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ORIGINAL ARTICLE

BOS172738, a selective RET inhibitor, for the treatment of patients with *RET*-altered tumors including *RET*-fusion-positive non-small-cell lung cancer and *RET*-mutant medullary thyroid cancer: a phase I dose-escalation/expansion multicenter study

P. Schöffski[1,2*], A. Gazzah[3], J. Trigo[4], A. Italiano[5,6], P. Gougis[7,8,9,10], V. Subbiah[11], J.-Y. Shih[12], H. H. Loong[13,14], B. Doger[15], M. Keegan[16], B. Jeglinski[16], K. Andreas[16] & B. C. Cho[17]

[1]Department of General Medical Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven; [2]Laboratory of Experimental Oncology, Department of Oncology, KU Leuven, Leuven, Belgium; [3]Department of Therapeutic Innovation and Early Trials (DITEP), Institut Gustave Roussy, Paris, France; [4]Department of Medical Oncology, Research and Development, Hospital Universitario Virgen de la Victoria, Málaga, Spain; [5]Department of Medicine, Institut Bergonié, Bordeaux; [6]University of Bordeaux, Bordeaux; [7]Department of Medical Oncology, Pitié-Salpêtrière Hospital, Sorbonne Université, Institut Universitaire du Cancer, Paris; [8]Assistance Publique-Hôpitaux de Paris (AP-HP), Paris; [9]Sorbonne Université, Institut National de la Santé et de la Recherche Médicale (INSERM), Assistance Publique-Hôpitaux de Paris (AP-HP), Clinical Investigation Center (CIC-1901), Regional Pharmacovigilance Centre, Department of Pharmacology, Pitié-Salpêtrière, Paris; [10]Residual Tumor & Response to Treatment Laboratory, RT2Lab, INSERM, U932 Immunity and Cancer, Institut Curie, Université Paris Cité, Paris, France; [11]Early-Phase Drug Development, Sarah Cannon Research Institute, Nashville, USA; [12]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [13]Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong; [14]Phase 1 Clinical Trial Centre, The Chinese University of Hong Kong, Hong Kong, China; [15]Department of Oncology, START Madrid-Fundación Jiménez Díaz (FJD), Early Phase Program, Fundación Jiménez Díaz Hospital, Madrid, Spain; [16]Boston Pharmaceuticals, Inc., Cambridge, USA; [17]Division of Medical Oncology, Department of Internal Medicine, Severance Hospital, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

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Background: This phase I dose-escalation (part A)/dose-expansion (part B) study evaluated the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BOS172738 [a selective rearranged during transfection (RET) inhibitor] in patients with *RET*-altered tumors including *RET*-fusion-positive non-small-cell lung cancer (NSCLC) and *RET*-mutant medullary thyroid cancer (MTC).

Patients and methods: Adult patients with advanced solid tumors with *RET* gene alteration received BOS172738 10-150 mg orally once daily in part A, and the recommended phase II dose (RP2D) in part B. Primary endpoints included safety (Common Terminology Criteria for Adverse Event v.4.03) and tolerability, and in part A, determining the maximum tolerated dose (MTD) and RP2D. Secondary endpoints included objective response rate (ORR; RECIST v.1.1), disease control rate (DCR), progression-free survival, duration of response (DoR), and pharmacokinetic assessments. Exploratory endpoints involved pharmacodynamic biomarkers.

Results: A total of 117 patients were enrolled (67 part A, 50 part B). Patients had advanced disease, were heavily pretreated, and 21% had brain metastases. In part A, three patients had dose-limiting toxicities, but MTD was not reached, with 75 mg recommended for part B. At final cut-off (November 2023), 85% had BOS172738-related treatment-emergent adverse events [54% grade $\geq$3, most common: blood creatine phosphokinase increased (25%), neutrophil count decreased (10%), and anemia (9%)]. In *RET*-fusion-positive NSCLC, 28% had an objective response and 59% disease control, with a median DoR (mDoR) of 10.17 months. In *RET*-mutant MTC, 30% had an objective response, and DCR was 74%, with a mDoR of 19.15 months.

Conclusions: BOS172738 showed preliminary efficacy and a manageable safety profile in *RET*-altered tumors, including those resistant to prior therapies and in patients with brain metastases.

Key words: BOS172738, RET inhibitor, *RET* gene alterations, non-small-cell lung cancer (NSCLC), medullary thyroid cancer (MTC)

*Correspondence to: Prof. Patrick Schöffski, Department of General Medical Oncology, Leuven Cancer Institute, University Hospitals Leuven, and Laboratory of Experimental Oncology, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium. Tel: +32-16-346900; Fax: +32-16-346901

E-mail: patrick.schoffski@uzleuven.be (P. Schöffski).

@schoffski

INTRODUCTION

The rearranged during transfection (*RET*) proto-oncogene, located on chromosome 10q11.2, encodes a transmembrane receptor tyrosine kinase that plays an important role in cell proliferation and survival.[1-3] Activation of RET occurs upon binding with its ligand, the glial cell line-derived neurotrophic factor family ligands (GFLs).[1-3] The RET—GFL complex leads to RET homodimerization and autophosphorylation, with activation of the downstream signaling pathways through mitogen-activated protein kinase (MAPK) (involving RAS/RAF/MEK/ERK signaling), phosphoinositide 3-kinase (PI3K), Janus kinase and signal transducer and activator of transcription (JAK—STAT), and protein kinase A (PKA).[1-3] The RET activation of the MAPK/PI3K/JAK—STAT/PKA pathways results in cell growth, proliferation, and survival.[1-3]

Alterations in the *RET* proto-oncogene can occur through two main mechanisms, namely gene fusion and point mutations, and both mechanisms are potent oncogenic drivers in various cancers, leading to constitutive RET activity.[4,5] *RET* alterations through gene fusion occur in cancers such as non-small-cell lung cancer (NSCLC) and *RET* fusions are present in ∼10%-20% of papillary thyroid carcinomas, ±1%-2% of NSCLC cases, and <1% of other solid tumors.[3,5-7] *RET* mutations are predominantly associated with medullary thyroid carcinoma (MTC), occurring in over 60% of sporadic cases and over 90% of hereditary MTC linked to the multiple endocrine neoplasia type 2 syndrome.[1,2,5,7,8]

The development of RET inhibitors has been a key area of interest in targeted cancer therapy.[5,7,9-11] First-generation multi-kinase inhibitors targeting RET, such as cabozantinib and vandetanib, had limited efficacy and poor safety characteristics due to low selectivity for RET and off-target effects.[9,10,12] These limitations resulted in either lower bioavailability in target tumor cells or suboptimal dosing, with modest efficacy through RET inhibition.[9,12-14] The therapeutic landscape for *RET*-altered tumors evolved with the development of more selective RET inhibitors, such as selpercatinib and pralsetinib.[9,12] These agents exhibit increased specificity for RET, leading to improved clinical responses and a more favorable safety profile. Selpercatinib and pralsetinib received regulatory approval in 2020 and they are now standard-of-care treatments for RET-aberrant cancers including RET-fusion-positive thyroid cancer, lung cancer, other solid tumors, and RET-mutant MTC.[9,10,12,13] However, the emergence of resistance mechanisms to RET inhibitors, such as resistant RET mutations (e.g. G810 solvent-front mutations: RET G810R, G810S, and G810C mutations) and activation of alternative signaling pathways, poses challenges to their long-term efficacy.[9,11-15] Furthermore, the development of brain metastases in patients with *RET*-fusion-positive NSCLC is common and is associated with a poor prognosis.[12] In patients with stage IV *RET*-rearranged lung cancer, the lifetime prevalence of developing brain metastases is 46%.[16] Overcoming resistance mechanisms and the need for effective blood—brain barrier penetration to treat brain metastases prompted continued research into next-generation RET-targeted therapies to improve outcomes for patients with *RET*-driven malignancies.[4,9-12,15]

The RET inhibitor BOS172738 is an orally available, highly potent, and selective RET inhibitor that has the potential to address the above limitations.[4,10,11,17] Preclinical studies and early clinical data have demonstrated its efficacy in targeting *RET* fusions and mutations across multiple tumor types, including *RET*-fusion-positive NSCLC and *RET*-mutant MTC.[4,11,17] BOS172738 has nanomolar ($k_d \leq 1$ nM) potency against RET, with >300-fold specificity to RET compared with vascular endothelial growth factor receptor 2.[4,17-19] BOS172738 has antitumor activity against resistant RET mutations and is also able to overcome RET G810 resistance.[10,17]

This phase I (BOS172738-01, NCT03780517) dose-escalation/dose-expansion study evaluated the safety, efficacy, pharmacokinetics, and pharmacodynamics of BOS172738, in patients with advanced solid tumors harboring *RET* alterations.

PATIENTS AND METHODS

Study design and patient selection

BOS172738-01 was a phase I, open-label, multicenter, dose-escalation (part A)/dose-expansion (part B) trial conducted to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BOS172738 in patients with advanced solid tumors with *RET* gene alterations. The primary objective was to assess the safety and tolerability of BOS172738, and in part A to establish the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) for the oral agent. Secondary objectives included the evaluation of the efficacy of BOS172738 based on objective tumor response criteria and characterization of the pharmacokinetics of the drug. Exploratory objectives included the relationship of *RET* gene status and treatment on efficacy outcomes, and evaluation of circulating free tumor DNA (cfDNA) as a potential biomarker for prediction of response.

Eligible patients included those ≥18 years of age, with a diagnosis of advanced solid tumors with documented *RET* gene alteration (determined locally by DNA- or RNA-based assays of tumor tissue or blood), measurable disease as assessed by the investigator, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and adequate bone marrow, renal, hepatic, and cardiac function. For part A, patients had no alternate therapy of proven benefit, but prior exposure to specific RET gene-targeted therapies was not allowed. For part B, patients had to have documented local diagnosis of either (i) advanced *RET* gene-fusion NSCLC, (ii) advanced *RET* gene-mutant MTC, or (iii) other *RET* gene-altered advanced

tumors or NSCLC/MTC with prior specific RET-targeted therapy; furthermore, NSCLC and MTC patients must have received at least one prior line of treatment that included an approved drug for their disease. Key exclusion criteria included inability to take oral medications or gastrointestinal conditions that could interfere with the swallowing or absorption of study medication; history of upper gastrointestinal bleeding, ulceration, or perforation within the prior 12 months; history of stroke or cerebrovascular accident within prior 6 months; human immunodeficiency virus infection or acquired immune deficiency syndrome; hepatitis B surface antigen positive or hepatitis C antibody positive (except if the latter had been successfully treated); serious active infections; uncontrolled or severe concurrent medical condition; concurrent malignancy other than the malignancies under study; and ongoing cancer-directed therapy.

The study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines; applicable International Council for Harmonisation Good Clinical Practice Guidelines; and applicable laws and regulations. All patients provided written informed consent.

Study treatment

In part A, patients received BOS172738 orally once daily in 28-day cycles at doses ranging from 10 to 150 mg. Part A used an accelerated titration design, followed by a 3 + 3 design (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105543). BOS172738 dosing began at 10 mg, and during escalations in the accelerated design, the dose was doubled for each subsequent accelerated cohort (e.g. 10 mg, 20 mg, 40 mg, etc.). When the 3 + 3 design was in use, the dose in subsequent cohorts was increased according to a standard Fibonacci series (67%, 50%, 40%, and 33%). In the accelerated design, each cohort consisted of a minimum of one patient. In the 3 + 3 design, each cohort consisted of at least three patients. Over-enrollment of the previous dose levels was deemed to be safe.

In part B, patients would receive BOS172738 at the RP2D established in part A.

Treatment was repeated every 28 days until disease progression or other discontinuation criteria were met. During part A, patients who were withdrawn from study treatment before completing cycle 1 (28 days of dosing) for reasons other than toxicity could be replaced so that a full cohort of patients completed cycle 1 safety evaluations.

The end of treatment visit occurred within 7 days after the last dose of BOS172738. The end of study (EOS) visit was completed 28 ± 3 days after the last dose of BOS172738.

Assessments

The primary endpoint was safety and tolerability, assessed through the incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events, related TEAEs, and TEAEs leading to study drug discontinuation. Adverse events (AEs) were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03. MTD was established based on dose-limiting toxicity (DLT), and the RP2D was the highest dose recommended for future clinical studies based on safety, efficacy, tolerability, pharmacokinetics, and compliance, including dose reductions and delay.

A DLT was defined as any toxicity attributable to BOS172738 that occurred before the end of cycle 1 and which included hematological toxicities (grade 4 neutropenia, grade 3 febrile neutropenia, grade 4 thrombocytopenia, grade 3 thrombocytopenia with bleeding) and non-hematological toxicities [grade 3 aspartate aminotransferase or alanine aminotransferase or increase in grade for patients with liver metastases, grade ≥3 non-hematologic toxicity (except untreated nausea, vomiting, constipation, pain, hyperbilirubinemia, and rash—these became DLTs if the AE persisted despite adequate treatment); any drug-related toxicity that resulted in a BOS172738 treatment interruption exceeding 7 consecutive days; and any intolerable grade >2 drug-related non-hematologic toxicity was considered a DLT following evaluation and agreement by the investigator, medical monitor, and sponsor].

Secondary endpoints included assessment of objective response rate (ORR) as per RECIST v.1.1, disease control rate (DCR), progression-free survival (PFS), duration of response (DoR), time to response, and duration of complete response (DoCR). Computed tomography (CT), positron emission tomography—CT, or magnetic resonance imaging scans were carried out for efficacy assessments at specific time points. Baseline/screening scans were carried out no more than 28 days before but as close as possible to the first BOS172738 dose. Subsequently, imaging was done between day 22 and 28 (before the beginning of the next cycle), in cycle 2, and every two cycles thereafter, and at the EOS. Evaluable or measurable disease and treatment response in accordance with RECIST v.1.1 were assessed by the investigator. Pharmacokinetic assessments of BOS172738 at pre-specified time points included maximum observed concentration (C_{max}), first time to maximum concentration (T_{max}), area under the concentration—time curve (AUC), terminal half-life ($t_{½}$), total body clearance for extravascular administration (Cl/F), and volume of distribution (V_z/F). The concentration of BOS172738 was quantified using a fully validated analytical method.

Exploratory endpoints included the evaluation of *RET* gene status by tumor response endpoints, the reduction in cfDNA correlated by tumor response endpoints, and reduction in cfDNA correlated by pharmacokinetic endpoints. Pre- and post-treatment blood samples for cfDNA isolation were collected from all patients in the study. Assessments of cfDNA for RET gene status were done at screening within 28 days before the first BOS172738 dose, at day 15 (±2 days) of the first cycle of treatment, and day 1 of the second cycle of treatment. cfDNA samples were used to confirm *RET* gene

alteration status. Archived tumor tissue samples were requested from all patients for retrospective central review of *RET* gene alterations and for comparison with cfDNA. The expression of the pharmacodynamic biomarkers in patient-derived tumor biopsies (in patients who consented to pre- and post-treatment biopsies) was measured by validated immunoassays and parameters such as percentage change from pre-dose or baseline derived.

Statistical analysis

No formal sample size estimation was carried out. Up to 114 patients could be enrolled in the study. For part A, the estimated sample size was up to 54 patients if 6 patients were assigned at each dose level, with up to nine dose levels being possible. However, additional patients could be added if exploration of intermediate dose level(s) of BOS172738 was warranted, or patient replacement occurred. The maximum total dose of BOS172738 to be administered was 450 mg daily. In part B, up to 60 additional patients with either *RET* gene-fusion NSCLC ($n = 20$), *RET* gene-mutant MTC ($n = 20$), or other *RET* gene-altered advanced tumors or NSCLC/MTC with prior specific *RET* gene-targeted therapy ($n = 20$) could be enrolled at the RP2D. In part B, a total of 60 enrolled patients would have resulted in ∼54 treated patients with evaluable post-baseline tumor data (∼18 per cohort), assuming no more than 10% patient withdrawal before post-baseline tumor assessments.

The safety analysis set was defined as all patients who received at least one dose of BOS172738. The evaluable analysis set included all patients who received at least one dose of BOS172738 and had an evaluable baseline tumor assessment and at least one evaluable post-baseline tumor assessment. The per-protocol set was a subset of the evaluable analysis set that could also be used to analyze select efficacy endpoints and was based on study drug exposure (compliance and/or time on study drug) and major protocol deviations. The pharmacokinetic analysis set included all patients who received at least one dose of BOS172738 and had at least one post-dose blood sample providing evaluable pharmacokinetic data for BOS172738.

Data were summarized descriptively. Tumor responses at each visit, best overall response (OR), ORR, and DCR were summarized and two-sided 95% exact confidence intervals (CIs) were calculated. Time-to-event analyses for PFS, DoR, DoCR, and time to response were assessed using Kaplan–Meier methods, as appropriate.

Before initiating part B, an interim analysis to determine the MTD and/or RP2D was carried out based on a review of safety, efficacy, tolerability, pharmacokinetics, and compliance.

For handling of missing data, any TEAEs missing causality to study drug were analyzed as being related to study treatment, and any TEAEs missing severity grade were analyzed as being grade 3.

All statistical analyses were carried out using Statistical Analysis System (SAS®) software version 9 or higher (SAS Institute Inc., Cary, NC).

RESULTS

Patients

Between 29 January 2019 and 13 August 2021, in total in parts A and B, 123 patients were screened, 117 patients received at least one dose of BOS172738 and were included in the safety analysis set, and 101 patients were included in the evaluable analysis set. At the time of the data cut-off for the interim report (01 April 2022), 95 patients had completed study treatment, and 22 patients were still on treatment (Supplementary Figure S2A and B, available at https://doi.org/10.1016/j.esmoop.2025.105543). The final data cut-off date (16 November 2023) included the final data from these 22 patients.

In part A, 69 patients were screened, 67 (97%) patients were included in the safety analysis set, 55 (80%) patients in the evaluable analysis set, 9 (13%) patients were still on treatment at the interim cut-off date, 58 (84%) patients discontinued study treatment [most frequently reasons for discontinuation included: 31 (45%) patients radiographic disease progression, and 18 (26%) patients AEs], and the mean duration on study treatment and duration on study were 41.8 weeks and 45.6 weeks, respectively. In part B, 54 patients were screened, 50 (93%) patients were included in the safety analysis set, 46 (85%) patients in the evaluable analysis set, 13 (24%) patients were still on treatment at the interim cut-off date, 37 (69%) patients discontinued study treatment [most frequently reasons for discontinuation included: 26 (48%) patients radiographic disease progression and 7 (13%) patients AEs], and the mean duration on study treatment and duration on study were 27.6 weeks and 30.1 weeks, respectively.

Overall, in parts A and B, 43 (37%) patients and 74 (63%) patients had a baseline ECOG PS of 0 and 1, respectively; the mean years with disease at screening was 3.20, the majority of patients had stage IV tumors at initial diagnosis [76 (65%) patients] and metastatic disease at study entry [114 (97%) patients], and the primary tumor type was NSCLC for 69 (59%) patients, MTC for 31 (26%) patients, and other for 17 (15%) patients. The specific *RET* gene alterations present in the greatest proportion were KIF5B [36 (31%) patients], CCDC6 [19 (16%) patients], and M918T [18 (15%) patients] (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105543). A history of brain metastases (stable at study entry) was reported in 24 (21%) patients. Baseline disease characteristics generally were similar between parts A and B.

In part A, the number of patients per dose level of BOS172738 was as follows: 10 mg ($n = 1$), 20 mg ($n = 1$), 40 mg ($n = 3$), 50 mg ($n = 10$), 75 mg ($n = 20$), 100 mg ($n = 19$), and 150 mg ($n = 13$). Two patients signed the informed consent form (ICF) and were screened but not assigned to a cohort. Of the 67 patients in the safety analysis set, the median age was 59 years (range 25-86 years), 38 (57%) were male, 62 (93%) had measurable target lesions, and patients were heavily pretreated with a median number of prior systemic regimens of 2 (range 0-6) [the two most common prior treatments were: 42 (63%)

Table 1. Patient baseline characteristics

Baseline characteristics	Dose escalation (part A)	Dose expansion (part B)				Overall	
	Total (all dose levels) ($n = 67$)	*RET* gene-fusion NSCLC BOS 75 mg ($n = 20$)	*RET* gene-mutant MTC BOS 75 mg ($n = 7$)	Other BOS 75 mg ($n = 23$)	Total ($n = 50$)	Total (all pooled data) BOS 75 mg ($n = 70$)	Total ($n = 117$)
Median age, years (range)	59.0 (25-86)	57.0 (22-78)	65.0 (43-79)	59.0 (33-79)	59.0 (22-79)	59.0 (22-86)	59.0 (22-86)
Male/female, *n* (%)	38 (57)/29 (43)	9 (45)/11 (55)	6 (86)/1 (14)	15 (65)/8 (35)	30 (60)/20 (40)	43 (61)/27 (39)	68 (58)/49 (42)
Race, *n* (%):							
Asian	17 (25)	14 (70)	1 (14)	9 (39)	24 (48)	30 (43)	41 (35)
White	20 (30)	4 (20)	2 (29)	8 (35)	14 (28)	20 (29)	34 (29)
Not reported	30 (45)	2 (10)	4 (57)	6 (26)	12 (24)	20 (29)	42 (36)
Presence of target lesions, *n* (%):							
Yes	62 (93)	20 (100)	7 (100)	23 (100)	50 (100)	69 (99)	112 (96)
No	5 (7)	0	0	0	0	1 (1)	5 (4)
Presence of non-target lesions, *n* (%):							
Yes	65 (97)	18 (90)	7 (100)	22 (96)	47 (94)	66 (94)	112 (96)
No	2 (3)	2 (10)	0	1 (4)	3 (6)	4 (6)	5 (4)
Median sum of target lesion diameter,[a] mm (range)	65.5 (11-205)	34.6 (13-116)	43.0 (32-130)	51.0 (13-302)	43.3 (13-302)	49.0 (13-302)	52.5 (11-302)
Median number of prior systemic regimens, *n* (range)	2 (0-6)	2 (0-4)	1 (1-3)	3 (1-7)	2 (0-7)	2 (0-7)	2 (0-7)
Number of prior systemic metastatic regimens, *n* (%):							
Median, *n* (range)	1.0 (0-6)	1.0 (0-4)	1.0 (0-3)	3.0 (0-7)	2.0 (0-7)	2.0 (0-7)	1.0 (0-7)
0	14 (21)	2 (10)	1 (14)	1 (4)	4 (8)	8 (11)	18 (15)
1	24 (36)	10 (50)	4 (57)	3 (13)	17 (34)	24 (34)	41 (35)
2	16 (24)	2 (10)	1 (14)	7 (30)	10 (20)	14 (20)	26 (22)
3	7 (10)	4 (20)	1 (14)	4 (17)	9 (18)	11 (16)	16 (14)
4	3 (4)	2 (10)	0	3 (13)	5 (10)	6 (9)	8 (7)
≥4	3 (4)	0	0	5 (22)	5 (10)	7 (10)	8 (7)
Treatment type,[b] *n* (%):							
Biological	4 (6)	0	0	1 (4)	1 (2)	3 (4)	5 (4)
Chemotherapy	42 (63)	18 (90)	1 (14)	16 (70)	35 (70)	48 (69)	77 (66)
Hormonal therapy	3 (4)	0	0	1 (4)	1 (2)	4 (6)	4 (3)
Immunotherapy	20 (30)	12 (60)	0	13 (57)	25 (50)	31 (44)	45 (38)
Targeted small molecule	24 (36)	(10)	7 (100)	20 (87)	29 (58)	37 (53)	53 (45)
Other	5 (7)	0	0	1 (4)	1 (2)	3 (4)	6 (5)
Therapy type,[b] *n* (%):							
Adjuvant	7 (10)	3 (15)	1 (14)	1 (4)	5 (10)	8 (11)	12 (10)
Neoadjuvant	6 (9)	0	0	1 (4)	1 (2)	2 (3)	7 (6)
Metastatic	53 (79)	18 (90)	6 (86)	22 (96)	46 (92)	62 (89)	99 (85)
Locally advanced	5 (7)	1 (5)	0	1 (4)	2 (4)	5 (7)	7 (6)
Other[c]	0	1 (5)	0	1 (4)	2 (4)	2 (3)	2 (2)
BOR,[d] *n* (%):							
CR	1 (1)	0	2 (29)	0	2 (4)	2 (3)	3 (3)
PR	20 (30)	7 (35)	1 (14)	14 (61)	22 (44)	28 (40)	42 (36)
SD	22 (33)	7 (35)	1 (14)	6 (26)	14 (28)	19 (27)	36 (31)
PD	7 (10)	2 (10)	1 (14)	3 (13)	6 (12)	9 (13)	13 (11)
NE	2 (3)	2 (10)	0	0	2 (4)	3 (4)	4 (3)
Unknown	7 (10)	1 (5)	2 (29)	0	3 (6)	7 (10)	10 (9)

BOR, best overall response; BOS, BOS172738; CR, complete response; MTC, medullary thyroid cancer; *n*, number of patients; NE, not evaluable; NSCLC, non-small-cell lung cancer; PD, progressive disease; PR, partial response; RET, rearranged during transfection; SD, stable disease.
[a]As per RECIST v.1.1.
[b]Patients are counted at most once per category.
[c]Other primary tumors included: sarcoma, pancreas, bladder, prostate, cholangiocarcinoma, and other tumors.
[d]The BOR was determined for prior cancer therapies by the following hierarchy: CR, PR, SD, PD, NE, and unknown.

received chemotherapy, followed by 24 (36%) receiving targeted therapy] (Table 1).

In part B, the number of patients per cohort who received BOS172738 75 mg included: *RET* gene-fusion NSCLC ($n = 20$), *RET* gene-mutant MTC ($n = 7$), other ($n = 23$). Four patients signed the ICF and were screened but not assigned to a cohort. Of the 50 patients in the safety analysis set, the median age was 59 years (range 22-79 years), 30 (50%) were male, 50 (100%) had measurable target lesions, and patients were heavily pre-treated with a median number of prior systemic regimens of 2 (range 0-7) [the two most common prior treatments were: 35 (70%) received chemotherapy, followed by 29 (58%) receiving targeted therapy] (Table 1).

Table 2. Summary of treatment-emergent adverse events (safety analysis set)

Safety parameters, *n* (%)	Dose escalation (part A)	Dose expansion (part B)				Overall	
	Total (all dose levels) ($n = 67$)	*RET* gene-fusion NSCLC BOS 75 mg ($n = 20$)	*RET* gene-mutant MTC BOS 75 mg ($n = 7$)	Other BOS 75 mg ($n = 23$)	Total ($n = 50$)	Total (all pooled data) BOS 75 mg ($n = 70$)	Total ($n = 117$)
Any TEAE	67 (100)	20 (100)	7 (100)	23 (100)	50 (100)	70 (100)	117 (100)
Grade ≥3	57 (85)	19 (95)	6 (86)	16 (70)	41 (82)	57 (81)	98 (84)
TEAE related to BOS							
Any	61 (91)	20 (100)	7 (100)	11 (48)	38 (76)	57 (81)	99 (85)
Grade ≥3	39 (58)	14 (70)	6 (86)	4 (17)	24 (48)	34 (49)	63 (54)
Serious TEAEs							
Any	39 (58)	9 (45)	2 (29)	17 (74)	28 (56)	35 (50)	67 (57)
Related to BOS	12 (18)	1 (5)	0	1 (4)	2 (4)	4 (6)	16 (14)
Any TEAE leading to							
BOS dose reduction	19 (28)	4 (20)	2 (29)	4 (17)	10 (20)	14 (20)	29 (25)
BOS dose interruption	45 (67)	17 (85)	5 (71)	11 (48)	33 (66)	46 (66)	78 (67)
BOS discontinuation	23 (34)	1 (5)	1 (14)	5 (22)	7 (14)	13 (19)	30 (26)
Study discontinuation	11 (16)	3 (15)	1 (14)	3 (13)	7 (14)	9 (13)	18 (15)
Any TEAE related to BOS leading to							
BOS discontinuation	14 (21)	0	1 (14)	1 (4)	2 (4)	6 (9)	16 (14)
Study discontinuation	4 (6)	0	1 (14)	0	1 (2)	2 (3)	5 (4)
Any TEAE resulting in death	9 (13)	1 (5)	0	1 (4)	2 (4)	3 (4)	11 (9)
TEAEs related to BOS of CTCAE grade ≥3 by preferred term in >1 patient[a]							
Blood creatinine phosphokinase increased	19 (28)	8 (40)	2 (29)	0	10 (20)	14 (20)	29 (25)
Neutrophil count decreased	5 (7)	5 (25)	1 (14)	1 (4)	7 (14)	9 (13)	12 (10)
Anemia	7 (10)	2 (10)	0	1 (4)	3 (6)	4 (6)	10 (9)
Neutropenia	4 (6)	0	0	0	0	2 (3)	4 (3)
Hypophosphatemia	3 (4)	0	2 (29)	1 (4)	3 (6)	4 (6)	6 (5)
Diarrhea	3 (4)	0	0	0	0	1 (1)	3 (3)
Lymphopenia	1 (1)	1 (5)	0	1 (4)	2 (4)	2 (3)	3 (3)
Muscular weakness	3 (4)	0	0	0	0	1 (1)	3 (3)
Myositis	2 (3)	0	0	0	0	0	2 (2)
Asthenia	2 (3)	0	0	0	0	1 (1)	2 (2)

Patients were counted at most once per category. TEAEs were defined as adverse events which started any time after first dose through 31 days after last dose of study drug. Related TEAEs were those the investigator found likely related to study drug or causality was missing.
TEAEs with a missing severity were classified as grade 3. TEAEs with missing seriousness were classified as serious. Adverse events were coded using MedDRA version 21.1.
BOS, BOS172738; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); MedDRA, Medical Dictionary for Regulatory Activities; MTC, medullary thyroid cancer; *n*, number of patients; NSCLC, non-small-cell lung cancer; RET, rearranged during transfection; TEAE, treatment-emergent adverse event.
[a]Total patients in part A.

At the final data cut-off, overall (in parts A and B), the mean treatment duration was 45.1 weeks (range 0.9-216.3 weeks); the mean treatment compliance was 90% (range 39%-101%). For the 117 patients who received at least one dose of BOS172738 (safety analysis set), treatment was discontinued primarily due to radiographically documented progressive disease (55%), TEAEs (20%), and subject withdrawal (17%).

Safety

In part A, three patients experienced DLTs, one patient each in the BOS172738 150 mg cohort (capillary leak syndrome which led to treatment withdrawal, but no intervention was required, and the event resolved), 100 mg cohort (muscle weakness and blood creatine phosphokinase increased), and 75 mg cohort (blood creatine phosphokinase increased). However, the MTD was not reached. Without a formal determination of MTD, a dose of 75 mg was recommended for further exploration in the expansion cohorts (part B).

Table 2 provides a summary of the TEAEs in parts A and B. At the final data cut-off, overall (in parts A and B, safety analysis set), 100% of patients experienced at least one TEAE, of which 98 (84%) had CTCAE grade ≥3 TEAEs. TEAEs related to BOS172738 occurred in 99 (85%) patients, with 63 (54%) having CTCAE grade ≥3 TEAEs. The most common TEAEs reported were blood creatine phosphokinase increased [72 (62%)], aspartate aminotransferase increased [48 (41%)], anemia [46 (39%)], diarrhea [41 (35%)], dyspnea [34 (29%)], fatigue [33 (28%)], facial edema [31 (26%)], hypophosphatemia [31 (26%)], and constipation [30 (26%)]. The three most common grade ≥3 TEAEs related to BOS172738 were blood creatine phosphokinase increased [29 (25%)], neutrophil count decreased [12 (10%)], and anemia [10 (9%)].

Serious TEAEs occurred in 67 (57%) patients, and serious TEAEs related to BOS172738 occurred in 16 (14%) patients. The three most common serious TEAEs were dyspnea [8 (7%)], pneumonia [7 (6%)], and anemia [4 (3%)]. The

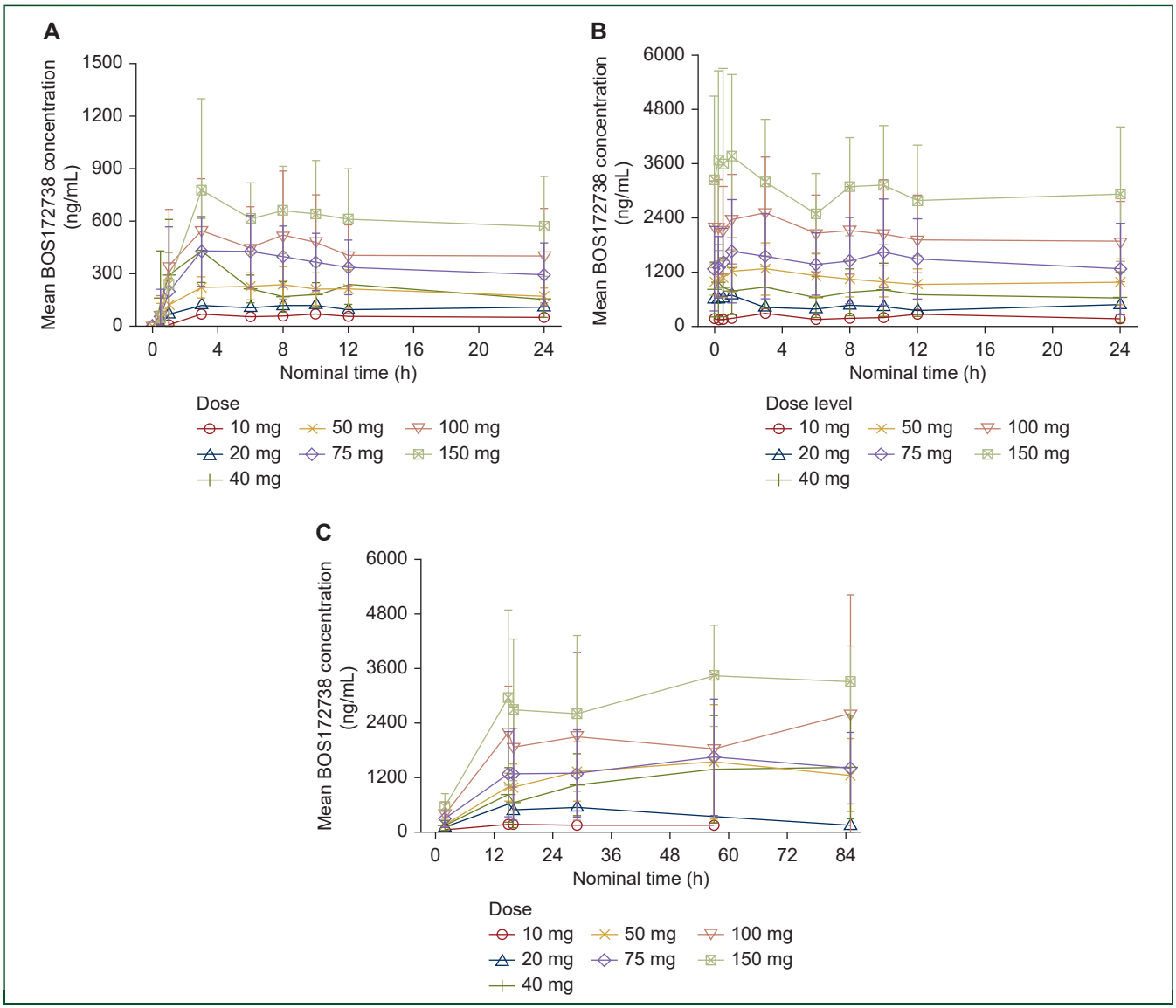


Figure 1. Mean observed BOS172738 plasma and trough concentrations versus time. (A) Plasma concentration versus time overlaid by dose level (cycle 1 day 1); (B) plasma concentration versus time overlaid by dose level (cycle 1 day 15); and (C) trough concentration versus time overlaid by dose level.

most common serious TEAEs related to BOS172738 were muscular weakness [3 (3%)] and myositis [2 (2%)]; the remainder occurred in one patient per preferred term.

Twenty-nine (25%) patients had TEAEs leading to dose reduction, 78 (67%) had dose interruption, 30 (26%) had discontinuation of BOS172738, and 16 (14%) had TEAEs related to BOS172738 leading to discontinuation of BOS172738.

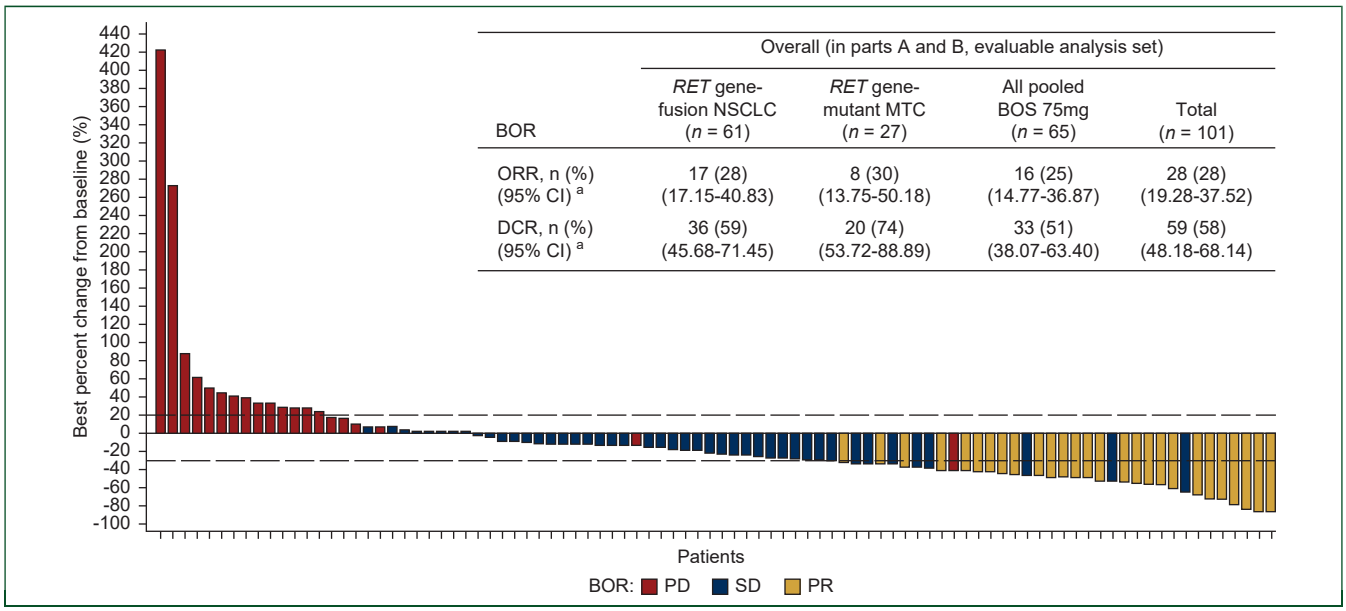
Overall, TEAEs resulted in death in 11 (9%) patients in total. None of the deaths reported were considered related to BOS172738. The only TEAE occurring in more than one patient within a preferred term was dyspnea (2%).

Pharmacokinetics

Mean BOS172738 plasma concentrations increased with increasing doses on cycle 1 day 1 (Figure 1A) and cycle 1 day 15 (Figure 1B), with secondary plasma concentration peaks being observed. After 12 h, concentrations slowly declined but remained quantifiable through 24 h. T_{max} ranged between 3 and 10 h across all dose levels on cycle 1 day 1, and between 1 and 3.1 h on cycle 1 day 15. Based on mean trough concentration and effective $t_{½}$ (geometric mean ranged from 41.9 to 84.1 h), steady state appears to be reached by day 15 in most treatment groups (Figure 1C). The AUC accumulation ratios ranged from 2.82 to 5.27 following once-daily administration. C_{max} and AUC were generally dose proportional with a point estimate of the slope near 1 on both cycle 1 day 1 and cycle 1 day 15. Variability was moderate for C_{max} and AUC on both days (geometric coefficient of variation % generally 35%-65%).

Efficacy

Overall, in parts A and B (evaluable analysis set), the ORR was 28% (28/101; 95% CI 19.28% to 37.52%) and the DCR was 58% (59/101; 95% CI 48.18% to 68.14%) (Supplementary Table S1, available at https://doi.org/10.



BOR	Overall (in parts A and B, evaluable analysis set)			
	RET gene-fusion NSCLC (*n* = 61)	*RET* gene-mutant MTC (*n* = 27)	All pooled BOS 75mg (*n* = 65)	Total (*n* = 101)
ORR, n (%) (95% CI) [a]	17 (28) (17.15-40.83)	8 (30) (13.75-50.18)	16 (25) (14.77-36.87)	28 (28) (19.28-37.52)
DCR, n (%) (95% CI) [a]	36 (59) (45.68-71.45)	20 (74) (53.72-88.89)	33 (51) (38.07-63.40)	59 (58) (48.18-68.14)

Figure 2. Waterfall plot of best overall response (evaluable analysis set). Horizontal lines represent criteria for target lesion response of PD (20% increase) and PR (30% decrease) (i.e. the patient's best response and change relative to baseline, with response based on RECIST v.1.1). ORR was the percentage of patients with confirmed complete or partial response. DCR was the percentage of patients achieving ORR or stable disease lasting ≥15 weeks (16 weeks—7-day window) from first dose.

BOR, best overall response; BOS, BOS172738; CI, confidence interval; DCR, disease control rate; MTC, medullary thyroid cancer; *n*, number of patients; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RET, rearranged during transfection; SD, stable disease.

[a]95% CI was calculated based on the exact Clopper—Pearson for binominal proportions.

1016/j.esmoop.2025.105543, Figure 2). No patients had a complete response. For patients with NSCLC, the ORR was 28% (17/61; 95% CI 17.15% to 40.83%) and the DCR was 59% (36/61; 95% CI 45.68% to 71.45%). For patients with MTC, the ORR was 30% (8/27; 95% CI 13.75% to 50.18%) and the DCR was 74% (20/27; 95% CI 53.72% to 88.89%). Responses were also observed in patients with brain metastases, one of whom had a 43% reduction in brain target lesions following BOS172738 treatment at the first post-baseline scan. Supplementary Figure S4A and B, available at https://doi.org/10.1016/j.esmoop.2025.105543, presents spider plots representing the percent of change from baseline in target lesion measurements over time in assessable patients by dose in part A, and by *RET*-fusion-positive NSCLC and *RET*-mutant MTC, respectively. Best OR by tumor type and dose is shown in Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2025.105543.

The median PFS (mPFS) was 7.16 months (95% CI 5.32-8.77 months). For patients with NSCLC and MTC, the mPFS was 6.18 months (95% CI 3.91-7.36 months) and 12.75 months (95% CI 5.32-21.95 months), respectively. Kaplan—Meier estimates for PFS in the evaluable analysis set are shown in Supplementary Figure S6A-F, available at https://doi.org/10.1016/j.esmoop.2025.105543, for overall, NSCLC, and MTC cohorts in parts A and B.

The median DoR (mDoR) for confirmed responders was 11.10 months (95% CI 5.78-20.99 months). For confirmed responders with NSCLC and MTC, the mDoR was 10.17 months (95% CI 4.57-22.51 months) and 19.15 months (95% CI 5.78 months-not available), respectively. The median time to response was 1.79 months (95% CI 1.74-1.87 months) for all confirmed responders.

Pharmacodynamics and biomarkers

Of the 117 patients in the safety analysis set, 112 patients had cfDNA samples analyzed, of which 74 had *RET* alterations [single nucleotide variant (SNV), fusion, or both]. Of these 74 patients, OR and percent change in tumor size from baseline were available for 58 patients (25 part A and 33 part B), and the 58 patients included 37 NSCLC, 13 MTC, and 8 other advanced tumors (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2025.105543). In these 58 patients, 29% (17/58) had partial responses (7 part A and 10 part B), 43% (25/58) had stable disease (12 part A and 13 part B), and 28% (16/58) had progressive disease as best response (6 part A and 10 part B).

These 58 patients included 64% (37/58) with *RET* fusions, 33% (19/58) with SNVs, and 3% (2/58) with *RET*-fusion-positive SNV. Of the 117 patients enrolled in the trial based on local *RET* results, 93 patients had associated efficacy data. Patients with *RET* fusions responded better and at a higher frequency than those with SNV; ORR and DCR were comparable between the patient cohort with cfDNA *RET* alterations ($n = 58$) and the cohort enrolled based on local results ($n = 93$) (Table 3). Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2025.105543, presents a waterfall plot of percent change in tumor size in the 58 patients with cfDNA-detected RET alterations and clinical response, by individual patient, tumor type, and dose.

DISCUSSION

In this phase I study, despite most patients having metastatic disease and being heavily pretreated at enrollment,

Table 3. Patients with cfDNA *RET* mutation or local *RET* and clinical outcome

BOR, *n* (%)	*RET* fusions (*n* = 37)	SNV (*n* = 19)	*RET* fusions + SNV (*n* = 2)	Total (*n* = 58)
Patients with cfDNA *RET* mutation and clinical outcome[a]				
PR	12 (32)	4 (21)	1 (50)	17 (29)
SD	19 (51)	6 (32)	0	25 (43)
PD	6 (16)	9 (47)	1 (50)	16 (28)
ORR	12 (32)	4 (21)	1 (50)	17 (29)
DCR	31 (84)	10 (53)	1 (50)	42 (72)
	***RET* fusions (*n* = 57)**	**SNV (*n* = 30)**	**Indel (*n* = 6)**	**Total (*n* = 93)**
Patients with local *RET* and clinical outcome[a]				
PR	21 (37)	6 (20)	1 (17)	28 (30)
SD	26 (46)	15 (50)	4 (67)	45 (48)
PD	10 (18)	9 (30)	1 (17)	20 (22)
ORR	21 (37)	6 (20)	1 (17)	28 (30)
DCR	47 (82)	21 (70)	5 (83)	73 (78)

DCR was calculated as PR + SD.

BOR, best overall response; cfDNA, circulating free tumor DNA; DCR, disease control rate; *n*, number of patients; ORR, objective response rate; PD, progressive disease; PR, partial response; RET, rearranged during transfection; SD, stable disease; SNV, single nucleotide variation.

[a]Clinical outcome: patients with results available for overall response and percent change in tumor size from baseline.

BOS172738 had a manageable toxicity profile and achieved durable antitumor activity in patients with *RET*-altered advanced solid tumors. While the primary objective was to establish MTD and the RP2D of BOS172738, the MTD was not reached among doses administered orally from 10 to 150 mg once daily. In the absence of an established MTD at the conclusion of part A, a 75 mg dose was recommended for further evaluation in part B. This decision was based on available pharmacokinetic, safety, and preliminary efficacy data, with a focus on minimizing potential increases in creatine phosphokinase and reducing the low incidence of low-grade muscle weakness that had been observed at higher dose levels. Further experience with BOS172738 showed that creatine phosphokinase elevations were generally asymptomatic and did not predict muscle weakness. Additionally, this infrequent muscle weakness was also found to be readily reversible with dose modifications and is considered an on-target effect given the role of RET in maintaining the neuromuscular junction.[20] A review of both safety and efficacy data from the 75 mg and 100 mg dose cohorts suggested that higher efficacy may be achieved at 100 mg compared with 75 mg, with an ORR of 57% versus 25%, respectively, without a considerable change in the overall safety profile. Further evaluation of BOS172738 at dose levels >75 mg may be warranted in future studies.

In this study, the incidence of TEAEs was comparable between BOS172738 75 mg (all pooled data, *n* = 70) patients and total patients (*n* = 117) (Table 2). Consistent with its RET-selective profile and lack of substantial off-target activity, BOS172738-related TEAEs were mostly grade 1-2. The most common grade ≥3 BOS172738-related TEAEs of blood creatine phosphokinase increased (25%), neutrophil count decreased (10%), and anemia (9%) were reversible with dose modifications. Most BOS172738-related TEAEs did not warrant dose interruption or modification, and only 4% of patients discontinued from the study due to BOS172738-related TEAEs. In the pooled data, elevated blood creatine phosphokinase led to treatment discontinuation in 2% of patients, dose reduction in 17%, and dose interruption in 28%; these events were reversible with dose modifications. In total, myositis led to dose interruption in 6% of patients. These TEAEs of blood creatine phosphokinase increased or myositis with dose interruptions mostly resolved in under 2 weeks. There was a low incidence of hypertension and hepatotoxicity in BOS172738-treated patients (2% of patients had a grade ≥3 TEAE of either hypertension or liver enzyme elevations), which contrasts with those reported for other selective RET inhibitors (e.g. around 11%-12% and 5%-7% grade ≥3 hepatotoxicity for selpercatinib and pralsetinib, respectively; and around 20% and 18% grade ≥3 hypertension for selpercatinib and pralsetinib, respectively).[21,22] The results from our study suggest that the long-term treatment of patients is feasible with BOS172738.

BOS172738 pharmacokinetics exhibited dose-dependent exposure, with rapid absorption and steady state achieved by day 15.

BOS172738 showed antitumor activity in heavily pretreated patients with advanced solid tumors harboring RET alterations. In *RET*-fusion-positive NSCLC, the ORR was 28%, DCR was 59%, mPFS was 6.18 months, and mDoR was 10.17 months. In *RET*-mutant MTC, the ORR was 30%, DCR was 74%, mPFS was 12.75 months, and mDoR was 19.15 months. These data suggest that patients had a meaningful benefit with BOS172738, even though they were pretreated with a median of two prior systemic therapies (some patients had up to seven prior systemic therapies) with prior treatment including 66% chemotherapy, 45% targeted therapy, and 38% immunotherapy; 88% of patients received prior therapy for metastatic disease. In these patients with multiple lines of prior therapy and advanced disease, the efficacy outcomes observed, along with patients being able to continuously receive treatment for >4 years, demonstrated that BOS172738 had durable antitumor activity in patients with both *RET*-fusion-positive NSCLC and *RET*-mutant MTC. These data also suggest that BOS172738 may be able to overcome resistance to prior lines of other therapies. Furthermore, the median time to response of 1.79 months indicates that most confirmed responders achieved a rapid response (i.e. by the first post-treatment radiological assessment). Notably, intracranial activity was also observed with BOS172738.

These preliminary efficacy results of BOS172738 show improvement on those previously achieved with the multikinase inhibitors with RET activity (i.e. 28% ORR and mPFS of 5.5 months with cabozantinib in patients with advanced *RET*-rearranged lung adenocarcinomas; 18% ORR and mPFS of 4.5 months with vandetanib in *RET*-fusion-positive

NSCLC; and 16% ORR and mPFS of 7.3 months with lenvatinib in patients with MTC harboring RET-M918T).[10,23] For selective RET inhibitors, in previously treated *RET*-fusion-positive NSCLC, an ORR of 64% and an mPFS of 16.5 months have been reported with selpercatinib (160 mg twice daily) and an ORR of 61% has been reported with pralsetinib (400 mg once daily).[24,25] In previously treated *RET*-fusion-positive solid tumors including *RET*-mutant MTC, an ORR of 44%-69%, an mPFS of 13.2 months, and a 1-year PFS of 82%, respectively, have been reported with selpercatinib (160 mg twice daily) and an ORR of 57%-61% with pralsetinib (400 mg once daily).[12,26-28] In part A of our study, BOS172738 at a dose of 100 mg had an ORR of 57% and an objective DCR (ODCR) of 93%, while lower doses had lower ORRs and ODCRs (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105543). From our study, BOS172738 shows preliminary efficacy data, but requires further evaluation and possibly at a higher dose to achieve higher efficacy.

Data from the biomarker analysis support that a cfDNA-based test can be used as a patient selection biomarker of response to BOS172738.

The BOS172738-01 study does have several limitations, including being an early-phase clinical trial, with a small sample size which limits generalizing findings across broader populations of patients with *RET*-fusion-positive NSCLC and *RET*-mutant MTC. Also, as it was a single-arm design, direct comparison with existing approved RET inhibitors was precluded, and as most of the enrolled patients were heavily pretreated, the outcomes could potentially be skewed due to baseline heterogeneity in disease progression and prior therapies. Another limitation of this study is that the MTD was not reached, raising the possibility that the selected dose for evaluation in part B may have been lower than optimal, potentially having an impact on the efficacy outcomes.

Conclusion

BOS172738 showed preliminary efficacy and manageable safety results in patients with *RET*-altered advanced solid tumors. Continued benefits from BOS172738 were observed at doses ranging from 10 to 150 mg, administered orally once daily for a duration exceeding 4 years, sustaining overall benefit with a notably encouraging safety profile.

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DISCLOSURE

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DATA SHARING

Datasets generated and analyzed are commercially sensitive and are not publicly available. Requests for data supporting findings in the manuscript should be made to the corresponding author and will be reviewed individually. Individual patient-level raw data containing confidential or identifiable patient information are subject to patient privacy and cannot be shared. Data can be shared in the form of aggregated summaries.

REFERENCES

1. Desilets A, Repetto M, Yang SR, Sherman EJ, Drilon A. *RET*-altered cancers-a tumor-agnostic review of biology, diagnosis and targeted therapy activity. *Cancers (Basel)*. 2023;15(16):4146.
2. Addeo A, Miranda-Morales E, den Hollander P, et al. RET aberrant cancers and RET inhibitor therapies: current state-of-the-art and future perspectives. *Pharmacol Ther*. 2023;242:108344.
3. Regua AT, Najjar M, Lo HW. RET signaling pathway and RET inhibitors in human cancer. *Front Oncol*. 2022;12:932353.
4. Schoffski P, Cho BC, Italiano A, et al. BOS172738, a highly potent and selective RET inhibitor, for the treatment of *RET*-altered tumors including *RET*-fusion+ NSCLC and *RET*-mutant MTC: phase 1 study results. *J Clin Oncol*. 2021;39(suppl 15):3008. 3008.
5. Thein KZ, Velcheti V, Mooers BHM, Wu J, Subbiah V. Precision therapy for RET-altered cancers with RET inhibitors. *Trends Cancer*. 2021;7(12):1074-1088.
6. Gandhi MM, Ricciuti B, Harada G, et al. Amplification of wild-type RET represents a novel molecular subtype of several cancer types with clinical response to selpercatinib. *JCO Precis Oncol*. 2023;7:e2300295.
7. Subbiah V, Cote GJ. Advances in targeting RET-dependent cancers. *Cancer Discov*. 2020;10(4):498-505.
8. Zhang Y, Zheng W-H, Zhou S-H, et al. Molecular genetics, therapeutics and RET inhibitor resistance for medullary thyroid carcinoma and future perspectives. *Cell Commun Signal*. 2024;22(1):460.
9. Miyazaki I, Odintsov I, Ishida K, et al. Vepafestinib is a pharmacologically advanced RET-selective inhibitor with high CNS penetration and inhibitory activity against RET solvent front mutations. *Nat Cancer*. 2023;4(9):1345-1361.
10. Zhao L, Wang N, Zhang D, Jia Y, Kong F. A comprehensive overview of the relationship between RET gene and tumor occurrence. *Front Oncol*. 2023;13:1090757.
11. Hamidi S, Hu MI. RET kinase inhibitors for the treatment of RET-altered thyroid cancers: current knowledge and future directions. *Ann Endocrinol*. 2024;85(2):118-126.
12. Clark L, Fisher G, Brook S, Patel S, Arkenau H-T. Selective RET inhibitors (SRIs) in cancer: a journey from multi-kinase inhibitors to the next generation of SRIs. *Cancers*. 2024;16(1):31.
13. Solomon BJ, Tan L, Lin JJ, et al. RET solvent front mutations mediate acquired resistance to selective RET inhibition in RET-driven malignancies. *J Thorac Oncol*. 2020;15(4):541-549.
14. Subbiah V, Shen T, Terzyan SS, et al. Structural basis of acquired resistance to selpercatinib and pralsetinib mediated by non-gatekeeper RET mutations. *Ann Oncol*. 2021;32(2):261-268.
15. Subbiah V, Gouda MA, Iorgulescu JB, et al. Adaptive Darwinian off-target resistance mechanisms to selective RET inhibition in RET driven cancer. *NPJ Precis Oncol*. 2024;8(1):62.
16. Novello S, Califano R, Reinmuth N, Tamma A, Puri T. RET fusion-positive non-small cell lung cancer: the evolving treatment landscape. *Oncologist*. 2023;28(5):402-413.
17. Keegan M, Wilcoxen K, Ho PT. Abstract 2199: BOS172738: A novel highly potent and selective RET kinase inhibitor in phase 1 clinical development. *Cancer Res*. 2019;79(suppl 13):2199.
18. Schoffski P, Aftimos PG, Massard C, et al. A phase I study of BOS172738 in patients with advanced solid tumors with RET gene alterations including non-small cell lung cancer and medullary thyroid cancer. *J Clin Oncol*. 2019;37(suppl 15):TPS3162.
19. Vodopivec DM, Hu MI. RET kinase inhibitors for *RET*-altered thyroid cancers. *Ther Adv Med Oncol*. 2022;14:17588359221101691.
20. Baudet C, Pozas E, Adameyko I, Andersson E, Ericson J, Ernfors P. Retrograde signaling onto Ret during motor nerve terminal maturation. *J Neurosci*. 2008;28(4):963-975.
21. RETEVMO® (selpercatinib) Prescribing Information. 2024. Available at https://pi.lilly.com/us/retevmo-uspi.pdf. Accessed January 8, 2025.
22. GAVRETO® (pralsetinib) Prescribing Information. 2023. Available at https://gavreto-hcp.com/downloads/pdf/GAVRETO-Full-Prescribing-Information.pdf. Accessed January 8, 2024.
23. Drilon A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol*. 2016;17(12):1653-1660.
24. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. *N Engl J Med*. 2020;383(9):813-824.
25. Gainor JF, Curigliano G, Kim DW, et al. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. *Lancet Oncol*. 2021;22(7):959-969.
26. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol*. 2022;23(10):1261-1273.
27. Subbiah V, Hu MI, Wirth LJ, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. *Lancet Diabetes Endocrinol*. 2021;9(8):491-501.
28. Subbiah V, Cassier PA, Siena S, et al. Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. *Nat Med*. 2022;28(8):1640-1645.