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# Linsitinib (OSI-906) for the Treatment of Adult and Pediatric Wild-Type Gastrointestinal Stromal Tumors, a SARC Phase II Study

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## ABSTRACT

**Purpose:** Most gastrointestinal stromal tumors (GIST) have activating mutations of *KIT, PDGFRA*, or uncommonly *BRAF*. Fifteen percent of adult and 85% of pediatric GISTs are wild type (WT), commonly having high expression of IGF-1R and loss of succinate dehydrogenase (SDH) complex function. We tested the efficacy of linsitinib, an oral TKI IGF-1R inhibitor, in patients with WT GIST.

**Patients and Methods:** A multicenter phase II trial of linsitinib was conducted. The primary endpoint was objective response rate. Secondary endpoints were clinical benefit rate: complete response, partial response, and stable disease (SD) $\geq$ 9 months, and quantitative 2[18F]fluoro-2-deoxy-D-glucose (FDG) metabolic response (MR) at week 8. Serum levels for glucose, insulin, IGF-1R ligand IGF1, and binding proteins were obtained to explore correlations to patient outcomes and FDG-PET results.

**Results:** Twenty patients were accrued in a 6-month period. Grade 3–4 toxicities possibly related to linsitinib were uncommon (8.5%). No objective responses were seen. Clinical benefit rate (CBR) at 9 months was 40%. Intense FDG uptake was observed at baseline, with partial MR of 12% and stable metabolic disease of 65% at week 8; these patients had RECIST 1.1 SD as their best response. Progression-free survival (PFS) and overall survival Kaplan–Meier estimates at 9 months were 52% and 80%, respectively. SDHA/B loss determined by IHC was seen in 35% and 88% of cases, respectively.

**Conclusions:** Linsitinib is well tolerated in patients with WT GIST. Although the 9-month CBR was 40%, and PFS at 9 months was 52%, no objective responses were observed. Rapid accrual to this study demonstrates that clinical trials of experimental agents in selected subtypes of GIST are feasible.

## Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal malignancies of the gut (1). In the adult population, GIST presents most commonly in the seventh to eighth decades of life with nonspecific gastrointestinal complaints, anemia, and/or gastrointestinal bleeding. Histologically, GIST can appear similar to leiomyosarcomas, but were recognized as distinct sarcomas by Mazur and Clark due to the presence of both smooth muscle and neural features (2). Subsequently, Hirota and colleagues demonstrated that GISTs express the KIT growth factor receptor (3). In 85% of cases in adults, mutant *KIT* serves as the oncogenic driver. Of the remaining tumors, 5% to 7% contain mutations in the platelet-derived growth factor alpha receptor (*PDGFRA*; ref. 4), with rare cases of *BRAF* mutations and *NF-1* biallelic inactivation (5, 6). Pediatric patients present with similar symptoms but frequently have multiple tumors of the stomach as well as lymph node metastases, with a median age of 12 at presentation. In the pediatric population, only 15% of tumors have mutations in *KIT* or *PDGFRA* (7). Historically, GIST tumors lacking *KIT, PDGFRA*, or *BRA*F mutations have been designated as wild type (WT), as the oncologic driver was unknown.

Studies of WT GIST using DNA arrays demonstrated a remarkable absence of genomic alterations (5, 8). In addition, they were noted to have elevated levels of IGF-1R expression compared with GIST with *KIT/PDGFRA* mutations (9, 10). More recently, the majority of WT GIST have been found to lack protein expression of the Kreb's cycle enzyme succinate dehydrogenase B subunit (SDHB; ref. 11). SDHB expression loss is secondary to biallelic inactivating mutations in one of the SDH family members (A, B, C, or D), or alternatively secondary to abnormal methylation (12). SDH-deficient (SDH-def) GIST, those with loss of SDHB protein expression, account for the majority of GIST in the pediatric population, adult WT gastric GIST, as well as GIST associated with the Carney Triad and the Carney–Stratakis Dyad (1, 13). Notably, SDH-def GIST commonly have increased expression of IGF-1R (10, 14, 15).

Trials of KIT-targeting tyrosine kinase inhibitors demonstrated a correlation between tumor response, progression-free survival (PFS), and overall survival with the type of mutation present (16, 17). In contrast to *KIT*-mutant GIST, WT tumors were reported to have poorer response rates and shorter PFS. Sunitinib malate, a multi-targeted tyrosine kinase inhibitor with activity against KIT, PDGFR, VEGFR, and FLT-1/KDR, has demonstrated no complete responses in WT patients, one PR response and stable disease (SD) for 6 months or more in 56% of patients (18). More recently, regorafenib was shown to provide disease control in some patients with SDHB-def tumors (19).

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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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## Translational Relevance

Wild-type gastrointestinal stromal tumors (WT GIST) demonstrate few genomic alterations and lack activating mutations in *KIT, PDGFRA*, or *BRAF*. They have high levels of IGF-1R and loss of succinate dehydrogenase B (SDHB) expression due to genetic/epigenetic mutation of *SDH* complex genes. WT GISTs are less responsive to standard tyrosine kinase inhibitors (TKI). Optimal medical treatment is unknown. Based on preclinical data, we hypothesized that WT GIST cells may be IGF-1R–dependent, and therefore targeting IGF-1R might inhibit tumor growth. Therefore, linsitinib, an oral IGF-1R TKI, was tested in patients with WT GIST. Tumors were assessed for IGF-1R expression, loss of SDHA/B expression, and activation of AKT and mTOR as potential biomarkers of response. Serum samples were analyzed for changes in glucose, insulin, and IGF-1R ligands and inhibitors during treatment. In addition, the efficacy of 2[18F]fluoro-2-deoxy-D-glucose-PET imaging in the setting of IGF-1R inhibitor therapy was evaluated given the association of hyperglycemia with IGF-1R inhibition.

Preclinical work utilizing RNA knockdown of IGF-1R and an IGF-1R inhibitor correlated with a decrease in growth of GIST-mutant cell lines *in vitro* (9). Given the limited benefit of standard therapies in patients with WT GIST, and preclinical data suggesting IGF-1R may be a therapeutic target, we hypothesized that the growth and proliferation of this subset of GIST might be IGF-1R dependent and inhibition of this receptor might lead to clinical benefit. To evaluate this hypothesis, a phase II multicenter trial of linsitinib, an oral kinase inhibitor with specificity for IGF-1R and the insulin receptor (IR), was performed.

## Patients and Methods

Eligible patients, age $\geq$18 years, with a confirmed diagnosis of GIST and WT genotype, defined as negative for *KIT, PDGFRA*, and *BRAF* mutations, were accrued between November, 2012, and April, 2013. Patients were stratified into pediatric (diagnosed prior to age 18, or GIST in the context of Carney Triad/Carney–Stratakis Dyad with progression on or intolerance to at least sunitinib) and adult cohorts (diagnosed after the age of 18 without a diagnosis of the Carney triad/Carney–Stratakis Dyad who had intolerance to or progression on at least prior imatinib). Other inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0–2, radiographically measurable tumor, and adequate organ function including QTcF interval average of < 450 msec at baseline without a history of significant cardiac disease or concomitant use of drugs known to prolong QTcF. Patients with diabetes were allowed as long as their disease was controlled on oral agents; all patients had to have a baseline fasting glucose of <150 mg/dL with an HbA1c of < 7%. The study was conducted in accordance with the Declaration of Helsinki, and all sites were required to obtain approval from their Institutional Review Board prior to enrolling study subjects. Signed informed consent was required prior to study procedures and participation.

Exclusion criteria included prior therapy with any IGF-1R–targeted therapy; history of brain metastases, Torsades de Pointes, or solid organ transplant; HIV infection on antiretroviral therapy; or currently pregnant. In addition, patients on medications metabolized by CYP1A2 and/or CYP2C9 were not excluded, but, if feasible, alternate medications were recommended.

### Study design and treatment

The study was a phase II open-label trial of linsitinib given at a dose of 150 mg orally twice daily. Using a Clopper–Pearson two-stage design, 20 patients were accrued to part 1 with an additional 20 to be accrued if at least one response was observed. Treatment was continuous throughout a 28-day cycle. Patients were seen at screening, days 1, 14, and 28 and then every 4 weeks through week 16 and then every 12 weeks until disease progression or discontinuation from therapy, with an end of study visit approximately 30 days after treatment ended. Complete blood count and complete metabolic panel were obtained at every visit and pregnancy tests for women with reproductive potential except for the day 14 visit.

### Study endpoints

The primary objective of the study was the response rate to linsitinib in patients with advanced WT GIST using RECIST 1.1 (20). In addition, the clinical benefit rate (SD $\geq$ 9months, PR or CR) using RECIST criteria was determined. Secondary objectives included assessing the duration of response, PFS, and overall survival as well as tolerability of treatment. Imaging objectives were to evaluate the metabolic response (MR) to linsitinib using 2[18F]fluoro-2-deoxy-D-glucose (FDG)-PET, to compare the changes in tumor metabolism to conventional cross-sectional imaging, and to determine if tumor MR correlated with anatomic response and clinical benefit. In addition, we explored patterns of protein expression in serum and tumor tissues as predictors of response and PFS in advanced WT GIST treated with linsitinib. The correlation between glucose, insulin and candidate tumor tissue, and blood biomarkers with FDG-PET MR was also investigated.

### Study assessments

FDG-PET/CT was performed within 2 weeks of starting therapy and at week 8 along with blood glucose, insulin, and blood biomarkers: total serum IGF-1, free serum IGF, and IGFBP1-4, 6, and 7. Serum biomarker data were evaluated at multiple time points and assessed for change from predose levels and stability on therapy.

### Biomarker analyses

IHC for SDHA/B was performed on 4-μm-thick formalin-fixed paraffin-embedded whole tissue sections following pressure cooker antigen retrieval (0.001 mol/L citrate buffer; pH 6.0), using a mouse anti-SDHA monoclonal antibody (1:750 dilution; 40-minute incubation; clone 2E3GC12FB2AE2; Abcam) and a mouse anti-SDHB monoclonal antibody (1:100 dilution; 40-minute incubation; clone 21A11AE7; Abcam). The Envision Plus detection system (Dako) was used as a secondary antibody. Expression was scored as "retained" when any granular cytoplasmic staining was observed in tumor cells or "deficient" when there was a complete absence of granular cytoplasmic staining in tumor cells with positive internal controls (J.L. Hornick). Nonneoplastic cells, such as endothelium, smooth muscle, and epithelium, served as internal positive controls.

IGF-1R and pAKT IHC for IGF-1R and pAKT was performed as previously described (9). All IGF-1R and pAKT IHC evaluation was performed in a blinded manner (D.B. Flieder) to assess distribution and intensity of positive tumor cell staining and summed to derive the staining for each marker. For distribution, absent tumor cell staining was scored as 0, <10% of positive tumor cells staining as 1, 10% to 50% of cells staining as 2, 50% to 90% of cells staining as 3, and >90 of cells staining as 4. For intensity, absent staining in tumor cells was scored as 0, equivocal as 1, clearly positive as 2, and strong positive staining as 3. The summed scoring was assigned: sum of 0, no staining (score 0); sum

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of 1 to 3, slight staining (score 1); sum of 4 to 5, low staining (score 2); and sum of 6 to 7, high staining (score 3).

Serum levels for IGF-1R–related biomarkers were determined by ELISA using DuoSet ELISA Development Systems (R&D Systems) according to the manufacturer's instructions. Biomarkers analyzed included IGF-1 and insulin, and the IGF-binding proteins (IGF-BP1-4, 6, and 7). Glucose levels were performed as part of standard of care blood work.

### Radiologic assessments

CT or MRI was performed at baseline, every 8 weeks through week 16, and then every 12 weeks. Tumor response was assessed using modified RECIST 1.1 (20). In addition, patients had a baseline FDG-PET/CT within 2 weeks prior to initiating therapy and within 7 days prior to the week 8 visit to assess metabolic activity and response. FDG-PET scans were performed in accordance with NCI consensus guidelines following a minimum fasting period of 6 hours and a 1-hour uptake of FDG (21). Fasting blood glucose was measured prior to injection of FDG. PET/CT data were interpreted independently by two readers (A.D. Van den Abbeele and J.T. Yap) without knowledge of the cross-sectional imaging results for semiquantitative analyses utilizing the modified European Organization for Research and Treatment of Cancer (EORTC) guidelines for FDG-PET (22). A separate consensus review session was performed with both reviewers to resolve any discordant interpretations. The detailed analysis plan for assessment of PET images is found in the Supplementary Materials Section.

### Statistical analysis

The primary objective of the study was to determine whether the oral IGF-1R kinase inhibitor increased the response rate from 5% to 20% at 6 months in patients with relapsed or refractory GIST. If no responses were seen in the first 20 patients, the study would not proceed to the second stage; the probability of early termination if the true response rate was 20% was 1.2%. If 5 or more patients had response in 40 patient population, the null hypothesis would be rejected with a 92% power and 0.05 significance level.

The clinical benefit rate, defined as SD $\geq$ 9 months, PR or CR, was also analyzed at 19, 28, and 37 weeks of treatment using Kaplan–Meier curves for the all treated and per protocol populations. Time to progression was evaluated using cumulative incidence.

The objective of the statistical analyses of biomarkers was exploratory. The identification of markers or combinations of markers which showed the best association with positive or negative clinical outcome of treatment with the oral IGF-1R kinase inhibitor was evaluated on a univariate level for their potential to predict clinical endpoints. Correlations of biomarker and response correlations were investigated using the Spearman test of rank correlation.

## Results

### Patient characteristics

Twenty patients were accrued to stage I of the study between November, 2012, and April, 2013 (**Table 1**). Sixty percent were female, with a median age of 41; 6 of the patients met the definition for the pediatric cohort. The most common primary disease site was stomach (85%), with liver and peritoneal disease being the most frequent sites of metastatic disease. All patients were previously treated with TKIs with 95% having received prior imatinib and sunitinib; no patient was noted to be intolerant to prior therapy.

**Table 1.** Patient and tumor characteristics.

| | |
|---|---|
| Female | 12 |
| Male | 8 |
| Age | 18–62, average 41 |
| Performance status | |
| 0/1/2 | 12/7/1 |
| Primary site | |
| Stomach (gastroesophageal) | 16 (1) |
| Small bowel | 2 |
| Peritoneum | 1 |
| Metastatic sites | |
| Liver | 17 |
| Peritoneum | 11 |
| Lymph nodes | 4 |
| Prior therapies | 1–7, median 3 |
| Biomarker (*N* samples) | *N* (%) with biomarker |
| SDHA deficient (17) | 6 (35) |
| SDHB deficient (17) | 15 (88) |
| IGF-1R High (14) | 10 (71) |
| pAKT High (14) | 6 (43) |

### Linsitinib treatment

All patients completed at least one cycle of therapy, with the median time on treatment of 7.7 months (range, 1–31.7). There were 4 patients who progressed rapidly on linsitinib, with a median of 1.7 months (range, 1–2); the remaining 16 patients had a median time on treatment of 9.4 months (range, 2–31.7), including 4 patients who discontinued therapy for reasons other than progressive disease (PD; toxicity: $n = 1$ month 2, adverse event: $n = 1$ month 7, and MD decision: $n = 2$ month 2.8 and 3.6); excluding those patients, the median treatment duration was 10.6 months (range, 5.6–31.7). The protocol was terminated on October 29, 2015, with the expiration of the CTEP CRADA for linsitinib; the remaining patient on study was free of progression, and transferred to an Astella rollover protocol. Females remained on study longer than males ($P = 0.049$), but site of primary disease or classification as Pediatric/Adult WT GIST did not affect length of time on study (Supplementary Table S1).

### Linsitinib tolerability

Treatment with linsitinib was well tolerated (**Table 2**). There were 285 adverse events reported; 35.4% were categorized as related to study drug (possible, probable, or definite) by the treating investigator. Of the related events, 1.8% were grade 3 or higher with no grade 5 events. The most common toxicities were fatigue (7.7%), musculoskeletal complaints including muscle cramps, myalgias, musculoskeletal, and back pain (7.4%), and nausea (6.0%). The most common related adverse events were nausea (4.9%), fatigue (3.2%), abnormal liver function tests (3.2%), and diarrhea (2.5%). Grade 4 abnormalities in laboratory investigations occurred only in liver function tests. There were 3 occurrences of grade 2–3 hyperglycemia ($n = 2$ and 1, respectively). The grade 3 hyperglycemia occurred with steroid premedication for iodine contrast allergy.

### Response to linsitinib

There were no RECIST-defined objective responses, although 4 of 19 patients with evaluable disease did have $\geq$ 10% decrease in tumor size (**Fig. 1A**). The CBR at 9 months was 40%. PFS and overall survival Kaplan–Meier estimates at 9 months were 52% and 80%, respectively (**Fig. 2**). Using modified EORTC criteria for MR, the partial metabolic response (PMR) rate was 12.5% and the stable metabolic disease

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**Table 2.** Toxicities for which four or more occurrences were reported.

| Toxicity | Total number, all grades *N* (%) | Related, all grades *N* (%) | Related, grade ≥ 3 *N* (%) |
|---|---|---|---|
| All | 285 (100%) | 101 (35.4%) | 5 (1.8%) |
| Abdominal pain | 20 (7.0%) | 2 (<1.0%) | 0 (0%) |
| Abnormal liver function tests | 11 (3.9%) | 9 (3.2%) | 3 (1.1%) |
| Anemia | 5 (1.8%) | 1 (<1.0%) | 0 (0%) |
| Anorexia | 7 (2.5%) | 4 (1.4%) | 0 (0%) |
| Chills | 4 (1.4%) | 0 (0%) | 0 (0%) |
| Constipation | 9 (3.2%) | 4 (1.4%) | 0 (0%) |
| Diarrhea | 13 (4.6%) | 7 (2.5%) | 0 (0%) |
| Dizziness | 6 (2.1%) | 3 (1.1%) | 0 (0%) |
| Dyspnea | 7 (2.5%) | 0 (0%) | 0 (0%) |
| Fatigue | 22 (7.7%) | 9 (3.2%) | 0 (0%) |
| Fluid retention | 9 (3.2%) | 3 (1.1%) | 1 (<1.0%) |
| Hyperglycemia | 4 (1.4%) | 4 (1.4%) | 1 (<1.0%) |
| Insomnia | 5 (1.8%) | 0 (0%) | 0 (0%) |
| Amylase and lipase increased | 10 (3.5%) | 0 (0%) | 0 (0%) |
| Musculoskeletal complaints | 21 (7.4%) | 4 (1.4%) | 0 (0%) |
| Nausea/vomiting | 29 (10.2%) | 19 (6.7%) | 0 (0%) |
| Skin and nail disorders | 13 (4.6%) | 8 (2.8%) | 0 (0%) |

(SMD) rate was 65% in 17 patients that had baseline and week 8 assessments (**Table 3**). The 2 patients with PMR remained on therapy for 7.2 and 11.3 months. There were 4 patients with progressive metabolic disease (PMD). Two had early progression and discontinued therapy at week 8. However, 1 patient had with RECIST 1.1 SD for 10.7 months, and another discontinued therapy for an adverse event at 6.9 months. Eight of 13 patients who demonstrated PMR or SMD at week 8 demonstrated CBR ≥ 9 months. Based on the fasting blood glucose measurements performed immediately prior to FDG-PET/CT imaging, hyperglycemia (e.g., FBG > 120 mg/dL) was only seen in one subject at the 8-week scan; this subject had glucose that increased from 91 mg/dL at baseline to 255 mg/d. Notably, this subject had the best MR with an SUV reduction of 64% (**Fig. 1B** and **C**). Although there was no RECIST response noted, there was a trend between the length of time on study and any decrease in the size of RECIST measurements ($P = 0.065$).

## Correlative analyses

Expression of SDHA and SDHB by IHC was assessed in 17 available patient samples (**Fig. 3A–D**; **Table 1**). Loss of SDHB was observed in 15 samples (88%), 6 of which (35%) also had loss of SDHA expression. All of these tumors arose in the stomach or gastroesophageal junction. The two GISTs with retained SDHB expression arose in the small bowel.

IGF-IR levels were assessed in 14 samples (**Fig. 3E** and **F**; **Table 1**); 10 (71%) had high IGF-1R expression and 4, including one small bowel tumor (29%), expressed intermediate levels. Six of 14 tumors (43%) had high to intermediate staining for phospho-AKT (**Fig. 3G** and **H**; **Table 1**). No on therapy samples were available for analysis, limiting our ability to assess pharmacodynamic effects of linsitinib. No correlation was found between biomarker status and the length of time a patient remained on drug (Supplementary Table S1).

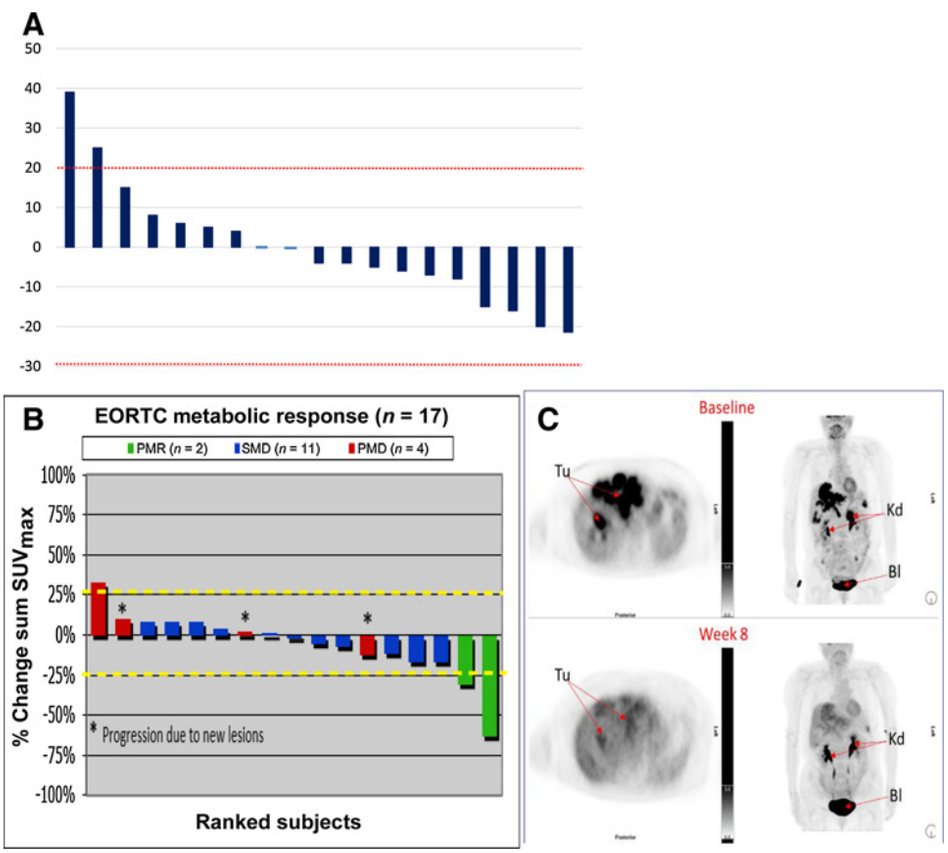


**Figure 1.**
Waterfall plots for CT and FDG-PET assessments. **A,** Waterfall plot illustrating the best response for 19 patients who underwent baseline imaging and at least one disease assessment. **B,** EORTC MR waterfall plot for 17 patients who underwent baseline and week 8 FDG-PET scans. **C,** FDG-PET [eyes-to-thighs view (right) and axial slice through the liver (left)] of a patient at baseline (upper row) and at week 8 post-linsitinib therapy showing PMR throughout all liver lesions (bottom row). This patient had a normal glucose level at baseline and was also the only patient with hyperglycemia at the time of FDG-PET imaging.

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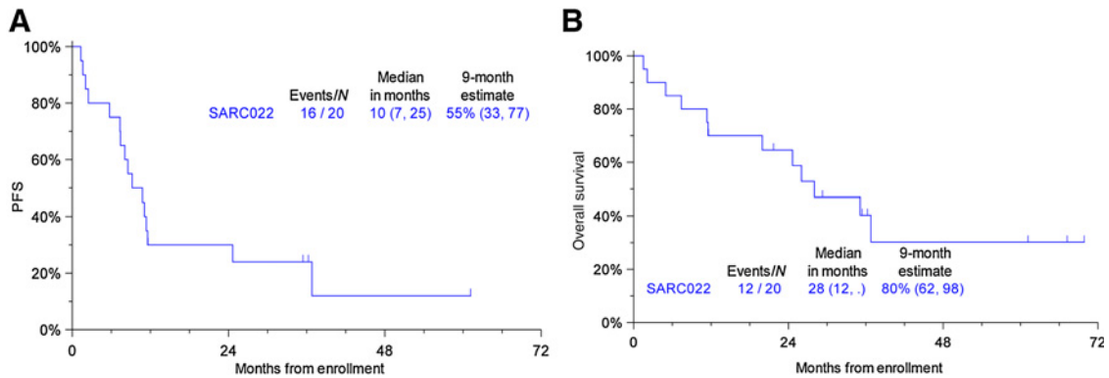


**Figure 2.**
Kaplan–Meier survival assessments. (**A**) PFS and (**B**) overall survival by Kaplan–Meier.

Serum biomarkers were assessed at baseline, cycle 1-day 14 (C1D14), cycle 2- and 3-day 1 (C2D1 and C3D1), at the end of treatment (EOT), and 30 days later (EOT+30); fewer patient samples were available for assessments on cycle 3 and beyond making correlations less certain. The levels of IGF-1 and insulin were statistically increased compared with baseline at all time points with the exception of the final follow-up assessment 30 days of therapy, consistent with the predicted effects from IGF-1R inhibition (**Fig. 4A** and **B**; Supplementary Table S2). Values of BP-3 and-4 increased from baseline levels to subsequent time points, whereas BP-6 decreased on drug (**Fig. 4C–E**; Supplementary Table S2); these changes were more variable than those observed with IGF-1 and insulin. There was no difference in the other serum markers assessed. We did not find a correlation with the baseline value of any of the biomarkers or change from baseline to C1D14 and the length of time on linsitinib.

### Imaging analyses

An endpoint of this trial was to evaluate the effect of an IGF-1R inhibitor on tumor FDG uptake using FDG-PET CT imaging, given the potential effect of IGF-1R inhibition upon glucose metabolism, as well as to compare MR with RECIST response using CT or MRI imaging. FDG-PET CT studies were performed at baseline and C3D1 on 17 patients. All patients demonstrated elevated tumor glycolysis at baseline prior to initiation of therapy (Supplementary Table S3), demonstrating the tumor's dependency on glucose metabolism as is observed with most mutation-positive GISTs. As discussed above, the finding of SMD or PMR was predictive of CBR $\geq$ 9 months in 61% of patients. However, 1 of 4 patients with PMD remained with disease control for > 9 months.

To assess the potential impact of changes from linsitinib on glucose metabolism from inhibition of IGF-1R and the IR, correlations between normal tissue and tumor SUVs and serum levels of glucose,

**Table 3.** EORTC response as correlated with length of time on therapy, reason off study, RECIST 1.1 response, and CB $\geq$ 9 months.

| EORTC PET response at week 8 | Patient number | Length of time on therapy (months) | Reason off study | RECIST 1.1 response at week 8 | Best RECIST 1.1 response | CB $\geq$ 9 months |
|---|---|---|---|---|---|---|
| Not performed | 2 | 1.1 | CPD | NA | NE | N |
| | 7 | 1.6 | CPD | SD | SD | N |
| | 1 | 1.9 | PD | PD | PD | N |
| Progressive metabolic disease | 17 | 1.9 | PD | PD | PD | N |
| | 14 | 2.8 | CPD | SD | SD | N |
| | 12 | 6.9 | AE | SD | SD | N |
| | 6 | 10.7 | PD | SD | SD | Y |
| Stable metabolic disease | 5 | 1.9 | AE | SD | SD | N |
| | 3 | 3.6 | MDC | SD | SD | N |
| | 9 | 5.6 | PD | SD | SD | N |
| | 19 | 8.1 | PD | SD | SD | N |
| | 15 | 8.6 | PD | SD | SD | Y |
| | 10 | 10.3 | PD | SD | SD | Y |
| | 13 | 10.5 | CPD | SD | SD | Y |
| | 8 | 11.2 | PD | SD | SD | Y |
| | 21 | 14.9 | PD | SD | SD | Y |
| | 20 | 16.7 | AE | SD | SD | Y |
| | 16 | 31.7 | SC | SD | SD | Y |
| Partial metabolic response | 4 | 7.2 | PD | SD | SD | N |
| | 11 | 11.3 | PD | SD | SD | Y |

Abbreviations: AE, adverse event; CB, clinical benefit rate; CPD, clinical progressive disease; MDC, MD choice; NA, not applicable; NE, nonevaluable; SC, study closure.

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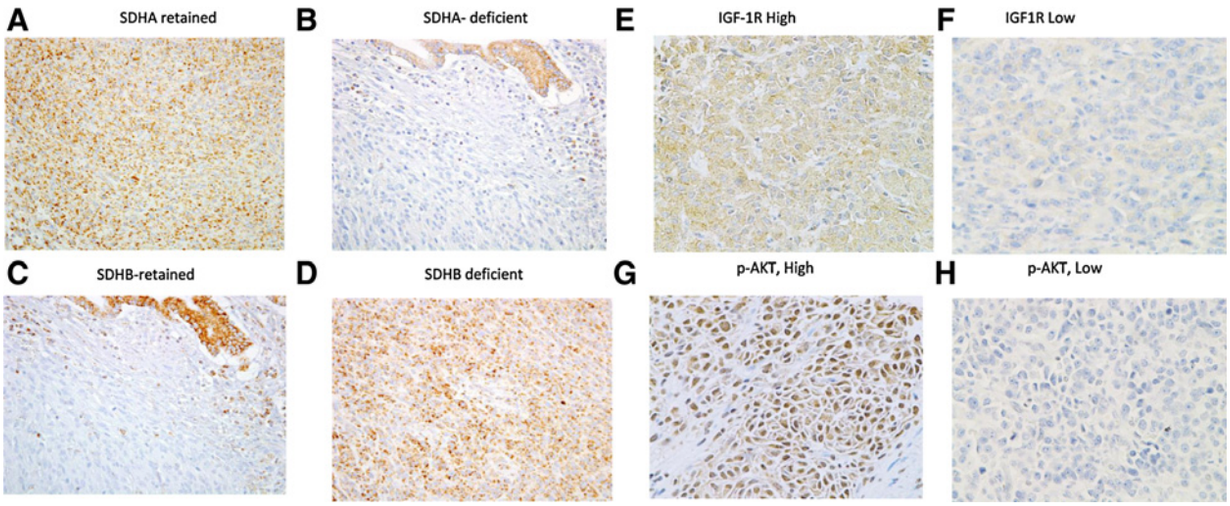


**Figure 3.**
IHC. Representative examples of staining of SDHA (**A** and **B**), SDHB (**C** and **D**), IGF-1R (**E** and **F**), and p-AKT (**G** and **H**) expression in baseline WT GIST samples; all images are at 40x. Percentage of samples with biomarker found in **Table 1**.

IGF-1, BP1-4, 6, and 7 at baseline, C3D1, EOT, and EOT+30 were analyzed. Insulin and BP6 levels at the C3D1 visit were correlated with the observed changes in SUV between baseline and the C3 PET scan ($P = 0.03494$ and $P = 0.02519$, respectively). There was no correlation between change in SUV (PMR) with change in RECIST measurements or with length of time on study drug.

## Discussion

Understanding of the biology of GIST has evolved since the initial discovery of *KIT* mutations as an oncogenic driver (3). Studies of approved TKI's have documented that response is strongly correlated with the presence and type of *KIT* and *PDGFRA* mutation (1). Tumors without these known mutations were historically called WT GIST and now are recognized as more than one biological subgroup (13). Other oncologic drivers identified include mutations in the *RAS/RAF* pathway including *BRAF* and *NF1*, novel translocations, as well as SDH deficiency (13, 23).

Prior studies in GIST did not preselect patients based upon genotype. This is the first clinical trial to test an agent for GIST tumors that lack *KIT, PDGFRA,* and *BRAF* mutations. The majority of patients accrued to this study were females with SDH-def GIST, based upon loss of SDHB expression by IHC, and stomach primaries. The two samples with retained SDHB expression were small bowel tumors. These clinicopathologic associations of gender, SDHB expression, and tumor site of origin are consistent with the literature concerning SDH-def GIST (12, 13).

The SDH family has four members (A–D), which form a tetramer on the inner mitochondrial membrane and are responsible for converting succinate to fumarate as well as functioning as complex II of the electron transport chain. Loss of SDHB protein expression occurs from biallelic inactivation of any of the *SDH* genes by mutation or hypermethylation of the *SDHC* gene promoter (24). Loss of expression of one member of the complex alters the structure or production of SDH proteins such that the complex is no longer able to form. This results in elevated intracellular levels of succinate leading to enhanced HIF 1a regulated gene transcription, as well as loss of demethylase activity (e.g. TET2). In the largest series of SDH-def tumors, *SDHA* was the most common SDH family member mutated (13). We had insufficient material to test for mutations or hypermethylation. However, loss of SDHA protein expression has been correlated with the presence of a mutation in *SDHA* (25), which would suggest that up to 35% of the patients in our study likely had this mutation.

SDH-def GISTs have been shown to have elevated expression of IGF-1R protein (9, 10). As in other malignancies, no mutations or amplification of IGF-1R has been reported in GIST. It has been hypothesized that the reason for the overexpression may be because SDH-def GIST arise from a more primitive stem cell than typical kinase-mutant GIST (26, 27). Although preclinical work utilizing RNA knockdown of IGF-1R and an IGF-1R inhibitor *in vitro* with mutant GIST cell lines did show some benefit (9), the testing was not conducted in SDH-def cell lines as none are available. There is a clear need for better models for drug development in SDH-def GIST.

Linsitinib was found to be well tolerated in this group of patients, and side effects were comparable with those seen in other studies. In our patients, drug-induced hyperglycemia was rarely noted, and the most common drug-related toxicities were elevated liver function tests, nausea, diarrhea, fatigue, and nail disorders. The phase I study of continuous dosing linsitinib found the dose-limiting toxicities were grade 3 QTc prolongation, hyperglycemia, and elevations of transaminases as well as grade 2 abdominal pain and nausea that led to linsitinib being held; they identified the MTD to be 400 mg daily or 150 mg twice daily (28). Other trials using the twice daily schedule as in our study noted grade 3/4 thrombocytopenia, fatigue and transaminase elevations, nausea, and hyperglycemia (29, 30).

No measurable responses were seen in this study suggesting that IGF-1R overexpression is not a driver of tumor growth or survival in WT GIST, or that linsitinib therapy at the dose used resulted in insufficient inhibition of IGF-1R kinase activity in tumor. Heinrich and colleagues reported that in advanced GIST, imatinib resulted in CR 4.5%, PR 33 %, SD 28.5%, PD 18% in non-*KIT*/non–*PDGFRA*-mutant GIST (16), whereas Debiec-Rychter and colleagues reported no complete responses, 23% PR, 50% SD, and 19% PD (17). These response rates to imatinib in adult patients with WT GIST are in marked contrast to outcomes reported in the literature in pediatric patients (16, 17, 31) and from the NIH Wild Type GIST clinic (13)

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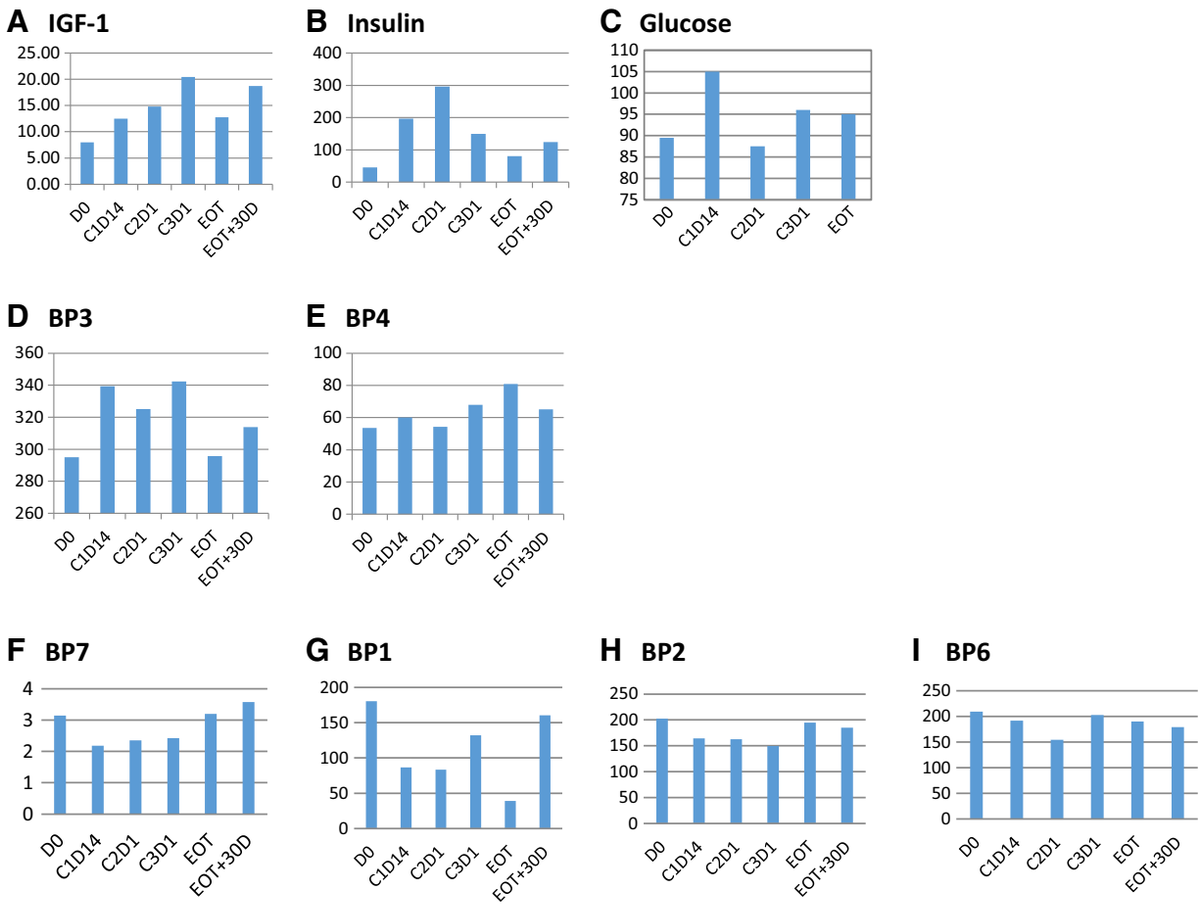


**Figure 4.**

**A–I,** Median values for serum biomarkers at different time points. Samples are measured in ng/mL, except for glucose which is in mg/dL. Sample numbers decreased over time: $N = 20$ for D0 and C1D14, $N = 18$ C2D1, $N = 16$ C3D1, $N = 10$ EOT, and $N = 5$, EOT+30. Glucose values were not collected at the EOT +30 visit.

where data from pediatric patients find SD is the best response observed. Reasons for the differences may be attributable to earlier sequencing methodologies that may have missed *KIT* or *PDGFRA* mutations and thus a higher response rate in the WT cohort; evaluation of WT patients in the studies of imatinib did not assess SDHB expression. Alternatively, differences may be due to selection bias (those seen at the NIH may have self-selected for poorer outcomes) or to an inherent difference in pediatric patients with WT tumors. Sunitinib and regorafenib have led to disease control (18), with only one PR reported in a pediatric patient with WT GIST (19).

The 9-month estimated PFS for linsitinib was 52%. This was chosen to represent a meaningful endpoint based upon available data from other TKI studies and as WT GIST can have an indolent course. In the U.S.-led phase III imatinib trial in advanced GIST, time to progression was shorter for patients with WT tumors compared with those with the more common exon 11 tumors: 25 months versus 13 months (16). Sunitinib resulted in 56% SD for 6 months or more (18). The median PFS of 6 SDH-def patients on regorafenib was 10 months with all patients deriving clinical benefit for $\geq$ 16 weeks (19). Comparing with these data, the observed PFS for linsitinib appears meaningful, particularly as all patients were pretreated with TKIs. The length of imatinib and sunitinib therapy for metastatic disease in the 10 patients who remained on linsitinib longer than 9 months ranged from 1 to 30 months and 1 to 51 months respectively, with a median of 3 and 9 months. It is possible that linsitinib may have altered tumor glucose metabolism resulting in modulated tumor growth kinetics; unfortunately, imaging prior to study enrollment was not collected to assess this. Female patients remained on study longer than male patients. This is not explained by tumors of the small bowel that were SDH intact, for whom we would have predicted no potential benefit from linsitinib. Of the 2 patients with these characteristics, one was a male and was treated for 2 months; the other was a female and treated for 8 months. Material was insufficient to assess the IGF-1R expression in the female patient.

IGF-1R exists as a homodimer or heterodimer with IR isoform A or B (32). It is activated by binding of free IGF-I or II. Insulin-like growth factor binding proteins (IGFBP) are a family of six proteins that are evolutionarily conserved with high affinity binding for IGF-1 and 2 (33). In the circulation, IGFBPs bind IGF-I and -II, limiting their bioavailability. IGFBP3 is the predominant circulating form. Serum biomarkers were analyzed and as expected from an IGF-1R inhibitor, levels of IGF-I increased following initiation of linsitinib; this is in agreement with other studies (28, 30) and suggests that IGF-1R was inhibited in patients on study. That said, it is still possible that

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intratumoral inhibition of IGF-1R was suboptimal as on-treatment biopsy material was not available for study. No prior studies of single-agent linsitinib have reported on other serum biomarkers. We observed an increase in insulin levels as well, consistent with linsitinib also inhibiting the IR. Three episodes of hyperglycemia were reported, all of which occurred in the setting of steroid use in 1 patient, and thus not due to linsitinib. Serum levels of 5 of 6 IGFBPs were assessed; an assay for IGFBP-5 was not available at the time of study initiation. IGFBP7, also known as MAC25, has low affinity binding to IGF-1 and II, and is not considered part of the IGFBP family.

Another goal of this trial was to understand whether therapy with an IGF-1R inhibitor would limit the utility of FDG-PET imaging, as these agents have been correlated with hyperglycemia, and could FDG-PET imaging be used as an early biomarker of objective tumor response subsequently observed by CT/MRI size criteria. We noted that WT GIST have a metabolic tumor phenotype that is highly dependent on glucose metabolism as demonstrated by high FDG uptake at baseline. There was also no evidence of altered FDG biodistribution following administration of linsitinib. The finding of qualitative MRs without corresponding RECIST-defined anatomic responses raises the possibility that the changes observed were due to an impact of linsitinib on glucose metabolism rather than on tumor metabolism; this is supported by the correlation between changes in insulin and BP-6 levels and SUV changes. Interestingly, 10 of 13 and 7 of 13 patients with PMR and SMD also had SD as their best RECIST 1.1 response at 6 and 9 months respectively, with extended lengths of time on study drug. This has to be contrasted with the outcomes in patients with PMD in which 2 of 4 patients had rapid progression; however, 1 patient remained on therapy for more than 9 months, with another discontinuing for an adverse event at 6.7 months.

In conclusion, this is the first therapeutic trial that prospectively enrolled patients with molecularly defined GIST with documented absence of *KIT, PDGFRA,* and *BRAF* mutations; we were able to accrue to this trial faster than our expected rate of 1 to 2 patients per month, indicating the feasibility of performing future studies in this rare molecular subtype of GIST. Linsitinib was well tolerated in this patient population, but did not result in any objective responses; the estimated PFS was prolonged beyond 9 months in the majority of patients, indicating a potential benefit of treatment and providing a benchmark for future studies. The FDG-PET demonstrated a metabolic tumor phenotype for WT GIST that is highly dependent on glucose metabolism with no evidence of altered biodistribution after linsitinib administration. The role of FDG-PET as potential biomarker to assess novel therapies in GIST requires further evaluation given inconsistent results when compared with RECIST 1.1 response assessment. Importantly, although there was not a high rate of hyperglycemia in this patient population, the observed changes in SUV correlated with metabolic changes induced by linsitinib; the metabolic changes were small and consistent with a lack of impact of IGF-1R TKIs on WT GIST glucose metabolism unlike the inhibitory effect of approved KIT/PGDFRA TKIs on the glucose metabolism of kinase-mutant GIST (34). However, the study showed that clinical benefit can be attained in patients with partial or stable response by either anatomic or functional criteria, whereas anatomic or metabolic PD had bad outcomes. We were not able to make meaningful conclusions about the benefit of CT scans versus FDG-PET imaging as the best modality for disease response assessments due to the limited number of patients with objective response using either criteria.

## Disclosure of Potential Conflicts of Interest

S. George is an employee/paid consultant for Blueprint Medicines, Deciphera Pharmaceuticals, Bayer, AstraZeneca, Eli Lilly, Exelixis, and Daiichi Sankyo. M.C. Heinrich is an employee/paid consultant for Deciphera Pharmaceuticals, Blueprint Pharmaceuticals, MolecularMD; reports receiving other commercial research support from Deciphera Pharmaceuticals and Blueprint Medicines; holds ownership interest (including patents) in MolecularMD and Novartis; and reports receiving other remuneration from Novartis. K.A. Janeway is an employee/paid consultant for Bayer. J.L. Hornick is an employee/paid consultant for Eli Lilly and Epizyme. R. Chugh reports receiving commercial research grants from Plexxikon. No potential conflicts of interest were disclosed by the other authors.

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Clinical Cancer Research

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