Poster discussion
Nosov D et al. Abstract No. 796PD
Eisen T et al. Abstract No. 795PD

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Tivozanib hydrochloride pharmacokinetic/pharmacodynamic analysis of blood pressure and soluble vascular endothelial growth factor receptor 2 (sVEGFR2) in patients with advanced renal cell carcinoma

Dmitry A. Nosov, Robert J. Motzer, John Loewy, Lee Hodge, Brooke Esteves, Anna Berkenblit, Wei Yin, Kevin Dykstra, Thomas E. Hutson, Monette M. Cotreau

VIENNA 2012 ESMO congress

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Nosov D et al. Abstract No. 796PD

Tivozanib pharmacokinetic/pharmacodynamic analysis of blood pressure and soluble vascular endothelial growth factor receptor 2 (sVEGFR2)
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- PK, BP, sVEGFR2 data from tivozanib-treated RCC
- from phase II discontinuation and phase III trials
- Tivozanib 1.5 mg/day, 3/1 week schedule
- 531 pts tivozanib-treated
- n=21 with PK data

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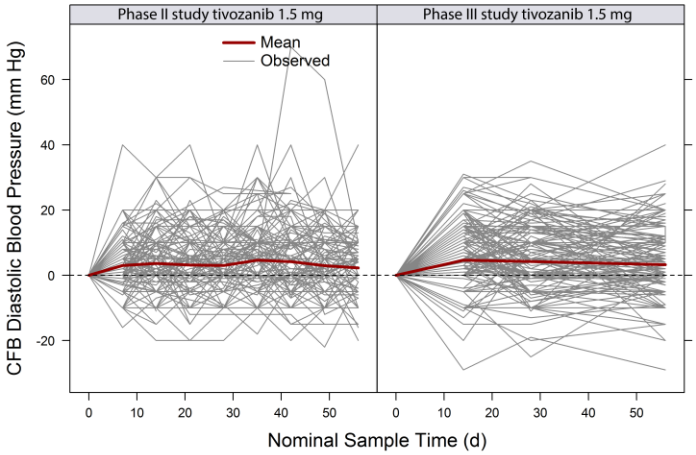
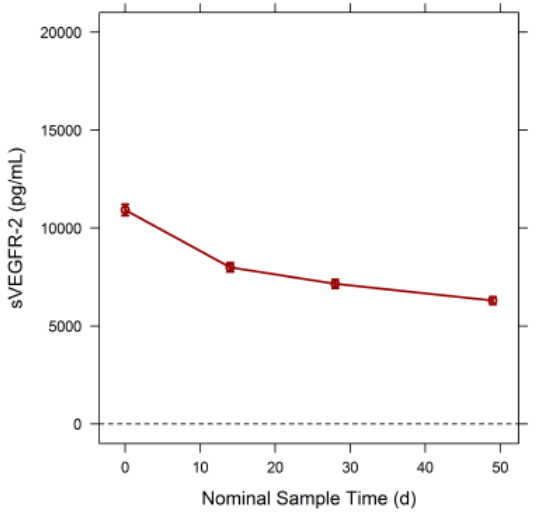
Tivozanib Exposure and Blood Pressure



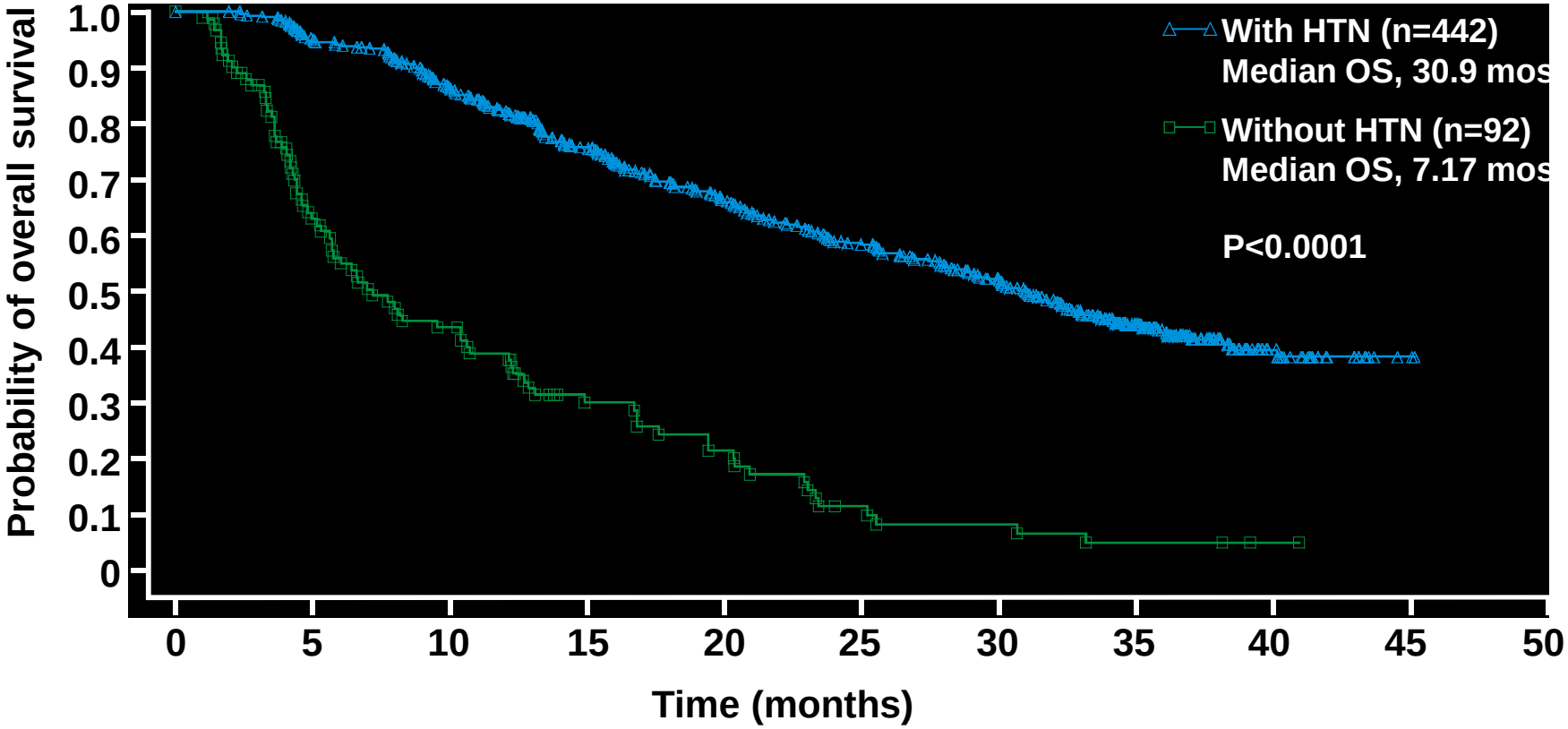
Pharmacodynamics and sVEGFR2



Conclusions

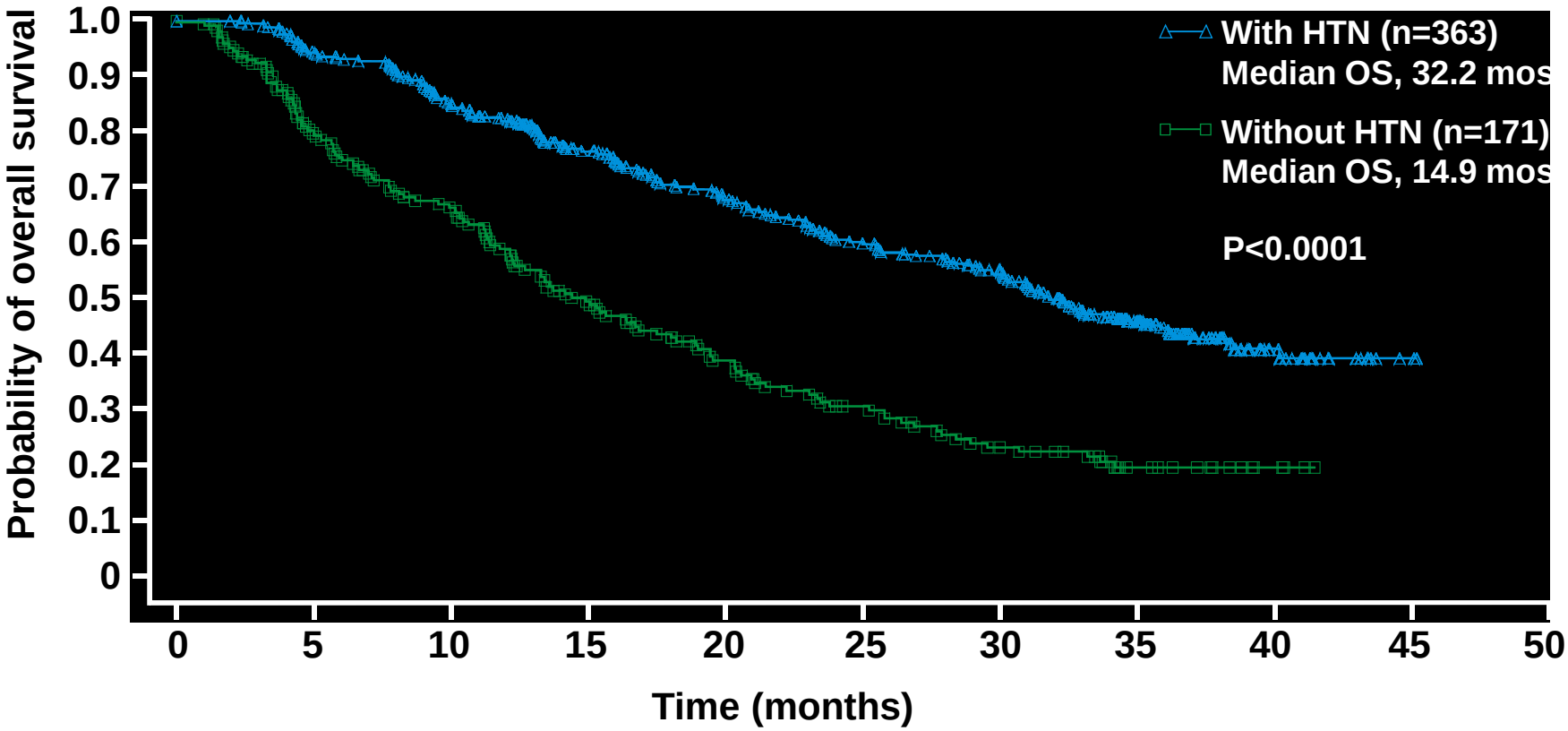
- median increase in DBP of 5 mm Hg on C1 Day 15 and C2 Day 1
- Levels of serum sVEGFR2 decrease with time, increase with tivozanib exposure, ? biomarker for disease progression
- significant association of tivozanib exposure and BP is likely, but has not been found in the present analysis
- due to infrequent monitoring of blood pressure in the phase III study

Median OS by HTN Status
Defined by Maximum SBP ≥ 140 mmHg
Sunitinib in RCC



Rini et al JNCI 2011

Median OS by HTN Status Defined by Maximum DBP ≥ 90 mmHg Sunitinib in RCC



Rini et al JNCI 2011

Reported Effects of Tyrosine Kinase Inhibitors on VEGF and sVEGFR-2 in Renal Cell Carcinoma Patients

Drug	Target	VEGF	sVEGFR-2
Sorafenib[1]	VEGF-1,-2, -3, PDGFR, RET, Raf	↑	↓
Sunitinib[2]	VEGF-1, -2, PDGFR, KIT, RET	↑	↓
Axitinib[3]	VEGF-1, -2, -3, PDGFR, KIT	↑	↓
Pazopanib[4]	VEGF-1, -2, -3, PDGFR	↑	↓
Cediranib[5]	VEGF-1, -2, -3, PDGFR, KIT	NA	↓

1. Bukowski 2007, 2. Motzer 2006, 3. Deprimo 2007,
4. George 2007, 5. Hixe 2005

Biomarkers in RCC

Soluble angiogenic	Matrix-derived angiogenic	Coagulation	Vascular activation + inflammation
bFGF	MMP2	Tissue Factor	Gro-α
HGF	MMP9	PAI-1 Active	IL-6
PIGF	TGFβ1	PAI-1 Total	IL-8
VEGF-A	TGFβ2	CRP	P-selectin
VEGF-C	Osteopontin	D-dimer	E-selectin
VEGF-D	TSP1	Von Willebrand	SDF-1b
ANG-2	TSP2	Factor	ICAM-1
PDGF-AA			VCAM-1
PPDGF-BB			MCP-1
IGFBP1			E-cadherin
IGEFBP3			TNF-α
PEDF			IFN-*y*
sVEGFR1			NT-proBMP
sVEGFR2			

SNPs and outcome in RCC

- **Pazopanib**
  - ***VEGF-A* -1154G>A assoc OS[1]**
  - **Reduction in ORR for *VEGFA* -1498CC genotype compared with TT genotypes (33% vs 51%)[1]**
- **Axitinib**
  - ***VEGF-A* SNPs asscoc PFS[2]**
  - **Shorter PFS observed for *VEGF-A* -1498 T/T vs *–1498* C/-variants in colorectal cancer (median PFS, 7.5 vs 11.1 months; *P*=0.0027)[5]**
- **Sunitinib**
  - ***CYP3A5*, *ABCB1*, *NR1/3* SNPs assoc PFS and OS[3]**
  - ***VEGFR-3* SNPs assoc TTP and OS[3]**

from Escudier ASO 2011

1. Xu C, et al. J Clin Oncol 2011 2. Escudier et al ASCO 2011
3. van der Veldt AA, et al. Clin Cancer Res 2011
4. Garcia-Donas J, et al. J Clin Oncol 2011

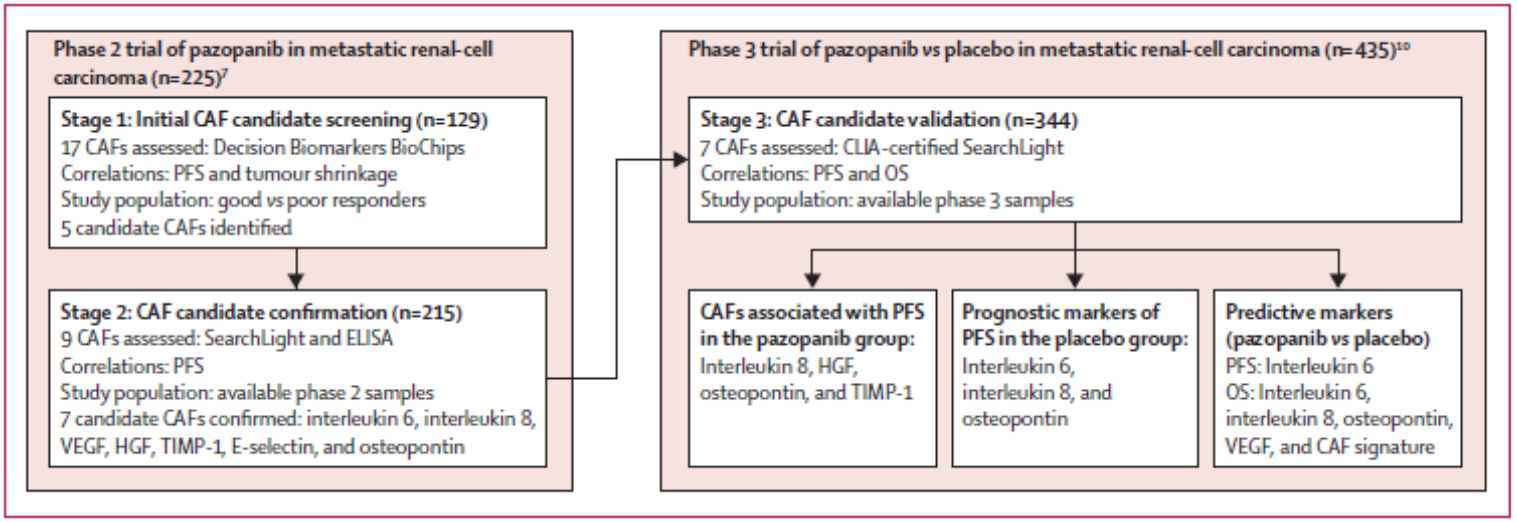
Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials

Hai T Tran, Yuan Liu, Amado J Zurita, Ying Lin, Katherine L Baker-Neblett, Anne-Marie Martin, Robert A Figlin, Thomas E Hutson, Cora N Sternberg, Rafael G Amado, Lini N Pandite, John V Heymach

Lancet Oncol 2012; 13: 827–37

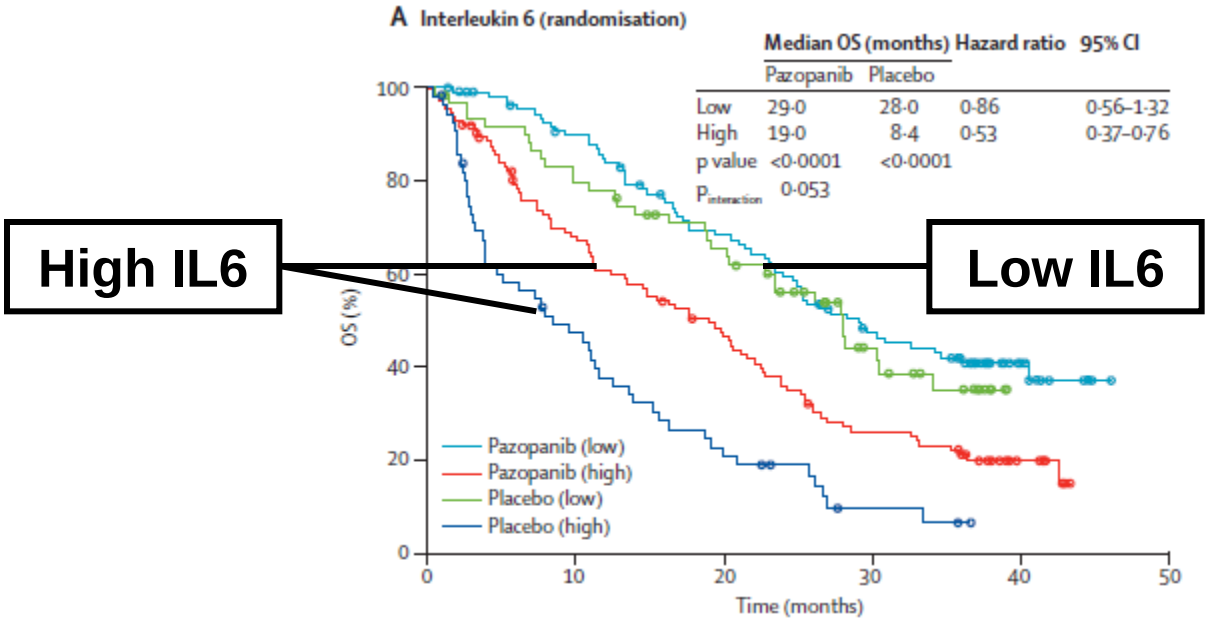
Cytokine and angiogenic factors (CAFs) as factors for prognostic and predicitve modeling

3-step methodology (screening, confirmation, validation)



Tran Lancet Oncol 2012

IL6 as a prognostic marker for OS



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CAFs stronger prognostic factors for PFS than standard clinical models

	PFS (weeks)	p value
CAF classification		
Interleukin 6		
Low	24·0	<0·0001
High	9·9	
Osteopontin		
Low	24·0	<0·0001
High	8·4	
Interleukin 8		
Low	23·9	0·002
High	8·4	
Standard clinical classification		
Eastern Clinical Oncology Group		
0	18·4	0·144
1	13·0	
Memorial Sloan Kettering Cancer Center[25]		
Favourable	24·0	0·011
Intermediate or poor	12·1	
Heng[26]		
Favourable	24·3	0·139
Intermediate or poor	12·6	

Table 4: Cytokine and angiogenic factors (CAFs) and clinical classifications as prognostic markers for progression-free survival (PFS) in the placebo group

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7 candidate CAFs as markers for PFS

HIGH
IL8
HGF
TIMP-1
SHORTER PFS (18wks)

	PFS (weeks)		HR (95% CI)	p value		
	Pazopanib	Placebo		Pazopanib	Placebo	Interaction
Interleukin 6						
Low	42·3	24·0	0·55 (0·38–0·81)	0·445	<0·0001	0·009
High	32·6	9·9	0·31 (0·21–0·44)			
Interleukin 8						
Low	49·1	23·9	0·41 (0·28–0·60)	0·006	0·002	0·472
High	31·3	8·4	0·39 (0·27–0·56)			
Osteopontin						
Low	49·3	24·0	0·43 (0·29–0·64)	0·0004	<0·0001	0·343
High	32·0	8·4	0·35 (0·24–0·51)			
VEGF						
Low	40·4	19·1	0·47 (0·32–0·69)	0·689	0·144	0·376
High	35·6	11·9	0·41 (0·28–0·60)			
Hepatocyte growth factor						
Low	48·1	15·6	0·40 (0·27–0·58)	0·010	0·237	0·520
High	32·1	13·0	0·46 (0·32–0·67)			
TIMP-1						
Low	49·1	18·0	0·38 (0·26–0·55)	0·006	0·052	0·922
High	32·6	13·0	0·40 (0·27–0·59)			
E-selectin						
Low	41·0	18·1	0·49 (0·33–0·71)	0·844	0·089	0·219
High	39·3	12·1	0·36 (0·25–0·52)			

TIMP=tissue inhibitor of metalloproteinases.

Table 2: Cytokine and angiogenic factors and progression-free survival (PFS) in the biomarker population of the phase 3 trial

Vaidation set:
344\435 pts (79%)
from phase 3, pazopanib vs placebo

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	PFS (weeks)		HR (95% CI)	p value		
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Table 2: Cytokine and angiogenic factors and progression-free survival (PFS) in the biomarker population of the phase 3 trial

HIGH
IL6
IL8
Osteopontin
SHORTER PFS (15wks)

Vaidation set:
344\435 pts (79%)
from phase 3, pazopanib vs placebo

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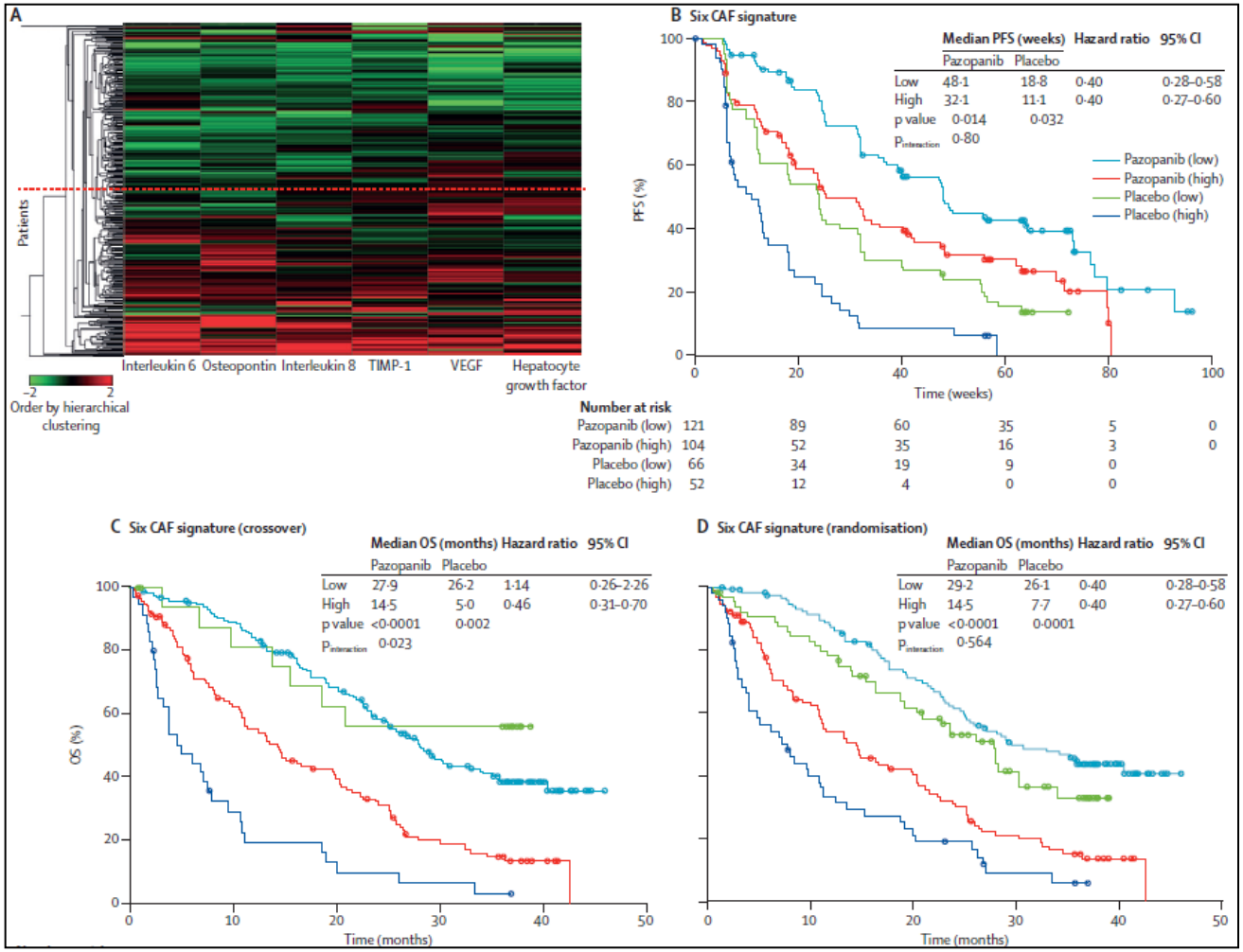
Hierarchical clustering analysis (6 CAFs grouping)
High vs low concentrations



HIGH CAF
(IL6, IL8, HGF, VEGF, Osteopontin , TIMP-1)

1. Shorter PFS
2. Greater benefit from pazopanib

Caveats in biomarker research

- poor history of ‘searching’ for biomarker
- best biomarkers have come from ‘single findings’
- need to be ‘all or nothing’ ie 80% predictive not enough
- ER, HER2, BRAF

Detailed comparison of the safety of tivozanib hydrochloride versus sorafenib in patients with advanced/metastatic renal cell carcinoma (mRCC) from a Phase III trial

Timothy Eisen, Cora N. Sternberg, Piotr Tomczak, Brooke Esteves, Robert Motzer

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Tivozanib versus sorafenib - safety comparison in patients in RCT
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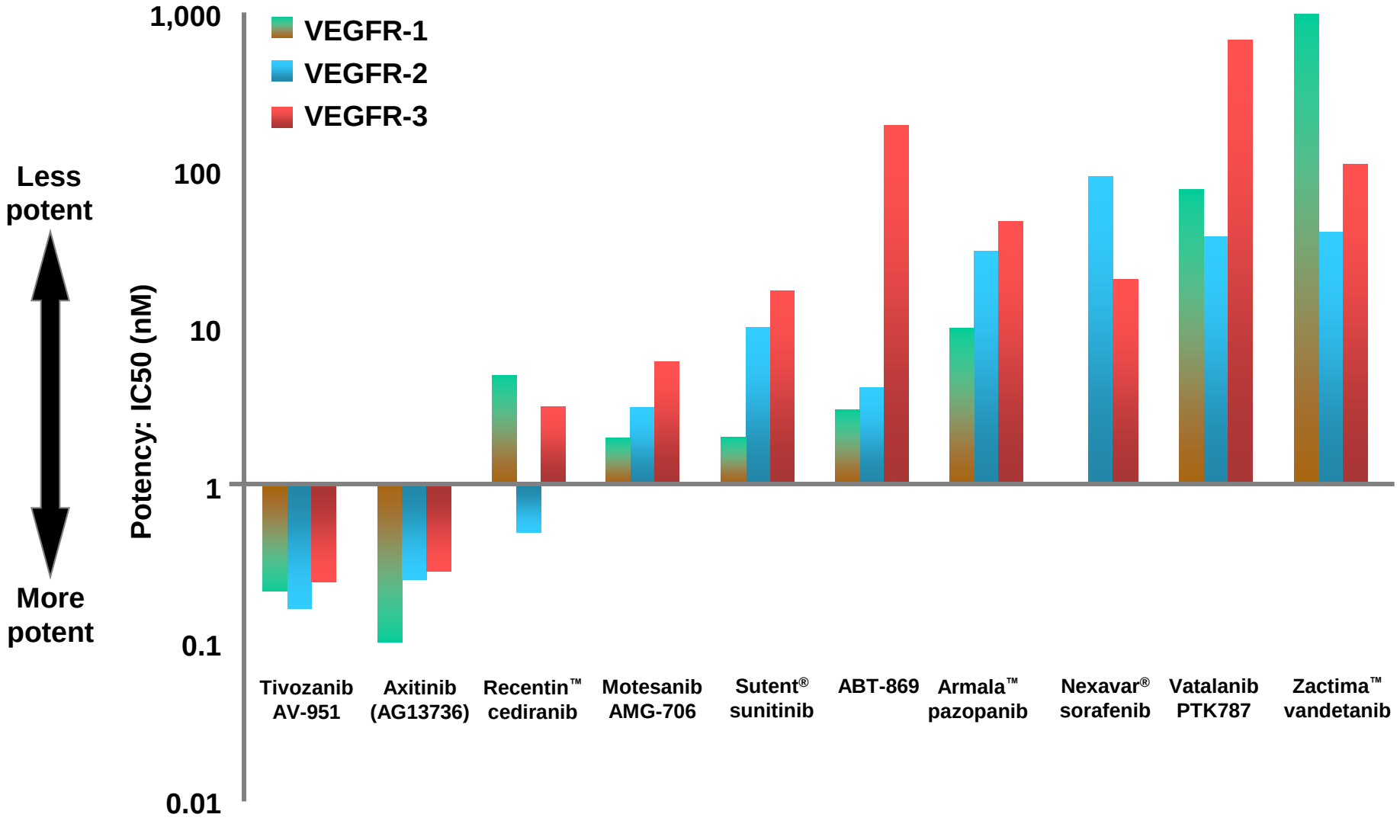
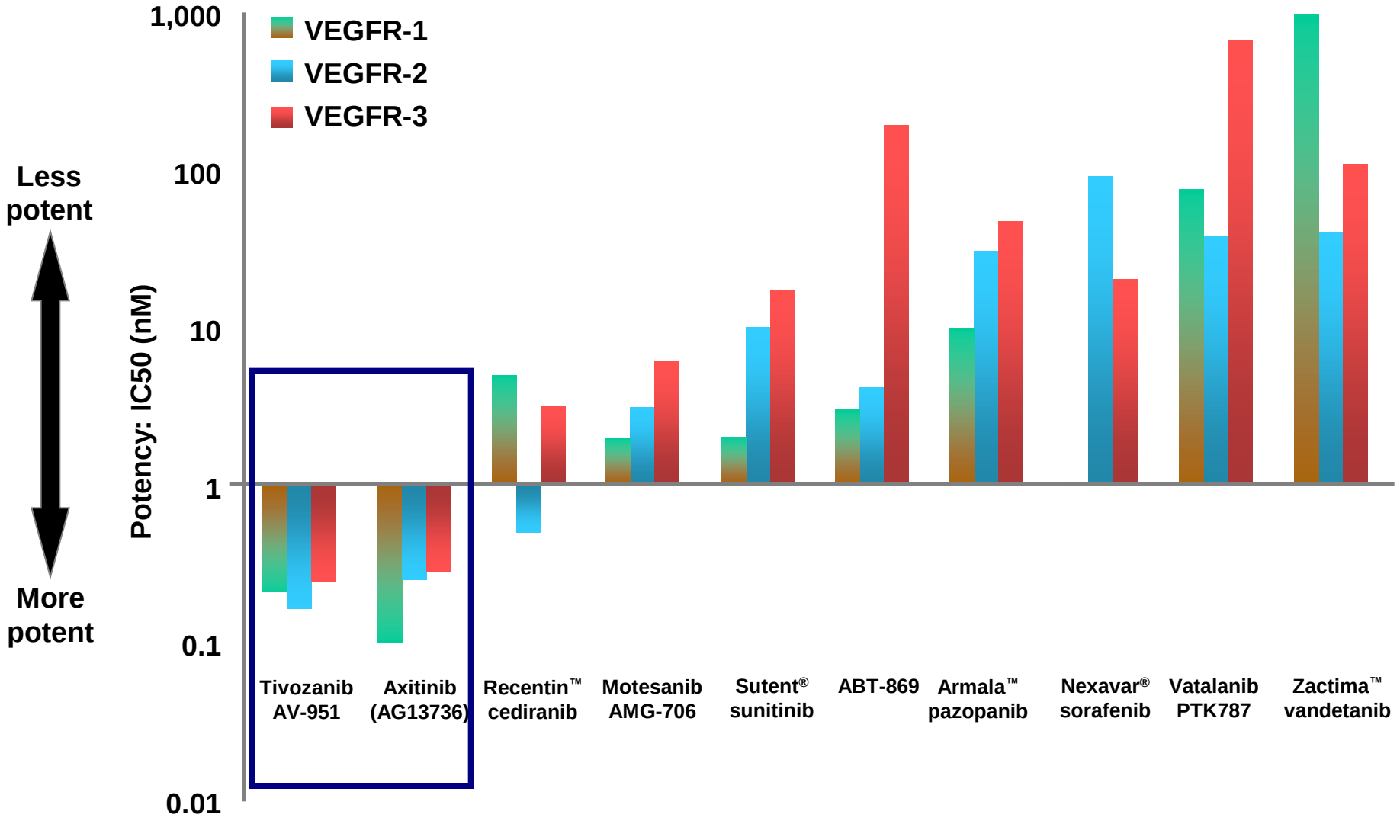
- clear cell mRCC
- prior nephrectomy
- ≤1 prior systemic treatment
- n = 517 pts

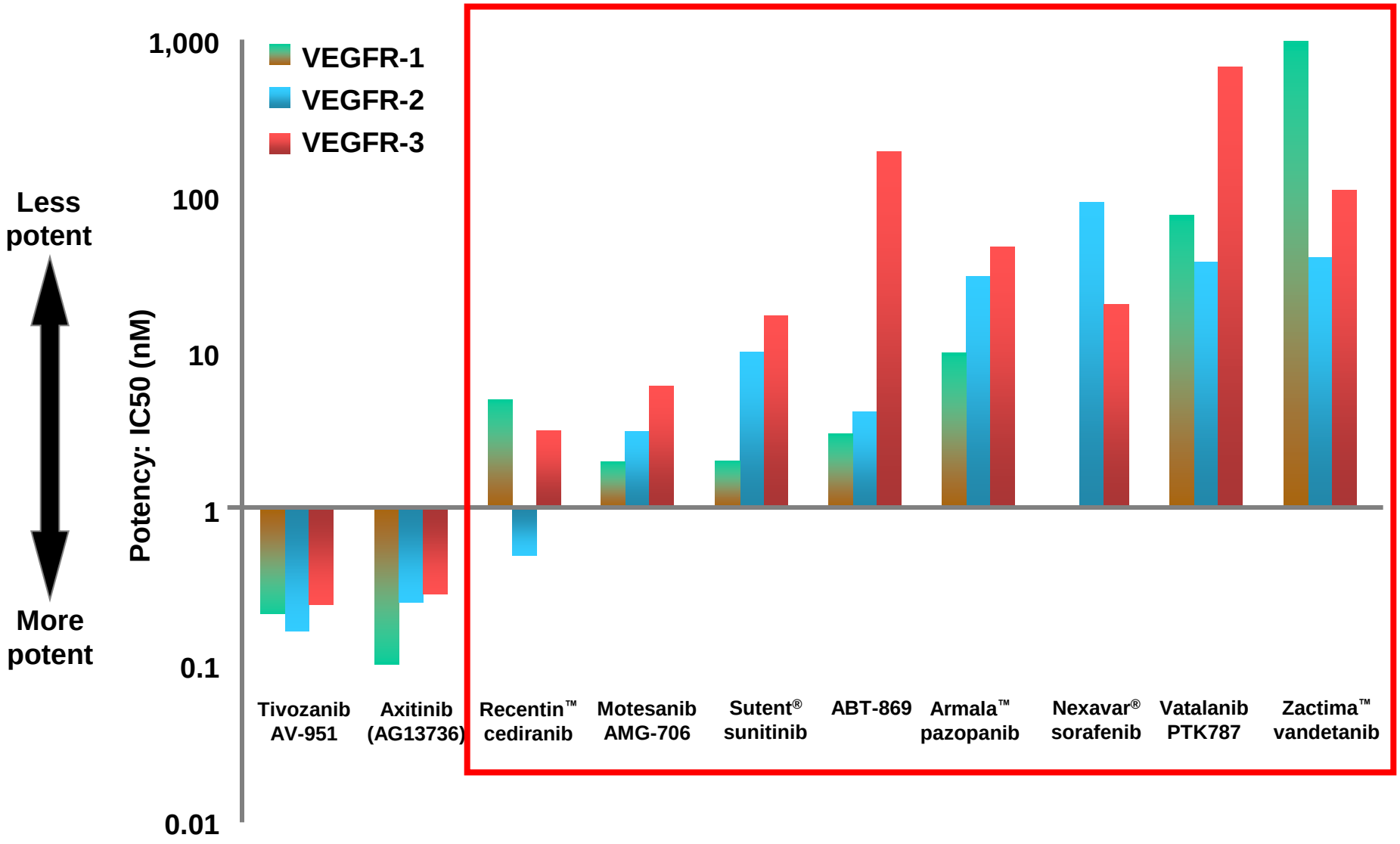
Relative Potencies of VEGFR TKIs



Relative Potencies of VEGFR TKIs



Relative Potencies of VEGFR TKIs



Tivozanib versus sorafenib - safety comparison in patients in RCT
Eisen T et al. Abstract No. 795PD

	Tivozanib (n=259)	Sorafenib (n=257)
All drug-related AEs	68	83
Hypertension	42%	31%
Dysphonia	18%	4%
Diarrhoea	18%	28%
PPE\HFS	13%	53%
Alopecia	2%	21%

on target vs off target
drug-related ≥Gr 3 AEs less with tivo
BP increase with tivo, no CVS sequelae

Tivozanib versus sorafenib - safety comparison in patients in RCT
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How to compare toxicities ?

Tivozanib versus sorafenib - safety comparison in patients in RCT
Eisen T et al. Abstract No. 795PD

How to compare toxicities ?

	Tivozanib (n=260)	Sorafenib (n=257)	*P* value
Discontinuations due to drug-related AEs	4.2%	5.4%	–
Dose interruptions due to AE, %	17.8	35.4	<0.001
Dose reductions due to AE, %	11.6	42.8	<0.001

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Reason for discontinuation	PD in 69.5%	PD in 79.7%	-
Relative dose intensity	94.3%	81.2%`	-

Tivozanib versus sorafenib - safety comparison in patients in RCT
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Reason for discontinuation	PD in 69.5%	PD in 79.7%	-
Relative dose intensity	94.3%	81.2%`	-

Selective vs multi-targeted TKIs
Comparative toxicites (Gd 3\4)

	Sunitinib n = 375	Sorafenib n=361	Pazopanib n =290	Axitinib n = 362	Tivozanib n = 272
Diarrhea	9%	7%	3%	11%	2%
Fatigue\Asthenia	11%	5%	2%	11%	2%
Hand-foot syndrome	9%	16%	NA	5%	<1%
Dysphonia	NA	11%	NA	28	18%
Hypertension	12%	11%	4%	16%	9%
Hypothyroidism	2%	0%	NA	1%	<1%
Nausea	5%	1%	<1%	3%	<1%
Mucositis/stomatitis	1	<1%	NA	1%	<1%
Vomiting	4%	1%	2%	3%	<1%

on target
off target

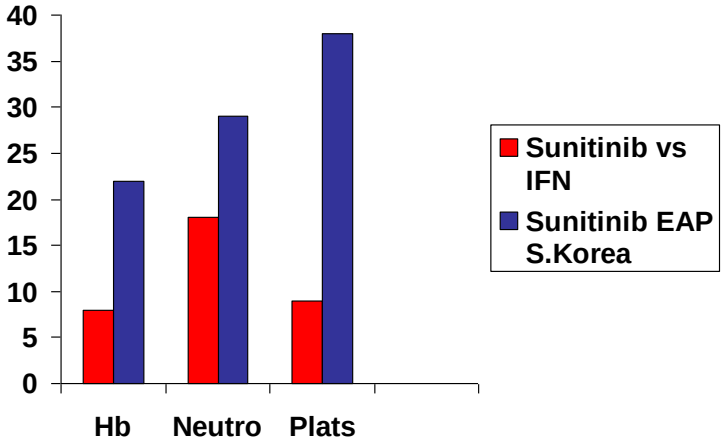
Motzer 2009, Sternberg 2010,
Bhargava 2010, Rini 2012

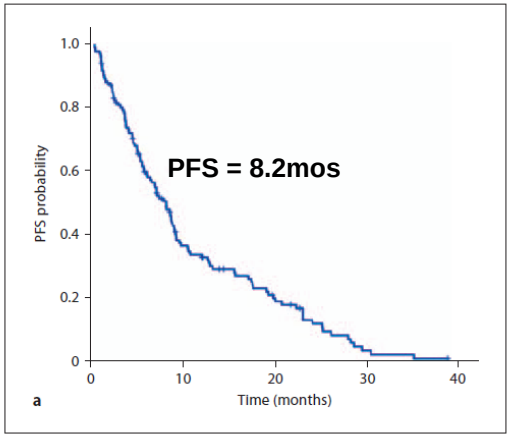
Polymorphisms genotyped
Factors relevant to sunitinib toxicity

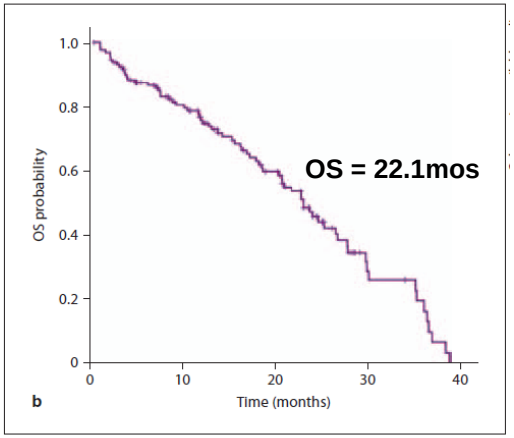
	Genotype	OR	95% CI	P
Any toxicity > grade 2 n = 183				
VEGFR2 1191C/T	CC ⌫ TC ⌫ TT	2.39	1.02 to 5.60	0.046
ABCG2 haplotype ξ	TT-TT+TT-other vs other-other	0.38	0.17 to 0.83	0.016
Mucosal inflammation n = 193				
CYP1A1 2455A/G	AA ⌫ AG ⌫ GG	4.03	1.24 to 13.09	0.021
Hand foot syndrome n = 182				
ABCB1 haplotype∞	TTT-TTT+TTT-other vs other-other	0.39	0.16 to 0.94	0.035

van Erp JCO 2009

Toxicity and ethnicity







Motzer JCO 2009

Kim Oncology 2011

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- **low grade toxicity for longer worse that high grade toxicity for shoreter**
- **on\off target toxicities**
- **what bothers the patient**
- **what bothers the doctor**
- **patient symptoms and doctor symptoms ie diarrhoea vs hypertension**

end