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Predictors of anti-VEGF drug-induced hypertension using different hypertension criteria: a secondary analysis of the COMPARZ study

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Abstract

Background: There is inconsistency in the criteria used to define anti-vascular endothelial growth factor (VEGF) drug-induced hypertension (AVEGF-HT) in published studies. It is unknown whether specific patient characteristics similarly predict AVEGF-HT using different criteria.

Methods: We assessed the associations between clinical and demographic factors ($n = 22$) and AVEGF-HT, using six criteria based on predefined on-treatment blood pressure (BP) thresholds or absolute BP elevations *versus* baseline, in a *post hoc* analysis of a phase III trial of 1102 patients with renal cell carcinoma (RCC) randomized to pazopanib or sunitinib (COMPARZ study).

Results: The cumulative incidence of AVEGF-HT at any time while on treatment ranged between 14.8% [criterion: grade ⩾3 toxicity, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0] and 58.8% (criterion: absolute systolic BP increase ⩾20 mmHg *versus* baseline). After adjusting for anti-VEGF treatment and baseline BP, the number of significant ($p < 0.05$) predictors ranged between one (criterion: absolute systolic BP increase ⩾20 mmHg, on-treatment systolic BP ⩾140 mmHg and diastolic BP ⩾90 mmHg) and nine (criterion: grade ⩾3 toxicity, NCI CTCAE v3.0). Age, use of antidiabetic drugs and use of antihypertensive drugs each significantly predicted four AVEGF-HT criteria. By contrast, sex, smoking, heart rate, proteinuria, Karnofsky performance status, and use of thiazide diuretics did not predict any criterion.

Conclusions: There was a significant variability in the incidence, number and type of predictors of AVEGF-HT, using six different criteria, in a *post hoc* analysis of the COMPARZ study. The use of specific criteria might affect the assessment of the interaction between anti-VEGF drugs, AVEGF-HT and cancer outcomes.

Keywords: anti-VEGF drugs, blood pressure, cancer, hypertension, outcomes, renal cell carcinoma

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Introduction

The vascular endothelial growth factor (VEGF) regulates angiogenesis, a key pathophysiological process in cancer, through the tyrosine kinase receptors VEGFR1 (Flt-1) and VEGFR2 (Flk-1) and the endogenous messenger nitric oxide.[1–4] Several drugs inhibiting the effects of VEGF (anti-VEGF drugs), either by targeting circulating VEGF or its receptors, have been shown to improve survival outcomes in different types of cancer.[5] However, anti-VEGF drugs also increase the risk of hypertension, particularly during the first few weeks of treatment.[3] There is a

significant variability, between 9% and 67%, in the reported incidence of anti-VEGF drug-induced hypertension (AVEGF-HT).[6]

Although AVEGF-HT might require anti-VEGF dose modification, withdrawal or treatment with antihypertensive drugs, it might also predict favourable survival outcomes in specific types of cancer, including renal cell carcinoma (RCC).[7–18] However, other studies have refuted this hypothesis.[19,20] Measurement of blood pressure (BP) in these studies was performed at different time points, using different protocols. Furthermore, there was a considerable variability in the criteria used for AVEGF-HT, which included 'hypertension' listed as diagnosis in medical records, the use of antihypertensive drugs, a predefined absolute BP increase from baseline, and on-treatment BP values above predefined thresholds.[7–17,19–21]

Theoretically, the lack of consistency in the criteria for AVEGF-HT might prevent the identification of patients requiring a more intensive BP monitoring, particularly during the first few weeks of treatment. However, no study has investigated whether specific clinical or demographic characteristics have similar capacity to predict AVEGF-HT, and possibly survival outcomes, using different criteria. We sought to address this issue by studying the capacity of a wide range of patient characteristics to predict AVEGF-HT, using six predefined criteria, in a completed phase III clinical trial of patients with RCC randomized to pazopanib or sunitinib.[22] Potential advantages of this approach were the rigorous assessment of demographic and clinical characteristics in the study cohort and the use of a predefined protocol for the measurement of BP, at the same time points in each patient, within a tightly controlled clinical trial environment.

Methods

Study design and patients

We conducted a *post hoc* analysis of a phase III randomized, open-label, parallel group trial investigating the efficacy and safety of pazopanib and sunitinib in RCC (COMPARZ study) [ClinicalTrials.gov identifier: NCT007720941].[22] The COMPARZ study enrolled adult patients with locally advanced or metastatic RCC with a clear-cell histology component, no prior systemic therapy, measurable disease according to the Response Evaluation Criteria in Solid Tumours Guidelines, and satisfactory renal, hepatic and hematologic parameters. Exclusion criteria were pregnancy or lactating female, history of another cancer, the presence of metastatic disease in the central nervous system, significant gastrointestinal abnormalities, uncontrolled infection, significant QT interval prolongation, cardiovascular events within the previous 12 months, history of stroke or transient ischaemic attack, history of thromboembolic events, poorly controlled hypertension [systolic BP (SBP) $\geqslant$150 mmHg or diastolic BP (DBP) $\geqslant$90 mmHg, despite the use of antihypertensive drugs], prior major surgery or trauma within the previous 28 days, and active bleeding or bleeding predisposition. Randomization to pazopanib or sunitinib was stratified according to the Karnofsky performance status score, the concentration of lactate dehydrogenase, and previous nephrectomy. Participants were randomized, in a 1:1 ratio, to either pazopanib 800 mg once daily continuously or sunitinib 50 mg once daily in 6-week cycles of dosing for 4 weeks of treatment, followed by 2 weeks without treatment.[22]

Pazopanib or sunitinib dose modification (dose reduction, dose interruption/delay or withdrawal) due to AVEGF-HT followed predefined scenarios and protocols: asymptomatic and persistent SBP at least 150 and less than 170 mmHg, or DBP at least 90 and less than 110 mmHg, or a clinically significant DBP increase of at least 20 mmHg (continue current anti-VEGF drug dose, adjust current dose of or initiate new antihypertensive drugs, titrate antihypertensive drugs during the next two weeks to achieve well controlled BP, defined as SBP $<$150 mmHg and DBP $<$90 mmHg); symptomatic, or SBP at least 170 mmHg, or DBP at least 110 mmHg, or failure to achieve BP control within two weeks in the first scenario (interrupt anti-VEGF drug, adjust current or initiate new antihypertensive drugs, titrate antihypertensive drugs during the next two weeks as indicated to achieve well controlled BP, restart anti-VEGF drug at the same dose or lower dose at the discretion of the study investigator, once BP control is achieved); at least two symptomatic episodes of hypertension despite the modification of antihypertensive drugs and reduction of the dose of anti-VEGF drug (discontinuation of anti-VEGF drug).

Patient data

Baseline demographic, clinical and laboratory data were collated. BP was assessed at baseline,

day 14, day 28 and day 42 of cycle 1, and then day 28 and day 42 of each cycle thereafter until discontinuation of study treatment. During each visit, after a resting period of at least 10 min, sitting BP was measured three times at approximately 2 min intervals using the cuff method. The mean SBP and DBP values of the three measurements were recorded. All BP measurements were performed on the same arm, using the same cuff size and equipment, throughout the study.[22]

The following baseline clinical and demographic parameters were assessed as possible predictors of AVEGF-HT in view of their plausible associations with BP elevations in epidemiological studies: age,[23,24] sex,[24] ethnicity,[25] body mass index,[26] family history of hypertension,[27] smoking,[28] heart rate,[29] neutrophil to lymphocyte ratio (a marker of inflammation),[30] prior nephrectomy,[31] proteinuria,[32] Karnofsky performance status and FKSI (Kidney Symptom Index)-19 score (measures of physical function and quality of life),[33] serum albumin concentrations,[34] haemoglobin concentrations,[35] haematocrit,[36] use of any antihypertensive drug (indicating pre-existing hypertension) and specific drug classes, use of antidiabetic drugs (indicating pre-existing diabetes),[37] and use of nonsteroidal anti-inflammatory drugs (NSAIDs).[38]

Anonymized patient level data were remotely accessed *via* a secure research environment following approval by an independent review panel of the clinical data transparency portal clinicalstudydatarequest.com (reference number: 668, access available until 28 July 2017) [ClinicalTrials.gov identifier: NCT02156310]. The study was approved by the institutional review board or ethics committee at each participating centre. All patients provided written informed consent before commencing the study.[22]

Study outcomes

We analysed six AVEGF-HT criteria, based on absolute elevations in SBP or DBP *versus* baseline, or on-treatment SBP or DBP values above predefined thresholds, according to current hypertension guidelines (SBP $\geqslant$140 mmHg or DBP $\geqslant$90 mmHg) or the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3.0, hypertension grade 3, SBP $\geqslant$160 mmHg or DBP $\geqslant$100 mmHg):[21,39,40] absolute SBP change *versus* baseline at least 10 mmHg, and on-treatment SBP at least 140 mmHg and DBP at least 90 mmHg; grade 3 and higher hypertension toxicity (NCI CTCAE v3.0);[21] on-treatment SBP at least 160 mmHg; absolute SBP change *versus* baseline at least 20 mmHg; on-treatment DBP at least 100 mmHg; and absolute DBP change *versus* baseline at least 20 mmHg. We assessed the incidence of AVEGF-HT at any BP assessment time point while on anti-VEGF treatment plus 28 days after study treatment cessation (primary outcome). We also assessed the cumulative incidence of AVEGF-HT within day 14 (week 2, cycle 1), day 42 (week 6, cycle 1), and day 84 (week 12, cycle 2) of treatment (secondary outcomes).

Statistical analysis

Data are expressed as means $\pm$ SD or frequencies. Comparisons of the AVEGF-HT rates between sunitinib and pazopanib were performed by χ^2 tests. Multivariable logistic regression was used to investigate the capacity of baseline clinical and demographic variables to predict AVEGF-HT, after adjusting for treatment (pazopanib or sunitinib) and baseline SBP and DBP values. As less than 5% of data were typically missing, a complete case analysis was reported. The type 1 error rate was set at p less than 0.05. All analyses were two sided and undertaken using the R statistical environment v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline characteristics of the study participants are described in Table 1. The majority of patients were male, white, had prior nephrectomy, pre-existing hypertension, and Karnofsky performance status score greater than 90. Mean on-treatment SBP values with both sunitinib and pazopanib were higher than baseline values, particularly at week 2. A similar trend was observed for DBP values (Table 2). The frequency of anti-VEGF dose modification (dose reduction, dose interruption/delay or withdrawal) due to AVEGF-HT was 2.2% within week 2, 4.2% within week 6, 5.3% within week 12 ($p = 0.16$ for trend) and 6.9% overall with sunitinib; and 4.2% within week 2, 10.8% within week 6, 12.6% within week 12 ($p < 0.001$ for trend) and 13.4% overall with pazopanib.

Incidence and predictors of AVEGF-HT

Although there were no significant differences in the overall incidence of AVEGF-HT between sunitinib

Table 1. Baseline characteristics of the COMPARZ study participants.

	(*n* = 1102)
Age, years, mean (SD)	61.1 (11.0)
Sex	
Female	295 (27%)
Male	807 (73%)
Race	
White	702 (64%)
Asian	378 (34%)
Other	22 (2%)
Body mass index, kg/m^2, mean (SD)	27.3 (5.9)
Missing	91 (8%)
Family history of hypertension	
No	761 (69%)
Yes	320 (29%)
Missing	21 (2%)
Smoking status	
Never smoked	468 (43%)
Former smoker	494 (45%)
Current smoker	134 (12%)
Missing	6 (<1%)
Prior nephrectomy	
No	181 (16%)
Yes	921 (84%)
Grade 1 proteinuria	
No	786 (71%)
Yes	177 (18%)
Missing	139 (13%)
Karnofsky performance status	
70 or 80	268 (24%)
90 or 100	828 (76%)
FKSI-19 total score	59.0 (10.2)
Heng risk group	
Favourable	279 (25%)
Intermediate	604 (55%)
Poor	195 (18%)
Missing	24 (2%)
Serum albumin	

Table 1. (Continued)

	(*n* = 1102)
⩾LLN	956 (89%)
<LLN	123 (11%)
Missing	23 (2%)
Haemoglobin	
⩾LLN	647 (59%)
<LLN	454 (41%)
Missing	1 (<1%)
Haematocrit	
⩾LLN	622 (56%)
<LLN	479 (44%)
Missing	1 (<1%)
Use of antihypertensive drugs	
Angiotensin system inhibitor	292 (27%)
Calcium channel inhibitor	240 (22%)
β blocker	189 (18%)
Thiazide	147 (14%)
Any of above	503 (53%)
Missing	39 (4%)
Use of drugs for diabetes	
No	934 (85%)
Yes	161 (15%)
Missing	7 (<1%)
Use of nonsteroidal anti-inflammatory drugs	
No	825 (75%)
Yes	250 (23%)
Missing	27 (3%)

FKSI-19, Functional Assessment of Cancer Therapy-Kidney Symptom Index 19; LLN, lower limit of normal; SD, standard deviation.

and pazopanib while on treatment, there was a significant variability using specific criteria, between 14.8% (criterion: grade ⩾3 toxicity, NCI CTCAE v3.0) and 58.8% (criterion: absolute increase in SBP ⩾20 mmHg from baseline, Table 3).

After adjusting for anti-VEGF treatment and baseline SBP and DBP, the number of significant ($p < 0.05$) predictors of AVEGF-HT while on treatment also depended on specific criteria, ranging between one (use of antidiabetic drugs; criterion: absolute SBP increase ⩾20 mmHg *versus* baseline, on-treatment SBP ⩾140 mmHg and DBP ⩾90 mmHg) and nine (ethnicity, family history of hypertension, neutrophil to lymphocyte ratio, FKSI-19 total score, serum albumin,

Table 2. Blood pressure values at baseline and at week 2, 6 and 12 of treatment with sunitinib and pazopanib.

	Baseline	Week 2	Week 6	Week 12
SBP, mmHg, mean (SD)				
Sunitinib	127.1 (13.8)	136.5 (17.3)	127.9 (15.0)	128.0 (14.8)
Missing, *n* (%)	1 (0.2%)	25 (4.5%)	62 (11.3%)	126 (23.0%)
Pazopanib	126.7 (13.7)	138.6 (17.7)	135.5 (15.7)	132.8 (13.7)
Missing, *n* (%)	2 (0.4%)	19 (1.3%)	64 (11.5%)	143 (25.8%)
DBP, mmHg, mean (SD)				
Sunitinib	75.6 (8.6)	83.8 (10.6)	76.7 (9.1)	76.6 (9.2)
Missing, *n* (%)	1 (0.2%)	25 (4.5%)	62 (11.3%)	126 (23.0%)
Pazopanib	75.6 (9.0)	84.7 (10.9)	83.8 (10.3)	82.3 (9.5)
Missing, *n* (%)	2 (0.4%)	19 (1.3%)	64 (11.5%)	143 (25.8%)

DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

haematocrit, use of any antihypertensive drug, use of calcium channel blockers, and use of any antidiabetic drug; criterion: grade ⩾3 toxicity, NCI CTCAE v3.0, Table 4).

Age, use of antidiabetic drugs and use antihypertensive drugs each predicted four AVEGF-HT criteria (Table 4). Age was an independent predictor of on-treatment SBP at least 160 mmHg, absolute SBP change *versus* baseline at least 20 mmHg, on-treatment DBP at least 100 mmHg, and absolute DBP change *versus* baseline at least 20 mmHg. Use of antidiabetic drugs independently predicted absolute SBP change *versus* baseline at least 10 mmHg and on-treatment SBP at least 140 mmHg and DBP at least 90 mmHg, grade 3 and higher hypertension toxicity (NCI CTCAE v3.0), on-treatment DBP at least 100 mmHg, and absolute DBP change *versus* baseline at least 20 mmHg. Use of antihypertensive drugs independently predicted grade 3 and higher hypertension toxicity (NCI CTCAE v3.0), on-treatment SBP at least 160 mmHg, absolute SBP change *versus* baseline at least 20 mmHg, and on-treatment DBP at least 100 mmHg. By contrast, sex, smoking, heart rate, proteinuria, Karnofsky performance status, and use of thiazide diuretics did not predict any AVEGF-HT criterion (Table 4).

The analysis of clinical and demographic predictors of AVEGF-HT within week 2, 6 and 12 did not show any significant time-dependent trends except for the following criteria: absolute increase in SBP at least 10 mmHg from baseline, on-treatment SBP at least 140 mmHg and DBP at least 90 mmHg: ethnicity, prior nephrectomy, serum albumin and use of calcium channel blocker (Supplementary Table 1); grade 3 and higher hypertension toxicity (NCI CTCAE v3.0): use of antihypertensive drugs (Supplementary Table 2); on-treatment SBP at least 160 mmHg: ethnicity, smoking status, prior nephrectomy and use of calcium channel blockers (Supplementary Table 3); absolute SBP change *versus* baseline at least 20 mmHg: prior nephrectomy and use of angiotensin system inhibitors (Supplementary Table 4); on-treatment DBP at least 100 mmHg: age, neutrophil to lymphocyte ratio, and haematocrit (Supplementary Table 5); absolute DBP change *versus* baseline at least 20 mmHg: age, neutrophil to lymphocyte ratio, prior nephrectomy, haematocrit, use of antihypertensive drugs, use of calcium channel inhibitors and use of NSAIDs (Supplementary Table 6).

Discussion

There is an increasing interest in the association between anti-VEGF drugs and AVEGF-HT. Specific clinical and demographic predictors of AVEGF-HT might allow the identification of patients benefitting from intensive BP monitoring, particularly during the first few weeks of treatment.[3] Studies conducted in patients with hypertension have shown that an earlier BP control with antihypertensive drugs is associated with better cardiovascular outcomes.[41] Furthermore, the reported association between AVEGF-HT and cancer outcomes might better identify treatment responders *versus* nonresponders, with significant

Table 3. Cumulative incidence of anti-VEGF-mediated hypertension using different criteria.

Hypertension definition	Sunitinib ($n = 548$)	Pazopanib ($n = 554$)	*p* value¶
SBP change* ⩾10 mmHg and SBP$ ⩾140 mmHg and DBP$ ⩾90 mmHg			
Overall‡	262 (48.7%)	297 (54.6%)	0.06
Within the first 2 weeks of treatment	77 (14.7%)	112 (20.9%)	0.008
Within the first 6 weeks of treatment	137 (25.7%)	206 (38.0%)	<0.001
Within the first 12 weeks of treatment	179 (33.5%)§	236 (43.6%)§	0.008
Grade ⩾3			
Overall‡	81 (14.8%)	82 (14.8%)	0.92
Within the first 2 weeks of treatment	27 (4.9%)	34 (6.1%)	0.45
Within the first 6 weeks of treatment	45 (8.2%)	68 (12.3%)	0.03
Within the first 12 weeks of treatment	62 (11.3%)§	72 (13.0%)§	0.45
SBP^2 ⩾160 mmHg			
Overall‡	156 (28.5%)	164 (29.6%)	0.73
Within the first 2 weeks of treatment	44 (8.0%)	64 (11.6%)	0.06
Within the first 6 weeks of treatment	74 (13.5%)	111 (20.0%)	0.005
Within the first 12 weeks of treatment	92 (16.8%)§	131 (23.6%)§	0.006
SBP change* ⩾20 mmHg			
Overall‡	322 (58.8%)	320 (57.8%)	0.78
Within the first 2 weeks of treatment	118 (21.5%)	160 (28.9%)	0.006
Within the first 6 weeks of treatment	193 (35.2%)	241 (43.5%)	0.006
Within the first 12 weeks of treatment	237 (43.2%)§	263 (47.5%)§	0.18
DBP$ ⩾100 mmHg			
Overall‡	131 (23.9%)	135 (24.4%)	0.92
Within the first 2 weeks of treatment	38 (6.9%)	46 (8.3%)	0.46
Within the first 6 weeks of treatment	65 (11.9%)	104 (18.8%)	0.002
Within the first 12 weeks of treatment	83 (15.1%)§	120 (21.7%)§	0.007
DBP change* ⩾20 mmHg			
Overall‡	193 (35.2%)	215 (38.8%)	0.24
Within the first 2 weeks of treatment	61 (11.1%)	73 (13.2%)	0.34
Within the first 6 weeks of treatment	106 (19.3%)	149 (26.9%)	0.004
Within the first 12 weeks of treatment	134 (24.5%)§	174 (31.4%)§	0.01

*Maximal change from baseline.
$Maximal value after baseline.
‡While on treatment and within the 28 days following treatment cessation.
§$p < 0.001$ (temporal trend).
¶Pazopanib *versus* sunitinib.
DBP, diastolic blood pressure; SBP, systolic blood pressure; VEGF, vascular endothelial growth factor.

Table 4. Association between baseline clinical and demographic characteristics and anti-VEGF-mediated hypertension while on treatment and within the 28 days following treatment cessation.

Variable	Hypertension* OR (95% CI)	Grade ⩾3$ OR (95% CI)	SBP‡ >160 mmHg OR (95% CI)	Max ΔSBP§ >20 mmHg OR (95% CI)	DBP‡ >100 mmHg OR (95% CI)	Max ΔDBP§ >20 mmHg OR (95% CI)
Age (per 10 years increment)	0.97 (0.86–1.10) $p = 0.62$	1.07 (0.90–1.27) $p = 0.45$	**1.48 (1.27–1.71) p < 0.0001**	**1.35 (1.18–1.54) p < 0.0001**	**0.74 (0.64–0.86) p < 0.0001**	**0.83 (0.73–0.95) p = 0.008**
Sex (male *versus* female)	0.95 (0.71–1.27) $p = 0.73$	1.07 (0.72–1.60) $p = 0.74$	1.03 (0.75–1.43) $p = 0.84$	1.12 (0.83– 1.51) $p = 0.44$	1.14 (0.80–1.62) $p = 0.45$	0.93 (0.69–1.25) $p = 0.61$
Race	$p = 0.21$	**p < 0.0001**	$p = 0.26$	**p = 0.02**	$p = 0.66$	$p = 0.19$
Other *versus* white	1.16 (0.46–2.92) $p = 0.76$	0.84 (0.19–3.75) $p = 0.82$	1.25 (0.49–3.18) $p = 0.64$	0.90 (0.36–2.28) $p = 0.83$	1.32 (0.48–3.65) $p = 0.59$	1.09 (0.42–2.82) $p = 0.86$
Asian *versus* White	0.79 (0.61–1.04) $p = 0.09$	**2.57 (1.80–3.68) p < 0.0001**	0.79 (0.58–1.07) $p = 0.13$	**0.68 (0.51–0.89) p = 0.006**	1.14 (0.83–1.56) $p = 0.42$	1.30 (0.98–1.72) $p = 0.07$
Body mass index (per kg/m^2 increment)	1.02 (0.99–1.04) $p = 0.16$	1.01 (0.97–1.03) $p = 0.88$	1.00 (0.98–1.03) $p = 0.96$	**1.03 (1.01–1.06) p = 0.01**	1.01 (0.98–1.04) $p = 0.43$	1.02 (0.99–1.04) $p = 0.19$
Family history of hypertension (yes *versus* no)	1.12 (0.85–1.47) $p = 0.42$	**1.79 (1.26–2.55) p = 0.0012**	0.92 (0.68–1.25) $p = 0.59$	**1.38 (1.03–1.84) p = 0.03**	0.93 (0.67–1.28) $p = 0.65$	1.30 (0.97–1.74) $p = 0.08$
Smoking status	$p = 0.18$	$p = 0.55$	$p = 0.69$	$p = 0.08$	$p = 0.99$	$p = 0.42$
Former smoker *versus* current smoker	1.20 (0.80–1.78) $p = 0.37$	1.23 (0.69–2.18) $p = 0.47$	1.09 (0.69–1.71) $p = 0.71$	1.26 (0.83–1.91) $p = 0.27$	0.97 (0.61–1.58) $p = 0.90$	1.07 (0.69–1.64) $p = 0.77$
Never smoked *versus* current smoker	0.93 (0.62–1.39) $p = 0.73$	1.36 (0.77–2.42) $p = 0.29$	1.20 (0.76–1.88) $p = 0.44$	0.92 (0.61–1.39) $p = 0.69$	0.97 (0.61–1.54) $p = 0.89$	1.25 (0.81–1.94) $p = 0.31$
Heart rate (per 10 bpm increment)	1.01 (0.92–1.12) $p = 0.81$	0.91 (0.79–1.04) $p = 0.17$	1.01 (0.90–1.13) $p = 0.86$	1.02 (0.92–1.13) $p = 0.77$	0.99 (0.88–1.11) $p = 0.86$	1.01 (0.91–1.12) $p = 0.83$
Neutrophil to lymphocyte ratio (per unit increment)	0.98 (0.93–1.03) $p = 0.37$	**0.82 (0.73–0.92) p = 0.0005**	1.01 (0.95–1.07) $p = 0.70$	1.01 (0.95–1.06) $p = 0.97$	0.94 (0.87–1.01) $p = 0.07$	**0.93 (0.88–0.99) p = 0.02**
Prior nephrectomy (yes *versus* no)	0.81 (0.57–1.15) $p = 0.24$	1.13 (0.70–1.84) $p = 0.62$	**0.59 (0.41–0.85) p = 0.005**	**0.69 (0.48–0.99) p = 0.04**	0.78 (0.52–1.17) $p = 0.23$	0.84 (0.59–1.19) $p = 0.33$
Proteinuria (grade 1, yes *versus* no)	0.98 (0.69,1.39) $p = 0.90$	0.74 (0.45–1.21) $p = 0.23$	1.02 (0.70–1.49) $p = 0.92$	0.99 (0.68–1.42) $p = 0.94$	1.24 (0.84–1.85) $p = 0.28$	1.07 (0.74–1.55) $p = 0.70$
Karnofsky performance status <90 (yes *versus* no)	0.94 (0.70–1.27) $p = 0.70$	0.78 (0.51–1.20) $p = 0.26$	1.22 (0.88–1.68) $p = 0.24$	1.11 (0.81–1.51) $p = 0.52$	0.89 (0.62–1.28) $p = 0.54$	0.83 (0.61–1.14) $p = 0.25$

Table 4. (Continued)

Variable	Hypertension* OR (95% CI)	Grade ⩾3$ OR (95% CI)	SBP‡ >160 mmHg OR (95% CI)	Max ΔSBP§ >20 mmHg OR (95% CI)	DBP‡ >100 mmHg OR (95% CI)	Max ΔDBP§ >20 mmHg OR (95% CI)
FKSI-19 total score (per unit increment)	1.01 (0.99–1.02) $p = 0.30$	**1.04 (1.02–1.06) p = 0.0006**	1.01 (0.99–1.02) $p = 0.60$	1.01 (1.00–1.03) $p = 0.16$	1.02 (1.00–1.03) $p = 0.08$	1.01 (1.00–1.03) $p = 0.15$
Albumin (per unit increment)	0.99 (0.96–1.01) $p = 0.32$	**1.04 (1.01–1.08) p = 0.03**	**0.96 (0.94–0.99) p = 0.01**	0.98 (0.95–1.01) $p = 0.08$	1.00 (0.97–1.03) $p = 0.91$	1.01 (0.98–1.03) $p = 0.60$
Haemoglobin (per unit increment)	1.0 (0.99–1.01) $p = 0.27$	1.01 (1.00–1.02) $p = 0.05$	1.00 (0.99–1.01) $p = 0.55$	1.00 (1.00–1.01) $p = 0.29$	**1.01 (1.00–1.02) p = 0.02**	1.01 (1.00–1.01) $p = 0.14$
Haematocrit (per 0.1% increment)	1.17 (0.91–1.51) $p = 0.21$	**1.42 (1.01–1.99) p = 0.04**	0.87 (0.66–1.16) $p = 0.34$	1.14 (0.88–1.48) $p = 0.32$	**1.38 (1.03–1.86) p = 0.03**	1.25 (0.96–1.64) $p = 0.10$
Use of antihypertensive drugs (yes *versus* no)	0.97 (0.74–1.26) $p = 0.80$	**1.67 (1.17–2.40) p = 0.005**	**1.38 (1.03–1.85) p = 0.03**	**1.70 (1.28–2.24) p = 0.0002**	**0.63 (0.46–0.86) p = 0.003**	0.89 (0.67–1.18) $p = 0.40$
Use of angiotensin system inhibitor (yes *versus* no)	0.92 (0.69–1.23) $p = 0.56$	1.21 (0.83–1.76) $p = 0.33$	**1.40 (1.03–1.91) p = 0.03**	**1.63 (1.20–2.21) p = 0.002**	0.87 (0.62–1.24) $p = 0.45$	0.99 (0.72–1.35) $p = 0.94$
Use of calcium channel inhibitor (yes *versus* no)	0.86 (0.63–1.17) $p = 0.33$	**1.66 (1.14–2.43) p = 0.009**	1.00 (0.74–1.44) $p = 0.84$	1.23 (0.89–1.69) $p = 0.20$	**0.48 (0.32–0.72) p = 0.0003**	**0.67 (0.48–0.94) p = 0.02**
Use of β blocker (yes *versus* no)	1.06 (0.75–1.49) $p = 0.73$	1.26 (0.82–1.94) $p = 0.29$	1.39 (0.97–1.98) $p = 0.0732$	**1.91 (1.33–2.76) p = 0.0005**	0.95 (0.64–1.42) $p = 0.81$	0.94 (0.65–1.35) $p = 0.74$
Use of thiazide-like diuretic (yes *versus* no)	0.88 (0.60–1.27) $p = 0.49$	0.75 (0.44–1.29) $p = 0.3023$	1.21 (0.82–1.80) $p = 0.34$	1.16 (0.79–1.70) $p = 0.45$	0.75 (0.47–1.19) $p = 0.22$	0.93 (0.62–1.38) $p = 0.70$
Use of a drug for diabetes (yes *versus* no)	**0.53 (0.37–0.76)** $p = 0.0005$	**0.58 (0.33–0.99) p = 0.048**	0.75 (0.50–1.11) $p = 0.1525$	1.01 (0.70–1.46) $p = 0.95$	**0.55 (0.34–0.88) p = 0.01**	**0.46 (0.31–0.70) p = 0.0002**
Use of a nonsteroidal anti-inflammatory drug (yes *versus* no)	0.76 (0.57–1.03) $p = 0.08$	0.91 (0.60–1.38) $p = 0.6659$	1.28 (0.93–1.77) $p = 0.1354$	1.11 (0.81–1.51) $p = 0.52$	**0.68 (0.47–1.00) p = 0.048**	**0.67 (0.48–0.93) p = 0.01**

Significant associations are highlighted in bold.
*Absolute increase in SBP ⩾10 mmHg from baseline, SBP ⩾140 mmHg and DBP ⩾90 mmHg.
$NCI CTCAE v3.0.
‡Maximal change from baseline.
§Maximal value after baseline.
CI, confidence interval; DBP, diastolic blood pressure; FKSI-19, Functional Assessment of Cancer Therapy-Kidney Symptom Index 19; OR, odds ratio; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SBP, systolic blood pressure; VEGF, vascular endothelial growth factor.

implications for a personalized medicine based approach.[7–17] However, it is unknown whether the wide range of anti-VEGF drugs, BP measurement methods, protocols and time points, and AVEGF-HT criteria studied might limit the generalizability of the available data on the complex interaction between anti-VEGF drugs, AVEGF-HT and cancer outcomes.[7–17] In a recent systematic review and meta-analysis of 15 studies on AVEGF-HT and survival in RCC,[18] nine studies investigated sunitinib alone,[42–50] one investigated sorafenib alone,[51] one investigated axitinib alone,[52] whereas the remaining four investigated two or more anti-VEGF drugs.[10,53–55] When considering the timing of AVEGF-HT, one study captured BP elevations at any time point,[42] five studies investigated the period between baseline and week 4, the week 4 time point, or the first treatment cycle,[10,43,44,50,53] three studies investigated the week 8 time point,[45,52,54] whereas six studies did not report any relevant details.[46–49,51,55] Furthermore, 11 studies defined AVEGF-HT using on-treatment SBP thresholds ranging between 110 and 160 mmHg,[10,42–45,47–50,52,54] one study used absolute BP changes *versus* baseline,[53] whereas the remaining three studies did not report any relevant details.[46,51,55]

The assessment of whether specific patient characteristics have similar capacity to predict AVEGF-HT regardless of anti-VEGF drug, assessment time points and specific criteria requires a well characterized study population in which each patient undergoes the same baseline and follow-up BP assessment. Using six predefined AVEGF-HT criteria in a *post hoc* analysis of the COMPARZ study, we observed a significant variability in the cumulative incidence of AVEGF-HT while on treatment plus 28 days after study treatment cessation (between 14.8% and 58.8%), the number of predictors for each criterion (between 1 and 9), and the number of criteria predicted by each patient characteristic. Age, use of antidiabetic drugs and use of antihypertensive drugs each predicted four AVEGF-HT criteria. By contrast, sex, smoking, heart rate, proteinuria, Karnofsky performance status and use of thiazide diuretics did not predict any criterion. The strength of the associations between specific predictors and AVEGF-HT criteria was also dependent on individual BP assessment time points.

Two studies have recently sought to identify the factors associated with AVEGF-HT. Hamnvik and colleagues analysed the electronic clinical data of 1120 patients with RCC, hepatocellular carcinoma, gastrointestinal stromal cancers or other cancers treated with sunitinib, sorafenib or pazopanib in a naturalistic setting.[10] BP elevations were assessed until the first anti-VEGF drug was either stopped or replaced with another anti-VEGF drug. In patients without pre-existing hypertension, AVEGF-HT was defined either as hypertension listed as a diagnosis in the electronic medical record, at least one prescription for antihypertensive medication, on-treatment SBP at least 160 mmHg or DBP at least 100 mmHg. In patients with pre-existing hypertension, AVEGF-HT was defined either as dose increase of a prior antihypertensive medication, addition of a new antihypertensive medication, on-treatment SBP at least 160 mmHg or DBP at least 100 mmHg.[10] In multivariable analysis, pre-existing hypertension [odds ratio (OR) 1.56, 95% confidence interval (CI) 1.27–1.92, $p < 0.0001$), age at least 60 years (OR 1.26, 95% CI 1.06–1.52, $p = 0.01$) and body mass index at least 25 kg/m^2 (OR 1.26, 95% CI 1.04–1.53) independently predicted AVEGF-HT. By contrast, no significant associations were observed with sex, ethnicity, type of cancer, anti-VEGF drug or type of antihypertensive drug at baseline.[10] Notably, age, body mass index and AVEGF-HT also predicted overall survival.[10] However, no information was provided regarding the method and protocol for BP measurement and the frequency of the BP assessments. Wicki and colleagues investigated 169 patients with colorectal cancer, breast cancer or other types of cancer treated with bevacizumab.[56] BP was measured once, after 10 min of rest, during each visit, using validated automatic devices. Visits occurred at baseline and after each cycle of bevacizumab treatment, approximately every 2–3 weeks. Pre-existing hypertension was defined as history of hypertension or treatment with at least one antihypertensive drug. The median on-treatment increase in both SBP and DBP values was greater in patients with pre-existing hypertension than in those without.[56] However, there was no assessment of the capacity of pre-existing hypertension, or other baseline characteristics, to predict AVEGF-HT in regression analysis.[56]

In agreement with the study of Hamnvik and colleagues, we observed that age and use of antihypertensive drugs (indicating pre-existing hypertension) predicted four AVEGF-HT criteria, whereas body mass index only predicted one criterion. Furthermore, the definitions of AVEGF-HT by Hamnvik and colleagues included on-treatment SBP at least 160 mmHg and DBP at

least 100 mmHg.[10] In our study, age and use of antihypertensive drugs independently predicted similar criteria, on-treatment SBP greater than 160 mmHg and DBP greater than 100 mmHg. However, while age and use of antihypertensive drugs independently predicted higher odds of SBP greater than 160 mmHg, they also predicted lower odds of DBP greater than 100 mmHg. This suggests that, in patients with older age or pre-existing hypertension, the BP elevations during anti-VEGF therapy are primarily driven by an increase in SBP and pulse pressure, the difference between SBP and DBP. This BP elevation pattern is commonly observed in older adults, including those with coexisting hypertension, and is associated with an increase in arterial stiffness.[57,58]

In our study, the use of antidiabetic drugs, indicating pre-existing diabetes, was negatively associated with four AVEGF-HT criteria. Although further research is required to confirm this finding and to identify the pathophysiological mechanisms involved in this association a recent systematic review and meta-analysis of 18 cohort studies reported that patients with RCC and diabetes have significantly worse cancer-specific, progression-free and overall survival rates.[59] Higher neutrophil to lymphocyte ratio, prior nephrectomy and use of NSAIDs were also associated with a reduced risk of AVEGF-HT according to two criteria. The neutrophil to lymphocyte ratio is being increasingly investigated as a marker of chronic inflammation in cancer.[60] A recent systematic review and meta-analysis of 15 studies in patients with RCC has shown that a higher neutrophil to lymphocyte ratio predicts poorer survival outcomes.[61] While cytoreductive nephrectomy in RCC has been widely utilized either before and during the immunotherapy era, its role in the context of targeted therapy with antiangiogenic drugs is uncertain despite the encouraging preliminary results of the SORCE study (a phase III randomized double-blind study comparing sorafenib with placebo in patients with resected primary renal cell carcinoma at high or intermediate risk of relapse).[62,63] Pending the outcomes of other randomized trials of nephrectomy followed by anti-VEGF therapy *versus* anti-VEGF therapy alone,[64] our results raise the concern that the reduced incidence of AVEGF-HT in patients with RCC and prior nephrectomy might potentially translate into poor survival outcomes. Given the established association between NSAID use and BP elevations in the general population,[65] our observation of a reduced risk of AVEGF-HT in patients with RCC treated with NSAIDs is surprising. However, the reduced risk of AVEGF-HT with NSAIDs is limited to elevations in DBP. Further studies are warranted to investigate the relationship between the presence of diabetes, neutrophil to lymphocyte ratio, prior nephrectomy, and use of NSAIDs, AVEGF-HT and survival outcomes in patients with RCC.

A recent study has challenged the hypothesis that AVEGF-HT predicts favourable outcomes in RCC. Goldstein and colleagues conducted a *post hoc* analysis of the COMPARZ study and other phase II–III studies of pazopanib.[53] AVEGF-HT at week 4 and 12 was defined using one of the following criteria: maximum absolute increase in mean BP [(DBP + 1/3(SBP – DBP)] at least 10 mmHg, maximum absolute increase in SBP at least 10 mmHg, on-treatment SBP greater than 140 mmHg or DBP greater than 90 mmHg. None of the criteria independently predicted progression-free or overall survival.[53] However, the different results between this study and the study by Hamnvik and colleagues might be explained, at least in part, by the use of mean BP values in the study by Goldstein and colleagues, and by the use of higher on-treatment SBP and DBP threshold values, at least 160 mmHg and at least 100 mmHg respectively, in the study by Hamnvik and colleagues.[10] This highlights, once again, the potential implications of using different AVEGF-HT criteria when assessing the interaction between anti-VEGF drugs, BP elevations and cancer outcomes.

The strengths of our study include a well characterized patient population, recruited using the strict inclusion and exclusion criteria of the COMPARZ study, the rigorous assessment of demographic and clinical characteristics, and the use of a predefined protocol for the measurement of BP at the same time points in each patient. Furthermore, in our analyses, we adjusted not only for anti-VEGF treatment (pazopanib or sunitinib) but also for baseline SBP and DBP values, thus preventing the well known statistical artefact, regression to the mean.[66] Potential limitations, in addition to the *post hoc* nature of the analyses, include the possibility of residual confounding and the lack of adjustment for the change in dose and type of antihypertensive drugs after commencing anti-VEGF treatment.

In conclusion, there was a significant variability in the cumulative incidence, number and type of predictors of AVEGF-HT, using six different criteria, in a phase III study of patients with RCC.

The use of specific AVEGF-HT criteria should be taken into account when assessing the association between anti-VEGF drugs, AVEGF-HT and survival outcomes in RCC and other types of cancer. In this context, the consistent use of standard, validated, protocols and time points for BP assessment is likely to significantly reduce the variability in the reported incidence of AVEGF-HT in different studies.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Supplementary material

Supplementary material is available for this article online.

References

1. Lee S, Chen TT, Barber CL, *et al*. Autocrine VEGF signaling is required for vascular homeostasis. *Cell* 2007; 130: 691–703.
2. Hoeben A, Landuyt B, Highley MS, *et al*. Vascular endothelial growth factor and angiogenesis. *Pharmacol Rev* 2004; 56: 549–580.
3. Thanigaimani S, Kichenadasse G and Mangoni AA. The emerging role of vascular endothelial growth factor (VEGF) in vascular homeostasis: lessons from recent trials with anti-VEGF drugs. *Curr Vasc Pharmacol* 2011; 9: 358–380.
4. Kimura H and Esumi H. Reciprocal regulation between nitric oxide and vascular endothelial growth factor in angiogenesis. *Acta Biochim Pol* 2003; 50: 49–59.
5. Ellis LM and Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nat Rev Cancer* 2008; 8: 579–591.
6. Escalante CP and Zalpour A. Vascular endothelial growth factor inhibitor-induced hypertension: basics for primary care providers. *Cardiol Res Pract* 2011; 2011: 816897.
7. Scartozzi M, Galizia E, Chiorrini S, *et al*. Arterial hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab. *Ann Oncol* 2009; 20: 227–230.
8. Dahlberg SE, Sandler AB, Brahmer JR, *et al*. Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. *J Clin Oncol* 2010; 28: 949–954.
9. Ryanne Wu R, Lindenberg PA, Slack R, *et al*. Evaluation of hypertension as a marker of bevacizumab efficacy. *J Gastrointest Cancer* 2009; 40: 101–108.
10. Hamnvik OP, Choueiri TK, Turchin A, *et al*. Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway. *Cancer* 2015; 121: 311–319.
11. Osterlund P, Soveri LM, Isoniemi H, *et al*. Hypertension and overall survival in metastatic colorectal cancer patients treated with bevacizumab-containing chemotherapy. *Br J Cancer* 2011; 104: 599–604.
12. Cai J, Ma H, Huang F, *et al*. Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer patients treated with bevacizumab: a systematic review and meta-analysis. *World J Surg Oncol* 2013; 11: 306.
13. Lombardi G, Zustovich F, Farina P, *et al*. Hypertension as a biomarker in patients with recurrent glioblastoma treated with antiangiogenic drugs: a single-center experience and a critical review of the literature. *Anti-cancer drugs* 2013; 24: 90–97.
14. Tahover E, Uziely B, Salah A, *et al*. Hypertension as a predictive biomarker in bevacizumab treatment for colorectal cancer patients. *Med Oncol* 2013; 30: 327.
15. Chen C, Sun P, Ye S, *et al*. Hypertension as a predictive biomarker for efficacy of bevacizumab treatment in metastatic colorectal cancer: a meta-analysis. *J BUON* 2014; 19: 917–924.
16. Nakaya A, Kurata T, Yokoi T, *et al*. Retrospective analysis of bevacizumab-induced hypertension and clinical outcome in patients with colorectal cancer and lung cancer. *Cancer Med* 2016; 5: 1381–1387.
17. Pant S, Martin LK, Geyer S, *et al*. Treatment-related hypertension as a pharmacodynamic biomarker for the efficacy of bevacizumab in advanced pancreas cancer: a pooled analysis of 4 prospective trials of gemcitabine-based therapy with bevacizumab. *Am J Clin Oncol* 2016; 39: 614–618.
18. Petrelli F, Dognini GP, Destro M, *et al*. Hypertension and survival in renal cell carcinoma treated with anti-VEGFR agents: a systematic review and meta-analysis. *J Onco-Nephrol* 2017; 1: 120–126.
19. Hurwitz HI, Douglas PS, Middleton JP, *et al*. Analysis of early hypertension and clinical

outcome with bevacizumab: results from seven phase III studies. *Oncologist* 2013; 18: 273–280.

20. Duffaud F, Sleijfer S, Litiere S, *et al*. Hypertension (HTN) as a potential biomarker of efficacy in pazopanib-treated patients with advanced non-adipocytic soft tissue sarcoma. A retrospective study based on European Organisation for Research and Treatment of Cancer (EORTC) 62043 and 62072 trials. *Eur J Cancer* 2015; 51: 2615–2623.
21. Karpenko I, Singh B, Beltran H, *et al*. Association of CTCAE v4 grading of hypertension with toxicity in patients with renal cancer receiving vascular endothelial growth factor (VEGF)-targeting agents. *J Clin Oncol* 2013; 31: 447.
22. Motzer RJ, Hutson TE, Cella D, *et al*. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013; 369: 722–731.
23. Vokonas PS, Kannel WB and Cupples LA. Epidemiology and risk of hypertension in the elderly: the Framingham Study. *J Hypertens Suppl* 1988; 6(Suppl. 1): S3–S9.
24. Gillespie CD, and Hurvitz KA and Centers for Disease Control and Prevention. Prevalence of hypertension and controlled hypertension – United States, 2007–2010. *MMWR Suppl* 2013; 62: 144–148.
25. Liu K, Ballew C, Jacobs DR Jr, *et al*. Ethnic differences in blood pressure, pulse rate, and related characteristics in young adults. The CARDIA study. *Hypertension* 1989; 14: 218–226.
26. Shihab HM, Meoni LA, Chu AY, *et al*. Body mass index and risk of incident hypertension over the life course: the Johns Hopkins Precursors Study. *Circulation* 2012; 126: 2983–2989.
27. Tozawa M, Oshiro S, Iseki C, *et al*. Family history of hypertension and blood pressure in a screened cohort. *Hypertens Res* 2001; 24: 93–98.
28. Halimi JM, Giraudeau B, Vol S, *et al*. The risk of hypertension in men: direct and indirect effects of chronic smoking. *J Hypertens* 2002; 20: 187–193.
29. Selby JV, Friedman GD and Quesenberry CP Jr. Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. *Am J Epidemiol* 1990; 131: 1017–1027.
30. Liu X, Zhang Q, Wu H, *et al*. Blood neutrophil to lymphocyte ratio as a predictor of hypertension. *Am J Hypertens* 2015; 28: 1339–1346.
31. Boudville N, Prasad GV, Knoll G, *et al*. Meta-analysis: risk for hypertension in living kidney donors. *Ann Intern Med* 2006; 145: 185–196.
32. Brantsma AH, Bakker SJ, de Zeeuw D, *et al*. Urinary albumin excretion as a predictor of the development of hypertension in the general population. *J Am Soc Nephrol* 2006; 17: 331–335.
33. Koizumi Y, Hamazaki Y, Okuro M, *et al*. Association between hypertension status and the screening test for frailty in elderly community-dwelling Japanese. *Hypertens Res* 2013; 36: 639–644.
34. Hu H, Sparrow D and Weiss S. Association of serum albumin with blood pressure in the normative aging study. *Am J Epidemiol* 1992; 136: 1465–1473.
35. Atsma F, Veldhuizen I, de Kort W, *et al*. Hemoglobin level is positively associated with blood pressure in a large cohort of healthy individuals. *Hypertension* 2012; 60: 936–941.
36. Cirillo M, Laurenzi M, Trevisan M, *et al*. Hematocrit, blood pressure, and hypertension. The Gubbio Population Study. *Hypertension* 1992; 20: 319–326.
37. Levin G, Kestenbaum B, Ida Chen YD, *et al*. Glucose, insulin, and incident hypertension in the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2010; 172: 1144–1154.
38. Johnson AG, Simons LA, Simons J, *et al*. Non-steroidal anti-inflammatory drugs and hypertension in the elderly: a community-based cross-sectional study. *Br J Clin Pharmacol* 1993; 35: 455–459.
39. Gabb GM, Mangoni AA, Anderson CS, *et al*. Guideline for the diagnosis and management of hypertension in adults - 2016. *Med J Aust* 2016; 205: 85–89.
40. Weber MA, Schiffrin EL, White WB, *et al*. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens* 2014; 32: 3–15.
41. Xu W, Goldberg SI, Shubina M, *et al*. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: population based retrospective cohort study. *BMJ* 2015; 350: h158.
42. Donskov F, Michaelson MD, Puzanov I, *et al*. Sunitinib-associated hypertension and neutropenia as efficacy biomarkers in metastatic renal cell carcinoma patients. *Br J Cancer* 2015; 113: 1571–1580.
43. Bono P, Rautiola J, Utriainen T, *et al*. Hypertension as predictor of sunitinib treatment outcome in metastatic renal cell carcinoma. *Acta Oncol* 2011; 50: 569–573.

44. Izzedine H, Derosa L, Le Teuff G, *et al*. Hypertension and angiotensin system inhibitors: impact on outcome in sunitinib-treated patients for metastatic renal cell carcinoma. *Ann Oncol* 2015; 26: 1128–1133.

45. Kucharz J, Dumnicka P, Kuzniewski M, *et al*. Co-occurring adverse events enable early prediction of progression-free survival in metastatic renal cell carcinoma patients treated with sunitinib: a hypothesis-generating study. *Tumori* 2015; 101: 555–559.

46. Keizman D, Gottfried M, Ish-Shalom M, *et al*. Active smoking may negatively affect response rate, progression-free survival, and overall survival of patients with metastatic renal cell carcinoma treated with sunitinib. *Oncologist* 2014; 19: 51–60.

47. Szmit S, Langiewicz P, Zlnierek J, *et al*. Hypertension as a predictive factor for survival outcomes in patients with metastatic renal cell carcinoma treated with sunitinib after progression on cytokines. *Kidney Blood Press Res* 2012; 35: 18–25.

48. Miyake M, Kuwada M, Hori S, *et al*. The best objective response of target lesions and the incidence of treatment-related hypertension are associated with the survival of patients with metastatic renal cell carcinoma treated with sunitinib: a Japanese retrospective study. *BMC Res Notes* 2016; 9: 79.

49. Rini BI, Cohen DP, Lu DR, *et al*. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 2011; 103: 763–773.

50. Eechoute K, van der Veldt AA, Oosting S, *et al*. Polymorphisms in endothelial nitric oxide synthase (eNOS) and vascular endothelial growth factor (VEGF) predict sunitinib-induced hypertension. *Clin Pharmacol Ther* 2012; 92: 503–510.

51. Nakano K, Komatsu K, Kubo T, *et al*. Hand-foot skin reaction is associated with the clinical outcome in patients with metastatic renal cell carcinoma treated with sorafenib. *Jpn J Clin Oncol* 2013; 43: 1023–1029.

52. Rini BI, Garrett M, Poland B, *et al*. Axitinib in metastatic renal cell carcinoma: results of a pharmacokinetic and pharmacodynamic analysis. *J Clin Pharmacol* 2013; 53: 491–504.

53. Goldstein D, Rosenberg JE, Figlin RA, *et al*. Is change in blood pressure a biomarker of pazopanib and sunitinib efficacy in advanced/metastatic renal cell carcinoma? *Eur J Cancer* 2016; 53: 96–104.

54. Motzer RJ, Escudier B, Tomczak P, *et al*. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol* 2013; 14: 552–562.

55. Iacovelli R, Verri E, Cossu Rocca M, *et al*. Prognostic role of the cumulative toxicity in patients affected by metastatic renal cells carcinoma and treated with first-line tyrosine kinase inhibitors. *Anticancer Drugs* 2017; 28: 206–212.

56. Wicki A, Hermann F, Pretre V, *et al*. Pre-existing antihypertensive treatment predicts early increase in blood pressure during bevacizumab therapy: the prospective AVALUE cohort study. *Oncol Res Treat* 2014; 37: 230–236.

57. Moore A, Mangoni AA, Lyons D, *et al*. The cardiovascular system. *Br J Clin Pharmacol* 2003; 56: 254–260.

58. Stella ML, Failla M, Mangoni AA, *et al*. Effects of isolated systolic hypertension and essential hypertension on large and middle-sized artery compliance. *Blood Press* 1998; 7: 96–102.

59. Chen L, Li H, Gu L, *et al*. The impact of diabetes mellitus on renal cell carcinoma prognosis: a meta-analysis of cohort studies. *Medicine (Baltimore)* 2015; 94: e1055.

60. Ocana A, Nieto-Jimenez C, Pandiella A, *et al*. Neutrophils in cancer: prognostic role and therapeutic strategies. *Mol Cancer* 2017; 16: 137.

61. Hu K, Lou L, Ye J, *et al*. Prognostic role of the neutrophil–lymphocyte ratio in renal cell carcinoma: a meta-analysis. *BMJ Open* 2015; 5: e006404.

62. Lawrence NJ, Martin A, David ID, *et al*. 881P – Predicted benefits of adjuvant sorafenib after nephrectomy for renal cell carcinoma (RCC) in SORCE: an international, placebo-controlled, randomised phase 3 trial. *Ann Oncol* 2017; 28(Suppl. 5): v295–v329.

63. Motzer RJ, Haas NB, Donskov F, *et al*. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. *J Clin Oncol* 2017; 35: 3916–3923.

64. Stewart GD, Aitchison M, Bex A, *et al*. Cytoreductive nephrectomy in the tyrosine kinase inhibitor era: a question that may never be answered. *Eur Urol* 2017; 71: 845–847.

65. Johnson AG, Nguyen TV and Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994; 121: 289–300.

66. Shepard DS and Finison LJ. Blood pressure reductions: correcting for regression to the mean. *Prev Med* 1983; 12: 304–317.