

Phase III Trial of Adjuvant Sunitinib in Patients with High-Risk Renal Cell Carcinoma: Exploratory Pharmacogenomic Analysis



Daniel J. George¹, Jean-Francois Martini², Michael Staehler³, Robert J. Motzer⁴, Ahmed Magheli⁵, Frede Donskov⁶, Bernard Escudier⁷, Sherry Li², Michelle Casey⁸, Olga Valota⁹, Brigitte Laguerre¹⁰, Allan J. Pantuck¹¹, Hardev S. Pandha¹², Anup Patel¹³, Maria Lechuga⁹, and Alain Ravaud¹⁴

Abstract

Purpose: In the S-TRAC trial, adjuvant sunitinib prolonged disease-free survival (DFS) versus placebo in patients with loco-regional renal cell carcinoma at high risk of recurrence after nephrectomy. An exploratory analysis evaluated associations between SNPs in several angiogenesis- or hypoxia-related genes and clinical outcomes in S-TRAC.

Patients and Methods: Blood samples were genotyped for 10 SNPs and one insertion/deletion mutation using TaqMan assays. DFS was compared using log-rank tests for each genotype in sunitinib versus placebo groups and between genotypes within each of three (sunitinib, placebo, and combined sunitinib plus placebo) treatment groups. *P* values were unadjusted.

Results: In all, 286 patients (sunitinib, *n* = 142; placebo, *n* = 144) were genotyped. Longer DFS [HR; 95% confidence inter-

val (CI)] was observed with sunitinib versus placebo for *VEGFR1* rs9554320 C/C (HR 0.44; 95% CI, 0.21–0.91; *P* = 0.023), *VEGFR2* rs2071559 T/T (HR 0.46; 95% CI, 0.23–0.90; *P* = 0.020), and *eNOS* rs2070744 T/T (HR 0.53; 95% CI, 0.30–0.94; *P* = 0.028). Shorter DFS was observed for *VEGFR1* rs9582036 C/A versus C/C with sunitinib, placebo, and combined therapies (*P* ≤ 0.05), and A/A versus C/C with sunitinib (*P* = 0.022). *VEGFR1* rs9554320 A/C versus A/A was associated with shorter DFS in the placebo (*P* = 0.038) and combined (*P* = 0.006) groups.

Conclusions: Correlations between *VEGFR1* and *VEGFR2* SNPs and longer DFS with sunitinib suggest germline SNPs are predictive of improved outcomes with adjuvant sunitinib in patients with renal cell carcinoma. Independent validation studies are needed to confirm these findings.

Introduction

Because of the increased use of radiologic and ultrasound imaging techniques, incidental detection of renal cell carcinoma (RCC) occurs more frequently today, contributing to an increase in the number of patients diagnosed with stage I to III (localized or

loco-regional) disease. Thus, optimizing the management of early-stage RCC is a key priority in clinical practice (1, 2). For patients with tumor, lymph nodes, metastasis (TNM) stage I and II RCC, surgery alone may be sufficient, with 5-year cancer-specific survival rates of 91% and 74% for stage I and II, respectively. However, a number of patients with stage III or IV nonmetastatic RCC (+/– regional lymph node involvement) will eventually relapse and progress to stage IV metastatic RCC (3). To try and identify those patients with the highest risk of relapse, there are several scoring systems in use, based on clinical and pathologic features (4–8). Based on risk stratification using the University of California Los Angeles Integrated Staging System (UISS), up to 15% of patients with non-metastatic RCC who undergo nephrectomy are considered at high risk (UISS III–IV) of recurrence and approximately 40% of these will relapse within 5 years (6, 9, 10).

Sunitinib is a multitargeted inhibitor of the VEGF signaling pathway and is approved for the treatment of metastatic RCC, and approved by the FDA as adjuvant therapy in patients at high risk for recurrent RCC post nephrectomy (11). In the randomized phase III S-TRAC trial, adjuvant sunitinib prolonged disease-free survival (DFS) versus placebo in patients with loco-regional RCC (≥T3 and/or N+) at high risk of recurrence following nephrectomy (based on blinded independent central review): HR 0.76; 95% confidence interval (CI), 0.59–0.98 (*P* = 0.03), and median DFS 6.8 years versus 5.6 years (12, 13).

The addition of a pharmacogenomic biomarker assay based on the understanding of host versus disease biology could potentially

¹Department of Medical Oncology, Duke Cancer Center, Durham, North Carolina.

²Global Product Development, Pfizer Inc, La Jolla, California. ³Department of Urology, University Hospital of Munich, Munich, Germany. ⁴Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, New York. ⁵Department of Urology, Charité Universitätsmedizin Berlin, Berlin, Germany. ⁶Department of Oncology, Aarhus University Hospital, Aarhus, Denmark. ⁷Department of Urology, Institut Gustave Roussy, Villejuif, France. ⁸Global Product Development, Pfizer Inc., Collegeville, Pennsylvania. ⁹Global Product Development, Pfizer S.r.L, Milan, Italy. ¹⁰Department of Medical Oncology, Centre Eugene Marquis, Rennes, France. ¹¹Department of Urology, Ronald Reagan UCLA Medical Center, Los Angeles, California. ¹²Department of Medical Oncology, University of Surrey, Surrey, United Kingdom. ¹³London, United Kingdom. ¹⁴Department of Medical Oncology, Bordeaux University Hospital, Bordeaux, France.

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Corresponding Author: Daniel J. George, Duke Cancer Center, 20 Duke Medicine Circle, Durham, NC 27710. Phone: 919-668-8108; E-Mail: daniel.george@duke.edu

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Translational Relevance

In patients with loco-regional renal cell carcinoma (RCC) at high risk of recurrence after nephrectomy, correlations between SNPs in *VEGFR1*, *VEGFR2*, and *eNOS* genes and improved disease-free survival (DFS) in the sunitinib group compared with the placebo group support the hypothesis that germline SNPs could have potential predictive value to identify patients who might derive more benefit from adjuvant sunitinib. Additionally, SNPs in *VEGFR1*, *VEGFR2*, and *CCDC26* demonstrated a potential trend toward prognostic value for either DFS or overall survival across treatment groups. Therefore, these data could be used in the development of a pharmacogenomic biomarker assay that could potentially improve risk assessment and help to select patients who are most likely to benefit from adjuvant treatment in the RCC setting.

improve risk assessment and help to select patients who are most likely to benefit from adjuvant treatment. The most common genetic DNA sequence variations are SNPs (14). A number of SNPs have been reported as potential predictors of efficacy and/or toxicity in patients with advanced RCC treated with anti-angiogenic tyrosine kinase inhibitors (15–23). The impact of these SNPs on the efficacy and safety of tyrosine kinase inhibitors range from modulating pharmacokinetics (e.g., through increased drug clearance) through to pharmacodynamics (e.g., increased expression of target proteins), and/or activation of downstream signaling pathways (15–29). With regards to SNPs in VEGF and VEGF receptors (VEGFR)-1, 2, or 3, various studies and analyses have reported that certain SNPs are associated with poorer response rate, overall survival (OS), and/or progression-free survival (PFS) in patients with metastatic RCC treated with sunitinib (19, 20, 24–29).

Therefore, the objectives of these exploratory, hypothesis-generating analyses were to evaluate potential associations between a subset of SNPs in genes known to be involved in angiogenesis and clinical outcomes by using data from a subset of patients enrolled in the S-TRAC trial.

Patients and Methods

Study design and patients

S-TRAC was a randomized, double-blind, phase III trial (ClinicalTrials.gov, NCT00375674) in patients with loco-regional RCC at high risk of tumor recurrence after nephrectomy (12, 13). Details on eligibility were previously reported (12, 13). Briefly, patients were ≥ 18 years old and had a histologic confirmation of clear-cell, loco-regional ($\geq T3$ and/or $N+$) RCC. Other inclusion criteria were: Eastern Cooperative Oncology Group performance status 0–2 before nephrectomy; no prior systemic therapy for RCC; and lack of macroscopic residual or metastatic disease, determined by blinded independent central review.

Patients were randomly assigned (1:1) to receive sunitinib 50 mg/day or placebo on a 4-weeks-on/2-weeks-off schedule for 1 year or until disease recurrence, diagnosis of secondary malignancy, unacceptable side effect, or consent withdrawal (12, 13). The trial was approved by the independent review board or ethics committee at each center and was conducted in accordance with

the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines and applicable local regulatory requirements and laws. All patients provided written informed consent.

Molecular biomarker assays

Anonymized blood samples were prospectively collected from patients in the S-TRAC trial who consented to the molecular profiling substudy. Samples were genotyped for 10 SNPs and one insertion/deletion mutation, some of which have been previously hypothesized to predict response to sunitinib in treatment of metastatic RCC (Table 1; refs. 19, 24–26).

Following sample de-identification and DNA extraction, DNA amplification was carried out using PCR. Commercially available TaqMan assays (Thermo Fisher Scientific) were used and analyzed on an Applied Biosystems QuantStudio 12K Flex Real-Time PCR System (Thermo Fisher Scientific; dba: Life Technologies), and was performed at Pfizer Clinical Pharmacogenomics Laboratory (Pfizer Inc.). The SNP *SH3GL2 rs10963287* was determined using a laboratory developed TaqMan assay. The region immediately surrounding SNP *rs10963287* contains a short interspersed nuclear elements [SINE] region; therefore, the assay to determine the genotype of *rs10963287* involved amplifying a region encompassing the SNP. The PCR product from this initial reaction was used as the input template for TaqMan analysis. For coiled-coil domain-containing protein 26 (*CCDC26*), the three nucleotide small insertion and deletion (INDEL) *rs60315789* was detected by amplifying a region around the insertion, sizing the fragment using an ABI3730xl DNA analyzer, and then analyzing the data using the GeneMapper 5.0 software (Thermo Fisher Scientific).

Statistical analyses

The pharmacogenomics population comprised all patients who received at least one dose of study medication (i.e., treatment assignments designated according to actual study treatment received) and who had at least one genotype result. The primary endpoint in S-TRAC was DFS, which was defined as time from randomization until recurrence or secondary malignancy, as assessed by blinded independent central review, or death. OS was assessed as a secondary endpoint.

Fisher exact test was used to compare baseline demographics and characteristics between treatment groups. Two-sided 95% CIs for allele frequency and genotype frequency were determined by exact method using the F distribution. All SNPs were examined for deviation from Hardy–Weinberg Equilibrium; *P* values were calculated using Pearson's Chi-squared test based on 10,000 replicates. Linkage disequilibrium analysis was also performed for SNP pairs. *D'*, *r*², and *P* values were calculated for each pair of SNPs within a given gene or on the same chromosome.

In exploratory analyses, DFS and OS between sunitinib and placebo groups were compared for each genotype with Kaplan–Meier estimates and an unstratified log-rank test. Estimated HR and its two-sided 95% CI were provided using Cox proportional hazards models. Genotype subgroups were also compared within each treatment group and for the combined sunitinib and placebo treatment groups ("combined group") using the same statistical approach, where applicable. *P* values were unadjusted for multiplicity. The log-rank *P* value and HR statistic were produced only when there were ≥ 10 events in both comparison groups. The data cut-off date for these analyses was April 7, 2016 (per the primary S-TRAC analyses; ref. 12).

Table 1. Candidate SNPs associated with response to anti-angiogenic therapy

Gene	Alternative name	SNP allele change	mRNA position allele change	Protein position and change
VEGFA	VPF, MVCD1, MGC70609	rs699947 A>C	-2055 A>C NM_001025366.2	-
VEGFA	VPF, MVCD1, MGC70609	rs833061 C>T	-958 C>T NM_001025366.2	-
FLT1	FLT, VEGFR1	rs9554320 A>C	3387-692 T>G NM_002019.4	-
FLT1	FLT, VEGFR1	rs9582036 C>A	3635+319 G>T NM_002019.4	-
KDR	VEGFR2, FLK1, CD309	rs2071559 T>C	-906 T>C NM_002253.2	-
KDR	VEGFR2, FLK1, CD309	rs1870377 T>A	1416 A>T NM_002253.2	Gln472His
FLT4	VEGFR3, PCL, FLT4I, LMPH1A	rs6877011 C>G	721 G>C NM_182925.4	-
LOXL2	LOR2, WS9-14	rs4872122 A>C	-84+12722 T>G NM_002318.2	-
NOS3	eNOS, ecNOS	rs2070744 T>C	-813 C>T NM_001160109.1	-
SH3GL2	CNSA2, SH3P4, EEN-B1, SH3D2A	rs10963287 C>T	-	-
CCDC26	RAM	rs60315789 -/TAT	-	-

Results

Patient population

Of 615 patients enrolled in S-TRAC, 610 received treatment ($n = 306$ and $n = 304$, sunitinib and placebo, respectively; ref. 12). Of these patients, 286 (46.9%; $n = 142$ and 144, sunitinib and placebo, respectively) consented to the pharmacogenomic analysis and provided a blood sample that was successfully genotyped. Because of ethnic or religious reasons, or regulations imposed by local health authorities, 324 patients did not consent or provide a blood sample that could be successfully genotyped. Demographics and baseline clinical characteristics of genotyped subgroups treated with sunitinib or placebo were generally comparable (Table 2). However, there were differences between 286 patients who were genotyped and the 324 who were not genotyped; a greater number of genotyped patients were older, white, and were categorized in the UISS high-risk group (Table 2).

Genotyping

There were no unexpected findings in allele and genotype frequencies for SNPs (Supplementary Tables S1 and S2).

For most SNPs, there were no deviations in genotype frequencies from the Hardy-Weinberg Equilibrium; however, two SNPs showed deviation from Hardy-Weinberg Equilibrium: *VEGFR2* rs1870377 ($P = 0.017$) and *VEGFR3* rs6877011 ($P < 0.001$). High linkage disequilibrium was detected between the following SNPs: *VEGFR2* rs1870377 and rs2071559 on chromosome 4 ($D' = 0.250$; $r^2 = 0.015$; $P = 0.036$); *VEGFA* rs699947 and rs833061 on chromosome 6 ($D' = 1.000$; $r^2 = 0.979$; $P < 0.001$); and *VEGFR1* rs9582036 and rs9554320 on chromosome 13 ($D' = 0.977$; $r^2 = 0.584$; $P < 0.001$).

Association between DFS and each genotype in sunitinib versus placebo group

The following genotypes were associated with a longer DFS in the sunitinib versus placebo group (Table 3): C/C genotype for *VEGFR1* rs9554320 (HR 0.44; 95% CI, 0.21–0.91; $P = 0.023$; Fig. 1A); T/T genotype for *VEGFR2* rs2071559 (HR 0.46; 95% CI, 0.23–0.90; $P = 0.020$; Fig. 1B); T/T genotype for *eNOS* rs2070744 (HR 0.53; 95% CI, 0.30–0.94; $P = 0.028$; Fig. 1C).

Table 2. Patient baseline characteristics

Variable, n (%)	All patients			Genotyped		
	Genotyped <i>n</i> = 286	Nongenotyped <i>n</i> = 324	<i>P</i> value ^a (genotyped vs. nongenotyped)	Sunitinib <i>n</i> = 142	Placebo <i>n</i> = 144	<i>P</i> value (Sunitinib vs. Placebo)
Age, years						
<65	195 (68.2)	258 (79.6)	0.002	95 (66.9)	100 (69.4)	0.704
≥65	91 (31.8)	66 (20.4)		47 (33.1)	44 (30.6)	
Sex						
Male	206 (72.0)	241 (74.4)	0.522	97 (68.3)	109 (75.7)	0.188
Female	80 (28.0)	83 (25.6)		45 (31.7)	35 (24.3)	
Race						
White	258 (90.2)	254 (78.4)	<0.001	127 (89.4)	131 (91.0)	0.097
Asian	17 (5.9)	59 (18.2)		11 (7.7)	6 (4.2)	
Other	11 (3.8)	11 (3.4)		4 (2.8)	7 (4.9)	
ECOG PS						
0	208 (72.7)	237 (73.1)	0.730	101 (71.1)	107 (74.3)	0.818
1	75 (26.2)	86 (26.5)		39 (27.5)	36 (25.0)	
2	1 (0.3)	0		1 (0.7)	1 (0.7)	
UISS group						
T3 low ^b	86 (30.1)	139 (42.9)	0.009	41 (28.9)	45 (31.3)	0.805
T3 high ^c	172 (60.1)	158 (48.8)		89 (62.7)	83 (57.6)	
T4, NO or NX, M0 ^d	5 (1.7)	3 (0.9)		2 (1.4)	3 (2.1)	
Any T, N+, M0 ^d	23 (8.0)	24 (7.4)		10 (7.0)	13 (9.0)	

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

^a*P* values calculated using Fisher exact test.

^bGenotyped vs. nongenotyped; unadjusted for multiplicity.

^cNO or NX, M0, any Fuhrman grade and ECOG PS 0 or NO or NX, M0, Fuhrman grade 1 and ECOG PS ≥1.

^dNO or NX, M0, Fuhrman grade ≥2 and ECOG PS ≥1.

^eAny Fuhrman grade and any ECOG PS.

Table 3. Comparison of DFS stratified by genotype and treatment group

Gene/SNP	Sunitinib vs. Placebo: HR (95% CI); P unadjusted		
VEGFA rs699947	A/A 0.78 (0.33–1.87); 0.579	A/C 0.65 (0.39–1.10); 0.107	C/C 0.81 (0.41–1.61); 0.547
VEGFA rs833061	C/C 0.78 (0.33–1.87); 0.579	C/T 0.65 (0.39, 1.08); 0.094	T/T 0.83 (0.41–1.68); 0.604
VEGFR1 rs9554320	A/A 1.32 (0.42–4.20); 0.636	A/C 0.85 (0.54–1.36); 0.507	C/C 0.44 (0.21–0.91); 0.023
VEGFR1 rs9582036	C/C 0.77 (0.08–7.49); 0.825	C/A 0.98 (0.61–1.59); 0.945	A/A 0.56 (0.30–1.02); 0.054
VEGFR2 rs2071559	T/T 0.46 (0.23–0.90); 0.020	T/C 1.03 (0.60–1.78); 0.914	C/C 0.72 (0.33–1.58); 0.417
VEGFR2 rs1870377	A/A Not done ^a	A/T 0.74 (0.39–1.40); 0.357	T/T 0.70 (0.43–1.15); 0.161
VEGFR3 rs6877011	C/C 0.72 (0.48–1.06); 0.096	C/G 1.38 (0.48–4.01); 0.550	G/G Not done ^a
LOXL2 rs4872122	A/A 0.81 (0.37–1.75); 0.589	A/C 0.72 (0.41–1.26); 0.245	C/C 0.75 (0.39–1.44); 0.388
eNOS rs2070744	T/T 0.53 (0.30–0.94); 0.028	T/C 0.96 (0.55–1.66); 0.879	C/C 0.85 (0.26–2.80); 0.794
SH3GL2 rs10963287	C/C 0.82 (0.50–1.32); 0.407	C/T 0.56 (0.28–1.10); 0.088	T/T 0.94 (0.29–3.10); 0.920
CCDC26 rs60315789	–/– 0.56 (0.24–1.28); 0.161	–/TAT 0.66 (0.38–1.12); 0.117	TAT/TAT 1.06 (0.53–2.10); 0.874

HR calculated using the unstratified Cox proportional hazards model. Two-sided *P* value from the unstratified log-rank test.

^aBecause of events <10 in both comparison groups.

A trend for a longer DFS in the sunitinib versus placebo group was observed for *VEGFR1* rs9582036 A/A (HR 0.56; 95% CI, 0.30–1.02; *P* = 0.054; Table 3). None of the genotypes for other tested SNPs showed differences in DFS between sunitinib and placebo (Table 3).

Association between DFS and genotype subgroups within each treatment group and the combined group

The following genotype subgroups were associated with a shorter DFS (Supplementary Table S3). The heterozygous genotype C/A of *VEGFR1* rs9582036 compared with the homozygous genotype C/C in the sunitinib (*P* < 0.001), placebo (*P* = 0.027), and combined (*P* < 0.001) groups; homozygous genotype A/A compared with genotype C/C only in the sunitinib group (*P* = 0.022; Fig. 2A and B); heterozygous genotype A/C of *VEGFR1* rs9554320 compared with the homozygous genotype A/A in the placebo (*P* = 0.038) and combined (*P* = 0.006) groups, with a trend in the sunitinib group (*P* = 0.051); and A/A genotype of *VEGFR2* rs1870377 compared with genotype T/T in the combined (*P* = 0.018) but not the placebo (*P* = 0.198) groups. No statistical test was performed in the sunitinib group because only seven patients had the A/A genotype.

None of the genotype subgroups for the other SNPs analyzed showed differences in DFS within each treatment group or when the treatments groups were combined.

Association between OS and genotypes

Correlation between the genotypes and OS was assessed by comparing sunitinib versus placebo within each SNP genotype subgroup. There were no other significant associations between SNP genotype and OS for sunitinib versus placebo; however, OS data were not mature at the time of data cut-off (Supplementary Table S4).

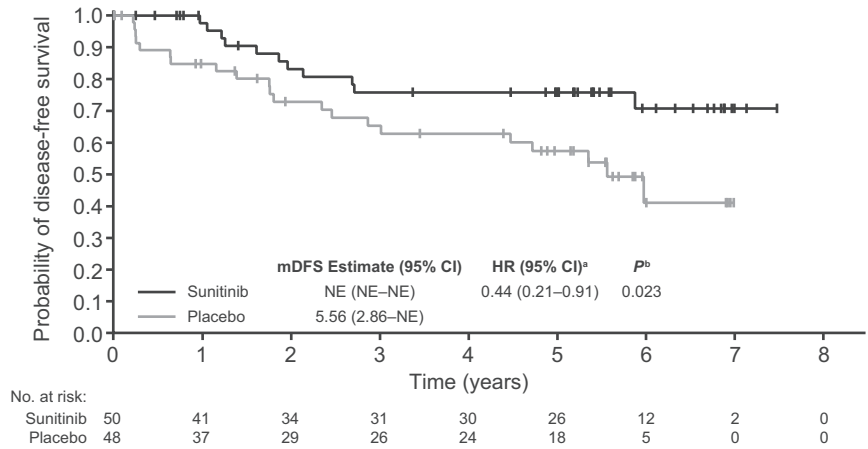
Correlations between OS and the SNP genotype subgroups were also carried out within each treatment group and by combining the two treatment groups. The genotype "–/–" (i.e., no

insertion) of *CCDC26* rs60315789 showed a trend toward longer OS versus the heterozygous –/TAT genotype in the sunitinib (HR 3.01; 95% CI, 0.88–10.31; *P* = 0.089) and placebo (HR 2.01; 95% CI, 0.74–5.44; *P* = 0.122) groups. A significant association was observed when the treatment groups were combined (HR 2.39; 95% CI, 1.11–5.16; *P* = 0.022). No other associations were reported for OS and genotypes within each treatment group or in the combined group.

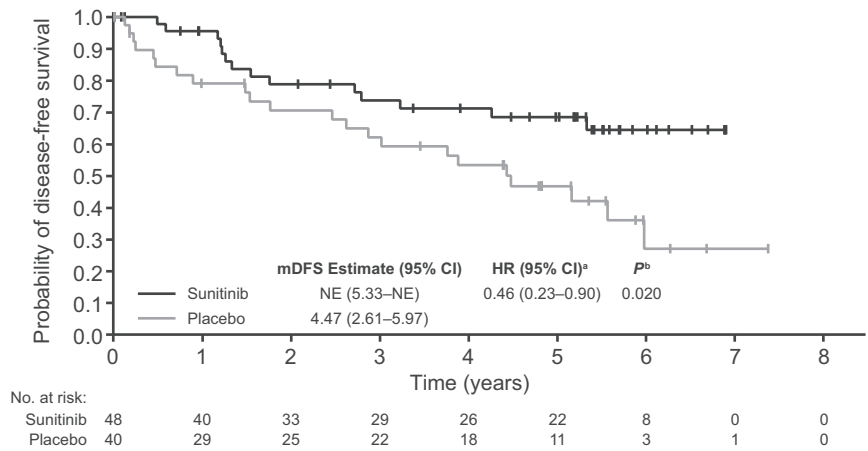
Discussion

In these exploratory analyses, correlations between 11 SNPs (including specific SNPs in *VEGFA*, *VEGFR1*, and *VEGFR3*) and DFS and OS were assessed in patients with locoregional RCC. Three of the 11 SNPs demonstrated improved DFS with sunitinib treatment over placebo with HRs between 0.44 and 0.56, compared with 0.76 for the overall population. This improvement in HR supports a predictive value for this biomarker-defined subset of patients receiving sunitinib treatment. In particular, the genotypes C/C for *VEGFR1* rs9554320, T/T for *VEGFR2* rs2071559, and T/T for *eNOS* rs2070744 were associated with a longer DFS with sunitinib versus placebo treatment. In addition, some SNPs demonstrated a potential trend toward prognostic value across treatment groups. The genotypes homozygous C/C of *VEGFR1* rs9582036 and A/A of *VEGFR1* rs9554320 showed trends toward longer DFS versus the heterozygous and other homozygous genotypes in the sunitinib, placebo, and combined treatment groups. For the *VEGFR2* rs1870377 SNP, the only significant association was observed when both treatment groups were combined; the A/A genotype showed an association with shorter DFS versus the T/T genotype only. Despite differences in baseline demographics, the effect of sunitinib treatment on DFS in the pharmacogenomic analysis cohort was similar to that overall S-TRAC population (HR 0.74; 95% CI, 0.51–1.07; *P* = 0.107), with median DFS of 7.07 and 5.56 years for sunitinib and placebo, respectively. With a limited number of OS events, there were no

A VEGFR1 rs9554320 C/C



B VEGFR2 rs2071559 T/T



C eNOS rs2070744 T/T

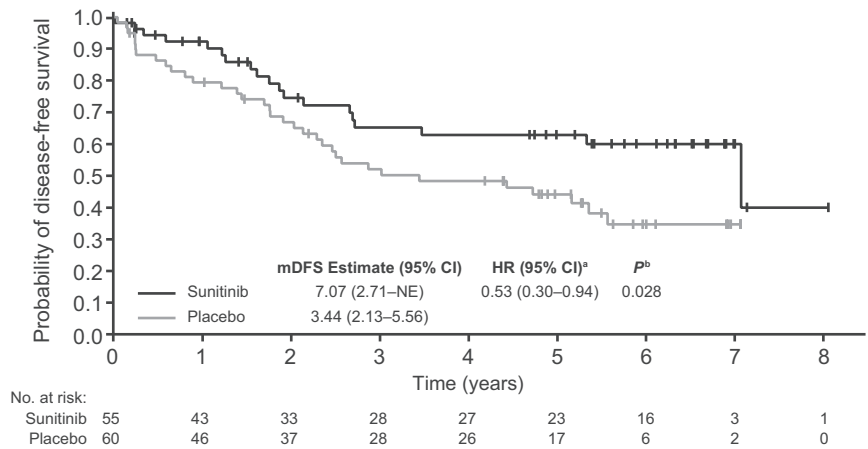


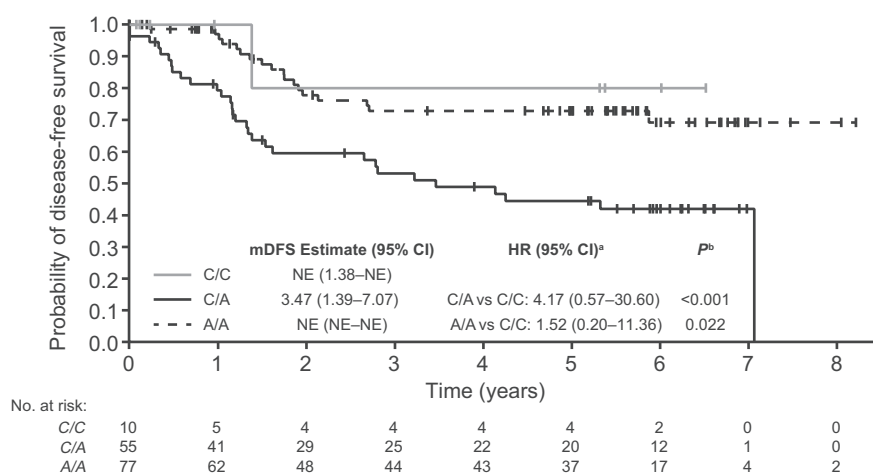
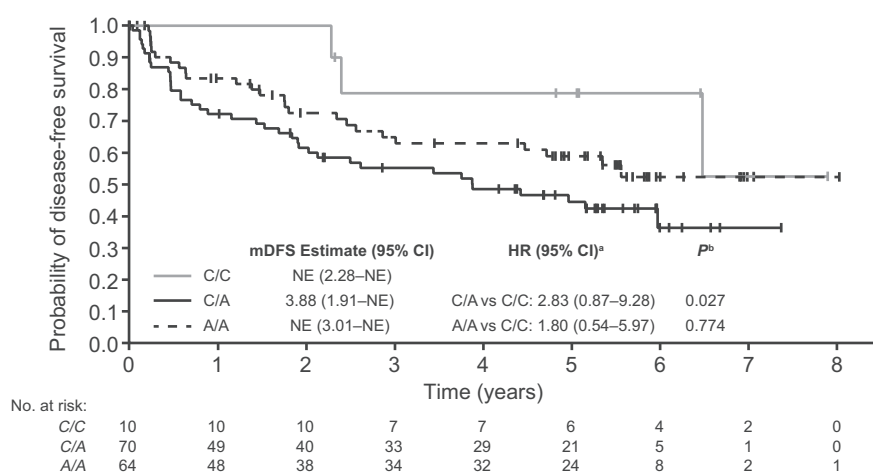
Figure 1.
A-C, Kaplan-Meier curve of DFS by genotype.
^aSunitinib vs. placebo. ^bUnstratified two-sided log-rank test. Abbreviation: NE, not estimable.

significant associations between SNP genotype and OS for sunitinib versus placebo. Still, for OS and genotypes within each treatment group and in the combined group, the genotype "-/-" (i.e., no insertion) of *CCDC26 rs60315789* showed a trend towards longer OS versus the heterozygous -/TAT genotype in the

sunitinib and placebo groups. A significant association was observed when the treatment groups were combined.

In the Renal EFFECT study, patients with metastatic RCC demonstrated marginally significant interactions between two sunitinib treatment arms and *VEGFR3 rs448012* for time-to-

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A Sunitinib arm**B Placebo arm****Figure 2.**

A and B, Kaplan-Meier curve of DFS by genotype subgroups for *VEGFR1 rs9582036*. ^aSunitinib vs. placebo. ^bUnstratified two-sided log-rank test. Abbreviation: NE, not estimable.

tumor progression, PFS, and OS; however, the study could not identify which treatment group had a significant association between genotype and the clinical outcome (28). The current analyses of patients in the adjuvant setting did not demonstrate any associations between efficacy and *VEGFR3* with sunitinib versus placebo, although longer DFS was seen for sunitinib versus placebo treatment in patients with C/C for *VEGFR1 rs9554320*, T/T for *VEGFR2 rs2071559*, and T/T for *eNOS rs2070744*. Genetic polymorphism in *eNOS rs2070744* has been previously identified as independently predicting a rise in blood pressure and/or development of severe hypertension, but not as a predictor of clinical outcome in sunitinib-treated patients with metastatic RCC (19, 30). A recent study has highlighted that endothelial nitric oxide synthase (*eNOS*) SNPs may have a role as predictive biomarkers for bevacizumab efficacy and toxicity in patients with metastatic colorectal carcinoma (31). Therefore, it will be necessary to explore the impact of *eNOS*, *VEGFR1*, *VEGFR2*, and *VEGFR3* SNPs on clinical outcomes in different treatment arms in patients with RCC or other tumor types.

In the current analyses, some SNPs in *VEGFR1*, *VEGFR2*, and *CCDC26* demonstrated potential for prognostic value in DFS or

OS outcomes across treatment groups in the adjuvant setting. To date, certain *VEGFR1* SNPs have been proposed as candidate prognostic biomarkers in patients with metastatic RCC (24, 25). In patients treated with first-line sunitinib, poorer response rate, PFS, and OS were observed in those with *VEGFR1 rs9554320* A/A and *rs9582036* C/C genotypes compared with more favorable genotypes (19, 24, 25). Dornbusch and colleagues also reported that poorer OS was observed in those with *VEGFR1 rs9582036* C/C genotypes versus A/A and A/C genotypes in patients with metastatic RCC treated with first-line sunitinib (26). However, they did not report any associations between *VEGFR1 rs9582036* and PFS or *VEGFR1 rs9554320* and PFS or OS (26).

Furthermore, SNPs in the *VEGFA* (*rs833061*, *rs699947*, *rs2010963*, and *rs3025039*), *VEGFR2* (*rs2305948*), and *VEGFR3* (*rs6877011*, *rs307826*, and *rs307821*) genes have been associated with varying clinical outcomes in patients with metastatic RCC treated with sunitinib (19, 20, 27, 29). For example, significantly longer PFS and OS were observed in patients with the C/C or C/T genotype of *VEGFA rs833061* compared with the T/T genotype; similar results were observed in patients with the A/A or A/C versus the C/C genotype of *VEGFA*

rs699947 (29). In patients with metastatic RCC treated with axitinib, certain SNPs in the *VEGFA* gene were associated with improved OS (19, 32). In contrast, in the Renal EFFECT study, Motzer and colleagues could not identify associations of certain SNPs (*VEGFA* rs699947, *VEGFA* rs1570360, *VEGFR3* rs448012, *VEGFR3* rs307821, and *VEGFR3* rs307826) with efficacy (PFS, OS, objective response, or time-to-tumor progression; refs. 19, 33). The contrasting observations for the impact of VEGF and VEGFR SNPs on sunitinib efficacy in RCC highlight the need to confirm exploratory studies and the differences reported. Additionally, some of the observations in the adjuvant setting appear to be divergent from the observations reported in the metastatic setting. These analyses were exploratory and were limited by small sample sizes in some subgroup analyses; therefore, further validation in independent adjuvant studies are needed to confirm if these SNPs can predict those patients who are most likely to derive benefit from adjuvant sunitinib treatment. Investigation into the association of SNPs and OS in the adjuvant setting would be of value; however, conservative estimates suggest that a suitably powered trial would require approximately 1,650 patients with a follow-up of 18.5 years to demonstrate a substantial impact on OS (13). Patients in the S-TRAC trial were followed-up for an additional year to further assess OS; however, only 16 additional events in the intent-to-treat population occurred between the data cut-off date and the final OS follow-up and data remained immature. Further analyses would therefore not be expected to provide additional insight. In lieu of mature OS data and given the clinical need, DFS can be considered a suitable endpoint, especially where survival may be prolonged. The importance of DFS as an endpoint is recognized by the FDA and formed the primary basis for the approval of other adjuvant therapies including colon cancer and hormonal and cytotoxic breast cancer therapies (34). Finally, additional analyses in the adjuvant setting should also address whether the frequency and outcomes associated with the identified SNPs are consistent across a more diverse range of ethnic groups.

Conclusions

Correlations between SNPs in *VEGFR1*, *VEGFR2*, and *eNOS* genes and improved DFS in the sunitinib compared with placebo groups support the hypothesis that germline SNPs could have potential predictive value to identify patients who might derive more benefit from adjuvant sunitinib. Additionally, SNPs in *VEGFR1*, *VEGFR2*, and *CCDC26* demonstrated a potential trend toward prognostic value for either DFS or OS across treatment groups. Further independent validation studies are necessary to confirm the potential predictive and prognostic value of these SNPs in the adjuvant setting.

Disclosure of Potential Conflicts of Interest

D.J. George receives other commercial research support from Acerta Pharmaceuticals, Astellas, Bayer H/C Pharmaceuticals, Bristol-Myers Squibb, Calithera, Dendreon, Exelixis, Innocrin, Janssen Pharmaceuticals, Novartis, Pfizer, and Sanofi, speakers bureau honoraria from Bayer H/C Pharmaceuticals, Sanofi, and Exelixis, is a consultant/advisory board member for Astellas, AstraZeneca, Bayer H/C Pharmaceuticals, Bristol-Myers Squibb, Capio Biosciences, Exelixis, Genentech, Innocrin, Janssen Pharmaceuticals, Merck Sharp & Dohme, Myovant Sciences, Pfizer, and Sanofi, receives other honorarium from EMD Serono, Michael J. Hennessey Associ-

ates, OnLive, Pfizer, and UroToday, is an independent contractor for Axess Oncology, is on the steering committees of NCI and Pfizer, and is on the independent data monitoring committees of Acceleron Pharmaceuticals and Janssen Pharmaceuticals. J.-F. Martini holds ownership interest (including patents) in Pfizer. M. Staehler reports receiving commercial research grants from Pfizer, Roche, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Bayer, Exelixis, and Novartis, speakers bureau honoraria from Pfizer, Ipsen, Novartis, EUSAPharm, and Eisai, and is a consultant/advisory board member for Pfizer, Ipsen, Novartis, EUSAPharm, and Eisai. R.J. Motzer reports receiving commercial research grants from Pfizer, Eisai, Exelixis, Bristol-Myers Squibb, Genentech/Roche, and Novartis, and is a consultant/advisory board member for Pfizer, Merck, Genentech, Exelixis, Eisai, and Novartis. A. Magheli is a consultant/advisory board member for Ipsen Pharma, and reports receiving speakers bureau honoraria from Pfizer, Astellas, Janssen, and Ipsen Pharma. F. Donskov reports receiving commercial research grants from Novartis, Pfizer, and Ipsen. B. Escudier is a consultant/advisory board member for Pfizer, Novartis, Bristol-Myers Squibb, Exelixis, and Roche, and reports receiving speakers bureau honoraria from Pfizer and Novartis. S. Li, M. Casey, O. Valota, and M.J. Lechuga hold ownership interest (including patents) in Pfizer. B. Laguerre receives honoraria from Pfizer. A.J. Pantuck and A. Patel are consultant/advisory board members for Pfizer. H.S. Pandha is a consultant/advisory board member for Ipsen and Eisai. A. Ravaud is a consultant/advisory board member for Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Roche, and Ipsen, and received travel support from Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Roche, Ipsen, and Merck Sharp & Dohme. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: D.J. George, J.-F. Martini, R.J. Motzer, B. Escudier, A.J. Pantuck, H.S. Pandha, A. Patel, M. Lechuga, A. Ravaud
Development of methodology: J.-F. Martini, B. Escudier, A. Patel, A. Ravaud
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Staehler, R.J. Motzer, A. Magheli, F. Donskov, B. Laguerre, A.J. Pantuck, M. Lechuga, A. Ravaud
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.J. George, J.-F. Martini, M. Staehler, R.J. Motzer, A. Magheli, F. Donskov, B. Escudier, S. Li, M. Casey, B. Laguerre, A.J. Pantuck, H.S. Pandha, A. Patel, M. Lechuga
Writing, review, and/or revision of the manuscript: D.J. George, J.-F. Martini, M. Staehler, R.J. Motzer, A. Magheli, F. Donskov, B. Escudier, S. Li, M. Casey, O. Valota, B. Laguerre, A.J. Pantuck, H.S. Pandha, A. Patel, M. Lechuga, A. Ravaud
Study supervision: D.J. George, J.-F. Martini, R.J. Motzer, A. Magheli, A.J. Pantuck, A. Patel, M. Lechuga, A. Ravaud
Other (Trial Global Steering Committee Member): D.J. George, M. Staehler, R.J. Motzer, A.J. Pantuck, H.S. Pandha, A. Patel, A. Ravaud

Data Sharing Statement

Upon request, and subject to certain criteria, conditions and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (i) for indications that have been approved in the United States and/or EU or (ii) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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