Short Communication

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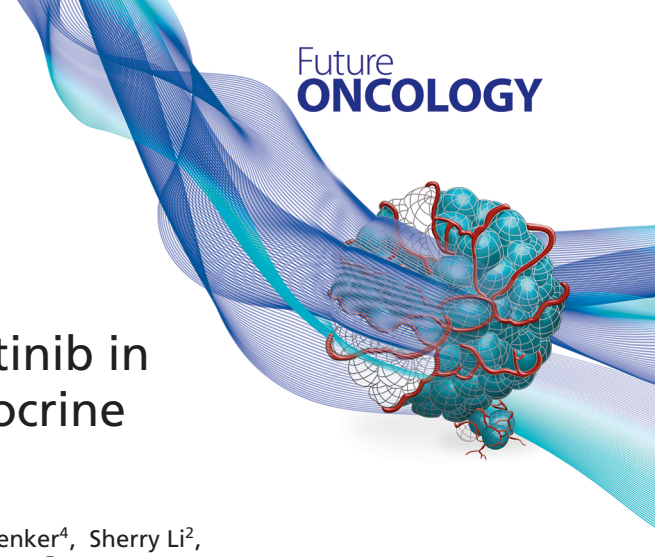

Pharmacogenomic analyses of sunitinib in patients with pancreatic neuroendocrine tumors

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Aim: Evaluate associations between clinical outcomes and SNPs in patients with well-differentiated pancreatic neuroendocrine tumors receiving sunitinib. **Patients & methods:** Kaplan–Meier and Cox proportional hazards models were used to analyze the association between SNPs and survival outcomes using data from a sunitinib Phase IV (genotyped, n = 56) study. Fisher's exact test was used to analyze objective response rate and genotype associations. **Results:** After multiplicity adjustment, progression-free and overall survivals were not significantly correlated with SNPs; however, a higher objective response rate was significantly associated with *IL1B rs16944* G/A versus G/G (46.4 vs 4.5%; p = 0.001). **Conclusion:** *IL1B* SNPs may predict treatment response in patients with pancreatic neuroendocrine tumors. VEGF pathway SNPs are potentially associated with survival outcomes.

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Pancreatic neuroendocrine tumors (panNETs) are rare malignancies; however, the incidence of these tumors appears to be increasing [1,2]. A number of options are available for the treatment of unresectable disease, including cytotoxic chemotherapy; somatostatin analogs; peptide receptor radionuclide therapy; and targeted agents, such as the mTOR inhibitor everolimus and the multitarget tyrosine kinase inhibitor (TKI) sunitinib [3]. However, most of these treatments may eventually be associated with either a primary resistance or a progressive loss of antitumor activity. Furthermore, not all therapies are approved by the European Medicines Agency (EMA) or US FDA [3].

Sunitinib is a TKI that inhibits the VEGFR signalling pathway, including VEGFR1–VEGFR3. panNETs are highly vascular tumors, and overexpression of VEGF has been shown to promote the growth of panNETs through increased angiogenesis [4]. Sunitinib is approved in the USA and Europe for the treatment of progressive, well-differentiated panNETs in patients with unresectable locally advanced or metastatic disease [5]. A Phase IV trial (ClinicalTrials.gov, NCT01525550) was conducted to provide additional information in previously treated patients and patients who were treatment-naive. Results in this Phase IV trial with a median progression-free survival (PFS) of 13.2 months, objective response rate (ORR) 24.5% and median overall survival (OS) of 37.8 months in sunitinib-treated patients with well-differentiated panNETs [6], were consistent with that of the Phase III study [5]. As a consequence of this demonstrated clinical activity, European Society of Medical Oncology (ESMO) clinical practice guidelines recommend sunitinib as a treatment option for patients with unresectable panNETs [7]. Despite publication of a treatment algorithm, the optimal allocation and sequence of treatments,

particularly among targeted therapies, requires an individualized approach, carefully balancing tolerability and efficacy considerations [8]. Real-world clinical experience with sunitinib in patients with panNETs demonstrates that sunitinib is a safe and effective treatment in patients with well-differentiated tumors [9] as well as heavily pretreated patients [10]. In two open-label extension studies of the sunitinib Phase III trial population, sunitinib was well-tolerated in the longer term [11], was consistent with the safety profile from the original Phase III trial [5] and other indications [12].

Not all patients treated with sunitinib experience benefit, and interpatient variability may be at least in part related with polymorphisms of sunitinib targets and other proteins involved in inflammation and metabolism. Being able to identify those patients most likely to benefit from a certain treatment may both improve the overall effectiveness of treatment and minimize unnecessary treatment-related adverse events. One way to achieve this is by defining predictive biomarkers. SNPs, the most common type of genetic variation, are stable single-base substitutions present in >1% of a population [13]. Germline SNPs, that is, those not arising from tumor cells, are attractive biomarker candidates as they are readily accessible via blood samples. As SNPs may alter drug metabolism and drug targets or effectors, there may be direct consequences for dosing, efficacy and safety [14]. Thus, pharmacogenomic evaluations have been developed as a per protocol ancillary analysis to evaluate potential associations between patient genotypes and clinical outcomes. The genes selected for this current study were *ABCB1*, *VEGFA*, *VEGFR2*/*KDR*, *VEGFR1* and *IL1B*, based on prior studies showing trends of correlations [15–19]. Therefore, the objectives of these exploratory analyses were to evaluate potential associations between clinical outcomes and SNPs in genes involved in angiogenesis, protein transport or inflammatory response, using a subset of patients from the Phase IV trial of sunitinib treatment in patients with panNETs.

Methods

Study design & patients

This was a single-arm, open-label, Phase IV clinical trial of sunitinib in patients with locally advanced unresectable/metastatic, well-differentiated panNETs. The study was conducted in accordance with the protocol, international ethical and clinical practice guidelines, the Declaration of Helsinki, and applicable local regulatory requirements and laws. All patients provided informed consent. The trial is registered on ClinicalTrials.gov (NCT01525550).

Patient eligibility has been reported previously [6]. Briefly, patients were ≥18 years old (in Japan, ≥ 20 years) with a histologically or cytologically proven diagnosis of well-differentiated panNETs and unresectable or metastatic disease with documented radiologic progression. Prior treatment with TKIs, anti-VEGF, non-VEGF angiogenesis inhibitors or mTOR inhibitors was not permitted [6].

Patients received 37.5 mg sunitinib orally once daily on a continuous daily dosing regimen. Dose modifications were permitted at the investigator's discretion. Patients were treated until death, unacceptable toxicity, withdrawal or the final analysis for the study was performed. Patients with evidence of disease progression could continue treatment if it was judged to have clinical benefit [6].

Molecular biomarker assays

Anonymized blood samples were prospectively collected from patients in the Phase IV trial who consented to the pharmacogenomics analyses. Samples were genotyped for 12 SNPs previously associated with panNET risk, prognosis or drug effect (Table 1). Samples underwent DNA extraction and DNA amplification using PCR. Commercially available TaqMan® assays (Thermo Fisher Scientific, MA, USA) 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, CT, USA).

Statistical analyses

The primary end point was investigator-assessed PFS per Response Evaluation Criteria In Solid Tumors (RECIST v1.0). PFS was defined as the time from enrollment to first progression of disease or death (in the absence of documented progressive disease), whichever occurred first. OS and ORR (investigator assessed) were assessed as secondary end points.

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. Fisher's exact test was used to compare baseline demographics and characteristics between treatment

Table 1. Candidate SNPs previously associated with pancreatic neuroendocrine tumor risk, prognosis or drug effect.

Official gene symbol	Alternate name	Official SNP & allele change	mRNA position & allele change	Protein position and changes
ABCB1	*CLCS; MDR1; P-GP; PGY1; ABC20; CD243; GP170*	*rs1128503* (C>T)	c.1236T>C, NM_000927.4	Gly412=
ABCB1	*CLCS; MDR1; P-GP; PGY1; ABC20; CD243; GP170*	*rs2032582* (tri-alletic) (G>T>A)	c.2677T>A, c.2677T>G NM_000927.4.	Ser893Ala/Thr
ABCB1	*CLCS; MDR1; P-GP; PGY1; ABC20; CD243; GP170*	*rs1045642* (C>T)	c.3435T>C, NM_000927.4:	Ile1145=
VEGFA	*VEGF, VPF, MVCD1, MGC70609*	*rs2010963* (C>G)	c.-94C>G, NM_001025366.2	–
VEGFA	*VEGF, VPF, MVCD1, MGC70609*	*rs833061* (T>C)	c.-958C>T, NM_001025366.2	–
VEGFA	*VEGF, VPF, MVCD1, MGC70609*	*rs833068* (G>A)	c.658+398G>A, NM_001025366.2	–
VEGFR2	*KDR, FLK1; CD309; VEGFR*	*rs7692791* (T>C)	c.798+54G>A, NM_002253.2	–
VEGFR2	*KDR, FLK1; CD309; VEGFR*	*rs1870377* (T>A)	c.1416A>T, NM_002253.2	Exon 11, Gln472His
VEGFR1	*FLT; FLT-1; VEGFR-1*	*rs9554320* (C>A)	c.3387-692T>G, NM_002019.4.	–
VEGFR1	*FLT; FLT-1; VEGFR-1*	*rs9582036* (A>C)	c.3635+319G>T, NM_002019.4	–
IL1B	*IL-1; IL1F2; IL1-BETA*	*rs16944* (G>A)	c.-598T>C, NM_000576.2:	–
IL1B	*IL-1; IL1F2; IL1-BETA*	*rs1143634* (C>T)	c.315C>T, NM_000576.2:	Phe27=

panNET: Pancreatic neuroendocrine tumor; SNP: Single nucleotide polymorphism.

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 as a quality control measure. All p-values were calculated using Pearson's χ^2 test based on 10,000 replicates. Linkage disequilibrium analysis was also performed for SNP pairs. D′, r2 and p-values were calculated for each pair of SNPs within a given gene or on the same chromosome.

In exploratory analyses, associations between SNPs and PFS or OS were assessed using Kaplan–Meier analysis and Cox proportional hazards models. Genotypes were compared within treatment-naive, previously treated and combined groups, and treatment groups were compared within genotypes. Fisher's exact test was used for association between ORR and genotype. All p-values were unadjusted for multiplicity; tests were significant if the p-value was <0.05.

To adjust for multiplicity in testing for an association between a genotype and a clinical end point, the Bonferroni multiplicity adjustment method was used. Considering the 12 SNPs in this study, the adjusted significance level was $0.05/12 = 0.0041$; tests were significant if the p-value was <0.0041. The data cut-off date for these pharmacogenomic analyses was 19 March 2016, per the primary analyses [6].

Results

Patients

From a total of 106 patients enrolled in the clinical study, 56 patients (25 treatment-naive and 31 previously treated) consented, provided a blood sample and were genotyped. Baseline demographics were generally comparable between groups (Table 2), with the following exceptions: there were more female patients (56.0%) in the treatment-naive cohort versus the previously treated cohort (25.8%). Additionally, there were no Asian patients in the genotyped subpopulation compared with 74.2% of the nongenotyped subpopulation.

Genotyping

There were no unexpected findings in allele and genotype frequencies for SNPs (Supplementary Tables 1 & 2). In general, there were no deviations from Hardy–Weinberg equilibrium; high-linkage disequilibrium was detected between SNPs *VEGFA rs2010963*, *VEGFA rs833068* and *VEGFA rs833061* on chromosome 6 ($D' = 1.000$, r2 ranging from 0.411 to 1.000; $p < 0.001$), between *VEGFR1 rs9554320* and *VEGFR1 rs9582036* on chromosome 13 ($D' = 1.000$, $r2 = 0.540$; $p < 0.001$), and between SNPs *ABCB1 rs1045642*, *ABCB1 rs1128503* and *ABCB1 rs2032582* on chromosome 7 ($D' > 0.9$, r2, ranging from 0.611 to 0.785; $p < 0.001$), as expected for SNPs located on the same gene.

Table 2. Patient baseline characteristics.

Characteristic	All patients			Genotyped		
	All genotyped (n = 56)	Nongenotyped (n = 50)	p-value† (genotyped vs nongenotyped)	Treatment-naive (n = 25)	Previously treated (n = 31)	p-value† (treatment naive vs previously treated)
Age, years						
<65	46 (82.1)	46 (92.0)	0.160	20 (80.0)	26 (83.9)	0.738
≥65	10 (17.9)	4 (8.0)		5 (20.0)	5 (16.1)	
Sex						
Male	34 (60.7)	29 (58.0)	0.844	11 (44.0)	23 (74.2)	0.029
Female	22 (39.3)	21 (42.0)		14 (56.0)	8 (25.8)	
Race						
White	55 (98.2)	12 (24.0)	<0.001	24 (96.0)	31 (100.0)	0.446
Black	1 (1.8)	1 (2.0)		1 (4.0)	0	
Asian		37 (74.0)		–	–	
ECOG PS						
0	36 (64.3)	33 (66.0)	1.000	14 (56.0)	22 (71.0)	0.256
1	19 (33.9)	17 (34.0)		11 (44.0)	8 (25.8)	
Not reported	1 (1.8)	–		–	1 (3.2)	

†p-value based on Fisher's exact test.
ECOG PS: Eastern Cooperative Oncology Group performance score.

Table 3. Summary of trends for objective response rate comparison between cohorts within SNP subgroups.

SNP subgroup	Treatment-naive	Previously treated	Combined
***VEGFR2 rs7692791*, T/T genotype**			
n	7	6	13
ORR (95% CI)	14.3 (0.4–57.9)	66.7 (22.3–95.7)	38.5 (13.9–68.4)
OR (95% CI)	0.08 (0.0–1.9)	–	–
p-value	0.103†	–	–
***VEGFA rs2010963*, G/G genotype**			
n	11	13	24
ORR (95% CI)	0.0 (0.0–28.5)	38.5 (13.9–68.4)	20.8 (7.1–42.2)
OR (95% CI)	0.00	–	–
p-value	0.041†	–	–
***VEGFA rs833068*, G/G genotype**			
n	11	13	24
ORR (95% CI)	0.0 (0.0–28.5)	38.5 (13.9–68.4)	20.8 (7.1–42.2)
OR (95% CI)	0.00	–	–
p-value	0.041†	–	–
***VEGFR1 rs9582036*, A/C genotype**			
n	10	13	23
ORR (95% CI)	0.0 (0.0–30.8)	38.5 (13.9–68.4)	21.7 (7.5–43.7)
OR (95% CI)	0.00	–	–
p-value	0.046†	–	–

†p-value based on Fisher's exact test.
OR: Odds ratio; ORR: Objective response rate.

Comparison between cohorts within each SNP subgroup

There were no significant associations between genotype and PFS or OS (Supplementary Tables 3 & 4). There were no statistically significant associations between genotype and ORR after Bonferroni adjustment (Supplementary Table 5). However, the following trends were reported (Table 3): higher ORR in the previously treated cohort versus the treatment-naive cohort for the homozygous genotype G/G of *VEGFA rs2010963* (38.5 vs 0.0%; p = 0.041);

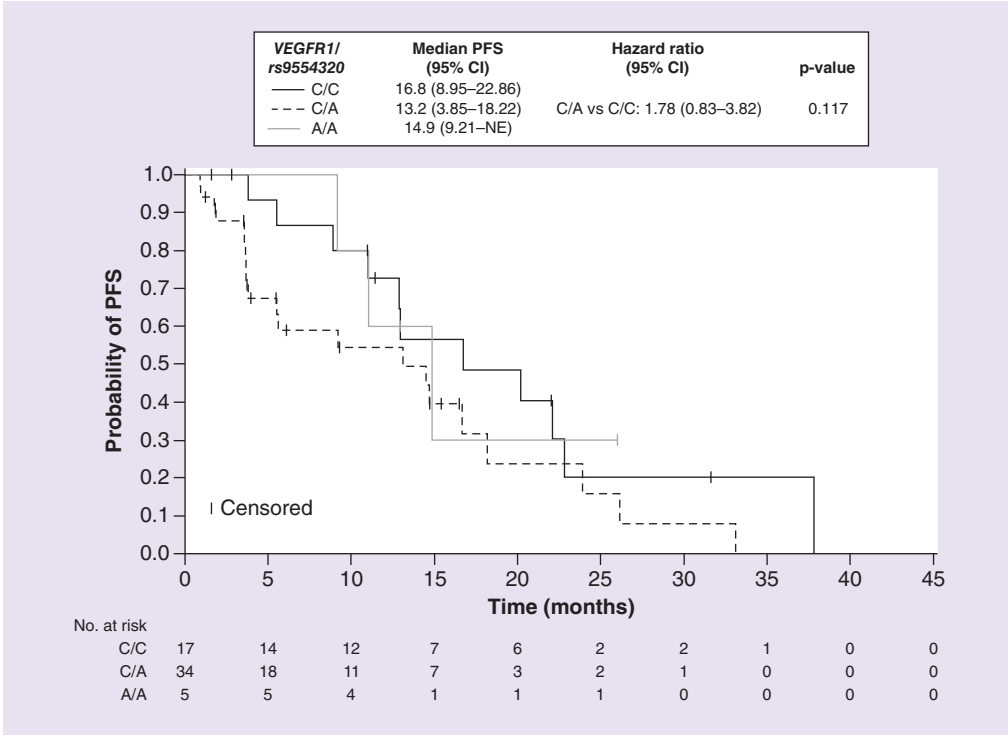

Figure 1. Kaplan–Meier plot of progression-free survival by *VEGFR1 rs9554320* genotype in the combined cohort.
NE: Non estimable; PFS: Progression-free survival.

the homozygous genotype G/G of *VEGFA rs833068* (38.5 vs 0.0%; p = 0.041); and the heterozygous genotype A/C of *VEGFR1 rs9582036* (38.5 vs 0.0%; p = 0.046). Additionally, the homozygous genotype T/T of *VEGFR2 rs7692791* showed a trend toward a lower ORR in the treatment-naive cohort compared with the previously treated cohort (14.3 vs 66.7%; odds ratio [OR]: 0.08; 95% CI: 0.0–1.9; p = 0.103).

Comparison of SNP genotype subgroups within each cohort & combined

There were no significant associations between genotype and PFS or OS, regardless of prior line of treatment (Supplementary Tables 6 & 7). However, there was a trend toward shorter PFS in patients with *VEGFR1 rs9554320* C/A versus C/C (hazard ratio: 1.78; 95% CI: 0.83–3.82; p = 0.117; Figure 1). Additionally, shorter PFS was also observed in patients with *VEGFR1 rs9582036* A/C versus A/A (hazard ratio: 1.88; 95% CI: 0.9–3.93; p = 0.102; Figure 2). Some patients (n = 31) were still in follow-up at the time of the analyses cut-off date (19 March 2016).

The heterozygous genotype G/A of *IL1B rs16944* was significantly associated with a higher ORR versus the homozygous genotype G/G (46.4 vs 4.5%; OR: 18.2; 95% CI: 2.2–809.3; p = 0.001; Table 4). In addition, in the previously treated cohort, there was a trend toward lower ORR in patients with the heterozygous genotype T/C of *VEGFR2 rs7692791* compared with patients with the homozygous genotype T/T (16.7 vs 66.7%; OR: 0.10; 95% CI: 0.0–1.2; p = 0.038). In the combined cohort, this trend was also observed (16.7 vs 38.5%; OR: 0.32; 95% CI: 0.1–1.8; p = 0.140; Table 4). No other associations between ORR and genotype were reported (Supplementary Table 8).

Discussion

In these exploratory analyses, after adjustment for multiplicity, no statistically significant correlations were observed between the VEGF pathway SNPs investigated and PFS or OS; however G/A of *IL1B rs16944* was significantly associated with a higher ORR than the homozygous genotype G/G. Although not statistically significant, a trend toward shorter PFS in patients with *VEGFR1 rs9554320* C/A versus C/C and *VEGFR1 rs9582036* A/C versus A/A was observed. A trend toward a lower ORR was also noted in patients with *VEGFR2 rs7692791* T/C versus T/T.

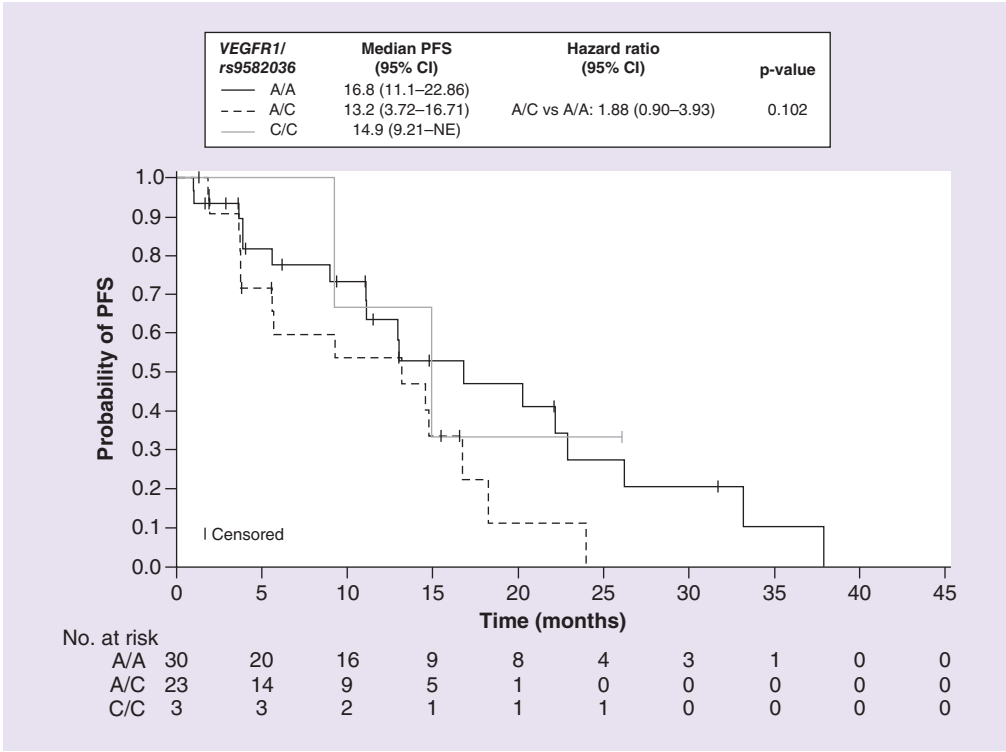

Figure 2. Kaplan–Meier plot of progression-free survival by *VEGFR1 rs9582036* genotype in the combined cohort.
NE: Non estimable; PFS: Progression-free survival.

Table 4. Summary of trends for objective response rate comparison of SNP genotype subgroups within each cohort and combined.

SNP genotype subgroup	Treatment-naive			Previously treated			Combined		
IL1B rs16944	G/G n = 13	G/A n = 9	A/A n = 3	G/G n = 9	G/A n = 19	A/A n = 3	G/G n = 22	G/A n = 28	A/A n = 6
ORR (95% CI)	7.7 (0.2–36.0)	33.3 (7.5–70.1)	33.3 (0.8–90.6)	0.0 (0.0–33.6)	52.6 (28.9–75.6)	0.0 (0.0–70.8)	4.5 (0.1–22.8)	46.4 (27.5–66.1)	16.7 (0.4–64.1)
OR (95% CI)	–	6.00 (0.4–340.6)	6.00 (0.1–509.0)	–	–	–	–	18.2 (2.2–809.3)	4.20 (0.0–344.9)
p-value	–	0.264†	0.350†	–	0.010†	–	–	0.001†	0.389†
VEGFR2 rs7692791	T/T n = 7	T/C n = 12	C/C n = 6	T/T n = 6	T/C n = 18	C/C n = 7	T/T n = 13	T/C n = 30	C/C n = 13
ORR (95% CI)	14.3 (0.4–57.9)	16.7 (2.1–48.4)	33.3 (4.3–77.7)	66.7 (22.3–95.7)	16.7 (3.6–41.4)	42.9 (9.9–81.6)	38.5 (13.9–68.4)	16.7 (5.6–34.7)	38.5 (13.9–68.4)
OR (95% CI)	–	1.20 (0.1–82.4)	3.00 (0.1–205.9)	–	0.10 (0.0–1.2)	0.38 (0.0–5.5)	–	0.32 (0.1–1.8)	1.00 (0.2–6.4)
p-value	–	1.000†	0.559†	–	0.038†	0.592†	–	0.140†	1.000†

†p-value based on Fisher's exact test.
OR: Odds ratio; ORR: Objective response rate; SNP: Single-nucleotide polymorphism.

Our results support that SNPs of VEGFR may play a role in clinical response to therapy in neuroendocrine tumors. In other tumor types, SNPs in *VEGFR1* (*VEGFR1 rs9582036* and *rs9554320*) have been associated with clinical outcomes (ORR, PFS and/or OS) in pancreatic cancer or metastatic colorectal cancer during treatment with bevacizumab, or during treatment with sunitinib in patients with metastatic renal cell carcinoma (RCC) or in the adjuvant RCC setting [18,20–24]. Despite conflicting reports, certain SNPs of *VEGFR1* appear to have an impact on clinical response across various tumor types, including in patients with panNETs. In the current analyses, there was a trend for higher ORR in previously treated patients compared with treatment-naive patients

for certain *VEGFA*, *VEGFR1* and *VEGFR2* genotypes. In the adjuvant RCC setting, longer disease-free survival was reported for sunitinib versus placebo in patients with homozygous genotypes C/C for *VEGFR1 rs9554320* and T/T for *VEGFR2 rs2071559* [24]. Although the study was not designed to identify associations between treatment groups, marginally significant interactions between two sunitinib treatment arms and *VEGFR3 rs448012* were seen for clinical outcomes in the RENAL EFFECT study in metastatic RCC [25]. Although no comparisons were made among different treatment groups, SNPs in the *VEGFA*, *VEGFR1*, *VEGFR2* and/or *VEGFR3* genes have been associated with varying clinical outcomes in other trials evaluating sunitinib-treated patients with metastatic RCC [17,18,20,23,26–29], as well as in bevacizumab-treated patients with metastatic colorectal or pancreatic cancer [18,21,22]. These data suggest that further evaluation of the effects of SNPs within *VEGFA*, *VEGFR1*, *VEGFR2* and *VEGFR3* on clinical outcomes across different treatment arms in patients with panNETs is warranted.

Establishing the predictive value of VEGFR SNPs could have important clinical implications. For example, in patients where it is necessary to achieve rapid regression of the tumor, due to pain or other symptoms, it may be possible to differentiate treatment. With relevance to this study, eligible patients with panNETs could be treated with sunitinib instead of chemotherapy, thus improving clinical outcomes and avoiding the toxicity associated with chemotherapy. Indeed, the ultimate goal of identifying SNPs associated with clinical outcome is to provide individualized treatment regimens that will optimize the effectiveness and safety of available treatments; however, several obstacles remain before SNP analysis can be routinely used in clinical practice. The majority of SNP studies are hypothesis generating and require validation in larger prospective studies. Furthermore, many SNP studies rely on PCR-based amplification of DNA and subsequent allelic discrimination assays. While minimally invasive, effective and relatively inexpensive, this method requires many steps and is of a low-moderate throughput [30]. The development of cost-effective, higher throughput diagnostic techniques would greatly aid the implementation of routine SNP analysis to the clinic.

Our analyses did not investigate *VEGFR3* SNPs, reported by others to be correlated with a decreased tumor response to pazopanib [31], divergent tumor responses to sunitinib [18,20,25,32–34] and poor prognosis in patients with gastroenteropancreatic neuroendocrine neoplasms [35]. A recent Spanish multicenter SNP analysis in patients with well-differentiated panNETs reported that *VEGFR3 rs307826* and *rs307821* predicted lower OS, but not PFS [34]; however, following correction for multiple testing, no correlations remained significant. Consistent with our study, no statistically significant correlation was observed between PFS or OS and the SNPs *VEGFA rs2010963*, *ABCB1 rs1128503* or *ABCB1 rs2032582* [34].

IL1B has been shown to be involved in panNET etiology and development [19,36]. Analysis of SNPs associated with tumor development may prove to be important in the diagnosis and identification of high-risk individuals. Polymorphisms in the displacement loop region of mitochondrial DNA have been identified that may be implicated in gastroenteropancreatic neuroendocrine neoplasms development [37] and survival [38]. Others have reported that polymorphisms in *CDKN2A/B* are risk factors for panNET development [39]. *IL1B* SNPs have been reported to be associated with the development of prostate cancer [40], but have no influence on outcomes in non-small-cell lung cancer [41]. However, this is the first report of *IL1B* SNPs leading to differences in treatment response in patients with panNETs. Therefore, specific further prospective investigation in patients with panNETs is warranted on this target to confirm the correlation with sunitinib treatment.

Our study adds to a growing body of evidence that SNPs in the VEGFR signalling pathway may help predict clinical responses in patients receiving sunitinib. Due to differences between genotyped and nongenotyped patients, the population used in this genotyping analysis could not be representative of the overall study population; thus, conclusions derived from the analysis of the genotyped population should not be extrapolated to the full study population. Due to the rare nature of panNETs, it is challenging to recruit large numbers of patients for clinical trials and subsequent analyses. The genotyped population (n = 56) of our study was of a comparable size with other SNP studies in patients with panNETs, including studies by Jiménez-Fonseca *et al.* (n = 43) [34], Karakaxas *et al.* (n = 51) [36] and Cigrovski Berković *et al.* (n = 60) [19]. Consequently, our analyses, like many SNP panNET studies, are also limited by the small sample sizes in some of the subgroups, as well as the exploratory nature of the study. Therefore, these findings will need to be validated in larger prospective studies in patients with panNETs.

Conclusion

No statistically significant correlations were observed between the VEGF pathway SNPs investigated and PFS or OS. A significant association was seen for *IL1B rs16944* and ORR, which is consistent with the role of *IL1B* in panNET etiology and development. Some associations were observed between ORR and SNPs in *VEGFA*, *VEGFR1*

and *VEGFR2* genotypes, although most correlations were not significant after adjustment for multiplicity. Further investigations in homogeneous, prospective studies are needed to elucidate the role of these SNPs in the treatment of patients with locally advanced unresectable/metastatic well-differentiated panNETs.

Summary points

- Well-differentiated pancreatic neuroendocrine tumors (panNETs) are highly angiogenic tumors whose incidence appears to be increasing.
- Sunitinib inhibits angiogenic activity through the VEGF pathway and has demonstrated improvements in progression-free survival (PFS) in patients with well-differentiated panNETs.
- Variability in the clinical response to sunitinib may be due to single-nucleotide polymorphisms in sunitinib targets.
- This study investigated potential associations between clinical outcomes and 12 SNPs in a subset of patients from a sunitinib Phase IV trial in patients with panNETs.
- Fifty-six (25 treatment-naive and 31 previously treated) patients consented and were genotyped.
- There were no significant associations between genotype and PFS or overall survival, but there was a trend toward shorter PFS (hazard ratio [95% CI]) in patients with *VEGFR1 rs9554320* C/A versus C/C (1.78 [0.83–3.82]; p = 0.117) and *VEGFR1 rs9582036* A/C versus A/A (1.88 [0.9–3.93]; p = 0.102).
- Correlations between overall response rate and *VEGFA rs2010963* and *rs833068*, *VEGFR1 rs9582036* and *VEGFR2 rs7692791* were observed, although they were not statistically significant.
- Higher ORR was significantly associated with *IL1B rs16944* G/A versus G/G (46.4 vs 4.5%; p = 0.001) in the combined group.
- This is the first report of *IL1B* SNPs leading to differentiated treatment responses in patients with panNETs.
- Further study is warranted to confirm the association of *IL1B* and *VEGFR1* SNPs with treatment response. These findings may have implications for future treatment decision making.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2018-0934

Author contributions

All authors were involved in the study conception/design, or the acquisition, analysis or interpretation of data. All authors contributed to the drafting of the manuscript and approved the final version. All authors contributed equally to the creation of this manuscript.

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Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of this data is: ClinicalTrials.gov, identifier NCT01525550.

Upon request, and subject to certain criteria, conditions and exceptions (see 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 for indications that have been approved in the USA and/or EU; or 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.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. For investigations involving human subjects, informed consent has been obtained from the participants involved.

Open access

Data disposition

The trial is registered on ClinicalTrials.gov, identifier NCT01525550.

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