Evidenze cliniche nel trattamento del RCC

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Napoli, 14 ottobre 2008

The past…

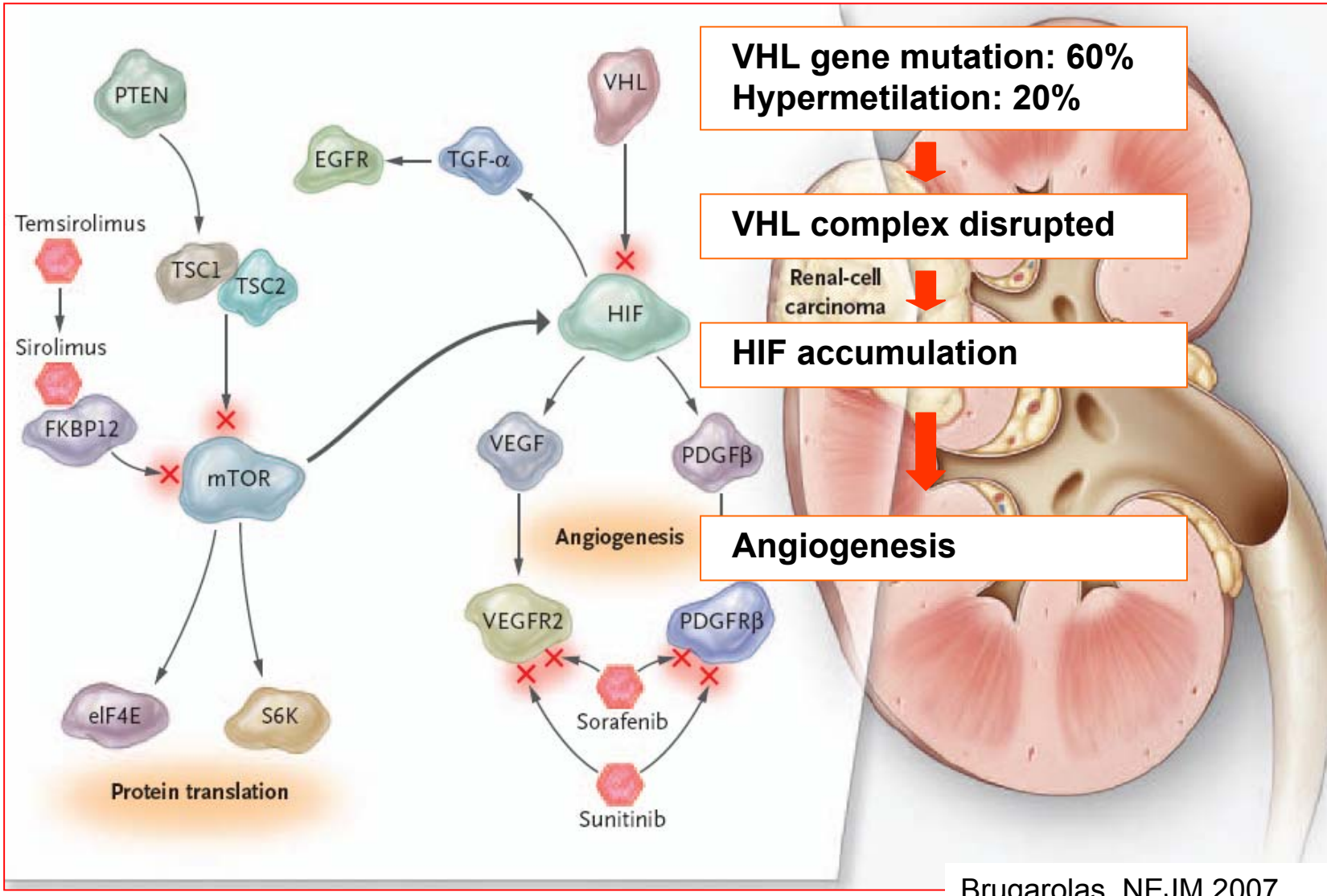
IL-2 and IFN in metastatic RCC

- **IL-2**
  - Responses:15%
  - CR: 5% (durable)
  - Survival benefit: not demonstrated in prospective trials
  - Toxicity: significant (high dose...)
- **IFN**
  - Responses:10%
  - CR: 2%
  - Survival benefit: increased median survival reported
  - Toxicity: dose correlated...

Advances in last years

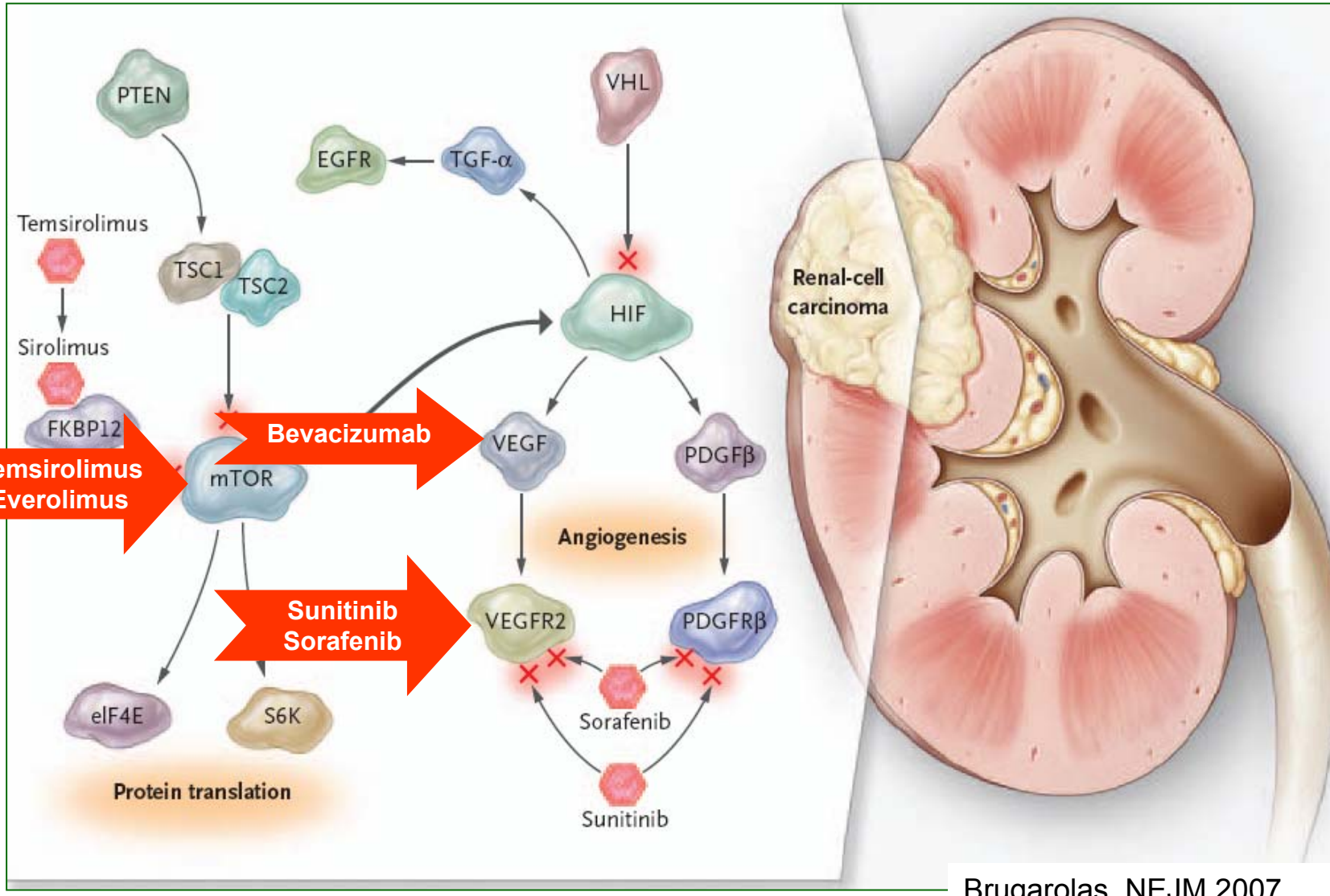
- In understanding the biology and genetics of renal cell carcinoma
- Availability of novel targeted approaches for the treatment of metastatic RCC

VHL Gene Mutation in Clear-Cell RCC



Brugarolas, NEJM 2007

New target-based agents

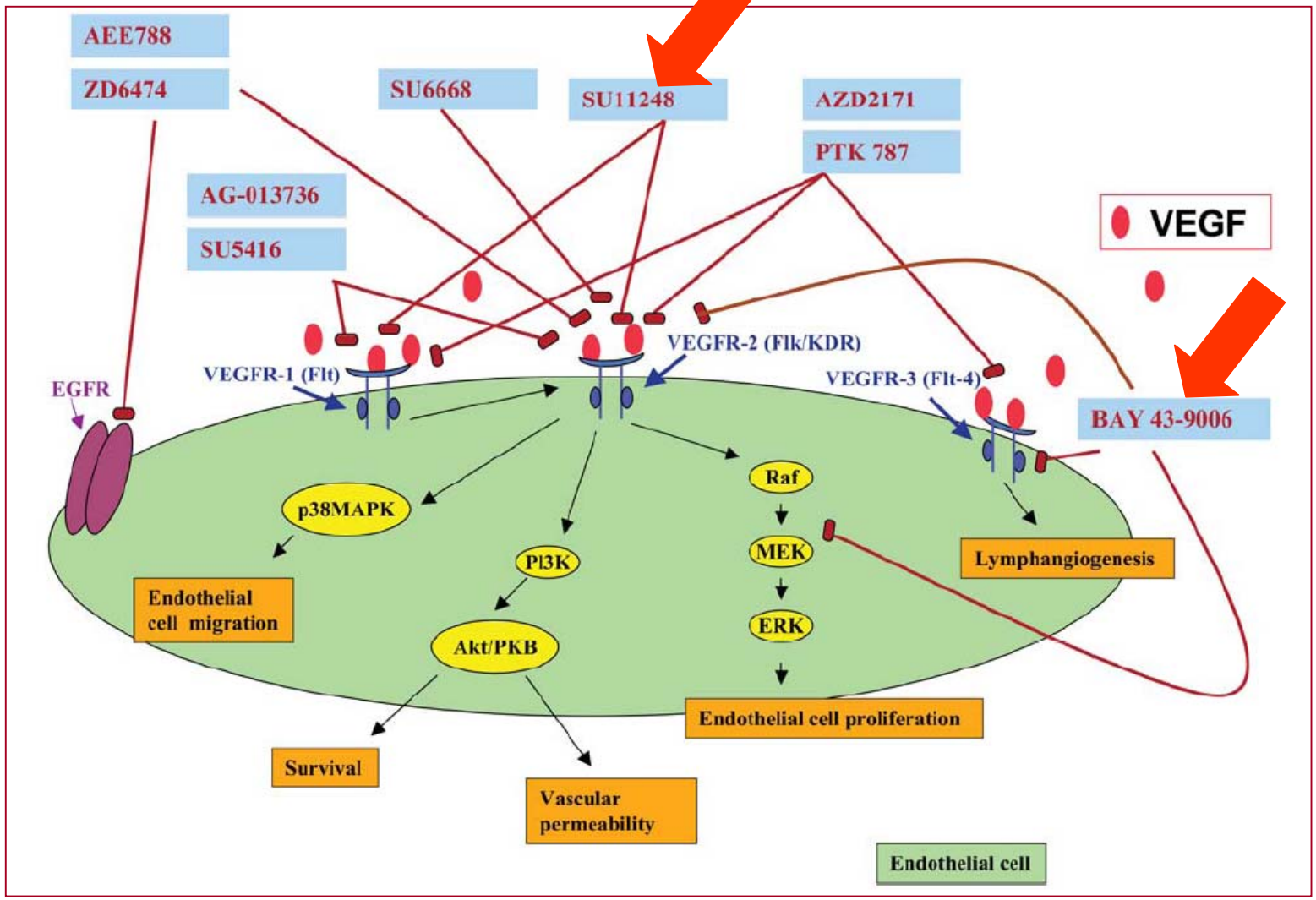


Brugarolas, NEJM 2007

Target-based agents in RCC: phase 3 trials

- Inhibitors of VEGF receptors
- Monoclonal antibody directed against VEGF
- Inhibitors of mTOR

Inhibitors of VEGF receptors



Morabito A, The Oncologist 2006

Sunitinib (SU11248)

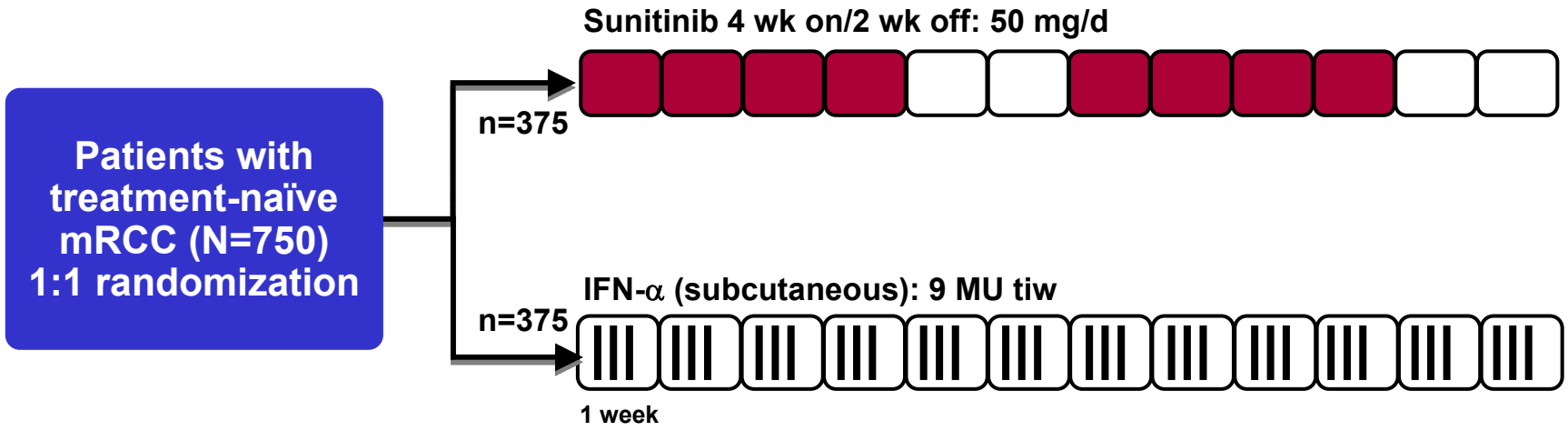
Sunitinib: phase 2 trials in RCC

- Two sequentially conducted multicenter phase 2 trials in second-line therapy
- Endpoint: response rate
- Overall response: **40%** and **34%**
- Stable disease: 28% and 23%

Motzer RJ, J Clin Oncol 2006; Motzer RJ, JAMA 2006

Sunitinib: Phase III Trial for first-line treatment of advanced RCC

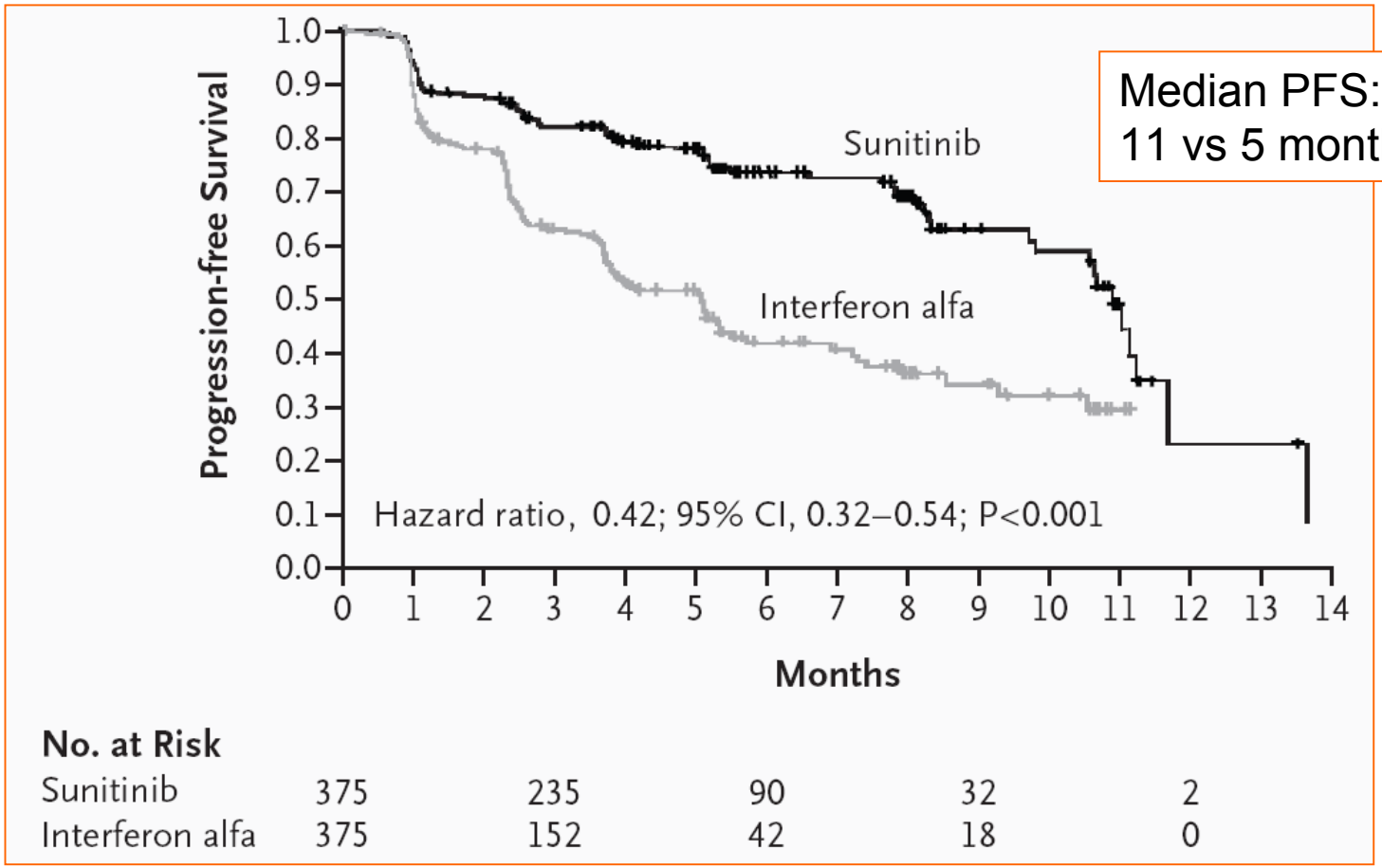
Study Design: Randomized, Multicenter Trial (Enrollment Complete)



Primary end-point: Progression-Free Survival

Motzer RJ, N Engl J Med 2007

Progression-Free Survival

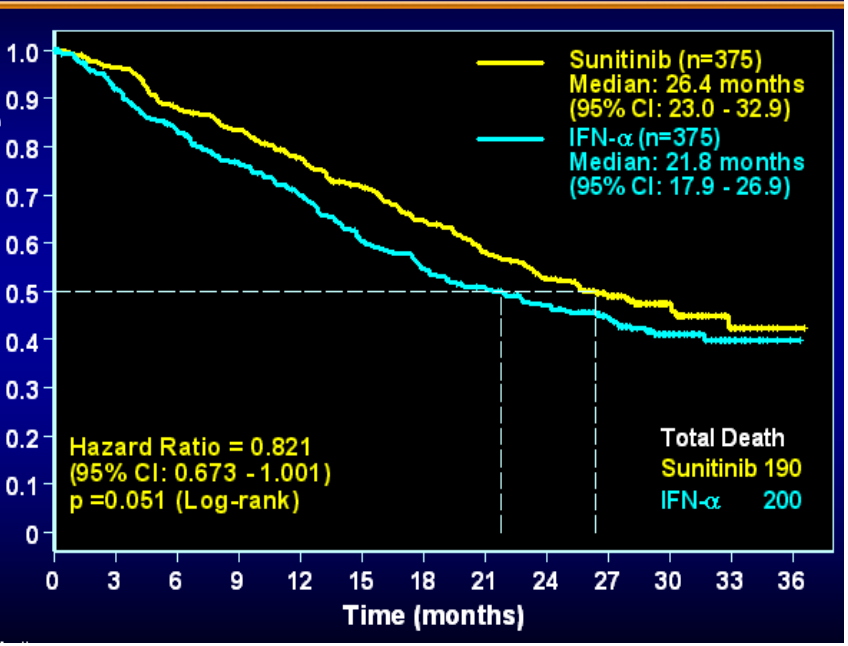


Median PFS:
11 vs 5 months

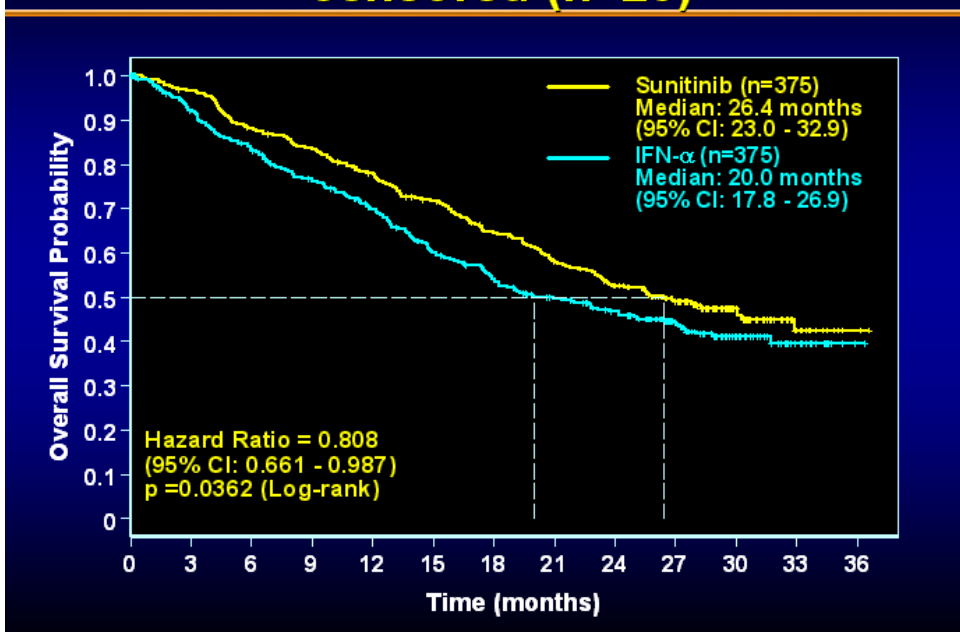
Motzer RJ, N Engl J Med 2007

Overall Survival

Final Overall Survival



Overall Survival: Crossover patients censored (n=25)



o-value: 0.0128 (Wilcoxon)

more appropriate test when the ratio of death rates between two reatment groups is not constant over time in situations where urvival data may be confounded by crossover or post-study reatments)

Figlin R, ASCO 2008

Quality of life

VOLUME 26 · NUMBER 22 · AUGUST 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Quality of Life in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib or Interferon Alfa: Results From a Phase III Randomized Trial

David Cella, Jim Z. Li, Joseph C. Cappelleri, Andrew Bushmakin, Claudie Charbonneau, Sindy T. Kim, Isan Chen, and Robert J. Motzer

Table 2. Average Treatment Differences for Quality-of-Life Instruments

Instrument	Least Squares Means		Difference	95% CI	*P*
	Sunitinib	IFN-α			
FKSI-DRS	29.4	27.4	1.98	1.46 to 2.51	< .0001
FKSI-15	45.3	42.1	3.27	2.36 to 4.18	< .0001
FACT-G	82.3	76.8	5.58	3.91 to 7.24	< .0001
PWB	21.3	19.9	1.42	0.796 to 2.04	< .0001
SFWB	23.5	22.3	1.20	0.667 to 1.73	< .0001
EWB	18.3	17.5	0.787	0.323 to 1.25	.0009
FWB	19.0	17.0	1.98	1.33 to 2.63	< .0001
EQ-5D Index	0.762	0.725	0.0364	0.0109 to 0.0620	.0052
EQ-VAS	73.4	68.7	4.74	2.60 to 6.87	< .0001

Sunitinib: conclusions

Author	Agent	Setting	Pts	PFS (months)	OR (%)	OS
Motzer (NEJM, 2007)	**Sunitinib** vs IFN	**1st line**	750	**11 vs 5** **(p<0.0001)**	31 vs 6 (p<0.001)	HR: 0.65 (p=0.02)*

- Sunitinib has consistently demonstrated improvements in progression-free survival, response rate and overall survival compared to IFN-α
- Sunitinib provided superior QoL compared with IFN- in mRCC patients
- Sunitinib is the reference **standard for the first-line** treatment of mRCC

Sorafenib

VOLUME 24 · NUMBER 16 · JUNE 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

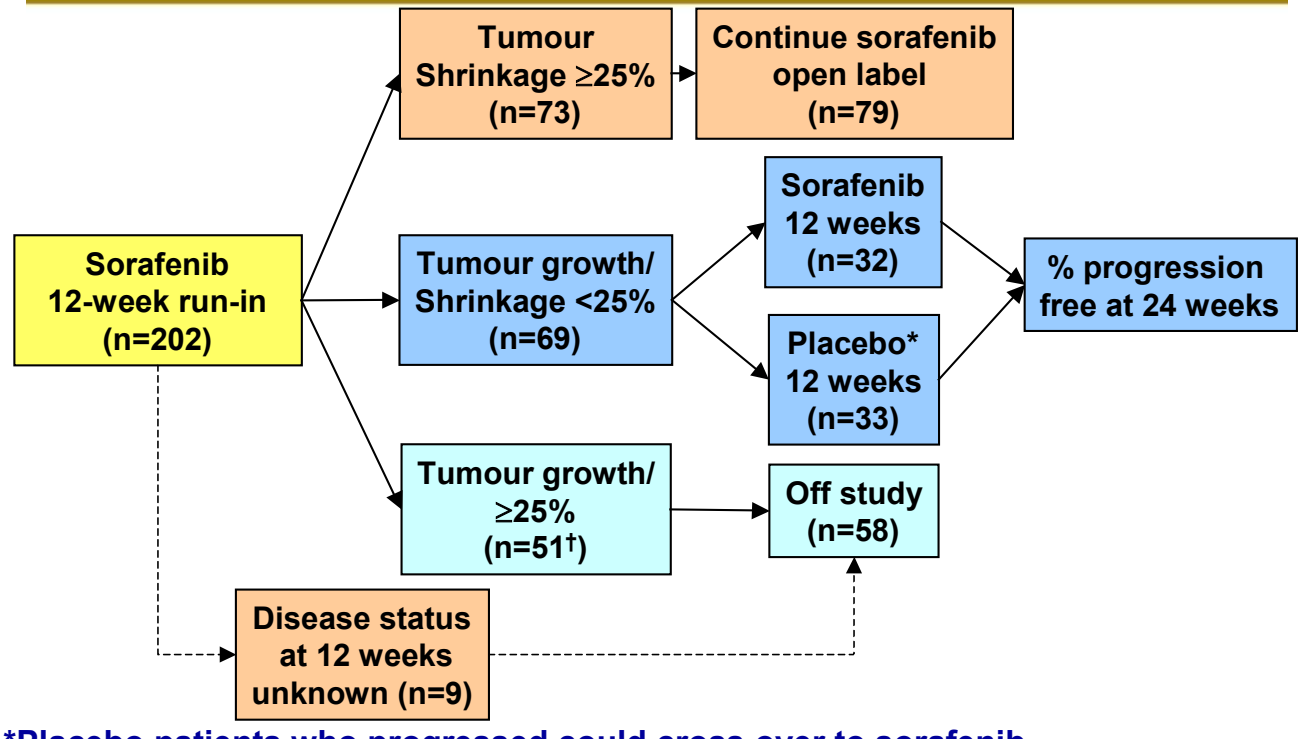
Phase II Placebo-Controlled Randomized Discontinuation Trial of Sorafenib in Patients With Metastatic Renal Cell Carcinoma

Mark J. Ratain, Tim Eisen, Walter M. Stadler, Keith T. Flaherty, Stan B. Kaye, Gary L. Rosner, Martin Gore, Apurva A. Desai, Amita Patnaik, Henry Q. Xiong, Eric Rowinsky, James L. Abbruzzese, Chenghua Xia, Ronit Simantov, Brian Schwartz, and Peter J. O'Dwyer

- **Methods**
  - **Study design:** randomized discontinuation trial
  - **Primary end-point**: progression-free survival (PFS) at 12 weeks

RCC

Patient flow



*Placebo patients who progressed could cross over to sorafenib
†including 36 patients without bidimensional tumor measurements, but with radiological evidence of progression

Ratain, ASCO 2005

Randomized discontinuation trial

- It is a rational phase II study design to demonstrate activity of a possibly cytostatic agent in a disease having substantial patient-to-patient variation in tumor growth rates, and for which disease stabilization is a clinically meaningful measure of activity

Rosner et al. JCO 2002

Sorafenib: phase 2 results

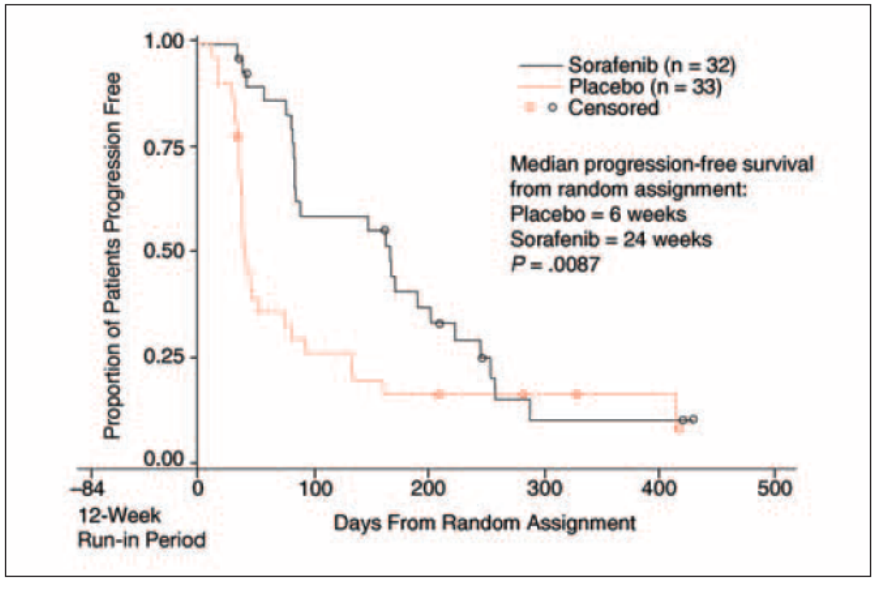
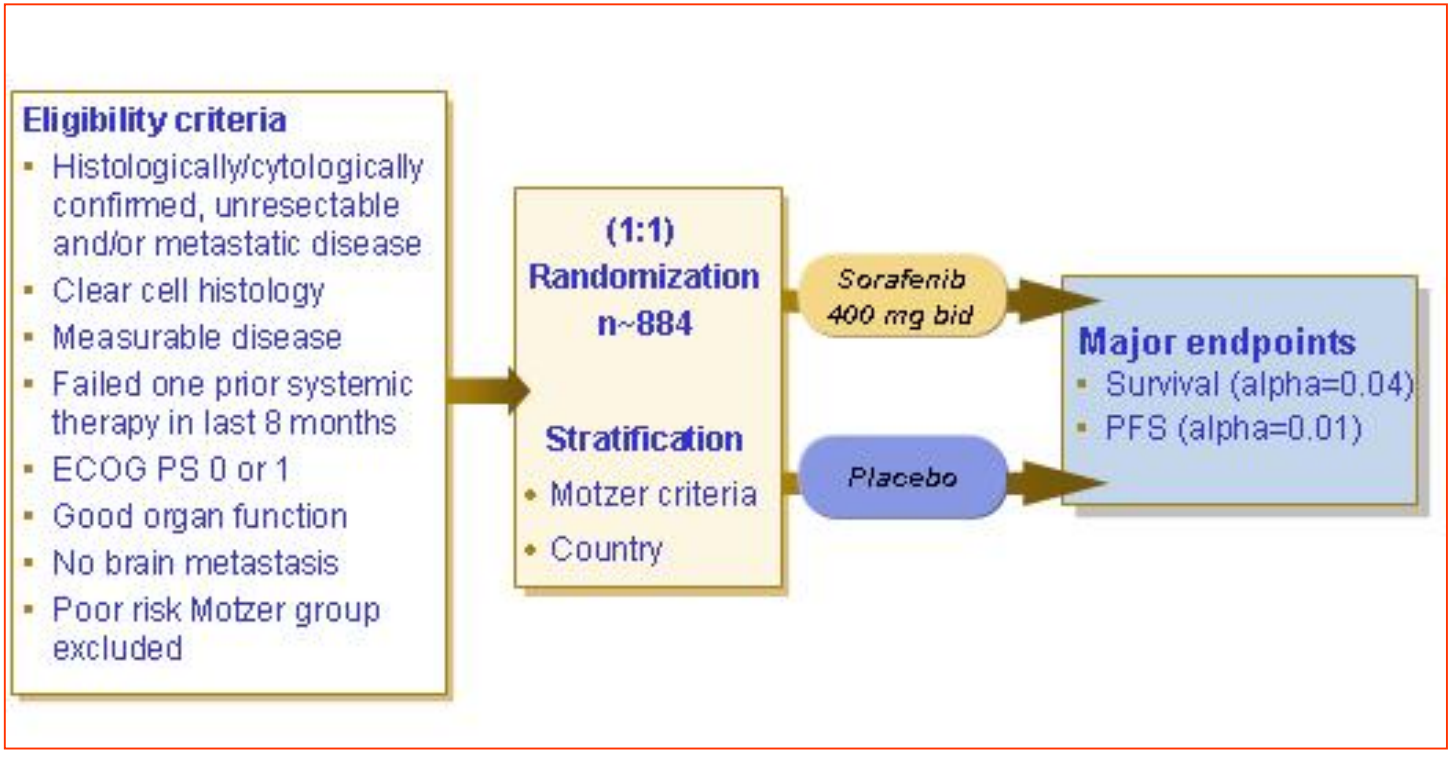


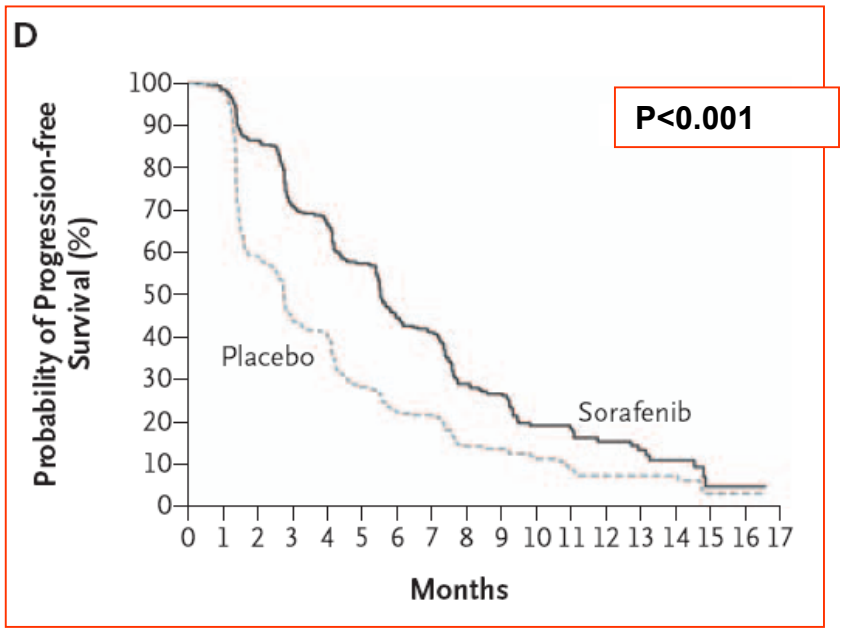
Fig 2. Kaplan-Meier plot of investigator-assessed progression-free survival from week 12 randomization for patients randomized to placebo (n = 33) or to sorafenib (n = 32).

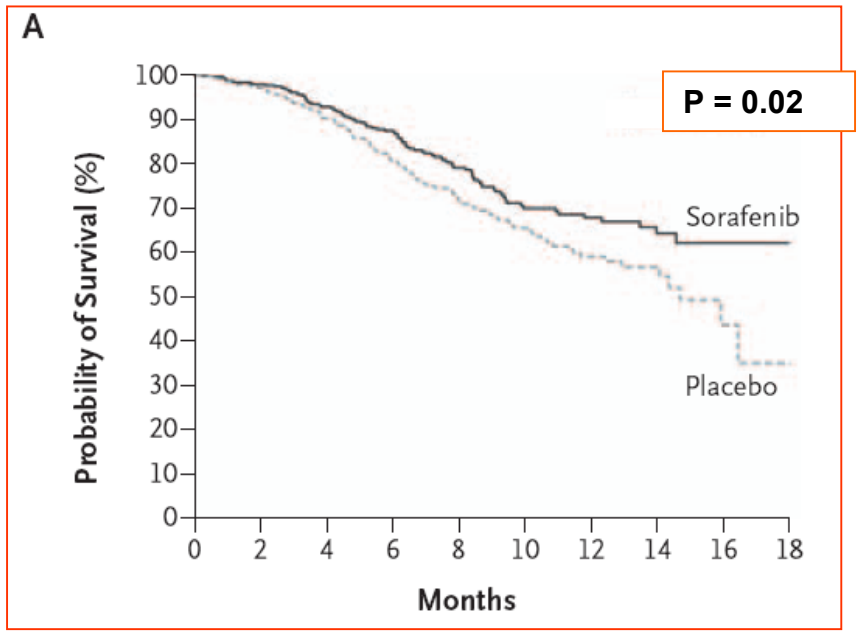
- **PFS at 12 weeks**: 50% with sorafenib vs 18% with placebo (p=0.0077)
- **Median PFS**: 24 weeks with sorafenib vs 6 weeks with placebo (p=0.0087)

Sorafenib: Phase III Trial for cytokine pretreated advanced RCC



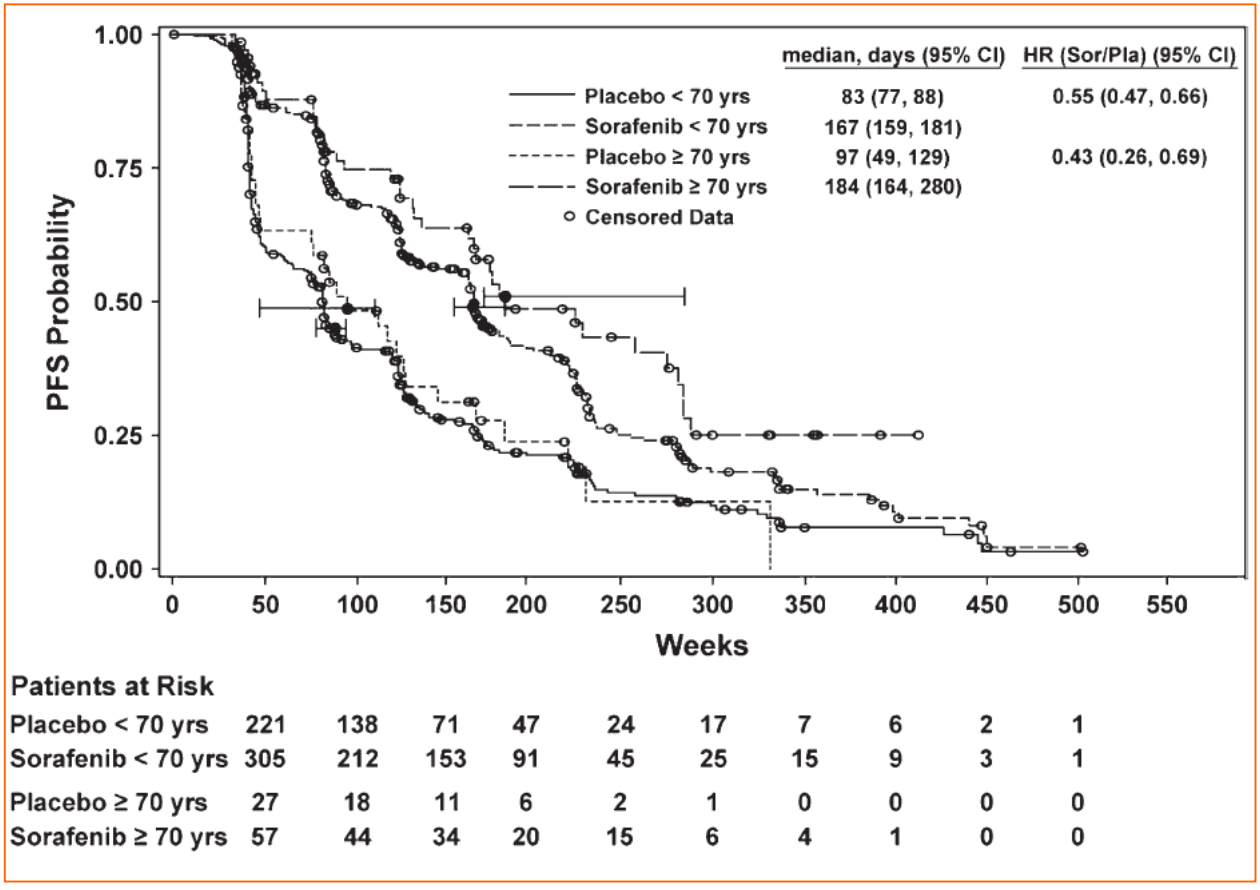
Progression-free and overall survival





Escudier B, N Engl J Med 2007

Sorafenib for older patients: subset analysis



> 70 years: 115 Patients

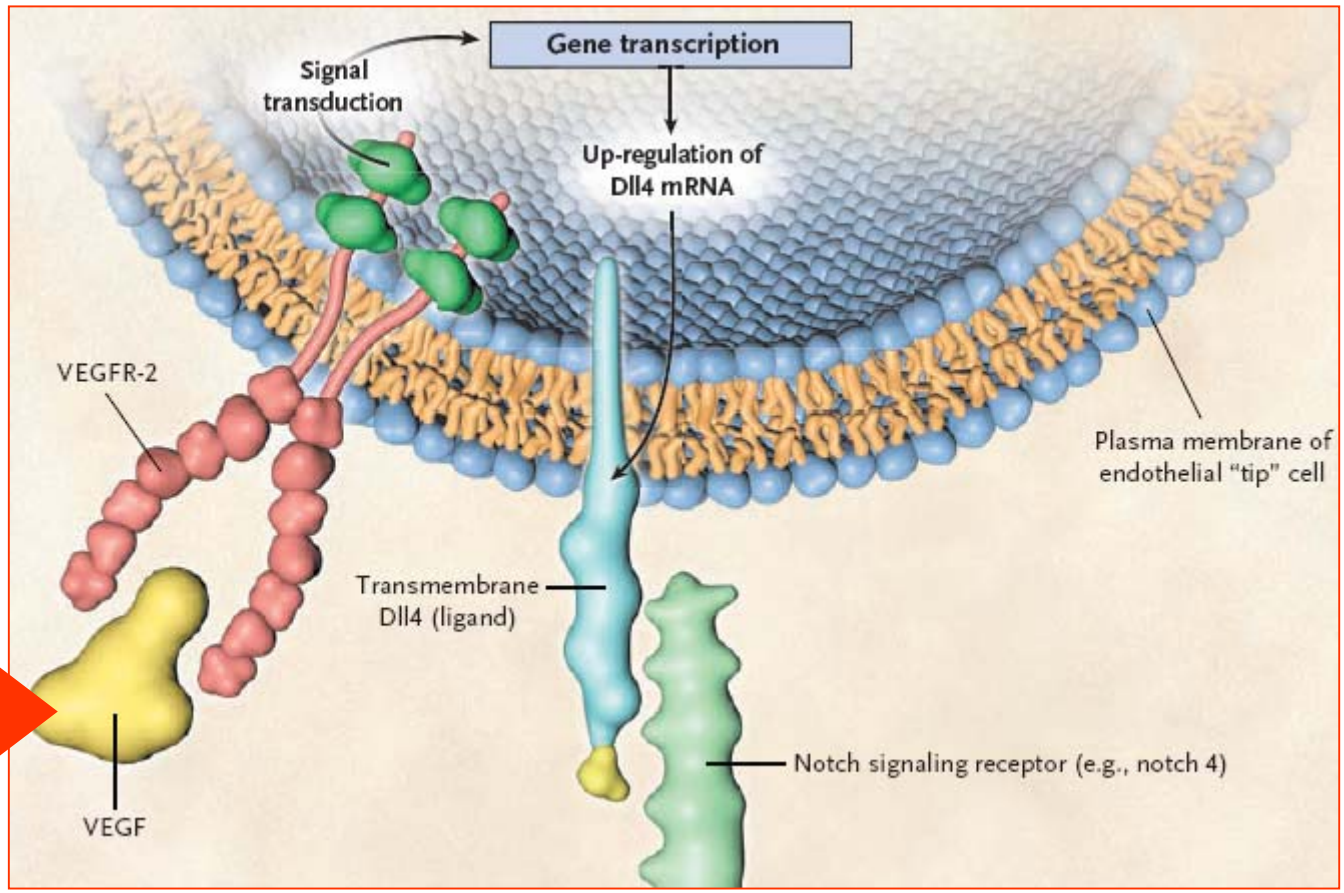
Eisen T, JNCI 2008

Sorafenib: conclusions

Author	Agent	Setting	Pts	PFS (months)	OR (%)	OS
Escudier (NEJM, 2007)	**Sorafenib** vs Placebo	**2nd line**	903	**5.5 vs 2.8** **(p<0.001)**	10 vs 2 (p<0.001)	HR: 0.72 (p=0.02)

- Sorafenib has demonstrated improvements in PFS compared to placebo
- Sorafenib is the reference **standard for the second-line** treatment of cytokine pretreated mRCC

Monoclonal antibody directed against VEGF



Kerbel RS, N Engl J Med 2008

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 31, 2003 VOL. 349 NO. 5

A Randomized Trial of Bevacizumab, an Anti–Vascular Endothelial Growth Factor Antibody, for Metastatic Renal Cancer

James C. Yang, M.D., Leah Haworth, B.S.N., Richard M. Sherry, M.D., Patrick Hwu, M.D., Douglas J. Schwartzentruber, M.D., Suzanne L. Topalian, M.D., Seth M. Steinberg, Ph.D., Helen X. Chen, M.D., and Steven A. Rosenberg, M.D., Ph.D.

- **Methods**
  - **Design:** randomized, double-blind, phase 2 trial, comparing placebo with bevacizumab at doses of 3 and 10 mg per kilogram of body weight, given every two weeks
  - **Primary end-point**: TTP (time to progression of disease)

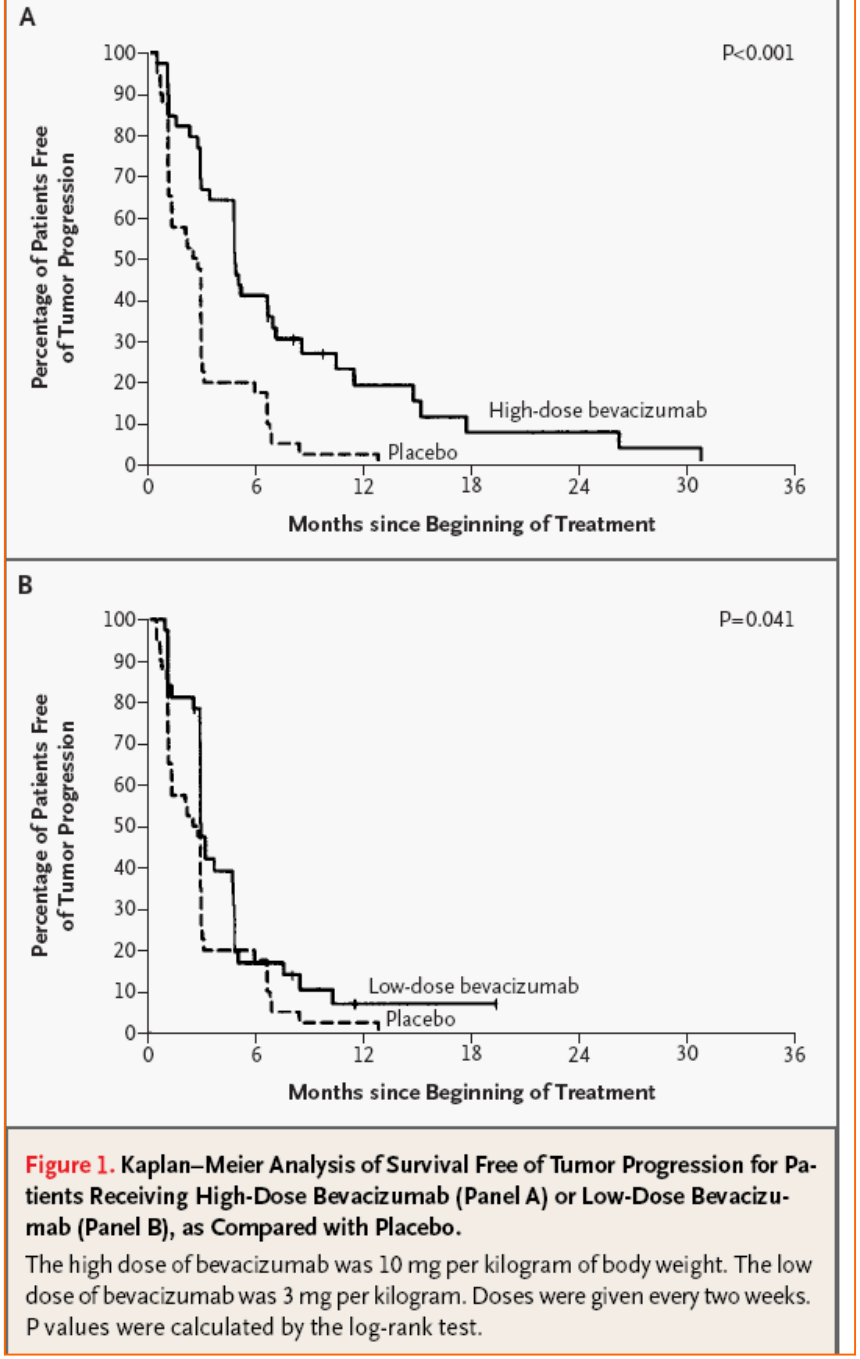


Figure 1. Kaplan–Meier Analysis of Survival Free of Tumor Progression for Patients Receiving High-Dose Bevacizumab (Panel A) or Low-Dose Bevacizumab (Panel B), as Compared with Placebo.

The high dose of bevacizumab was 10 mg per kilogram of body weight. The low dose of bevacizumab was 3 mg per kilogram. Doses were given every two weeks. P values were calculated by the log-rank test.

p<0.01

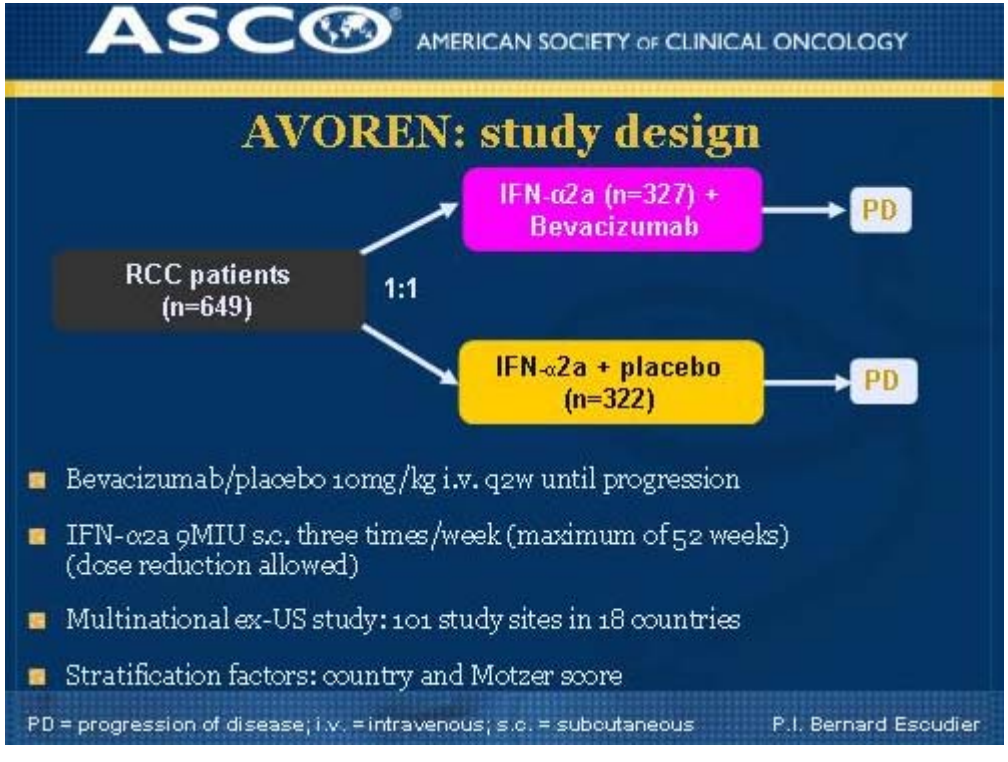
RO = 10%
(95% CI: 2.9-24.2%)

p=0.041

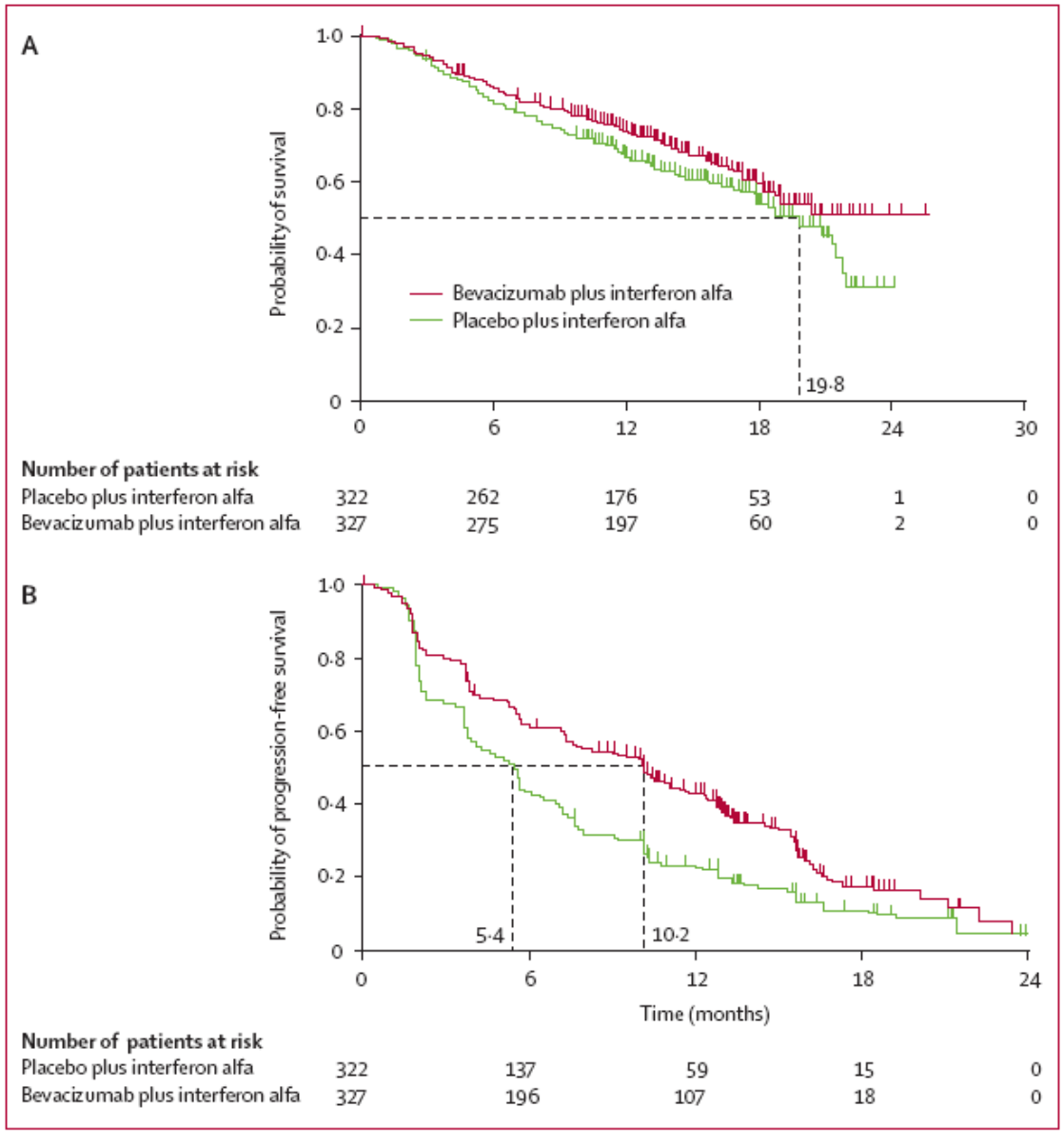
RO = 0%

Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial

*Bernard Escudier, Anna Pluzanska, Piotr Koralewski, Alain Ravaud, Sergio Bracarda, Cezary Szczylik, Christine Chevreau, Marek Filipek, Bohuslav Melichar, Emilio Bajetta, Vera Gorbunova, Jacques-Olivier Bay, Istvan Bodrogi, Agnieszka Jagiello-Gruszfeld, Nicola Moore, for the AVOREN Trial investigators**



Escudier B, Lancet 2007

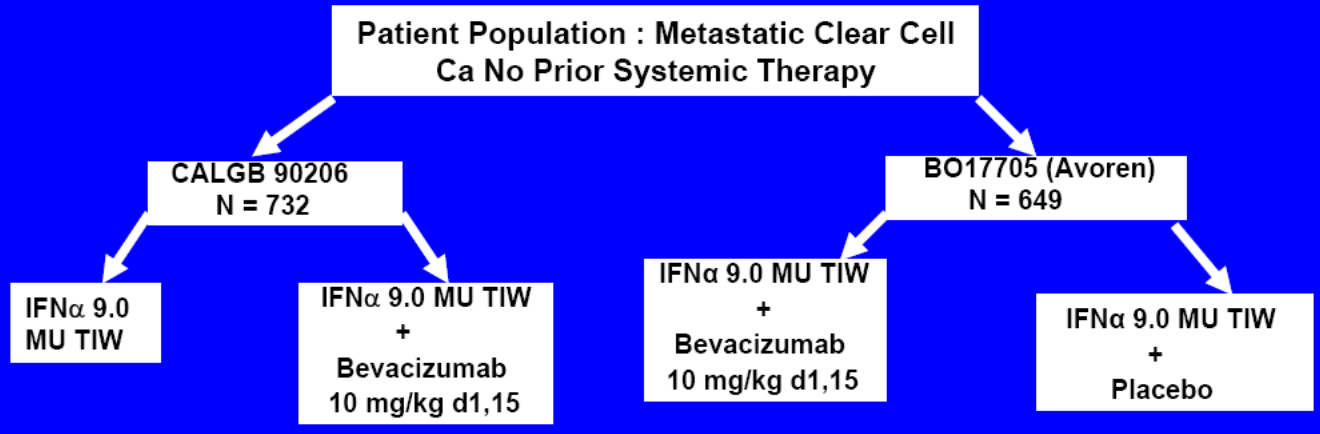


OS

PFS

Figure 2: **Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival**
Interim analysis of overall survival based on 251 of 450 scheduled events. Median overall survival had not been reached in the bevacizumab plus interferon alfa group. Final analysis of progression-free survival based on 505 progression events.

Bevacizumab : Phase 3 Trials in Renal Cell Carcinoma



	CALGB 90206[1]		AVOREN[2]	
Therapy	IFNα	IFNα + Bev	IFNα + Bev	IFNα + Placebo
ORR	13.1%	25.5%	31%	13%
PFS (med)	5.2 mos	8.5 mos	10.2 mos	5.4 mos

[1] Rini, B : GU Malignancy Symposium, ASCO 2/08; [2] Escudier, B et al : The Lancet, 2007

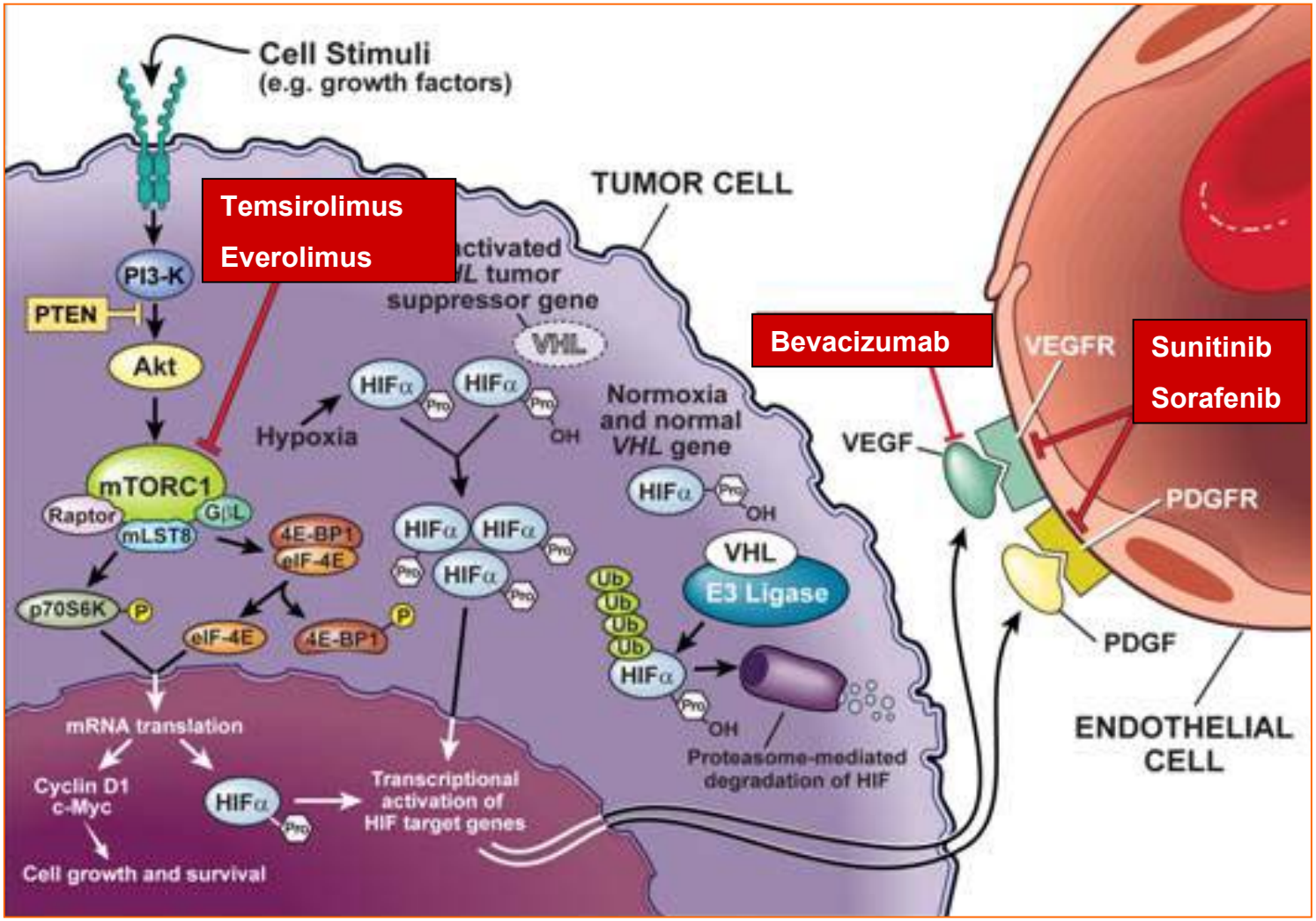
Bukowski RM, Berlin 2008

Bevacizumab: conclusions

Author	Agent	Setting	Pts	PFS (months)	OR (%)	OS
Escudier (Lancet, 2007)	**Bevacizumab + IFN** vs placebo+IFN	**1st line**	649	**10.2 vs 5.4 (p<0.0001)**	31 vs 13 (p<0.0001)	HR: 0.75 (p<0.0026)*

- Bevacizumab + interferon has demonstrated improvements in PFS compared to interferon + placebo
- Bevacizumab + interferon can be considered an alternative treatment for the **first-line therapy** of mRCC

Inhibitors of mTOR



Rini BI, ASCO 2008

Temsirolimus

SIFO

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase II Study of Multiple Dose Levels of CCI-779, a Novel Mammalian Target of Rapamycin Kinase Inhibitor, in Patients With Advanced Refractory Renal Cell Carcinoma

Michael B. Atkins, Manuel Hidalgo, Walter M. Stadler, Theodore F. Logan, Janice P. Dutcher, Gary R. Hudes, Young Park, Song-Heng Liou, Bonnie Marshall, Joseph P. Boni, Gary Dukart, and Matthew L. Sherman

Table 3. Tumor Response Rates of RCC Patients Treated With CCI-779

Response	CCI-779 Dose Level							
	Total (n = 111)		25 mg (n = 36)		75 mg (n = 38)		250 mg (n = 37)	
	No.	%	No.	%	No.	%	No.	%
CR	1	0.9	0	0	0	0	1	2.7*
PR	7	6.3	2	5.6	3	7.9	2	5.4
CR/PR	8	7.2	2	5.6	3	7.9	3	8.1
95% CI	3.2 to 13.7		0.7 to 18.7		1.7 to 21.4		1.7 to 21.9	
MR†	29	26.1	5	13.9	13	34.2	11	29.7
SD ≥ 8 weeks, < 24 weeks	23	20.7	8	22.2	6	15.8	9	24.3
SD ≥ 24 weeks	19	17.1	12	33.3	5	13.2	2	5.4
CR/PR/MR/SD ≥ 24 weeks	56	50.5	19	52.8	21	55.3	16	43.2
95% CI	40.8 to 60.1		35.5 to 69.6		38.3 to 71.4		27.1 to 60.5	
PD	22	19.8	6	16.7	9	23.7	7	18.9
Unknown	10	9.0	3	8.3	2	5.3	5	13.5

Table 7. Classification of RCC Patients Treated With CCI-779 Into Risk Groups for Survival

	CCI-779 Dose Level							
	Total (n = 111)		25 mg (n = 36)		75 mg (n = 38)		250 mg (n = 37)	
Risk Group	No.	%	No.	%	No.	%	No.	%
Good	8	7	2	6	2	5	4	11
Intermediate	48	43	14	39	14	37	20	54
Poor	49	44	20	56	19	50	10	27
Unknown*	6	5	0	0	3	8	3	8

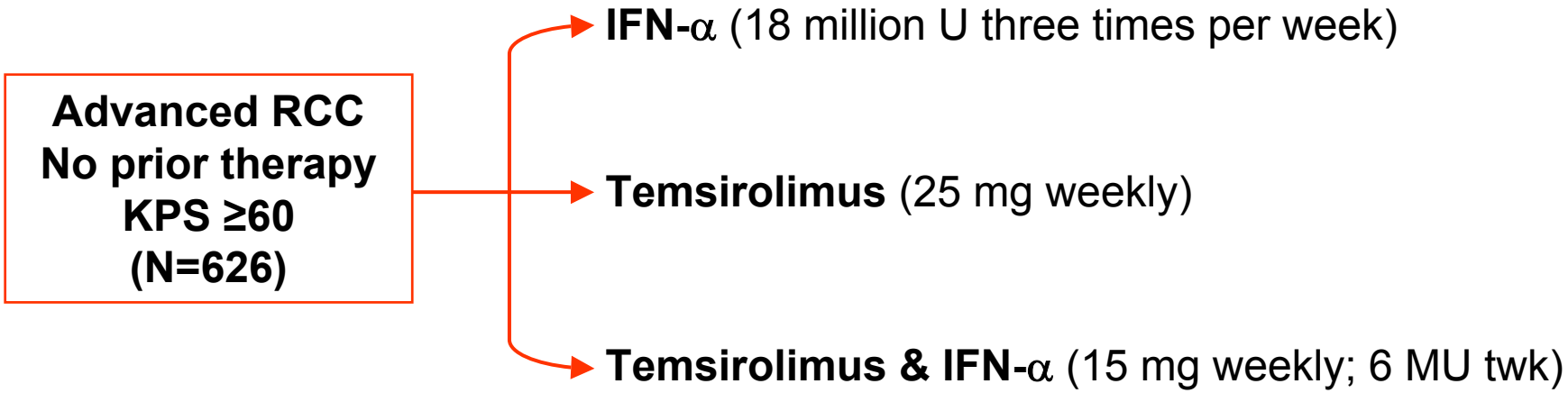
Abbreviation: RCC, renal cell carcinoma.
*Patients had data missing for one or more of the prognostic factors and could not be assigned to a risk group.

Table 8. Median Survivals of CCI-779-Treated RCC Patients by Risk Group

	Good				Intermediate				Poor			
	Patients		Median Survival		Patients		Median Survival		Patients		Median Survival	
CCI-779 Dose Level	No.	%	(months)	95% CI	No.	%	(months)	95% CI	No.	%	(months)	95% CI
25 mg (n = 36)	2	6	18.4	18.4 to 23.6	14	39	23.0	12.5 to NA	20	56	7.1	4.1 to 15.0
75 mg (n = 35)*	2	6	NA	24.1 to NA	14	40	20.9	10.4 to 26.1	19	54	8.6	7.3 to 10.3
250 mg (n = 34)*	4	12	22.4	14.4 to NA	20	59	19.3	16.5 to 29.5	10	29	8.4	3.9 to 17.3
All (n = 105)	8	8	23.8	17.7 to 27.1	48	46	22.5	16.9 to 25.7	49	47	8.2	7.0 to 10.1

Abbreviations: RCC, renal cell carcinoma; NA, not available.
*Three patients had data missing for one or more of the prognostic factors and could not be assigned a risk group.

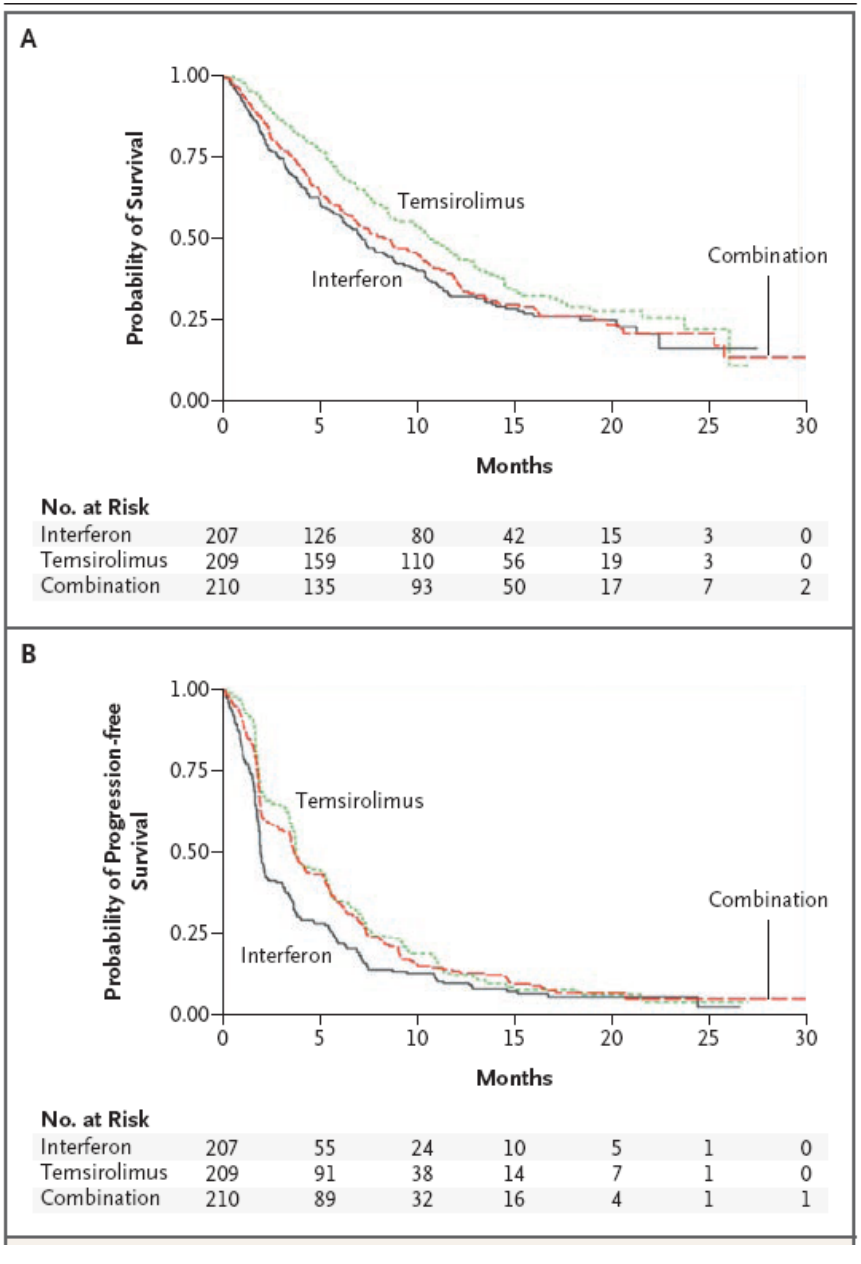
Temsirolimus: Phase III trial for first-line therapy of poor-risk RCC



- **Primary end point**: Overall Survival
- Demographics
  - MSKCC **poor-risk patients** (modified criteria)
  - Predominately clear-cell carcinoma

Poor-risk patients

- At least three of the following six predictors of short survival were required:
  - **LDH** > 1.5 times the upper limit of the normal range
  - **Hemoglobin** level below the lower limit of the normal range
  - **Calcium** level > 10 mg per deciliter
  - **Time from initial diagnosis** of renal-cell carcinoma to randomization < 1 year
  - **Karnofsky performance score** of 60 or 70
  - **Metastases** in multiple organs



Temsirolimus vs IFN

OS: 10.9 vs 7.3 months
HR: 0.73; p=0.008

Temsirolimus vs IFN

PFS: 3.8 vs 1.9 months
p<0.001

Temsirolimus: conclusions

Author	Agent	Setting	Pts	PFS (months)	OR (%)	OS
Hudes (NEJM, 2007)	**Temsirolimus** vs IFN vs TEMSR+IFN	**1st line, poor-risk**	626	3.7 vs 1.9 vs 3.7	9 vs 7 vs 11	**HR: 0.73** **(p=0.0069)**

- Temsirolimus as a single agent (25 mg iv weekly) significantly improves outcomes as first-line therapy of **poor-risk mRCC patients**
- The combination of temsirolimus + IFN-α did not significantly improve survival vs IFN-α

* No statistically significant according to O'Brien-Fleming

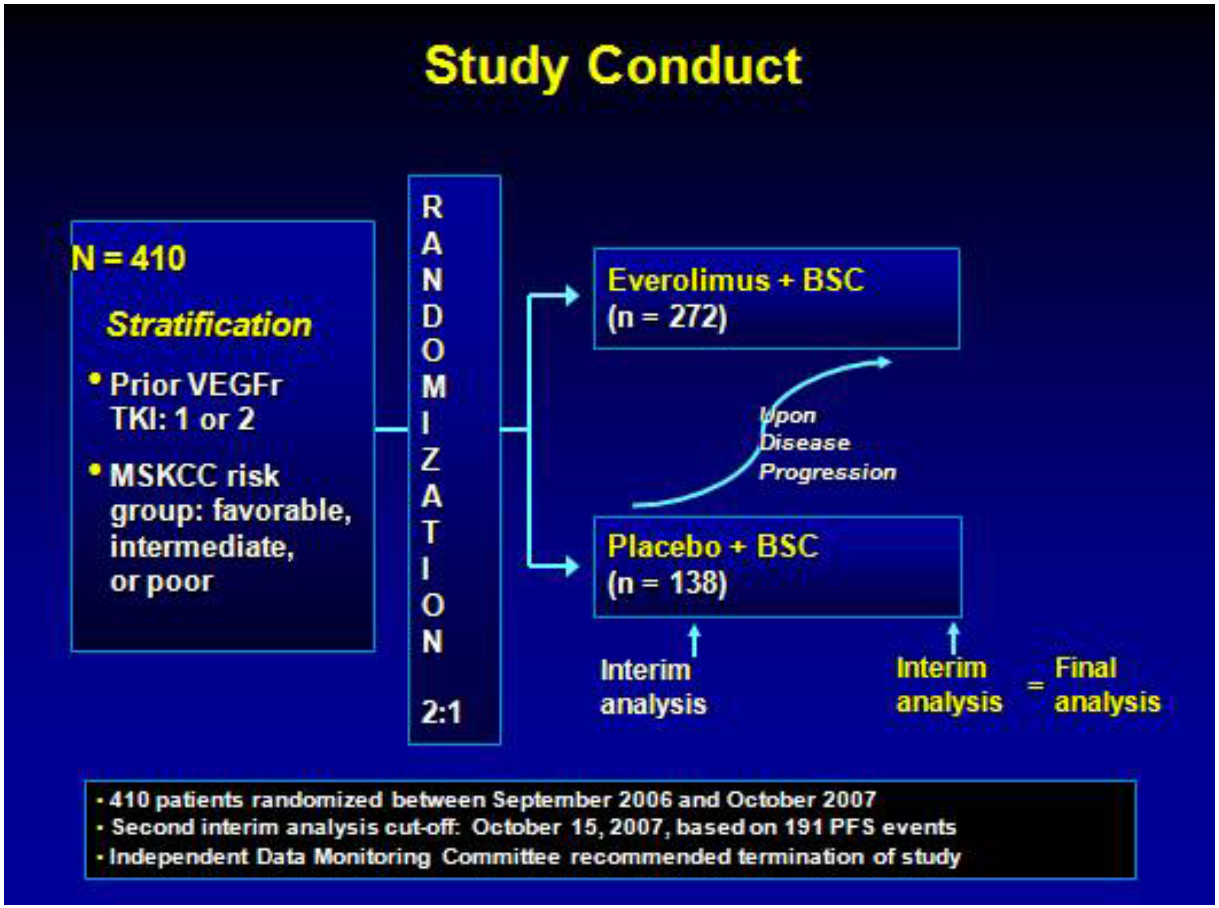
Everolimus

Everolimus: phase 2 trial

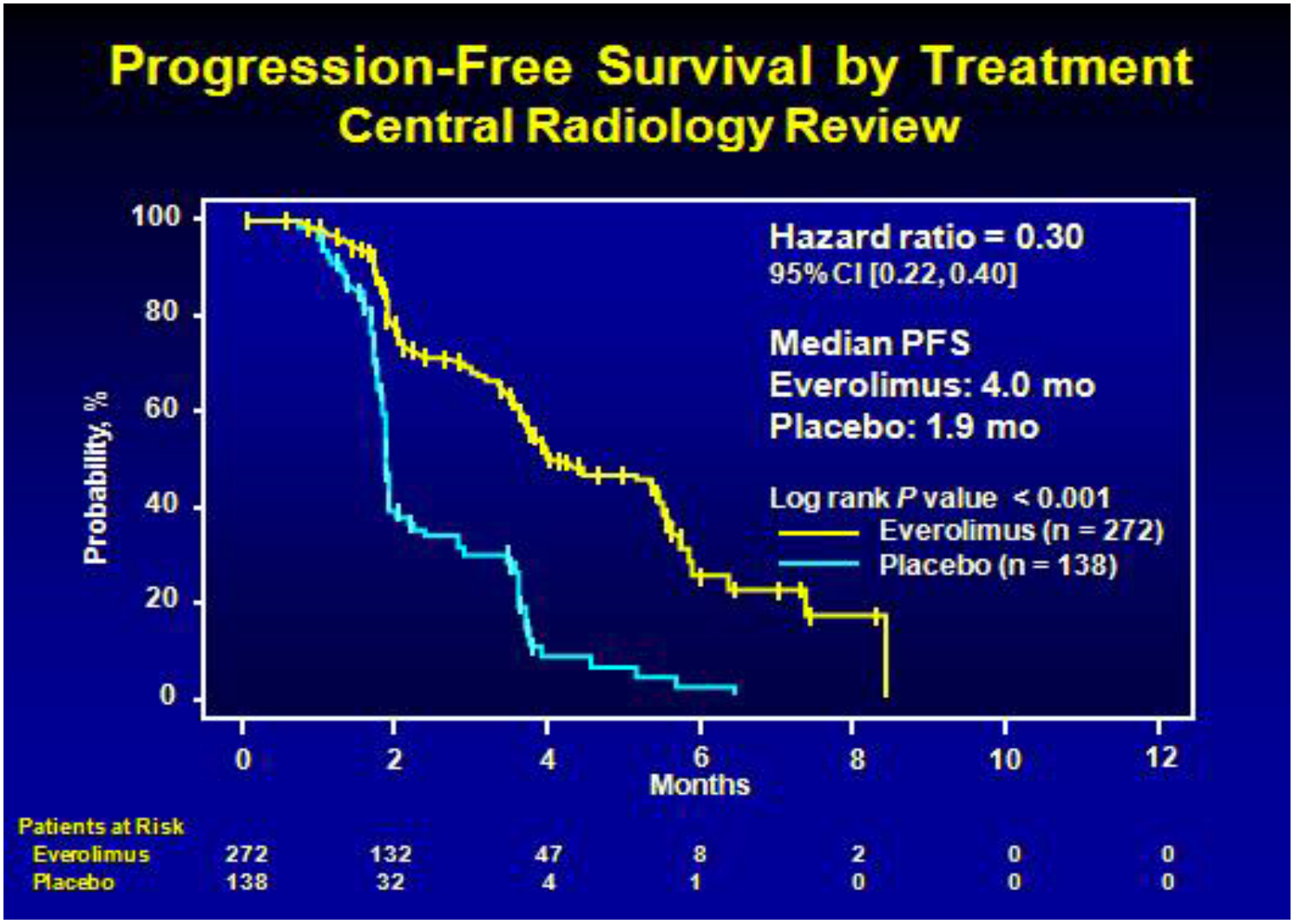
- Everolimus is an oral mTOR inhibitor
- Promising anti-tumor activity in patients with pretreated RCC:
  - response rate 32%
  - stable disease 51%

Jac J, ASCO 2007

Everolimus: Phase III Trial for advanced RCC patients pretreated with inhibitors of VEGFR



Motzer R, ASCO 2008



Motzer R, ASCO 2008

Everolimus: conclusions

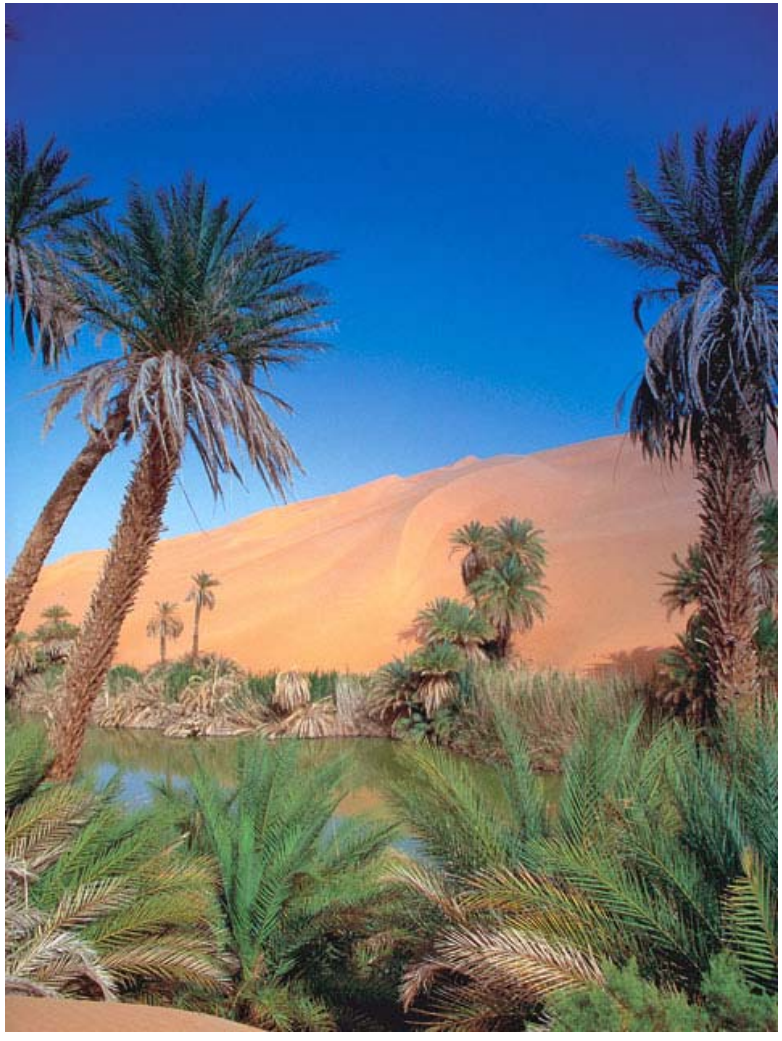
Author	Agent	Setting	Pts	PFS (months)	OR (%)	OS
Motzer (Lancet, 2008)	**Everolimus** vs placebo	**2nd line**	410	**4.0 vs 1.9 (p<0.001)**	1 vs 0	HR: 0.83 (p=0.23)

- Everolimus is the first and only agent with established clinical benefit for the treatment of patients with advanced renal cancer **after therapy with inhibitors of VEGF receptors**

RCC Therapeutic algorithm: 2008

Patients	Setting	Therapy (level 1)	Options (level ≥2)
Untreated	MSK Risk: good or intermediate	**Sunitinib** or **Bevacizumab + IFN**	HD IL-2 Clinical Trials Observation
	MSK Risk: poor	**Temsirolimus**	Sunitinib Clinical trials
Refractory	Cytokine refractory	**Sorafenib**	Sunitinib Bevacizumab
	Refractory to angiogenesis inhibitors	**Everolimus** Clinical Trials	Investigational

The present…:
an embarrassment of riches ?

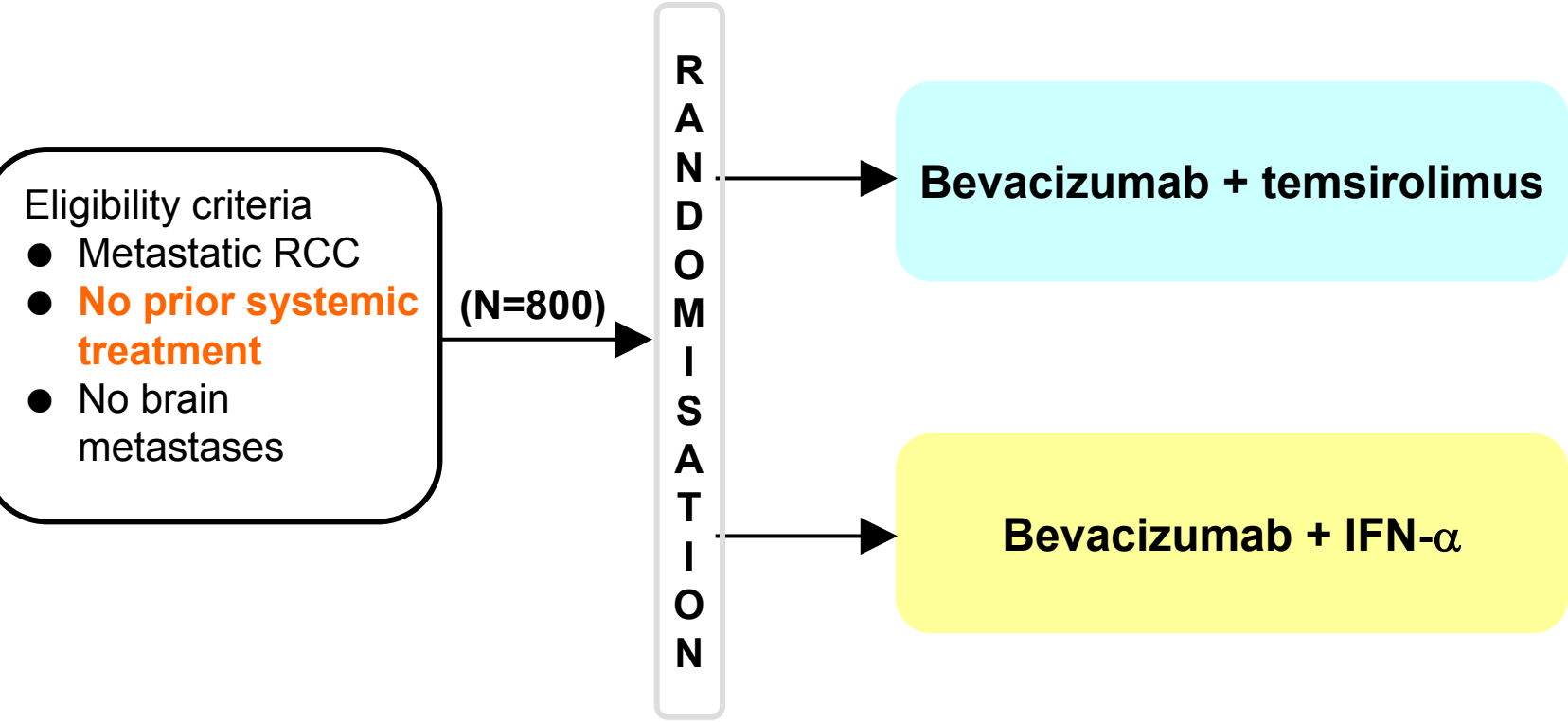


Targeted therapies: challenges and future directions

- Combination therapy
- New schedules
- Sequential strategies
- Role of cytokines
- New agents
- Predictive biomarkers
- Adjuvant and neo-adjuvant therapy

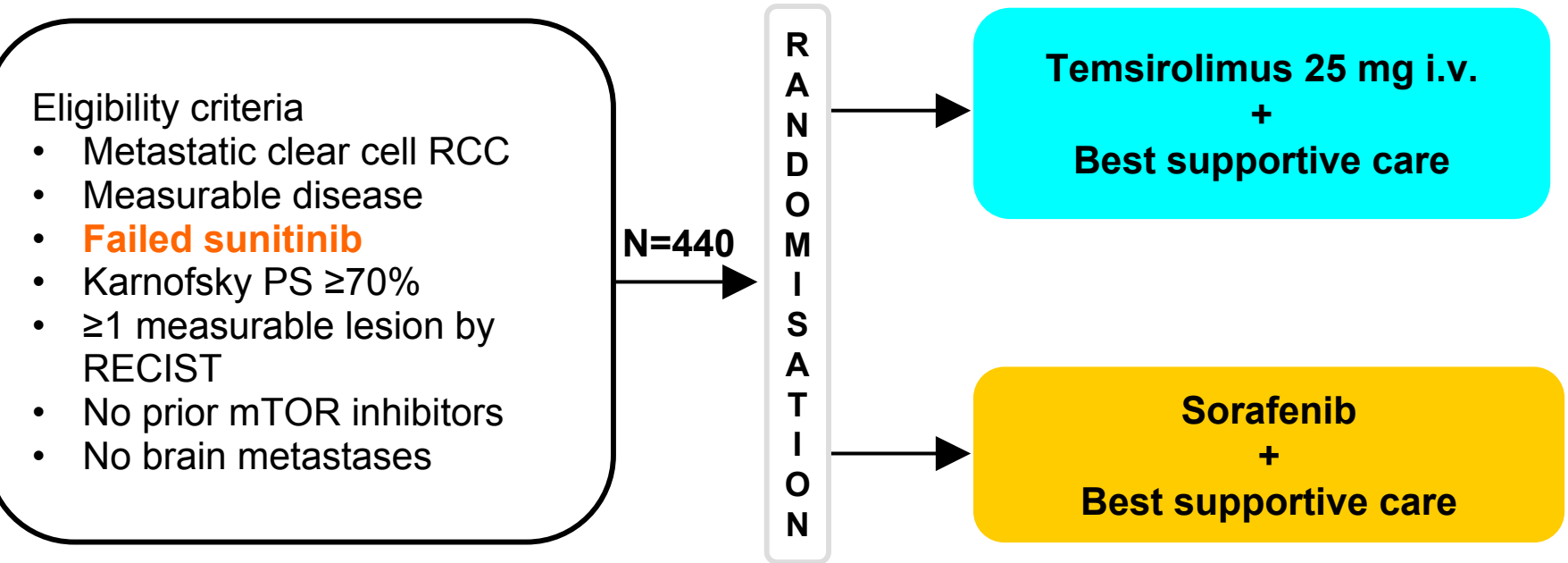
Ongoing studies…

Phase III Study of Bevacizumab plus Temsirolimus vs Bevacizumab plus IFN for First-line Treatment of mRCC



Primary end-point: PFS

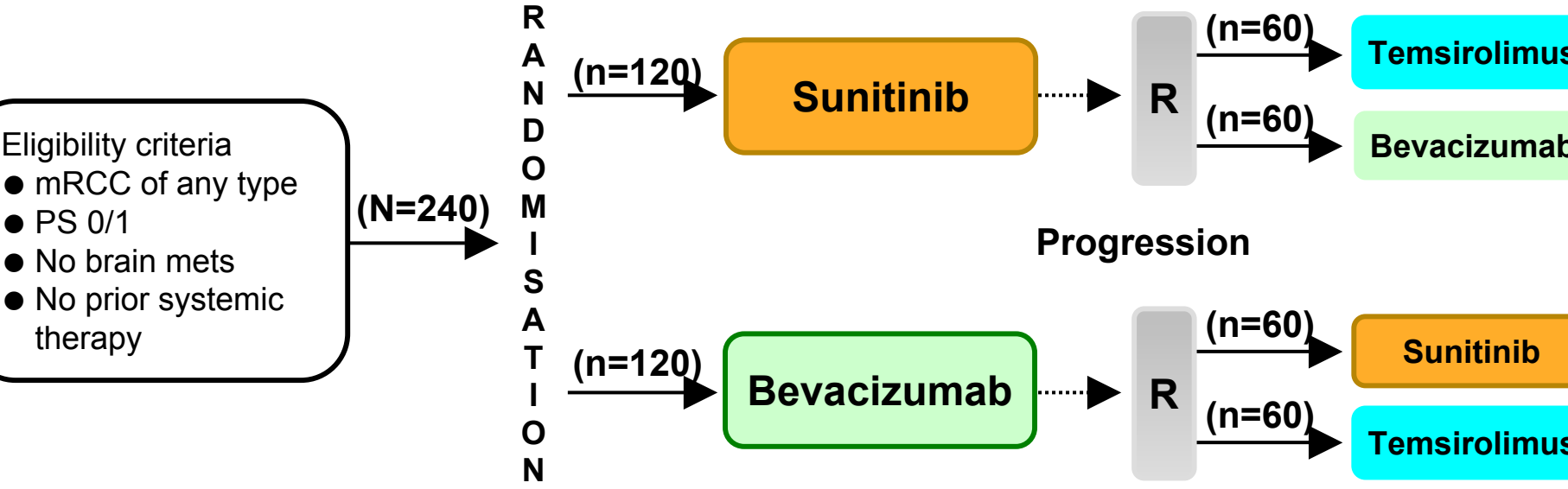
Randomised Phase III Study of Temsirolimus vs Sorafenib as second-line Therapy in mRCC



Primary end-point: PFS

NCT00474786. www.clinicaltrials.gov

START: Randomised Phase II Sequential Two-agent Assessment in RCC Therapy



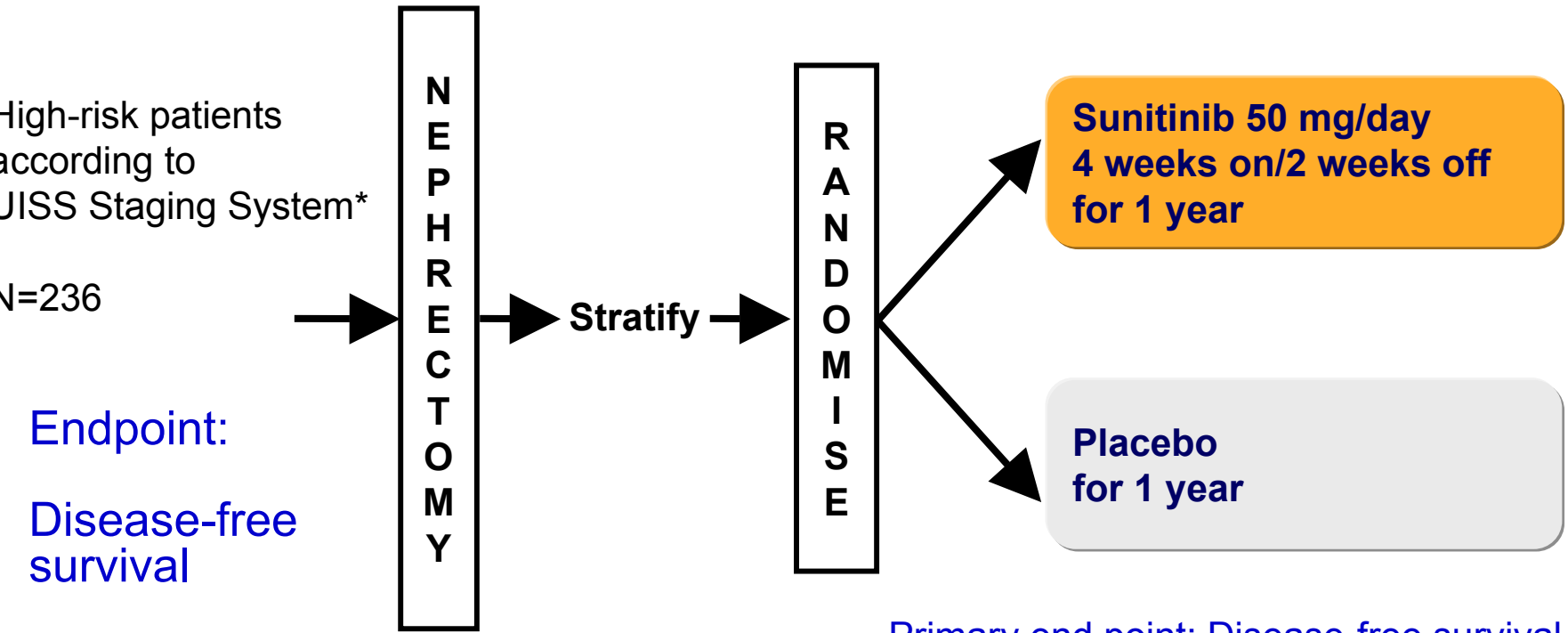
Stratification:

- Clear cell vs non–clear cell
- Prior nephrectomy (yes/no)
- PS (0/1)

Objectives:

Estimate TTP1 and ORR with each drug (first-line setting)
Estimate TTP2 and ORR with each drug (second-line setting)
Estimate and rank TTP1 + TTP2 for each sequence

S-TRAC:
Sunitinib Phase III Trial in Adjuvant Renal Cancer



Endpoint:

Disease-free survival

T3 N0 or NX, M0, Fuhrman's grade ≥2, ECOG ≥1 or T4 N0 or NX, M0, any Fuhrman's grade, and any ECOG status or Any T, N1-2, M0, any Fuhrman's grade, and any ECOG status

Primary end point: Disease-free survival

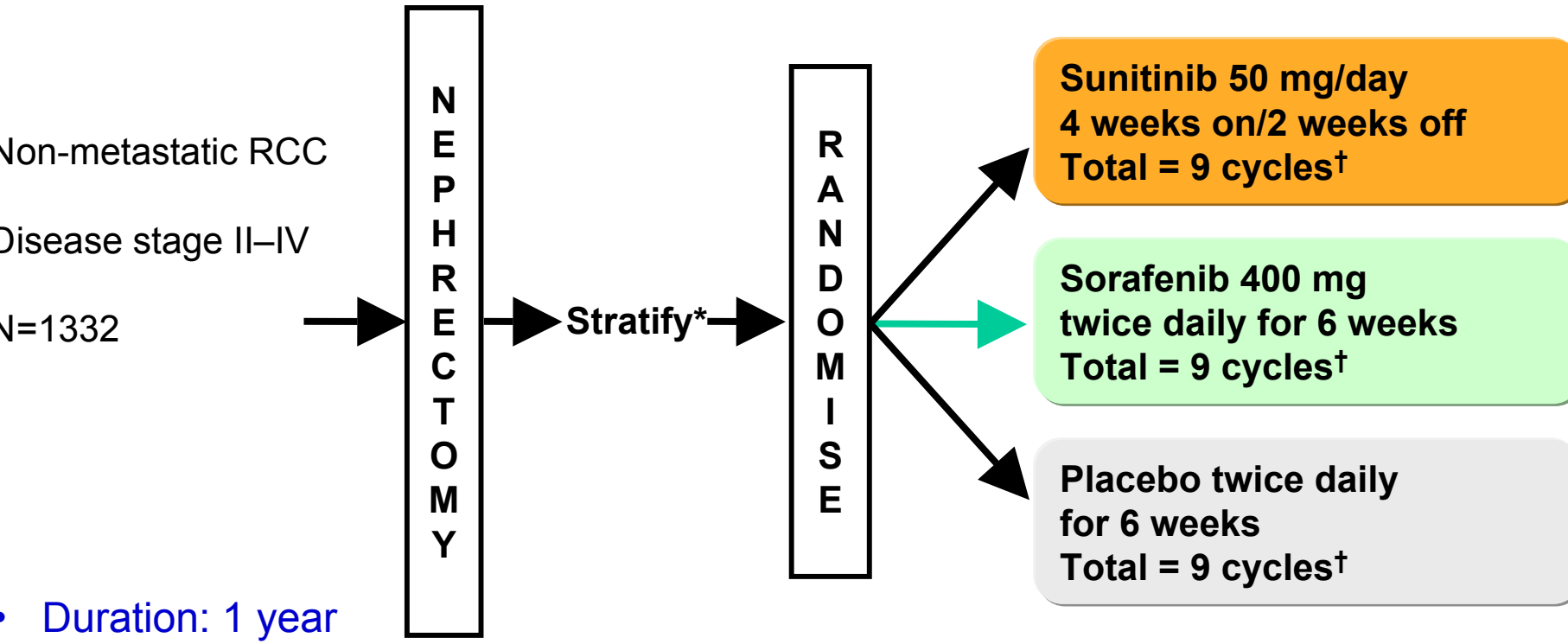
Secondary end points: OS, safety, patient-related outcomes, association of molecular markers with regression - free survival

Start Date: September 2007; recruiting

NCT00375674. www.clinicaltrials.gov

ASSURE:
Adjuvant Sorafenib or Sunitinib for Unfavourable RCC

ECOG-sponsored, randomised, double-blind, multicentre phase III trial; currently recruiting



- Duration: 1 year
- Primary endpoint: DFS

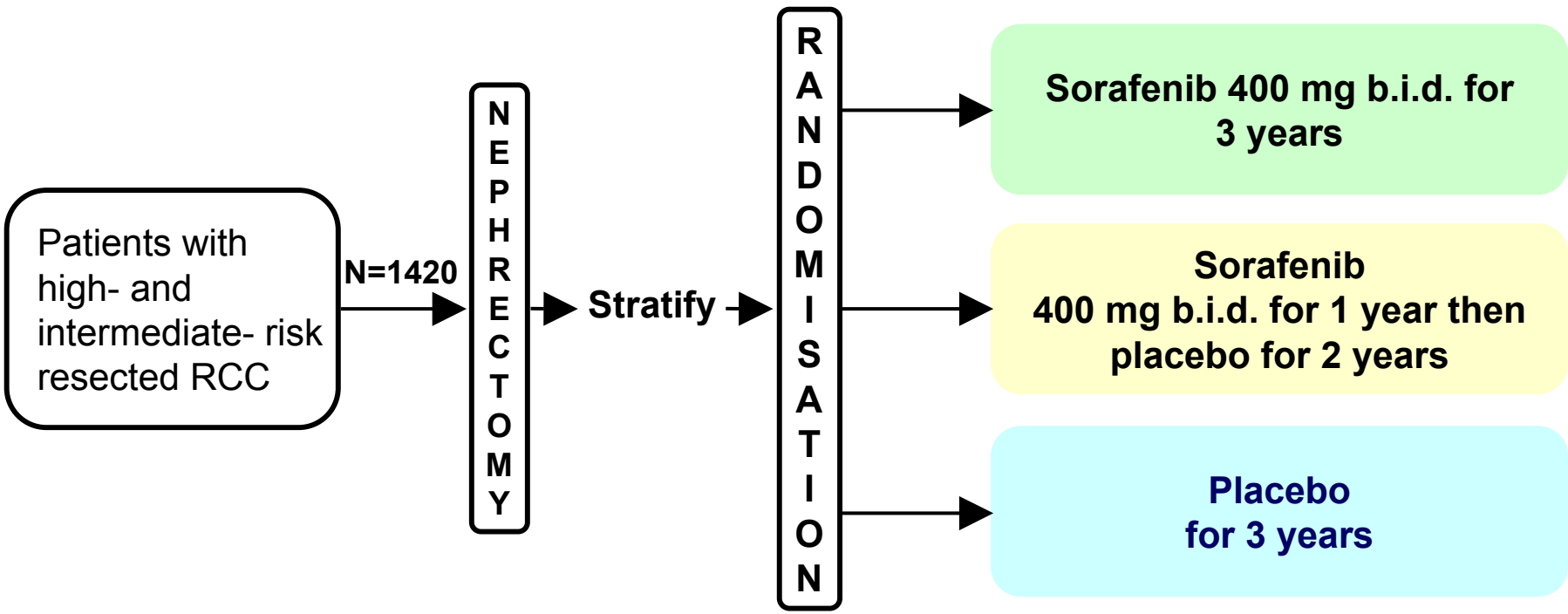
UISS (II–V); Histologic subtype clear cell/non-clear cell
Biopsy at recurrence

tart Date: May 2006; recruiting

NCT00326898. www.clinicaltrials.gov

SORCE:

Sorafenib in Patients with Resected Primary RCC at High or Intermediate Risk of Relapse



Endpoint: time to metastases

Duration: 1 vs 3 years

Start Date: June 2007; recruiting

NCT00492258. www.clinicaltrials.gov

In the next years....

- Ongoing studies will clarify:
  - The role of combination therapy (also including cytokines…)
  - The optimal sequence of therapy
  - Therapy for resistant disease
  - Long term toxicities...
  - Molecular biomarkers defining groups benefiting from anti-VEGF therapy