 281/2065 (13%)**
- **US experience (Pal S et al, ASCO GU 2013): 812/6937 (11.7%)**
  - **IMDC (Heng et al, ASCO 2013): 460/2703 (17%)**
    Overall, Around 50% receive a second line
  - **less than 20% of patients do receive third line treatment…..**

Changes in Third-Line Recommendation

ESMO Clinical Practice Guidelines 2016



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Following years of negative trials, it comes the era of targeted agents ...

Adjuvant trials of Targeted Agents

SORCE (MRC/EORTC) Sorafenib 1 year (+ 2 years placebo) vs. Sorafenib 3 years vs. placebo 3 years	1656	Enrolling patients with a Leibovich score of 3 to 8. Primary end-point: DFS	Data not mature yet
ASSURE (ECOG) Sunitinib 1 year vs. Sorafenib 1 year vs. placebo 1 year	1923	Enrollment completed (patients with T3b-4 N0, T1-4 N+, or T1-4 with positive margins or vascular invasion) Primary end-point: DFS	Data published
S-TRAC (Pfizer) Sunitinib 1 year vs. placebo 1 year	856	Enrolling patients with high risk according to UISS. Primary end-point: DFS	Data published
EVEREST (SWOG) Everolimus vs. placebo (days 1-42; treatment repeats every 6 weeks for 9 courses)	1218	Enrolling patients considered pathologically either intermediate high-risk or very high-risk. Primary end-point: DFS	Data not mature yet
VEG113387 PROTECT study (GSK) Pazopanib 1 year vs. placebo 1 year	1500	Enrolling patients with intermediate and high risk. Primary end-point: DFS	Data presented

ADJUVANT PHASE III TRIALS WITH VEGFR-TKI OR MTOR INHIBITORS

Trial	N	Patient Characteristics	Treatment Arms	Treatment Duration	Primary End Point
S-TRAC: Sunitinib Trial in Adjuvant Renal Cancer Treatment	**615**	**High-risk patients according to UISS**	**Sunitinib Placebo**	**1 year**	**DFS HR 0.76**
ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable RCC	**1,943**	**Non-metastatic RCC; disease stage II–IV selected by UISS**	**Sunitinib Sorafenib Placebo**	**1 year**	**DFS HR 1.02**
SORCE: Sorafenib in Patients with Resected Primary RCC at High/Intermediate Risk of Relapse	1,656	Patients with Leibovich high- and intermediate-risk resected RCC	Sorafenib Sorafenib/ Placebo Placebo	1 year 3 years	DFS
EVEREST: Everolimus for Renal Cancer Ensuing Surgical Therapy	1,537	Pathological stage intermediate or very high-risk patients with full or partial nephrectomy	Everolimus Placebo	9 treatment cycles	RFS
PROTECT: Pazopanib as an Adjuvant Treatment for Localized RCC	1,540	Patients with moderately high or high risk after nephrectomy of localized or locally advanced RCC by AJCC TNM v.2010	Pazopanib Placebo	1 year	DFS
ATLAS: Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients	700	High-risk, non-metastatic RCC with nephrectomy by AJCC TNM v.2010	Axitinib Placebo	3 years	DFS

Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT)

Robert Motzer, Naomi Haas, Frede Donskov, Marine Gross-Goupil, Sergei Varlamov, Evgeny Kopyltsov, Jae-Lyun Lee, Bohuslav Melichar, Brian Rini, Toni Choueiri, Milada Zemanova, Lori Wood, Dirk Fahlenkamp, Martin Reaume, Arnulf Stenzl, Weichao Bao, Paola Aimone, Christian Doehn, Paul Russo, Cora Sternberg for the PROTECT investigators

Abstract 4507

PROTECT, **P**azopanib as adjuvant the**R**apy in l**O**calized/locally advanced RCC af**T**er n**E**phre**CT**omy (VEG113387).

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

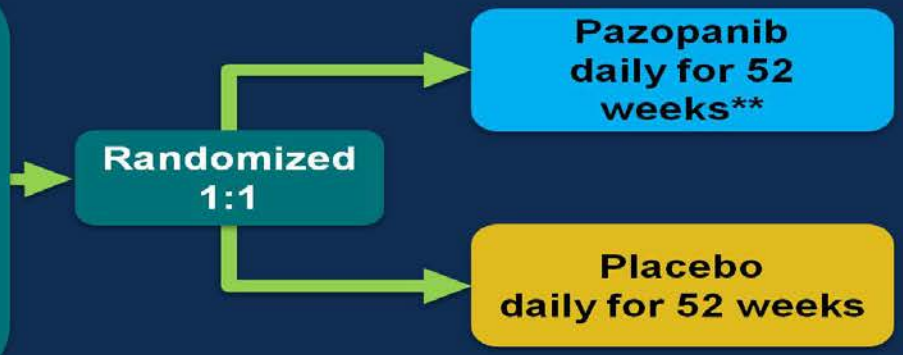
Presented by: Robert Motzer, MD

Presented By Robert Motzer at 2017 ASCO Annual Meeting

Study Design

Key eligibility criteria

- Resected non-metastatic clear-cell RCC histology and pathologic staging*
  - –pT2, G3 or G4, N0
  - –pT3, G_{any}, N0
  - –pT4, G_{any}, N0
  - –pT_{any}, G_{any}, N1
- Baseline imaging assessment by independent radiologist review that excluded metastasis
- Adequate PS and organ function



Stratification: partial vs radical nephrectomy; pathologic staging

**Starting dose 600 mg assessed for safety at 8-12 weeks and could be escalated to 800 mg or maintained at 600 mg based on patient's tolerability

*Staging based on TNM classification per the American Joint Committee on Cancer (AJCC) 2010 version and Fuhrman nuclear grades

Primary Analysis of DFS in ITT$_{600mg}$

The median duration of follow up was 30.4 months and 30.7 months for the pazopanib and placebo arms, respectively.

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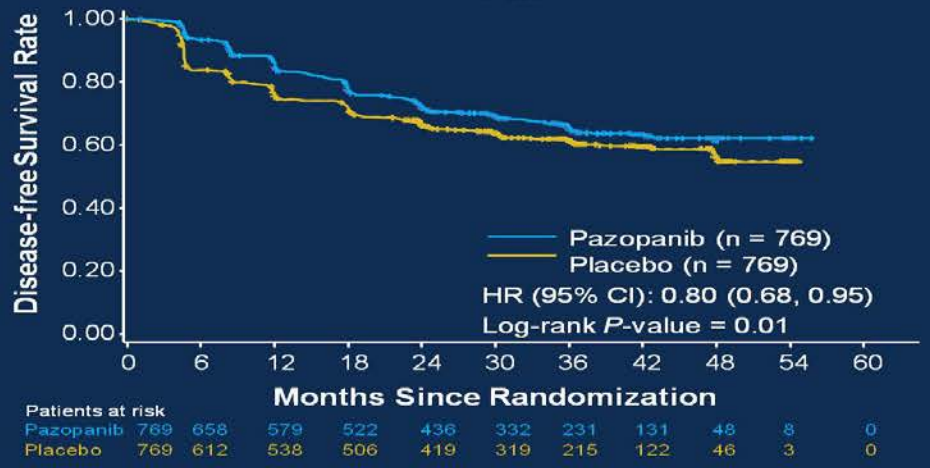
Secondary Analyses of DFS

ITT_{800mg}

ITT_{All}



The median duration of follow up for both treatment arms in the ITT_{800mg} group was 47.9 months, the median duration of follow up for the pazopanib and placebo arms was 35.5 and 35.9 months, respectively.

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Quality-of-Life Assessment by FKSI-19 for ITT_{600mg} vs Placebo

Evaluable patients (n)										
Pazopanib	558	435	485	451	423	364	335	253	161	71
Placebo	547	513	493	432	401	359	340	252	153	74

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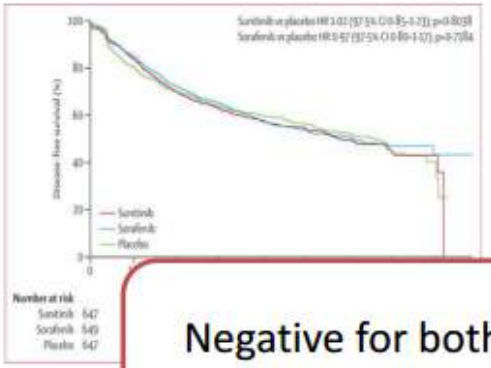
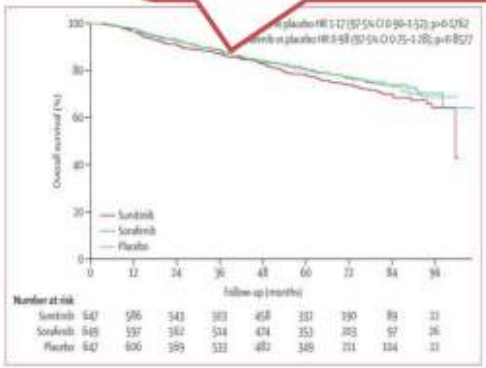
ASSURE, S-TRAC and PROTECT

ASSURE trial[1]

DFS



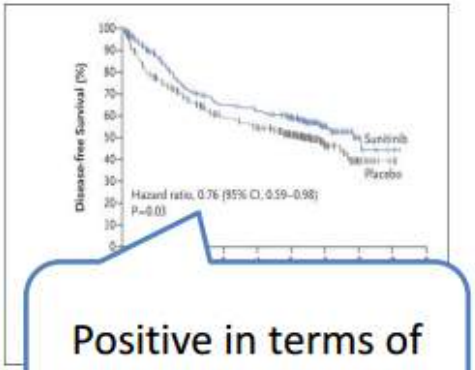
OS



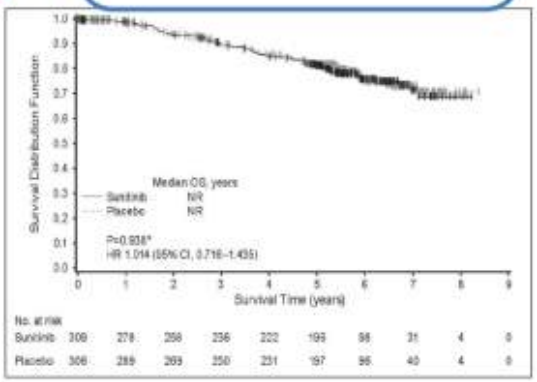
Negative for both DFS as well as OS

S-TRAC trial[2]

DFS



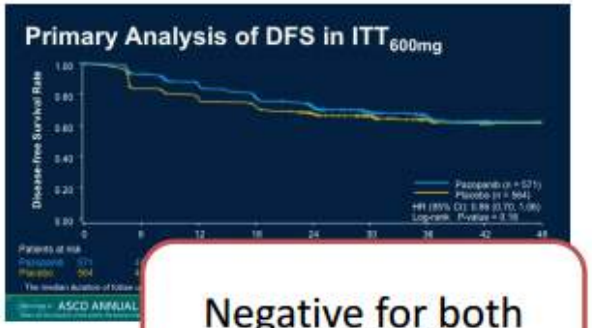
OS



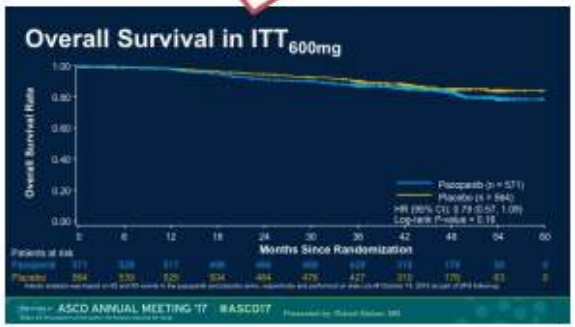
Positive in terms of DFS, but not of OS

PROTECT trial[3]

DFS



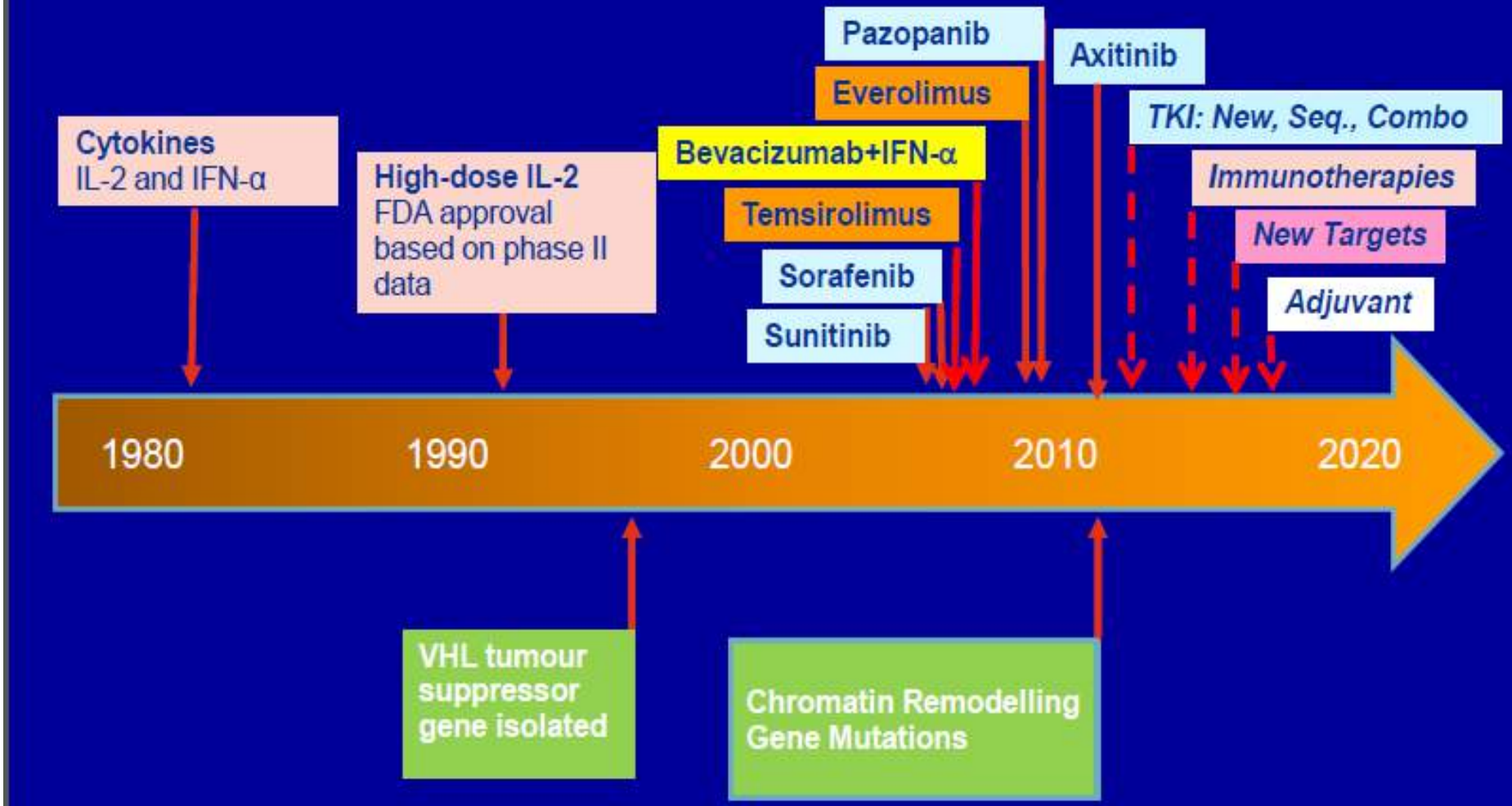
OS



Negative for both DFS as well as OS

1. Haas NB, et al. *Lancet* 2016;387:2008-16; 2. Ravaud A, et al. *N Engl J Med* 2017; 3. Motzer RJ, et al. *J Clin Oncol* 2017;

40 Years of Developing mRCC Treatments



Conclusion

- **Current first-line treatment landscape allows choices**
- **First-line therapy should always be a TKI (Exception: Poor PS poor-risk patients)**
- **In the absence of predictive factors, efficacy as well as patient and agent/patient-specific factors are the drivers of treatment selection**
- **Multiple new agents are currently in clinical development and immunotherapy has arrived in the treatment of RCC and those agents may change the landscape yet again in the near future.**

Ramathibodi Comprehensive Cancer Center
and Multidisciplinary Team

RCC Master Class 2017

THANK YOU IN YOUR ATTENTION