

# A Phase II Trial of Vandetanib in Children and Adults with Succinate Dehydrogenase–Deficient Gastrointestinal Stromal Tumor



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## Abstract

**Purpose:** Gastrointestinal stromal tumors (GIST) are resistant to cytotoxic chemotherapy and radiotherapy. Most GIST in children are wild-type for *KIT* and *PDGFRA* (WT GIST) and deficient in expression of succinate dehydrogenase (dSDH GIST). We tested the activity of vandetanib, an oral small-molecule inhibitor of VEGFR2, EGFR, and RET, in patients with dSDH GIST.

**Patients and Methods:** Phase II study of vandetanib (300 mg orally once daily to patients  $\geq 18$  years, and 100 mg/m<sup>2</sup>/dose to patients  $< 18$  years) on a continuous dosing schedule (1 cycle = 28 days) to assess the clinical activity (partial and complete response rate RECIST v1.1) in patients with dSDH GIST. A Simon optimal two-stage design (target response rate 25%, rule out 5%) was used: If  $\geq 1$  of 9 patients in stage 1 responded, enrollment

would be expanded to 24 patients, and if  $\geq 3$  of 24 responded, vandetanib would be considered active.

**Results:** Nine patients (7 female and 2 male; median age, 24 years; range, 11–52) with metastatic disease were enrolled. Three of the initial 5 adult patients developed treatment-modifying toxicities. After a protocol amendment, two adults received vandetanib at 200 mg/dose with improved tolerability. The two children ( $< 18$  years old) enrolled did not experience treatment-modifying toxicities. No partial or complete responses were observed (median number of cycles, 4; range, 2–18).

**Conclusions:** Vandetanib at a dose of 300 mg daily was not well tolerated by adults with dSDH GIST. Two of 9 patients had prolonged stable disease, but no partial or complete responses were observed, and vandetanib is thus not considered active in dSDH GIST.

## Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract with an annual incidence of approximately ten per million (1–3). The primary therapy for GIST is surgical, and the tumor is resistant to both cytotoxic chemotherapy and radiotherapy (4). The majority of GIST in adult patients harbor activating mutations in *KIT* or *PDGFRA* and can be effectively treated with KIT-targeting tyro-

sine kinase inhibitors (TKI; ref. 5). However, 85% of GIST in pediatric patients as well as 10% to 15% in adults are wild-type for both *KIT* and *PDGFRA* (6), and KIT-targeting TKIs such as imatinib have minimal efficacy for this group. WT GIST are primarily due to succinate dehydrogenase (SDH) deficiency because of mutations in one of the subunits of the SDH complex or lack of expression of SDHC due to hypermethylation of the SDHC promoter (epimutant; refs. 5, 7). SDH-deficient GIST (dSDH GIST) have a gastric predilection, increased incidence in females, and frequent multifocal presentation (6). They are typically indolent; however, metastatic disease can cause significant morbidity.

SDH (as SDH–ubiquinone complex II) is a component of the Krebs cycle and the respiratory chain and is composed of four subunits (A, B, C, and D). A group of SDH-deficient tumors are now recognized including approximately 30% to 40% of hereditary paragangliomas (8), a small subset of GIST (9), and rare renal cell carcinomas (10). In dSDH GIST, succinate dehydrogenase B (SDHB) protein expression evaluated using IHC is markedly decreased or absent (9). This unique feature brings up the consideration of using SDHB IHC early in the GIST diagnostic process. The specific mechanism of tumorigenesis in SDH-deficient tumors is not known. However, a number of metabolic derangements have been characterized. An autosomal-dominant inherited tumor predisposition syndrome that includes gastric GIST as well as paragangliomas was reported in 2002, and the

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### Translational Relevance

Approximately 85% of gastrointestinal stromal tumors (GIST) in pediatric patients are wild-type for both *KIT* and *PDGFRA* and have limited response to KIT inhibitors such as imatinib. The majority of these tumors are deficient in succinate dehydrogenase (SDH) due to genetic or epigenetic mechanisms (dSDH GIST). In preclinical models, SDH deficiency leads to increased levels of hypoxia-inducible factor-1 $\alpha$  (HIF1 $\alpha$ ). We hypothesized that inhibition of the HIF1 $\alpha$ -induced VEGF pathway would decrease the growth of dSDH GIST. Vandetanib, an orally available TKI with activity targeting VEGFR2, was tested in patients with dSDH GIST. No complete or partial responses were seen. Novel therapies are needed for this subgroup of patient.

underlying mutations in SDH subunits were subsequently identified (9, 11, 12). The SDH complex is a component of the Krebs cycle and electron transport chain catalyzing the oxidation of succinate to fumarate. Impaired SDH activity leads to accumulation of succinate within the cell causing a constellation of metabolic changes. The family of  $\alpha$ -ketoglutarate-dependent dioxygenases is inhibited by succinate. Among this family of enzymes is the hypoxia-inducible factor- $\alpha$  (HIF $\alpha$ ) prolyl-hydroxylase. Inhibition of HIF1 $\alpha$  prolyl-hydroxylase leads to von Hippel-Lindau-independent stabilization of HIF1 $\alpha$  and constitutive activation of hypoxia signaling (13–15). This causes increased expression of downstream targets such as EGFR and VEGF (14). There is a lack of preclinical models of dSDH GIST; however, vandetanib has been shown to inhibit cell growth in preclinical models of fumarate hydratase-deficient renal cell cancer, another tumor associated with a Krebs cycle enzyme deficiency, and increased levels of HIF1 $\alpha$  (16). This suggests that drugs targeting HIF1 $\alpha$ -dependent processes may have a role in the treatment of dSDH GIST. Vandetanib (CAPRELSA; ZD6474; Sanofi Genzyme) is a small-molecule receptor tyrosine kinase inhibitor, given as a once-daily oral drug that inhibits VEGFR2 and EGFR-dependent signaling. Vandetanib has activity in medullary thyroid carcinoma in adults at doses ranging from 100 to 300 mg once daily on a continuous dosing schedule and in children receiving 100 to 150 mg/m<sup>2</sup>/dose (17, 18). To test the activity of vandetanib in dSDH GIST, a small two-stage phase II study was performed.

## Patients and Methods

### Patient population

Patients  $\geq$  3 years of age with histologically confirmed GIST with the absence of *KIT* and *PDGFRA* mutation and measurable disease were eligible. Disease progression at the time of study entry was not required for eligibility. Other eligibility criteria included recovery from toxic effects of prior therapy; Karnofsky/Lansky performance score  $\geq$  50%; interval from prior therapy  $\geq$  4 weeks from prior surgical procedures with complete healing of surgical sites,  $\geq$  28 days from a last dose of cytotoxic chemotherapy and at least 7 days from prior biological therapy including immunomodulatory agents, vaccines, and differentiating agent; at least 30 days from a prior dose of a monoclonal antibody or any investigational agent; and  $\geq$  4 weeks from external beam radio-

therapy. Patients must have recovered from the acute toxic effects of prior therapy to grade 1. Patients were required to have normal organ and marrow function including adequate renal function (age-adjusted normal serum creatinine, or a creatinine clearance  $\geq$  50 mL/min/1.73m<sup>2</sup>) and adequate liver function [total bilirubin  $\leq$  1.5x institutional upper limit of normal (ULN; in patients with documented Gilbert's Disease, an elevated bilirubin was not an exclusion criterion), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)  $\leq$  2.5x ULN]. AST and ALT could be up to 5x ULN in patients with hepatic metastases. Adequate bone marrow function was required and defined as an absolute neutrophil count  $\geq$  1,500/ $\mu$ L and transfusion-independent platelet count of  $\geq$  100,000/ $\mu$ L. Participants 18 years of age and younger were required to have a blood pressure  $\leq$  95th percentile for age, height, and gender without any treatment for hypertension. In adult patients, preexisting hypertension was required to be controlled for enrollment. Adult patients with blood pressure  $>$ 160 mmHg systolic or  $>$  100 mmHg diastolic who were unable to achieve blood pressure control with antihypertensive therapy were excluded.

This trial conformed to the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the NCI's Institutional Review Board. Investigators obtained written consent from all patients or their legal guardians indicating their understanding of the investigational nature and risks of this study. Assent was obtained according to institutional guidelines.

### Drug administration and study design

The study was conducted as a small, Simon optimal two-stage phase II trial in order to rule out an unacceptably low overall response rate of 5% (ORR;  $p_0 = 0.05$ ), in favor of a response rate of 25% ( $p_1 = 0.25$ ). With  $\alpha = 0.10$  and  $\beta = 0.10$ , if  $\geq 1$  of 9 patients in stage 1 responded, enrollment would be expanded to 24 patients, and if  $\geq 3$  of 24 responded, vandetanib would be considered active. Vandetanib was supplied by AstraZeneca to the NCI and administered under an investigator-held IND (BB-IND 77570). Vandetanib was administered orally once a day on a continuous dosing schedule. The planned cycle duration was 28 days. Patients 18 years of age and older were started on a fixed dose of 200 mg once daily with a planned increase in vandetanib dose to 300 mg daily after the third cycle if the drug was tolerated. Patients younger than 18 years of age at the time of enrollment were started at a dose of 100 mg/m<sup>2</sup> based on a dosing nomogram with a planned increase in the dose to 150 mg/m<sup>2</sup>/day after the third cycle if the drug was tolerated.

### Toxicity assessment and disease evaluations

Monitoring for vandetanib-related toxicity included physical examination with blood pressure measurement as well as complete blood count with differential serum chemistries including electrolytes, calcium, phosphate, magnesium, creatinine, glucose, blood urea nitrogen, albumin, AST, ALT, total bilirubin, and total protein at baseline, day 14 of cycle 1, prior to cycle 2, 3, and 4, and subsequently after every third cycle. Thyroid function testing, urinalysis, and electrocardiogram were performed at baseline and prior to cycles 2, 3, and 4 and then following every third cycle thereafter. Pregnancy testing was done in postpubertal female patients, and unilateral knee MRI to assess for growth plate toxicity in patients with open growth plates was performed at baseline and prior to cycles 4, 7, 10, and 13 and then after every sixth cycle. Prothrombin time (PT) and partial thromboplastin

time (PTT) were performed at baseline. Adverse events were graded according to the Common Toxicity Criteria v. 4.

Response was evaluated using Response Criteria in Solid Tumors guideline version 1.1 (19) at baseline and prior to cycles 4, 7, 10, and 13 and then after every sixth cycle. Assessment of disease was performed using radiologic evaluation which could include CT scan of the chest, abdomen, and pelvis for primary tumor, and MRI of the abdomen/pelvis. A consistent method of disease evaluation was used for each patient throughout the study. 2[18F]fluoro-2-deoxy-D-glucose (FDG)-PET was performed on all patients at baseline and prior to cycle 4, and an optional PET scan was performed on adult patients on days 3 to 6 of cycle 1. CT attenuation coefficient (density) was measured using VuePACS version 12.2.2.0105. An average pixel value was determined over a region of interest of each target lesion, and average CT density was calculated.

### Definition of treatment-limiting toxicity

Hematologic treatment-limiting toxicity (TLT) was defined as grade 3 neutropenia (<1,000/ $\mu$ L) on two consecutive measurements drawn at least 72 hours apart or any grade 4 neutropenia (neutrophil count below 500/ $\mu$ L); thrombocytopenia (<50,000/ $\mu$ L, grade 3) on two consecutive measurements drawn at least 72 hours apart or any grade 4 thrombocytopenia (<25,000/ $\mu$ L); and grade 3 or 4 decrease in hemoglobin that could not be corrected to at least 8.0 g/dL (grade 2). Grade 3 or 4 leucopenia or lymphopenia was not considered a TLT. Any nonhematologic toxicity grade 3 or higher was considered treatment-limiting with the exception of grade 3 nausea or vomiting that was controlled with antiemetics within 48 hours, any grade 3 diarrhea that was tumor-related or vandetanib-related but controlled by symptomatic treatment within 48 hours, grade 3 AST or ALT elevation that returned to grade 2 or less within 14 days of holding drug and did not recur with reinstitution of the drug, or grade 3 electrolyte abnormalities that were asymptomatic and correctable to grade 2 within 48 hours. Treatment-limiting hypertension was defined as previously described (20). Treatment-limiting QTc prolongation was defined as a single QTc value  $\geq$ 500 ms. Compliance was assessed by diary which was evaluated at each clinic visit.

### Quality of life assessment

Health-related quality of life was evaluated by patient and parent report (for pediatric patients) using PROMIS short-form measures (anxiety, depression, fatigue, pain interference, and physical function). The measures were administered to all con-

senting English- or Spanish-speaking patients with parallel Parent Proxy instruments administered to parents of patients ages 8 to 17. These instruments were administered at baseline, at the first restaging visit (3 months), and at the time a patient was taken off treatment.

## Results

### Patient characteristics

Nine patients (2 male and 7 female; median age, 24 years; range, 11–52) were enrolled from May 7, 2014, to June 11, 2015. Table 1 provides a summary of demographic, clinical, and baseline disease characteristics. All patients had SDH-deficient tumors as determined by genomic analysis or tumor IHC showing negative staining for SDHB. Two patients had tumors with loss of SDHB by IHC but no identified SDH subunit mutation suggesting that these patients had loss of SDHC due to hypermethylation of the SDHC promoter (SDHC-epimutant tumors) as previously described (21). Eight of 9 patients had received prior TKI therapy including imatinib (7), sunitinib (5), and regorafenib (3). All patients had a gastric primary tumor, and sites of disseminated disease included hepatic, pulmonary, peritoneal, and lymph node metastases.

### Toxic effects and duration of treatment

Three of 5 adult patients initially treated at a vandetanib dose of 300 mg/dose developed TLT: Grade 3 hypertension ( $n = 1$ ), grade 2 seizure ( $n = 1$ ), grade 3 pneumonitis ( $n = 1$ ), and grade 2–3 abdominal pain (Table 2). The 300 mg dose was thus not tolerable, and following a protocol amendment, the two subsequent adults received vandetanib at 200 mg/dose with improved tolerability and no TLT. The two children enrolled did not experience toxicities requiring dose changes. No partial or complete responses were observed, and the best response was stable disease (median number of completed cycles, 4; range, 2–18). Three patients were taken off study at the request of the patient, and 6 patients were taken off study for progressive disease. Toxicities possibly, probably, or definitely related to vandetanib requiring dose reduction in later cycles included grade 2 pruritus intolerable to the patient (cycle #7) and gr3 diarrhea (cycle#6)

### Response evaluation

Because there were no partial or complete responses observed, the study was terminated after stage 1. In the 6 patients who were taken off study for progressive disease, the growth modulation index (GMI) was assessed and ranged from 0.28 to 1.3 (Table 3).

**Table 1.** Baseline and treatment characteristics

Patient number	Age (years)	Gender (M, F)	Sites of disease	SDHB IHC	SDH subunit mutation	Treatment cycles (number)
1	35	M	Liver, peritoneum, lymph nodes	NEG	SDHA	3
2	19	F	Liver, stomach	NEG	SDHC	18
3	52	F	Lung, liver peritoneum, lymph nodes	NEG	SDHA	2
4	39	F	Liver, lymph nodes	NEG	SDHA	13
5	24	F	Liver	NEG	SDHC	3
6	11	F	Liver, lymph nodes, spleen	NEG	SDHB	3
7	21	F	Liver, peritoneum	NEG	Wild-type	6
8	27	M	Lungs, liver, spleen, peritoneum, lymph nodes	NEG	SDHA	4
9	14	F	Liver, peritoneum, spleen	NEG	Wild-type	4

Abbreviations: F, female; M, male.

**Table 2.** Number of patients (highest grade/patient) with possibly, probably, or definitively grade 2, 3, or 4 vandetanib-related toxicities

Toxicity grade CTCAEv4	2	3	4
Gastrointestinal toxicity			
Nausea	1		
Diarrhea	1	1	
Oral mucositis	1		
Stomach pain	1		
Hepatic toxicity			
Alkaline phosphatase ↑	2		
AST ↑	1		
ALT ↑		1	
Metabolic/laboratory toxicity			
Calcium ↓	1		
Glucose ↑		1	
Constitutional toxicity			
Fatigue	1		
Anorexia	2		
Hematologic toxicity			
Lymphocyte count ↓	1	1	
Skin toxicity			
Rash acneiform	2		
Pruritus	1		
Neurologic toxicity			
Headache	1		
Seizure	1		
Genitourinary toxicity			
Proteinuria	2		
Vascular disorders			
Hypertension	4	2	
Pulmonary			
Pneumonitis		1	
Dyspnea	1		
Hypoxia	1		

All 4 adult patients who underwent the optional PET scan had a decrease in  $SUV_{max}$  in the time frame of day 3 through 6 of cycle 1. Eight patients were evaluated with FDG-PET prior to cycle 4. Three of eight patients had a decrease in  $SUV_{max}$  prior to cycle 4 compared with baseline (Table 3). Neither decreases in  $SUV_{max}$  at days 3 to 6 of cycle 1 nor prior to cycle 4 predicted long-term stabilization of disease. Three patients continued therapy for at least 5 cycles, and 1 patient had surgery to remove tumor and discontinued therapy after 13 cycles. Progression-free survival (PFS) and overall survival (OS) at 12 months were 44.4% [95% confidence interval (CI), 13.6%–71.9%] and 88.9% (95% CI, 43.3%–98.4%), respectively (Fig. 1). Median PFS was 5.1 months (95% CI, 1.8–24.1 months).

**Table 3.** Growth, FDG-PET, and tumor density evaluation

Patient number	Time to progression (months)	GMI	Pretreatment FDG-PET $SUV_{max}$	Day 3–6 FDG-PET $SUV_{max}$	Pre-cycle 4 FDG-PET $SUV_{max}$	Pretreatment mean density (HU)	First restaging mean density (HU)
1	2.7	0.63	30.7	19.3	11.5	36.1	49.8
2	22.4	1.3	15.6	7.5	8.9	103.1	122.4
3	2	1.3	16.2	NP	NP	64.6	54.7
4	NA	NA	21.4	NP	21.4	109.5	105.0
5	5	0.28	17.9	10.5	19.3	122.4	115.1
6	2.8	0.82	11.6	NP	13.8	102.2	98.8
7	NA	NA	25.3	NP	31.4	79.6	71.7
8	4.3	0.93	24.4	22.0	17.8	63.6	64.2
9	NA	NA	25.3	NP	27.4	90.4	89.1

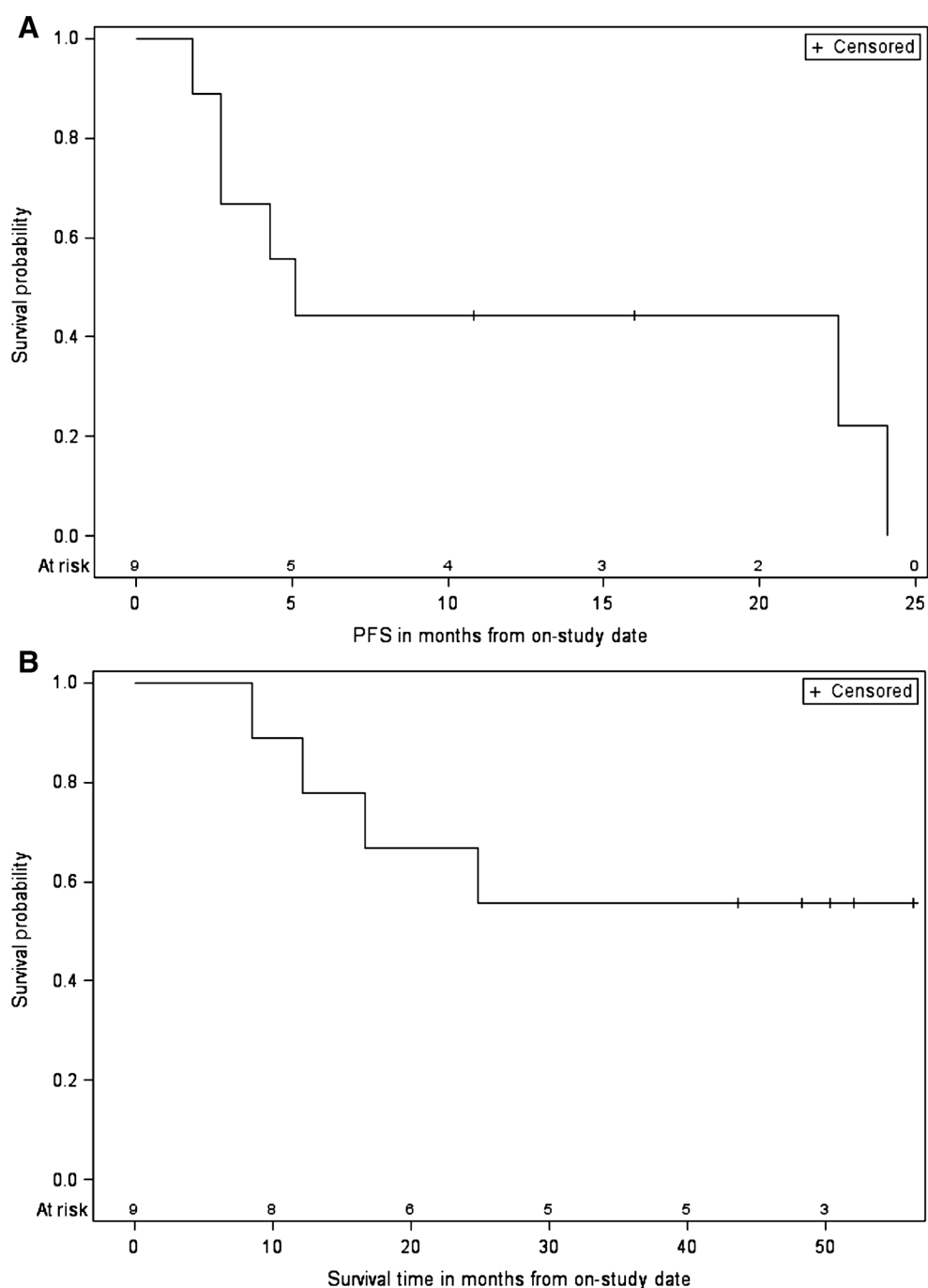
Abbreviations: HU, hounsfield units; NA, not available; NP, not performed;  $SUV_{max}$ , maximum standardized uptake value.

### Quality of life evaluation

All 9 patients completed the baseline PROMIS measures with 8 of 9 completing the pre-cycle 4 evaluation and 3 of 9 the end of therapy evaluation. The small number of patients precluded evaluation of changes in t-scores over time in any of the domains. The baseline evaluations were notable for 6 of 9 patients endorsing symptoms of anxiety and 5 of 9 mild or moderate symptoms of depression.

### Discussion

The use of imatinib and other KIT- and PDGFRA-targeting TKIs has dramatically improved the outcome for patients with GIST leading to increases in 5-year survival rates in those with advanced disease from 10% to nearly 50% (22, 23). However, TKIs targeting KIT and PDGFRA have had limited benefits for patients with dSDH GIST. Earlier trials of imatinib included patients with *KIT*/*PDGFRA* mutant as well as WT GIST, and investigators have subsequently analyzed molecular subgroups of patients treated on these trials. Heinrich and colleagues identified 12 patients with dSDH GIST within a population of 395 participants in a phase III SWOG study of imatinib in advanced GIST (24). In this group, 1 of 12 patients achieved a partial response, and there were no complete responses. In a follow-up analysis of a study of regorafenib in patients with metastatic or unresectable GIST after failure of therapy with imatinib and sunitinib, 6 patients with dSDH GIST derived clinical benefit (CR, PR, or SD lasting  $\geq 16$  weeks; ref. 25). Of these 6 patients, 2 experienced a PR with one complete metabolic response as measured by FDG-PET. In a retrospective study of 9 pediatric patients (age 11–21 years old) with wild-type GIST treated with sunitinib, a best response of stable disease was observed in 7 patients with a median PFS of 15 months (1 to >73 months; ref. 26). A single patient with SDH-deficient GIST was also reported to have prolonged disease control (17 months) on pazopanib (27). The paucity of patients with dSDH GIST who achieve a response is a common finding in previous reports as well as this study. The median PFS of 5.1 months that we found is less than that reported for patients receiving regorafenib. However, differences in patient selection as well as the indolent nature of SDH-deficient GIST make it difficult to determine the impact of treatment in patients with longer periods of disease stabilization. Patients with subtypes of dSDH GIST may have different rates of disease progression and potentially a different response to therapy further complicating the evaluation of these data. Improved characterization of the natural history of the disease in patients with dSDH GIST, including the



**Figure 1.** **A**, Progression-free survival. Median PFS, 5.1 months (95% CI, 1.8–24.1 months); 12-month PFS probability: 44.4% (95% CI, 13.6%–71.9%). **B**, Overall survival. Median OS not reached, 12 month OS: 88.9% (95% CI, 43.3%–98.4%), 24-month OS: 66.7% (95% CI, 28.2%–87.8%), 36-month OS: 55.5% (95% CI, 20.4%–80.5%).

differentiation of patients with SDH subunit mutations and those with SDHC deficiency due to promoter hypermethylation, will be important in designing future therapeutic trials.

We hypothesized that inhibition of the HIF1 $\alpha$ -induced VEGF pathway by vandetanib would decrease the growth of dSDH GIST. However, at the recommended adult dose of 300 mg daily, vandetanib was not well tolerated in adults with dSDH GIST.

Although not a dose-finding study, 3 of the initial 5 adult patients enrolled experienced toxicity requiring dose modification including grade 2 seizure, grade 3 hypertension, grade 3 pneumonitis, and grade 2–3 abdominal pain. In later cycles, patients developed grade 2 acne intolerable to the patient and grade 3 diarrhea. The inability of patients to tolerate full-dose vandetanib has been seen in other studies. In adult patients with medullary thyroid

carcinoma and advanced non-small cell lung cancer, 35% to 53% of patients required a dose reduction from a starting dose of vandetanib of 300 mg daily with diarrhea, hypertension, and rash being common adverse events (17, 28). Both well-described toxicities of vandetanib such as diarrhea and hypertension as well as uncommon toxicities including seizure and pneumonitis were seen on this study. Two of 9 patients experienced grade 3 hypertension. A meta-analysis of cancer patients receiving vandetanib reported a 6.4% incidence of grade 3–4 hypertension in 3,154 patients (29). In a study of 16 pediatric patients with medullary thyroid carcinoma treated with vandetanib, no patients had grade 3–4 hypertension in the first two cycles; however, approximately one third of patients developed grade 1–2 hypertension (18). A single patient developed pneumonitis, a toxicity not commonly associated with vandetanib. However, other TKIs with anti-EGFR activity are associated with pneumonitis in patients with non-small cell lung cancer (30). It is possible that this population of patients could have decreased tolerability of vandetanib. Pharmacokinetic analysis was not included in this study, but variations in drug metabolism could also contribute to differences in drug tolerability. After a protocol amendment, vandetanib was tolerated at a dose of 200 mg daily in adults, and no TLT were experienced in 2 pediatric patients enrolled at the recommended pediatric dose of 150 mg/m<sup>2</sup>/dose.

We did not observe partial responses, and stable disease was the best response. No improvement in quality of life was identified. Given the more indolent clinical behavior of dSDH GIST, stable disease cannot be clearly attributed to the effect of treatment. The study was designed to identify the more stringent criteria of response by RECIST. Although changes in FDG-PET were seen in some patients in response to vandetanib, this did not correspond to longer periods of tumor stabilization (Table 3). The small number of patients on this study makes it difficult to evaluate the significance of these findings; however, the rapid disease progression in several patients with decreased SUV<sub>max</sub> at the day 3–6 FDG-PET suggests that vandetanib may affect FDG uptake without affecting the disease course in patients with SDH-deficient GIST. *Post hoc* evaluation of the rate of tumor growth before and on therapy with vandetanib as well as changes in tumor density for patients with sequential imaging available prior to enrollment on study was performed. Meaningful changes in the rate of tumor growth or tumor density were not observed with vandetanib treatment (Table 3). The lack of activity of vandetanib does not preclude the possibility that other strategies targeting the HIF1 $\alpha$  pathway may be effective in treating this disease.

Other aspects of the metabolic abnormalities seen in dSDH GIST are being explored as possible therapeutic targets. Increased levels of cellular succinate also lead to global DNA hypermethylation. TET-DNA hydroxylases catalyze the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, an important step in DNA demethylation, which leads to a global increase in DNA methylation. This has been supported by showing that clinical SDH-deficient GIST samples have decreased 5-hydroxymethylcytosine levels (31) and consequently global epigenetic dysregulation (32). Strategies for targeting DNA hypermethylation in the treatment of patients with dSDH GIST are currently being tested.

Although SDH-deficient GIST is often an indolent entity, inexorable progression leads to significant morbidity, and patients continue to succumb to the disease. One of the most significant challenges for development of new therapies in this

rare disease is the lack of representative preclinical models. Although there are several groups currently pursuing this issue, clinical trials have been designed mostly on the basis of hypotheses that could not be completely tested in the laboratory. Continued improvement in our understanding of the molecular consequences of cellular SDH-deficiency as well as a more complete understanding of the natural history of these diseases is also needed. Ongoing studies are taking SDH-deficient mechanisms as a starting point to identify therapeutic targets and predictive biomarkers that allow the design of innovative therapeutic strategies. Collaborative initiatives are critical in order to detect associations and draw conclusions from the clinical history of these patients, identify therapeutic targets and predictive biomarkers, and design and evaluate innovative therapeutic strategies for patients with dSDH GIST.

### Disclosure of Potential Conflicts of Interest

F.I. Arnaldez is an employee of and has ownership interests (including patents) at MacroGenics, Inc. J.K. Killian is an employee of and has ownership interests (including patents) at Foundation Medicine. R. Srinivasan is a consultant/advisory board member for and reports receiving commercial research support from Peloton, Inc. L. Helman has ownership interests (including patents) at MedImmune/AstraZeneca, is a consultant/advisory board member for SpringWorks and PharmaMar, and reports receiving commercial research grants from Abbvie. No potential conflicts of interest were disclosed by the other authors.

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