Αντιμετώπιση του μεταστατικού καρκίνου του νεφρού

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ΓΝΑ "Γ. ΓΕΝΝΗΜΑΤΑΣ"

Αθήνα, 8 Μαρτίου 2017

Εισαγωγή

- 1/3 των ασθενών με RCC → M+ στη διάγνωση
- 30% μετά ριζική θεραπεία → M+
- Όχι ανταπόκριση σε EBRT, ΧΜΘ
- Ανοσοθεραπεία
  - Ανεπιθύμητες ενέργειες
  - Μη ικανοποιητική ανταπόκριση

→ Ανάγκη "νέων" θεραπειών

Parikh RA et al, Clin Genitourin Cncer (in press)

The NEW ENGLAND JOURNAL of MEDICINE

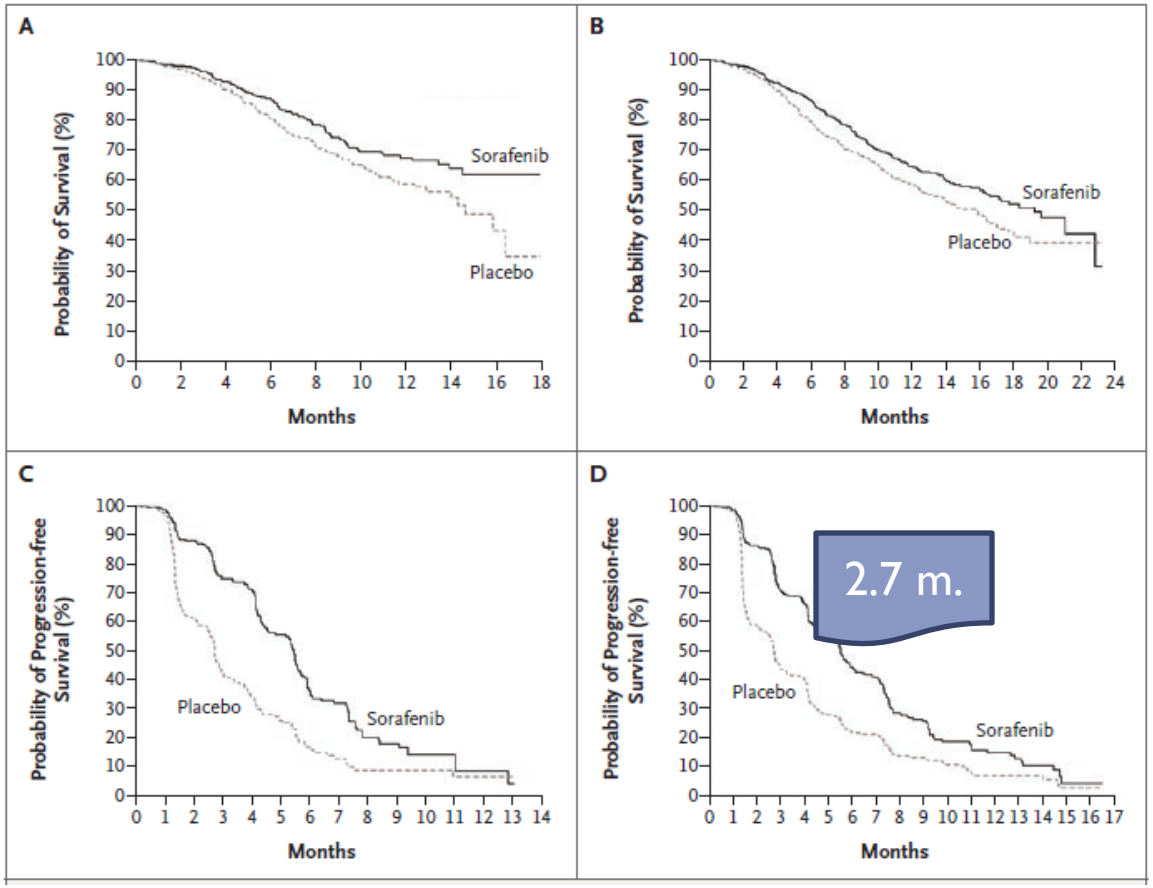
ORIGINAL ARTICLE

Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma

Bernard Escudier, M.D., Tim Eisen, M.D., Walter M. Stadler, M.D., Cezary Szczylik, M.D., Stéphane Oudard, M.D., Michael Siebels, M.D., Sylvie Negrier, M.D., Christine Chevreau, M.D., Ewa Solska, M.D., Apurva A. Desai, M.D., Frédéric Rolland, M.D., Tomasz Demkow, M.D., Thomas E. Hutson, D.O., Pharm.D., Martin Gore, M.D., Scott Freeman, M.D., Brian Schwartz, M.D., Minghua Shan, Ph.D., Ronit Simantov, M.D., and Ronald M. Bukowski, M.D., for the TARGET Study Group*

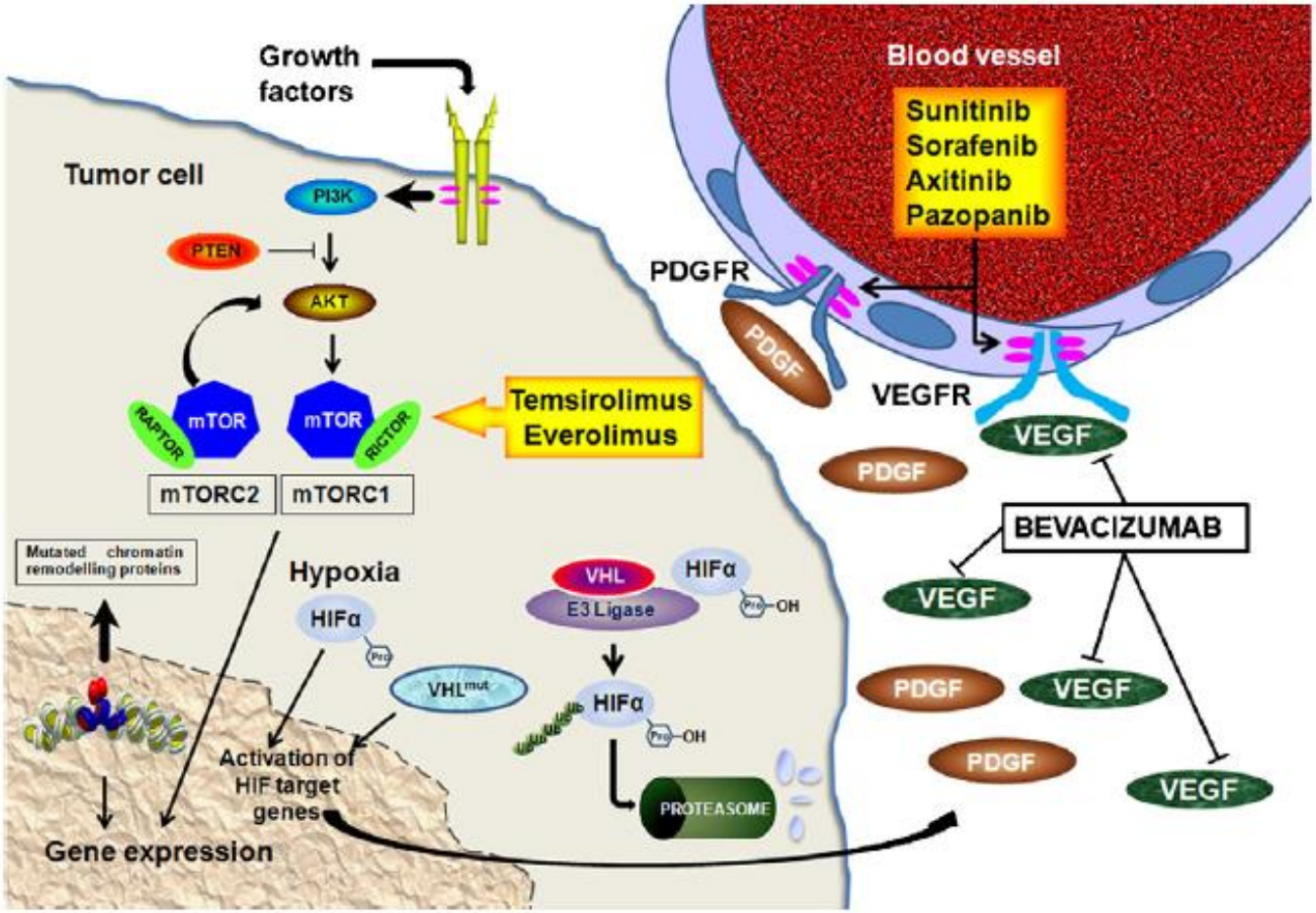
Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma

- Primary End-point: OS



Escudier B et al, N Engl J Med 2007;356:125

Μηχανισμός δράσης



Oosterwijk E et al, Eur Urol 2011;60:622

FDA Approval

- Sorafenib → 2005
- Sunitinib → 2006
- Pazopanib → 2009
- Axitinib → 2012

- Bevacizumab → 2007

- Temsirolimus → 2007
- Everolimus → 2009

Parikh RA et al, Clin Genitourin Cancer (in press)

MSKCC vs IMDC

MSKCC

- Karnofsky < 80%
- Διάγνωση → θεραπεία < 1 έτος
- Υπερασβεστιαιμία (10 mg/dl)
- Αναιμία
- LDH > 1,5 UNL

IMDC

- Karnofsky < 80%
- Διάγνωση → θεραπεία < 1 έτος
- Υπερασβεστιαιμία (10 mg/dl)
- Αναιμία
- Πολυμορφοπυρήνωση
- Θρομβοκυττάρωση

Motzer RJ et al, CJ Clin Oncol 2002;20:289
Heng D et al, CJ Clin Oncol 2009;27:5794

The NEW ENGLAND JOURNAL of MEDICINE

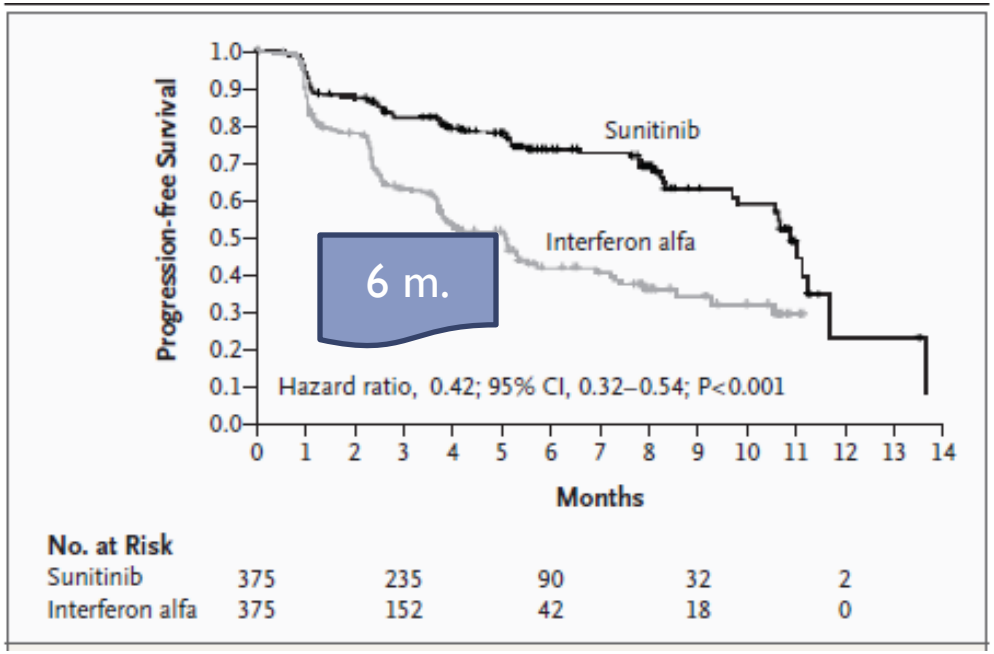
ESTABLISHED IN 1812 JANUARY 11, 2007 VOL. 356 NO. 2

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., Pharm.D., Piotr Tomczak, M.D., M. Dror Michaelson, M.D., Ph.D., Ronald M. Bukowski, M.D., Olivier Rixe, M.D., Ph.D., Stéphane Oudard, M.D., Ph.D., Sylvie Negrier, M.D., Ph.D., Cezary Szczylik, M.D., Ph.D., Sindy T. Kim, B.S., Isan Chen, M.D., Paul W. Bycott, Dr.P.H., Charles M. Baum, M.D., Ph.D., and Robert A. Figlin, M.D.*

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

- Untreated pts
- 95% MSKCC 0-2
- Primary End-point: PFS

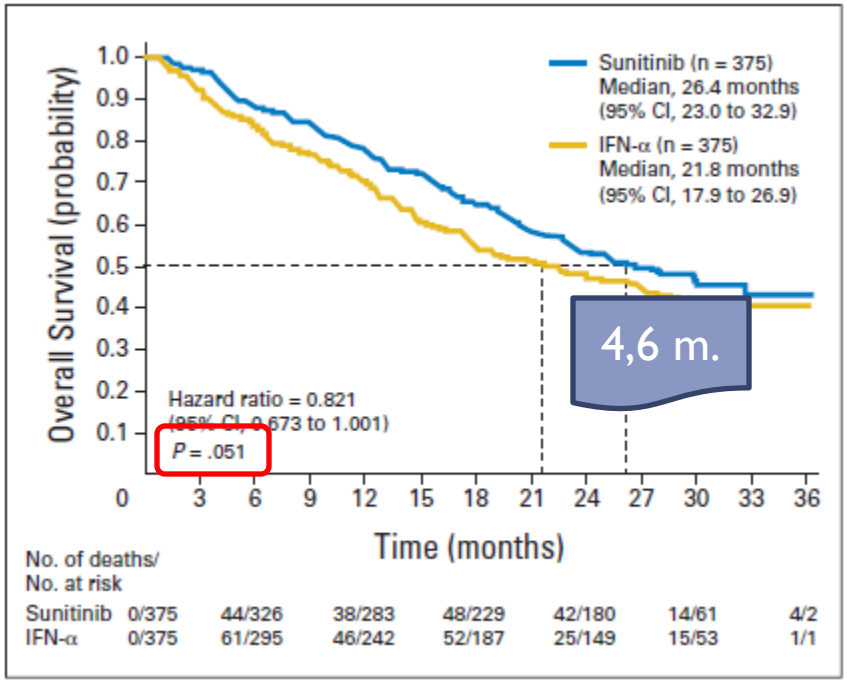


CONCLUSIONS

Progression-free survival was longer and response rates were higher in patients with metastatic renal-cell cancer who received sunitinib than in those receiving interferon alfa (ClinicalTrials.gov numbers, NCT00098657 and NCT00083889).

Motzer RJ et al, N Engl J Med 2007;356:115

Overall Survival and Updated Results for Sunitinib Compared With Interferon Alfa in Patients With Metastatic Renal Cell Carcinoma



- Οριακή υπεροχή του Sunitinib στη συνολική επιβίωση

Motzer RJ et al, J Clin Oncol 2009;27:3584

VOLUME 28 · NUMBER 6 · FEBRUARY 20 2010

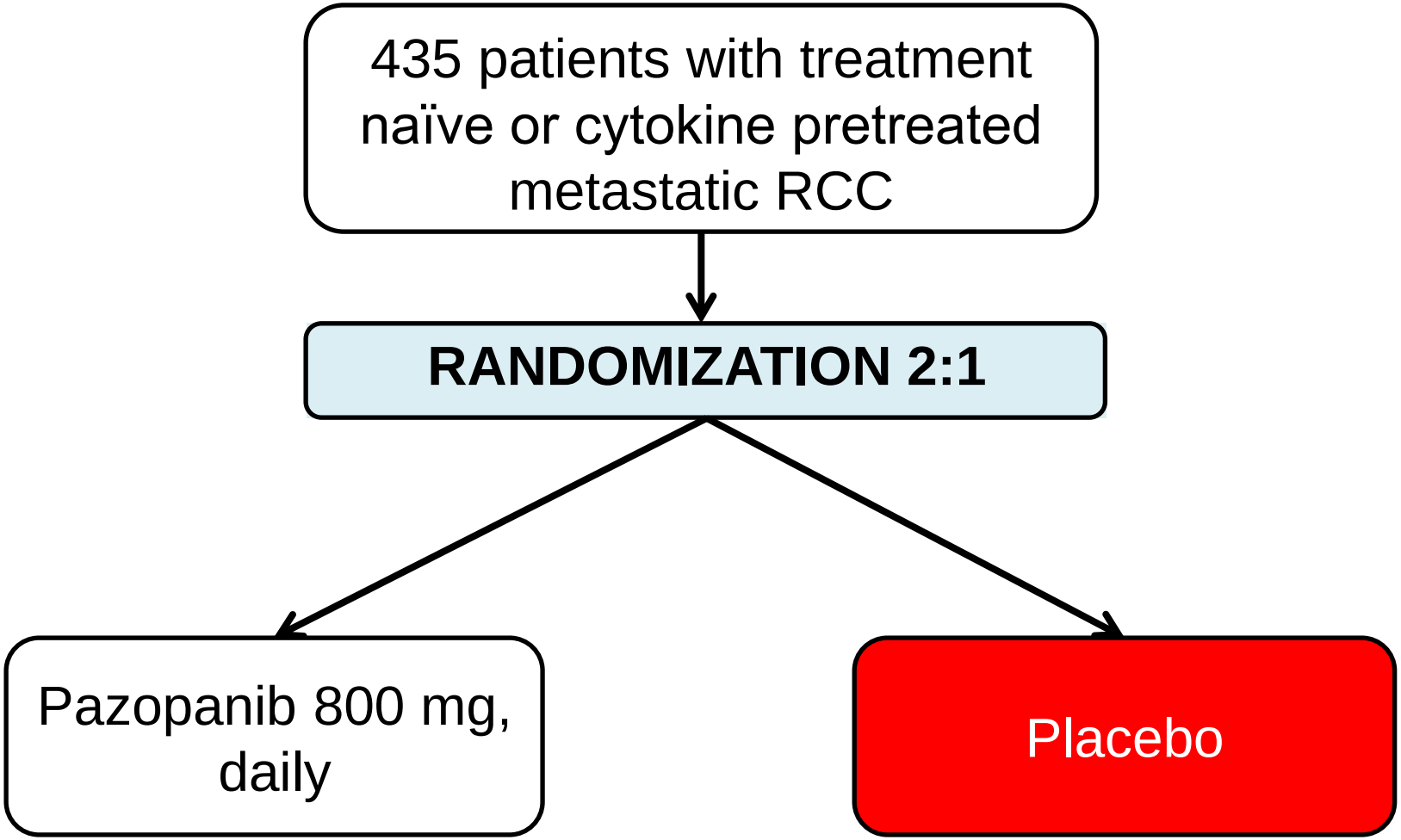
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

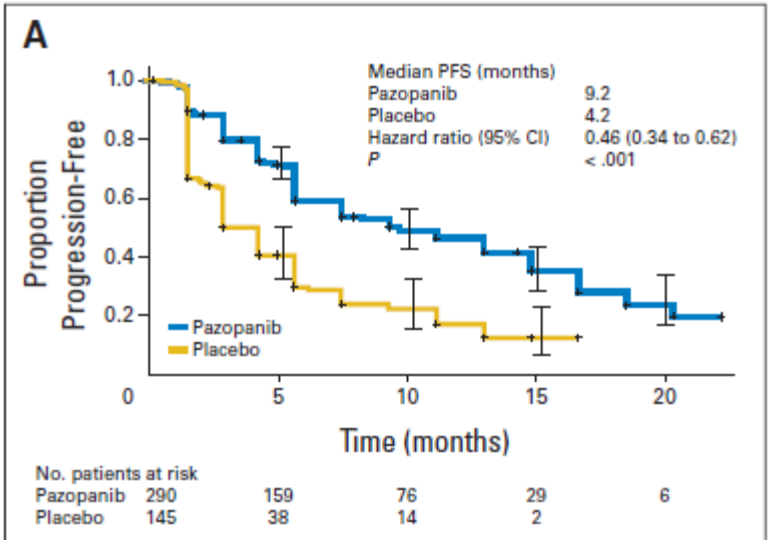
Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomized Phase III Trial

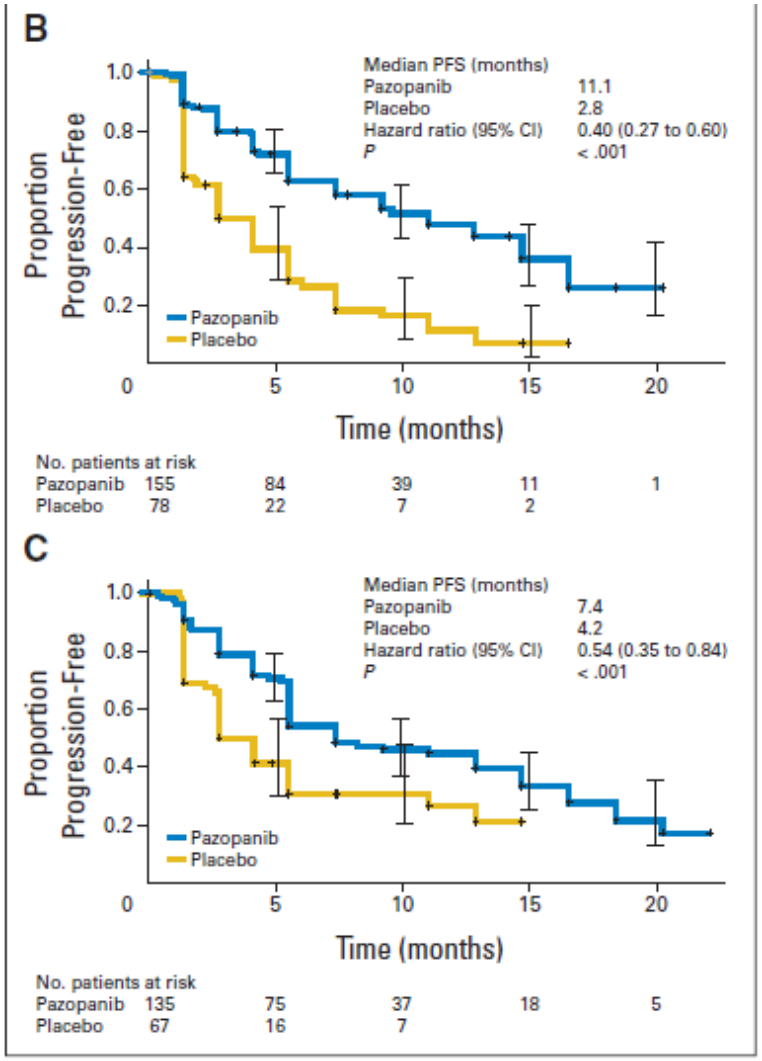
Cora N. Sternberg, Ian D. Davis, Jozef Mardiak, Cezary Szczylik, Eunsik Lee, John Wagstaff, Carlos H. Barrios, Pamela Salman, Oleg A. Gladkov, Alexander Kavina, Juan J. Zarbá, Mei Chen, Lauren McCann, Lini Pandite, Debasish F. Roychowdhury, and Robert E. Hawkins

Trial Design



Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomized Phase III Trial





- Υπεροχή του Pazopanib στο PFS
  - Συνολικά
  - Treatment naive
  - Cytokine pretreated

Sternberg CN et al, J Clin Oncol 2010;28:1061

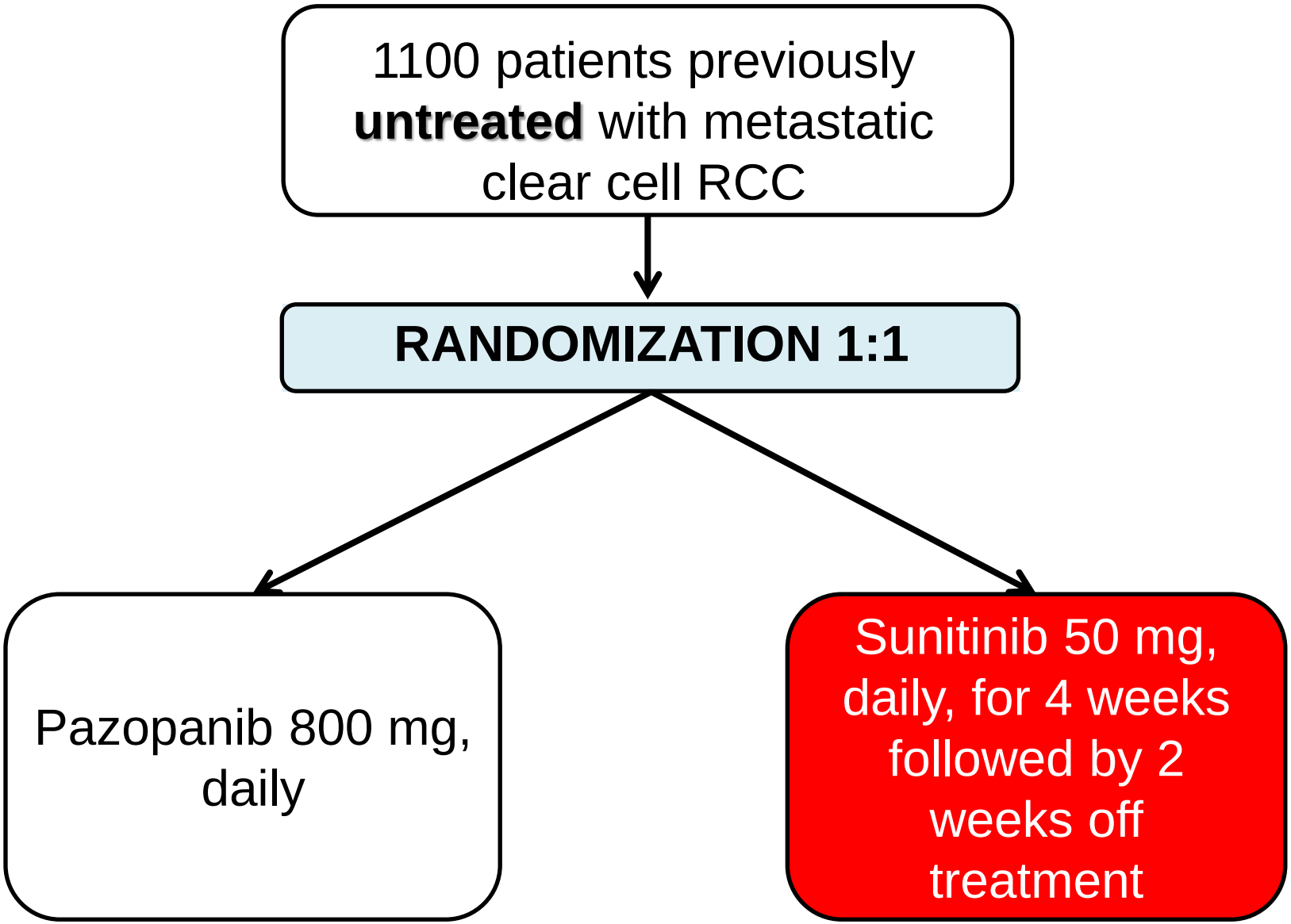
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

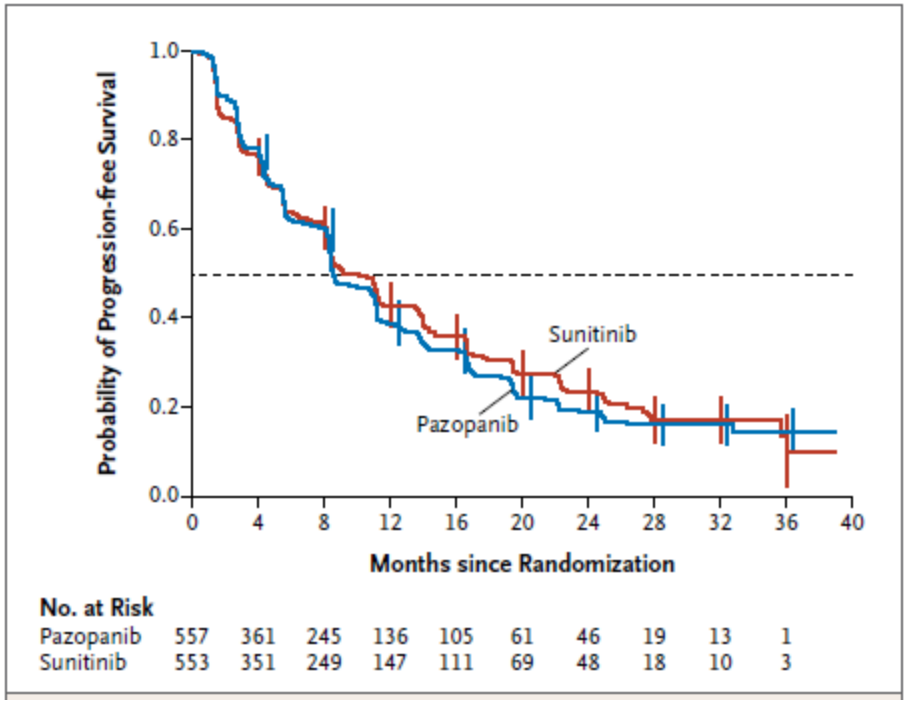
Robert J. Motzer, M.D., Thomas E. Hutson, D.O., David Cella, Ph.D., James Reeves, M.D., Robert Hawkins, M.B., B.S., Ph.D., Jun Guo, Ph.D., Paul Nathan, M.B., B.S., Ph.D., Michael Staehler, M.D., Paul de Souza, M.B., B.S., Ph.D., Jaime R. Merchan, M.D., Ekaterini Boleti, M.D., Ph.D., Kate Fife, M.D., Jie Jin, M.D., Robert Jones, Ph.D., Hirotsugu Uemura, M.D., Ph.D., Ugo De Giorgi, M.D., Ulrika Harmenberg, M.D., Ph.D., Jinwan Wang, M.D., Cora N. Sternberg, M.D., Keith Deen, M.S., Lauren McCann, Ph.D., Michelle D. Hackshaw, Ph.D., Rocco Crescenzo, D.O., Lini N. Pandite, M.D., and Toni K. Choueiri, M.D.

COMPARZ Trial Design



Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

- Primary End-point: PFS



CONCLUSIONS

Pazopanib and sunitinib have similar efficacy, but the safety and quality-of-life profiles favor pazopanib. (Funded by GlaxoSmithKline Pharmaceuticals; COMPARZ ClinicalTrials.gov number, NCT00720941.)

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

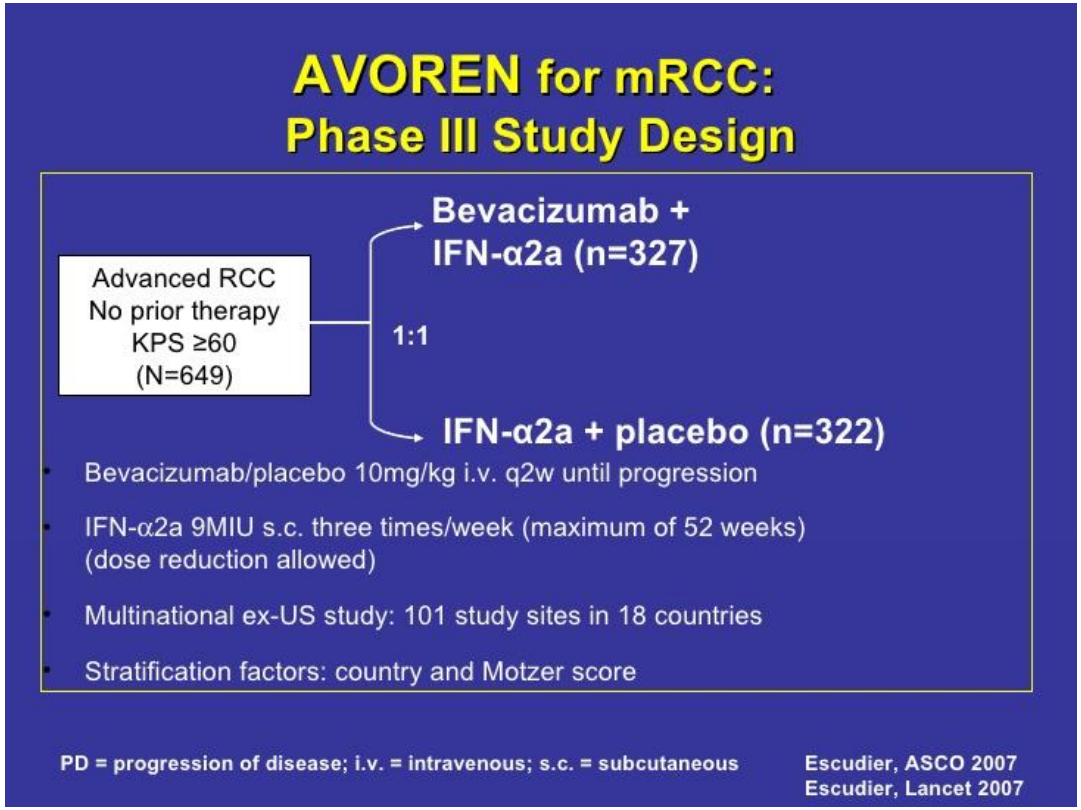
Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

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)
Hypertension	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

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

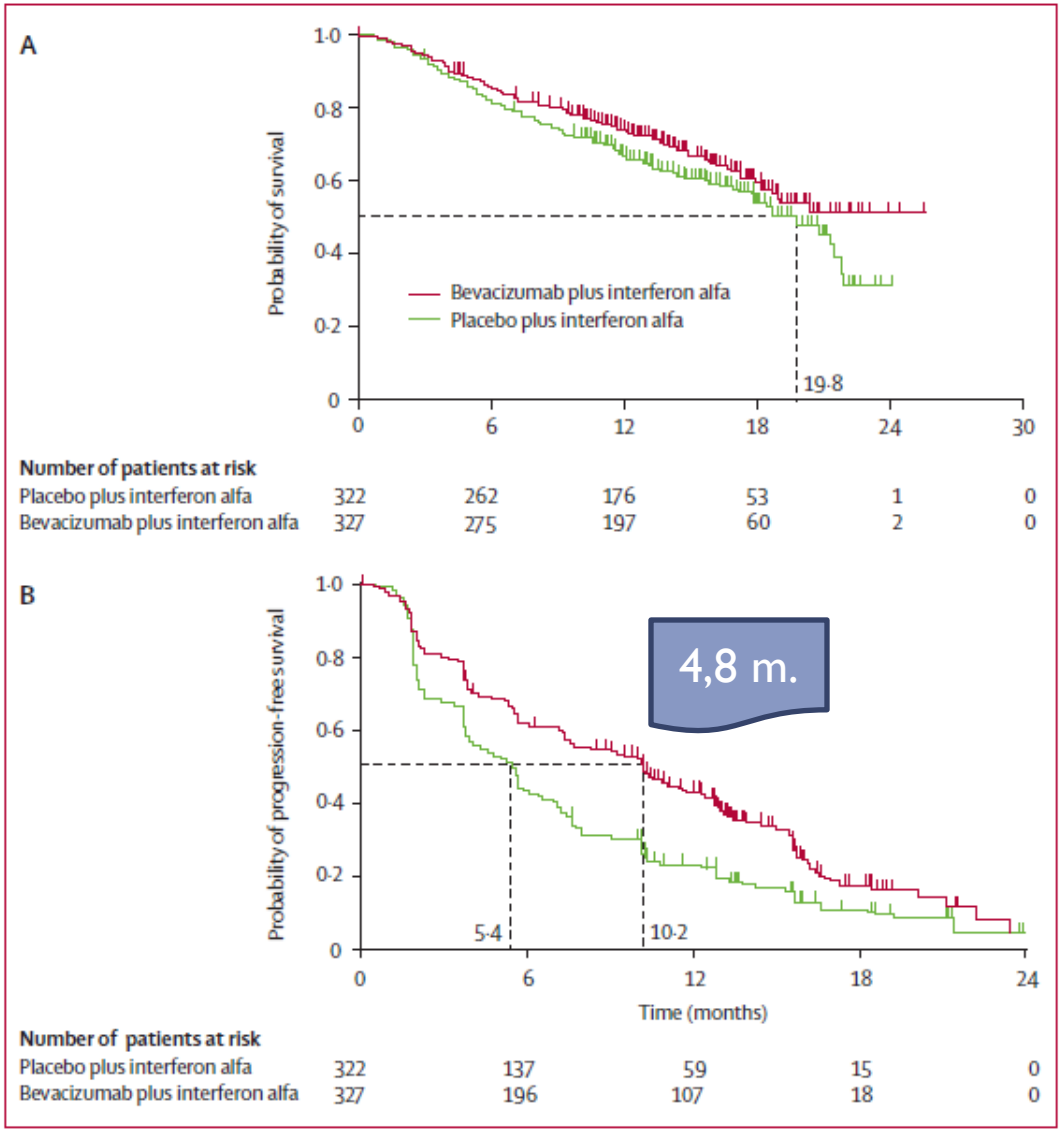
Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial



➢ Primary End-point: OS

Escudier B et al, Lancet 2007;370:2103

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

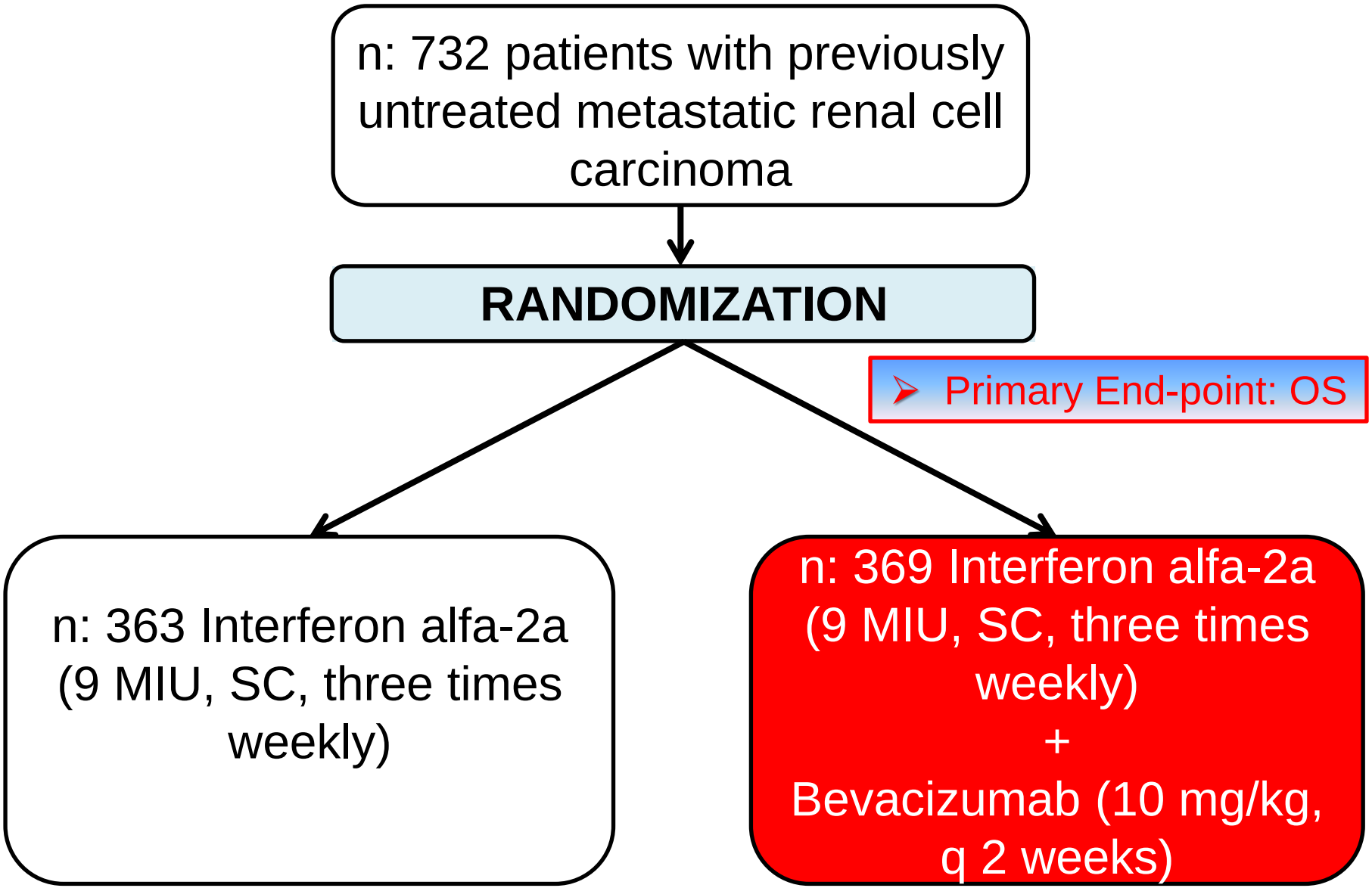


✓ OS

✓ PFS

Escudier B et al, Lancet 2007;370:2103

CALGB 90206 Trial Design



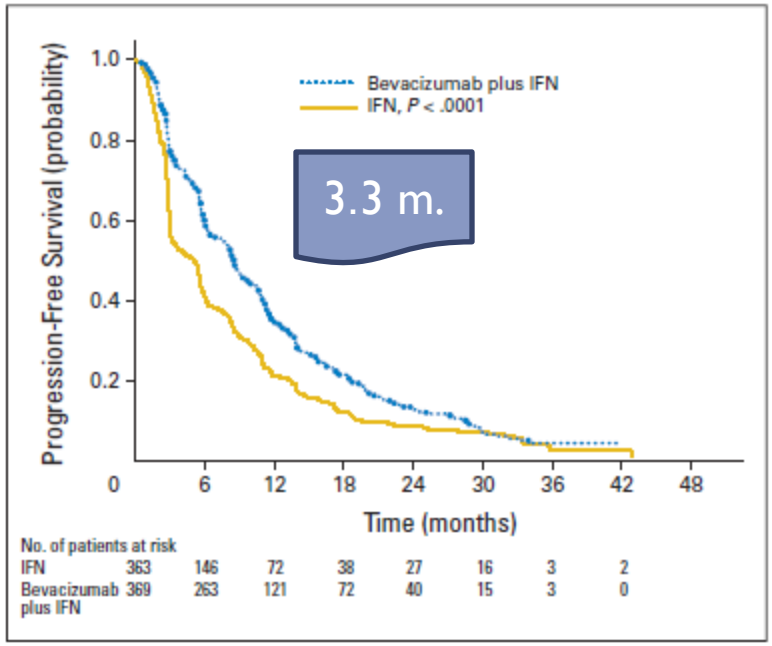
VOLUME 26 · NUMBER 33 · NOVEMBER 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bevacizumab Plus Interferon Alfa Compared With Interferon Alfa Monotherapy in Patients With Metastatic Renal Cell Carcinoma: CALGB 90206

Brian I. Rini, Susan Halabi, Jonathan E. Rosenberg, Walter M. Stadler, Daniel A. Vaena, San-San Ou, Laura Archer, James N. Atkins, Joel Picus, Piotr Czaykowski, Janice Dutcher, and Eric J. Small



✓ PFS

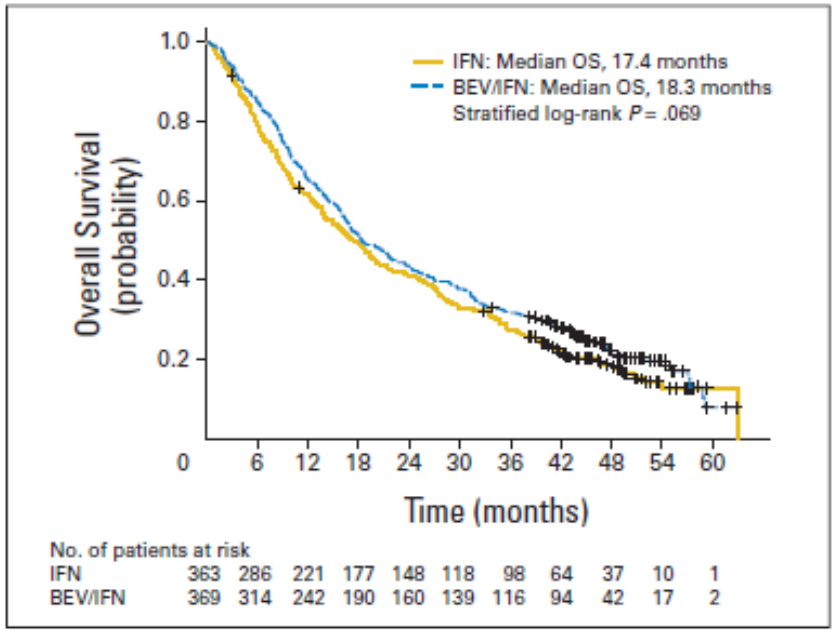
Rini BI et al, J Clin Oncol 2008;26:5422

VOLUME 28 · NUMBER 13 · MAY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial of Bevacizumab Plus Interferon Alfa Versus Interferon Alfa Monotherapy in Patients With Metastatic Renal Cell Carcinoma: Final Results of CALGB 90206



✓ OS

Conclusion

OS favored the bevacizumab plus IFN-α arm but did not meet the predefined criteria for significance. HTN may be a biomarker of outcome with bevacizumab plus IFN-α.

Rini BI et al, J Clin Oncol 2010;28:2137

The NEW ENGLAND JOURNAL of MEDICINE

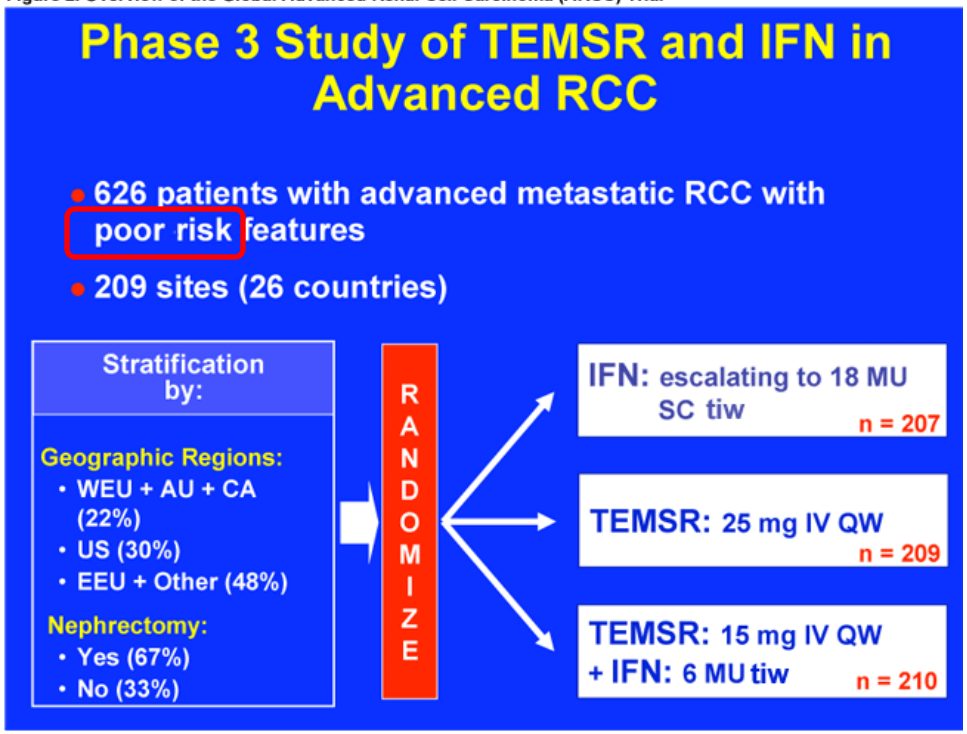
ORIGINAL ARTICLE

Temsirolimus, Interferon Alfa, or Both for Advanced Renal-Cell Carcinoma

Gary Hudes, M.D., Michael Carducci, M.D., Piotr Tomczak, M.D., Janice Dutcher, M.D., Robert Figlin, M.D., Anil Kapoor, M.D., Elzbieta Staroslawska, M.D., Jeffrey Sosman, M.D., David McDermott, M.D., István Bodrogi, M.D., Zoran Kovacevic, M.D., Vladimir Lesovoy, M.D., Ingo G.H. Schmidt-Wolf, M.D., Olga Barbarash, M.D., Erhan Gokmen, M.D., Timothy O'Toole, M.S., Stephanie Lustgarten, M.S., Laurence Moore, M.D., Ph.D., and Robert J. Motzer, M.D., for the Global ARCC Trial*

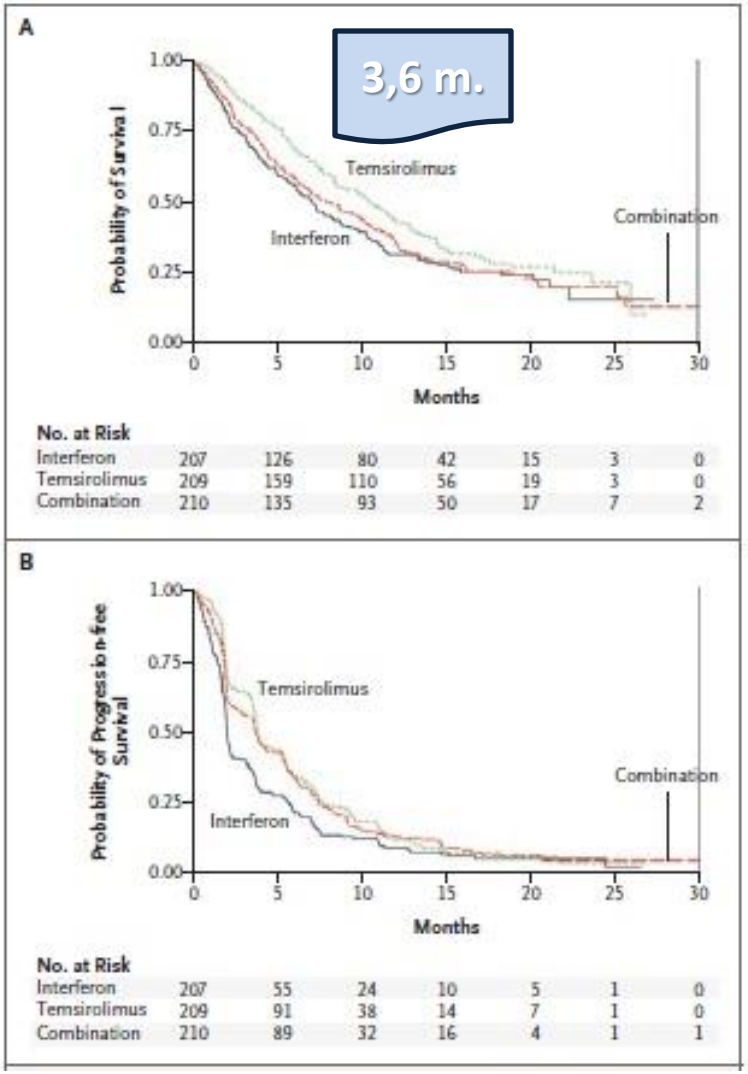
Temsirolimus, Interferon Alfa, or Both for Advanced Renal-Cell Carcinoma

Figure 2. Overview of the Global Advanced Renal Cell Carcinoma (ARCC) Trial



IFN = interferon; RCC = renal cell carcinoma; TEMSR = temsirolimus; tiw = three times a week.

MSKCC risk classification — no. (%)‡				
Poor risk (≥3 of 5 factors)	157 (76)	145 (69)	160 (76)	462 (74)
Intermediate risk (1 or 2 of 5 factors)	50 (24)	64 (31)	50 (24)	164 (26)



- Primary End-point: OS

- TEMSR > IFN
- TEMSR + IFN = IFN

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

2ης γραμμής θεραπεία

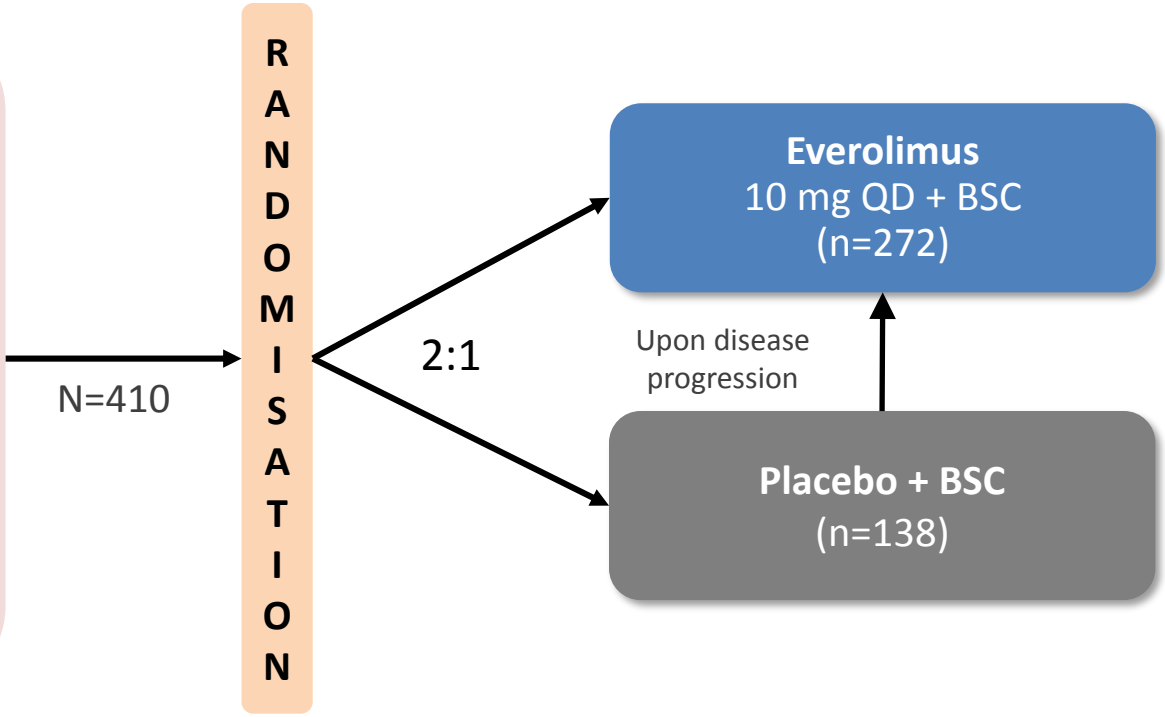
RECORD-1: phase III study design of everolimus versus placebo in second line

Eligibility:

- mRCC (clear-cell component)
- PD during or within 6 months of stopping VEGFR-TKI

Stratification:

- MSKCC prognostic criteria for patients with previously treated mRCC (favourable, intermediate or poor)
- Prior VEGFR-TKI therapy (1 vs 2 prior VEGFR-TKIs)



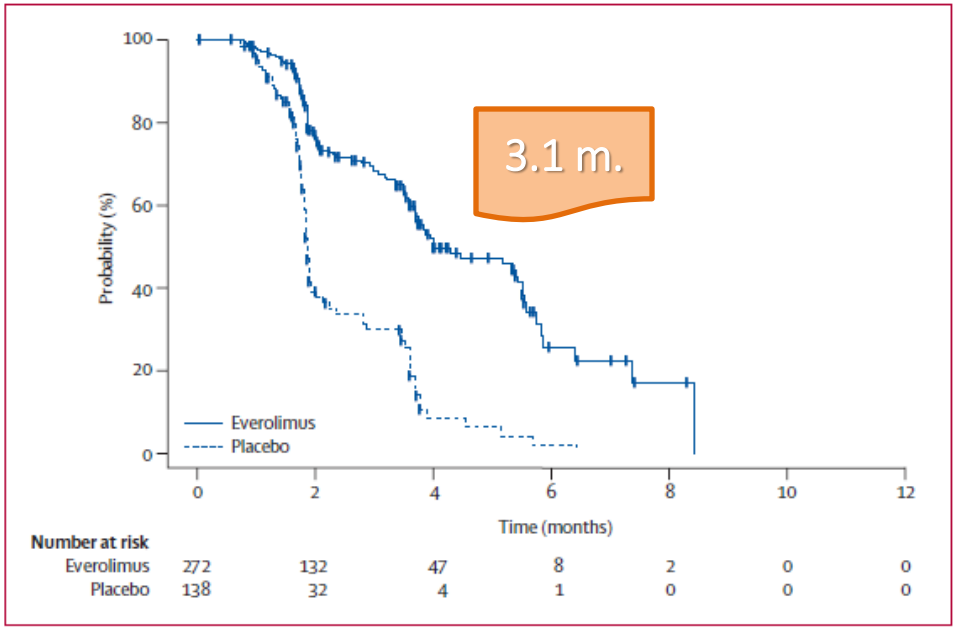
Primary endpoint: PFS

Secondary endpoints: OS, ORR, safety and quality of life

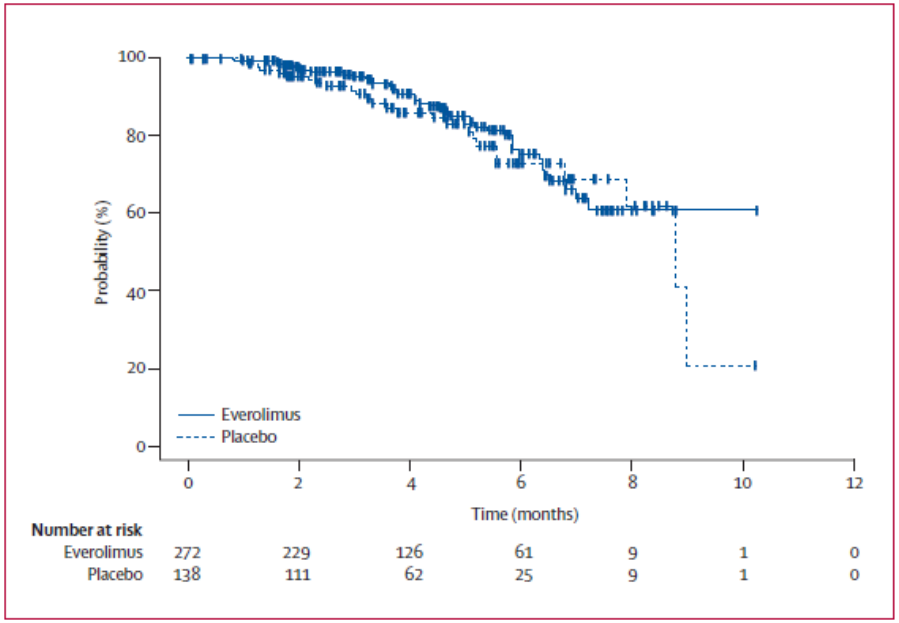
BSC, best supportive care; MSKCC, Memorial Sloan Kettering Cancer Center; RECIST, Response Evaluation Criteria in Solid Tumours

Motzer RJ et al, Lancet 2008;372:449

Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial



✓ PFS



✓ OS

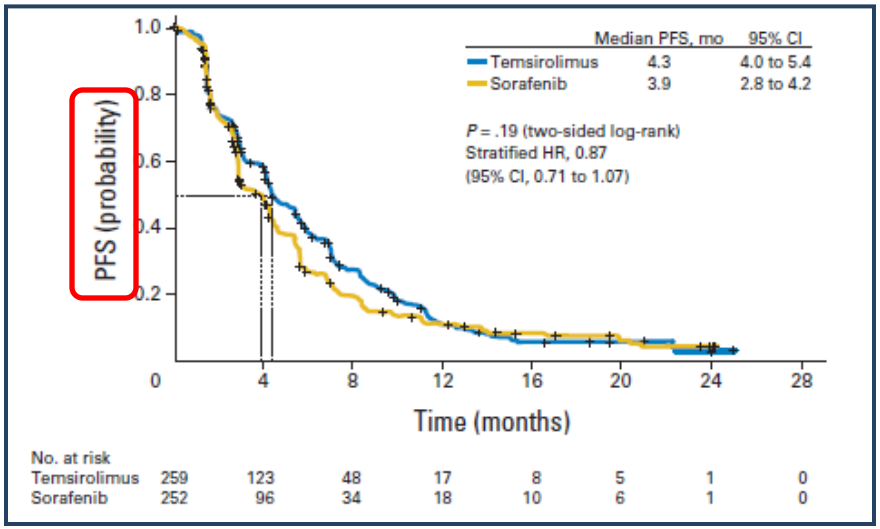
Interpretation Treatment with everolimus prolongs progression-free survival relative to placebo in patients with metastatic renal cell carcinoma that had progressed on other targeted therapies.

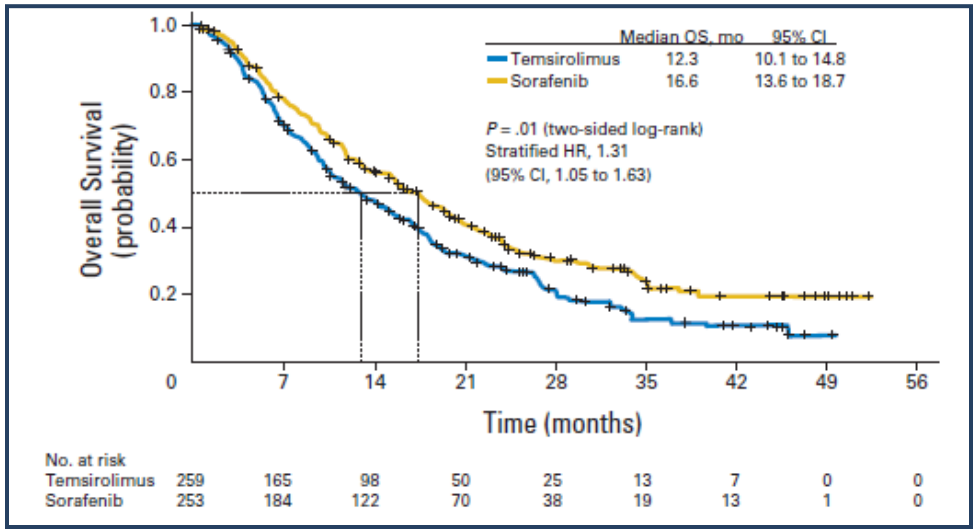
Motzer RJ et al, Lancet 2008;372:449

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

- **INTORSECT**
- Only Sunitinib-resistant
- n: 512 pts

- Primary End-point: PFS



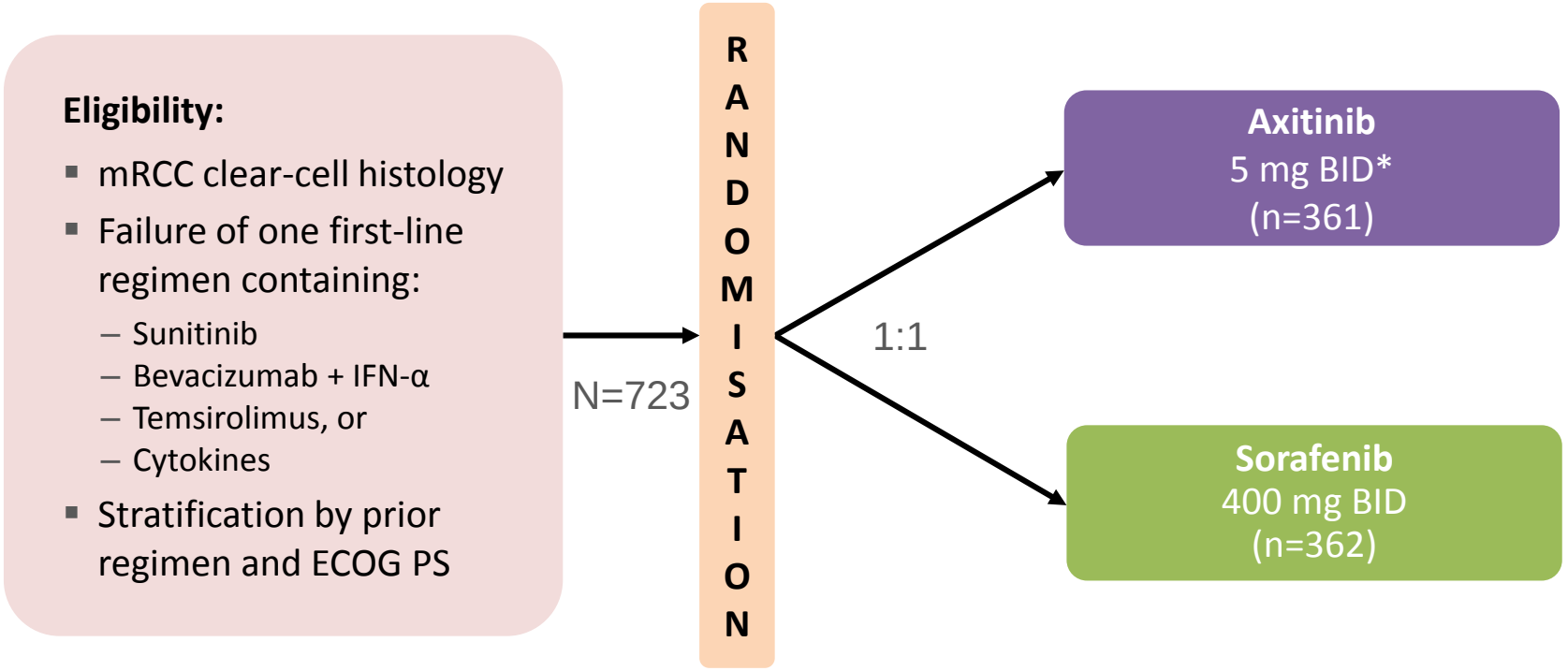


Conclusion

In patients with mRCC and progression on sunitinib, second-line temsirolimus did not demonstrate a PFS advantage compared with sorafenib. The longer OS observed with sorafenib suggests sequenced VEGFR inhibition may benefit patients with mRCC.

Hutson TE et al, J Clin Oncol 2013;32:760

AXIS: phase III study design with axitinib

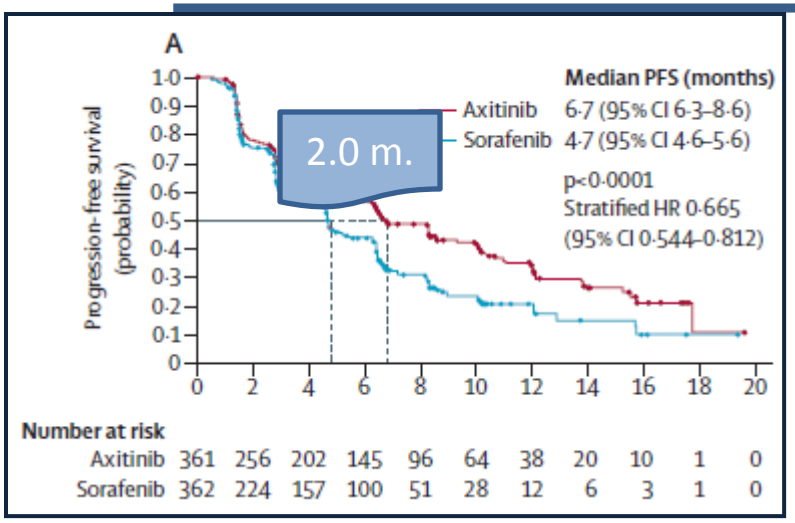


First phase III, head-to-head study vs a targeted agent in second-line mRCC

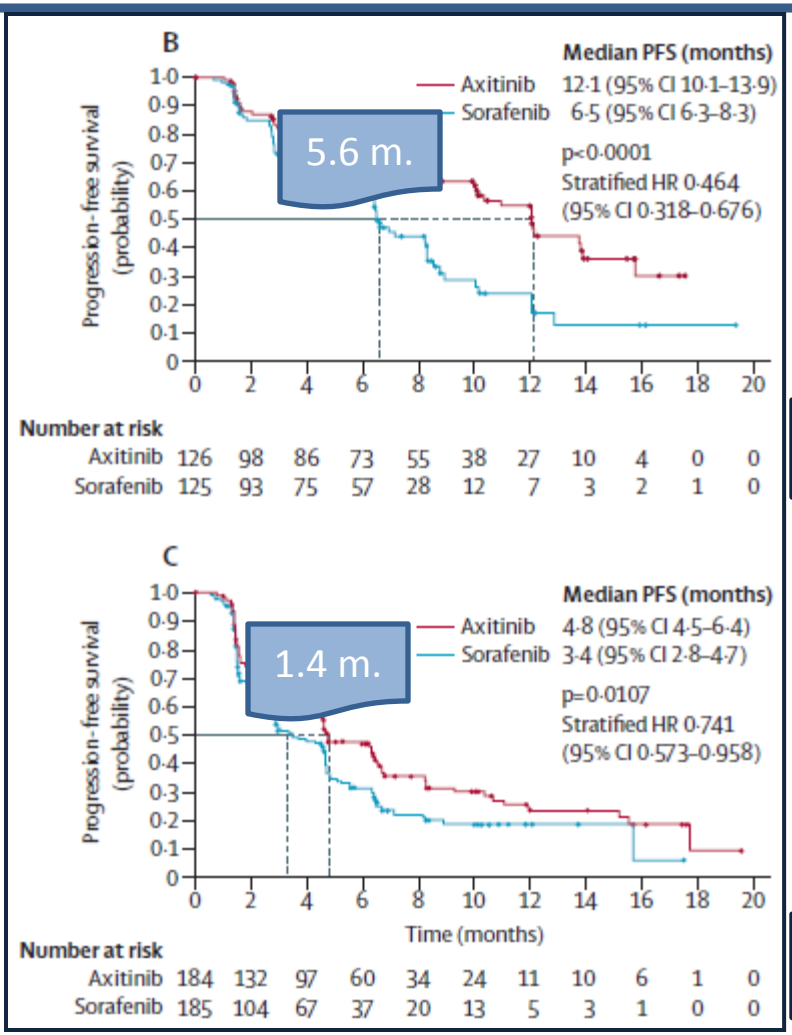
Primary endpoint: PFS

*Starting dose 5 mg BID with option for dose escalation to 7 mg BID then 10 mg BID
BID, twice daily

Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial



➢ All pts



➢ Previously Cytokine-based

➢ Previously Sunitinib-based

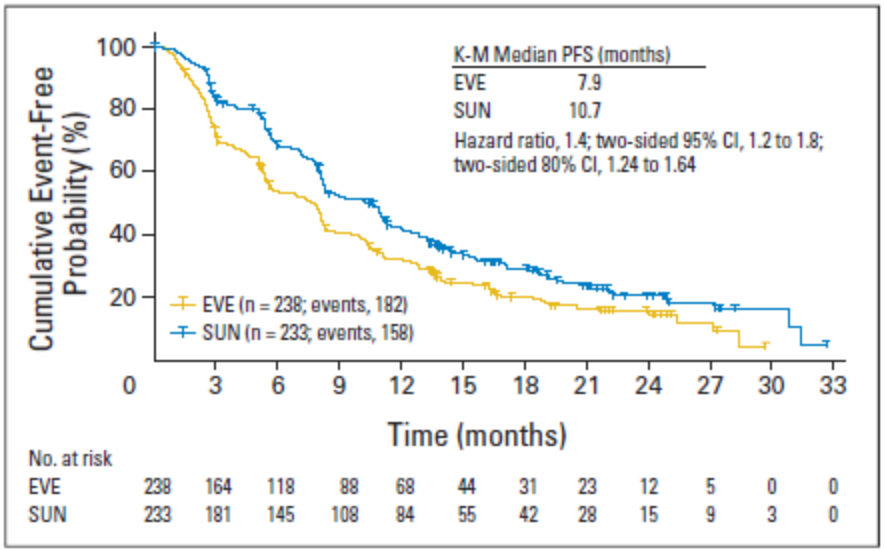
Interpretation Axitinib resulted in significantly longer PFS compared with sorafenib. Axitinib is a treatment option for second-line therapy of advanced renal cell carcinoma.

Rini BI et al, Lancet 2011;378:1931

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

- **RECORD-3**
- **n: 471**
  - n: 238: Eve + Sun
  - n: 233: Sun + Eve

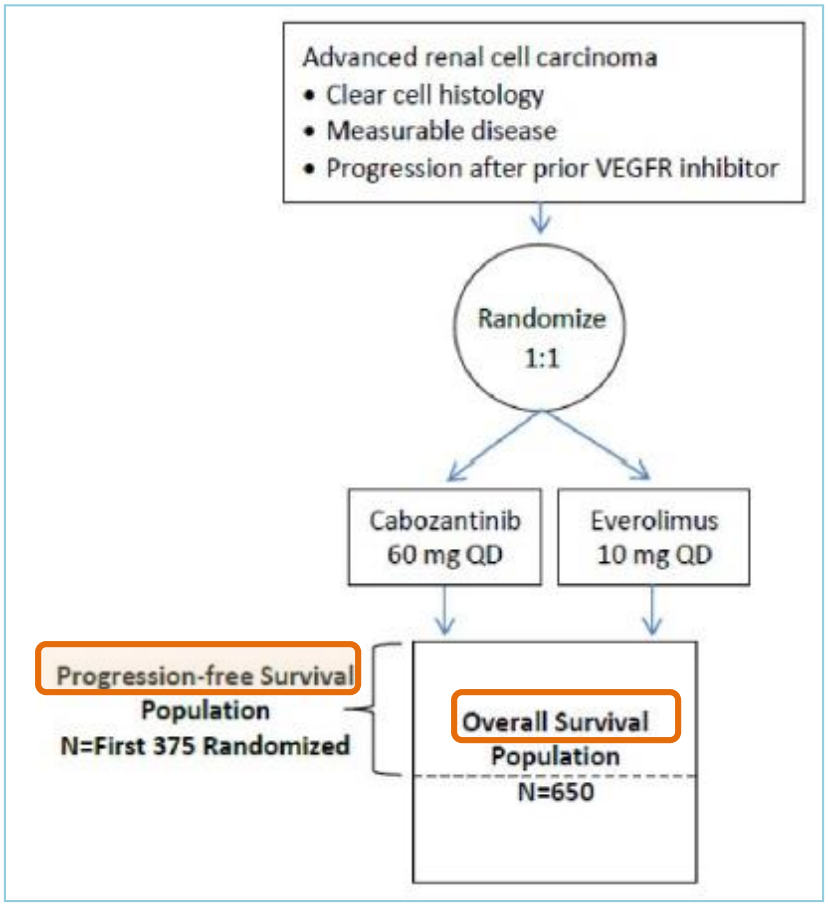
- Primary End-point: PFS
  Non-inferiority of Eve + Sun

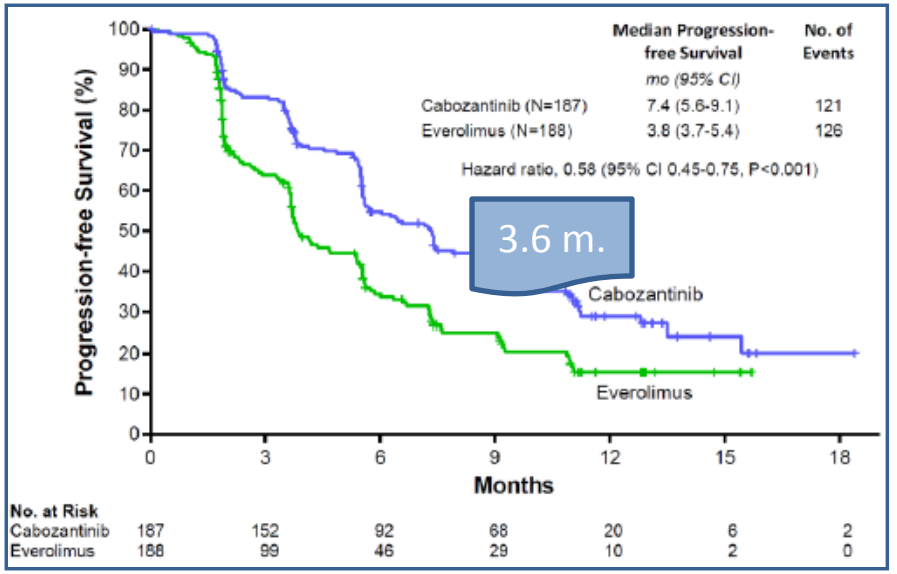


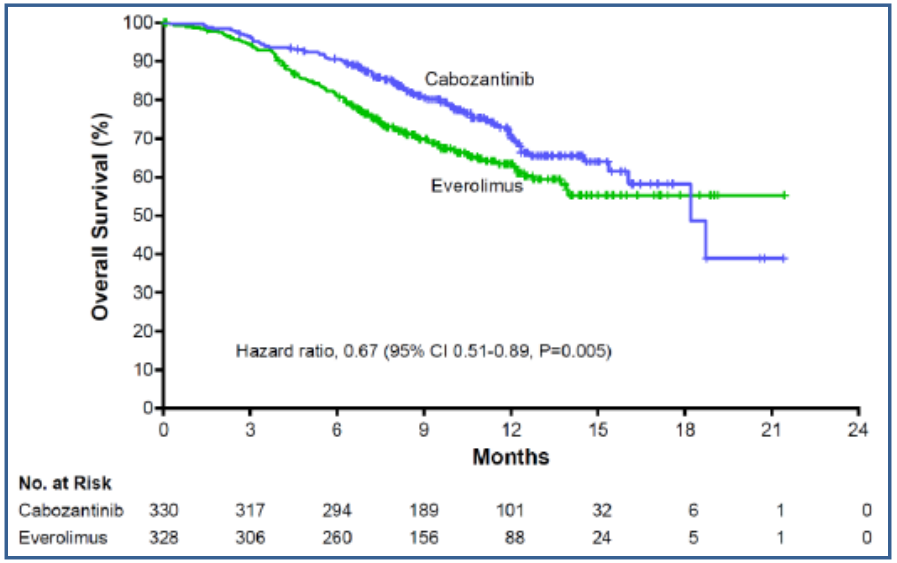
Conclusion
Everolimus did not demonstrate noninferiority compared with sunitinib as a first-line therapy. The trial results support the standard treatment paradigm of first-line sunitinib followed by everolimus at progression.

Motzer RJ et al, J Clin Oncol 2014;32:2765

Cabozantinib versus everolimus in advanced renal cell carcinoma

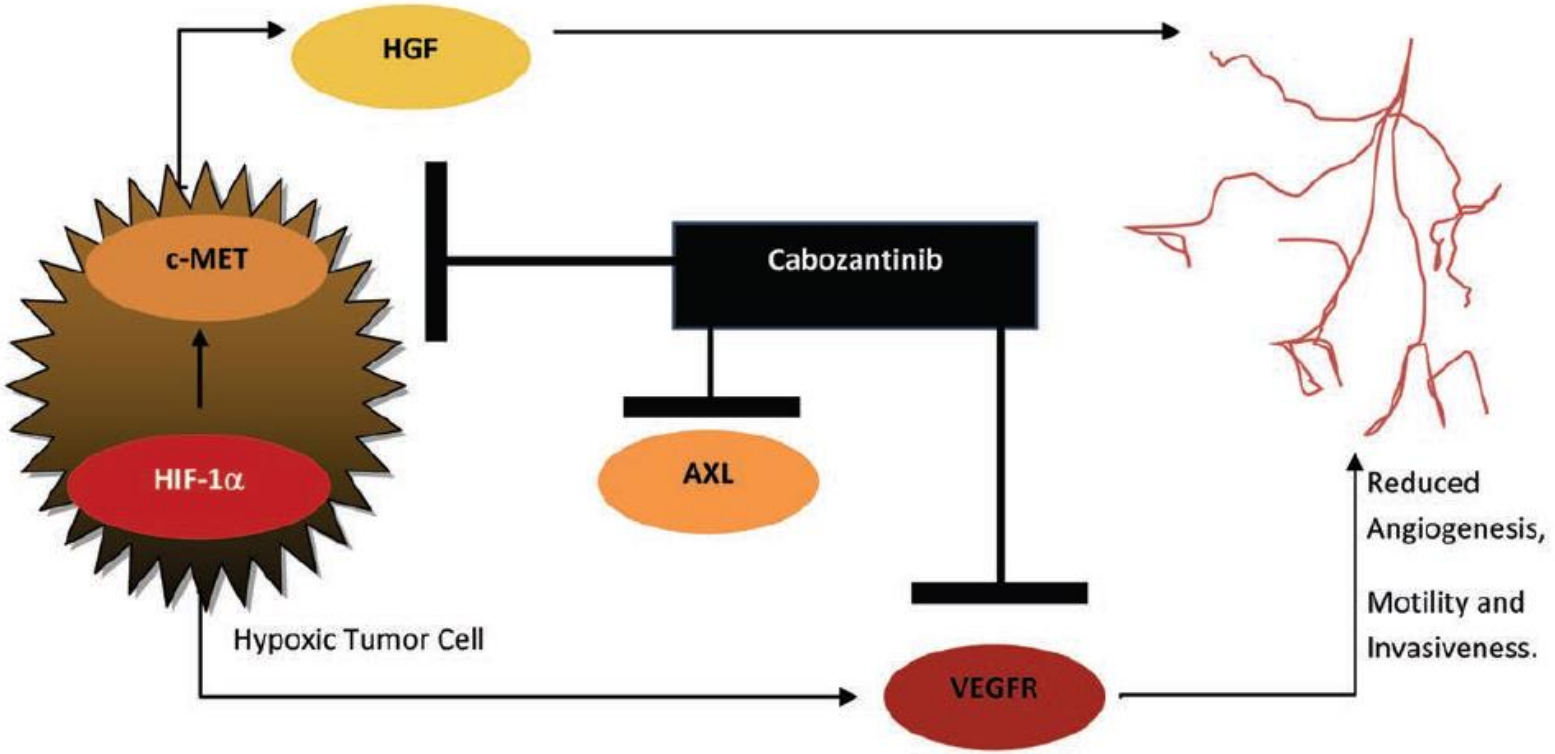






Choueiri T et al, N Engl J Med 2015;373:1814

Μηχανισμός δράσης



Stukalin I et al, Oncol Rev 2016:10:295

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

Study design and endpoints

Randomized, open-labeled phase III study to compare nivolumab with everolimus in patients with advanced RCC after prior systemic therapy (NCT01668784)

Enrolled patients
- Previously treated advanced or metastatic clear-cell RCC
- 1 or 2 prior anti-angiogenic treatments

Randomize 1:1

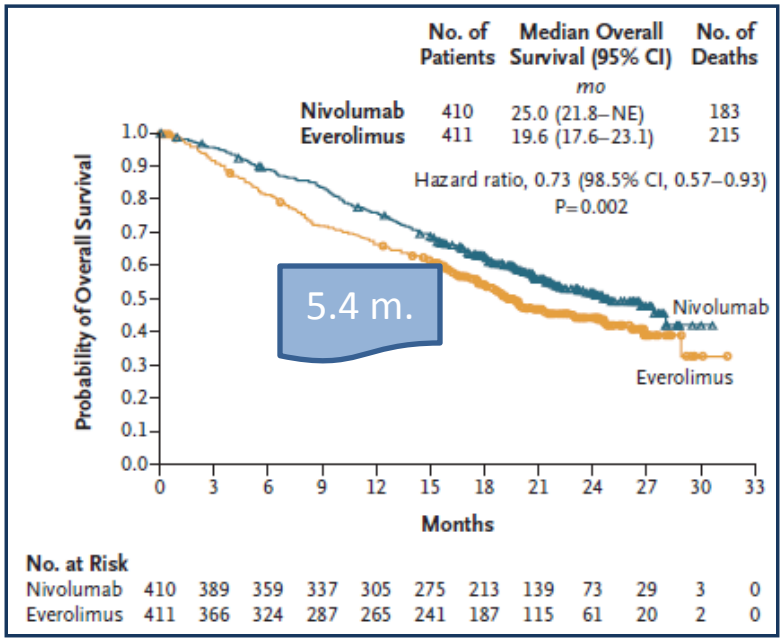
Nivolumab (N = 410) 3 mg/kg every 2 weeks intravenous

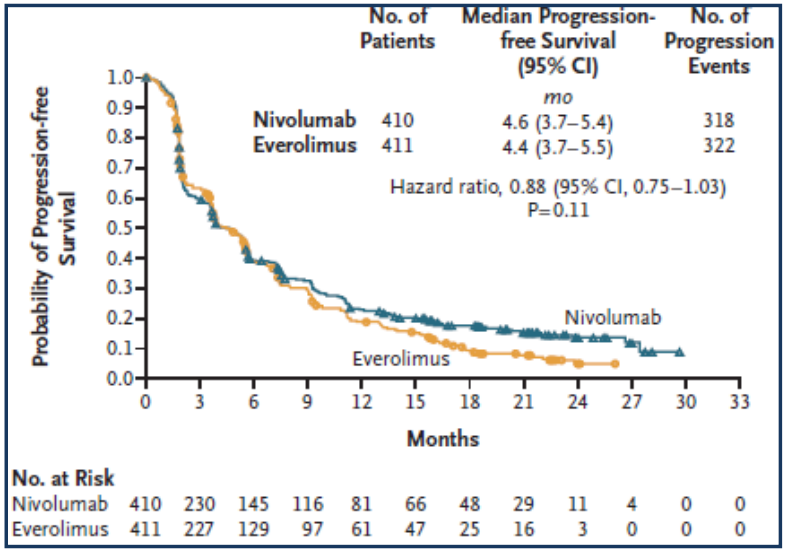
Everolimus (N = 411) 10 mg/day oral

- Treat until progression or intolerable toxicity
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

Disease assessments
- Every 8 weeks from randomization through 12 months
- Then every 12 weeks until progression or treatment discontinuation

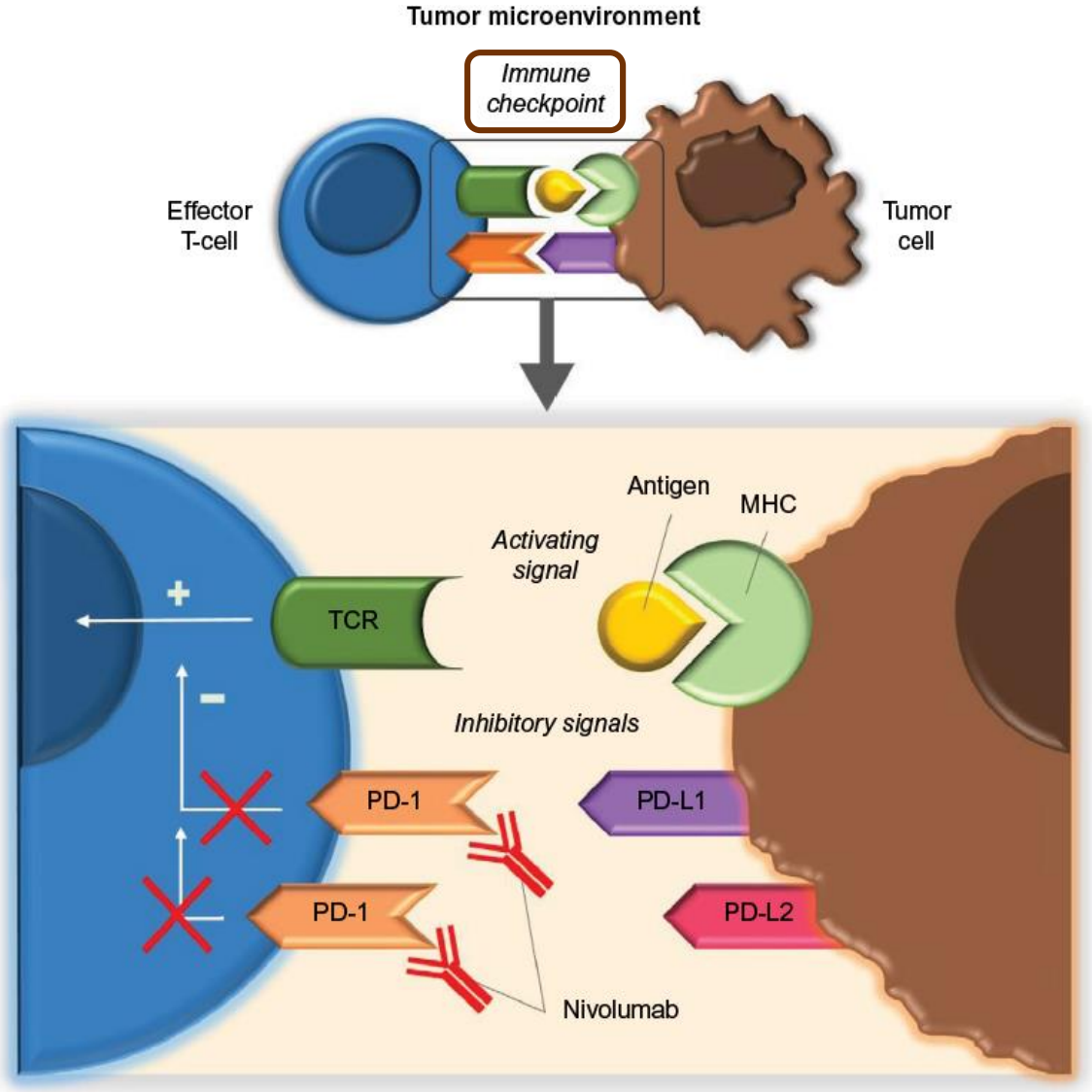
Primary endpoint
- Overall survival (OS)





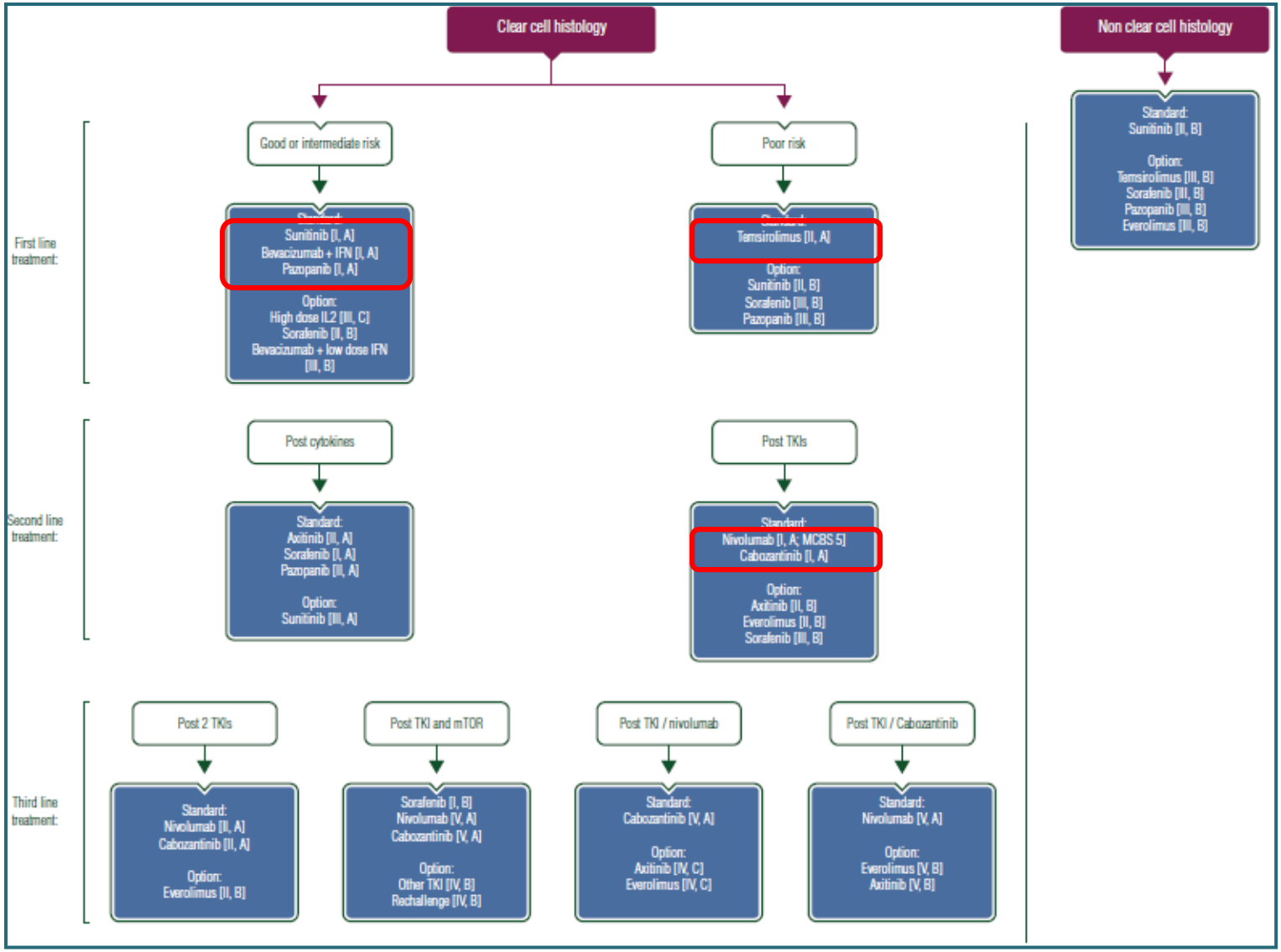
Motzer RJ et al, N Engl J Med 2015;373:1803

Μηχανισμός δράσης Nivolumab



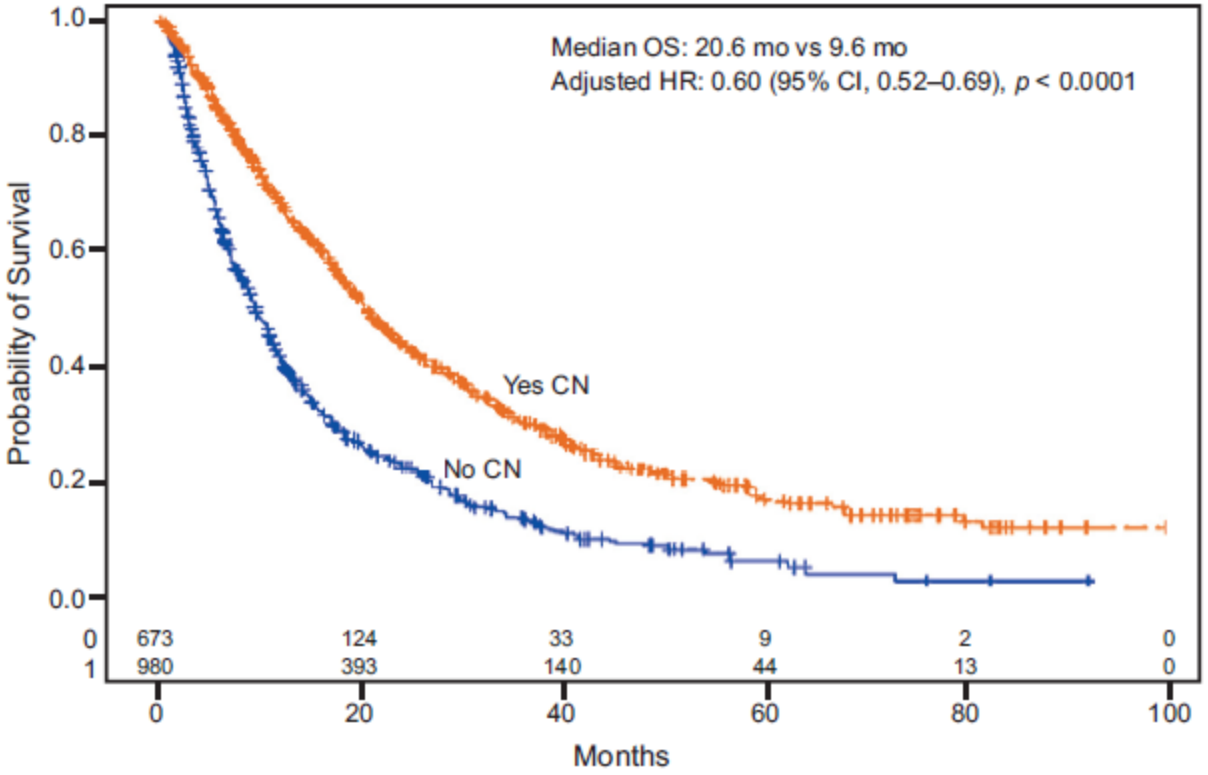
Zago G et al, Biologics 2016;10:103

Sequencing



Escudier B et al, Ann Oncol 2016;27(Suppl 5):v58

Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium



- Η CN φαίνεται ότι προσφέρει στην επιβίωση
- Όχι σε:
  - ≥ 4 IMDC
  - Survival < 12 m.

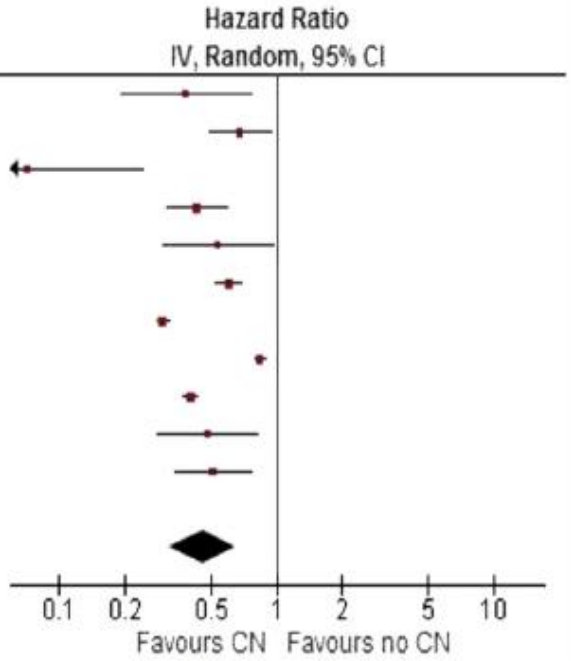
Heng DY et al, Eur Urol 2014;66:704

Ογκομειωτική νεφρεκτομή (CN)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Warren 2009	-0.9676	0.3537	7.5%	0.38 [0.19, 0.76]	2009
Choueiri 2011	-0.3857	0.1672	9.8%	0.68 [0.49, 0.94]	2011
Stroup 2013	-2.6451	0.6215	4.6%	0.07 [0.02, 0.24]	2013
Aizer 2013	-0.844	0.1669	9.8%	0.43 [0.31, 0.60]	2013
Bamias 2014	-0.6162	0.2999	8.2%	0.54 [0.30, 0.97]	2014
Heng 2014	-0.5108	0.073	10.5%	0.60 [0.52, 0.69]	2014
Vaishampayan 2014	-1.204	0.0352	10.7%	0.30 [0.28, 0.32]	2014
Conti 2014	-0.1744	0.0249	10.7%	0.84 [0.80, 0.88]	2014
Abern 2014	-0.9163	0.0398	10.6%	0.40 [0.37, 0.43]	2014
Tatsugami 2015	-0.734	0.275	8.5%	0.48 [0.28, 0.82]	2015
Mathieu 2015	-0.6733	0.2069	9.3%	0.51 [0.34, 0.77]	2015
Total (95% CI)			100.0%	0.46 [0.32, 0.64]	

Heterogeneity: Tau² = 0.29; Chi² = 667.29, df = 10 (P < 0.00001); I² = 99%

Test for overall effect: Z = 4.47 (P < 0.00001)



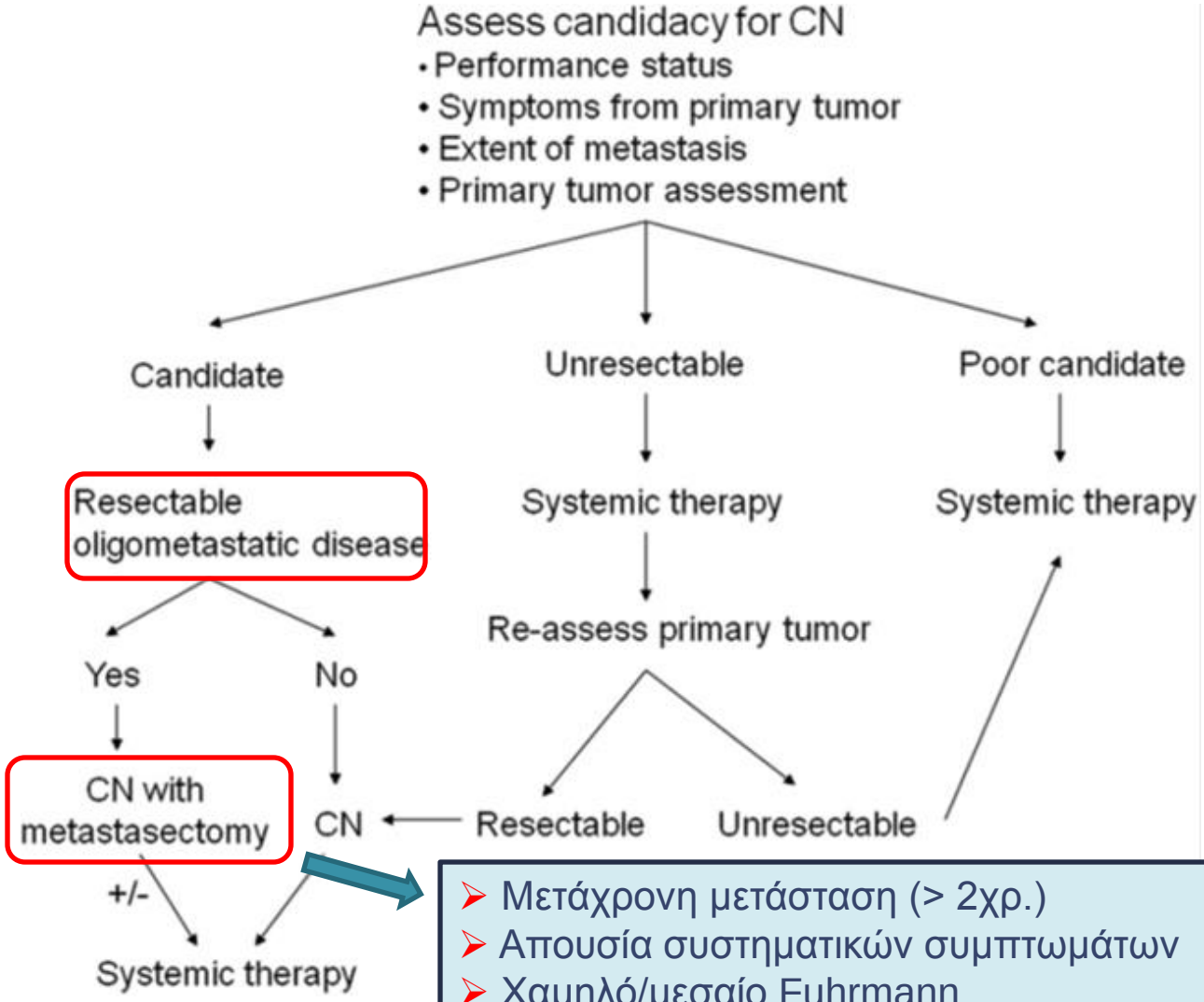
- Η CN φαίνεται ότι προσφέρει στην επιβίωση
- Απαιτούνται κι άλλες μελέτες

- Risk of overall mortality

- Καλό PS
- Ευμεγέθης/συμπτωματική 1παθής εστία
- Μικρό μεταστατικό φορτίο

Petrelli F et al, Clin Genitourin Cancer 2016;14:465

Ο ρόλος της μεταστασεκτομής



- Μετάχρονη μετάσταση (> 2χρ.)
- Απουσία συστηματικών συμπτωμάτων
- Χαμηλό/μεσαίο Fuhrmann

Pattard JJ et al, Eur Urol 2011;60:684


THANK YOU FOR
YOUR ATTENTION!
ANY QUESTIONS?
NO? GREAT!
BYE.