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Original Research

Dose-escalation study of a second-generation non-ansamycin HSP90 inhibitor, onalespib (AT13387), in combination with imatinib in patients with metastatic gastrointestinal stromal tumour☆

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KEYWORDS
Onalespib (AT13387);
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Abstract ***Background:*** Gastrointestinal stromal tumours (GIST) treated with the tyrosine kinase inhibitor (TKI) imatinib can become resistant when additional mutations in the receptor tyrosine kinases KIT or PDGFRA block imatinib activity. Mutated KIT requires the molecular chaperone heat-shock protein 90 (HSP90) to maintain stability and activity. Onalespib (AT13387) is a potent non-ansamycin HSP90 inhibitor. We hypothesised that the combination of onalespib and imatinib may be safe and effective in managing TKI-resistant GIST.

Patients and methods: In this dose-escalation study, we evaluated the safety and efficacy of combination once-weekly intravenous onalespib for 3 weeks and daily oral imatinib in 28-d cycles. Twenty-six patients with TKI-resistant GIST were enrolled into four sequential dose cohorts of onalespib (dose range, 150–220 mg/m^2) and imatinib 400 mg. The relationship between tumour mutational status (*KIT*/*PDGFRA*) and efficacy of treatment was explored.

Results: Common onalespib-related adverse events were diarrhoea (58%), nausea (50%), injection site events (46%), vomiting (39%), fatigue (27%), and muscle spasms (23%). Overall, 81% of patients reported more than one onalespib-related gastrointestinal disorder. Nine patients (35%) had a best response of stable disease, including two patients who had *KIT* mutations known to be associated with resistance to imatinib and sunitinib. Disease control at 4 months was achieved in five patients (19%), and median progression-free survival was 112 d (95% confidence interval 43–165). One patient with *PDGFRA*-mutant GIST had a partial response for more than 376 d.

Conclusion: The combination of onalespib plus imatinib was well tolerated but exhibited limited antitumour activity as dosed in this TKI-resistant GIST patient population.

Trial registration ID: clinicaltrials.gov: NCT01294202

1. Introduction

Gastrointestinal stromal tumours (GIST) are commonly driven by activating mutations in the KIT or PDGFRA receptor tyrosine kinases. Although the initial response rates for newly diagnosed GIST to the tyrosine kinase inhibitor (TKI) imatinib can be ≥50%, most tumours ultimately become resistant [1], commonly through secondary mutations [2–3] or through alternative pathways [4].

Mutated forms of KIT and PDGFRA are reliant on the heat-shock protein 90 (HSP90) chaperone for their functional stabilisation [5–6]. Inhibition of HSP90 function causes degradation of KIT *in vitro* and inhibits tumour growth in GIST models [7–11]. In a phase 1 trial of the geldanamycin analogue HSP90 inhibitor IPI-504, stable disease (assessed by RECIST 1.0) was observed in 70% of patients with metastatic and/or unresectable GIST (n = 37), with one partial response; metabolic partial responses were observed in 38% of these patients [12]. In a phase 2 trial of the non-ansamycin HSP90 inhibitor BIIB021, stable disease (assessed by RECIST 1.0) was observed in 43% of patients with GIST refractory to imatinib and sunitinib, with a 22% metabolic partial response rate [13].

Onalespib is a potent non-ansamycin HSP90 inhibitor that shows activity in many preclinical models, including imatinib-sensitive and -resistant GIST [11,14–15]. Preliminary antitumour activity was observed in patients with GIST in a phase 1 study of onalespib monotherapy [16]. The combination of onalespib with imatinib was well tolerated in mice and was shown to inhibit tumour growth in a TKI-resistant model [11]. Here, we describe a phase 1 study investigating the safety and efficacy of onalespib in combination with imatinib in patients with GIST. Imatinib was given in combination with onalespib for the possibility that a subpopulation of tumour cells may still be sensitive to imatinib [4,17] and that combining partial kinase inhibition with reduced KIT levels would lead to a synergistic or additive decrease in oncogenic KIT signalling.

2. Patients and methods

2.1. Patient selection

Patients included in the study were ≥18 years of age, ECOG performance status 0 or 1, with unresectable and/or metastatic GIST with objective progression of disease following previous treatment with a maximum of three TKIs, including imatinib. The trial was carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent and the study was approved by local institutional review boards.

2.2. Study objectives

The primary objective of this study was to evaluate the antitumour effects of onalespib in combination with imatinib. Secondary objectives were to evaluate the safety, maximum tolerated dose (MTD), and pharmacokinetic (PK) profile of onalespib plus imatinib and to

explore how treatment effects might vary with tumour mutational status.

2.3. Study design and treatment administration

A standard 3+3 dose-escalation design was used to define the MTD of intravenous (i.v.) onalespib administered once weekly for 3 weeks of each 4-week cycle in combination with daily oral imatinib (400 mg).

Four sequential dose levels were tested following safety monitoring committee (SMC) recommendations: 180 mg/m^2 (Cohort 1), 150 mg/m^2 (Cohort 2), 180 mg/m^2 (Cohort 3), and 220 mg/m^2 (Cohort 4). Patients who exhibited evidence of clinical benefit and continued to meet the eligibility criteria were allowed to remain on study until they withdrew consent or experienced disease progression or until the study was terminated.

Adverse event (AE) severity grades were determined using NCI-CTCAE v4.03. Standard criteria were used for dose-limiting toxicities (DLTs), with the exception of nausea, vomiting, or diarrhoea in the absence of appropriate prophylaxis; in addition, the omission of more than one dose during the first cycle of treatment because of toxicity related to onalespib was considered a DLT.

Tumour images (computed tomography or magnetic resonance imaging scans) were evaluated using RECIST 1.1 [18]. The primary end-point was disease control rate (i.e. the proportion of subjects who exhibited reduction or stabilisation of tumour size) at 4 months per RECIST 1.1.

Serum onalespib concentrations and PK parameters were measured as described previously [16]. Tumour *KIT* and *PDGFRA* genotypes were determined from historical records or from new or archived tumour biopsies, as previously described [19].

This study is registered in the clinicaltrials.gov under the identifier NCT01294202.

3. Results

3.1. Patient disposition and characteristics

Twenty-six patients were enrolled in the study between May 2011 and April 2013. All patients ($n = 26$) had received prior TKI therapy for GIST. Most patients ($n = 24$, 92%) had undergone prior surgical treatment and three patients (12%) had received radiotherapy. Patient demographics and baseline characteristics are summarised in Table 1.

The median number of onalespib cycles administered per patient was 2 (range 1–14 cycles); three patients (11.5%) received six or more cycles. Overall, 11 patients (42%) stopped treatment due to disease progression and 12 (46%) withdrew for personal reasons or as a result of an AE, including events that were primarily the result of GIST progression. One patient (4%) was withdrawn from study treatment due to protocol non-compliance. For two patients (8%), the primary reason for withdrawal from study was death due to disease progression or complications of disease progression. Patient screening, enrolment, and disposition are summarised in Fig. 1.

3.2. Dose-limiting toxicities

Patients were assessed for DLTs during Cycle 1. Two renal events (Grade II increased creatinine in one patient and Grade IV acute renal failure in another) in Cohort 1 (180 mg/m^2) were classified as DLTs. Both patients were taking antihypertension medications; one had slightly elevated serum creatinine at baseline (1.6–1.9 mg/dl, normal range 0.7–1.3) and the other had a history of a kidney tumour, renal injury, and ongoing nephrolithiasis. Because of these events, the SMC recommended de-escalating onalespib to 150 mg/m^2 for Cohort 2 and amending the protocol eligibility criteria to exclude patients who had elevated serum creatinine or reduced estimated creatinine clearance. After the protocol eligibility criteria were amended, no further treatment-related AEs indicative of a decline in renal function greater than Grade I were reported.

Two non-renal DLTs also occurred. In Cohort 3 (180 mg/m^2), Grade III subcapsular hepatic haemorrhage led to discontinuation of study treatment in a patient with pre-existing coagulopathy and extensive hepatic metastases. In Cohort 4 (220 mg/m^2), Grade IV increased blood creatine phosphokinase (CPK) and was reported in one patient. The study was terminated early, without identifying an MTD, for several non-safety-related reasons, including subject recruitment challenges, limited antitumour activity, and increasing availability of alternative treatment options.

3.3. Safety

The most common AEs (occurring in ≥20% of patients) considered to be related to onalespib were diarrhoea (58%), nausea (50%), injection site events (46%), vomiting (39%), fatigue (27%), and muscle spasms (23%) (Table 2). Overall, 81% of patients reported one or more onalespib-related gastrointestinal (GI) disorders; other GI disorders reported in ≥5% of patients included dry mouth, abdominal distention, and dyspepsia. AEs reported as "ongoing" at the time of last assessment in ≥10% of subjects were diarrhoea (26.9%), fatigue (23.1%), muscle spasms (11.5%), anaemia (11.5%), hypokalaemia (11.5%), and decreased appetite (11.5%). For more information on injection site events, visual disturbances (23%), and systemic infusion reactions (19%), see Supplementary data.

The most common imatinib-related AEs (in ≥20% of patients) were diarrhoea (54%), nausea (50%), vomiting (39%), fatigue (27%), and muscle spasms (23%). Seven patients (27%) had one or more Grade III or IV AEs

Table 1
Patients' baseline characteristics.

Demographic characteristics[a]	Cohort 1, 180 mg/m^2 (N = 7)	Cohort 2, 150 mg/m^2 (N = 7)	Cohort 3, 180 mg/m^2 (N = 6)	Cohort 4, 220 mg/m^2 (N = 6)	Total (N = 26)
Age (years)					
Mean ± SD	61.0 ± 16.2	60.0 ± 4.2	56.0 ± 8.0	58.8 ± 10.3	59.1 ± 10.2
Median	64.0	60.0	56.0	53.0	58.5
Sex					
Females	4 (57.1)	1 (14.3)	0	2 (33.3)	7 (26.9)
Males	3 (42.9)	6 (85.7)	6 (100.0)	4 (66.7)	19 (73.1)
ECOG performance status					
0	4 (57.1)	5 (71.4)	0	5 (83.3)	14 (53.8)
1	3 (42.9)	2 (28.6)	6 (100.0)	1 (16.7)	12 (46.2)
Previous therapies					
Surgery	6 (85.7)	7 (100.0)	5 (83.3)	6 (100.0)	24 (92.3)
Chemotherapy	0	0	0	0	0
Radiotherapy	0	2 (28.6)	0	1 (16.7)	3 (11.5)
TKI therapy	7 (100.0)	7 (100.0)	6 (100.0)	6 (100.0)	26 (100.0)
Other therapies	0	0	0	0	0
Number of previous TKIs received[b]					
None	0	0	0	0	0
1	1 (14.3)	0	1 (16.6)	0	2 (76.3)
2	4 (57.1)	4 (57.1)	3 (50.0)	3 (50.0)	14 (53.4)
3	2 (28.6)	3 (42.3)	2 (33.3)	3 (50.0)	10 (38.5)

ECOG = Eastern Cooperative Oncology Group; SD = standard deviation; TKI = tyrosine kinase inhibitor.
[a] Unless noted otherwise, the values show the numbers and percentages (in parentheses) of patients.
[b] The number of different TKI agents that were previously received, not the number of TKI regimens received.

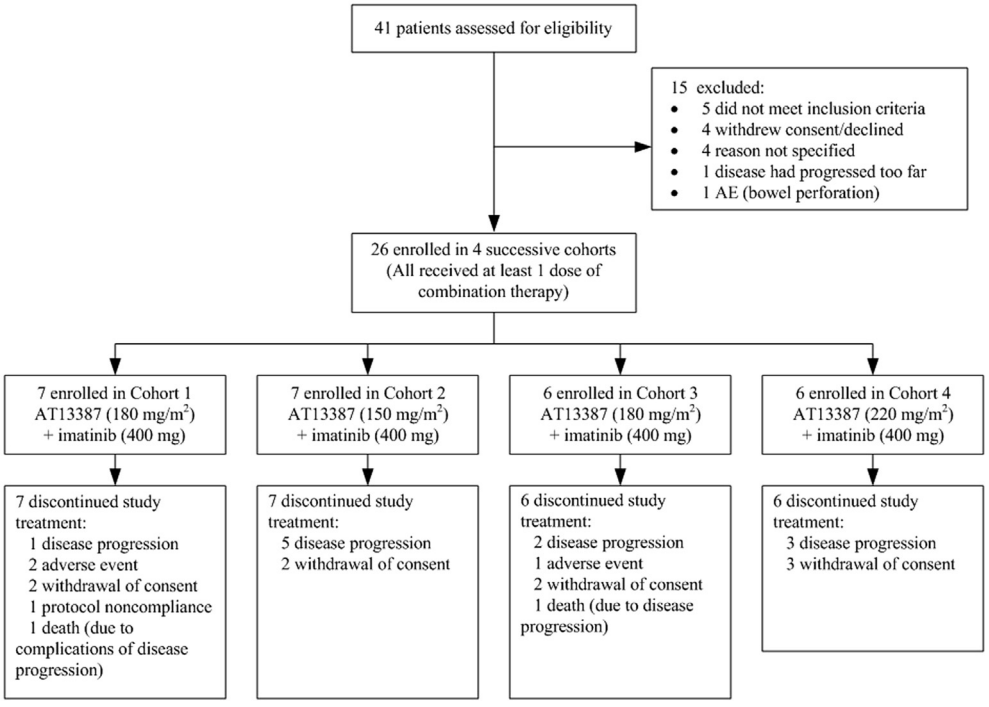

Fig. 1. Screening, enrolment, and disposition flow chart.

related to imatinib. The safety profile of imatinib in this study was similar to that reported in the prescribing information.

One patient died on study (31 d after the last infusion of onalespib in Cycle 5) as a result of a serious AE considered unrelated to study treatment (renal failure). Five patients died as a result of disease progression within 30 d after the last dose of onalespib or imatinib.

The majority of onalespib-related AEs were Grade I or II. Eight patients (31%) were reported to have one or more Grade III or IV AEs related to onalespib, including the following: anaemia (n = 4, 15%); increased blood CPK (n = 2, 8%); increased aspartate

Table 2
Summary of AEs related to onalespib treatment occurring in ≥10% of patients, n (%).

AE[a] MedDRA system organ class preferred term/grouped term	Cohort 1, 180 mg/m^2 (N = 7)	Cohort 2, 150 mg/m^2 (N = 7)	Cohort 3, 180 mg/m^2 (N = 6)	Cohort 4, 220 mg/m^2 (N = 6)	Total (N = 26)	CTCAE Grade III+IV AEs
GI disorders	6 (85.7)	5 (71.4)	5 (83.3)	5 (83.3)	21 (80.8)	
Diarrhoea	5 (71.4)	5 (71.4)	2 (33.3)	3 (50.0)	15 (57.7)	1 (3.8)
Nausea	3 (42.9)	4 (57.1)	2 (33.3)	4 (66.7)	13 (50.0)	0
Vomiting	3 (42.9)	2 (28.6)	4 (66.7)	1 (16.7)	10 (38.5)	0
Dry mouth	0	2 (28.6)	1 (16.7)	0	3 (11.5)	0
General disorders and administration site conditions	5 (71.4)	5 (71.4)	3 (50.0)	5 (83.3)	18 (69.2)	
Injection site events[b]	4 (57.1)	4 (57.1)	1 (16.7)	3 (50.0)	12 (46.2)	0
Fatigue	0	2 (28.6)	3 (50.0)	2 (33.3)	7 (26.9)	0
Systemic infusion reaction[b]	1 (14.3)	1 (14.3)	1 (16.7)	2 (33.3)	5 (19.2)	0
Oedema peripheral	1 (14.3)	0	1 (16.7)	1 (16.7)	3 (11.5)	0
Investigations	3 (42.9)	1 (14.3)	3 (50.0)	3 (50.0)	10 (38.5)	
ECG QT prolonged	1 (14.3)	1 (14.3)	0	2 (33.3)	4 (15.4)	0
AST increased	1 (14.3)	0	2 (33.3)	0	3 (11.5)	1 (3.8)
Metabolism and nutrition disorders	3 (42.9)	1 (14.3)	2 (33.3)	3 (50.0)	9 (34.6)	
Hypokalaemia	2 (28.6)	1 (14.3)	1 (16.7)	1 (16.7)	5 (19.2)	0
Decreased appetite	1 (14.3)	0	0	3 (50.0)	4 (15.4)	1 (3.8)
Hypomagnesaemia	1 (14.3)	1 (14.3)	1 (16.7)	1 (16.7)	4 (15.4)	0
Musculoskeletal and connective tissue disorders	2 (28.6)	2 (28.6)	1 (16.7)	4 (66.7)	9 (34.6)	
Muscle spasms	2 (28.6)	1 (14.3)	1 (16.7)	2 (33.3)	6 (23.1)	0
Psychiatric disorders	0	2 (28.6)	3 (50.0)	2 (33.3)	7 (26.9)	
Insomnia	0	2 (28.6)	2 (33.3)	1 (16.7)	5 (19.2)	0
Blood and lymphatic system disorders	2 (28.6)	0	2 (33.3)	2 (33.3)	6 (23.1)	
Anaemia	2 (28.6)	0	1 (16.7)	2 (33.3)	5 (19.2)	4 (15.4)
Nervous system disorders	2 (28.6)	2 (28.6)	1 (16.7)	1 (16.7)	6 (23.1)	
Headache	1 (14.3)	2 (28.6)	1 (16.7)	1 (16.7)	5 (19.2)	0
Eye disorders	2 (28.6)	2 (28.6)	1 (16.7)	1 (16.7)	6 (23.1)	
Visual disturbances[b]	2 (28.6)	1 (14.3)	0	0	3 (11.5)	0

AE = adverse event; AST = aspartate transaminase; ECG QT = electrocardiogram QT interval; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities.

[a] AEs considered possibly, probably, or definitely related to onalespib treatment.

[b] In this study, the group term 'injection site events' included the following specific AE preferred terms: infusion site extravasation, infusion site pain, injection site pain, and injection site reaction. The group term 'systemic infusion reaction' included flushing, hyperhidrosis, and infusion-related reactions, if they were definitely or possibly related to onalespib and occurred within 24 h of a dose. The group term 'visual disturbances' included photopsia, vision blurred, visual impairment, and vitreous floaters.

transaminase (AST), alanine transaminase (ALT), and bilirubin (n = 1 each); and decreased neutrophil count, coagulopathy, diarrhoea, abdominal pain, dehydration, decreased appetite, hyponatremia, myalgia, renal failure acute, subcapsular hepatic haemorrhage, and hypertension (n = 1 each).

Onalespib-related AEs leading to permanent discontinuation of study treatment were reported in four patients (15%): dehydration and acute renal failure (both in one patient), hepatic haemorrhage (in one patient), blood CPK increased (in one patient), and blood creatinine increased (in one patient). Additionally, in nine patients (35%), one or more doses of onalespib were omitted, interrupted, or reduced, predominantly due to AEs (although not all attributable to onalespib). Infusion interruption in three patients and dose reduction in one patient were due to injection site events.

Overall, no clinically significant or treatment-related trends were observed in clinical laboratory assessments. The most common laboratory parameters reported as treatment-related AEs were anaemia (five patients, four cases Grade III), hypokalaemia (five patients, all Grade I or II), and hypomagnesaemia (four patients, all Grade I or II). Six subjects (23%) had one or more onalespib-related laboratory AEs that were ongoing at the end of the study, all of which were Grade I or II; most were considered to be related to imatinib. For further discussion of laboratory values reported as treatment-related AEs, see Supplementary data and Table S1.

Effects on liver function were mild and unrelated to onalespib, with the exception of one patient in Cohort 3 who had Grade IV AEs of elevated ALT (23× upper limit of normal [ULN]) and AST (33× ULN) on study day 9. These events were likely related to ongoing Grade III subcapsular hepatic haemorrhage, which resolved with sequelae in 84 d.

Central analysis of cardiac repolarisation (Fridericia-corrected QT interval [QTcF] duration) in this small sample revealed no clinically significant prolongation.

3.4. PK analyses

The exposure of onalespib increased in a dose-proportional manner over the dosing range of 150–220 mg/m^2 per dose following once-weekly i.v. infusion (see Supplementary data Table S2, and Fig. S1) and is consistent with the experience from the phase I single-agent study [16]. There was no evidence of an effect of imatinib on onalespib elimination.

3.5. Antitumour activity

Based on the investigators' response assessments, disease control at 4 months was achieved in five patients (19.2%, 95% CI 6.6–39.4) and at 6 months in three patients (11.5%, 95% CI 2.4–30.2). Median progression-free survival (PFS) was 112 d (95% CI 43–165) and median overall survival was 184 d (lower 95% CI 141, upper 95% CI unknown).

One patient (3.8%, 95% CI 0.1–19.6) exhibited a partial response that was ongoing when the patient withdrew from the study after 376 d. Nine patients (34.6%) had a best response of stable disease, which in one case lasted for approximately 10 months (303 d). Nine patients (34.6%) had disease progression as best response, and seven (26.9%) were not evaluable. For patients with measurable disease, each patient's best percentage change in tumour size is shown in Fig. 2.

3.6. Relationship of antitumour activity to KIT and PDGFRA mutational status

The *KIT* and *PDGFRA* mutational status of the target tumour was determined for 23 of the 26 patients. Biopsies for genotyping were obtained from two patients during the study screening process. For the remainder of the patients (>90%), mutation data were obtained either from patient records or from genotyping performed on archived biopsies that had been obtained up to 12.5 years (median, ~5 years) prior to the subjects' entry into the study.

Fourteen of 23 patients (62%) had tumours with only primary mutations in *KIT* exons 9 or 11 (data not shown). Six of these 14 patients (43%) had a best response of stable disease (range 94–182 d); five subjects were non-evaluable and three subjects had progressive disease. The majority (>75%) of the biopsies were collected ≥2 years prior to first dose of onalespib; so, these patients could have acquired additional mutations prior to the start of the study.

Five of 23 patients (22%) had tumours with *KIT* mutations associated with imatinib or sunitinib resistance [4,20]; two of these five patients had a best response of stable disease (89 and 165 d, respectively) (Table 3). One of 23 patients (4%) had a tumour with a deletion in exon 18 of the activation loop of PDGRFA (DIMH 842-845), which is associated with sensitivity to

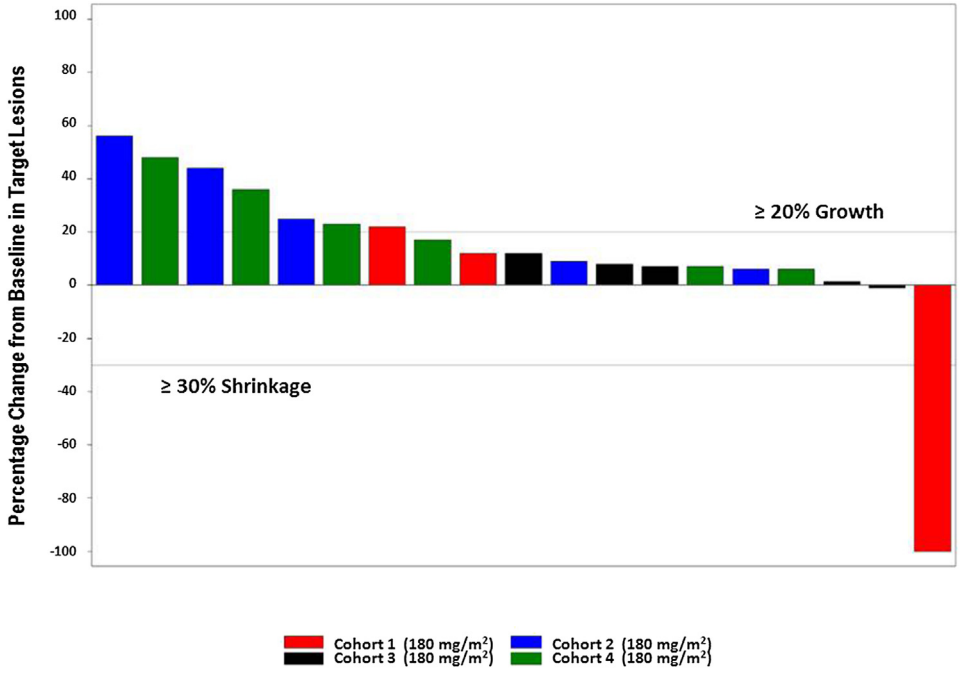

Fig. 2. Best percentage change in tumour size from baseline, based on target lesion assessments by investigator. Each bar in the waterfall plot represents, for a given patient, either (a) the largest percentage 'decrease' in tumour size from baseline (if there was any tumour shrinkage) or (b) the smallest percentage 'increase' in tumour size from baseline (if there was no tumour shrinkage), at any time point. The largest percentage decrease in tumour size was observed in a patient who received 14 cycles of study treatment; this patient was determined to have an objective (partial) response. One patient received ten cycles of study treatment and one patient received six cycles; for both of these patients, the best overall response was stable disease. All other patients received five or less cycles.

Table 3
KIT or PDGFRA mutation status of GIST and best response to combination therapy.

Patient	Type of *KIT* or *PDGFRA* mutation, if any	Time elapsed since tumour biopsied for genotyping	Previous TKI therapy(ies)	Overall disease assessment: best response (duration)
KIT mutations associated with resistance to imatinib or sunitinib				
107201	Exon 13 V654A	4 years	Regorafenib, imatinib, sunitinib,	Disease progression
108305	Exon 17 D816E	4 months	Imatinib, sunitinib	Stable disease (165 d)
107401	Exon 13 V654A	3.5 years	Imatinib, sunitinib, sorafenib	Disease progression
105404	Exon 17 D820E	<1 month (new/current biopsy)	Imatinib, sunitinib, sorafenib	Disease progression
107405	Exon 17 ND 819 and 820, exon 13 V654A	9 months	Imatinib, sunitinib	Stable disease (89 d)
PDGFRA mutations				
106102	Exon 18 deletion DIMH 842-845	5.5 years	Imatinib, sunitinib	Partial response (376 d)[a]
Wild-type for *KIT* and *PDGFRA*				
102105	None	8.5 years	Imatinib, sunitinib, nilotinib	Not assessed
103303	None	4.5 years	Imatinib, sunitinib	Stable disease (303 d)
103406	None	8 months	Imatinib, sunitinib	Disease progression

GIST = gastrointestinal stromal tumours; TKI = tyrosine kinase inhibitor.
Notes: The 14 patients whose GIST had only primary KIT mutations at the time of biopsy were not included. Six of the 14 patients had a best response of stable disease; the other patients either were not assessed or had disease progression. All five patients who had KIT mutations associated with resistance to imatinib or sunitinib also had a primary mutation in KIT exon 11.
[a] Ongoing at last patient contact, when patient withdrew consent.

imatinib [2]. This patient was the only one to have a partial response to combination therapy in this study. Finally, one of the three patients who had tumours without identifiable mutations in *KIT* or *PDGFRA* had stable disease for 303 d.

4. Discussion

Treatment with the combination of onalespib plus imatinib was generally well tolerated, and the safety profile was consistent with published reports of patients treated with onalespib and imatinib as monotherapies. The MTD of onalespib in combination therapy was not defined, as the study was terminated early due to insufficient efficacy and other non-safety-related reasons after Cohort 4 (220 mg/m^2) was complete. For comparison, 260 mg/m^2 was the recommended phase 2 dose for onalespib monotherapy using a similar dosing regimen (once-weekly i.v. administration [16]).

Antitumour activity was limited with study drugs as dosed in this study, with a single partial response (3.8%, 95% CI 0.1–19.6). The median PFS in this study (~3.5 months) compared favourably with the median PFS (1.8 months) recently reported in a study of patients with TKI-resistant metastatic GIST who resumed treatment with imatinib monotherapy [17]. While the results may be viewed as encouraging, it is not possible to make a definitive conclusion about efficacy from this small exploratory study. The occurrence of stable disease in two patients with *KIT* mutations associated with resistance to imatinib or sunitinib and prolonged disease stabilisation in one of three patients with no identifiable activating mutations is consistent with a potentially better outcome than seen with other investigational agents in a proportion of patients with GIST with biologically unfavorable characteristics (reviewed in 20). Interpretation of the genotyping results is confounded by the fact that the majority of the tumour biopsy samples were collected several years prior to the initiation of study dosing with onalespib plus imatinib.

5. Conclusions

The MTD of onalespib in combination with standard dose imatinib was not reached, as the study was closed early. The highest dose of onalespib that was safely administered in combination with imatinib in patients with baseline normal renal function was 220 mg/m^2 once weekly for 3 weeks of every 4-week cycle. Treatment with the combination of onalespib and imatinib was well tolerated, and treatment-related toxicities were consistent with those previously reported following single-agent therapy with either imatinib or onalespib. The appearance of renal toxicity following a relatively low dose of onalespib was unexpected, but may have been due to pre-existing renal impairment or vascular disease. In this exploratory dose-finding study, combination therapy achieved limited efficacy in TKI-resistant GIST.

Role of the funding source

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Conflict of interest statement

RFR, CLC, GDD, MCH, and MA report a financial relationship with Novartis. In addition, RFR reports a financial relationship with Glaxo SmithKline and EMD Serono; GDD reports a financial relationship with Bayer, Pfizer, Ariad, Astra-Zeneca, Kolltan Pharmaceuticals, and Blueprint Medicines; MCH reports a financial relationship with Ariad, Molecular MD, Astex, Blueprint Medicines, and Pfizer. MY is a consultant to Astex. AO, JL, and HK are employees of Astex Pharmaceuticals. All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.03.076.

References

[1] Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472–80.
[2] Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342–9.
[3] Chen LL, Trent JC, Wu EF, Fuller GN, Ramdas L, Zhang W, et al. A missense mutation in KIT kinase domain 1 correlates with imatinib resistance in gastrointestinal stromal tumors. Cancer Res 2004;64:5913–9.
[4] Gramza AW, Corless CL, Heinrich MC. Resistance to tyrosine kinase inhibitors in gastrointestinal stromal tumors. Clin Cancer Res 2009;15:7510–8.
[5] Solit DB, Rosen N. Hsp90: a novel target for cancer therapy. Curr Top Med Chem 2006;6:1205–14.
[6] Fumo G, Akin C, Metcalfe DD, Neckers L. 17-Allylamino-17-demethoxygeldanamycin (17-AAG) is effective in down-regulating mutated, constitutively activated KIT protein in human mast cells. Blood 2004;103:1078–84.
[7] Bauer S, Yu LK, Demetri GD, Fletcher JA. Heat shock protein 90 inhibition in imatinib-resistant gastrointestinal stromal tumor. Cancer Res 2006;66:9153–61.
[8] Dewaele B, Wasag B, Cools J, Sciot R, Prenen H, Vandenberghe P, et al. Activity of dasatinib, a dual SRC/ABL kinase inhibitor, and IPI-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor-associated PDGFRAD842V mutation. Clin Cancer Res 2008;14:5749–58.
[9] Floris G, Sciot R, Wozniak A, Van Looy T, Wellens J, Faa G, et al. The novel heat shock protein 90 inhibitor, IPI-493, is highly effective in human gastrostrointestinal stromal tumor (GIST) xenografts carrying heterogeneous KIT mutations. Clin Cancer Res 2011;17:5604–14.
[10] Floris G, Debiec-Rychter M, Wozniak A, Stefan C, Normant E, Faa G, et al. The heat shock protein 90 inhibitor IPI-504 induces KIT degradation, tumor shrinkage and cell proliferation arrest in xenografts models of gastrointestinal stromal tumors. Mol Cancer Ther 2011;10:1897–908.
[11] Smyth T, Van Looy T, Curry JE, Rodriguez-Lopez AM, Wozniak A, Zhu M, et al. The HSP90 inhibitor, AT13387, is effective against imatinib-sensitive and -resistant gastrointestinal stromal tumor models. Mol Cancer Ther 2012;11:1799–808.
[12] Wagner AJ, Chugh R, Rosen LS, Morgan JA, George S, Gordon M, et al. A phase I study of the HSP90 inhibitor retaspimycin hydrochloride (IPI-504) in patients with gastrointestinal stromal tumors or soft tissue sarcomas. Clin Can Res 2013;19:6020–9.
[13] Dickson MA, Okuno SH, Keohan ML, Maki RG, D'Adamo DR, Akhurst TJ, et al. Phase II study of the HSP90 inhibitor BIIB021 in gastrointestinal stromal tumors. Ann Oncol 2013;24:252–7.
[14] Woodhead AJ, Angove H, Carr MG, Chessari G, Congreve M, Coyle JE, et al. Discovery of (2,4-dihydroxy-5-isopropylphenyl)-[5-(4-methylpiperazin-1-ylmethyl)-1,3-dihydroisoindol-2-yl]methanone (AT13387), a novel inhibitor of the molecular chaperone Hsp90 by fragment based drug design. J Med Chem 2010;53:5956–69.
[15] Graham B, Curry J, Smyth T, Fazal L, Feltell R, Harada I, et al. The heat shock protein 90 inhibitor, AT13387, displays a long duration of action in vitro and in vivo in non-small cell lung cancer. Cancer Sci 2012;103:522–7.
[16] Shapiro GI, Kwak E, Dezube BJ, Yule M, Ayrton J, Lyons J, et al. First-in-human phase 1 dose-escalation study of a second-generation non-ansamycin HSP90 inhibitor, AT13387, in patients with advanced solid tumors. Clin Cancer Res 2015;21:87–97.
[17] Kang YK, Ryu MH, Yoo C, Ryoo BY, Kim HJ, Lee JJ, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2013;14:1175–82.
[18] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
[19] Corless CL, Ballman KV, Antonescu CR, Kolesnikova V, Maki RG, Pisters PW, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol 2014;32:1563–70.
[20] Maleddu AR, Pantaleo MA, Nannini M, Di Battista M, Saponara M, Lolli C, et al. Mechanisms of secondary resistance to tyrosine kinase inhibitors in gastrointestinal tumours (review). Oncol Rep 2009;21:1359–66.