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Sitravatinib in patients with solid tumors selected by molecular alterations: results from a Phase Ib study

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ABSTRACT

Aim: We report clinical activity and safety of sitravatinib in patients with advanced cancer from basket cohorts with specific molecular alterations, in a Phase Ib study.

Materials & methods: Patients with advanced solid tumors harboring amplification, mutation, or rearrangement of *MET*, *AXL*, *RET*, *NTRK*, *DDR2*, *KDR*, *PDGFRA*, *KIT* or *CBL* received sitravatinib once daily. Primary end point was confirmed objective response rate (ORR).

Results: In total, 113 patients were enrolled following a median of 3 (range 1–18) prior systemic regimens. Altered *RET* (n = 31), *CBL* (n = 31) and *MET* (n = 17) were most frequent cohorts. Overall, 68.9% had reduced tumor volume and most (61.5%) had a best objective response of stable disease. ORR was highest in patients with *RET*-rearranged non-small cell lung cancer (21.1%) but did not differ significantly from the null hypothesis (ORR $\leq$15%; $p = 0.316$). Median progression-free survival and overall survival (5.7 and 24.2 months, respectively) were also longest in the *RET*-rearranged non-small cell lung cancer cohort. Diarrhea (61.1%), fatigue (50.4%) and hypertension (46.9%) were the most frequent treatment-emergent adverse events. Most treatment-emergent adverse events were mild-to-moderate in severity. The study closed before the planned number of patients were enrolled in all cohorts.

Conclusion: Sitravatinib had a manageable safety profile with modest signals of clinical activity in patients with molecularly selected solid tumors.

Clinical trial registration: www.clinicaltrials.gov identifier is NCT02219711

PLAIN LANGUAGE SUMMARY

We report findings from a clinical study of sitravatinib which included patients with cancer that could not be removed by surgery or had spread to other parts of the body. The tumors of these patients contained specific molecular changes in one of the following genes: *MET*, *AXL*, *RET*, *NTRK*, *DDR2*, *KDR*, *PDGFRA*, *KIT* or *CBL*. All patients received treatment with sitravatinib once a day. Change in tumor size over time was assessed to see how effective treatment with sitravatinib was.

In total, 113 patients joined the study. Most patients had already received a median of three different types of medicines for their cancer (and up to 18 different types of anticancer medicines). Most patients had tumors that contained alterations in *RET*, *CBL* or *MET* genes.

During the study, the percentage of patients who had a decrease in the tumor size was highest in the group with non-small cell lung cancer that contained an altered *RET* gene (21.1%). However, this level of response to sitravatinib was not considered high enough to be medically important.

The most common side effects during the study were diarrhea (61.1%), fatigue (50.4%) and high blood pressure (46.9%). Most side effects were mild or moderate in severity. The study provided the

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opportunity to assess sitravatinib as a treatment for cancers with specific gene mutations that are uncommon; the study closed before the planned number of patients were enrolled.
In conclusion, the side effects seen in patients who received sitravatinib were manageable. Signals of how well sitravatinib worked were modest in patients with cancer that had spread to other parts of the body and contained specific molecular changes.

1. Introduction

Receptor tyrosine kinases (RTK) play a key role in regulating numerous key cellular processes including proliferation, differentiation and migration through a variety of interconnected signaling pathways [1,2]. Molecular alterations such as gain-of-function mutations, genomic amplification and chromosomal rearrangement can lead to aberrant RTK downstream signaling that is not subject to normal 'checks and balances'. Indeed, constitutive RTK activation disrupts the balance between cell proliferation and death, and can trigger oncogenesis [1]. RTK inhibitors are central for the treatment of numerous cancer types with hallmark of dysregulated RTK signaling. However, apart from rare exceptions, cancer is not cured by treatment with a single RTK inhibitor, due in part to emerging resistance mechanisms [3]. Consequently, new treatment approaches are needed.

Sitravatinib (MGCD516) is an oral small molecule inhibitor that targets a spectrum of closely related RTKs implicated in oncogenesis, predominantly TAM family (TYRO3, AXL, MERTK) and split family (VEGFR2, MET, RET, KIT) receptors [4,5]. Sitravatinib demonstrated antiproliferative effects in several cancer cell lines and was a potent suppressor of tumor growth in xenograft models of tumors with RTK dysfunction [5–7]. The first-in-human study of sitravatinib evaluated pharmacokinetics (steady absorption supported once-daily administration) and dosing in patients with advanced solid tumors [4]. Safety and clinical activity were further assessed in Phase Ib expansion cohorts that enrolled patients with advanced, refractory tumors of selected histologic diagnoses (clear cell renal cell carcinoma or castrate-resistant prostate cancer with bone metastases) or molecular alterations relevant to the mechanism of sitravatinib; the latter utilized a basket study approach.

Use of basket trials in oncology settings has gained momentum. This approach is based on the drive for precision oncology to ensure patients receive treatment based on the molecular signature of their disease, and to overcome the recruitment challenges of prospective studies in settings of rare genetic alterations [8,9]. Simultaneously enrolling patients with a variety of tumor types containing specific target gene alterations enables signals of clinical activity to be identified as they are observed across multiple indications, with potential to further investigate signals of clinical activity in expansion cohorts [8]. While most basket trials are exploratory, this approach has resulted in approval of a limited number of cancer treatments. For example, larotrectinib was approved for solid tumors with *NTRK* gene fusions based in part on data from the SCOUT and NAVIGATE basket trials [10,11].

A basket-cohort approach was selected for the Phase Ib portion of the first-in-human sitravatinib clinical trial to facilitate enrollment of patients with tumors harboring molecular alterations relevant to the mechanism of action of sitravatinib. This included gene alterations in the targets of sitravatinib such as *MET*, *RET* and *AXL*, as well as amplification of chromosomal segment 4q12 (Chr4q12) which encodes several relevant oncogenic driver RTKs including *KIT*, *PDGFRA* and *KDR* [12]. Loss of function alterations in *CBL* were also included. *CBL* encodes E3-ubiquitin ligase which facilitates the degradation of several RTKs implicated in carcinogenesis, including targets of sitravatinib [13–15]. Consequently, inactivation of *CBL* was postulated to lead to increased RTK density and signaling, thereby contributing to oncogenesis.

We report clinical activity and safety with sitravatinib in patients with solid tumors harboring genetic alterations relevant to the mechanism of action of sitravatinib, who participated in the Phase Ib basket study cohorts of the first-in-human study.

2. Materials & methods

2.1. Study design

This open-label, Phase I/Ib clinical trial (NCT02219711, 14 August 2014) included periods evaluating the pharmacokinetics (lead-in period), dosing (Phase I), and clinical activity (Phase Ib) of sitravatinib. Details of the study design have been reported [4]. Enrollment into the Phase Ib cohorts was based on a histologic diagnosis of renal cell carcinoma or castrate-resistant prostate cancer (reported separately) or by selected molecular alterations relevant for sitravatinib mechanism of action irrespective of histologic diagnosis (detailed below).

Patients in the Phase Ib portion of the study received sitravatinib at the maximum-tolerated dose established in the Phase I cohort: 150 mg/day [4]. During the study, the starting dose was reduced to 120 mg/day following evaluation of cumulative safety and tolerability data.

Dose reductions and interruptions were permitted for adverse events (AEs) assessed by the study investigators as related to study medication, and study treatment was continued at the discretion of the investigator until disease progression, unacceptable toxicity or withdrawal of consent.

2.2. Study population

Eligible patients were ≥18 years and had advanced, unresectable, or metastatic solid tumors for which standard treatment was not available. Patients also had a life expectancy of ≥3 months and Eastern Cooperative Oncology Group (ECOG) performance status 0–2. There were no restrictions on the number of prior lines of therapy, and prior treatment with specific therapies targeting molecular markers of interest were permitted on a case-by-case basis. Patients had not received anticancer therapy for ≥2 weeks prior to their first dose of study treatment and had recovered from any AEs to baseline or Grade 1 (except for alopecia). Patients were excluded with unacceptable hepatic, renal and bone marrow function, symptomatic or uncontrolled brain metastases, or significant cardiac abnormalities within the prior 6 months. Other exclusion criteria included prolonged QTc interval (>480 ms), left ventricular ejection fraction <40%, uncontrolled arterial hypertension, another active cancer (excluding basal cell carcinoma or cervical intraepithelial neoplasia), and major surgery ≤4 weeks before the first dose of study medication.

Patients with tumors harboring amplification, mutation, or rearrangement of *MET*, *AXL*, *RET*, *NTRK*, *DDR2*, *KDR*, *PDGFRA*, *KIT* or *CBL* were enrolled into an overall basket cohort as they were identified (amplifications of *MET*, *Chr4q12* and *AXL* were defined as *MET*: chromosome 7 centromere [CEP7] ratio ≥5:1, *KIT*:CEP7 ratio of 5:1, and *AXL* ≥8 copies, respectively). Molecular alterations were identified in tumor tissue or ctDNA using quantitative RT-PCR (*MET* exon 14 skipping mutations), fluorescence *in situ* hybridization (*RET* rearrangements and *MET* amplification) and next-generation sequencing (any genetic alterations). Tumor samples were required for retrospective central laboratory confirmation if molecular eligibility was established locally.

While sufficient patients with *RET* alterations were required to evaluate the clinical activity of sitravatinib, the feasibility of enrolling enough individuals with other relatively rare gene alterations into potential dedicated molecular cohorts within a reasonable timeframe was taken into consideration. Populations of interest emerged from the basket cohort as clinical activity signals were observed in clusters of patients with unifying targeted gene alterations (with or without a specific histologic diagnosis).

2.3. Study objectives & assessments

The primary objective in the Phase Ib molecular cohorts was to assess the clinical activity and safety of sitravatinib. Confirmed objective response rate (ORR), the primary efficacy end point, was assessed in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Scans (computed tomography or magnetic resonance imaging) of known or suspected disease sites were obtained at baseline and at 6-week intervals during the study. Duration of response, progression-free survival (PFS) and overall survival (OS) were also assessed. Treatment-emergent adverse events (TEAEs) were graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. Additional safety assessments included clinical laboratory parameters, physical examinations, vital sign, electrocardiogram and left ventricular ejection fraction measurements.

2.4. Statistical analysis

A two-stage Simon optimal design was used to identify specific molecular alterations for further study. If an objective response was seen in ≥2 of eight patients with the same molecular alteration (or a subgroup with the same histologic diagnosis and molecular alteration), an additional 16 patients were enrolled. Further cohort expansion was permitted if objective responses were seen in ≥7 of these 24 patients.

Summaries of ORR and corresponding 95% CI were calculated using the binomial proportions confidence interval method. Exact test for single proportion (one-sided alpha = 2.5%) tested the alternative hypothesis of ORR >15% (null hypothesis of ORR ≤15%).

Duration of response (time from first documentation of completed response [CR] or partial response [PR]) to disease progression [PD] per RECIST v1.1, or death due to any cause), PFS (time from first dose of study medication to PD or death due to any cause]) and OS (time from first dose of study medication to death due to any cause) were estimated using Kaplan–Meier methodology. Other data were summarized using descriptive statistics.

Response was assessed in the clinical activity evaluable population which included patients who received ≥1 cycle of therapy at ≥80% of assigned dose and had ≥1 on-study disease assessment. Other clinical activity assessments and safety were evaluated in the modified intent-to-treat population which comprised patients who

received ≥1 dose of study medication. The primary data cut-off was 31 July 2020. Data from patients who remained on treatment (n = 2 in *AXL* cohort) and long-term follow-up are included up to 10 October 2022.

3. Results

3.1. Patient characteristics

Genetic testing data were available for 639 of 734 patients screened between 27 August 2014 and 5 February 2020. Overall, 113 of 152 patients with qualifying genetic alterations were enrolled into distinct molecular cohorts.

Thirty-one patients had *RET* alterations in any tumor type. This cohort included a subgroup with non-small cell lung cancer (NSCLC) and any *RET* rearrangement (n = 23) which included fusion partners *KIF5B* (n = 13), *CCDC6* (n = 3), DSP (n = 1) and not specified (n = 6). Thirty-one patients were also enrolled into the *CBL* alteration cohort which included missense mutations (n = 25), indel (n = 5), or splice site mutation (n = 1) resulting in CBL inactivation. The *MET* altered cohort included patients (n = 17) with tumors harboring *MET* exon 14 skipping (n = 9), *MET* amplification (n = 4), *MET* point mutations D1246H (n = 1), R988C (n = 1), R988C with *MET* amplification (n = 1) and MET overexpression (n = 1). Sixteen and seven participants were enrolled with amplification of chromosome segment 4q (Chr4q) and *AXL* amplification, respectively. The cohort with other molecular alterations (n = 11) included changes that involved *KIT* (n = 5), *KDR* (n = 3), *NTRK* (n = 2), or *DDR2* (n = 1); one patient with both Chr4q amplification and *KIT* alteration was included in the Chr4q amplification cohort.

Across the cohorts, patients had a median age of 66 (range 36–87) years and NSCLC was the most frequent histologic diagnosis (46.9%). In general, participants were heavily pretreated, having received a median of 3 (range 1–18) prior systemic regimens and over half had received prior radiotherapy (54.0%). Baseline demographic and disease characteristics were broadly balanced across the molecular alteration cohorts (Table 1). Prior RET inhibitor treatment was reported in three patients with medullary (neuroendocrine) thyroid cancer and prior MET inhibitor treatment was reported in two patients with NSCLC in the *RET* alteration and *MET* alteration cohorts, respectively.

Across all patients, the most frequent reasons for study discontinuation were death (71.7%, n = 81) and withdrawal of consent (16.8%, n = 19). Objective disease progression (50.4%, n = 57), AEs (16.8%, n = 19) and withdrawal of consent (14.2%, n = 16) were the most frequent reasons for discontinuing study treatment. Reasons for discontinuation from the study and study treatment were balanced across the molecular cohorts (Figure 1).

3.2. Antitumor activity

Across the molecular alteration cohorts, 68.9% (51 of 74 with evaluable data) of patients experienced reductions in tumor volume, which were particularly pronounced in some individuals with *RET* alterations (Figure 2). Confirmed ORRs did not differ significantly from the null hypothesis in any cohort (Table 2). In the *RET* altered cohort, ORR was 19.2% (five of 26 evaluable patients achieved PR). Four of five PRs were seen in patients with NSCLC and *RET* rearrangement (lung adenocarcinoma with *RET* alteration not specified [n = 2], *CCDC6-RET* rearrangement [n = 1], *KIF5B-RET* rearrangement [n = 1]) and one PR occurred in a patient with hormone receptor (HR)-positive breast adenocarcinoma with *RET* C634R. Duration of responses ranged from 1.8 to 10.2 months with a Kaplan–Meier estimate of 40.0% (95% CI: 5.2–75.3) for ongoing response at 6 months. Maximum reported change in target lesion ranged from -34.1 to -100% in responders (Figure 2A). SD occurred in 61.5% (16/26 evaluable patients), including one patient with unconfirmed response and maximum target lesion change of -36.7%. Of note, SD (maximum target lesion change -24.5% lasting 5.3 months) was reported in one of three patients enrolled with medullary or neuroendocrine thyroid cancer and *RET* activating mutations, who were previously treated with ≥2 RET inhibitors.

In the *MET* alteration cohort confirmed ORR was 15.4% with PR reported in 2/13 evaluable patients (NSCLC with MET overexpression [n = 1] and *MET* exon 14 skipping [n = 1]). While nine of 11 evaluable patients experienced some reduction in tumor volume, maximum target lesion change was -41.6 and -49.4% in the responders (Figure 2B). Duration of response was 3.0 months in one patient and the second was censored at 5.6 months. Most patients in the *MET* alteration cohort achieved SD (76.9%, n = 10/13 evaluable patients) including n = 2 (both with *MET* exon 14 skipping alterations) with unconfirmed response and maximum target lesion changes of -34.8 and -50.0%.

There were no objective responses in the Chr4q12 amplification cohort, with most patients having SD (81.8%; 9/11 evaluable patients [Figure 2C]). In 18 evaluable patients with *CBL* alteration 44.4% (n = 8) had SD and the was one PR (ORR 5.6%) which lasted 14.2 months and occurred in an individual with sinonasal melanoma and *CBL* Y368C. Maximum target lesion change was -50.5% (Figure 2D). One additional PR which lasted 4.3 months (maximum target lesion change -77.4%) was observed in a patient with NSCLC and *CBL* C384R who received

Table 1. Demographic and disease characteristics of the molecular alteration cohorts (modified intent-to-treat population).

n (%)	All patients (N = 113)	*RET* alteration			*MET* alteration (N = 17)	Chr4q12 amplification[b] (N = 16)	*CBL* alteration (N = 31)	*AXL* amplification (N = 7)	Other (N = 11)
		Overall *RET* cohort (N = 31)	NSCLC and *RET* rearrangement[a]						
			All patients (N = 23)	*KIF5B-RET* (N = 13)					
Median age (range), years	66 (36–87)	62 (45–81)	62 (45–71)	58 (46–71)	70 (36–81)	67 (50–77)	69 (44–87)	65 (43–74)	68 (49–79)
Male	47 (41.6)	12 (38.7)	9 (39.1)	4 (30.8)	6 (35.3)	7 (43.8)	14 (45.2)	3 (42.9)	5 (45.5)
Ethnicity									
White	78 (69.0)	16 (51.6)	10 (43.5)	4 (30.8)	13 (76.5)	9 (56.3)	25 (80.6)	6 (85.7)	9 (81.8))
African American	8 (7.1)	2 (6.5)	2 (8.7)	1 (7.7)	2 (11.8)	3 (18.8)	1 (3.2)	0	0
Asian	21 (18.6)	10 (32.3)	9 (39.1)	6 (46.2)	2 (11.8)	4 (25.0)	3 (9.7)	1 (14.3)	1 (9.1)
Other	6 (5.3)	3 (9.7)	2 (8.7)	2 (15.4)	0	0	2 (6.5)	0	1 (9.1)
Primary diagnosis									
Head and neck cancer	2 (1.8)	0	0	0	0	1 (6.3)	0	1 (14.3)	0
Hormone-refractory prostate cancer	3 (2.7)	0	0	0	1 (5.9)	1 (6.3)	1 (3.2)	0	0
NSCLC	53 (46.9)	24 (77.4)	23 (100)	13 (100)	12 (70.6)[c]	4 (25.9)	10 (32.3)	1 (14.3)	2 (18.2)
Breast cancer	4 (3.5)	2 (6.5)	0	0	0	1 (6.3)	1 (3.2)[e]	0	0
Colon/rectal cancer	7 (6.2)	1 (3.2)	0	0	2 (11.8)	0	3 (9.7)	0	1 (9.1)
Melanoma	10 (8.8)	0	0	0	0	3 (18.8)	5 (16.1)	0	2 (18.2)
Soft tissue sarcoma	7 (6.2)	0	0	0	0	1 (6.3)	4 (12.9)[e]	0	2 (18.2)
Other	29 (25.7)	4 (12.9)[d]	0	0	3 (17.6)	5 (31.3)	8 (2.6)	5 (71.4)	4 (36.4)
ECOG performance score									
0	33 (29.2)	9 (29.0)	8 (34.8)	5 (38.5)	2 (11.8)	3 (18.8)	11 (35.5)	4 (57.1)	4 (36.4)
1	70 (61.9)	17 (54.8)	11 (47.8)	6 (46.2)	15 (88.2)	12 (75.0)	16 (51.6)	3 (42.9)	7 (63.6)
2	10 (8.8)	5 (16.1)	4 (17.4)	2 (15.4)	0	1 (6.3)	4 (12.9)	0	0
Prior surgery	70 (61.9)	16 (51.6)	10 (43.5)	7 (53.8)	8 (47.1)	10 (62.5)	20 (64.5)	7 (100)	9 (81.8)
Prior radiotherapy	61 (54.0)	21 (67.7)	14 (60.9)	9 (69.2)	9 (52.9)	13 (81.3)	14 (45.2)	1 (14.3)	3 (27.3)
Prior systemic therapy	101 (89.4)	30 (96.8)	22 (95.7)	13 (100)	14 (82.4)	15 (93.8)	26 (83.9)	5 (71.4)	11 (100)
Median (range) number of prior regimens	3 (1–18)	3 (1–11)[f]	2 (1–6)	3 (1–4)	3 (1–9)[g]	3 (1–18)	3 (1–6)	4 (2–5)	3 (1–7)

[a]Includes patients with NSCLC and *RET* fusion partner *KIF5B*, *CCDC6*, *DSP* or not specified.
[b]Includes one patient with Chr4q12 amplification and *KIT* alteration.
[c]One patient had concurrent NSCLC and renal cell carcinoma.
[d]Includes three patients with thyroid cancer.
[e]One patient had two primary diagnoses (soft tissue sarcoma and breast cancer).
[f]Prior treatment with ≥2 RET inhibitors (vandetanib, cabozantinib and lenvatinib) was reported in three patients with thyroid cancer.
[g]Prior treatment with a MET inhibitor (crizotinib and/or salvolitinib) was reported in two patients with NSCLC.
ECOG: Eastern Cooperative Oncology Group; NSCLC: Non-small cell lung cancer.

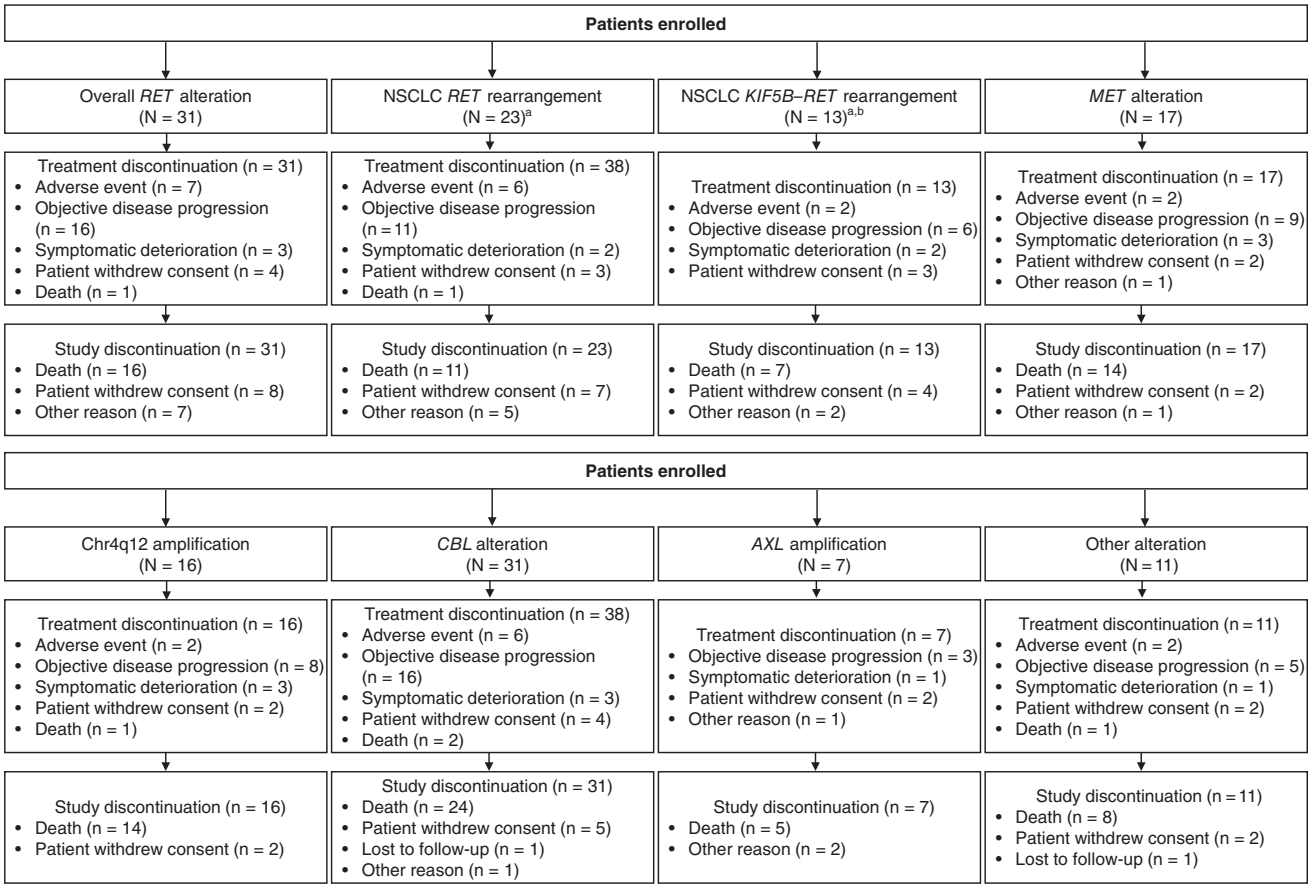


Figure 1. Disposition of patients enrolled in the molecular alteration basket cohorts (modified intent-to-treat population).
[a]Subgroup of 'Overall *RET* alteration' cohort;
[b]Subgroup of 'Overall *RET* alteration' and 'NSCLC *RET* rearrangement' cohorts.

a total dose <80% in Cycle 1; while this patient did not qualify for the clinical activity evaluable population, they received sufficient study treatment overall to be considered clinically evaluable.

In the *AXL* amplification cohort, PR lasting 3.1 months was seen in 1/6 evaluable patients (ORR 16.7%, Table 2) and occurred in a patient with bladder adenocarcinoma who had a maximum target lesion change of -32.1% (Figure 2E). Most patients (66.7%) had SD, including an individual with NSCLC who had achieved PR of approximately 3.6 years in a prior glesatinib clinical trial and was progression free at study completion. The patient then enrolled into the current study with two non-target lung lesions and remained progression free at last on-study assessment (prolonged SD >2 years 1 month [followed for 776 days]) and continues to be progression free following enrolment into an ongoing sitravatinib rollover study (2.4 years; ongoing disease control for ~8 years). In the cohort comprising patients with other relevant molecular alterations ORR was 12.5% (Table 2). One of eight evaluable patients (thymic carcinoma with *KIT* V560 deletion) had a PR that lasted for 15.2 months and a maximum target lesion change of -48.6% (Figure 2F). Most patients (62.5%) achieved SD.

Median PFS was 5.7 months in patients with NSCLC harboring *RET* rearrangement, and specifically *KIF5B-RET*, and 6-month PFS estimates were 40.3 and 36.4%, respectively (Figure 3A). Median PFS and 6-month PFS estimates were shorter in the Chr4q12 amplification, *MET* and *CBL* alteration cohorts, ranging from 2.0–2.9 months and 12.3–23.8%, respectively (Figure 3A). While median PFS was not reported for the *AXL* amplification cohort, 6-month PFS estimate was the longest of the molecular alteration cohorts (71.4%). Two patients in the *AXL* amplification cohort who continued study treatment following primary data cutoff had PFS of 351 days and censored PFS of 776 days (patient was progression-free at last recorded follow-up, described above). The longest duration of OS was seen in patients with NSCLC harboring *RET* rearrangement, including the *KIF5B-RET* subgroup (median OS 24.2 months in both cohorts; 12-month OS estimate 73.2 and 79.5%, respectively). In patients with tumors harboring Chr4q12 amplification and *MET*, *CBL* or *AXL* alterations, median OS and 12-month OS

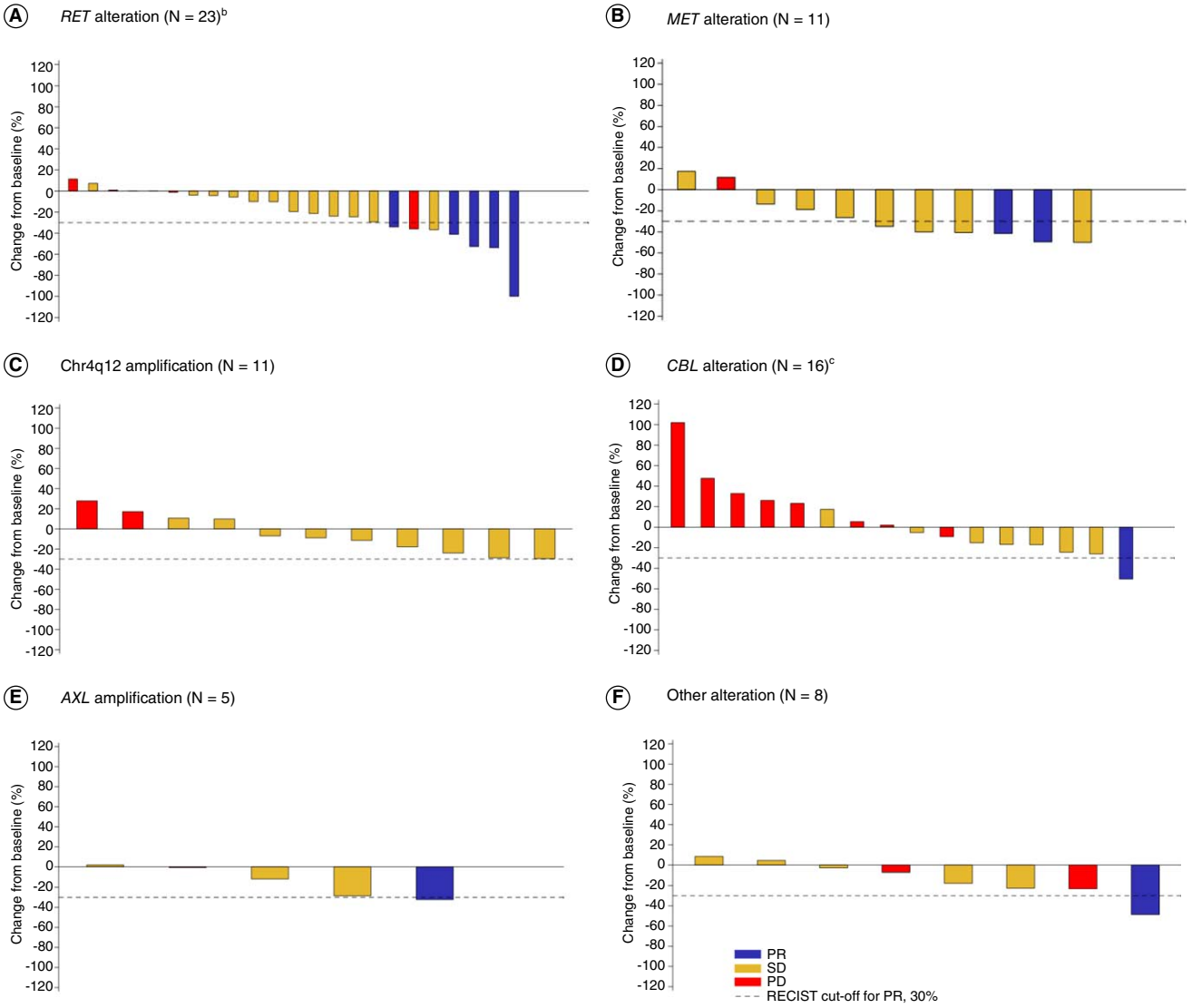


Figure 2. Percentage change in tumor burden grouped by molecular alteration (clinical activity evaluable population[a]).
(A) *RET* alteration (N = 23)[b]. **(B)** *MET* alteration (N = 11). **(C)** Chr4q12 amplification (N = 11). **(D)** *CBL* alteration (N = 16)[c]. **(E)** *AXL* amplification (N = 5). **(F)** Other alteration (N = 8).
[a]Patients were excluded with missing data for change from baseline.
[b]Overall *RET* alteration cohort is shown.
[c]One additional PR (maximum target lesion change -77.4%) was observed in a patient with NSCLC and *CBL* C384R who did not qualify for the CAE population (total dose of sitravatinib <80% in Cycle 1) but received sufficient study treatment overall to be considered clinically evaluable.
CAE: Clinical activity evaluable; NSCLC: Non-small cell lung cancer; PD: Disease progression; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: Stable disease.

estimate ranged from 5.0–9.5 months and 20.2–35.2%, respectively (Figure 3B).

3.3. Study treatment exposure

Across the molecular alteration cohorts the starting dose of sitravatinib was 150 mg QD and 120 mg QD in n = 60 and n = 53, respectively. Patients started a median of 4.0 cycles of study treatment and relative dose intensity was 80.5%. The two patients in the *AXL* alteration cohort who continued study treatment following the primary data cutoff started 39 cycles and 16 cycles of sitravatinib (relative dose intensity was 92.1 and 73.8%, respectively). Exposure to sitravatinib across the molecular alteration cohorts was broadly similar (Supplementary Table 1).

3.4. Safety

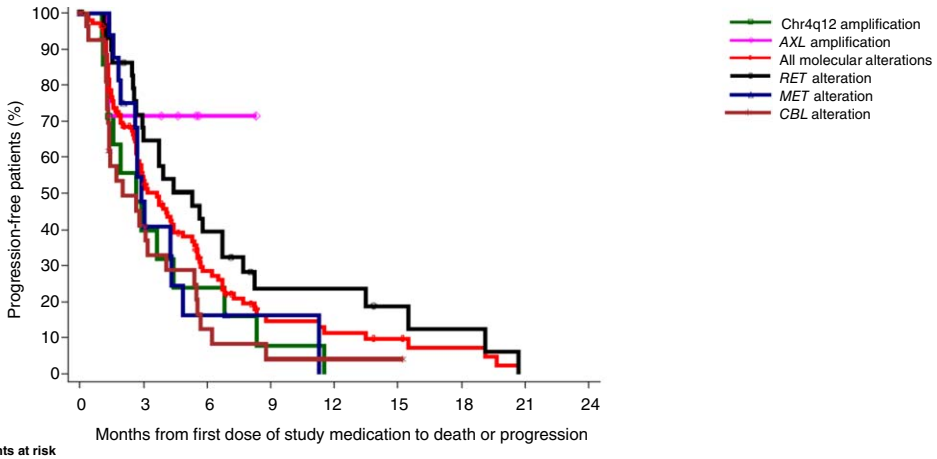
Across all the molecular alteration cohorts, the most frequent all-cause TEAEs were diarrhea (61.1%

Table 2. Best overall response with sitravatinib in patients with tumors harboring molecular alterations (clinical activity evaluable population).

n (%)	*RET* alteration			*MET* alteration (N = 13)	Chr4q12 amplification (N = 11)	*CBL* alteration (N = 18)	*AXL* amplification (N = 6)	Other (N = 8)
	Overall *RET* cohort (N = 26)	NSCLC *RET* rearrangement[a]						
		All patients (N = 19)	*KIF5B-RET* (N = 9)					
Best overall response, n (%)								
ORR	5 (19.2)	4 (21.1)	1 (11.1)	2 (15.4)	0	1 (5.6)	1 (16.7)	1 (12.5)
95% CI	6.6–39.4	6.1–45.6	0.3–48.2	9.1, 45.4	0.0–28.5	0.1–27.3	0.4–64.1	
P value[b]	0.350	0.316	0.768	0.602	>0.999	0.946	0.623	
CR	0	0	0	0	0	0	0	0
PR	5 (19.2)	4 (21.1)	1 (11.1)	2 (15.4)	0	1 (5.6)[c]	1 (16.7)	1 (12.5)
SD	16 (61.5)	12 (63.2)	5 (55.6)	10 (76.9)	9 (81.8)	8 (44.4)	4 (66.7)	5 (62.5)
PD	5 (19.2)	3 (15.8)	3 (33.3)	1 (7.7)	2 (18.2)	8 (44.4)	1 (16.7)	2 (25.0)
NE	0	0	0	0	0	1 (5.6)	0	0
Median DoR, months	2.8	2.3	10.2	N/A[d]	N/A	N/A[e]	3.1[f]	15.2
(range)	(1.8, 10.2)	(1.8, 10.2)	(10.2, 10.2)	(3.0, 5.6)	N/A	(14.2, 14.2)	(3.1, 3.1)	(15.2, 15.2)

[a]Includes patients with NSCLC and *RET* fusion partner *KIF5B*, *CCDC6*, *DSP* or not specified.
[b]Exact test for single proportion (null hypothesis ORR ≤15%).
[c]One additional patient with limited dosing in Cycle 1 (did not qualify for CAE population) also had PR (not shown).
[d]One patient experienced PD at 3.0 months and the second was censored at 5.6 months.
[e]Duration of response was 14.2 months (duration of response was 4.3 months in the additional patient with PR who did not qualify for the CAE population).
[f]PR ongoing at study withdrawal.
CAE: Clinical activity evaluable; CR: Complete response; DoR: Duration of response; N/A: Not applicable; NSCLC: Non-small cell lung cancer; PD: Disease progression; PR: Partial response; SD: Stable disease.

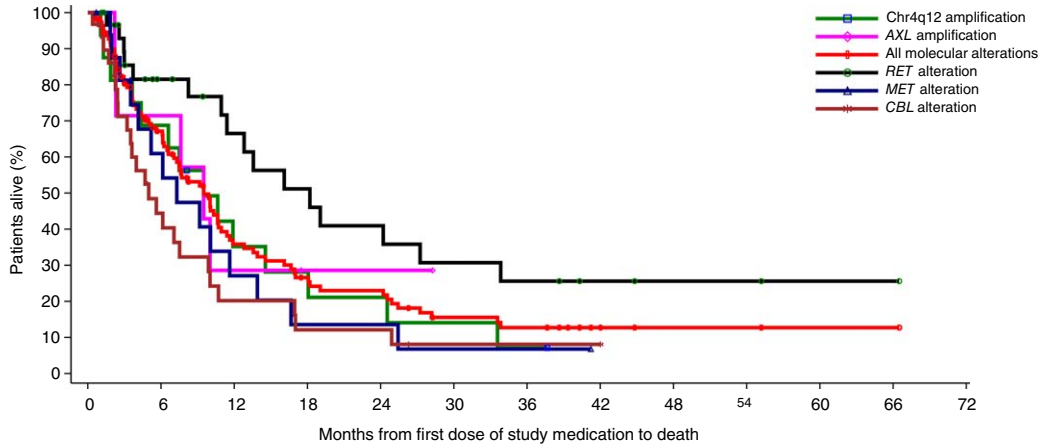
Ⓐ PFS



Number of patients at risk								
All molecular alterations	113	50	23	9	7	5	3	0
Chr4q12 amplification	16	5	3	1	0			
AXL amplification	7	5	1	0				
RET alteration	31	18	11	5	5	3	2	0
MET alteration	17	7	2	1	0			
CBL alteration	31	10	3	1	1	1	0	

PFS Summary n (%)	All patients (N = 113)	*RET* alteration			*MET* alteration (N = 17)	Chr4q12 amplification (N = 16)	*CBL* alteration (N = 31)	*AXL* amplification (N = 7)
		Overall *RET* cohort (N = 31)	NSCLC *RET* rearrangement[a]					
			All patients (N = 23)	*KIF5B-RET* (N = 13)				
Median PFS, months	3.6	5.3	5.7	5.7	2.9	2.7	2.0	NR
(95% CI)	(2.7, 4.4)	(3.0, 6.7)	(3.0, 13.5)	(1.5, 13.5)	(1.9, 4.3)	(1.3, 4.4)	(1.3, 4.1)	(1.2, NE)
6-month PFS KM estimate, %	28.5	39.5	40.3	36.4	16.4	23.8	12.3	71.4
(95% CI)	(19.6, 38.0)	(21.8, 56.7)	(19.5, 60.4)	(11.2, 62.7)	(2.8, 40.0)	(5.8, 48.5)	(3.1, 28.3)	(25.8, 92.0)

Ⓑ OS



Number of patients at risk													
All molecular alterations	113	63	31	22	19	11	9	4	2	2	1	1	0
Chr4q12 amplification	16	11	5	4	3	2	1	0					
AXL amplification	7	5	2	1	1	0	0			2			
RET alteration	31	18	13	10	8	6	5	3	2	2	1	1	0
MET alteration	17	9	4	2	2	1	1	0					
CBL alteration	31	11	5	3	3	1	1	1	0				

OS Summary n (%)	All patients (N = 113)	*RET* alteration			*MET* alteration (N = 17)	Chr4q12 amplification (N = 16)	*CBL* alteration (N = 31)	*AXL* amplification (N = 7)
		Overall *RET* cohort (N = 31)	NSCLC *RET* rearrangement[a]					
			All patients (N = 23)	*KIF5B-RET* (N = 13)				
Median OS, months	9.5	18.2	24.2	24.2	7.3	9.5	5.0	9.5
(95% CI)	(7.1, 10.9)	(10.9, 33.8)	(10.9, NE)	(10.9, NE)	(3.5, 13.9)	(3.6, 18.1)	(3.2, 9.9)	(2.2, NE)
12-month OS KM estimate, %	35.8	66.5	73.2	79.5	27.1	35.2	20.2	28.6
(95% CI)	(26.2, 45.6)	(43.3, 82.0)	(46.6, 88.1)	(39.3, 94.5)	(8.4, 50.2)	(13.3, 58.2)	(7.4, 37.3)	(4.1, 61.2)

Figure 3. Progression-free survival and overall survival with sitravatinib in patients with tumors harboring molecular alterations (modified intent-to-treat population).
(A) PFS. **(B)** OS.
[a]Includes patients with NSCLC and *RET* fusion partner *KIF5B*, *CCDC6*, *DSP* or not specified.
CI: Confidence interval; KM: Kaplan–Meier; NE: not evaluable; NR: not reported; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival.

[n = 69]), fatigue (50.4% [n = 57]), hypertension (46.9% [n = 53]) and nausea (38.9% [n = 44]; Table 4). These events were frequently considered by the study investigators to be related to study treatment (diarrhea 54.0% [n = 61], fatigue 43.4% [n = 49], hypertension 42.5% [n = 48] and nausea 31.0% [n = 35]). Nausea and hypertension were also the most frequent serious AEs considered by the investigators to be related to study medication (both n = 3 [2.7%]); other treatment-related serious AEs were reported in one or two patients only. Most AEs were mild-to moderate in severity. Except for hypertension (n = 31 [27.4%]), fatigue (n = 12 [10.6%]) and diarrhea (n = 11 [9.7%]), Grade ≥3 TEAEs were reported in fewer than 6% of patients (Table 3). There were no marked differences in the incidence of treatment-related TEAEs across the molecular alteration cohorts.

Dose reductions or interruptions due to AEs were reported in 71.7% (n = 81), and discontinuation of sitravatinib due to AEs was reported in 20.4% (n = 23). All-cause AEs resulting in study treatment discontinuation included alanine aminotransferase increased, aspartate aminotransferase increased, diarrhea, hypertension and sepsis (n = 2, each). Disease progression was also reported as an all-cause AE resulting in sitravatinib discontinuation in three patients (other AEs were reported as single events).

Across the molecular alteration cohorts, 14 patients died during the study. Most deaths were due to disease progression (n = 11), and two and one patient died of sepsis and pneumonia, respectively.

4. Discussion

We report the clinical activity and safety of sitravatinib, an inhibitor of several oncogenic RTKs, including split and TAM family members, in a subset of a Phase Ib population who were enrolled using a basket approach. These patients had malignancies with molecular alterations relevant to the mechanism of action of sitravatinib. This included amplification, mutation, or rearrangement of sitravatinib molecular targets: *MET*, *AXL*, *RET*, *NTRK*, *DDR2*, *KDR*, *PDGFRA* and *KIT*. Patients with tumors harboring amplification of Chr4q12 were also enrolled as this genetic segment encodes several relevant oncogenic driver RTKs including *KIT*, *PDGFRA* and *KDR* [12]. Furthermore, durable clinical benefit has been reported in some patients with Chr4q12 amplified tumors who received other TKIs with known anti-PDGFRA and anti-KIT activity [12]. Patients were also enrolled with tumors containing loss-of-function alterations in *CBL*. The resulting loss of E3-ubiquitin ligase may result in decreased degradation of several RTKs implicated in carcinogenesis, including targets of sitravatinib, potentially leading to increased RTK density and signaling, thereby contributing to oncogenesis [13–15].

Sitravatinib was previously reported to have modest clinical activity (ORR 11.8%) across all evaluable patients in this Phase I/Ib study, which also including those enrolled into cohorts based on histologic diagnosis alone [4]. However, the basket approach for the molecular alteration cohorts was designed to have flexibility to facilitate identification of patients who are most likely to benefit from treatment with sitravatinib. The molecular alteration cohorts could evolve from a broad population with regards to alteration for a given gene to become more refined (e.g., all tumor types with *RET* rearrangement to NSCLC with *KIF5B-RET* rearrangement), with the same Simon two-stage design used for the parent and refined cohorts. However, while clinical activity was seen in several molecular alteration cohorts, their low frequency combined with variability in the type of alteration within a specific gene and differing tumor types limited the feasibility to complete enrollment in all cohorts within a relevant timescale, and the trial was closed.

Across the molecular alteration cohorts, clinical activity signals with sitravatinib were most pronounced in patients with previously treated *RET* altered tumors, although the response rate did not differ significantly from the null hypothesis. Most patients experienced reductions in tumor volume, including PRs in four individuals with NSCLC harboring *RET* rearrangements at several different loci (confirmed ORR 21.1%) and in one patient with *RET* C634R-mutated HR-positive breast cancer; of note response duration was ≥7 months in two of 26 evaluable patients with previously treated disease. Clinical meaningful disease control (SD lasting 5.3 months) was also observed in one of three patients with thyroid cancer harboring *RET* rearrangement. Of note, all three patients with thyroid cancer had received prior treatment with two or three non selective RET inhibitors (vandetanib, cabozantinib and lenvatinib) which have potential to evoke RET-targeted resistance mechanisms.

During the course of our study ORRs of 57–64% and 89–100% were reported in patients with *RET* fusion-positive NSCLC and *RET* fusion-positive thyroid cancer, respectively, across clinical trials of the RTK inhibitors, selpercatinib and pralsetinib [16,17]. These findings resulted in FDA approval of both drugs in these settings [16,17]. While direct comparison of outcomes across studies is not recommended due to differences in study design and patient populations, the ORR with selpercatinib and pralsetinib in patients with *RET*-altered NSCLC and thyroid cancer exceeds the modest, preliminary

Table 3. Frequent all-cause treatment-emergent adverse events (≥10% of patients) in study participants with tumors harboring molecular alterations (modified intent-to-treat population).

n (%)	All patients (N = 113)		
	All Grade	Grade 3	Grade 4
Gastrointestinal disorders			
Diarrhea	69 (61.1)	11 (9.7)	0
Nausea	44 (38.9)	1 (0.9)	0
Constipation	40 (35.4)	0	0
Vomiting	31 (27.4)	3 (2.7)	0
Abdominal pain	26 (23.0)	3 (2.7)	0
Dry mouth	19 (16.8)	0	0
Stomatitis	19 (16.8)	2 (1.8)	0
Oral pain	13 (11.5)	0	0
General disorders/administration site conditions			
Fatigue	57 (50.4)	12 (10.6)	0
Peripheral edema	16 (14.2)	0	0
Asthenia	12 (10.6)	0	0
Metabolism and nutrition disorders			
Decreased appetite	43 (38.1)	3 (2.7)	0
Dehydration	20 (17.7)	1 (0.9)	0
Hyponatremia	15 (13.3)	6 (5.3)	1 (0.9)
Hypokalemia	13 (11.5)	2 (1.8)	0
Hypophosphatemia	13 (11.5)	6 (5.3)	0
Respiratory, thoracic and mediastinal disorders			
Dysphonia	30 (26.5)	0	0
Dyspnea	18 (15.9)	1 (0.9)	0
Cough	15 (13.3)	0	0
Vascular disorders			
Hypertension	53 (46.9)	31 (27.4)	0
Investigations			
ALT increased	30 (26.5)	4 (3.5)	0
AST increased	29 (25.7)	1 (0.9)	0
Weight decreased	27 (23.9)	2 (1.8)	0
Lipase increased	14 (12.4)	4 (3.5)	2 (1.8)
Skin and subcutaneous tissue disorders			
Hand–foot syndrome	21 (18.6)	6 (5.3)	0
Rash	16 (14.2)	2 (1.8)	0
Nervous system disorders			
Dizziness	23 (20.4)	0	0
Headache	23 (20.4)	2 (1.8)	0
Musculoskeletal and connective tissue disorders			
Back pain	16 (14.2)	0	0
Pain in extremity	15 (13.3)	1 (0.9)	0
Arthralgia	13 (11.5)	1 (0.9)	0
Infections and infestations			
Urinary tract infection	13 (11.5)	3 (2.7)	0
Endocrine disorders			
Hypothyroidism	28 (24.8)	0	0
Blood and lymphatic system disorders			
Anemia	19 (16.8)	6 (5.3)	0
Renal and urinary disorders			
Proteinuria	14 (12.4)	1 (0.9)	0

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

clinical activity observed with sitravatinib in these cohorts in our study. While durable responses were seen with sitravatinib in two patients with *RET*-altered tumors, additional refinement of predictive indicators would be required to warrant further investigation of sitravatinib in this setting.

While this study was closed prior to enrollment of the n = 24 planned patients eligible for clinical activity in the other molecular cohorts, some signals of clinical activity were seen, including PRs in 2 of 18 evaluable patients with *CBL* missense mutations. A prolonged PR (14.2 months) was reported in a patient with sinonasal

melanoma and *CBL* Y368C that was resistant to several prior treatments, leading to the hypothesis that inhibiting PDGFRα and/or KIT may result in clinical activity in this setting. Another PR of clinically meaningful duration (4.3 months) occurred in a patient with NSCLC and *CBL* C384R with prior EGFR inhibitor failure, leading to the hypothesis that *CBL* mutation may result in resistance to EGFR inhibition through increased MET activity. Of note, a large proportion (11/39 [39%]) of patients with *CBL* altered tumors were not eligible for clinical activity evaluation, largely due to on-study death and sitravatinib dose modifications, suggesting *CBL* inactivation may be associated with poor prognosis. These observations suggest further refinement of *CBL* alteration type would be required to warrant future study of sitravatinib in patients with tumors harboring this molecular alteration.

Most evaluable patients with tumors harboring altered *MET* experienced reductions in tumor volume, including confirmed responses in two of 13 (15.4%) patients, both of whom had NSCLC, one harboring *MET* overexpression and one with *MET* exon 14 skipping. Since the onset of this study, capmatinib and tepotinib received FDA approval for patients with NSCLC and *MET* exon 14 skipping alterations, with ORRs of 45–68% and 41–45% in treatment-naive and previously treated patients, respectively [18–20]. While the clinical activity of sitravatinib in MET-altered NSCLC appears lower than that of capmatinib and tepotinib, both approved MET inhibitors are associated with toxicities that can be challenging in some patients including edema, pulmonary symptoms and hepatotoxicity [18]. This underscores the challenges of developing effective treatments that are well tolerated in this setting. Clinical activity signals were also observed in tumors harboring *AXL* amplification, with five of six evaluable patients having disease control (n = 1 PR and n = 4 SD), including one patient with NSCLC who achieved ongoing disease control for approximately 8 years with glesatinib (in a prior study) followed by sitravatinib. Given the roles of AXL in cell proliferation, survival, migration, regulation of natural killer cell development, and drug resistance mechanisms, along with the lack of approved treatments in this setting [21], further investigation of sitravatinib may be warranted for patients with *AXL*-altered tumors.

In this study, the safety assessment of sitravatinib showed gastrointestinal events were among the most frequent TEAEs considered by the investigators to be related to study treatment (diarrhea 54%, nausea, 31%) along with hypertension (42.5%) and fatigue (43.4%). These findings are aligned with safety observations previously reported across all patients enrolled in this Phase I/Ib study, as well as in smaller studies of sitravatinib in combination with nivolumab [4,22–24]. No safety signals were identified that would impact further development of this investigational agent. Over half the patients in the molecular alteration cohorts received sitravatinib at the previously established MTD of 150 mg QD (n = 60 of 113) [4]. However, based on tolerability observations during the course of the study, 120 mg QD was identified as the recommended dose, which was received by n = 53 in the molecular alteration cohorts. The tolerability profile of sitravatinib is likely better with this lower dose. Furthermore, 120 mg QD was considered a clinically active dose of sitravatinib based on concentration-dependent modulation of VEGF-A and soluble-VEGF-receptor 2 in plasma samples obtained from patients before and after sitravatinib administration [4]. However, further evaluation of clinical activity according to dose would be required, along with consideration of the exposure–response relationship for each molecular target. In addition, consideration of other molecular alterations present in the tumor may also be required, given the potential that the driver mutation may differ from the alteration selected for investigation. Sitravatinib may also have potential as combination therapy with immunotherapy, given the impact of targeting TAM receptors on immunosuppression in the tumor microenvironment [6]. However, while, combining sitravatinib with an anti-programmed cell death protein 1 antibody (tislelizumab) demonstrated preliminary signals of antitumor activity in patients with hepatocellular and gastric cancer, clinically meaningful responses were not seen with sitravatinib plus nivolumab in patients with urothelial cancer [25,26].

5. Conclusion

Single-agent sitravatinib demonstrated modest clinical activity with a manageable safety profile in patients with heavily pretreated advanced tumors including NSCLC in molecularly defined cohorts (*RET* rearrangement, *MET* alterations, *CBL* alterations and *AXL* amplification). Further refining molecular alteration subtype in some target genes could identify populations in whom sitravatinib may have potential clinical utility. However, despite the basket cohort-approach to enrollment, given the low frequency of these alterations this was not feasible in the timeframe for this study. Further development of sitravatinib is not anticipated.

Article highlights

- Basket trials that enroll cohorts of patients with various tumor types that harbor specific molecular alterations can inform the activity of novel treatments for rare genetic drivers, helping ensure patients receive treatment that is based on the molecular signature of their disease.
- Sitravatinib (MGCD516) is an oral small molecule inhibitor that targets a spectrum of closely related receptor tyrosine kinases involved in cancer development, predominantly TAM family

(TYRO3, AXL, MERTK) and split family (VEGFR2, MET, RET, KIT) receptors.
- We report clinical activity and safety with sitravatinib in patients with advanced solid tumors that harbored genetic alterations relevant to the mechanism of action of sitravatinib, who participated in the Phase Ib basket study cohorts of the first-in-human study.
- Overall, 113 heavily pre-treated patients were enrolled; patients with tumors containing alterations in *RET* (n = 31), *CBL* (n = 31) and *MET* (n = 17) were the most frequent cohorts.
- Overall, the clinical activity of sitravatinib was modest: while most patients (68.9%) experienced a reduction in tumor volume, the majority (61.5%) had a best objective response of stable disease.
- Objective response rate was highest in patients with *RET*-rearranged NSCLC (21.1%) but this did not differ significantly from the null hypothesis (ORR $\leq$15%; $p = 0.316$).
- Despite the basket-cohort approach to enrollment, fewer patients than planned were enrolled across the cohorts in the timeframe of the study; this prevented further refinement of molecular alteration subtypes for which sitravatinib may have clinical utility.
- Sitravatinib had a manageable safety profile: most adverse events were mild-to-moderate in severity, with diarrhea (61.1%), fatigue (50.4%) and hypertension (46.9%) being most frequently observed.

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Preliminary outcomes from these molecular alteration cohorts were reported by Bauer et al. Invest New Drugs 2022;40:990–1000 and presented at World Congress on Lung Cancer; October 2017; Yokohama, Japan (Bazhenova L et al. *CBL* mutations as potential mediators of EGFR TKI resistance effectively treated with sitravatinib. Poster P3.01–048) and European Society for Medical Oncology Annual Meeting; October 2018; Munich, Germany (Bazhenova L et al. Sitravatinib demonstrates activity in patients with novel genetic alterations that inactivate CBL. Oral presentation 408O).

Author contributions

All authors contributed to data interpretation, development of the manuscript, approved the final draft for submission and take responsibility for data integrity. In addition, L Bazhenova, DW Kim, BC Cho, S Goel, R Heist, TL Werner, KD Eaton, JS Wang, S Pant, DR Adkins, C Blakely and T Bauer contributed to data collection; X Yan was responsible for data analysis and contributed to data presentation; S Neuteboom was responsible for coordinating the research and contributed to data presentation; JG Christensen and R Chao were responsible for conception and design of the study and contributed to data presentation.

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Competing interests disclosure

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Ethical conduct of research

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, defined by the International Council for Harmonisation, and was approved by the institutional review board at each participating site. Western Institutional Review Board served as the central institutional review board in conjunction with 23 local institutional review boards. All participants provided written, informed consent.

Data availability

Mirati Therapeutics Inc. (a Bristol Myers Squibb company) is committed to patient care, advancing scientific understanding, and enabling the scientific community to learn from and build upon our research. We will honor legitimate requests from qualified researchers and investigators for our clinical trial data in order to conduct methodologically sound research. We will share clinical trial data, as well as study protocols, clinical study reports and statistical analysis plans for this study. Sharing is subject to protecting patient privacy and respect for the patient's informed consent. Data will generally be made available for specific requests approximately 2 years after clinical trial completion. For additional information on data sharing collaborations with Mirati Therapeutics, please email medinfo@mirati.com.

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