Oncologia e Rene

Il trattamento della malattia metastatica: dalle linee guida alle novità 2014

Maurizio Nicodemo

Ospedale Sacro Cuore-Don Calabria Negrar (VR)

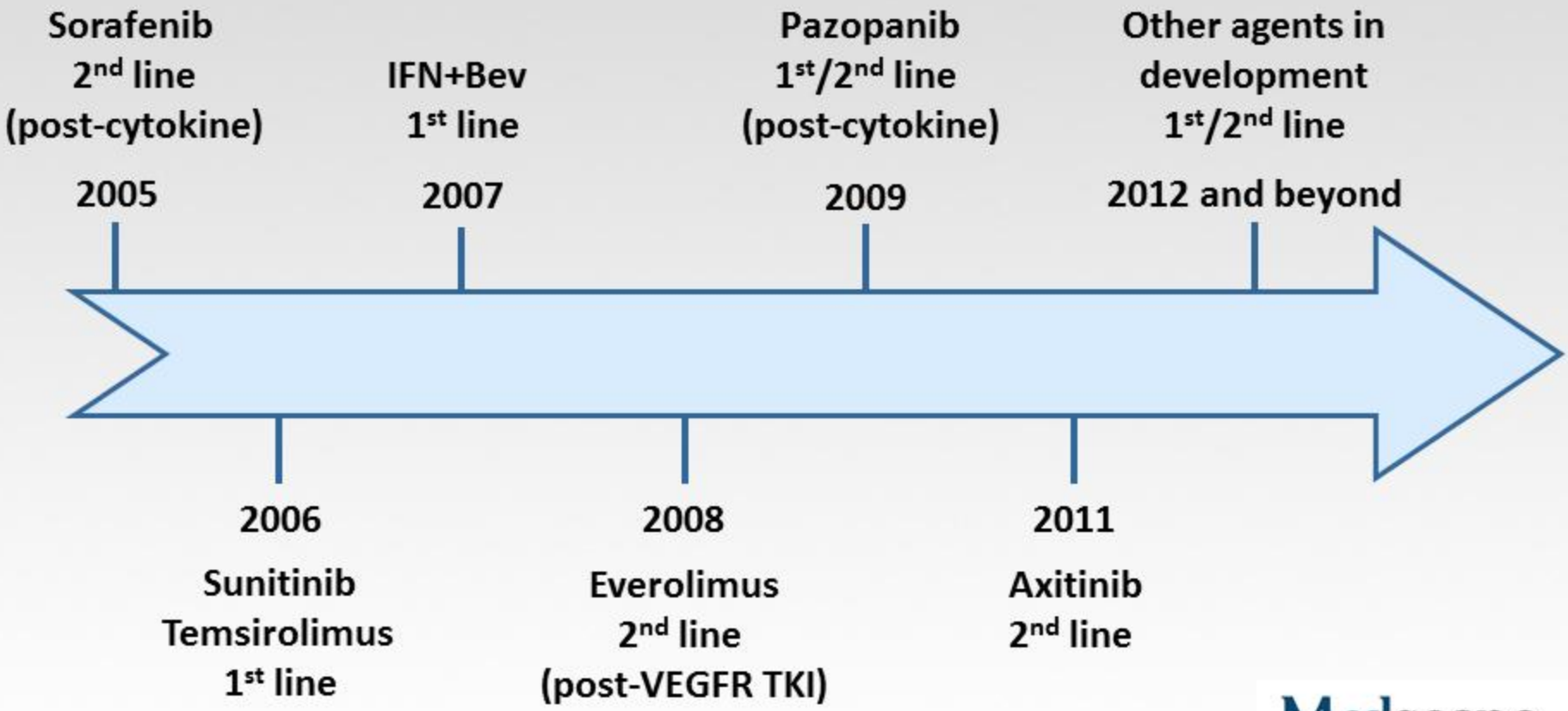
Epidemiology

- Clear cell RCC is the most common form of kidney cancer[a]
- Worldwide, it accounts for 270,000 cases and 116,000 deaths annually[b]
- Approximately 2/3 of patients present with localized disease[a]
- At this stage, the 5-year survival rate > 90%[a]
- One-third present with metastatic disease[a]
- Up to 40% develop metastatic disease after nephrectomy[c]
- At this stage, the 5-year survival rate is approximately 10%[c]

a. Kane CJ, et al. *Cancer*. 2008;113(1):78-83.
b. GLOBOCAN 2008.
c. Chin AI, et al. *Rev Urol*. 2006;8(1):1-7.

Milestones in Clinical Development of Targeted Agents for RCC

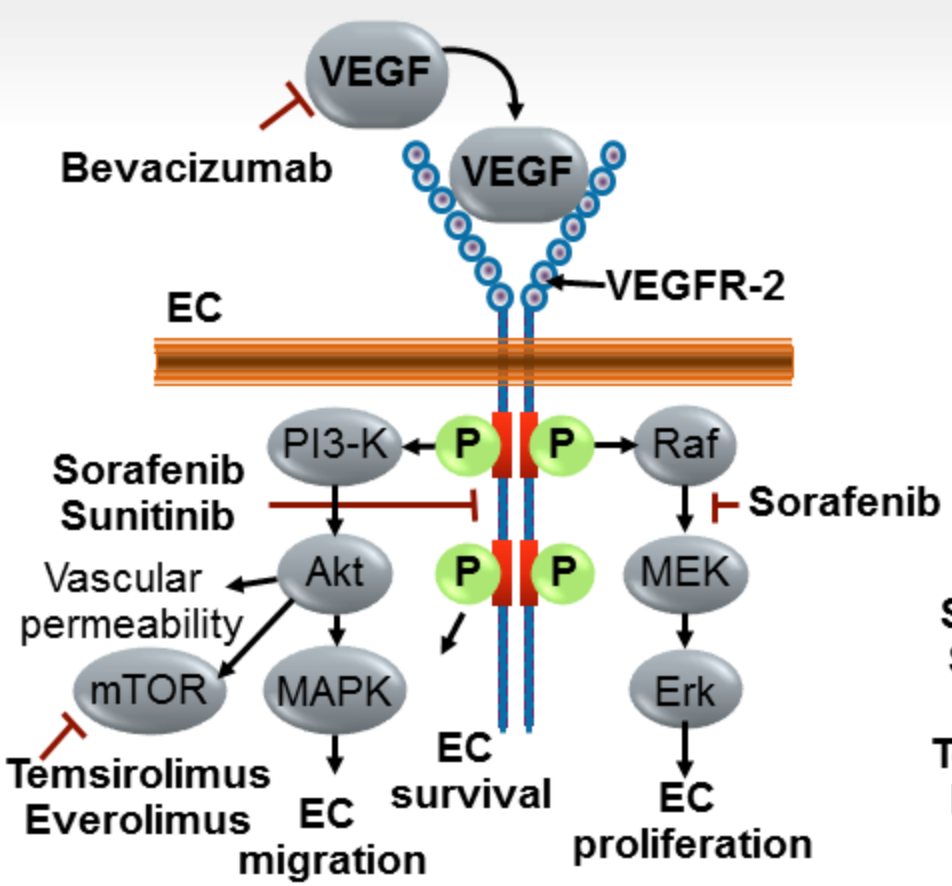
First Presentation of Clinical Trial Results

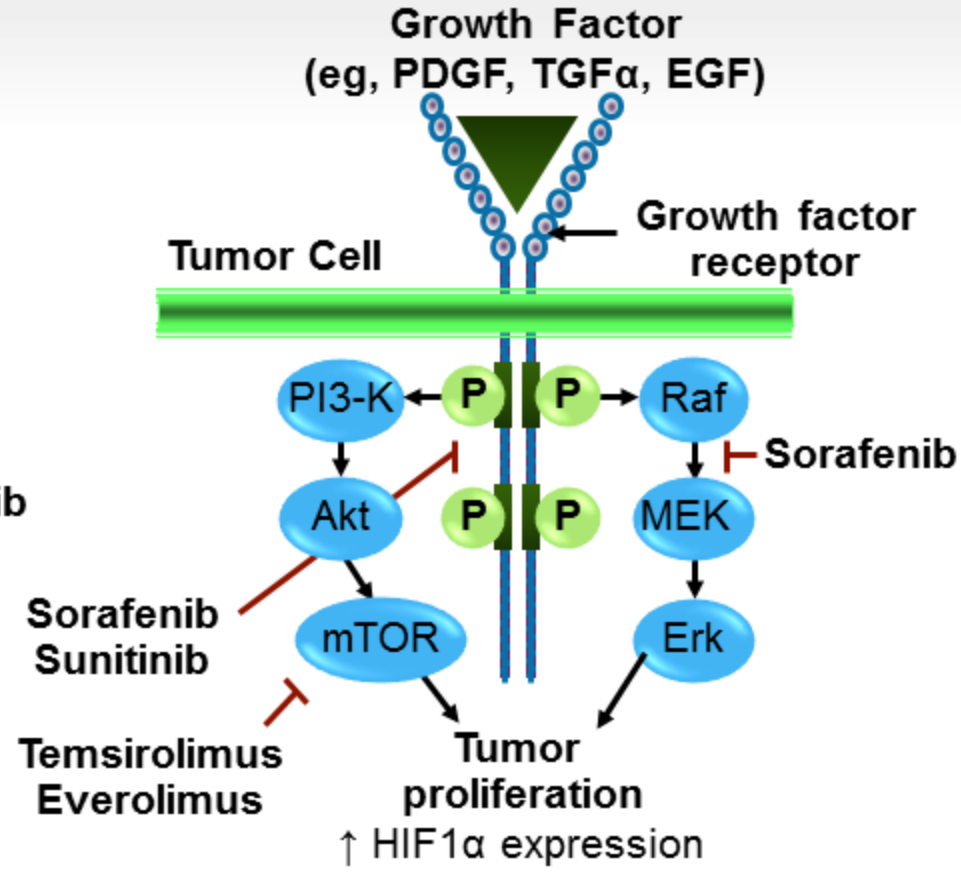


BEV = bevacizumab

Medscape EDUCATION

Signaling Pathways and Selective Inhibitors





EC = endothelial cell; EGF = epidermal growth factor; Erk = extracellular receptor kinase; MAPK = mitogen-activated protein kinase; MEK = mitogen and extracellular kinase; PI3-K = phosphoinositide 3-kinase; TGF = transforming growth factor.

EMA Approved Targeted Therapies

Mechanism of Action	Agent	Approved Line of Therapy
VEGFR TKI	Sorafenib	After failure of IFN or cytokine
	Sunitinib	Unrestricted
	Pazopanib	Unrestricted
	Axitinib	After failure of sunitinib or cytokine
Anti-VEGF mAb	Bevacizumab	Unrestricted (in combination with IFN)
mTOR Inhibitor	Temsirolimus	Unrestricted
	Everolimus	After failure of VEGF-targeted therapy

EMA = European Medicines Agency; IFN = interferon; mAb = monoclonal antibody; TKI = tyrosine kinase inhibitor

Risk assessment is important in mRCC: IMDC classification

- 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

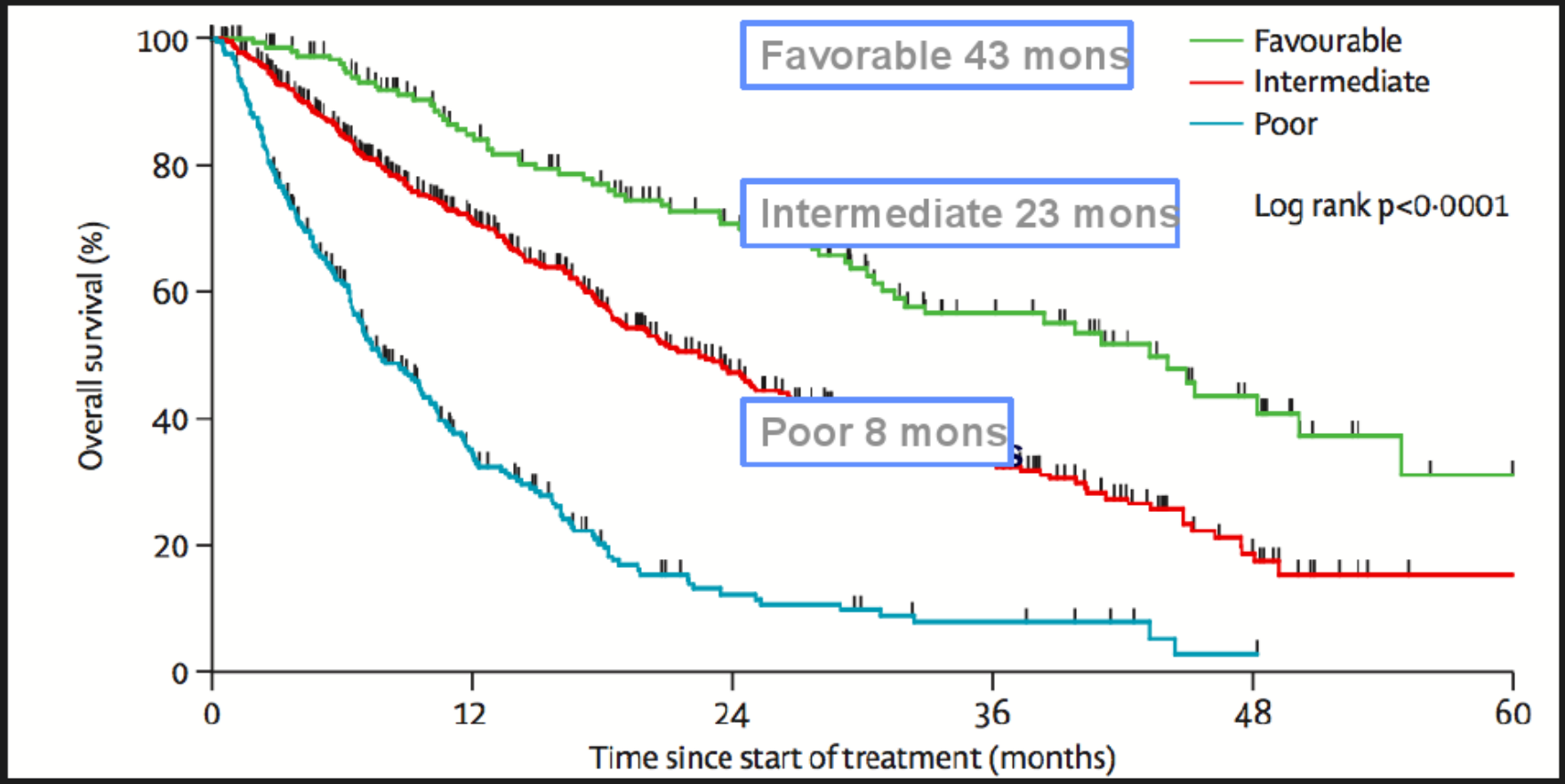
Risk groups are useful

If patient has 0 factors:
Favorable Prognosis

If patient has 1-2 factors:
Intermediate Prognosis

If patient has 3-6 factors:
Poor Prognosis

IMDC Prognostic Factors



Heng et al Lancet Oncology 2013

Annals of Oncology 25 (Supplement 3): iii49–iii56, 2014
doi:10.1093/annonc/mdu259

Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Table 6. Algorithm for systemic treatment in mRCC

Histology and setting	Risk group	Standard	Option
Clear-cell first line	Good or intermediate risk	Sunitinib [I, A]	High-dose IL2 [III, C]
		Bevacizumab + IFN-α [I, A]	Sorafenib [II, B]
		Pazopanib [I, A]	Bevacizumab + low-dose IFN-α [III, A]
	Poor risk	Temsirolimus [II, A]	Sunitinib [II, B]
			Sorafenib [III, B]
Clear-cell second line	Post cytokines	Axitinib [I, A]	Sunitinib [III, A]
		Sorafenib [I, A]	
		Pazopanib [II, A]	
	Post TKIs	Axitinib [I, B]	Sorafenib [II, A]
		Everolimus [II, A]	
Clear-cell third line	Post 2 TKIs	Everolimus [II, A]	
	Post TKI and mTOR	Sorafenib [I, B]	Other TKI [IV, B]
			Rechallenge [IV, B]
Non-clear-cell histology			Temsirolimus [III, B]
			Sunitinib [III, B]
			Sorafenib [III, B]

Pazienti		Terapia di prima scelta	Opzioni di seconda scelta
Non pretrattati	**Rischio prognostico**: basso o intermedio	**Sunitinib** **Bevacizumab + IFN-α** **Pazopanib**	IL-2 alte dosi Sorafenib Osservazione
	Rischio prognostico: *poor risk*	**Temsirolimus** **Sunitinib**	*Trial* clinici
Pretrattati	**con citochine**	**Sorafenib** **Axitinib**	Pazopanib Sunitinib
	con farmaci *anti VEGF/VEGFr*	**Everolimus** **Axitinib**	Sorafenib

Tabella 8: Trattamento medico dell' mRCC - istologia a cellule chiare

Figura 2. Trattamento medico mRCC istotipo a cellule chiare

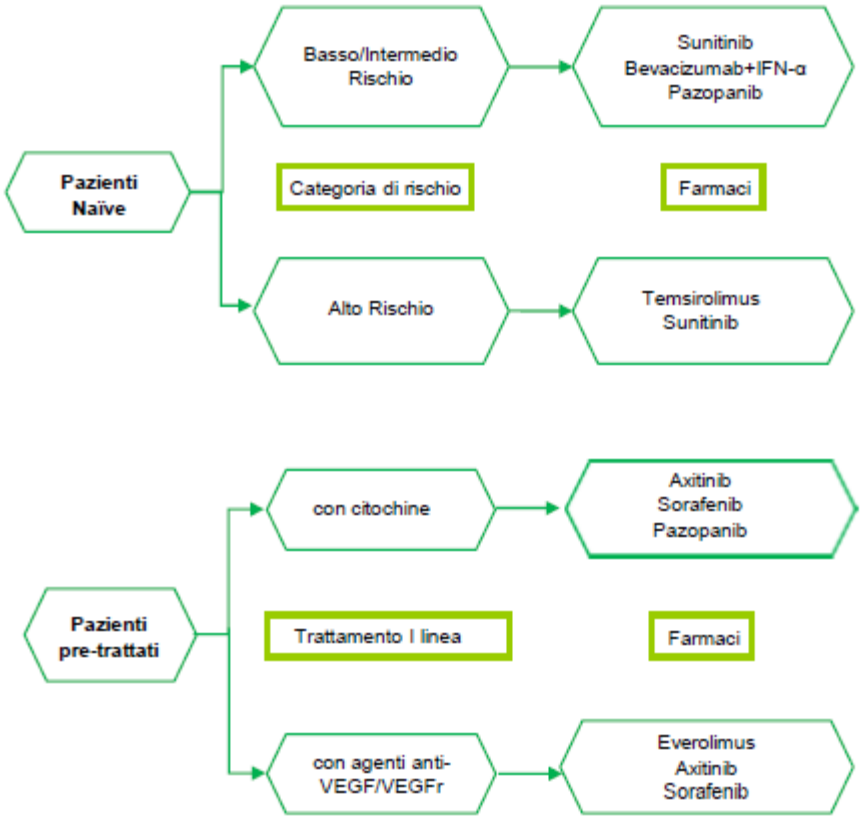
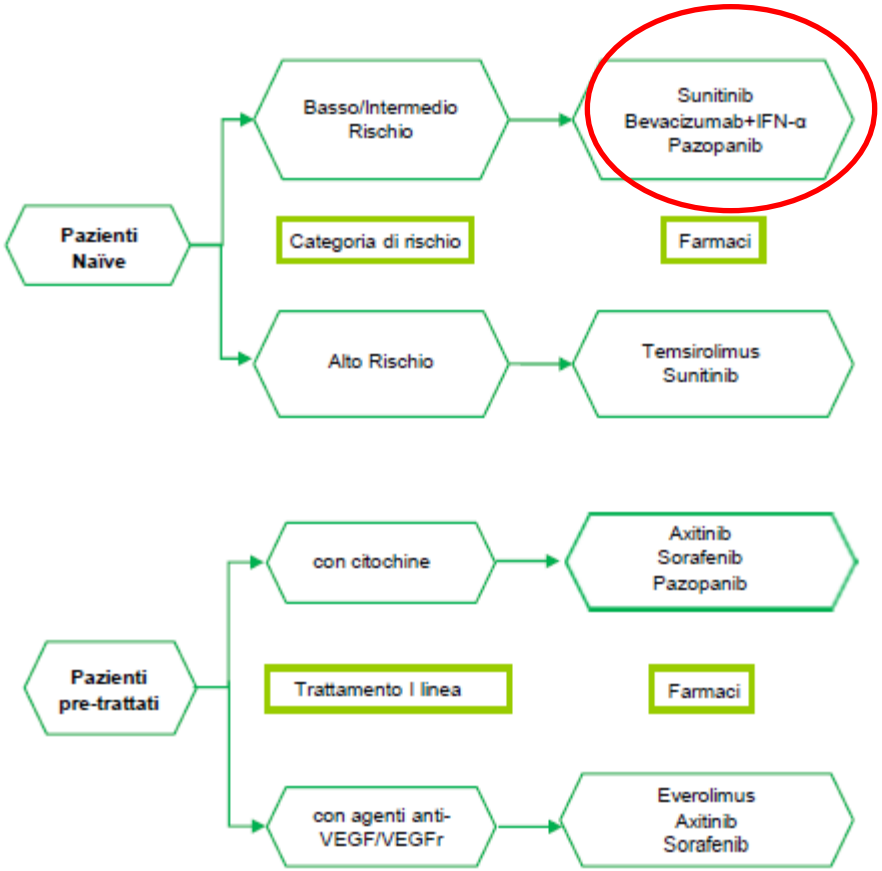
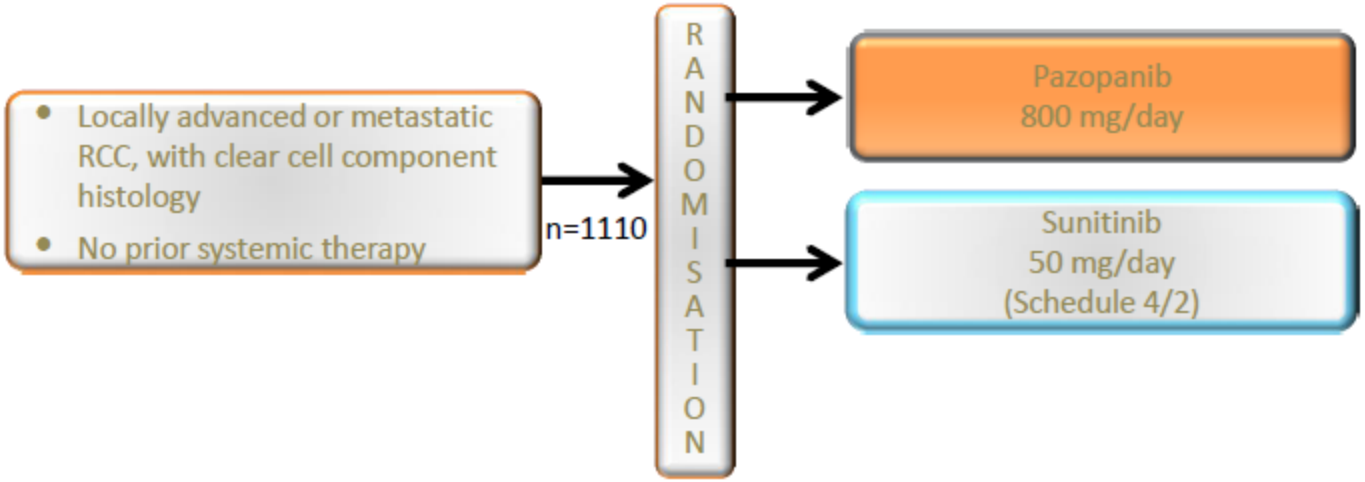


Figura 2. Trattamento medico mRCC istotipo a cellule chiare

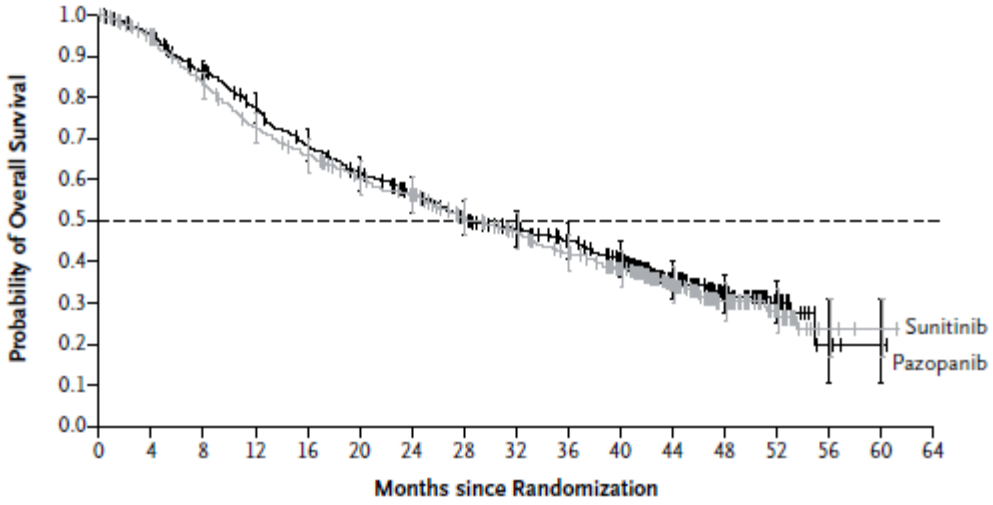


COMPARZ: Sunitinib vs Pazopanib



Motzer et al, NEJM 2013

Overall Survival in Renal-Cell Carcinoma with Pazopanib versus Sunitinib

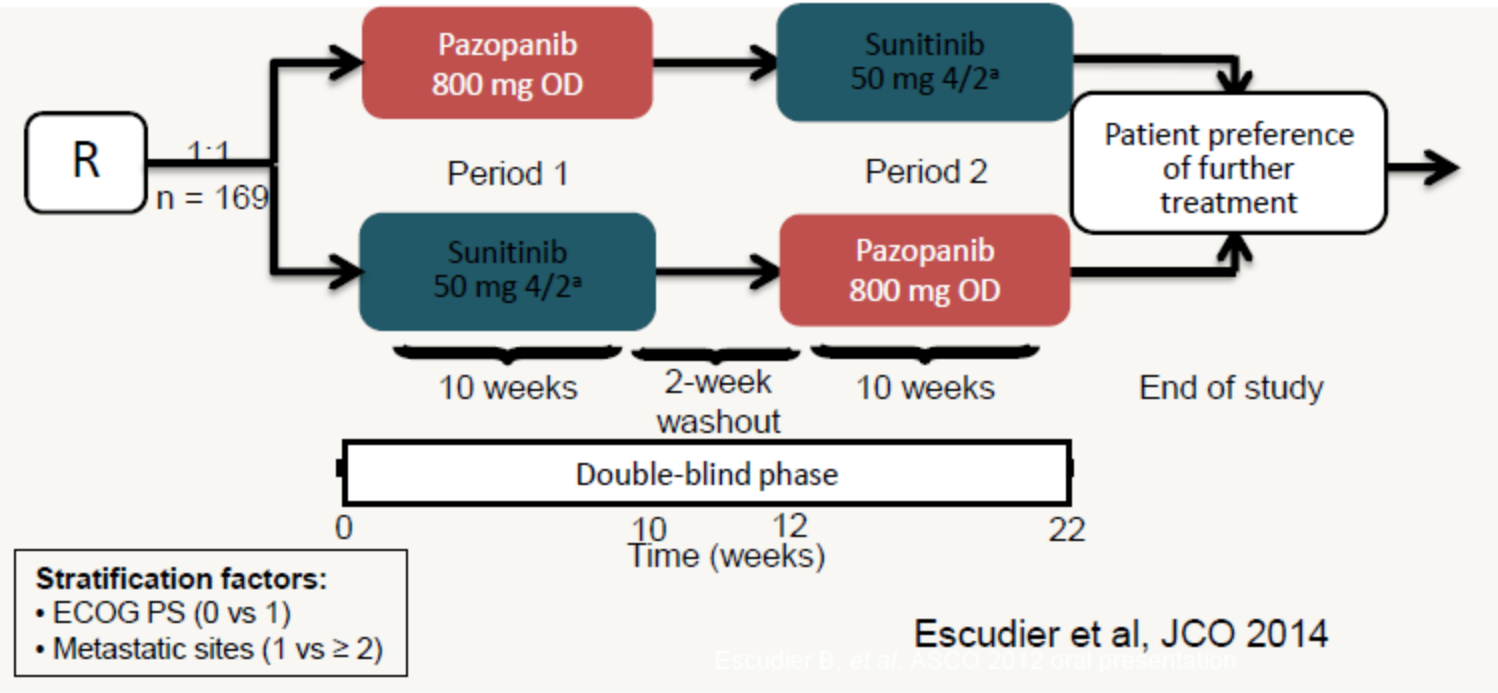


No. at Risk

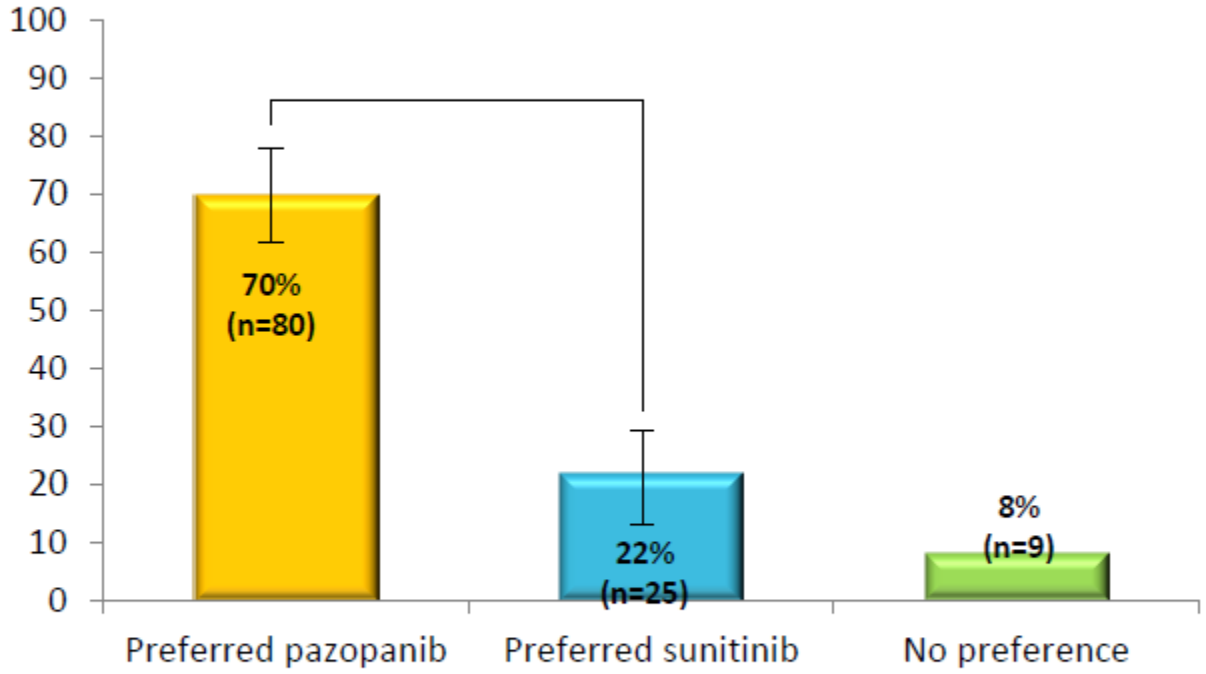
Pazopanib	557	521	462	409	360	320	284	243	221	197	169	99	51	21	4	1	0
Sunitinib	553	501	435	377	339	304	281	237	211	180	153	100	45	20	4	1	0

Figure 1. Kaplan–Meier Curves for Overall Survival in the Intention-to-Treat Population.
The dashed line represents the median (0.5), and vertical lines represent 95% confidence intervals.

PISCES: Sunitinib vs Pazopanib



PISCES: Sunitinib vs Pazopanib

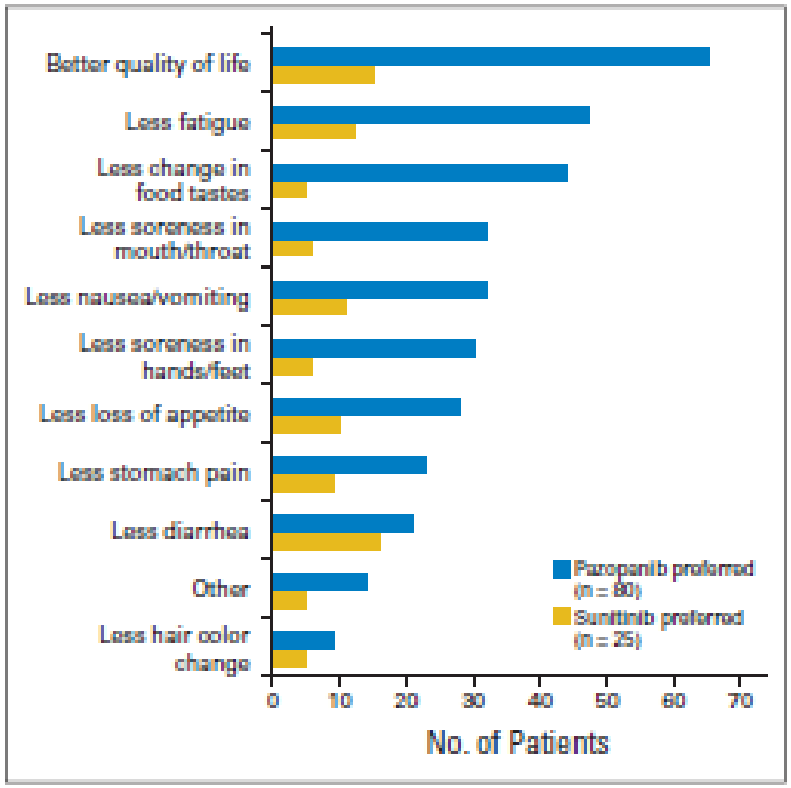


Escudier et al, JCO 2014

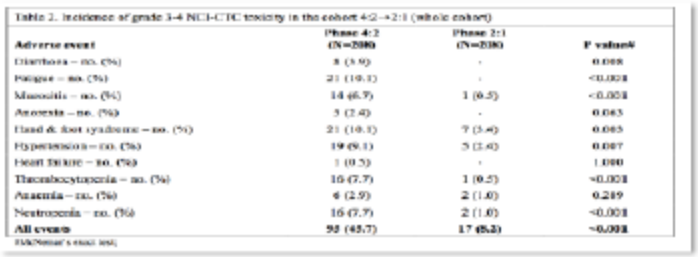
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized, Controlled, Double-Blind, Cross-Over Trial Assessing Treatment Preference for Pazopanib Versus Sunitinib in Patients With Metastatic Renal Cell Carcinoma: PISCES Study

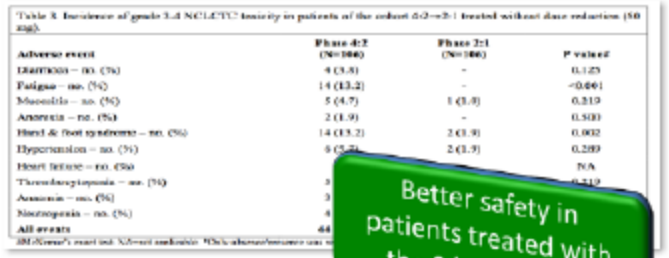
Bernard Escudier, Camillo Porta, Piotr Bono, Thomas Powles, Tim Eisen, Cora N. Sternberg, Jürgen E. Gschwend, Ugo De Giorgi, Omi Parikh, Robert Hawkins, Emmanuel Sevin, Sylvie Négrier, Sadya Khan, Jose Diez, Suman Reddy, Faisal Mehmud, and David Cella



New schedule of sunitinib might change the scene…



Adverse event	Phase 4:2 (N=280)	Phase 2:1 (N=280)	P value§
Diarrhoea – no. (%)	8 (3.9)	-	0.008
Fatigue – no. (%)	21 (10.1)	-	<0.001
Mucositis – no. (%)	14 (6.9)	1 (0.5)	<0.001
Anorexia – no. (%)	5 (2.4)	-	0.063
Hand & foot syndrome – no. (%)	21 (10.1)	7 (3.4)	0.005
Hypertension – no. (%)	19 (9.1)	5 (2.4)	0.007
Heart failure – no. (%)	1 (0.5)	-	1.000
Thrombocytopenia – no. (%)	16 (7.7)	1 (0.5)	<0.001
Anaemia – no. (%)	6 (2.9)	2 (1.0)	0.289
Neutropenia – no. (%)	16 (7.7)	2 (1.0)	<0.001
All events	93 (45.7)	17 (8.2)	<0.001



Adverse event	Phase 4:2 (N=106)	Phase 2:1 (N=106)	P value‡
Diarrhoea – no. (%)	4 (3.8)	-	0.125
Fatigue – no. (%)	14 (13.2)	-	<0.001
Mucositis – no. (%)	5 (4.7)	1 (1.0)	0.219
Anorexia – no. (%)	2 (1.9)	-	0.500
Hand & foot syndrome – no. (%)	14 (13.2)	2 (1.9)	0.002
Hypertension – no. (%)	6 (5.7)	2 (1.9)	0.289
Heart failure – no. (%)			NA
Thrombocytopenia – no. (%)			
Anaemia – no. (%)			
Neutropenia – no. (%)			
All events	44		

Better safety in patients treated with the 2/1 schedule[1]

- Group A (**schedule 2/1 after toxicity**) – median treatment duration: 28.2 months; **median PFS: 38.6 months**
- Group B (**schedule 2/1 *ab initio***) – median treatment duration: 7.8 months; **median PFS: 9.6 months**
- Group C (**schedule 4/2**) – median TD treatment duration: 10.[illegible] **PFS: 10.9 months**

Longer PFS in patients treated with the 2/1 schedule[1]

[1]Bracarda S, et al. *J Clin Oncol* 2014;36(Suppl.):abs. 461.

When no treatment is the best treatment?

Outcomes of treatment cessation in metastatic renal cell carcinoma (mRCC) patients

Kriti Mittal[1] MD, MS, Lisa Derosa[2] MD, Laurence Albiges[2] MD, Laura Wood[1] RN, Paul Elson[1] ScD,
Timothy Gilligan[1] MD, Jorge A. Garcia[1] MD, Robert Dreicer[1] MD,
Bernard Escudier[2] MD, Brian Rini[1] MD

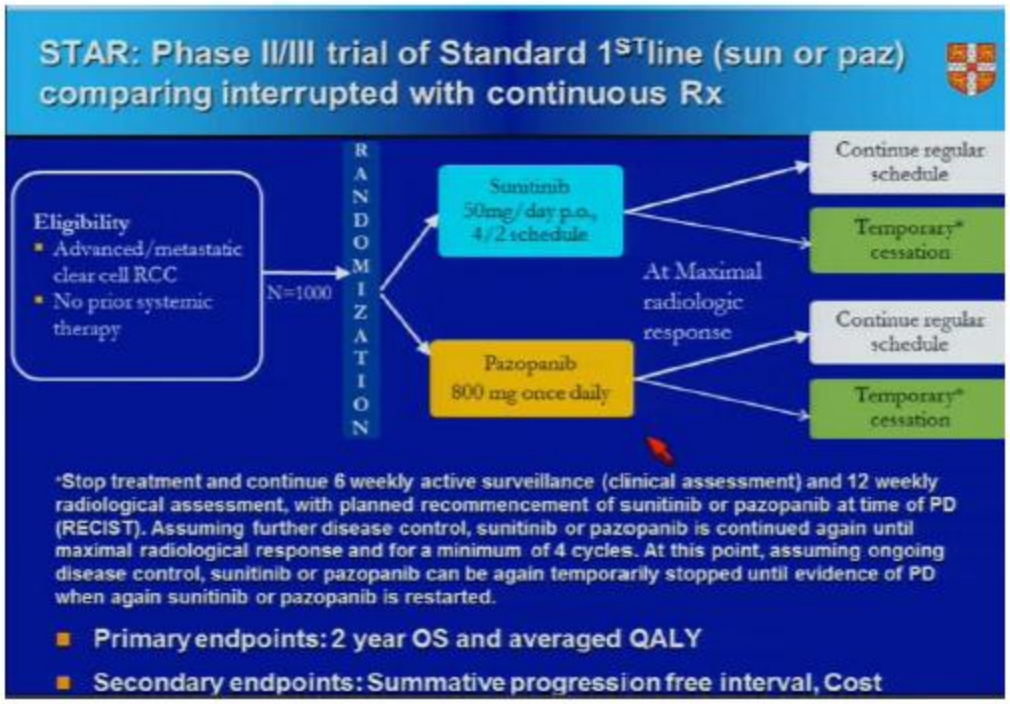
[1]Cleveland Clinic, Cleveland, Ohio
[2]Institut Gustave Roussy, Villejuif, France

When no treatment is the best treatment?

Treatment	Number of pts. starting treatment	Median duration of therapy in months (95% CI)	Number of pts. on treatment break	Median duration of break in months (95% CI)
A	112	13.5 (11-16.4)	112	16.8 (12.5-26.4)
B	68	16.1 (11.4-20)	24	9.5 (4.6-10.3)
C	43	14.8 (12-17.2)	10	7.1
D	15	13.8 (5.7-18.6)	3	15.9

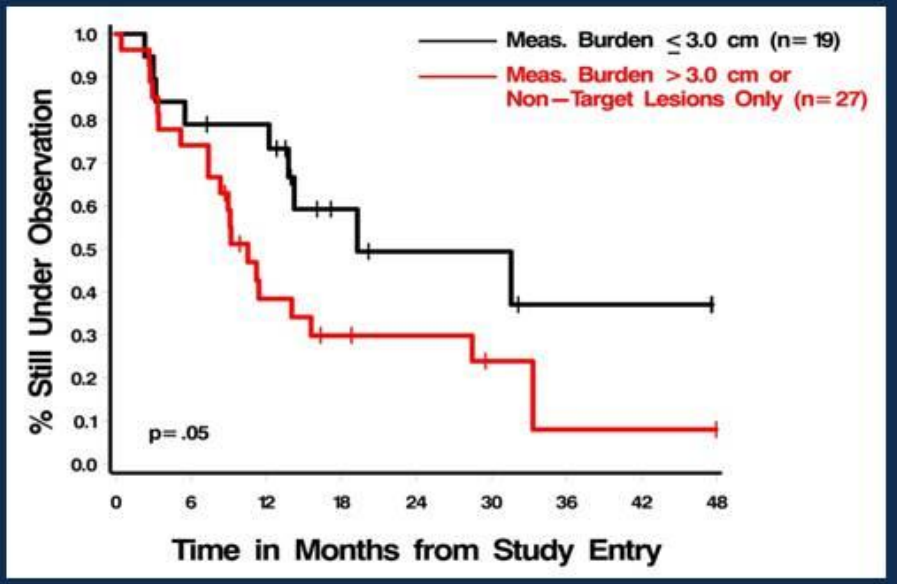
Sequential lines of therapy were defined as treatment A, B, C, D, etc.

When no treatment is the best treatment?



Prospective Data: Rini BI ASCO 2014, abstract 4520

- n=49 patients, mostly cc-RCC,
- KPS > 80%: 94%;
- **Median time on observation: 14.1 months**
- **ORR on following treatment: 43%,** PFS nr
- Median tumor burden at baseline 3.2 cm (0.8-19.6)
- Median change in tumor burden: 0.09 cm/month (range -0.51-3.6 cm)
- No changes in baseline anxiety/depression score during observation
- Significant decrease of anxiety at final evaluation



- Neither Heng group, nor location nor number of metastases impacted length of observation

VOLUME 33 · NUMBER 8 · MARCH 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial of Temsirolimus and Bevacizumab Versus Interferon Alfa and Bevacizumab in Metastatic Renal Cell Carcinoma: INTORACT Trial

Brian I. Rini, Joaquim Bellmunt, Jill Clancy, Rongrong Wang, Andreas G. Nathanson, Subramanian Hariharan, and Bernard Escudier

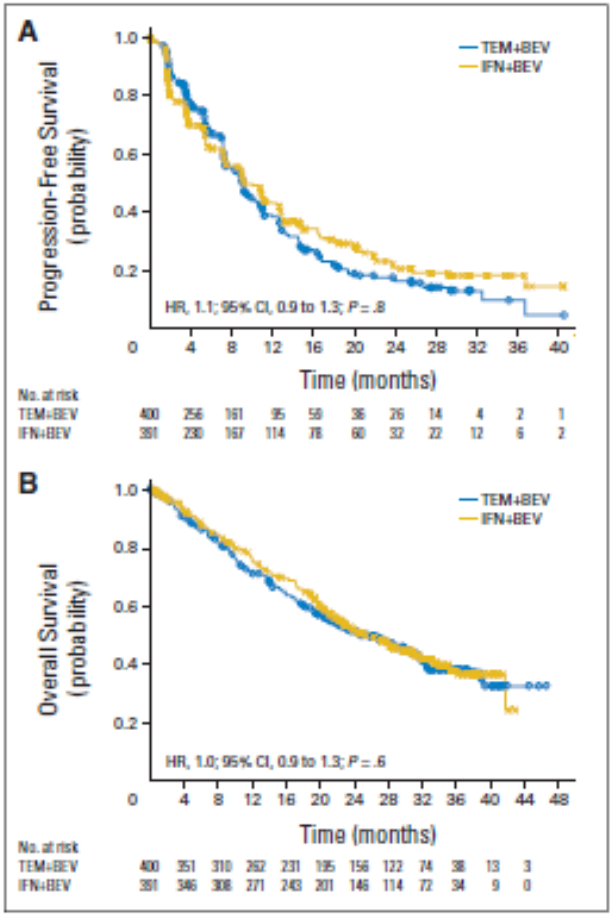
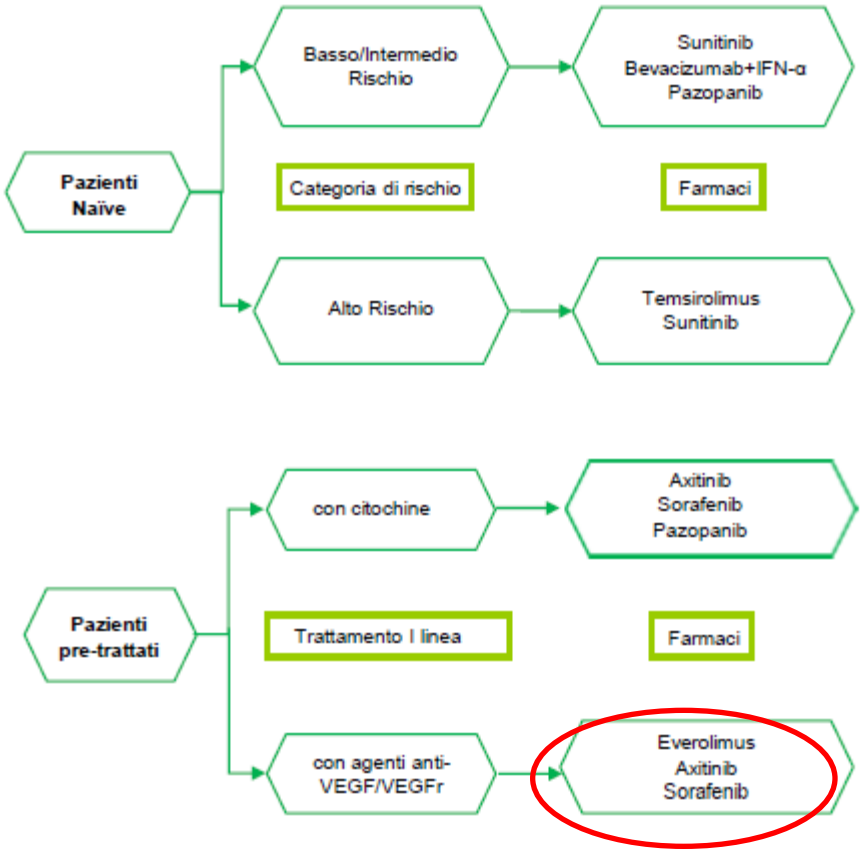
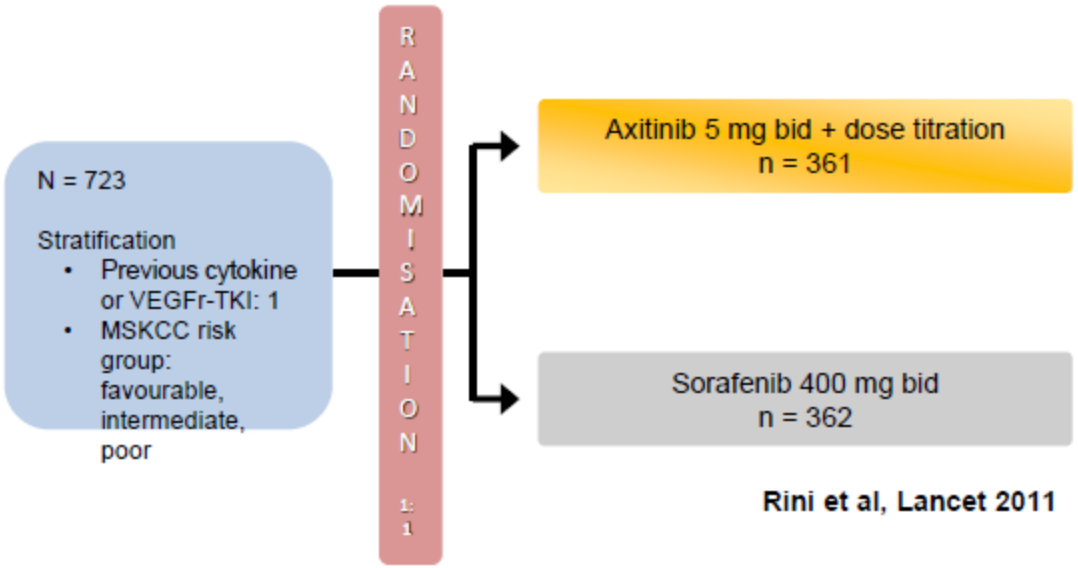


Figura 2. Trattamento medico mRCC istotipo a cellule chiare



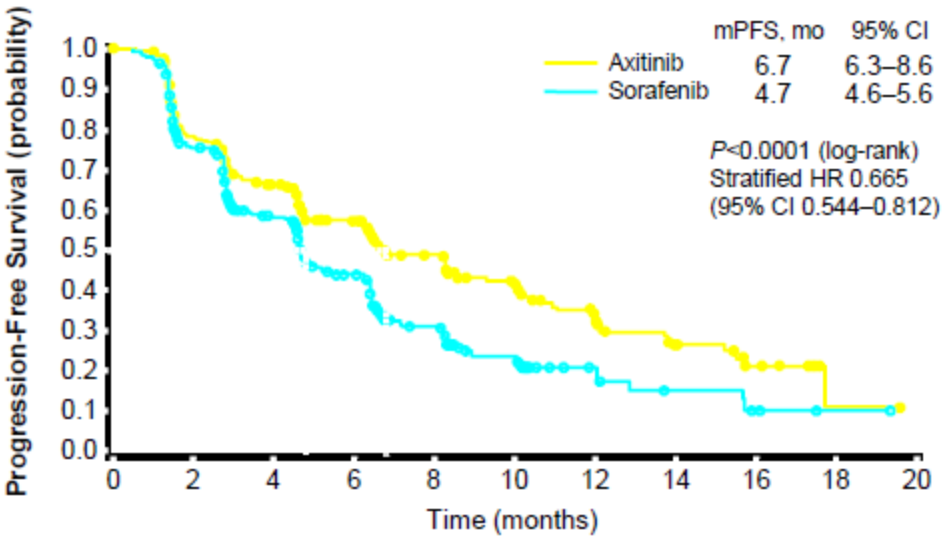
Choice of second line treatment

Now available AXITINIB…….



Rini et al, Lancet 2011

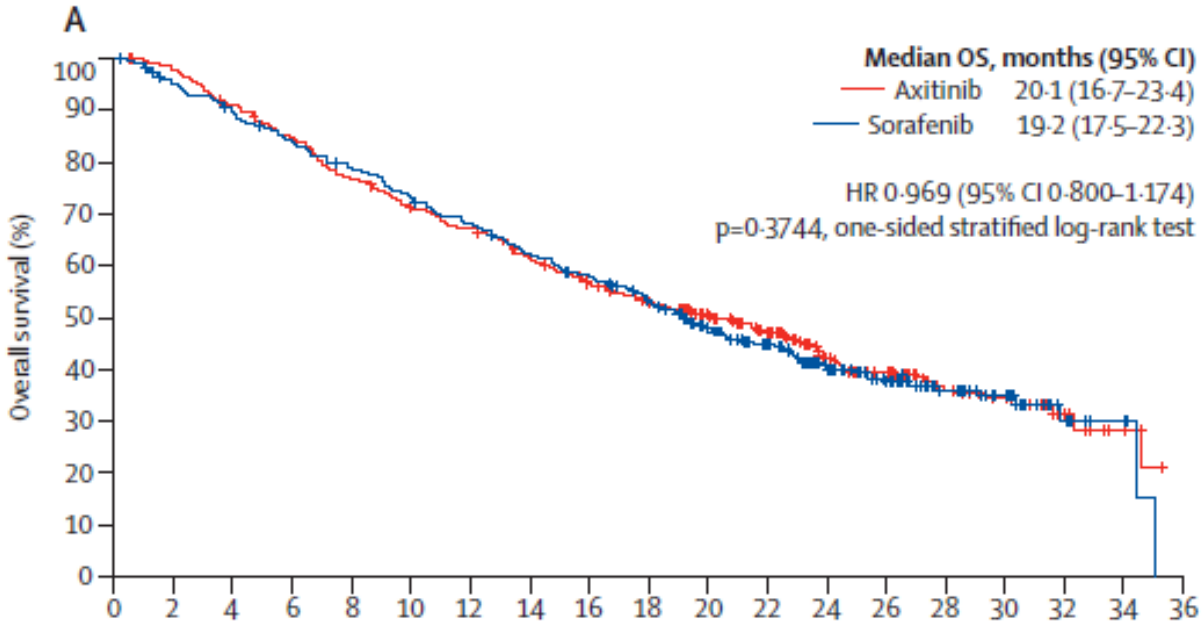
AXIS PFS final analysis



Rini et al, Lancet 2011

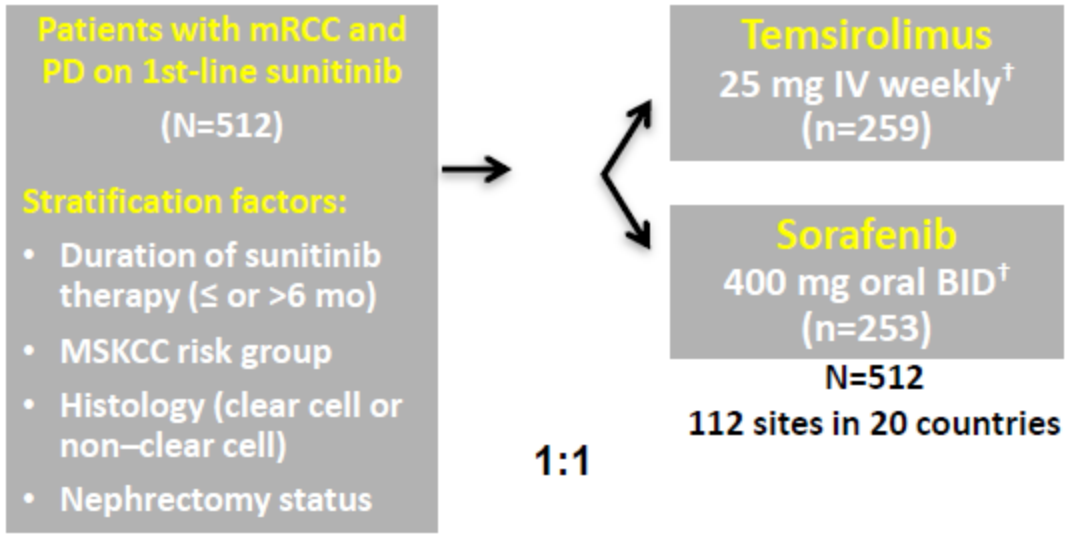
Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial

Robert J Motzer, Bernard Escudier, Piotr Tomczak, Thomas E Hutson, M Dror Michaelson, Sylvie Negrier, Stephane Oudard, Martin E Gore, Jamal Tarazi, Subramanian Hariharan, Connie Chen, Brad Rosbrook, Sinil Kim, Brian I Rini



Lancet Oncol 2013; 14: 552–62

How to select second line treatment?



Hutson et al, JCO 2014

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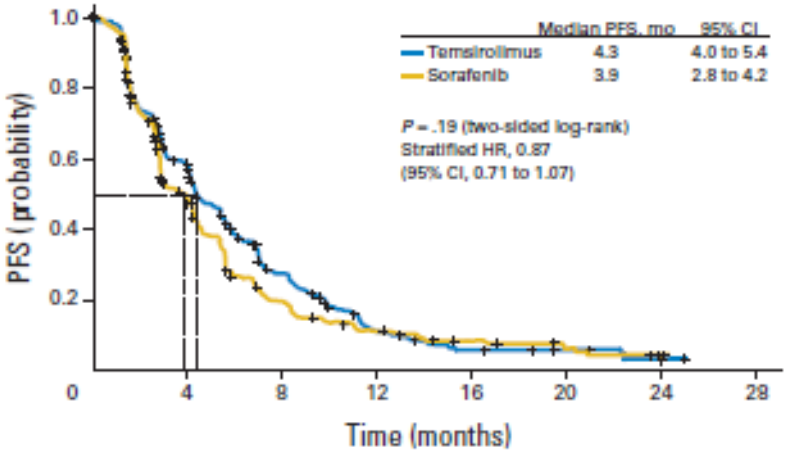
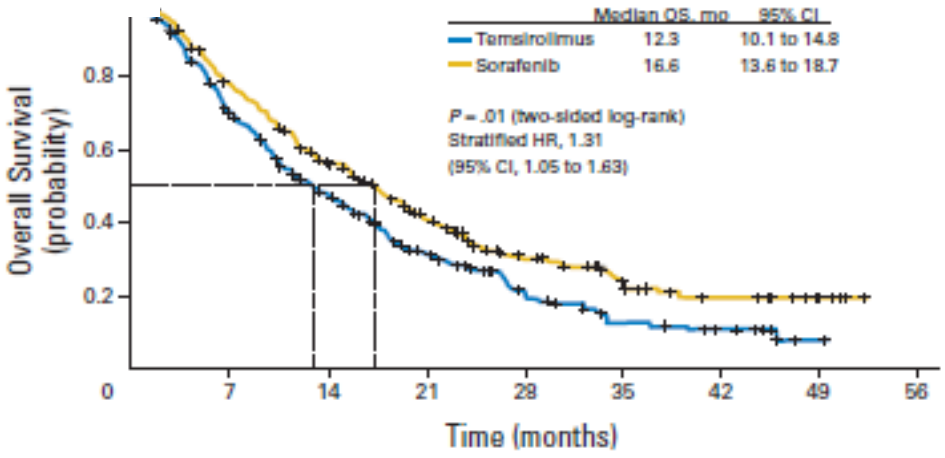
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial of Temsirolimus Versus Sorafenib As Second-Line Therapy After Sunitinib in Patients With Metastatic Renal Cell Carcinoma

Thomas E. Hutson, Bernard Escudier, Emilio Esteban, Georg A. Bjarnason, Ho Yeong Lim, Kenneth B. Pittman, Peggy Szczylik, Andreas Nathan, Dongrai Ray Lu, Subramanian Hariharan, and Robert J. Motzer





VOLUME 32 · NUMBER 25 · SEPTEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Randomized Trial Comparing Sequential First-Line Everolimus and Second-Line Sunitinib Versus First-Line Sunitinib and Second-Line Everolimus in Patients With Metastatic Renal Cell Carcinoma

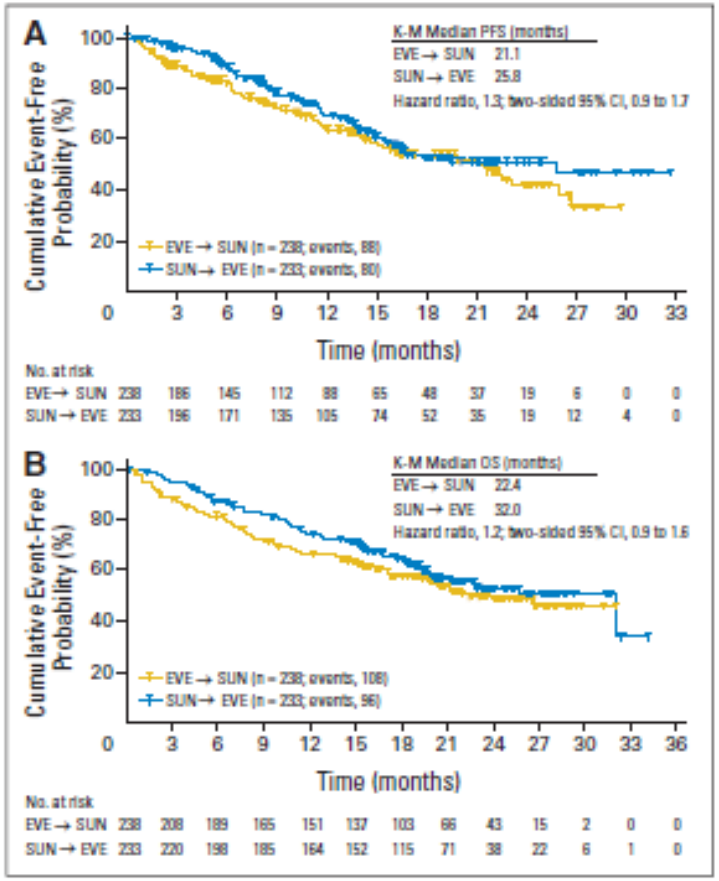


Fig 3. Combined first-line and second-line (A) progression-free survival (PFS; Kaplan-Meier [K-M]) and (B) overall survival (OS; K-M). EVE, everolimus; SUN, sunitinib.

Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial

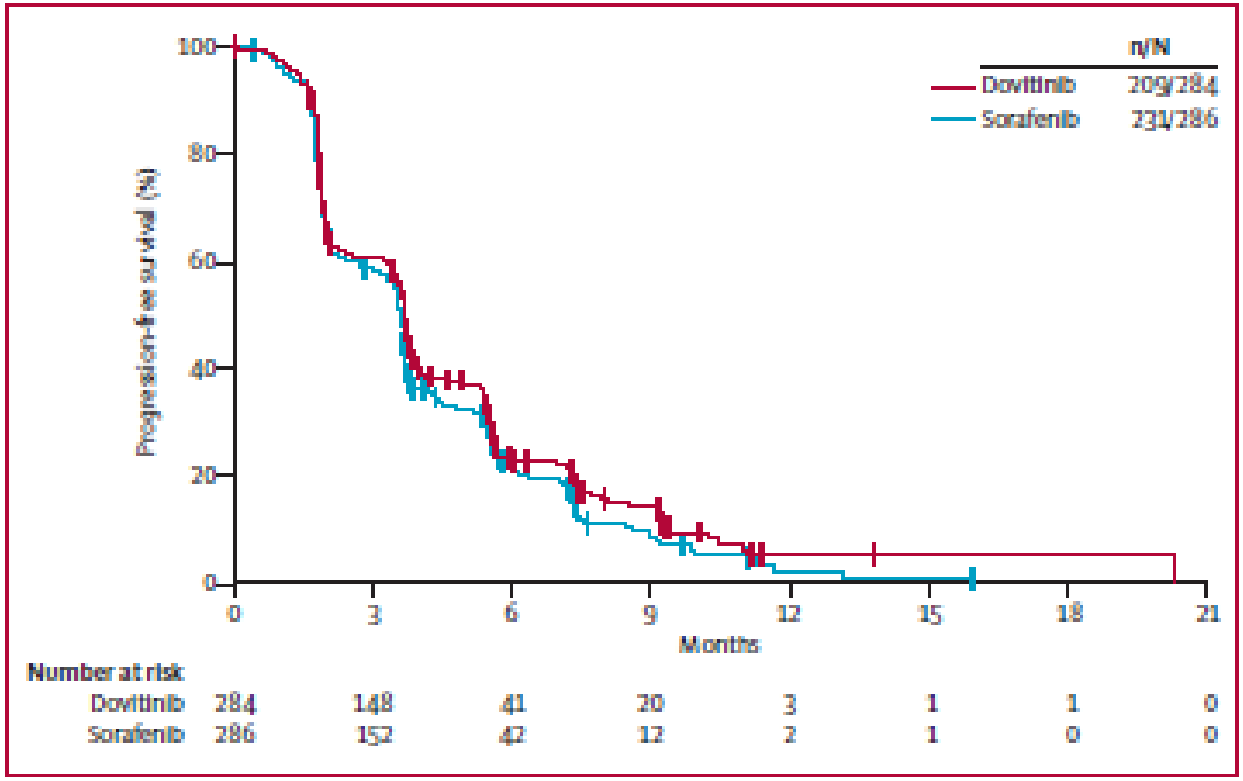


Figure 2: Kaplan-Meier curves of progression-free survival (by central analysis)

Lancet Oncol 2014; 15: 286–96

Second line options

- Everolimus and axitinib are standard of care
- Sorafenib is another option
- Differences in toxicity profile are important
- Intorsect study should be interpreted with caution, although supporting the use of TKI after TKI

Choosing a Second-line Treatment: Factors to Consider

- Clinical factors
  - Aggressiveness of disease
  - Performance status
  - Safety; toxicity in first-line; quality of life
  - Response to first-line?
- Nonclinical factors
  - Physician experience with drugs
  - Availability of and access to drugs
  - Patient preference

New targets

- VEGF and mTOR inhibition have reached a plateau:
  - PFS 8-11 months
  - OS 26-29 months
- New targets are urgently needed to further improve outcome

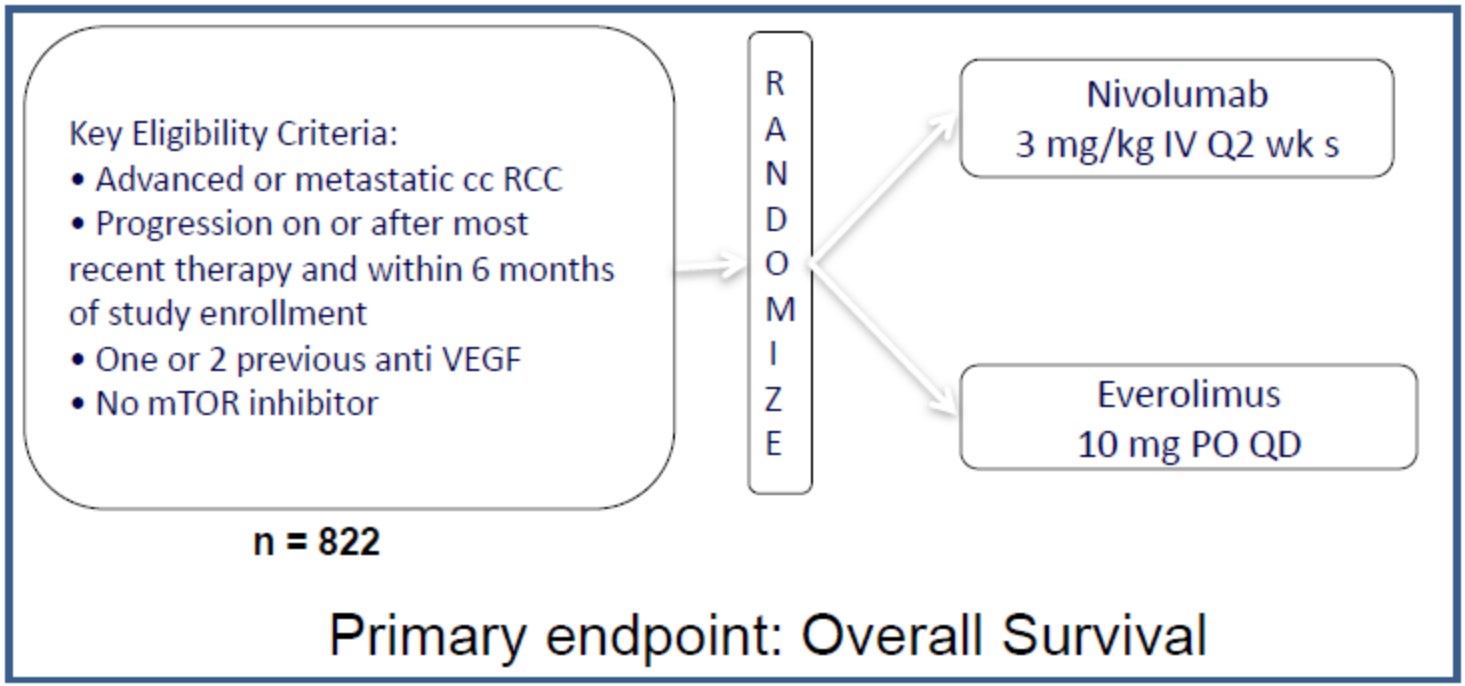
New targets

- PD1/PDL1 pathway: nivolumab
  - Promising activity:

    Single agent (MOTZER and CHOUEIRI ASCO 2014)

    Phase I combination studies (AMIN, Nivo+VEGF TKI and HAMMERS, Nivo+Ipi, ASCO 2014)
  - Does PD-L1 expression alone reliably predict responders?

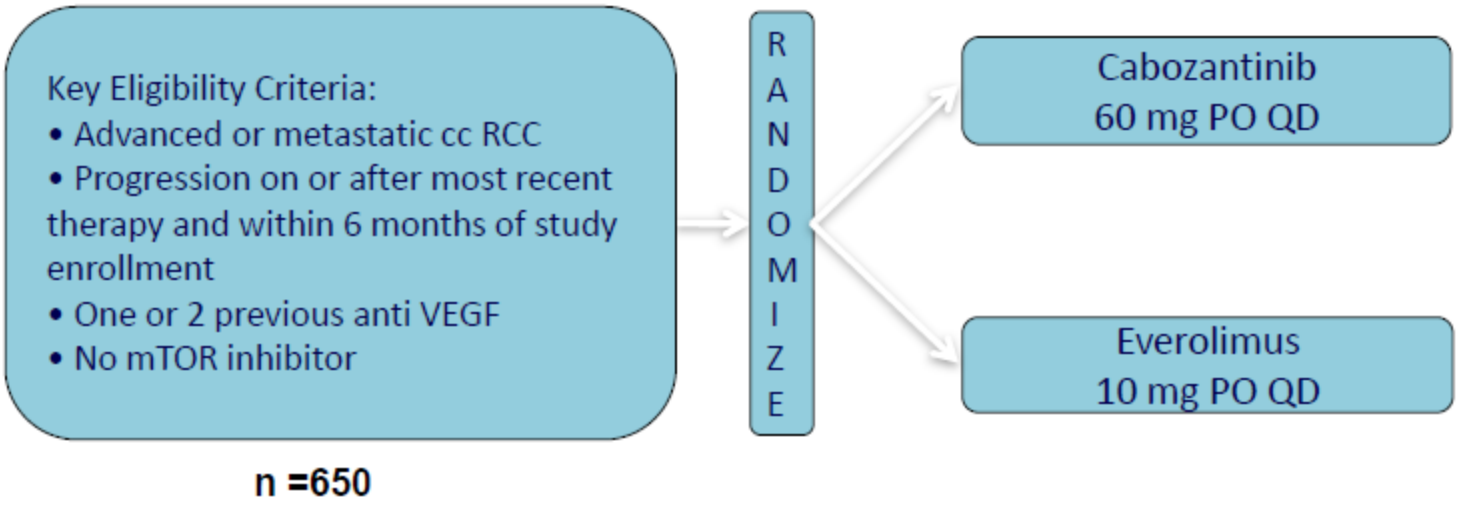
BMS study


Key Eligibility Criteria:
• Advanced or metastatic cc RCC
• Progression on or after most recent therapy and within 6 months of study enrollment
• One or 2 previous anti VEGF
• No mTOR inhibitor
n = 822
RANDOMIZE
Nivolumab
3 mg/kg IV Q2 wk s
Everolimus
10 mg PO QD
Primary endpoint: Overall Survival

New targets

- PD1/PDL1 pathway
- cMET pathway:
  - Strong rationale :
    - cMET overexpressed in many ccRCC
    - cMET induced by VEGF inhibition

METEOR study



Primary endpoint: PFS

Choueiri et al, ASCO 2014