Abstract 785O

Comparative Assessment of Sunitinib-associated Adverse Events as Potential Biomarkers of Efficacy in Metastatic Renal Cell Carcinoma (mRCC)

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Disclosure

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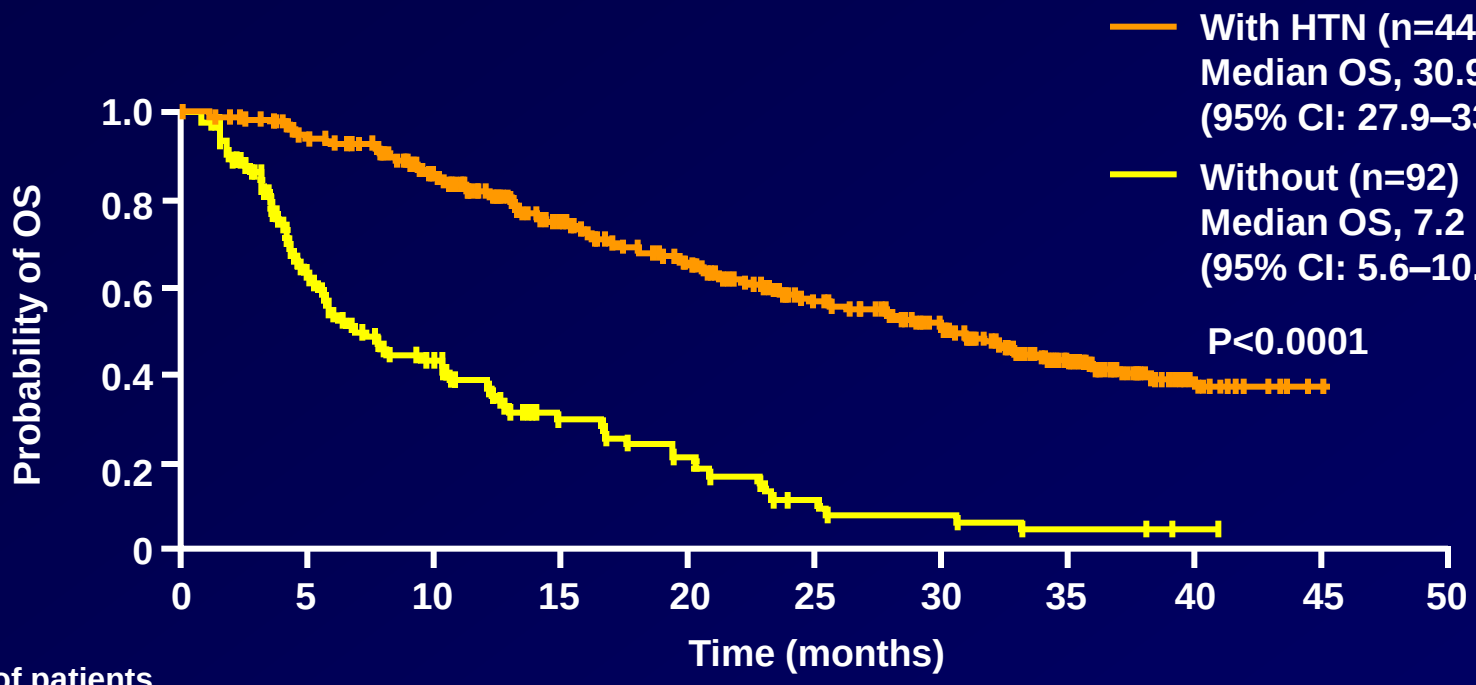
Introduction

- Prior retrospective analyses of pooled data from five clinical mRCC trials have separately identified the following treatment-associated AEs as potential biomarkers of sunitinib efficacy:
  - hypertension[1]*
  - neutropenia[3]
  - asthenia/fatigue[4]
  - hand–foot syndrome[2]
  - thrombocytopenia[3]
- AEs were chosen for study if they were common, manageable, readily and systematically measurable, and potentially reflective of intended target inhibition with sunitinib
- We assessed the relative strength and independence of each biomarker in a combined analysis using the same database

*This efficacy biomarker analysis included three trials, excluding two trials that used continuous daily dosing (CDD), rather than the approved Schedule 4/2

1. Rini BI, et al. *J Natl Cancer Inst* 2011;103:763–773; 2. Michaelson MD, et al. *J Clin Oncol* 2011;29(suppl 7; abstr 320); 3. Donskov F, et al. *Eur J Cancer* 2011;47:S136(abstr 1141); 4. Davis MP, et al. *Eur J Cancer* 2011:47:S135(abstr 1139).

Sunitinib-associated Hypertension (HTN) Has Been Associated with Improved Clinical Outcomes

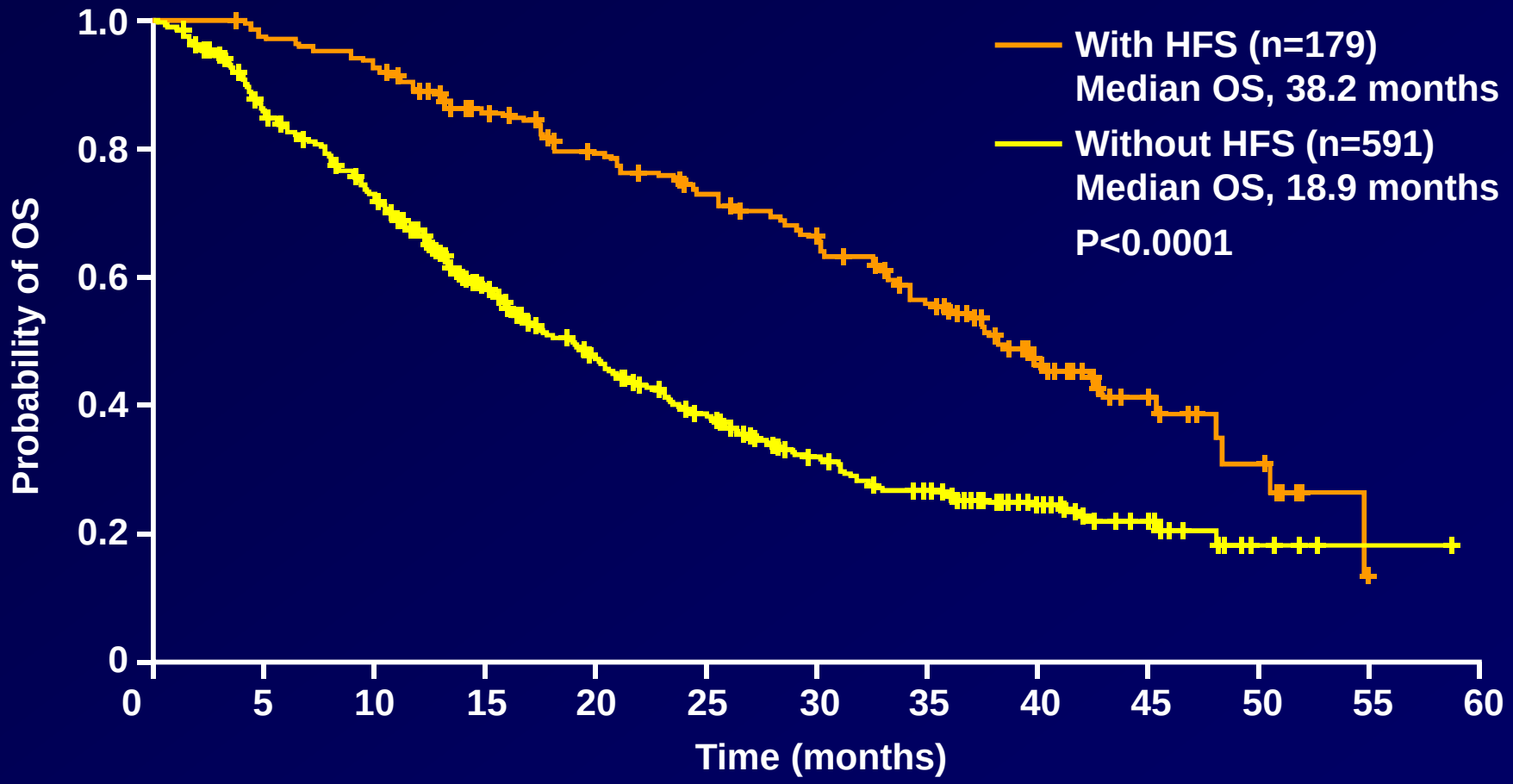


No. of patients at risk									
With HTN	442	418	377	308	257	224	190	106	29
Without HTN	92	55	38	21	15	7	5	3	1

- HTN-associated complications were investigated by expanding the safety analysis with 4,373 patients from an expanded access trial
  - AE rates were similar for patients with and without SBP-defined HTN; however, patients with HTN had somewhat more renal AEs (5% vs. 3%; P=0.013)

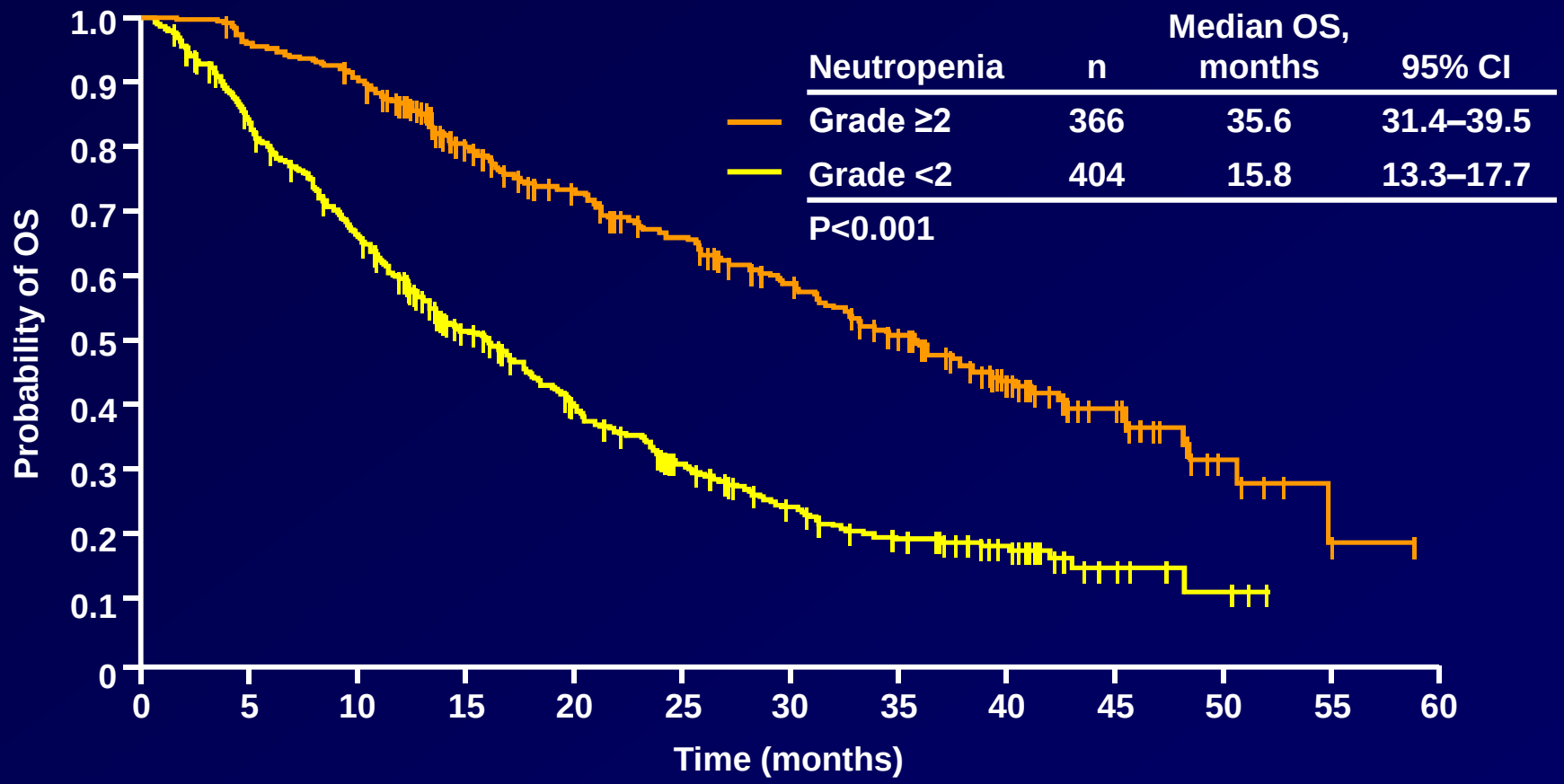
Rini BI, et al. *J Natl Cancer Inst* 2011;103:763–773.

Sunitinib-associated Hand–foot Syndrome (HFS) Has Been Associated with Improved Clinical Outcomes



Michaelson MD, et al. Poster presented at ASCO GU, Orlando, Florida, USA, February 17–19, 2011.

Sunitinib-associated Myelosuppression Has Been Associated with Improved Clinical Outcomes



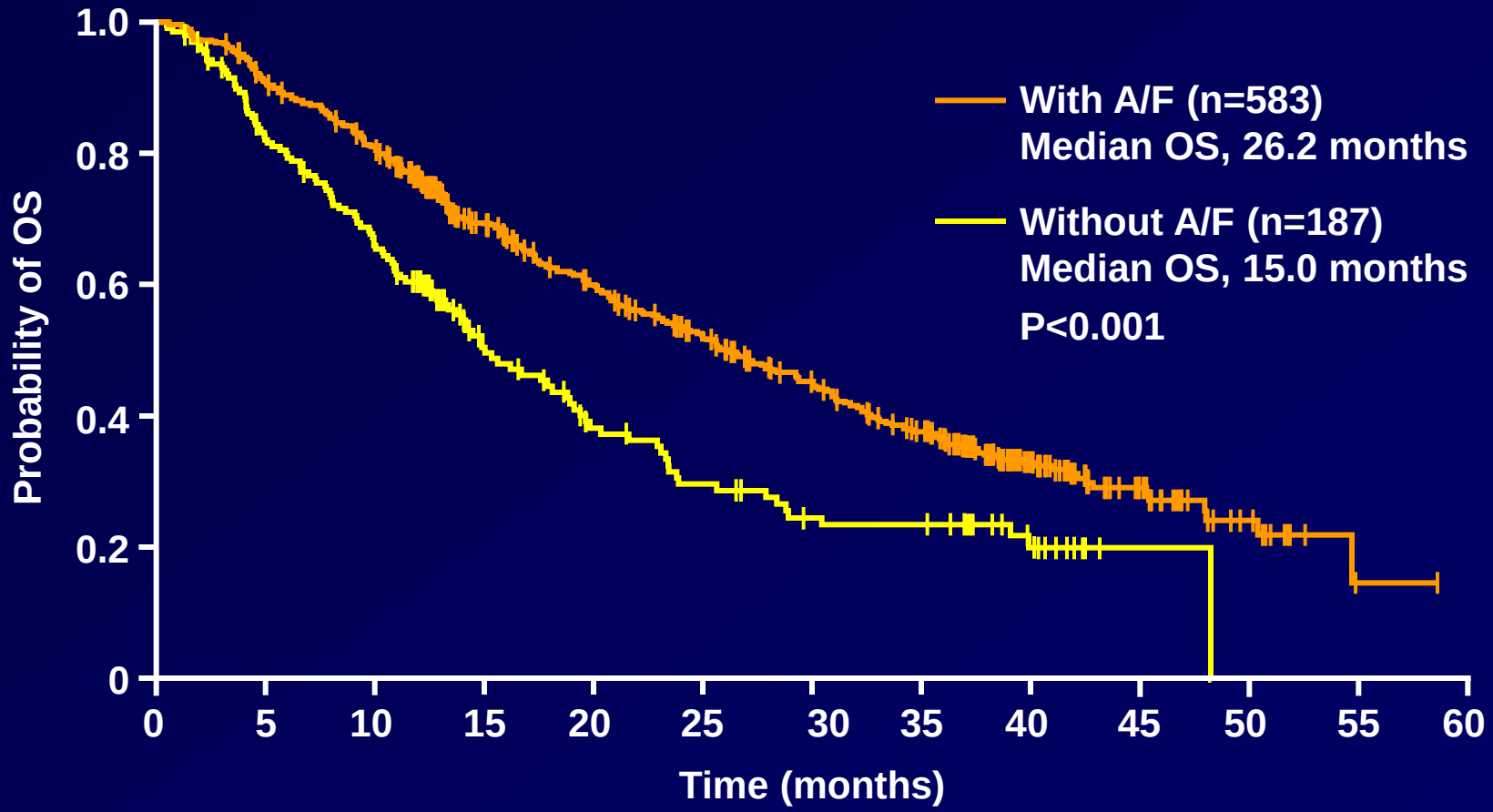
Neutropenia	n	Median OS, months	95% CI
Grade ≥2	366	35.6	31.4–39.5
Grade <2	404	15.8	13.3–17.7

P<0.001

- Neutropenia- and thrombocytopenia-related AEs were investigated by expanding the safety analysis with 4,388 patients from an expanded access trial
  - Related AEs were more frequent with neutropenia grade ≥2 and thrombocytopenia grade >1 (P<0.001)

Donskov F, et al. Poster presented at ECCO-ESMO, Stockholm, Sweden, September 23–27, 2011.

Sunitinib-associated Asthenia/Fatigue (A/F) Has Been Associated with Improved Clinical Outcomes



Davis MP, et al. Poster presented at ECCO-ESMO, Stockholm, Sweden, September 23–27, 2011; Pfizer data on file.

Study Designs and Treatments

- A retrospective analysis with pooled data from 770 mRCC patients who received sunitinib in five clinical trials[1–5]
  - 1st-line (n=494; 64%)
  - 2nd-line (n=276; 36%)

- Oral sunitinib was administered at:
  - 50 mg once daily on Schedule 4/2 (n=544; 71%)
  - 37.5 mg CDD (n=226; 29%)

1. Motzer RJ, et al. *J Clin Oncol* 2006;24:16–24;
2. Motzer RJ, et al. *JAMA* 2006;295:2516–2524;
3. Escudier B, et al. *J Clin Oncol* 2009;27:4068–4075;
4. Motzer RJ, et al. *J Clin Oncol* 2009;27:3584–3590;
5. Barrios CH, et al. *Cancer* 2012;118:1252–1259.

Patient Eligibility

- Eligibility criteria common to all patients were:
  - age 18 years or older
  - histologically confirmed mRCC
  - adequate organ function
  - presence of measurable disease
  - no known presence of brain metastases
  - Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1

Statistical Methods

- A multivariate Cox proportional-hazard regression model was used to analyze potential independent AE biomarkers
  - repeated using a 12-week landmark to address potential bias from longer treatment (ie, AEs evaluated up to the first 12 weeks)
  - performed separately for patients on Schedule 4/2 and both schedules combined
- The following were used as covariates for prediction of PFS and OS:
  - hypertension (SBP ≥140 mmHg)*
  - neutropenia and thrombocytopenia (both CTCAE grade >1)
  - any CTCAE grade hand–foot syndrome and asthenia/fatigue
  - dose reduction (adjusted for time on treatment)
  - relative dose intensity for the overall treatment period
  - previously identified prognostic factors[1–3]

*Results of prior biomarker analyses were similar using DBP-defined hypertension[4]

1. Motzer RJ, et al. *J Clin Oncol* 2002;20:289–296;
2. Heng DY, et al. *J Clin Oncol* 2009;27:5794–5799;
3. Patil S, et al. *Ann Oncol* 2011;22:295–300;
4. Rini BI, et al. *J Natl Cancer Inst* 2011;103:763–773.

Baseline Patient Characteristics

Characteristic	2nd-line, Schedule 4/2 Phase II trial[1] (n=63)	2nd-line, Schedule 4/2 Phase II trial[2] (n=106)	1st-line, Schedule 4/2 Phase III trial[3] (n=375)*	1st-line, Schedule CDD Phase II trial[4] (n=119)	2nd-line, Schedule CDD Phase II trial[5] (n=107)
Median (range) age, years	60 (24–87)	56 (32–79)	62 (27–87)	58‡ (24–78)	59 (29–80)
ECOG PS, n (%)					
0	34 (54)	58 (55)	231 (62)	63 (53)	61 (57)
1	29 (46)	48 (45)	144 (38)	56 (47)	45 (42)
≥2	0	0	0	0	1 (1)
Prior nephrectomy, n (%)	58 (92)	106 (100)	340 (91)	112 (94)	100 (93)
Prior cytokine therapy, n (%)	63 (100)	106 (100)	0	0	107 (100)
No. of disease sites, n (%)					
1	8 (13)	13 (12)	55 (15)	30 (25)	12 (11)
≥2	55 (87)	93 (88)	320 (85)	87 (73)¶	95 (89)

*The 375 patients cited in the table are those who received sunitinib in this trial
‡Mean value presented
¶Data missing for two patients

1. Motzer RJ, et al. *J Clin Oncol* 2006;24:16–24; 2. Motzer RJ, et al. *JAMA* 2006;295:2516–2524;
3. Motzer RJ, et al. *J Clin Oncol* 2009;27:3584–3590; 4. Barrios CH, et al. *Cancer* 2012;118:1252–1259;
5. Escudier B, et al. *J Clin Oncol* 2009;27:4068–4075.

Final Multivariate Models of Associations Between AEs and Survival for mRCC Patients on Schedule 4/2

AE	Endpoint	AE at any time point			AE by the 12-week landmark		
		HR	95% CI	P value*	HR	95% CI	P value*
Hypertension	PFS	0.29	0.22–0.40	<0.0001	–	–	NS
	OS	0.30	0.24–0.43	<0.0001	0.65	0.51–0.84	0.0008
Hand–foot syndrome	PFS	0.75	0.60–0.94	0.0148	–	–	NS
	OS	0.58	0.44–0.77	0.0001	0.67	0.46–0.98	0.0415
Asthenia/ fatigue	PFS	0.49	0.38–0.64	<0.0001	–	–	NS
	OS	0.72	0.54–0.96	0.0245	–	–	NS
Neutropenia	PFS	–	–	NS	–	–	NS
	OS	–	–	NS	–	–	NS
Thrombocytopenia	PFS	–	–	NS	–	–	NS
	OS	–	–	NS	–	–	NS

NS, not significant
*Wald chi-square test

Results, cont'd

- Neutropenia and thrombocytopenia were not significant in any of the multivariate analyses, possibly due to a statistically significant correlation of both with hypertension and asthenia/fatigue ($r \geq 0.08$; $P < 0.05$, Fisher's exact test), but not with hand–foot syndrome
- Dose reduction, adjusted for time on treatment, was not associated with clinical outcome
- Results were similar with both schedules (Schedule 4/2 and CDD) combined

Conclusions

- Combined multivariate analyses indicate that hypertension and hand–foot syndrome, and to a lesser degree asthenia/fatigue, may serve as independent on-treatment biomarkers of sunitinib efficacy in mRCC
- The inconsistent landmark results warrant further study, but suggest that hypertension and hand–foot syndrome may be more reliable early predictors of OS than of PFS with sunitinib
- Neutropenia and thrombocytopenia were not significant in the multivariate analyses; however, a statistically significant correlation of both with hypertension and asthenia/fatigue was seen
- Further study into underlying biological mechanisms is warranted
- Providers who observe these AEs are encouraged to continue sunitinib therapy, managing AEs with standard medical treatment with or without dose reduction as clinically indicated

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