

Αλγόριθμος αντιμετώπισης καρκίνου νεφρού

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ΓΝΑ ΑΛΕΞΑΝΔΡΑ



Αιχμές στην Παθολογία

01-02 ΑΠΡΙΛΙΟΥ 2016

Ενοδοχείο **Crowne Plaza** ΑΘΗΝΑ

Δηλώνω ότι έχω δεν έχω

(προσωπικά ή ως μέλος εργασιακής/ερευνητικής ομάδας) ή μέλος της οικογένειάς μου οποιοδήποτε οικονομικό ή άλλου είδους όφελος* από τις εταιρείες/επιχειρήσεις που διοργανώνουν /χρηματοδοτούν την άνω εκδήλωση κατά τη διάρκεια των τελευταίων 4 ετών.

<u>Περιγραφή οφέλους</u>	<u>Έτος Διακοπής οφέλους</u>
έρευνας	2016
συμβουλευτική	2016
εκπαιδευτική	2015

Χορηγοί: ABBVIE, AMGEN, ASTELLAS, ASTRazeneca, BAYER, BOEHRINGER INGELHEIM, DEMO, ENOPAZIS, GENESIS PHARMA, GILEAD, JANSSEN, LEO, LILLY, MAVROGENIS COLOPLAST, MENARINI, MERCK, MSD, NOVARTIS, PFIZER, ROCHE, SANOFI GENZYME

Ως οικονομικό ή άλλου είδους όφελος ορίζεται :

- ✓ Οποιαδήποτε πληρωμή για την πραγματοποίηση εργασίας ή έρευνας ή εκπαίδευσης κατά τη διάρκεια των τελευταίων 4 ετών από την επιχείρηση / όμιλο επιχειρήσεων που χρηματοδοτεί τη συγκεκριμένη εκδήλωση, καθώς και
- ✓ Οποιαδήποτε υπαλληλική, συμβουλευτική ή διευθυντική ή άλλη θέση τα τελευταία 4 χρόνια ή είναι τώρα υπό διαπραγμάτευση – επί πληρωμή ή όχι – στην επιχείρηση / όμιλο επιχειρήσεων που χρηματοδοτεί την συγκεκριμένη εκδήλωση.

Αντιμετώπιση καρκίνου νεφρού

Τοπική νόσος

- ▶ T1-4N0M0

Μεταστατική νόσος

- ▶ N+
- ▶ M1



ΤΟΠΙΚΗ ΝΟΣΟΣ

Αντιμετώπισης μάζας νεφρού

- ▶ Κλινικό στάδιο T1
 - ▶ Surveillance
 - ▶ Non surgical procedures
 - ▶ RFA
 - ▶ Cryoablation
- ▶ Surgical procedures
 - ▶ Partial nephrectomy
 - ▶ Open
 - ▶ Laparoscopic
 - ▶ Traditional
 - ▶ Robotic

Αντιμετώπισης μάζας νεφρού

- ▶ Κλινικό στάδιο T2
 - ▶ Radical nephrectomy
 - ▶ Partial nephrectomy
- ▶ Κλινικό στάδιο T3-4
 - ▶ Radical nephrectomy
 - ▶ Removal of thrombus
- ▶ No routine LND
- ▶ No adrenalectomy
- ▶ No adjuvant
- ▶ Neoadjuvant-Downsizing

Θεραπεία των ασθενών με μεταστατικό καρκίνο νεφρού

- ▶ Χειρουργική αντιμετώπιση?
- ▶ Συστηματική Θεραπεία?

Watchful waiting

- ▶ Slow progression
- ▶ Selection criteria undefined

CN-Prognostic features

	Nephrectomy				No-nephrectomy				p
	n	G	I	P	n	G	I	P	
Choueiri	201	12%	58%	30%	113	1%	37%	62%	
Bamias	186	24%	56%	20%	36	9%	48%	43%	0.027
Heng	935	9%	63%	28%	676	1%	45%	54%	<0.0001

CN-Αποτελέσματα

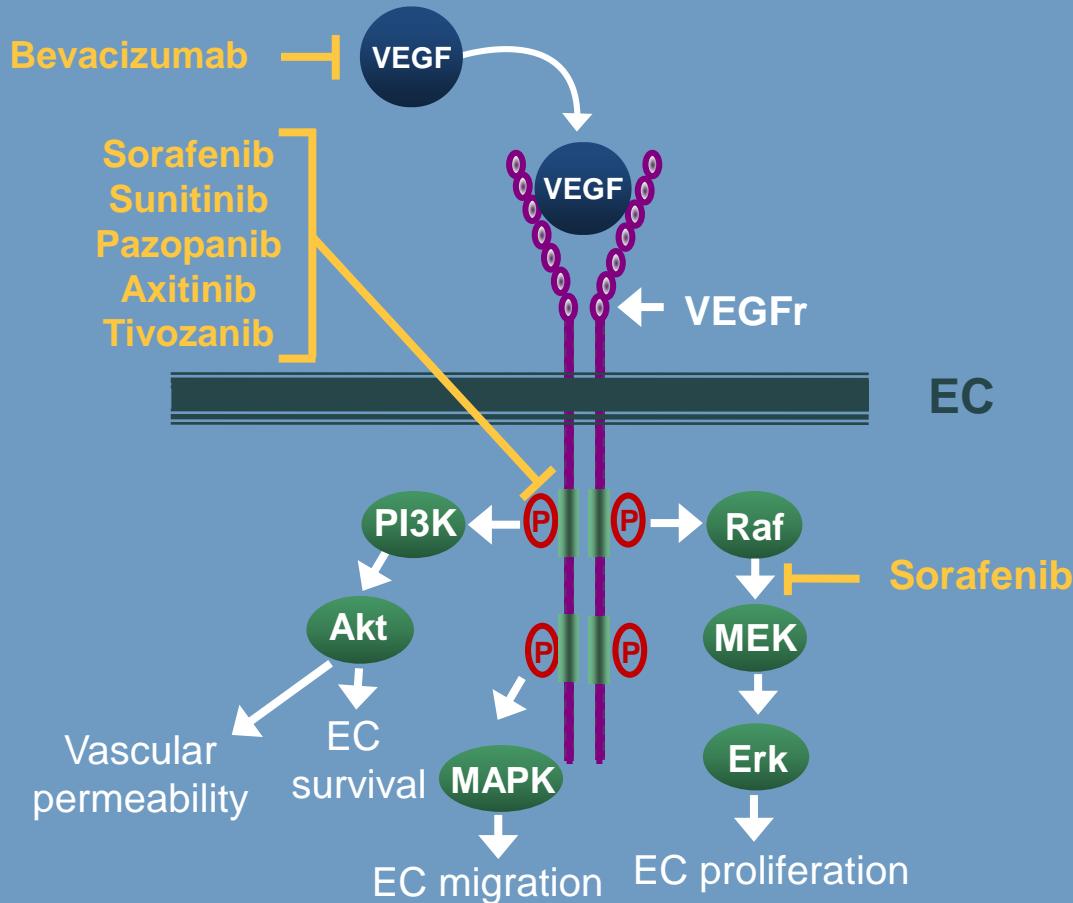
Μεταστασεκτομή

- ▶ Αρχική Θεραπεία
- ▶ Για επίτευξη ΠΥ
- ▶ Σε διαφορετική ανταπόκριση
- ▶ Πρέπει να επιδιώκεται
- ▶ Καλύτερη η χειρουργική έναντι της ΑΚΘ
- ▶ Απουσία κριτηρίων επιλογής
- ▶ 'Όχι pseudo-adjuvant

Επιλογή Θεραπείας 1ης γραμμής

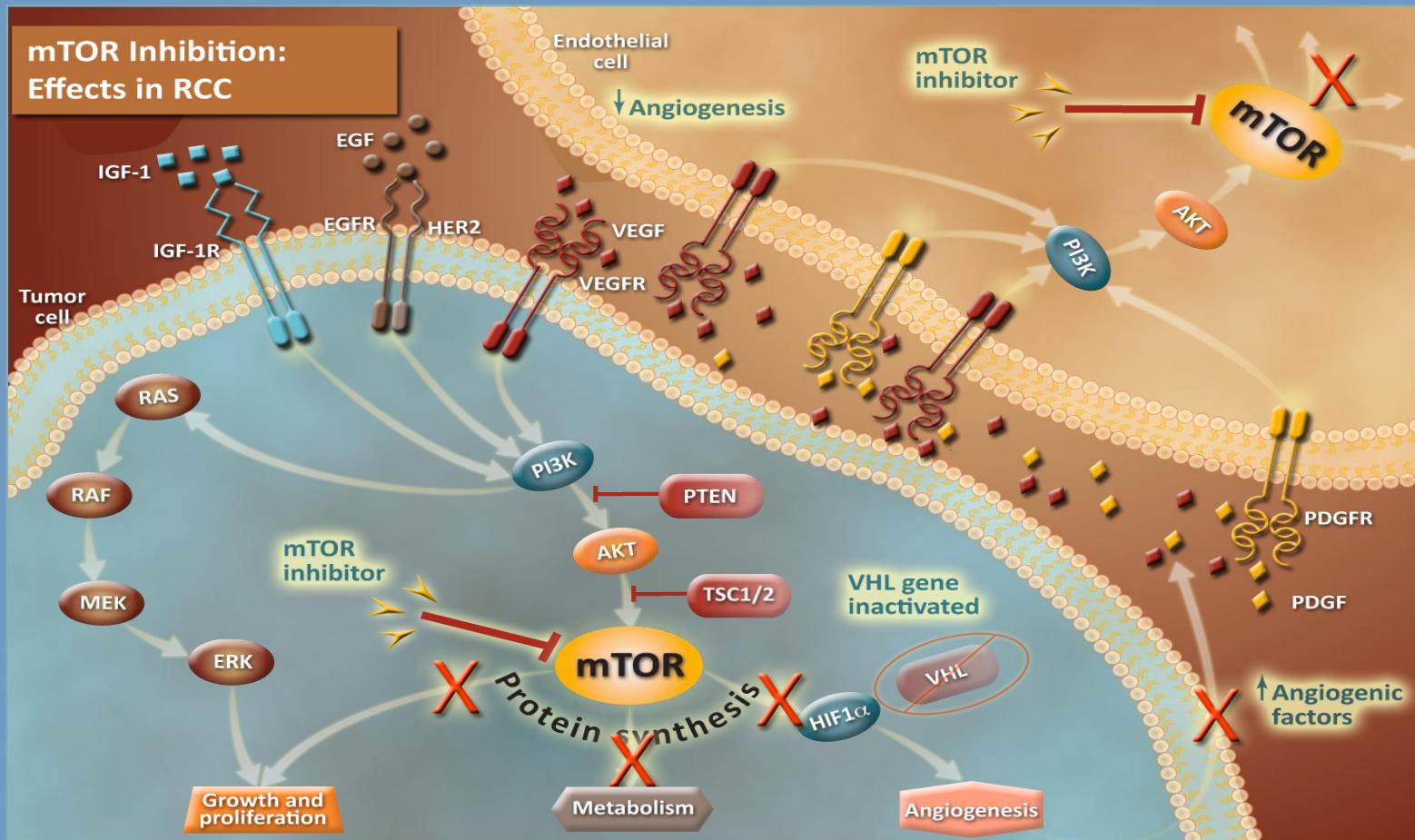


VEGF Signaling Pathway Inhibitors: Approved and Investigational Agents



EC, endothelial cell; Erk, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein/extracellular signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B

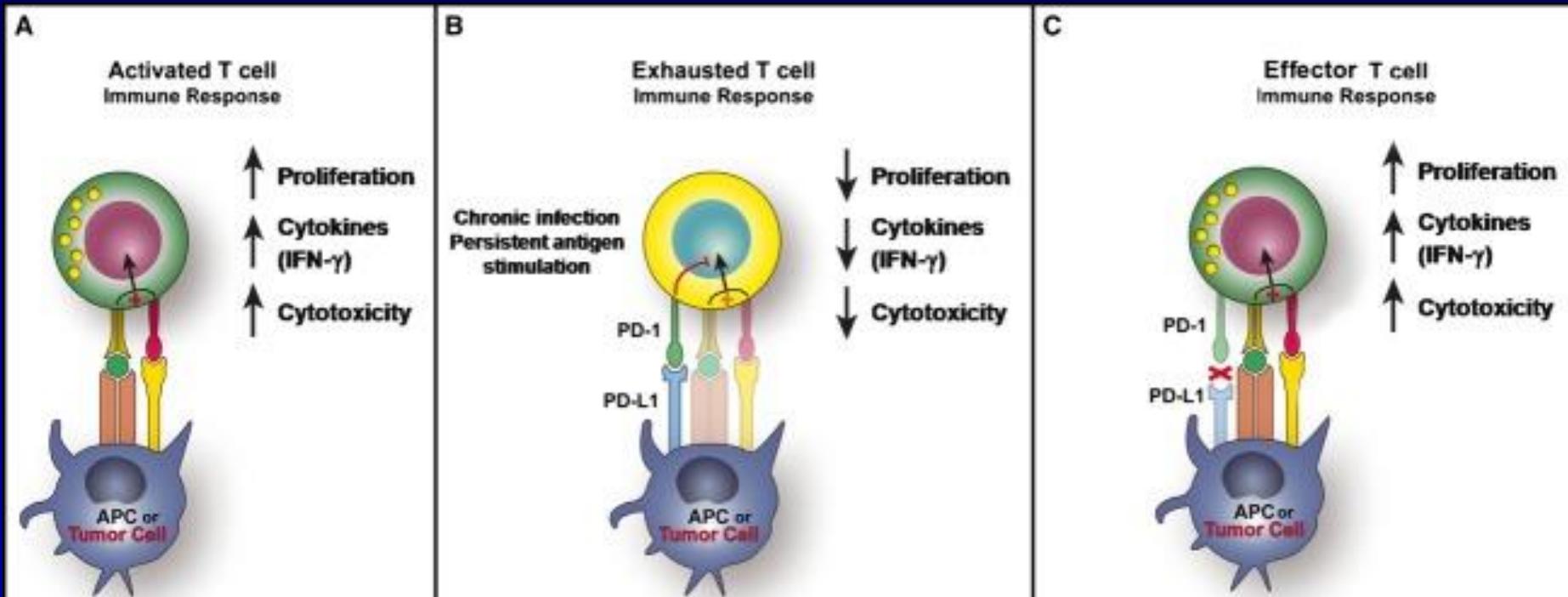
mTOR Signaling Pathway Inhibition



EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HIF-1 α , hypoxia-inducible factor 1 α ; IGF-1R, insulin-like growth factor receptor; PDGFR, platelet-derived growth factor receptor; PTEN, phosphatase and tensin homolog; TSC1/2, tuberous sclerosis type 1/2; VHL, Von Hippel-Lindau



Πρόσφατες εξελίξεις ΑΝΟΣΟΕΠΙΤΗΡΗΣΗ ΤΟΥ ΟΓΚΟΥ



CD80,
CD86

CD28

MHC

Peptide
Antigen

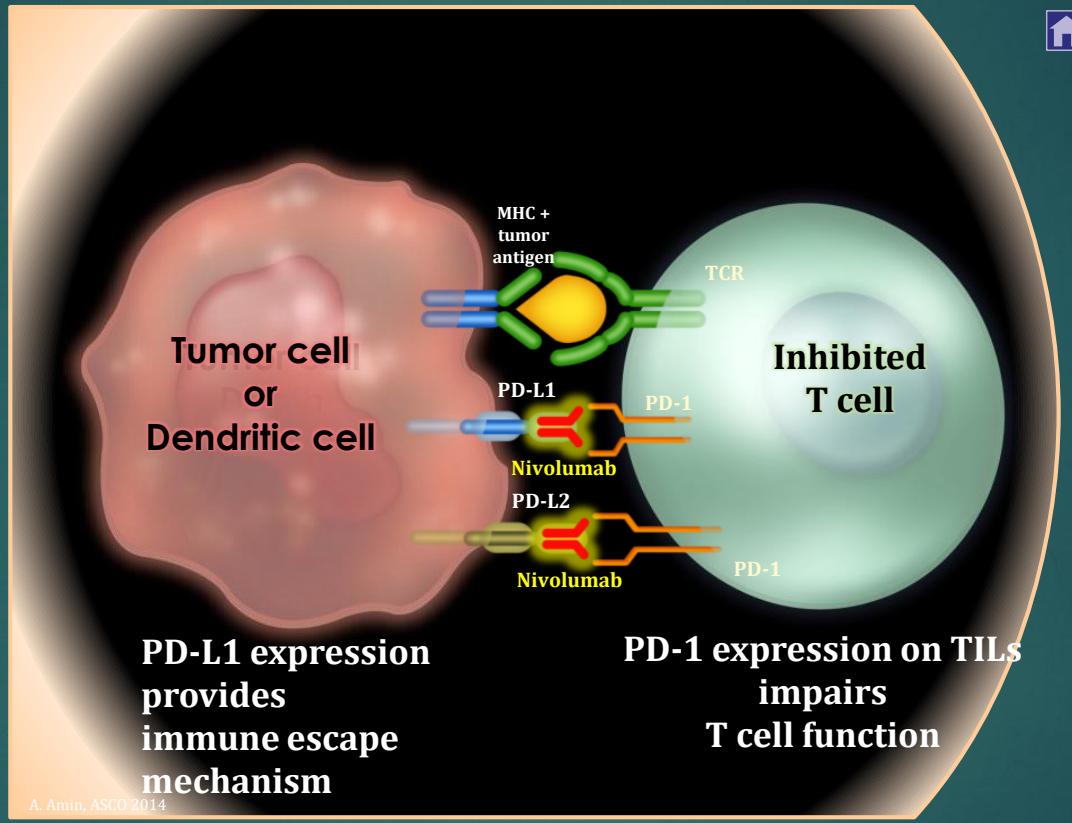
TCR

PD-L1

PD-1

Blocking
Antibody

Immunosuppressive tumor microenvironment



PD-1, programmed death-1; PD-L1, programmed death ligand-1.
Gabrilovich D, et al. *Nat Med.* 1996;2:1096-103; Gabrilovich D, et al. *Nat Rev Immunol.* 2009;9:162-74; Bronte V, et al. *J Immunother.* 2001;24:431-46; Finke JH, et al. *Clin Cancer Res.* 2008;14:6674-82; Ko JS, et al. *Clin Cancer Res.* 2009;15:2148-57; Thompson RH, et al. *Clin Cancer Res.* 2007;13:1757-61; Thompson RH, et al. *Proc Natl Acad Sci U S A.* 2004;101:17174-9.

RECORD-3: PFS results

- Non-inferiority of PFS for 1st line everolimus compared with sunitinib was not achieved in this randomized phase II trial of mRCC patients

RECORD-3	Everolimus 1 st line (n=238)	Sunitinib 1 st line (n=233)
Median PFS (95% CI)	7.9 months (5.6-8.2)	10.7 months (8.2-11.5)
HR (95%CI)		1.43 (1.15-1.77)

RECORD-3	EVE→SUN	SUN→EVE
Median OS (95% CI)	22.4 months (17.9-NA)	32.0 months (20.5-NA)
HR (95%CI)		1.24 (0.94-1.64)

Table 1. Vancouver RCC classification

Clear-cell renal cell carcinoma

Multi-locular clear-cell renal cell neoplasm of low malignant potential

Papillary renal cell carcinoma

Number of risk factors	Risk group	Median overall survival (OS), months	2-year OS (%)
0	Favourable	43	75
1–2	Intermediate	27	53
3–6	Poor	8.8	7

Reprinted from the American Journal of Surgical Pathology [2]. Copyright © 2013, with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health.

Current guidelines

Guidelines	Treatment								
	1 st -line			2 nd -line				3 rd -line	
	CC		NCC	CC		NCC		Any histotype	
	Favourable-Intermediate	Poor	Any risk	Any risk				Any risk	
EAU	Sunitinib (1b,A) Pazopanib (1b,A) BEV+IFN (1b,A)	Temsirolimus (1b,A) Sunitinib (1b,A) Pazopanib (1b,A)	Sunitinib (2a) Temsirolimus (2b) Everolimus (2b)	Sorafenib (1b) Axitinib (2a) Pazopanib (2a)	Axitinib (2a,A) Everolimus (2a,A) Sorafenib (2a)	Any targeted agent	Any targeted agent (4)	Everolimus (2a)	Sorafenib (1b)
ESMO	Sunitinib (1,A) Pazopanib (1,A) BEV+IFN (1,A) Sorafenib (2,B) BEV+LD IFN (3,A) HD IL2 (3,C)	Temsirolimus (2,A) Sunitinib (2,B) Sorafenib (3,B)	Temsirolimus (3,B) Sunitinib (3,B) Sorafenib (3,B)	Sorafenib (1,A) Axitinib (1,A) Pazopanib (2,A) Sunitinib (3,A)	Axitinib (1,B) Everolimus (2,A) Sorafenib (2,A)			Everolimus (2,A)	Sorafenib (1,B) Other TKI (4,B) Rechallenge (4,B)
NCCN	Sunitinib (1) Temsirolimus (2B) BEV + IFN (1) Pazopanib (1) HD IL-2 (2B) Axitinib (2B) Sorafenib (2B) Clinical trial (2B)	Sunitinib (1) Temsirolimus (1) BEV + IFN (1) Pazopanib (1) HD IL-2 (2B) Axitinib (2B) Sorafenib (2B) Clinical trial (2B)	Temsirolimus (2A)* Temsirolimus (1) [#] Sorafenib (2B) Sunitinib (2B) Pazopanib (2B) Axitinib (2B) Everolimus (2B) BEV (2B) Erlotinib (2B) Clinical trial (2B)	Axitinib (1) Sorafenib (1) Sunitinib (1) Pazopanib (1) Temsirolimus (2B) BEV (2B)	Everolimus (1) Axitinib (1) Sorafenib (2B) Sunitinib (2B) Pazopanib (2B) Temsirolimus (2B) BEV (2B) Clinical trial (2B) HD IL-2 (2B)				

mTORI in 1st-line

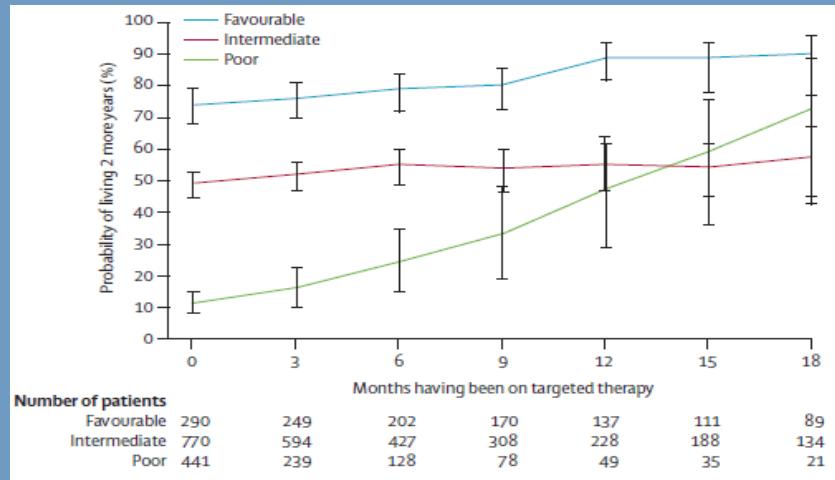
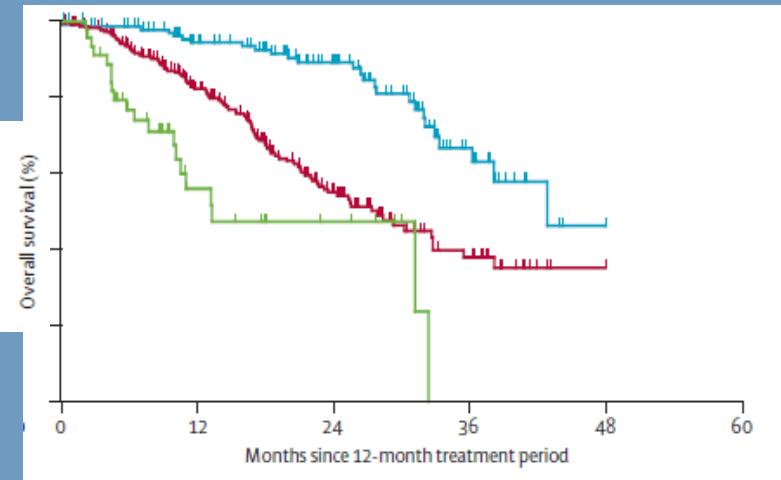
	TEM	EVE
IMDC	2%	<1%
UK	0.8%	6.4%
HGUCG	3.5%	4.4%



Conditional survival of patients with metastatic renal-cell carcinoma treated with VEGF-targeted therapy: a population-based study



Lauren C Harshman, Wanling Xie, Georg A Bjarnason, Jennifer J Knox, Mary MacKenzie, Lori Wood, Sandy Srinivas, Ulka N Vaishampayan, Min-Han Tan, Sun-Young Rha, Frede Donskov, Neeraj Agarwal, Christian Kollmannsberger, Scott North, Brian I Rini, Daniel Y C Heng*, Toni K Choueiri*



ASPEN: Everolimus vs Sunitinib in NCRCC

Stratified by histology (papillary vs chromophobe vs unclassified), MSKCC risk group

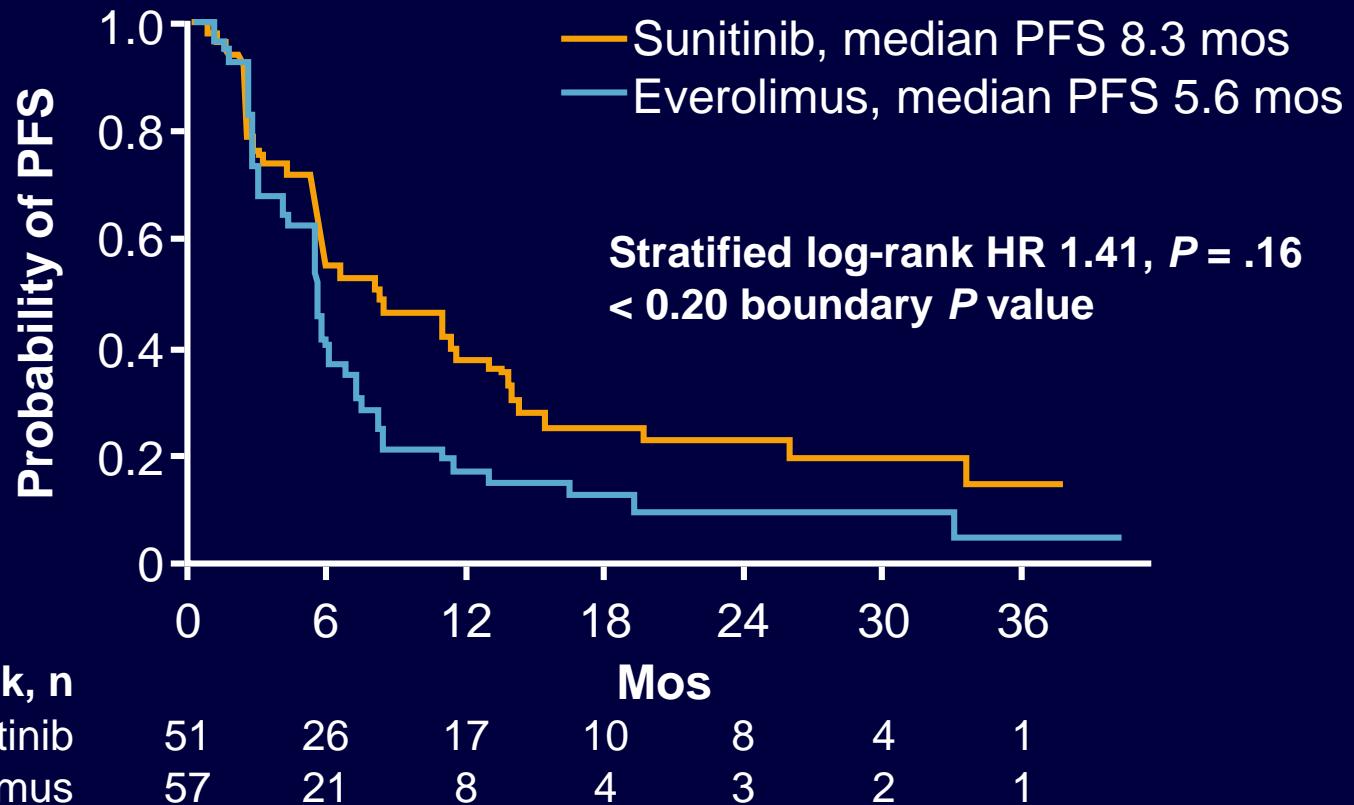
Untreated pts with metastatic NCRCC,
KPS ≥ 60
(N = 108)

Everolimus 10 mg QD
daily in 6-wk cycles
(n = 57)

Sunitinib 50 mg QD
Days 1-28 in 6-wk cycles
(n = 51)

- Primary endpoint: radiographic PFS
- Secondary endpoints: OS; PFS at 6, 12, 24 mos; ORR; CBR; time to metastasis; QoL

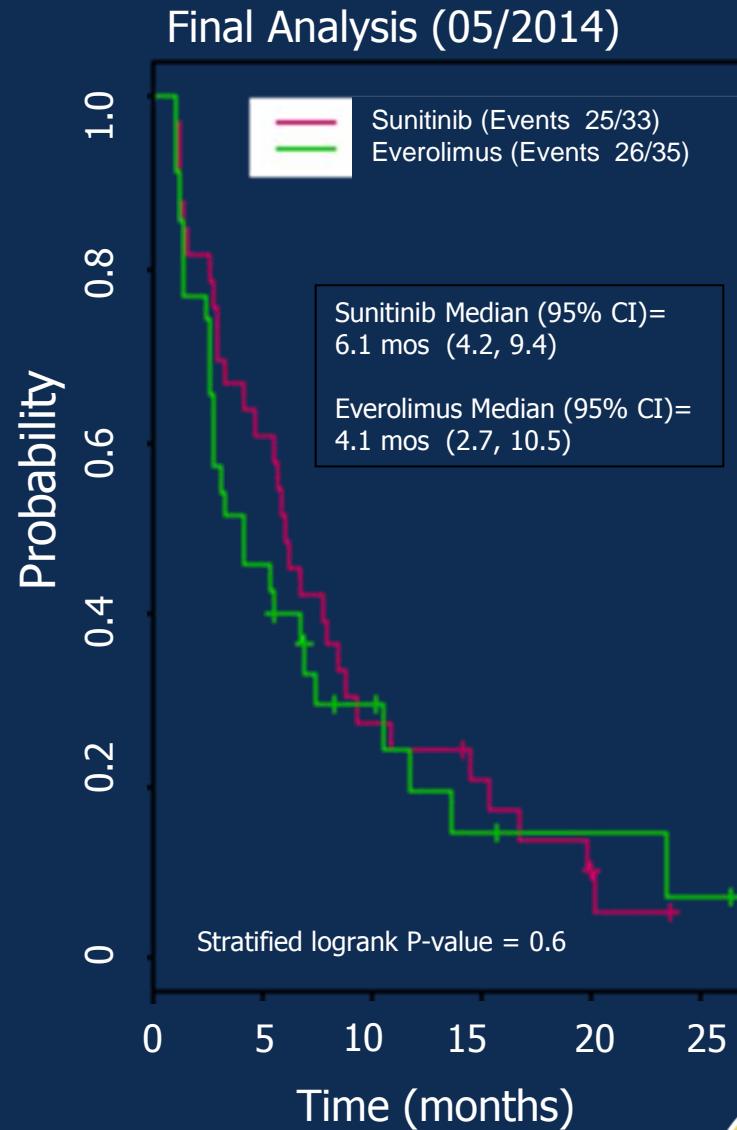
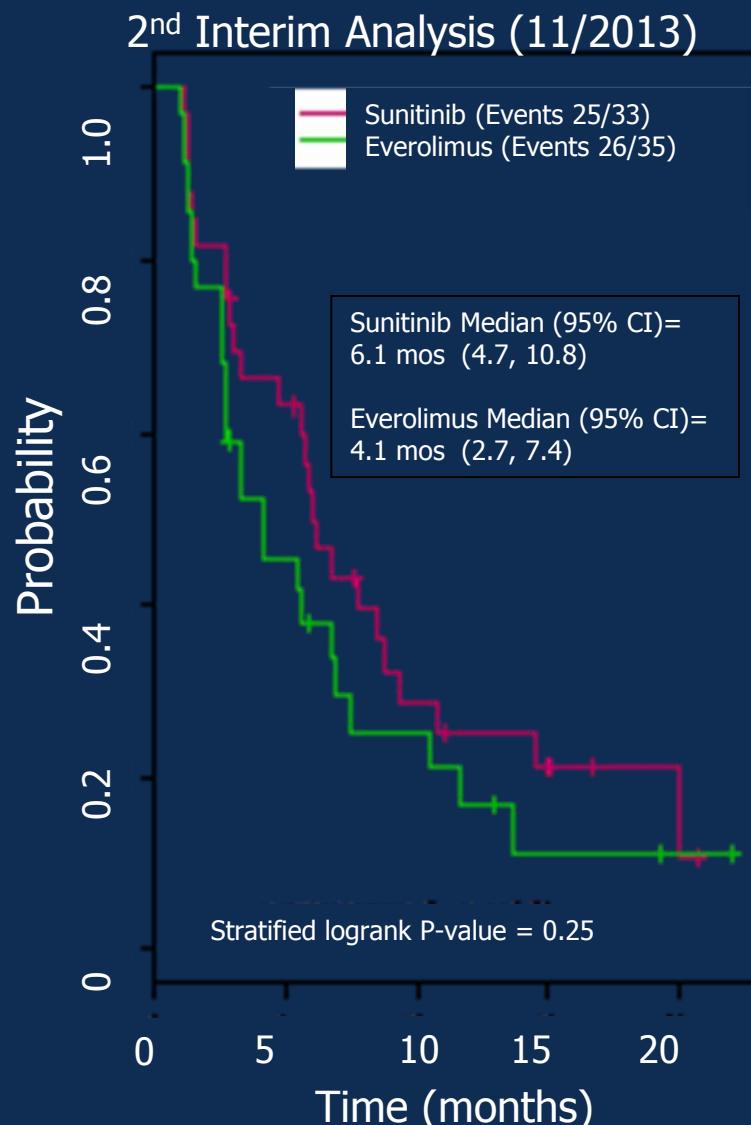
ASPEN: Progression-Free Survival



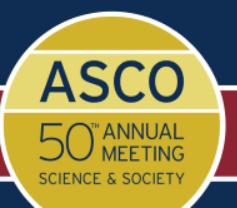
- Median OS: sunitinib vs everolimus: 32 (95% CI: 15-NR) vs 13 mos (95% CI: 10-38) (HR: 1.12; $P = .60$)

Armstrong AJ, et al. ASCO 2015. Abstract 4507. Reprinted with permission.

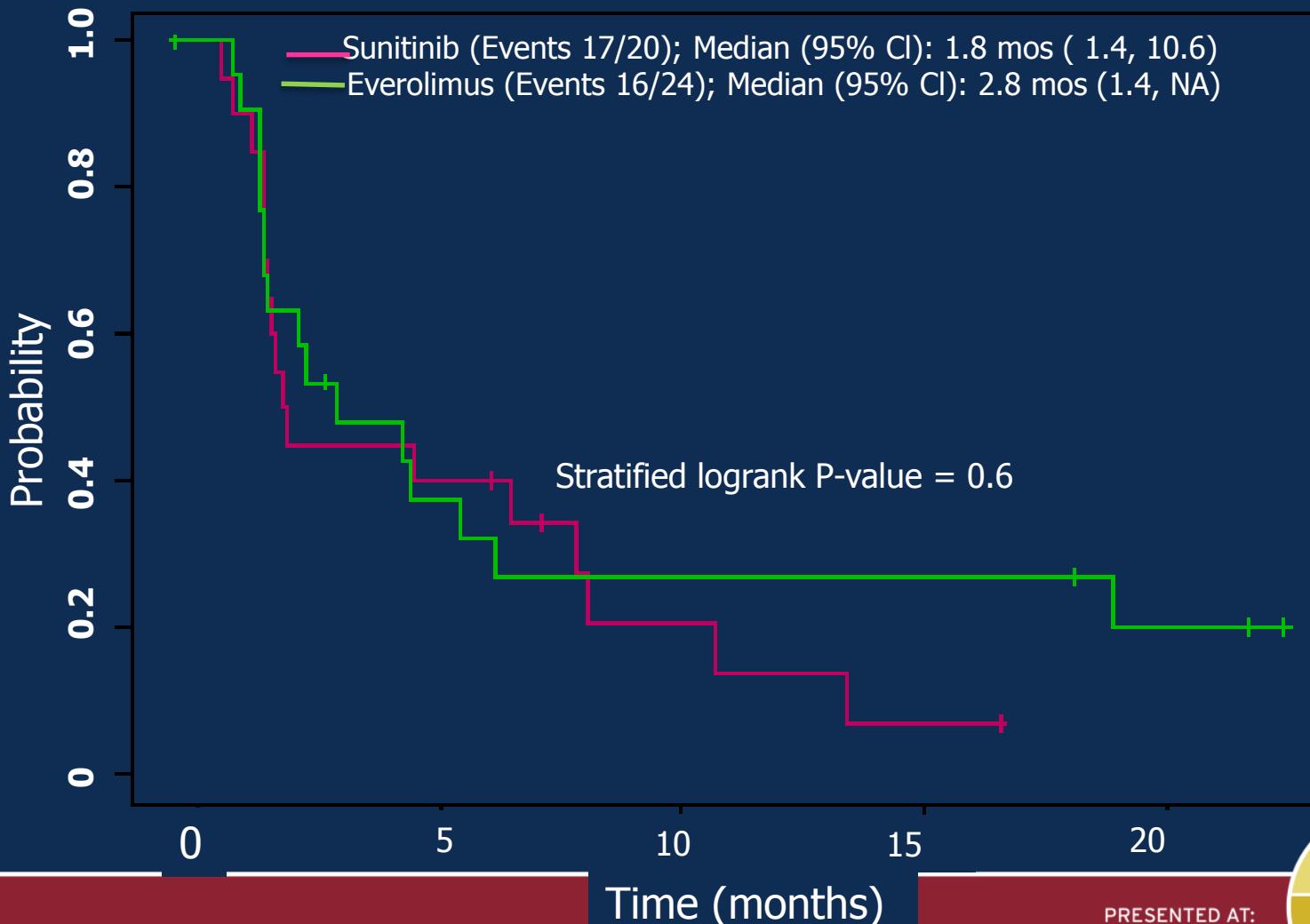
PFS in First-Line



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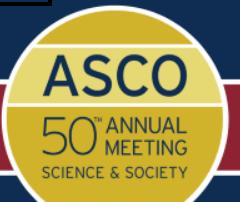


PFS in Second-line



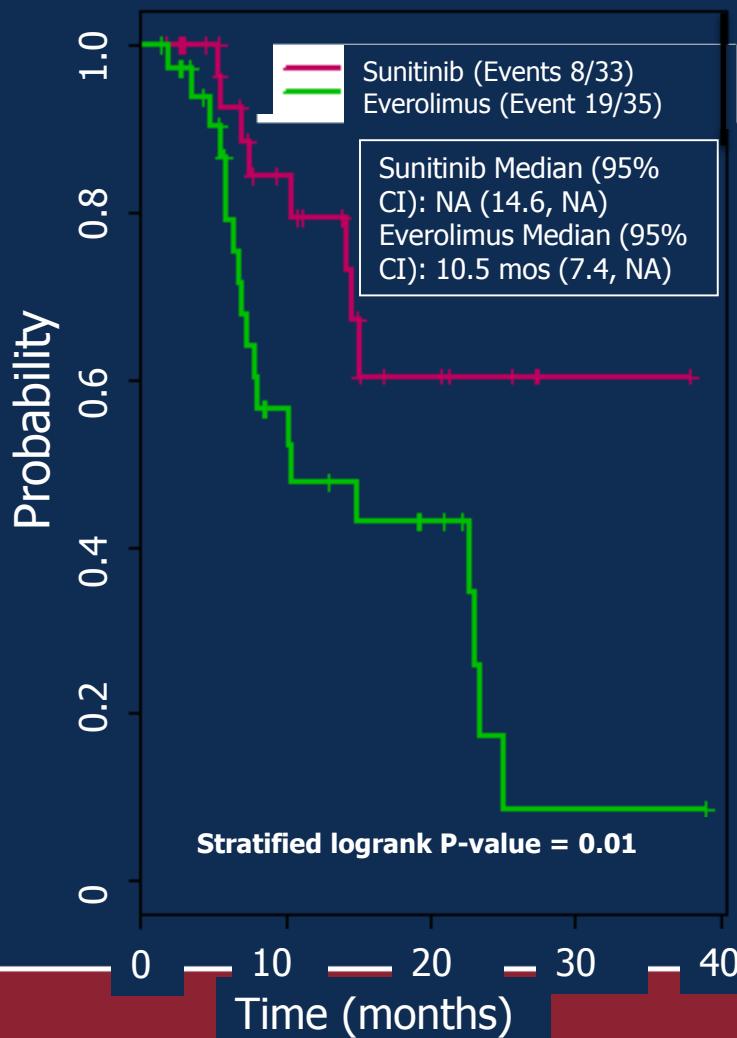
Time (months)

PRESENTED AT:

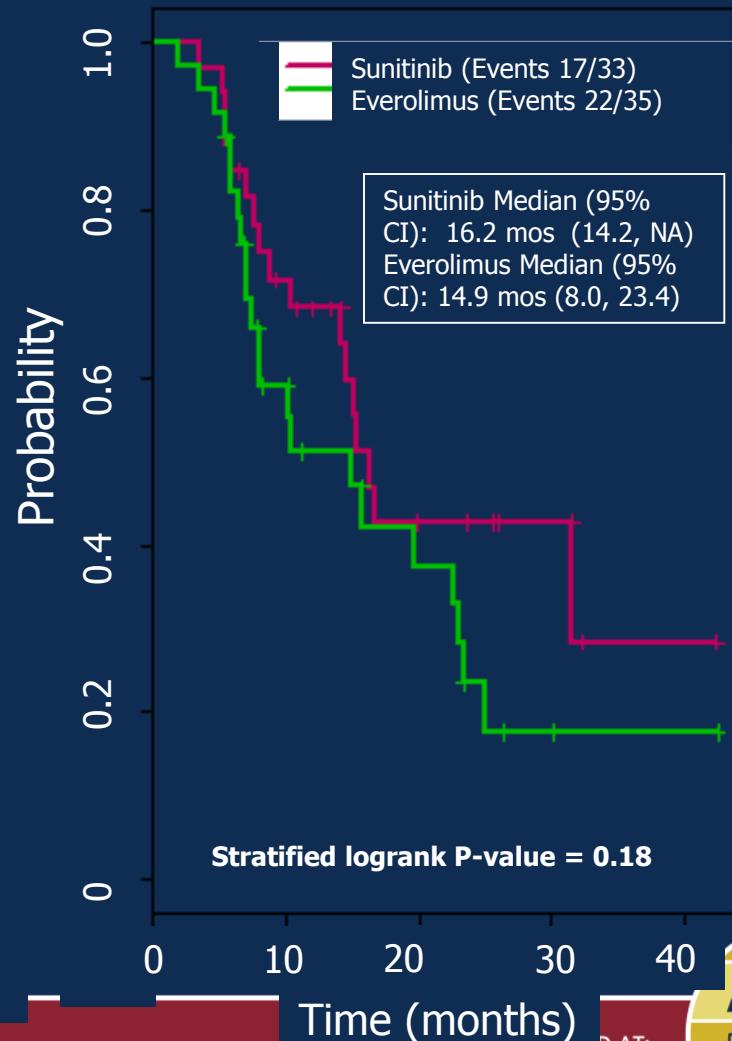


Overall Survival

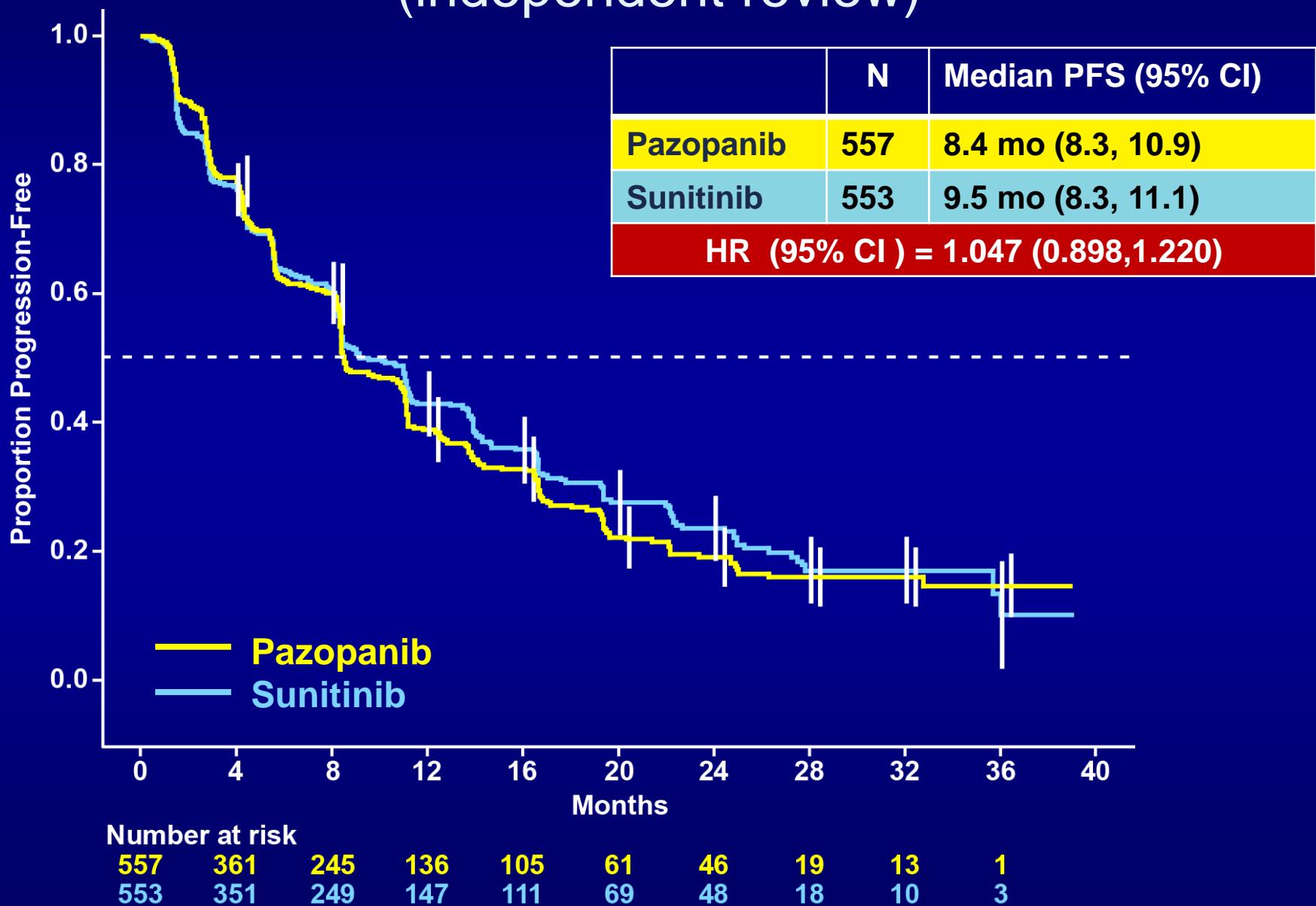
Second Interim Analysis 11/2013



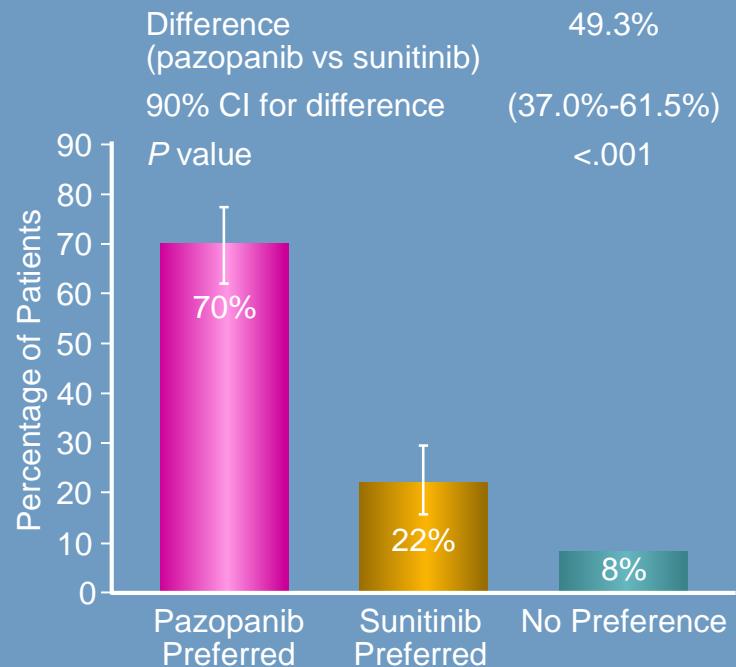
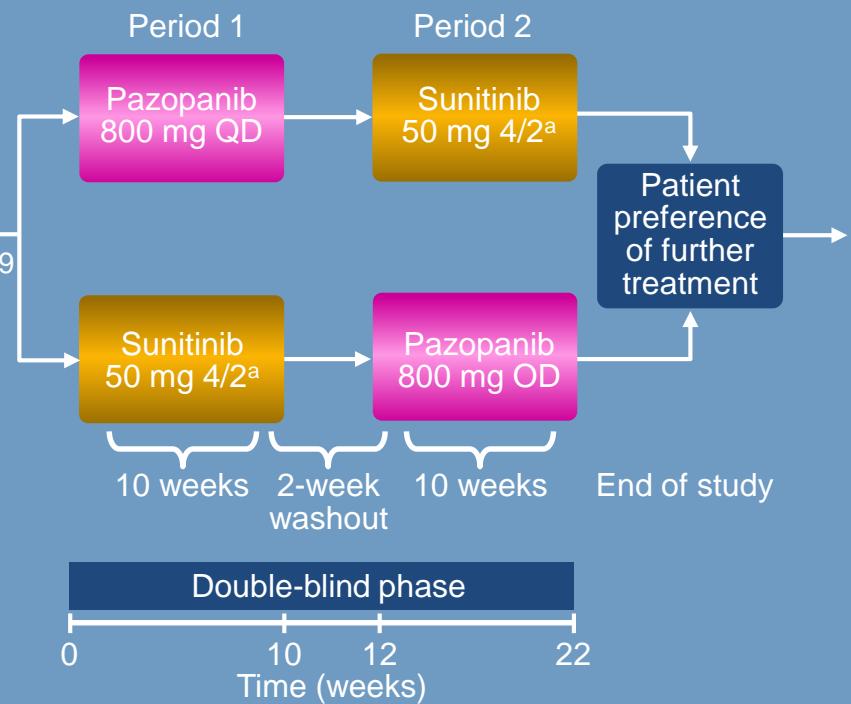
Final Analysis 05/2014



Primary Endpoint: Progression-free Survival (independent review)



PISCES: Patient Preference Between Pazopanib and Sunitinib

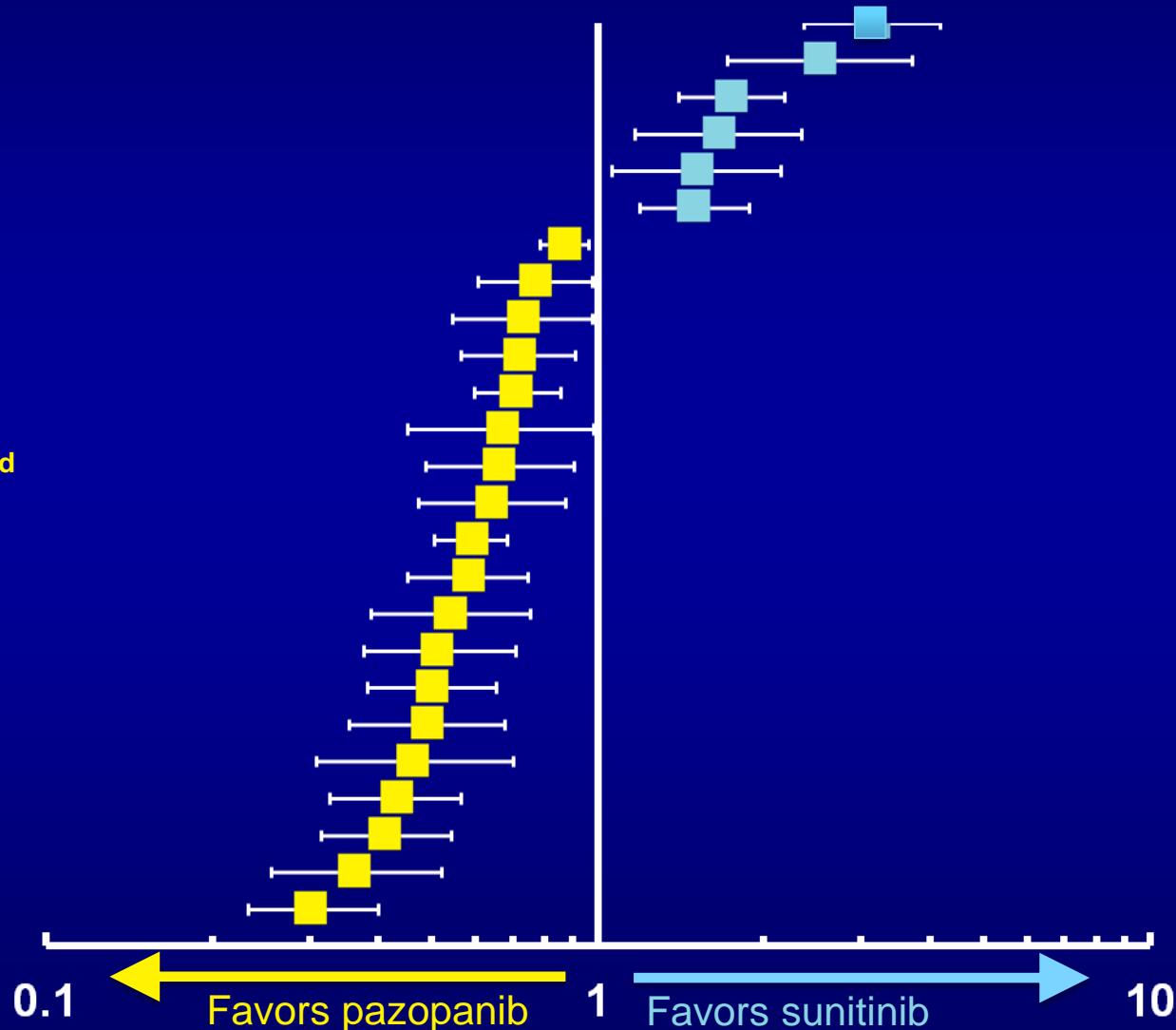


QD, once daily; CI, confidence interval.

Relative Risk in Adverse Events

AE occurrence $\geq 10\%$ in either arm; 95% CI for RR does not cross 1

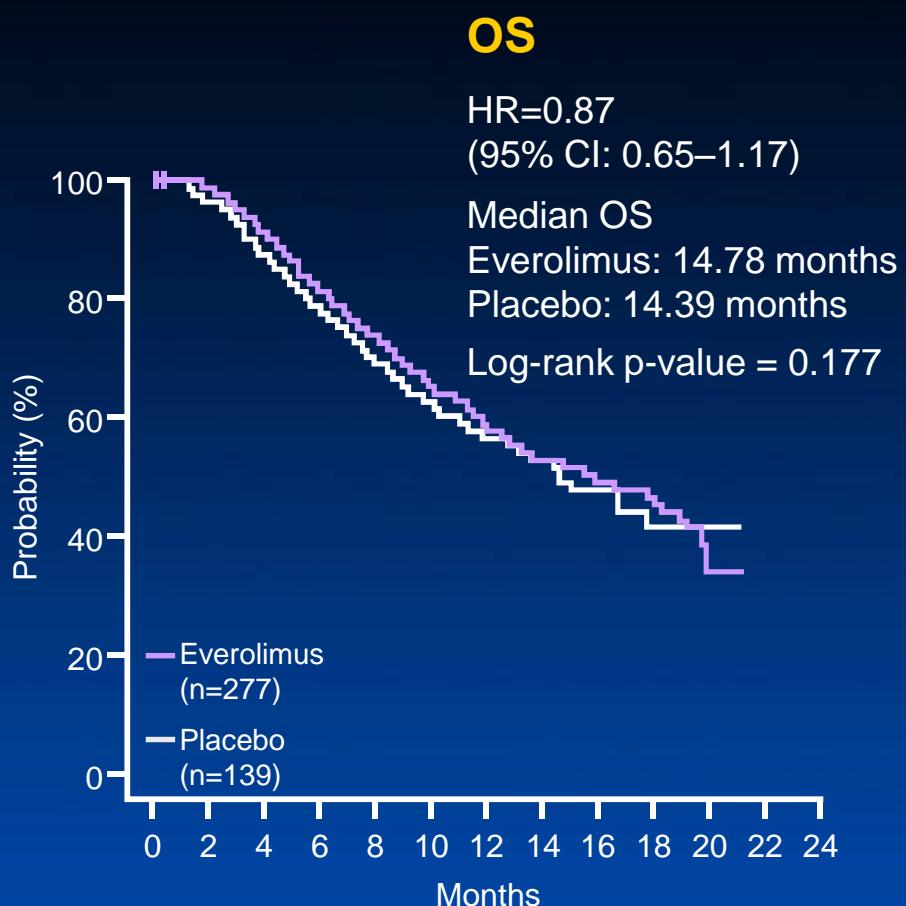
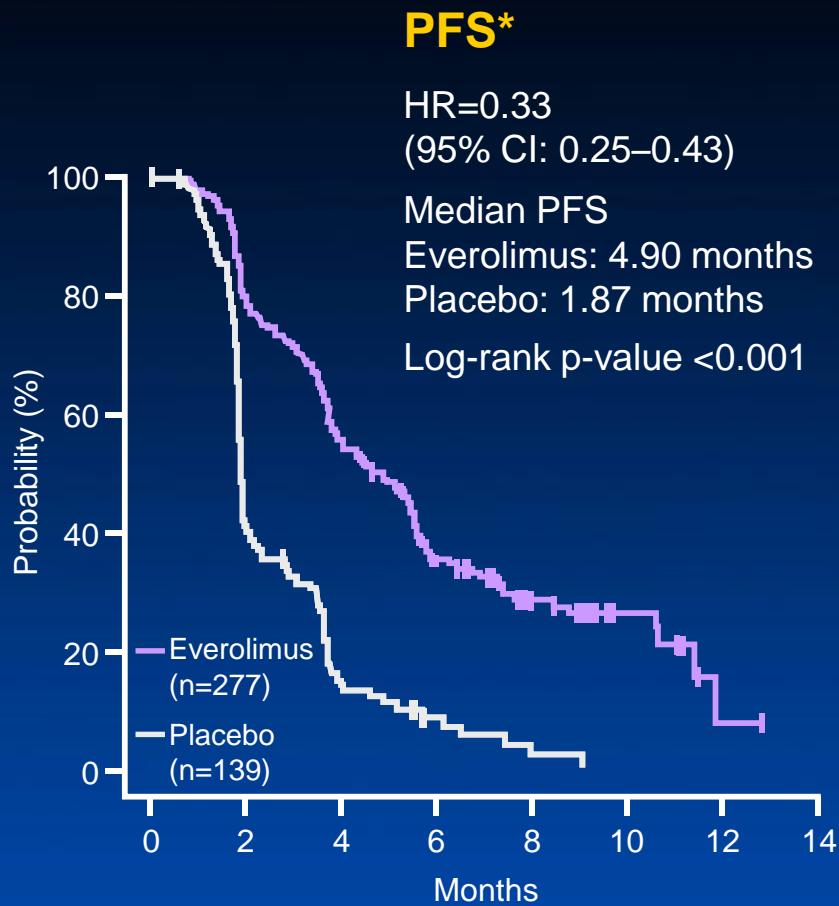
- Hair color change
- Weight decreased
- Serum ALT increased
- Alopecia
- Upper abdominal pain
- Serum AST increased
- Fatigue
- Rash
- Pain in extremity
- Constipation
- Taste Alteration
- LDH increased
- Serum creatinine increased
- Peripheral edema
- Hand-foot syndrome
- Dyspepsia
- Pyrexia
- Leukopenia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



Επιλογή Θεραπείας 2^{ης} γραμμής

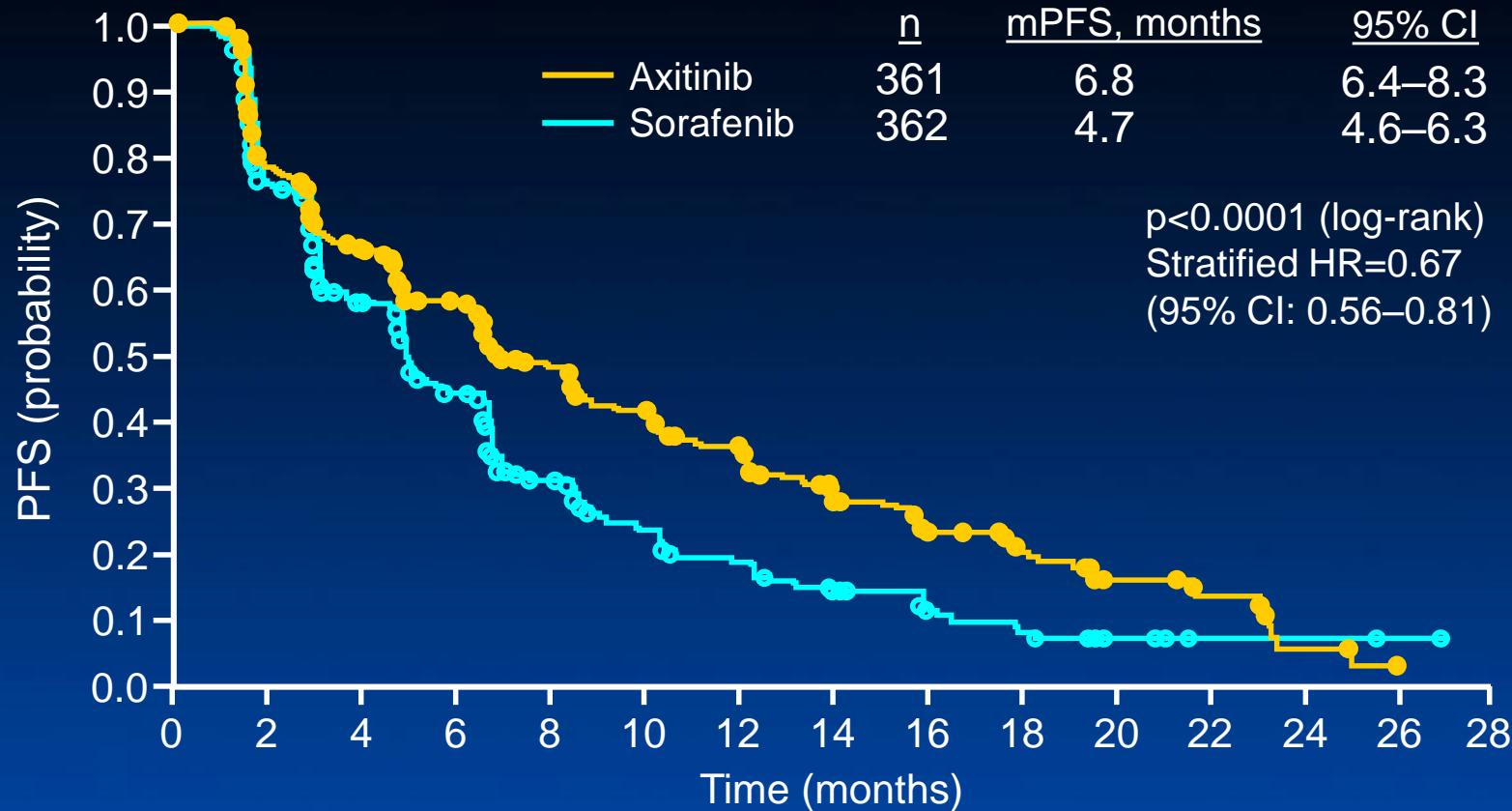


RECORD-1: PFS and OS results



*Central radiology review

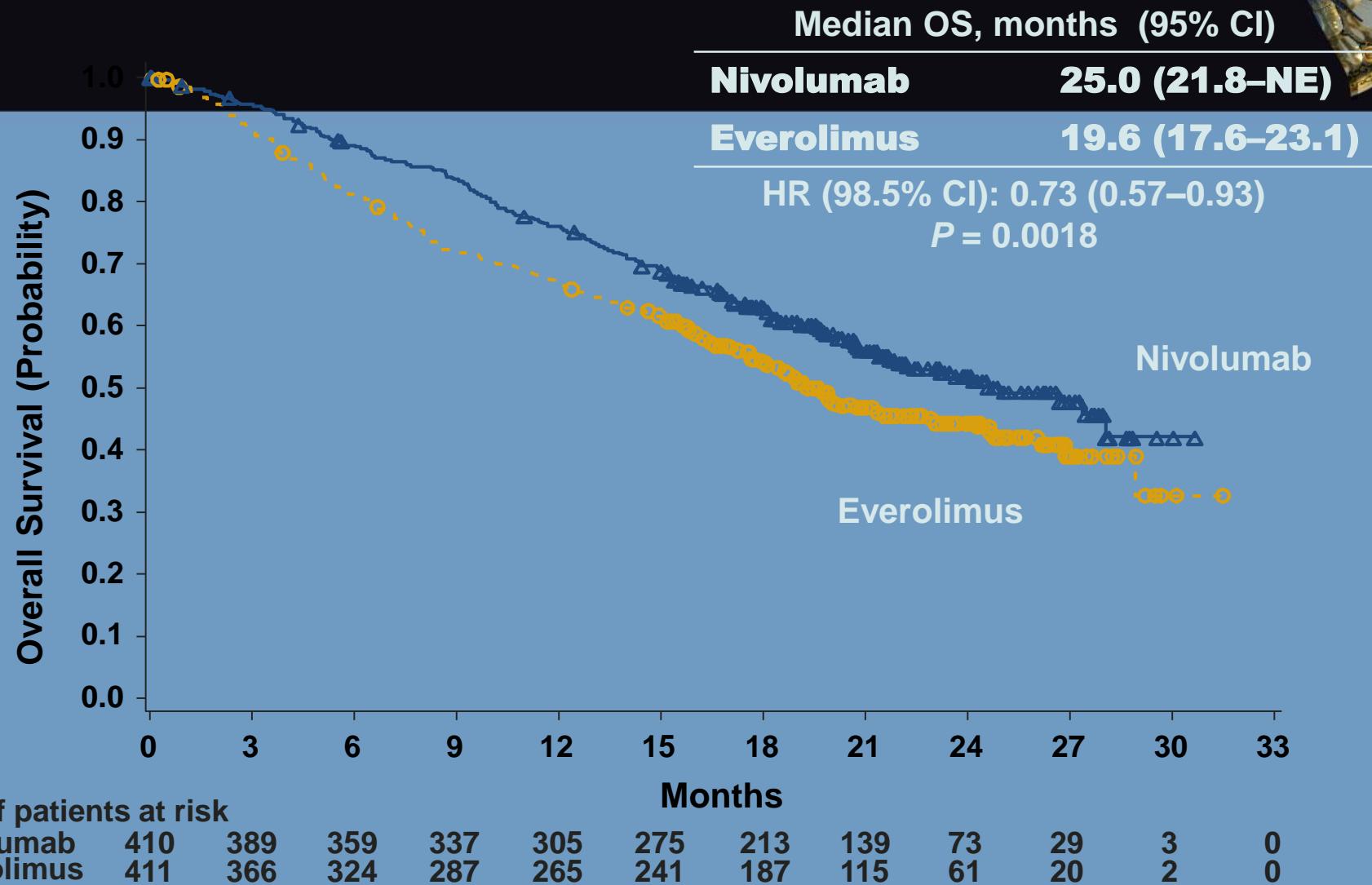
AXIS: Axitinib significantly prolonged PFS vs sorafenib



Updated data cut-off requested for SmPC June 03, 2011



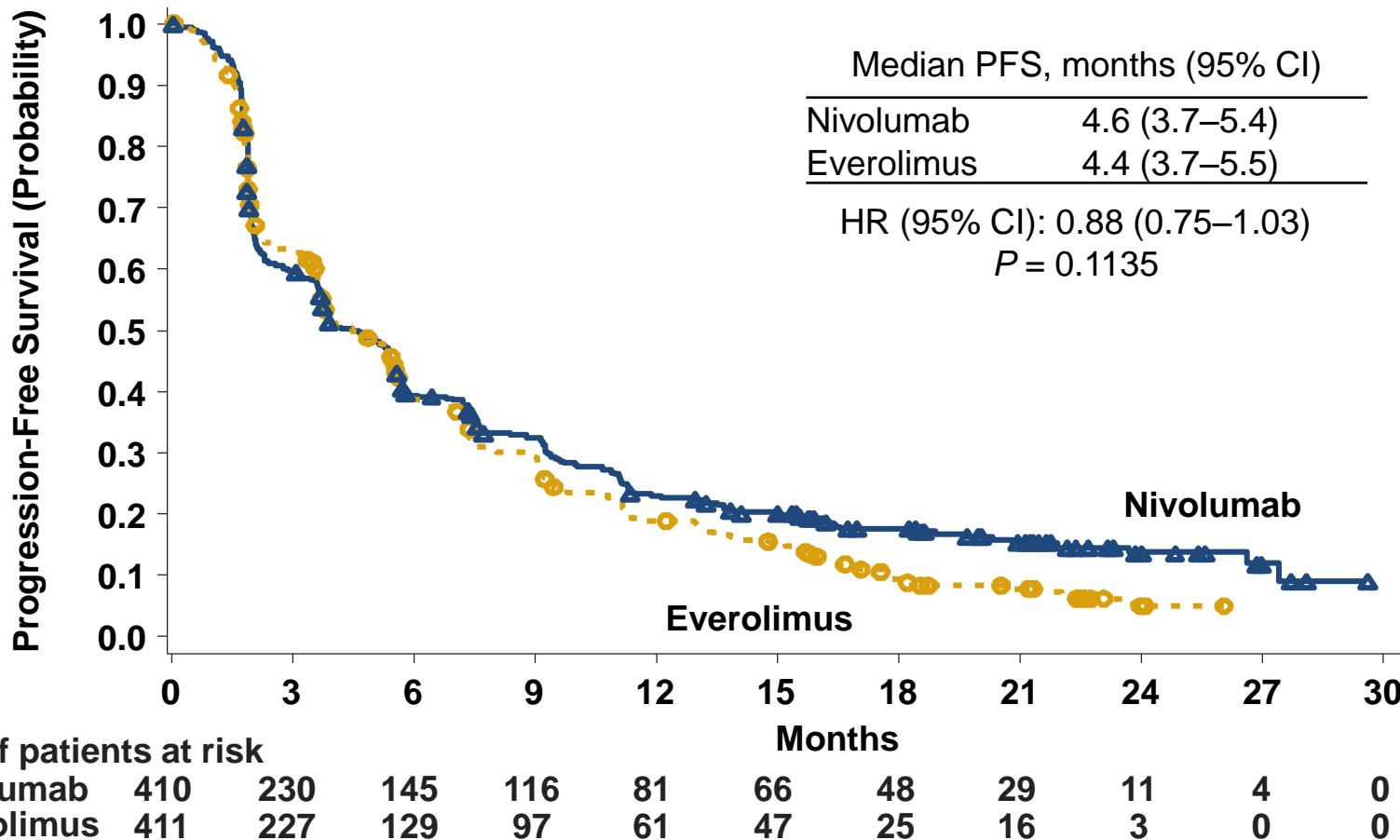
Overall survival



Minimum follow-up was 14 months.

NE, not estimable.

Progression-free survival

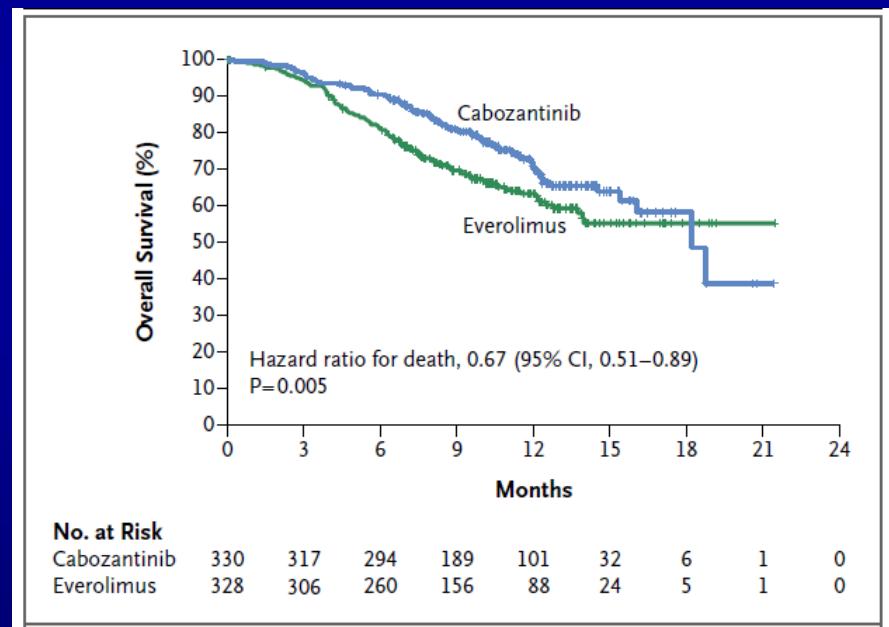
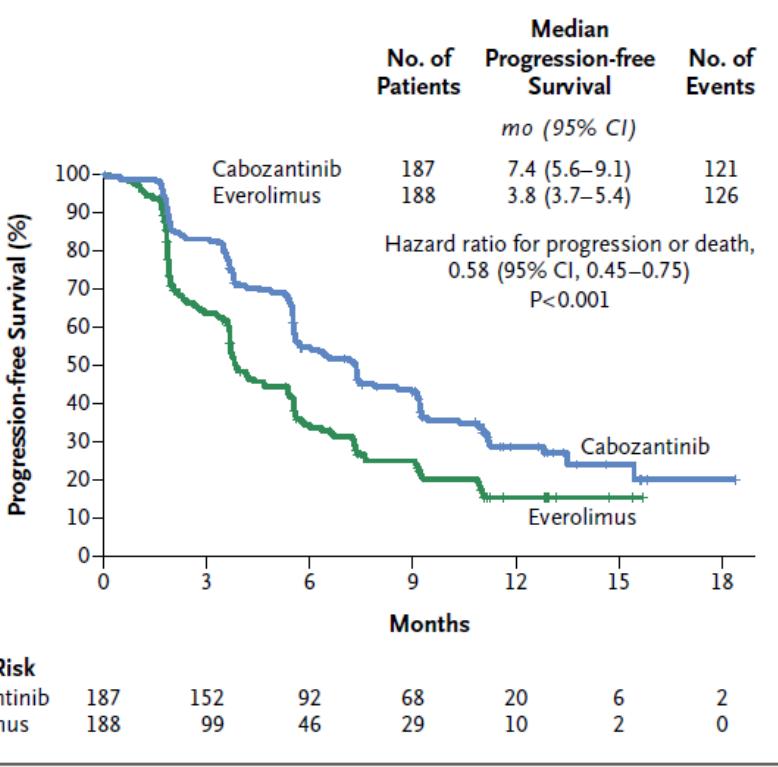


- In a post-hoc analysis of patients who had not progressed or died at 6 months, median PFS was 15.6 months for nivolumab vs 11.7 months for everolimus (HR (95% CI): 0.64 (0.47–0.88))

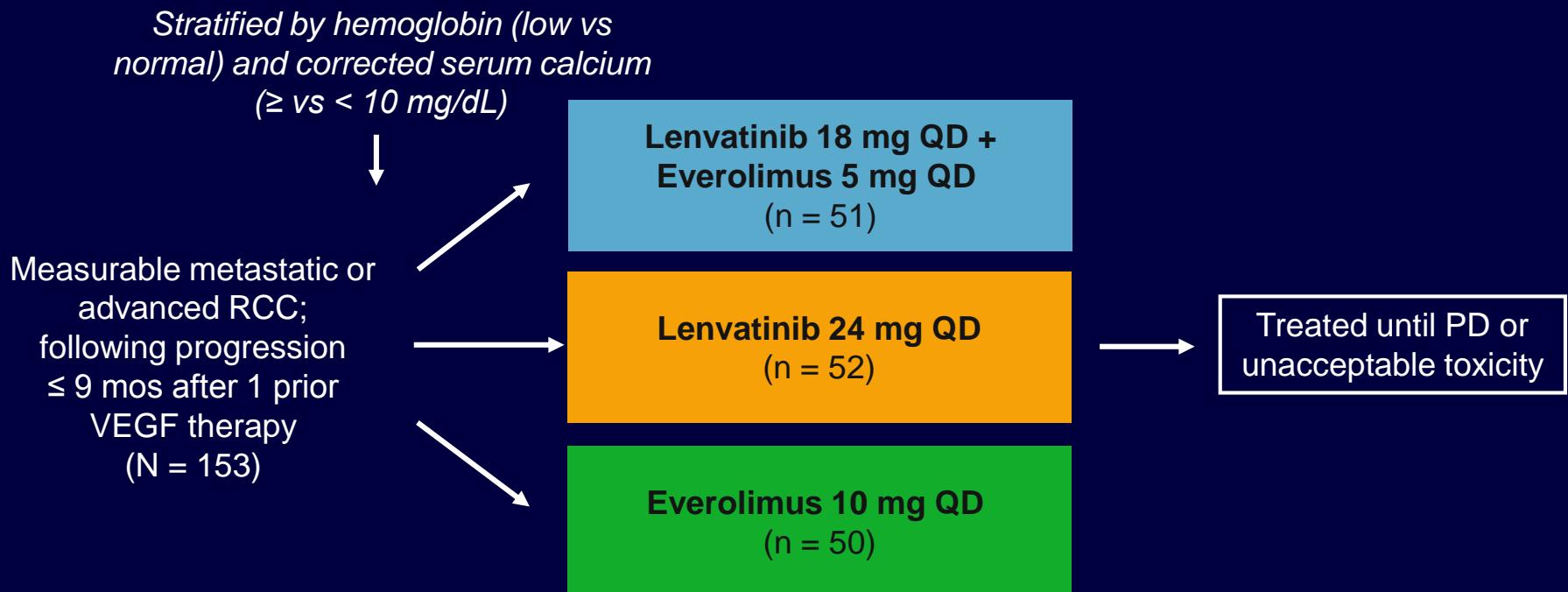
ORIGINAL ARTICLE

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*



Lenvatinib ± Everolimus in mRCC: Randomized, Open-Label Phase II Study



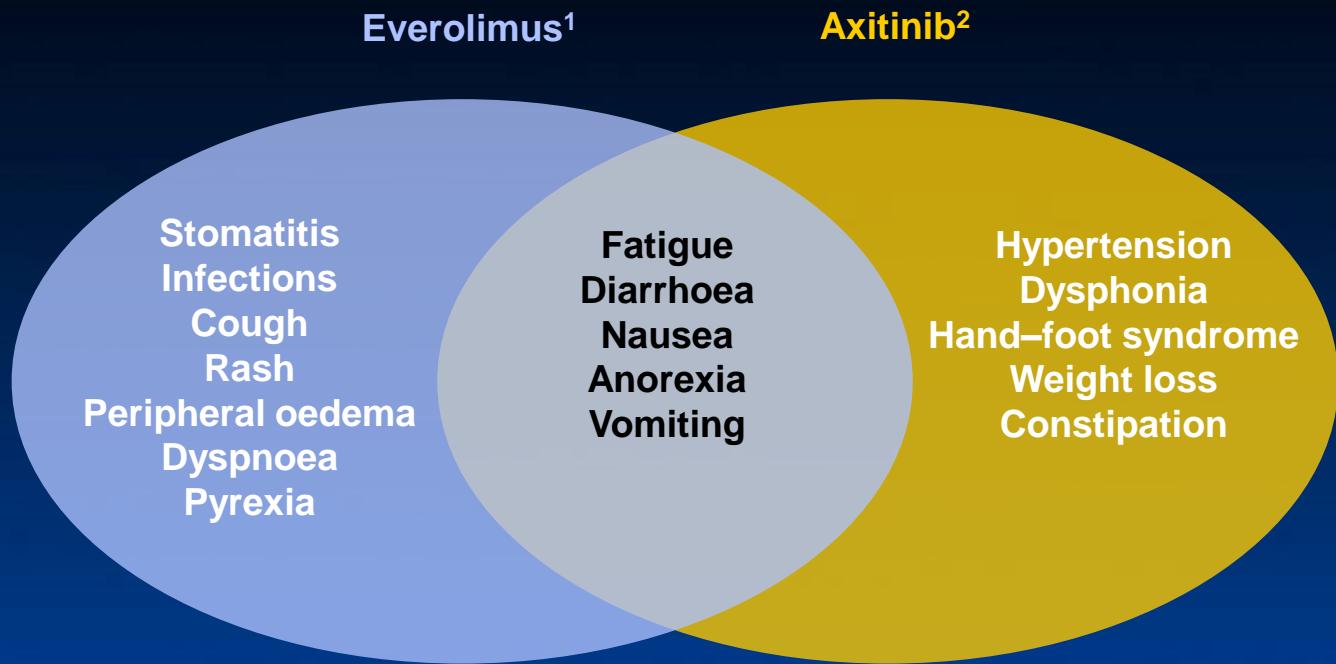
- Primary endpoint: PFS with lenvatinib ± everolimus vs everolimus alone
- Secondary endpoints: PFS with combination vs lenvatinib alone, ORR, OS, safety/tolerability

Lenvatinib \pm Everolimus in mRCC: Efficacy

Response	Lenvatinib/ Everolimus (n = 51)	Lenvatinib (n = 52)	Everolimus (n = 50)
Median PFS, mos	14.6 HR: 0.40; $P < .001$ vs everolimus	7.4 HR: 0.61; $P = .048$ vs everolimus	5.5
ORR, %	43 $P < .001$ vs everolimus	27 $P = .007$ vs everolimus	6
Median OS,* mos	25.5 HR: 0.51; $P = .024$ vs everolimus	19.1 HR: 0.68; $P = .118$ vs everolimus	15.4

*Updated analysis.

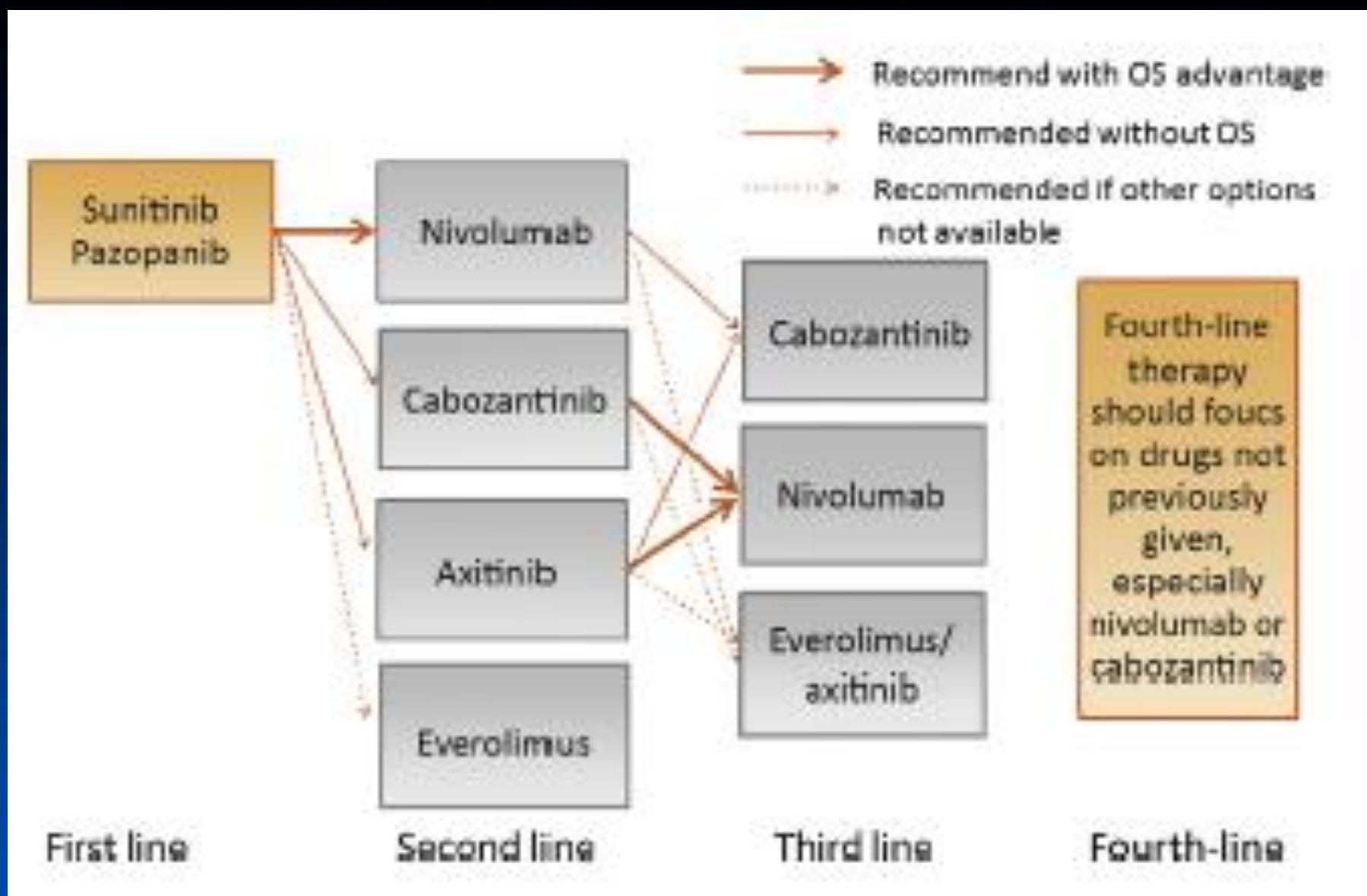
Frequent all-causality AEs ($\geq 20\%$)*



*Outcomes from different clinical trials should not be compared directly due to differences in trial design and patient populations

1. Escudier B, et al. Cancer 2010;4256–65; 2. Rini BI, et al. Lancet 2011;378:1931–9

EAU guidelines

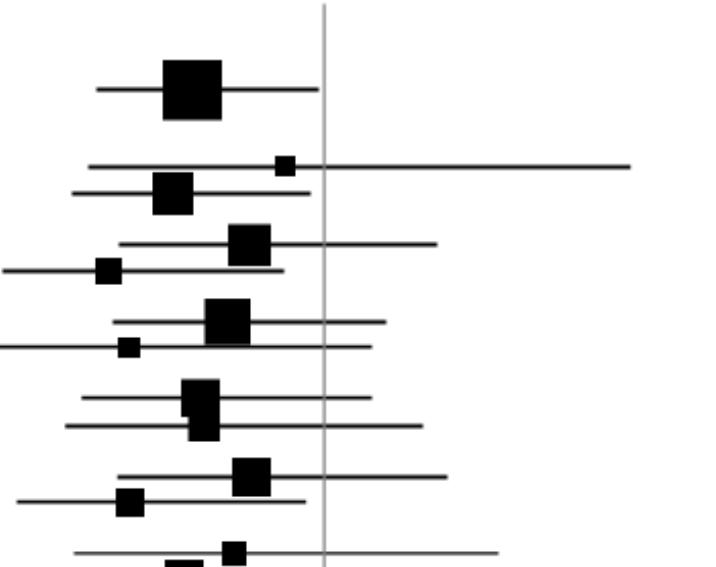


COMBO VS MONO ?

Σημασία της προηγούμενης ανταπόκρισης στην επιλογή της 2^ης γραμμής

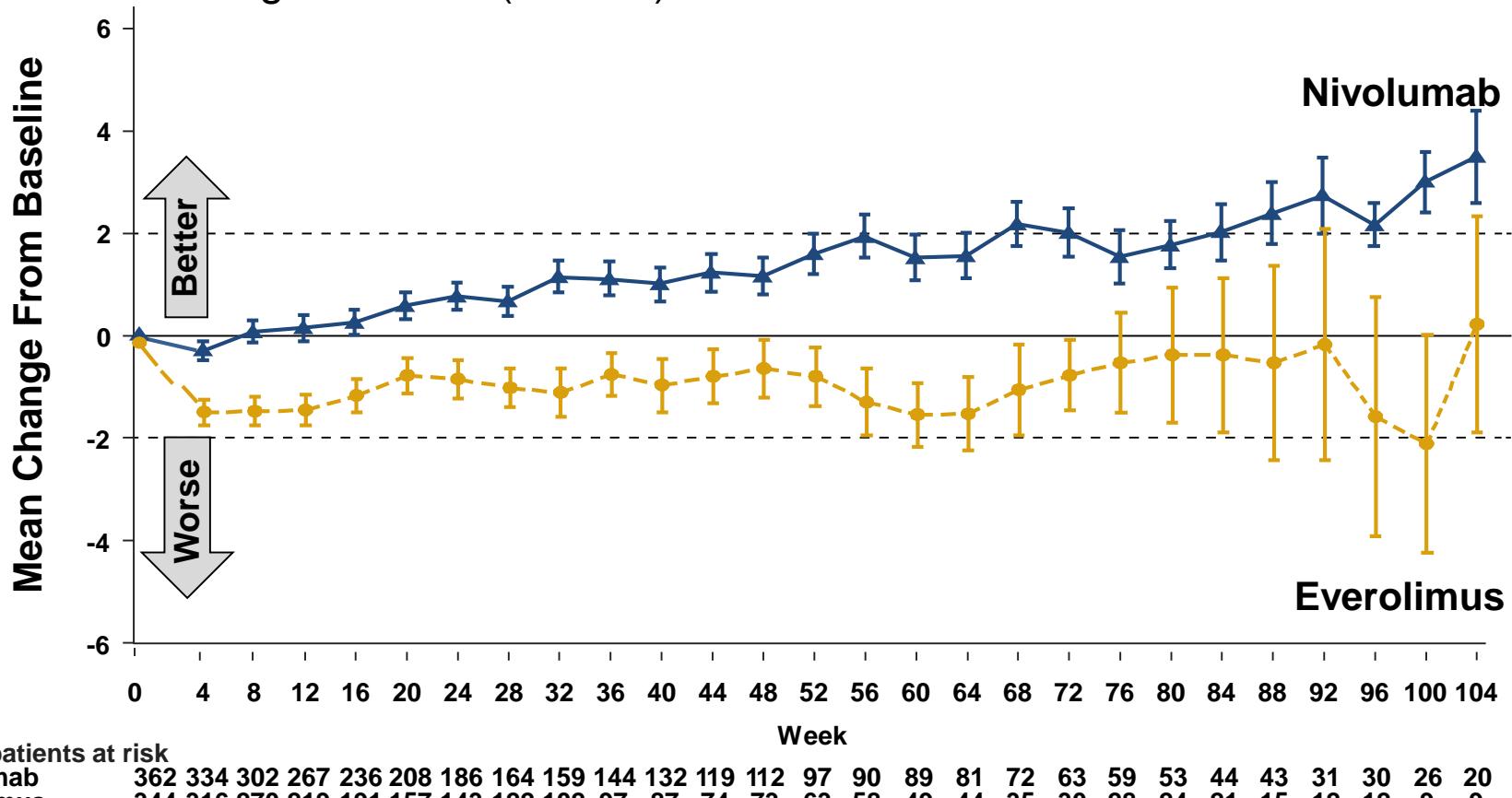


- Αντικρουόμενα αποτελέσματα
- Βασικό μειονέκτημα: οι early progressors συμπεριλαμβάνονται στις περισσότερες αναλύσεις

Subgroup	N (TKI/mTORi)	Hazard Ratio	Test for heterogeneity
Overall (TKI/mTORi)	118/123		p-value*
Fuhrman grade			0.414
I-II	27 / 41		
III-IV	91 / 82		
Number of metastatic sites			0.182
<=2	81 / 79		
> 2	37 / 44		
Presence of bone metastases			0.411
No	93 / 92		
Yes	25 / 31		
Best OR to 1st TKI			0.850
SD	76 / 60		
CR/PR	42 / 63		
ECOG-PS prior to 1st line			0.268
0	69 / 71		
> 0	49 / 52		
ECOG-PS prior to 2nd line			0.660
0	38 / 45		
> 0	80 / 78		
IMDC score prior to 1st line			0.243
Favourable/Intermediate	74 / 87		
Poor	44 / 36		
IMDC score prior to 2nd line			0.279
Favourable/Intermediate	69 / 77		
Poor	49 / 46		
Time on 1st TKI (m)			
6-12	46 / 50		
12-18	28 / 24		0.151
18-24	20 / 19		0.176
> 24	24 / 30		0.028
Time on 1st TKI (m)			
6-11	39 / 41		
11-22	51 / 42		0.020
> 22	28 / 40		0.698

Change from baseline in quality of life scores on FKSI-DRS

- Mean change from baseline in the nivolumab group increased over time and differed significantly from the everolimus group at each assessment through week 76 ($P<0.05$)

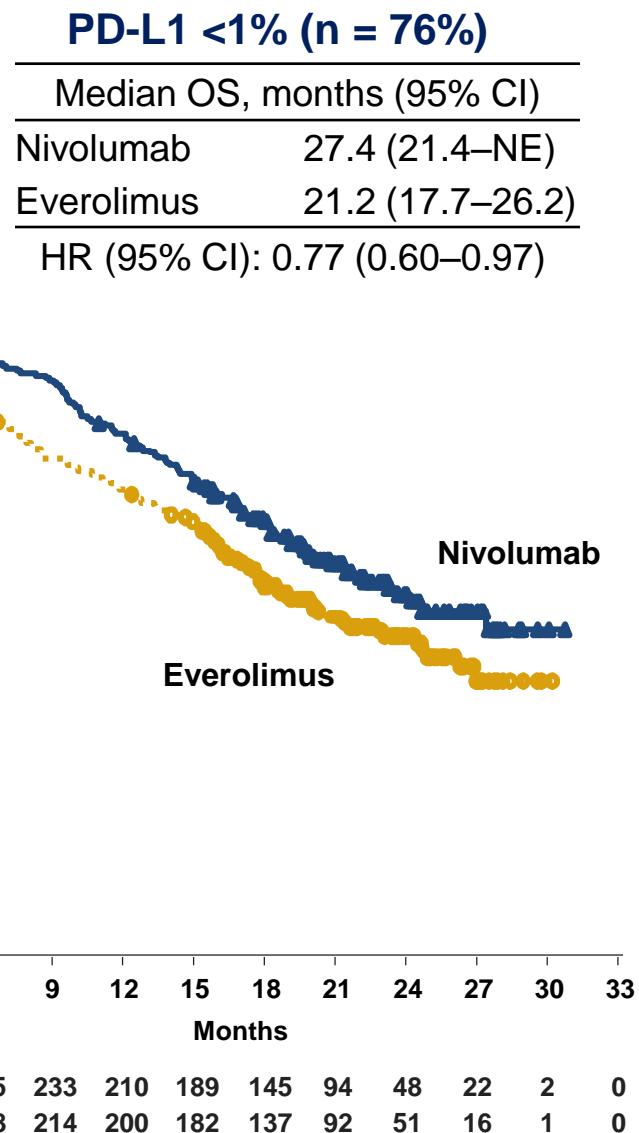
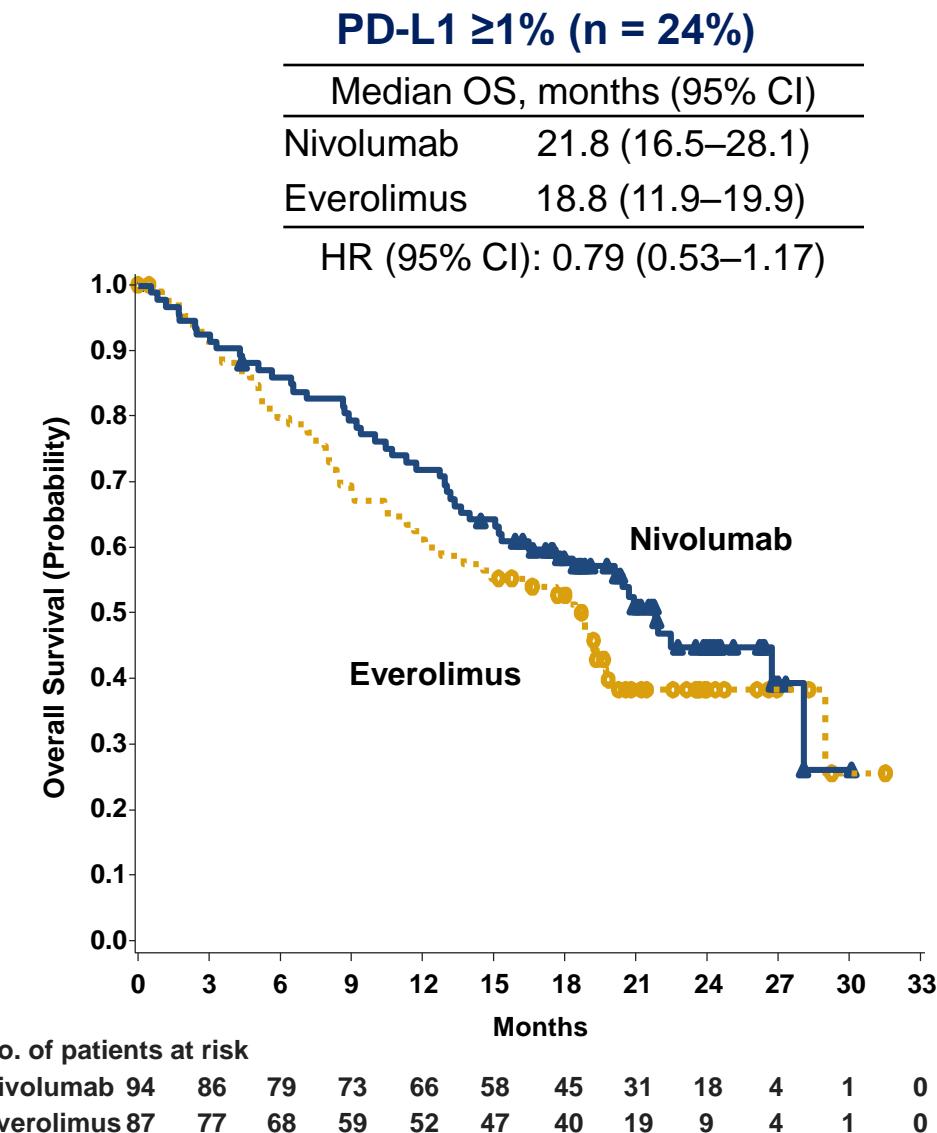


No. of patients at risk

Nivolumab	362	334	302	267	236	208	186	164	159	144	132	119	97	74	73	63	58	49	44	35	30	28	24	21	15	12	31	30	26	9	20
Everolimus	344	316	270	219	191	157	143	122	102	97	87	74	73	63	58	49	44	35	30	28	24	21	15	12	31	30	26	9	20		

Questionnaire completion rate: $\geq 80\%$ during the first year of follow-up.

Overall survival by PD-L1 expression



Treatment holidays



- Μελέτες: until PD or intolerance
- Real world: ?safe interruption after achieving CR (with or without surgery)

ΣΥΜΠΕΡΑΣΜΑΤΑ



- Ο μεταστατικός καρκίνος νεφρού είναι χρόνια νόσος με πολλές θεραπευτικές επιλογές
- Η επιλογή της θεραπείας βασίζεται σε κλινικά κριτήρια και στα δεδομένα τοξικότητας, τα οποία, όμως, δεν επαρκούν για αποτελεσματική επιλογή των ασθενών.
- Η σύγχρονη έρευνα εστιάζεται στην ιδεατή διαδοχική χρήση των στοχευμένων θεραπειών και στην ανεύρεση βιολογικών και κλινικών παραμέτρων για την επιλογή ασθενών που μπορεί να έχουν μεγαλύτερο όφελος από τον ένα ή τον άλλο παράγοντα