Investigational New Drugs (2019) 37:282–290
https://doi.org/10.1007/s10637-018-0648-z

PHASE I STUDIES

A phase Ib study of BGJ398, a pan-FGFR kinase inhibitor in combination with imatinib in patients with advanced gastrointestinal stromal tumor

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Received: 27 March 2018 / Accepted: 18 July 2018 / Published online: 13 August 2018

Summary

Background Preclinical studies suggest that imatinib resistance in gastrointestinal stromal tumor (GIST) can be mediated by MAP-kinase activation via fibroblast growth factor (FGF) signaling. In FGF stimulated GIST cell lines, BGJ398, a pan-FGFR kinase inhibitor in combination with imatinib, was cytotoxic and superior to imatinib therapy alone. In FGF-dependent GIST, the combination of BGJ398 and imatinib may provide a mechanism to overcome imatinib resistance. *Methods* This phase Ib study of BGJ398 and imatinib was performed in patients with imatinib refractory advanced GIST. A standard 3 + 3 dosing schema was utilized to determine the recommended phase II dose (RP2D). Two treatment schedules were evaluated incorporating imatinib 400 mg daily in combination with (A) BGJ398 daily 3 weeks on, 1 week off or (B) BGJ398 daily 1 week on, 3 weeks off. *Results* 16 patients enrolled. The median age was 54 years (range: 44–77), 81% were male, and the median number of lines of prior therapy was 4 [range: 2–6, 13 patients had ≥3 prior therapies]. 12 patients received treatment on schedule A [BGJ398 dose range: 25 – 75 mg]: 2 patients experienced dose limiting toxicities (DLT) ($n = 1$, myocardial infarction & grade (G)4 CPK elevation; $n = 1$, G3 ALT elevation) on schedule A (BGJ398 75 mg), significant hyperphosphatemia, an on-target effect, was not observed, implying the maximum tolerated dose was below the therapeutic dose. Following protocol amendment, 4 patients enrolled on schedule B [BGJ398 dose range: 75 − 100 mg]: no DLTs were observed. The most common treatment related adverse events occurring in >15% of patients included CPK elevation (50%), lipase elevation (44%), hyperphosphatemia (24%), anemia (19%), and peripheral edema (19%). Among the 12 evaluable patients, stable disease (SD) was the best response observed in 7 patients by RECIST v1.1 and 9 patients by CHOI. Stable disease ≥ 32 weeks was observed in 3 patients (25%). Median progression free survival was 12.1 weeks (95% CI 4.7–19.5 weeks). *Conclusions* Toxicity was encountered with the combination therapy of BGJ398 and imatinib. Due to withdrawal of sponsor support the study closed before the RP2D or dosing schedule of the combination therapy was identified. In heavily pre-treated patients, stable disease ≥ 32 weeks was observed in 3 of 12 evaluable patients. Trial Registration: NCT02257541.

Keywords Gastrointestinal stromal tumor · Imatinib · BGJ 398 · FGFR inhibition · Phase I

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Introduction

The majority of gastrointestinal stromal tumors (GIST) harbor activating oncogenic mutations in the KIT receptor tyrosine kinase. Imatinib is a small molecule tyrosine kinase inhibitor of KIT. It represents the standard first–line therapy for the management of patients with advanced GIST. The majority of patients experience clinical benefit from imatinib with an objective response rate of approximately 50% and an overall disease control rate of 80%. [1, 2] The median progression free survival is 20–24 months following initiation of imatinib therapy. [1–3] Second and third line options are sunitinib and regorafenib. Both of these tyrosine kinase inhibitors yield low response rates (around 4–7%) and the median PFS with these agents is 4–6 months [4, 5].

Mechanisms of imatinib resistance in GIST are complex and heterogeneous. Primary and early resistance to imatinib therapy occurs in approximately 20% of patients. The majority of patients experience progression of disease after 2–3 years of imatinib therapy. Secondary KIT mutations are rarely identified in primary resistance but are found in 56–67% of patients who develop secondary resistance to imatinib. [6–8] Other mechanisms of resistance are still being defined and include activation of alternative signaling pathways downstream of KIT including the MAP kinase pathway. Preclinical studies suggest that imatinib resistance (IR) in a subset of GIST is mediated by signaling crosstalk between KIT and fibroblast growth factor receptor 3 (FGFR3) which activates the mitogen-activated protein kinase (MAPK) pathway. [9] Combination KIT and FGFR inhibition has been shown to be synergistic in abrogating MAP kinase signaling and suppressing growth of FGF-dependent imatinib resistant GIST cell lines. [9, 10] In FGF-dependent GIST, the combination of a pan-FGFR kinase inhibitor and imatinib may provide a mechanism to overcome imatinib resistance.

The primary objective of this study was to assess the safety and tolerability and to establish the recommended phase II dose (RP2D) and schedule of treatment with BGJ398, a pan-FGFR kinase inhibitor, in combination with imatinib in patients with locally advanced or metastatic GIST.

Methods

Study population

Eligible patients were ≥ 18 years old with pathologically confirmed, locally advanced or metastatic GIST that had progressed on imatinib; measurable disease (RECIST 1.1); and an Eastern Cooperative Oncology Group performance status 0–1.

Study design and procedures

This was a single-center, phase IB study performed at Memorial Sloan Kettering Cancer Center (New York, NY). The primary objective of the trial was to evaluate the safety and tolerability of treatment with BGJ398 in combination with imatinib and to determine the maximum tolerated dose (MTD), the RP2D and schedule of the combination therapy in patients with advanced GIST. The secondary objectives of the study were to assess the pharmacokinetics of BGJ398 and imatinib and to determine the response rate by 32 weeks by both RECIST 1.1 [11] and Choi criteria [12], the progression free survival and clinical benefit rate [CR + PR + stable disease (SD)] at 32 weeks of the combination therapy.

The design of this phase Ib trial included imatinib administered at 400 mg once a day, with escalating doses of BGJ398 starting at 75 mg daily with 5 dose levels ranging between 25 and 125 mg daily (Table 1). A standard 3 + 3 dose escalation design was used. BGJ398 was initially administered using schedule A (3 weeks on followed by one week off). Once the MTD was reached using this schedule, the protocol was amended to change the schedule of administration of BGJ398 for subsequently enrolled patients to 1 week on followed by 3 weeks off (schedule B). This schedule was chosen on the basis of preclinical data which conveyed that in the context of continuous KIT inhibition with imatinib, transient inhibition of FGFR with BGJ 398 was sufficient to drive tumor cell death after just 2–3 days of the combination therapy. [10] Both drugs were given by oral administration. A cycle of treatment consisted of 28 days. In the absence of a dose limiting toxicity (DLT) or overt clinical progression, imatinib was administered daily with BGJ administered daily using the dosing schedule A or B.

Safety

Toxicity was graded according to the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE v 4.03). Any unexpected adverse event or abnormal laboratory value assessed as at least possibly related to the study medication that met the criteria defined in the protocol, which occurred ≤28 days (first cycle) following the first dose of BGJ398 was considered a DLT for the purposes of dose escalation to the next dose level. Patients that stopped study therapy before completing the DLT period for reasons other than toxicity were replaceable and considered not evaluable for the purpose of determining the MTD of the combination therapy. The highest tolerated dose for each given dosing schedule was defined as the maximum dose of BGJ398 administered in combination with imatinib at which no more than 1 of 6 patients experienced a DLT.

Table 1 Dose escalation schema & dosing schedule

Dose level (DL)	Imatinib daily	BGJ398 daily
3	400 mg qd	125 mg qd
2	400 mg qd	100 mg qd
1	400 mg qd	75 mg qd
−1	400 mg qd	50 mg qd
−2	400 mg qd	25 mg qd
Dosing schedule		
A	Imatinib 400 mg daily & BGJ 398 3 weeks on, 1 week off	
B	Imatinib 400 mg daily & BGJ 398 1 week on, 3 weeks off	

Evaluation of clinical activity

Baseline imaging was conducted within 4 weeks of starting the study therapy. Tumor assessments were performed every 8 weeks × 4 and then every 12 weeks thereafter. Response was assessed using RECIST 1.1 and Choi criteria. Response and progression as defined by RECIST v1.1 was used for all clinical decision making in this trial. Patients were allowed to remain on the study until the time of confirmed progressive disease as defined by the modified RECIST v1.1 (20% increase in tumor burden) or the development of unacceptable toxicity.

Pharmacokinetic (PK) analysis

Plasma concentrations of BGJ398, imatinib and its pharmacologically active metabolite (CGP 74588) were measured in blood samples collected at prespecified timepoints during cycle 1. Plasma concentrations of these compounds were determined using a validated liquid chromatography - tandem mass spectrometry method. [13] PK testing was performed at Wuxi AppTec Com., Ltd. Shanghai, China. PK parameters, including maximum plasma concentration, area under the plasma concentration-time curve and time to reach maximum plasma concentration were calculated using non-compartmental methods.

Results

Patient characteristics

Between November 2014 and October 2016, a total of 17 patients were enrolled. One patient was considered a screen failure and did not receive treatment on study. The remaining 16 patients received at least one dose of BGJ398 in combination with imatinib. The median age was 54 years (range, 44–77). The molecular characteristics of thirteen of the patient's tumors were available and are reported in Table 2. None of the thirteen patients with molecular information available on their tumor had a known genomic alteration in the FGFR gene. Other key baseline demographics are presented in Table 3.

Reasons for study discontinuation included radiographically documented progressive disease (PD) ($n = 10$, 62%); symptomatic deterioration/clinical progression ($n = 3$, 19%); and withdrawal of consent ($n = 2$, 12.5%). One of these patients withdrew consent after experiencing a DLT.

All 16 patients were included in the safety population. Fourteen patients were evaluable for DLT assessment. Two patients were not considered evaluable for the primary endpoint of DLT assessment due to study withdrawal in one patient and clinical progression in another patient. Twelve patients were evaluable for response; 4 patients did not have restaging imaging performed because they discontinued study treatment before the first imaging time point. Two of these patients discontinued the study because of symptomatic deterioration.

Dose escalation and MTD

The first twelve patients received treatment on schedule A. In dose level 1, schedule A, the first patient treated experienced a grade 3, non-ST elevation myocardial infarction and associated grade 4 CPK elevation. This 64 y/o man experienced exertional chest pain that occurred on cycle 1 day 5 after increased physical activity. He also had evidence of grade 2 anemia present at baseline. He had known cardiovascular risk factors including a 20-pack year smoking history, controlled hypertension and type II diabetes mellitus without a known personal or family history of ischemic heart disease. The patient was managed conservatively and withdrew consent from the study. The second patient enrolled in this initial cohort also withdrew consent prior to completing the first cycle of treatment. Following this event, a decision was made to enroll the next cohort on dose level − 2. This dose level was well tolerated and a further three patients were enrolled on dose level − 1 without incident. Dose level 1 was then expanded

Table 2 Tumor molecular characteristics

Molecular characteristics	N (%)
Primary oncogenic mutation:	
KIT exon 11	10 (62)
KIT exon 9	3 (19)
Unknown	3 (19)
Secondary KIT mutations	8(50)

Table 3 Baseline patient characteristics, $N = 16$

Characteristic	N (%)
Age (years), median (range)	54 (44–77)
Gender:	
Male	13 (81)
Female	3 (19)
ECOG PS:	
PS 0	14 (87.5)
PS 1	2 (12.5)
Number of prior therapies, median (range)	4 (2–6)
≥ 3 prior therapies	13 (81)
Imatinib	16 (100%)
Sunitinib	16 (100%)
Regorafenib	12 (75%)
Pazopanib	4 (25%)
Sorafenib	2 (12.5%)
Clinical trial	4 (25%)

with 3 more patients. One patient with known liver metastases experienced a DLT with a grade 3 elevation in alanine transaminase at dose level 1. In light of two DLTs at dose level 1 the maximum tolerated dose on schedule A was determined to be dose level − 1 (400 mg of imatinib and 50 mg of BGJ398). Significant hyperphosphatemia, an on target effect of BGJ398, was not observed at the MTD, raising concern that the dose was insufficient to achieve adequate FGFR inhibition. The protocol was therefore amended (amendment #5; IRB approved on Mar 22nd 2016) to change the dosing schedule from BGJ398 three weeks out of four to BGJ 398 one week out of four with imatinib 400 mg once daily (schedule B) and allow for further dose escalation of BGJ 398. Four patients received treatment on schedule B; three patients at dose level 1 and one patient at dose level 2. No DLTs were experienced in patients that received treatment on dosing schedule B. The sponsor closed the study before the MTD for dosing schedule B was determined. Figure 1 is a consort diagram highlighting the study flow and the DLTs encountered during this study.

Safety

Of the 16 evaluable patients, 15 of 16 (94%) experienced treatment-related AEs of any grade. The most common treatment-related AEs of any grade were CPK increased (50%), lipase increased (44%), hyperphosphatemia (19%), anemia (19%), edema in limbs (19%), ALT increased (13%), constipation (13%), dry eye (13%), dysgeusia (13%), reduced ejection fraction (13%), fatigue (13%) and nausea (13%) (Table 4).

Grade 3 AEs included a myocardial infarction medically managed in one patient, ALT increased, hypertension, lipase increased and non-cardiac chest pain each occurring in one patient respectively. Two patients experienced grade 4 increase in creatinine phosphokinase level. There were 10 serious AEs that occurred during the course of

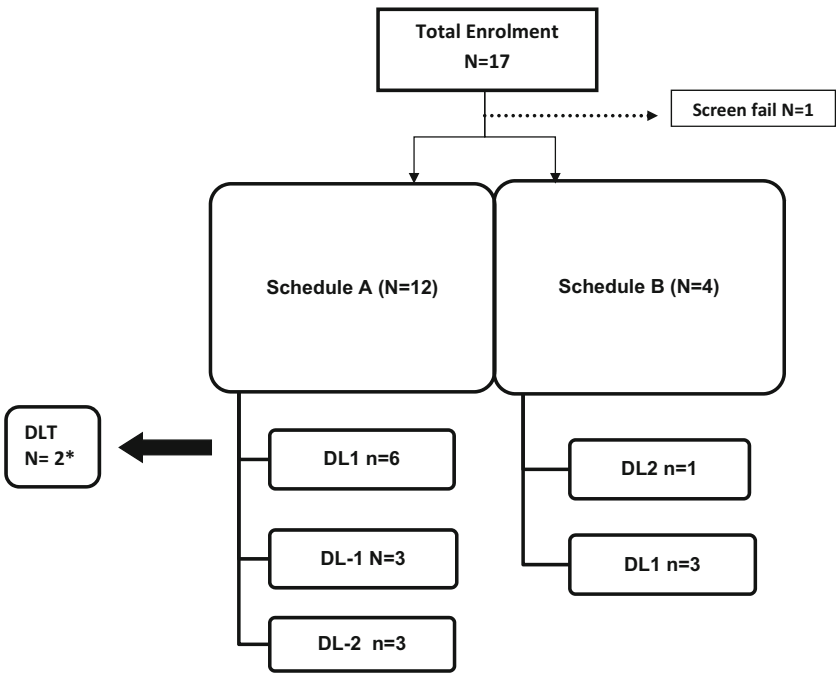

Fig. 1 Consort diagram. Abbreviations: N, number of study participants; Schedule A, BGJ 398 3 weeks on, 1 week off & imatinib 400mg once daily; Schedule B, BGJ 398 1 week on, 3 weeks off & imatinib 400mg once daily; DL, dose level; DLT, dose limiting toxicity. *Two patients experienced a DLT at DL1 on schedule A. The DLTs included a grade 3 non-ST elevation myocardial infarction together with grade 4 CPK elevation and a grade 3 elevation in alanine transaminase

Table 4 All grade toxicity possibly, probably or definitely related to study therapy by dose level

Schedule	A (BGJ 398 3 wks on, 1 wk. off, imatinib continuously)						B (BGJ398 1 wk. on, 3 wks off, imatinib continuously)			
Dose level	1 ($n=6$) BGJ 398 75 mg		−1 ($n=3$) BGJ 398 50 mg		−2 ($n=3$) BGJ 398 25 mg		1 ($n=3$) BGJ 398 75 mg		2 ($n=1$) BGJ 398100 mg	
Grade	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4
ALT increased		1(6%)							1(6%)	
AST increased			1(6%)							
Anemia			2(13%)						1(6%)	
Anorexia										
Bilirubin increased	1(6%)									
Constipation	1(6%)		1(6%)							
CPK increased	2(13%)	1(6%)	1(6%)	1(6%)	1(6%)		2(13%)			
Creatinine increased							1(6%)			
TSH decreased			1(6%)							
Dry eye	1(6%)						1(6%)			
Dry skin	1(6%)									
Dysguesia	2(13%)									
Dyspepsia										
Edema in limbs			1(6%)		1(6%)		1(6%)			
Ejection fraction decreased					1(6%)				1(6%)	
Prolonged QTc interval					1(6%)					
Fatigue			2(13%)							
Flashing lights			1(6%)							
Gastritis					1(6%)					
Hyperphosphatemia	1(6%)		1(6%)		1(6%)		1(6%)			
Hypophosphatemia			1(6%)							
Hypertension						1(6%)				
Lipase increased	2(13%)		2(13%)		1(6%)	1(6%)	1(6%)	1(6%)		
Memory Impairment	1(6%)									
Myalgia			1(6%)							
Myocardial Infarction		1(6%)								
Nausea					1(6%)		1(6%)			
Non-cardiac chest pain		1(6%)								
Periorbital edema					1(6%)					
Serum amylase increased							1(6%)			
Skin hyperpigmentation							1(6%)			
Vomiting			1(6%)							
Watery eyes	1(6%)									

Abbreviations: *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CPK* creatinine phosphokinase, *TSH* thyroid stimulating hormone, *n* number of patients

the study. Four of these were treatment related and are highlighted in Table 5.

Clinical activity

Of the 16 patients evaluable for toxicity, 12 patients reached their first disease assessment and were evaluable for radiographic response. Two patients came off study prior to their

Table 5 Treatment related serious adverse events (SAE)

	SAE	Grade
1.	CPK increased	4
2.	Hypertension/Ejection Fraction Decreased	3/2
3.	Lipase Increased	4
4.	CPK increased/Myocardial Infarction	4/3

Table 6 Best response and clinical benefit rate by RECIST 1.1 (evaluable population)

Best tumor radiographic response	
CR	0
PR	0
SD	7 (44%)
PD	5 (31%)
Not evaluable	4 (25%)
Clinical benefit rate (CR + PR + SD) at 32 weeks	
N (%)	3 (25%)

CR complete response, *PD* progressive disease, *PR* partial response, *SD* stable disease, *N* number of patients

first imaging due to clinical progression of their disease. Two patients withdrew consent to treatment prior to their first disease assessment.

No objective responses were observed in the evaluable population by either RECIST v1.1 or Choi criteria (Table 6). Stable disease was observed in 7 patients by RECIST v1.1 and 9 patients by Choi criteria.

The clinical benefit rate at 32 weeks was 25% ($n = 3$). The patient and tumor characteristics of the 3 patients where disease stability was maintained at 32 weeks are highlighted in Table 7. The median PFS was 12.1 weeks (95% CI 4.7–19.5 weeks). The duration of time on study for each patient is highlighted in Fig. 2. There is one patient that continues to receive treatment, 21 months from the initiation of study therapy.

Pharmacokinetic analysis

BGJ 398 was absorbed relatively quickly. The median time to achieve maximal concentration was 4.5 h (range 4-5 h). The plasma concentrations of BGJ 398, imatinib and its active metabolite (CGP 74588) taken on day 1 of cycle one are recorded in Tables 8 and 9. The mean AUC of BGJ 398 varied in a non-linear fashion relative to the BGJ 398 dose level. The mean imatinib and CGP 74588 concentrations taken 24 h after starting imatinib and BGJ 398 varied also between the BGJ 398 dose levels in a non-linear fashion.

Discussion

The majority of GIST harbor oncogenic mutations in KIT or PDGFRα that play a fundamental role in their development and provide the scientific rationale for the use of tyrosine kinase inhibitors (TKI) in their management. Most GIST are initially sensitive to TKI therapy but the beneficial effects are generally not durable with most patients developing resistance to first line TKI therapy within 2–3 years. Secondary resistance to TKI therapy in KIT mutant GIST is commonly associated with the development of secondary resistant KIT mutations. Other mechanisms of resistance to tyrosine kinase inhibition continue to be elucidated. Activation of signaling pathways downstream of KIT/PDGFRα including the phosphatidyl-inositol-3-kinase (PI3K) pathway and the mitogen-activated protein kinase (MAPK) pathway have been implicated [14, 15].

The fibroblast growth factor signaling network plays a diverse role in the control of cell proliferation, differentiation and angiogenesis. Dysregulation of the FGF signaling pathway through somatic alterations affecting FGF receptor genes and overexpression of the FGF ligands has been observed in many human cancers and is a recognized therapeutic target currently under investigation. [16–18] Preclinical studies have identified the FGF pathway as a possible mediator in the development of imatinib resistance in a subset of GIST patients. [9, 10] Direct crosstalk between KIT and the FGF signaling pathway has been observed in imatinib resistant GIST cell lines without evidence of secondary KIT mutations. [9] In imatinib sensitive GIST cell lines activation of FGF signaling desensitized GIST to imatinib via upregulation of the MAPK pathway. Activation of FGF signaling also re-activated KIT signaling. Preclinical work has also shown that imatinib can abrogate MAPK activity in FGF non-stimulated GIST cell lines but not in FGF stimulated GIST cell lines. However, in

Table 7 Characteristics of patients that experienced durable disease stability

Dose level	Schedule	Age/ Sex	# prior Rx	Molecular characteristics	Reason to stop	PFS (wk)	Hyperphosphatemia	Survival status
−1	A	48 M	5	KIT ex 11 splice variant KIT exon 13 p.V654A SETD2 exon3 p.I277T	POD	32	Yes, Grade 1	Unknown
−1	A	65 M	2	KIT exon 11 p.T574_H580dup AR exon1 p.L56Q PHOX2B exon2 p.K97 N	Remains on Rx	n/a	No	Alive
1	A	52 F	4	KIT exon9 p.A502_Y503dup MLL2 exon11 p.L1271 V PPP2R1A exon5 p.L189 V	POD	60	No	Alive

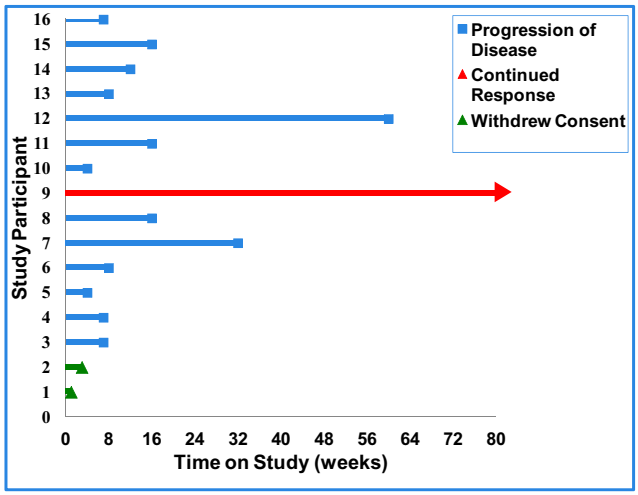

Fig. 2 Duration of time on study

FGF-stimulated GIST cell lines a pan-FGFR inhibitor can abrogate MAPK signaling. This suggests that in FGF-dependent GIST MAPK activation is dependent on FGF, more so than KIT signaling. The combination of FGFR inhibition and KIT inhibition has consistently been shown to be synergistic in suppressing GIST growth compared to either drug alone in preclinical models in the presence or absence of FGF stimulation. In FGF stimulated GIST combination FGFR and KIT inhibition was also shown to be superior over combination MEK and KIT inhibition however, the converse was evident in FGF non-stimulated GIST.

It is hypothesized that some patients with imatinib resistant GIST may rely on FGF signaling which mediates MAPK activation. In this population combination FGFR and KIT inhibition may suppress GIST growth and potentially can overcome FGF mediated imatinib resistance. This provided the scientific rationale for investigating the combination of imatinib and BGJ398 in this GIST specific phase I study.

The primary end point of this study was to determine the safety of the combination therapy (imatinib and BGB 398), to identify the maximum tolerated dose and the recommended phase II dose and schedule. The imatinib dose, as the known active agent, remained consistent throughout all dose levels and schedules in this study. An intermediate dose level of BGJ398 was chosen in combination with imatinib as dose level 1. In this small heavily pretreated population ($n = 16$) tolerability of the combination therapy was difficult to establish. The first patient enrolled on dose level 1 (schedule A) experienced a myocardial infarction deemed at least possibly related to study treatment. A second patient observed a DLT at this dose level and schedule. They experienced a grade 3 elevation in ALT in the setting of preexisting liver metastases and discontinued the study shortly after this DLT due to clinical progression of disease. The MTD (BGJ398 50 mg) on dosing schedule A did not result in significant hyperphosphatemia, an on-target effect of FGFR inhibition. This dose and schedule was felt to be insufficient to achieve the effective level of FGFR inhibition required to produce an anti-cancer effect. An alternative dosing schedule with pre-existing scientific data to support it allowed for escalation in BGJ 398 dose level safely. [9] However, the study closed prematurely before the MTD with this dose schedule was reached. The study sponsor made an internal decision to close their pan-FGFR kinase inhibitor clinical trial portfolio. Consequently, the study closed early.

The median progression free survival of 12.1 weeks with the combination therapy is superior to that achieved with imatinib re-challenge. [19] The combination therapy yielded a disease control rate at 32 weeks of 25%. One patient continued study treatment (schedule A, dose level-1) after 21 months on study. At a molecular level this patient had KIT exon 11 mutant disease without evidence of secondary KIT mutations at the time of progression after 9 years of imatinib therapy for metastatic GIST. A second patient with KIT exon 9 mutant GIST remained on study for 15 months with stable disease before progression on study therapy (schedule A, dose level 1). Again next generation sequencing analysis did not reveal secondary KIT mutations. Tumor tissue sequenced in this case was taken following imatinib exposure but with continued response to imatinib at the time of tissue biopsy. The third patient with stable disease at 32 wks had evidence of a secondary KIT exon 13 mutation. This patient received study therapy on schedule A at dose level − 1. Next generation sequencing of tumor tissue from these 3 patients did not identify any genomic alterations in genes involved in the FGFR

Table 8 Mean pharmacokinetic parameters of BGJ-398 after once daily dosing of BGJ-398 and imatinib (day 1)

Dose level	Patients (n)	AUC (0 − 24 h) (h x ng/mL)	Cmax (ng/mL)	Tmax (h)
2	1	309	33	5
1	9	487 (32–1153)	57 (45–79)	4
−1	1	25	2.49	4
−2	3	61 (4–61)	12.6 (2–13)	5

Abbreviations: *AUC* area under the plasma concentration time curve, *Cmax* maximum concentration, *Tmax* time of occurrence of Cmax

Table 9 Mean pharmacokinetic parameters of imatinib and its metabolite (CGP74588) after once daily dosing of BGJ-398 and imatinib (day 1)

Dose level	Patients (n)	Concentration of imatinib (ng/mL) day 1 24 h	Concentration of metabolite (ng/mL) day 1 24 h
2	1	3130	1040
1	9	977 (468–1750)	149 (56–395)
−1	3	364 (183–562)	54 (26–84)
−2	3	1142 (390–2340)	131 (67–209)

signaling pathway. The incidence of FGF-mediated imatinib resistance is unknown and the study did not select patients based on the presence or absence of FGF mediated imatinib resistance. FGF ligand testing was beyond the scope of this phase I study, the primary endpoint of which was focused on determining the safety of the combination therapy. The study may or may not have captured patients with tumors exhibiting FGF mediated imatinib resistance. However, the absence of secondary KIT mutations in two of these patients suggests an alternative mechanism of resistance to imatinib that the study therapy may have been suppressing. However, low grade hyperphosphatemia was observed among only one of the three patients with durable disease control. The median PFS previously observed with imatinib re-challenge is 1.8 months (95% CI 1.7–3.6). [19] Therefore the effects of imatinib re-challenge is unlikely to account for the observed durable stabilization of disease among these three patients. It is also possible that BGJ398 and imatinib may have other synergistic anticancer effects when administered concurrently.

Pharmacokinetic analyses failed to provide an explanation for the toxicity encountered or the prolonged stabilization of disease observed in 25% of the evaluable cohort.

Conclusion

The scientific data supporting the clinical concept of this study is based on evidence that combination KIT and FGFR inhibition are synergistic in suppressing GIST growth in tumors with evidence of FGF-dependent MAPK pathway activation. This study was not designed to explore this hypothesis and further trials rich in correlative studies are necessary to answer questions about the role of FGF-signaling as a mediator of imatinib resistance in GIST. Durable stabilization of disease lasting at least 32 weeks was observed in 25% of the evaluable study cohort. This finding is intriguing and remains unexplained. A larger study is required to evaluate the true clinical activity of this combination therapy in patients with advanced GIST. Evaluating this combination therapy earlier in the treatment course prior to the development of polyclonal mutation resistance would be reasonable. However, motivation for further study of this combination therapy must be balanced against toxicity, a factor that limited the ability of this study to meet its primary end point.

Acknowledgements This study received funding from Novartis Pharmaceuticals. The study was also supported by a grant from the Jennifer Linn Fund through Cycle for Survival. WuXi AppTec Com., Ltd. Shanghai, China performed the pharmacokinetic analyses.

Funding This study received funding from Novartis Pharmaceuticals and a grant from the Jennifer Linn Fund through Cycle for Survival.

Compliance with ethical standards

Conflict of interest CMK: Declares that she has no conflict of interest.

ANS: consulting or advisory role – Castle biosciences, Immunocore, Vaccinex; Research funding – Bristol Myers Squibb, Immunocore; Travel, Accommodation, Expenses – Bristol Myers Squibb.

LXQ: Declares that she has no conflict of interest.

SPD: Consulting or Advisory Role – Amgen, EMD Serono, Nektar.

MAD: Declares that he has no conflict of interest.

MMG: Honoraria – Amgen, Daiichi Sankyo, Karyopharm Therapeutics, TRACON Pharma; Consulting or Advisory Role – Amgen, Daiichi Sankyo, Epizyme, Karyopharm Therapeutics; Speakers' Bureau – Amgen; Travel, Accommodations, Expenses – Amgen, Daiichi Sankyo, Karyopharm Therapeutics.

MLK: Declares that she has no conflict of interestCM: Declares that she has no conflict of interest.

AS: Declares that she has no conflict of interest.

SS: Declares that he has no conflict of interest.

RPD: Declares that he has no conflict of interest.

SH: Declares that she has no conflict of interest.

MHH: Declares that he has no conflict of interestJHF: Declares that she has no conflict of interest.

CRA: Declares that she has no conflict of interest.

PC: Honararia - Novartis.

WDT: Consulting or Advisory Role – Adaptimmune, Daiichi Sankyo, Eisai, EMD Serono, Immune Design, Janssen, Lilly, Novartis, Plexxikon, TRACON Pharma.

Ethical approval All procedures performed in this study (ClinicalTrials.govNCT02257541) which involved human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all individual participants included in this study.

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