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

Evan Rosenbaum,a,t Ciara Kelly,a,b† Sandra P. D’Angelo,a,b Mark A. Dickson,a,b Mrinal Gounder,a,b Mary L. Keohan,a,b Sujana Movva,a Mercedes Condy,a Travis Adamson,a Chloe R. McFadyen,a Christina R. Antonescu,a Sinchun Hwang,a Sam Singer,a,b Li-Xuan Qin,a William D. Tap,a,b Ping Chi,a,b

aMemorial Sloan Kettering Cancer Center, New York, New York, USA; bWeill Cornell Medical College, New York, New York, USA
†Co-first authors.

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
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/PDGFRα 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/PDGFRα 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
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.

**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%       |
### 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     |

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 untreated 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 (IC50) 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 oncogenesis [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/PDGFRα 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.

Acknowledgments

We thank the patients and their families, the investigators, and the clinical and research staff who participated in this study. The study was supported by Plexxikon and Array BioPharma, grants from the National Cancer Institute (P50 CA140146 and P50 CA217694 to Drs. Chi, Qin, Antonescu, Singer, and Tap; P30-CA008748 to Drs. Chi, Antonescu, Singer, and Tap; GIST Cancer Research Fund to Drs. Chi and Antonescu; the Shuman Fund to Drs. Chi, Antonescu, and Tap; the GIST Cancer Awareness Fund to Dr. Chi; and the Cycle for Survival fund to Drs. Chi and Tap.

Disclosures

Mark A. Dickson: AADi, Eli Lilly & Co. (RF); Minral Gounder: Daiichi Sankyo, Amgen, Karyopharm, Springworks Therapeutics, Bayer, Epizyme (C/A); Sujana Movva: Novartis, Takeda, Eli Lilly & Co.; William D. Tap: Deciphera, Eli Lilly & Co., Eisai, Janssen, Immune Design, Adaptimmune, Daiichi Sankyo, Blueprint, GlaxoSmithKline,
The Ras-RasGAP complex: Structural basis for gastrointestinal stromal tumors in patients with neurofibromatosis 1: A clinical and genetic study of 45 cases. Am J Surg Pathol 2006;30:90–96.

10. Scheffzek K, Ahmadian MR, Kabsch W et al. The Ras-RasGAP complex: Structural basis for GTPase activation and its loss in oncogenic Ras mutants. Science 1997;277:333–338.

11. Nissan MH, Pratillas CA, Jones AM et al. Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence. Cancer Res 2014;74:2340–2350.

12. Ran L, Chen Y, Sher J et al. FOXF1 defines the core-regulatory circuitry in gastrointestinal stromal tumor. Cancer Discov 2018;8:234–251.

13. Xie Y, Cao Z, Wong EW et al. COP1/DET1/ETS axis regulates ERK transcriptome and sensitivity to MAPK inhibitors. J Clin Invest 2018;128:1442–1457.

14. Hirota S, Isozaki K, Moriyama Y et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577–580.

15. Demetri GD. Identification and treatment of chemoresistant inoperable or metastatic GIST: Experience with the selective tyrosine kinase inhibitor imatinib mesylate (STI571). Eur J Cancer 2002;38(suppl 5):S52–S59.

16. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumors: Origin and molecular oncology. Nat Rev Cancer 2011;11:865–878.

17. Heinrich MC, Corless CL, Duensing A et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003;299:708–710.

18. Heinrich MC, Corless CL, Demetri GD et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342–4349.

19. von Mehren M, Joensuu H. Gastrointestinal stromal tumors. J Clin Oncol 2018;36:136–143.

20. Agaram NP, Wong GC, Guo T et al. Novel V600E BRAF mutations in imatinib-naive and imatinib-resistant gastrointestinal stromal tumors. Genes Chromosomes Cancer 2008;47:853–859.

21. van Oosterom AT, Judson I, Verweij J et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: A phase I study. Lancet 2001;358:1421–1423.
### 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*                            |
| 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) |

*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.