The Oncologist®

Clinical Trial Results

A Phase I Study of Binimetinib (MEK162) Combined with Pexidartinib (PLX3397) in Patients with Advanced Gastrointestinal Stromal Tumor

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT03158103
- **Sponsor(s):** Memorial Sloan Kettering Cancer Center
- **Principal Investigator:** Ping Chi
- **IRB Approved:** Yes

Lessons Learned

- The combination of pexidartinib and binimetinib was safe and tolerable and demonstrated encouraging signs of efficacy in two patients with advanced gastrointestinal stromal tumor (GIST) refractory to tyrosine kinase inhibitors (TKIs).
- Molecular profiling of GISTs at diagnosis and upon progression may provide insight into the mechanisms of response or resistance to targeted therapies.
- Additional trials are needed to further explore combined KIT and MEK inhibition in treatment-naïve and TKI-refractory patients with advanced GIST.

Abstract

Background. Nearly all patients with advanced gastrointestinal stromal tumor (GIST) develop resistance to imatinib, and subsequent treatments have limited efficacy. Dual inhibition of KIT and MAPK pathways has synergistic antitumor activity in preclinical GIST models.

Methods. This was an investigator-initiated, phase I, dose escalation study of the MEK inhibitor binimetinib combined with pexidartinib, a potent inhibitor of CSF1R, KIT, and FLT3, in patients with advanced or metastatic GIST who progressed on imatinib. The primary endpoint was phase II dose determination; secondary endpoints included safety, tolerability, and efficacy. An expansion cohort to further evaluate safety and efficacy was planned.

Results. Two patients were treated at dose level one (binimetinib 30 mg b.i.d. and pexidartinib 400 mg every morning and 200 mg every evening), after which the study was terminated by the manufacturer. No dose-limiting toxicities (DLTs) were reported, and treatment was well tolerated. The only grade ≥3 treatment-emergent adverse event (TEAE) was asymptomatic elevated creatine phosphokinase (CPK). Both patients had a best response of stable disease (SD) by RECIST. Progression-free survival (PFS) and overall survival (OS) were 6.1 and 14.6 months, respectively, in one patient with five prior lines of therapy. The second patient with *NF1*-mutant GIST had a 27% decrease in tumor burden by RECIST and remains on study after 19 months of treatment.

Conclusion. Pexidartinib combined with binimetinib was tolerable, and meaningful clinical activity was observed in two imatinib-refractory patients. ***The Oncologist*** 2019;24:1309–e983

Discussion

The rationale for combining MEK and KIT inhibitors in advanced GIST is based on preclinical studies demonstrating that MAPK signaling downstream of KIT stabilizes ETV1, a transcriptional regulator essential for GIST cell proliferation [1, 2]. Although a pharmaceutical supporter closed the trial prematurely, two patients were treated with binimetinib and pexidartinib at dose level one. Both tolerated treatment

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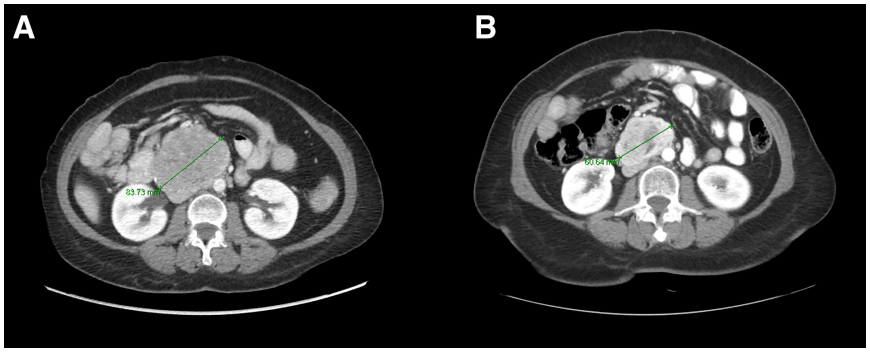

Figure 1. Computed tomography scans demonstrate tumor shrinkage of metastatic gastrointestinal stromal tumor, measured on axial image, on pexidartinib and binimetinib. Baseline image **(A)** and on-treatment image **(B)**.

without DLTs. Elevated blood CPK, an expected side effect of binimetinib [3], was the only grade ≥3 TEAE. This TEAE was not clinically significant, and the patient remained asymptomatic without myalgias.

The current standard of care in imatinib-refractory GIST includes a multitargeted tyrosine kinase inhibitor (TKI), either sunitinib or regorafenib. The median PFS of these agents in phase III trials was less than 7 months [4, 5]. Both patients on this study achieved a clinically meaningful PFS. One has been on treatment for 19 months with a decrease in tumor burden (−27% by RECIST) and remains on treatment. Targeted sequencing of this patient's tumor with MSK-IMPACT [6] identified a loss-of-function mutation in exon 42 (pX2143_splice) of *NF1*, with no detectable mutation in other GIST-associated oncogenes.

NF1 loss is associated with the development of GIST in the absence of known genetic drivers [7, 8], and these tumors often have unique clinicopathologic features [9]. Loss-of-function of NF1, a negative regulator of RAS [10], leads to constitutive activation of RAS and downstream MEK and ERK. MEK inhibitors contribute to antitumor activity in *NF1*-mutant tumors by suppressing downstream ERK [11]. MEK inhibition alone is ineffective in GIST because of MEK inhibitor-induced feedback reactivation of upstream receptor tyrosine kinases, such as KIT or platelet-derived growth factor receptor A (PDGFRA), in part through ETV1 [3, 12, 13]. These mechanisms highlight the scientific rationale for using combination targeted treatment in GIST, including in *KIT/PDGFRA* wild-type GIST.

The other study patient had received five lines of prior TKI before enrollment. MSK-IMPACT found a *KIT* exon 11 founder mutation (D579del) in both the primary and the imatinib-resistant tumors. Furthermore, the resistant tumor harbored activating mutations in *KRAS* exon 2 (G12V) and *PIK3CA* exon 21 (H1047R), which confer resistance to imatinib. This patient achieved a best response of SD (4.3% by RECIST) lasting more than 6 months. A mixed response on the last radiographic assessment led to removal from the study for clinical progression.

Although definitive conclusions cannot be drawn from this trial, clinically meaningful activity was seen in the two patients treated, most strikingly in *NF1*-mutant *KIT/PDGFRA* wild-type GIST. These clinical responses, each lasting longer than 6 months, support our hypothesis that combined KIT and MAPK pathway inhibition decrease ETV1-mediated GIST survival. An ongoing study of binimetinib combined with imatinib (NCT01991379) in treatment-naïve GIST will shed more light on the safety and efficacy of this treatment mechanism. Correlative studies to evaluate pharmacodynamic inhibition of KIT, MAPK signaling, and ETV1 are needed to confirm the hypothesis of this study.

Trial Information	
Disease	GIST
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	1 prior regimen
Type of Study – 1	Phase I
Type of Study – 2	3 + 3
Primary Endpoints	Safety Tolerability Recommended phase II dose
Secondary Endpoint	Efficacy

Additional Details of Endpoints or Study Design

Phase I Dose Escalation Portion Study Design and Endpoint Assessment: The primary endpoint of the dose escalation portion of the phase I study was to determine the recommended phase II dose of MEK162 and pexidartinib administered in combination in patients with GISTs. The dose escalation study was pursued in standard 3 + 3 format, based on toxicities encountered during the first cycle of therapy. The secondary endpoints of the dose escalation portion were (a) response rate (RR) defined by RECIST 1.1 criteria and by Choi criteria evaluated within 32 weeks and (b) PFS. RR was to be estimated as the

proportion of patients who have complete response or partial response for each criterion. PFS was to be calculated using Kaplan-Meier estimate among all patients enrolled, and median PFS will be estimated. Patients who did not experience the event of interest by the end of the study would be censored at the time of the last follow-up. The dose escalation portion of the study was to have a minimum sample size of 6 patients and a maximum of 30.

Investigator's Analysis	Drug tolerable, hints of efficacy

Drug Information

Drug 1	
Generic/Working Name	Pexidartinib (PLX3397)
Company Name	Plexxikon
Drug Type	Small molecule
Drug Class	FMS, KIT, FLT3
Dose	Per flat dose
Route	p.o.
Drug 2	
Generic/Working Name	Binimetinib (MEK162)
Trade Name	Mektovi
Company Name	Array BioPharma
Drug Class	MEK
Dose	Per flat dose
Route	p.o.

Dose Escalation Table (three patients enrolled, two patients evaluable for toxicity)

Dose level	Dose of drug: pexidartinib (PLX3397)	Dose of drug: binimetinib (MEK162)
–2	200 mg a.m./200 mg p.m.	15 mg b.i.d.
–1	400 mg a.m./200 mg p.m.	15 mg b.i.d.
1	400 mg a.m./200 mg p.m.	30 mg b.i.d.
2	400 mg a.m./400 mg p.m.	30 mg b.i.d.
3	400 mg/400 mg	45 mg b.i.d.

Patient Characteristics

Number of Patients, Male	1
Number of Patients, Female	2
Stage	IV
Age	Median (range): 61 (59–78)
Number of Prior Systemic Therapies	Median (range): 3 (1–5)
Performance Status: ECOG	0 — 1 1 — 2 2 — 3 — Unknown —
Cancer Types or Histologic Subtypes	GIST, 3

Primary Assessment Method	
Title	Response rate
Number of Patients Enrolled	3
Number of Patients Evaluable for Toxicity	2
Number of Patients Evaluated for Efficacy	2
Evaluation Method	RECIST 1.1
Response Assessment SD	*n* = 1 (50%)
Response Assessment PD	*n* = 1 (50%)
Outcome Notes	One patient withdrew prior to initiating study treatment. One of two patients continues on study treatment.

Secondary Assessment Method	
Title	Response rate
Number of Patients Screened	3
Number of Patients Enrolled	2
Number of Patients Evaluable for Toxicity	2
Number of Patients Evaluated for Efficacy	2
Evaluation Method	Other (specify): Choi
Response Assessment SD	*n* = 1 (50%)
Response Assessment PD	*n* = 1 (50%)
Outcome Notes	One patient withdrew consent prior to initiating study treatment. One of two patients remains on study treatment at the time of manuscript submission.

Adverse Events, All Cycles

Name	NC/NA	1	2	3	4	5	All grades
Alanine aminotransferase increased	0%	100%	0%	0%	0%	0%	100%
Alopecia	0%	100%	0%	0%	0%	0%	100%
Anemia	0%	67%	33%	0%	0%	0%	100%
Arthralgia	0%	100%	0%	0%	0%	0%	100%
Aspartate aminotransferase increased	0%	100%	0%	0%	0%	0%	100%
Bladder infection	0%	100%	0%	0%	0%	0%	100%
Blurred vision	0%	100%	0%	0%	0%	0%	100%
Nail loss	0%	0%	100%	0%	0%	0%	100%
CPK increased	1%	0%	33%	33%	33%	0%	99%
Depression	0%	100%	0%	0%	0%	0%	100%
White blood cell decreased	0%	100%	0%	0%	0%	0%	100%
Weight gain	0%	100%	0%	0%	0%	0%	100%
Vulval infection	0%	100%	0%	0%	0%	0%	100%
Vomiting	0%	50%	50%	0%	0%	0%	100%
Vaginal discharge	0%	100%	0%	0%	0%	0%	100%
Urinary frequency	0%	100%	0%	0%	0%	0%	100%
Urinary tract pain	0%	100%	0%	0%	0%	0%	100%
Pharyngolaryngeal pain	0%	100%	0%	0%	0%	0%	100%
Skin hypopigmentation	0%	100%	0%	0%	0%	0%	100%
Pain in extremity	0%	100%	0%	0%	0%	0%	100%
Rash maculo-papular	0%	50%	50%	0%	0%	0%	100%
Rash acneiform	0%	100%	0%	0%	0%	0%	100%

Pruritus	0%	100%	0%	0%	0%	0%	100%
Pneumonitis	0%	50%	50%	0%	0%	0%	100%
Edema face	0%	100%	0%	0%	0%	0%	100%
Tumor pain	0%	100%	0%	0%	0%	0%	100%
Nausea	0%	0%	100%	0%	0%	0%	100%
Respiratory, thoracic and mediastinal disorders—nasal congestion	0%	100%	0%	0%	0%	0%	100%
Myalgia	0%	100%	0%	0%	0%	0%	100%
Memory impairment	0%	100%	0%	0%	0%	0%	100%
Fatigue	0%	75%	25%	0%	0%	0%	100%
Localized edema	0%	100%	0%	0%	0%	0%	100%
Hypophosphatemia	0%	50%	50%	0%	0%	0%	100%
Hypomagnesemia	0%	100%	0%	0%	0%	0%	100%
Hypertension	0%	50%	25%	25%	0%	0%	100%
Voice alteration	0%	100%	0%	0%	0%	0%	100%
Gastrointestinal disorders—GERD	0%	100%	0%	0%	0%	0%	100%
Diarrhea	0%	67%	33%	0%	0%	0%	100%
Dry eye	0%	50%	50%	0%	0%	0%	100%
Dry mouth	0%	100%	0%	0%	0%	0%	100%
Edema limbs	0%	100%	0%	0%	0%	0%	100%
Infections and infestations—flu-like symptoms	0%	100%	0%	0%	0%	0%	100%

Adverse Events Legend: The table captures all toxicities of the two patients, which may have ranged in grade depending on the assessment period.
Abbreviations: CPK, creatine phosphokinase; GERD, gastroesophageal reflux disease; NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
Lower gastrointestinal hemorrhage	2	Unrelated
Rectal pain	2	Unrelated

Serious Adverse Events Legend	Both serious adverse events (SAEs) occurred prior to initiation of the dose escalation in the same patient. This patient withdrew consent prior to initiating the dose escalation. There were no treatment-related SAEs.

Dose-Limiting Toxicities

Dose level	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity
1	3	2	0

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated Reason	Company stopped development
Investigator's Assessment	Drug tolerable, hints of efficacy

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract arising from the interstitial cells of Cajal (ICC), primordial pacemaker cells located within the muscle layers of the GI tract [14]. Primary GISTs often demonstrate intramural or submucosal growth and remain asymptomatic until they are large enough to cause bowel obstruction, bleeding, or rupture [15]. Approximately 75%–80% of GISTs are characterized by gain-of-function mutations in the proto-oncogene *KIT*, leading to constitutive activation of the KIT receptor tyrosine kinase

[14, 16, 17]. The most common *KIT* mutation involves the juxtamembrane domain located in exon 11 [14, 18]. Genetic alterations in other oncogenes, including *PDGFRA*, *SDHA/B/C/D*, *NF1* or *BRAF*, have been detected in *KIT* wild-type cases [17, 19, 20].

Imatinib revolutionized the treatment of advanced GIST by eliciting remarkable clinical responses in a once uniformly fatal and untreatable disease [15, 21, 22]. The overall response rate (ORR) to imatinib approaches 50%, with an additional 25% of patients deriving clinical benefit from treatment [22]. The median progression-free survival (PFS) and overall survival on first-line imatinib therapy are approximately 20 and 55 months, respectively [23].

Despite imatinib's remarkable clinical activity, a sizeable portion of patients (10%–15%) harbor primary resistance to therapy, and nearly all patients with advanced GIST demonstrate secondary resistance over time [22]. Whereas patients with *KIT* exon 11 mutant GIST respond most favorably, fewer responses are noted in *KIT* exon 9 or *PDGFRA* exon 18 mutation carriers, and even fewer are seen in patients with wild-type *KIT* [18, 24]. Patients with *PDGFRA* D842V mutation are markedly resistant to imatinib, with a half maximal inhibitory concentration (IC_{50}) 10 - 20 fold higher than other *PDGFRA* mutant isoforms [18].

Sunitinib and regorafenib are U.S. Food and Drug Administration approved for second- and third-line treatment after imatinib, respectively; but objective responses to these agents are rare, and the duration of response is brief. The ORR to sunitinib is 7% with a median PFS of 6.4 months, whereas the ORR of regorafenib is 4.5% with a median PFS of 4.8 months [4, 5]. The limited response rates of second- and third-line agents represents the emergence of resistance to available tyrosine kinase inhibitor (TKI) therapy, which develops because of secondary mutations, reactivation of signaling pathways downstream of KIT, tumor heterogeneity, or the tumor microenvironment [25, 26]. Novel tyrosine kinase inhibitors, such as avapritinib and ripretinib, are currently under study in patients with primary resistant or TKI-refractory GISTs (NCT03465722 and NCT03673501) [27, 28].

The ETS family transcription factor ETV1 is required for the development and lineage-specification of GIST and its precursor ICC; ETV1 is highly expressed in all GISTs at the transcript and protein levels and functions as a master regulator of the transcriptional program in both ICC and GIST [1, 2]. Additionally, activated MAPK signaling, including the RAF-MEK-ERK pathway downstream of activated KIT signaling, facilitates GIST oncogenesis by stabilizing ETV1 and augmenting the ETV1-dependent transcriptome. The stabilized ETV1 protein can enhance *KIT* expression, and both KIT and ETV1 then cooperate in GIST pathogenesis [2]. In vivo, preclinical GIST models combining imatinib with the MEK inhibitor binimetinib result in the synergistic inhibition of MAPK signaling, a dramatic reduction in GIST tumor size, and durable inhibition of ETV1 protein levels compared with either treatment alone [1]. Thus, targeting the ETV1 protein through dual MEK and KIT inhibition may lead to profound and durable responses in patients with advanced GISTs, regardless of prior exposure to imatinib or *KIT/PDGFRA* mutational status.

The novel TKI pexidartinib, a potent dual-specific inhibitor of KIT and FMS, has more anti-GIST activity compared with imatinib. In transgenic and human GIST xenograft mouse models, pexidartinib reduced tumor weight, resulted in 90% fewer KIT tumor cells, and induced more hypocellularity, necrosis, and fibrosis in GIST tumors than imatinib. The increased potency of this agent led to reduced *KIT* expression per cell and to decreased downstream mediators of KIT signaling [29]. We hypothesized that the combination of pexidartinib with binimetinib would lead to antitumor activity through durable inhibition of the MAPK pathway and destabilization of the ETV1 protein.

We enrolled three patients onto this phase I dose escalation trial with expansion, prior to its premature closure (Table 1). One patient withdrew consent before starting the treatment combination. The remaining two patients were treated at dose level one with 400 mg of pexidartinib in the morning and 200 mg at night, orally, combined with 30 mg of binimetinib twice daily orally. The most frequent adverse events included fatigue, anemia, leukopenia, diarrhea, dry mouth and dry eye, hypomagnesemia and hypophosphatemia, skin and nail changes, edema, elevated aspartate aminotransferase, and elevated creatine phosphokinase (CPK). Treatment-emergent adverse events were grade ≤2, except for an asymptomatic grade 3 elevation of CPK. Plexxikon withdrew trial support after the first two patients were treated.

One patient with a loss-of-function mutation of *NF1* achieved tumor shrinkage (best response—27% by RECIST) and remains on study treatment (Fig. 1). In addition to downregulation of ETV1, MEK inhibition targets the activated MAPK pathway, which results from *NF1* loss [12]. The other patient on this study with multiply refractory *KIT*-mutant GIST had a PFS of 6.1 months before demonstrating clinical progression.

Although the investigation of combined pexidartinib and binimetinib was halted, studying alternative treatment combinations incorporating KIT and MEK inhibition in advanced GIST, particularly in *NF1*-mutant tumors, is warranted. Pharmacodynamic studies and additional correlative analyses are needed to determine the signaling pathways affected by this treatment combination and to identify other potentially targetable mechanisms of resistance.

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Disclosures

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Table

Table 1. Patient characteristics and treatment response

Characteristic	Patient 1	Patient 2
Sex	Female	Female
Ethnicity	Hispanic	Hispanic
Age, years	61	59
ECOG performance status	1	0
Number of prior systemic treatments	5	1
Best response (RECIST)	4.3%	−27.4%
Best response (Choi)	−12.7%	−9.3%
Progression-free survival, months	6.1	Not reached
Overall survival, months	14.6	Not reached
Duration on study treatment, months	6.1	19.6[a]
Reason for treatment discontinuation	Progression	N/A
Molecular profile of primary tumor	KIT exon 11 (pD579del)	NF1 exon 42 (pX2143_splice)
Molecular profile of metastasis after prior TKI	KIT exon 11 (pD579del) KRAS exon 2 (pG12V) PIK3CA exon 21 (pH1047R) NRAS deletion (−6.7-fold)	NF1 exon 42 (pX2143_splice) TSC1 exon 15 (pV531M) SPEN intragenic deletion (1p36.21)

[a]Patient remains on study treatment at the time of manuscript submission.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; N/A, not applicable; TKI, tyrosine kinase inhibitor.