High-dose alectinib for *RET* fusion-positive non-small cell lung cancer in the Blood First Assay Screening Trial

Rafal Dziadziuszko[1], Nir Peled[2,3], Tony Mok[4], Solange Peters[5], Santiago Ponce Aix[6], Jorge Alatorre-Alexander[7], Brian D. Vicuna[8], Margaret Maclennan[9], Vijay Bhagawati-Prasad[10], Sarah M. Shagan[11], Erica Schleifman[11], Thorsten Ruf[12], Michael S. Mathisen[11], Shirish M. Gadgeel[13]

[1]Department of Oncology and Radiotherapy and Early Clinical Trials Centre, Medical University of Gdańsk, Gdańsk, Poland
[2]Soroka Medical Centre and Ben-Gurion University, Beer-Sheeva, Israel
[3]Helmsley Cancer Centre, Shaare Zedek Medical Centre, Hebrew University, Jerusalem, Israel (currently)
[4]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Chinese University of Hong Kong, Hong Kong
[5]Lausanne University Hospital, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[6]Hospital Universitario 12 de Octubre, Madrid, Spain
[7]Health Pharma Professional Research, Mexico City, Mexico
[8]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA
[9]Syneos Health, Edinburgh, UK
[10]F. Hoffmann-La Roche, Ltd., Welwyn Garden City, UK
[11]Genentech, Inc., South San Francisco, CA, USA
[12]F. Hoffmann-La Roche, Ltd., Basel, Switzerland
[13]Department of Internal Medicine, Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI, USA

Introduction: This paper presents results from Cohort B (rearranged during transfection [*RET*], fusion-positive) of the Blood First Assay Screening Trial in patients with advanced non-small cell lung cancer (NSCLC) screened for genetic alterations using blood-based next-generation sequencing.

Material and methods: Adults with advanced *RET* fusion-positive NSCLC received alectinib 900 mg twice daily (BID) in Phase I. Enrolment closed prematurely with Phase II uninitiated.

Results: Among eight treated patients, confirmed best overall responses in evaluable patients were stable disease (4/5) and progressive disease (1/5). One dose-limiting toxicity (death, unknown cause) was considered by the investigator to be related to treatment and underlying disease. Serious adverse events (SAEs) occurred in five patients, and SAEs that may be related to treatment occurred in two patients.

Conclusions: Alectinib showed limited activity in advanced *RET* fusion-positive NSCLC, and further investigation was not conducted due to the development of selective RET inhibitors pralsetinib and selpercatinib. No new safety signals were observed, and the safety profile of alectinib was in line with previous reports at the 600 mg BID dose.

Key words: alectinib, blood-based assay, Blood First Assay Screening Trial (BFAST), non-small cell lung cancer, NSCLC, *RET* fusion, ctDNA, circulating tumour DNA, liquid biopsy, NGS.

Contemp Oncol (Pozn) 2023; 27 (4): 217–223
DOI: https://doi.org/10.5114/wo.2023.135246

Introduction

Alectinib is a highly selective and potent tyrosine kinase inhibitor that targets both anaplastic lymphoma kinase (*ALK*) and the rearranged during transfection (*RET*) oncogene products [1, 2]. Alectinib monotherapy is approved in the United States (US) and European Union (EU) as a first-line and later-line treatment for adults with advanced/metastatic *ALK*-positive non-small cell lung cancer (NSCLC) at a recommended dose of 600 mg taken orally twice daily (BID) [3, 4]. However, previous *in vitro* research has shown that the half maximal inhibitory concentration (IC_{50}) of alectinib for *RET* is greater than that for *ALK* (4.8 vs. 1.9 nmol/l, respectively), suggesting the need to explore a higher dose for the treatment of patients with advanced *RET* fusion-positive NSCLC [1].

The Blood First Assay Screening Trial (BFAST; NCT03178552) is an open-label, multi-cohort study investigating the activity of multiple targeted therapies or immunotherapy in patients with unresectable, advanced or metastatic NSCLC who are screened for actionable genetic alterations exclusively using next-generation sequencing (NGS) of circulating tumour DNA (ctDNA) [5]. Seven interventional BFAST cohorts and one natural history cohort have been initiated to date, including *ALK*-positive, *RET* fusion-positive, high blood-based tumour mutational burden, *ROS1*-positive, v-raf murine sarcoma viral oncogene homologue B1 (*BRAF*) V600 mutation-positive, epidermal growth factor receptor (*EGFR)* exon 20 mutation-positive and Kirsten rat sarcoma virus (*KRAS*) G12C mutation-positive, each with their own treatment and biomarker-specific eligibility criteria [5–7]. Previously published outcomes from

the *ROS1*-positive and *ALK*-positive cohorts of the BFAST study have shown the clinical feasibility of blood-based NGS in identifying patients with *ROS1*-positive NSCLC to be treated with entrectinib and *ALK*-positive NSCLC to be treated with alectinib, respectively [6, 8].

When the BFAST study was initiated in 2017, treatment options were limited for patients with advanced *RET* fusion-positive NSCLC because platinum-based chemotherapy was the only standard of care for treatment-naïve patients. Subsequently, specific RET inhibitors such as pralsetinib and selpercatinib have demonstrated clinically meaningful activity in *RET* fusion-positive NSCLC and have thus been approved in the US and EU for the treatment of advanced/metastatic *RET* fusion-positive NSCLC [9–13].

Herein, we present results from BFAST Cohort B (alectinib in *RET* fusion-positive NSCLC), which was planned to comprise a Phase I dose-escalation phase followed by a Phase II dose expansion at the recommended Phase II dose. However, enrolment to this cohort was closed prematurely and the dose-expansion phase was not initiated due to the clinical development of pralsetinib and selpercatinib, which were not available when the BFAST study was initiated.

Material and methods

Study design and treatment

Blood First Assay Screening Trial (NCT03178552) is an ongoing, open-label, global, multicohort study; patients that were identified as having unresectable, advanced/metastatic *RET* fusion-positive NSCLC by blood-based NGS were enrolled into Cohort B of BFAST. The global, single-arm BFAST Cohort B study consisted of a Phase I dose-escalation step followed by a Phase II dose-expansion study at the recommended Phase II dose. Staggered enrolment was employed in Phase I to ensure that a maximum of two patients received treatment simultaneously during the dose-limiting toxicity (DLT) assessment window (Cycle 1, Days 1–28). The dose-limiting toxicity were defined as adverse events (AEs) assessed by the investigator to be at least possibly attributable to alectinib, including Grade 3/4 myelosuppression events or Grade ≥ 3 non-haematological toxicities.

The initial dose of alectinib to be tested in Phase I was 900 mg BID given orally with food until progressive disease (PD), unacceptable toxicity, or withdrawal of consent. The study protocol was designed to potentially test a dose of up to 1200 mg BID and allowed for dose reduction in cases of unsatisfactory tolerability.

Patients

Eligible patients were aged ≥ 18 years, with histologically or cytologically confirmed stage III/IV *RET* fusion-positive NSCLC, confirmed by a central blood-based ctDNA NGS assay, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, life expectancy ≥ 12 weeks, and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Patients with asymptomatic brain or leptomeningeal metastases at baseline were allowed to enrol. Prior systemic treatment for advanced or metastatic NSCLC was not permitted.

The protocol was approved by the institutional review board at each study site, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before initial blood screening and enrolment into a treatment cohort.

Endpoints

The primary endpoint of BFAST Cohort B was confirmed objective response rate (ORR) per investigator, defined as the proportion of patients with a complete response or partial response according to RECIST v1.1 on two assessments separated by ≥ 4 weeks. Secondary endpoints included the following: investigator-assessed duration of response (DoR), clinical benefit rate (CBR), and progression-free survival (PFS); independent review facility-assessed confirmed ORR, DoR, CBR, and PFS; overall survival; percentage of patients with AEs/safety; and the pharmacokinetic (PK) profile of alectinib. Safety was determined by the occurrence of any DLTs associated with alectinib at escalating doses. Incidence, type, and severity of AEs were based on the National Cancer Institute Common Terminology Criteria for AEs (V4.0).

Assessments

Patients were screened for actionable *RET* fusions using the Foundation Medicine Assay for Circulating Tumour DNA (FoundationACT™), a hybrid capture-based NGS assay, which was an earlier version of the FoundationOne®Liquid CDx assay (Foundation Medicine). FoundationACT™ was validated for genomic profiling of ctDNA from blood and demonstrated rearrangement detection at 100% sensitivity for mutation allele frequencies ≥ 0.5% [14]. Tumour assessments were performed at baseline and every 8 weeks during the study. Magnetic resonance imaging of the brain was required at each tumour assessment, irrespective of baseline central nervous system (CNS) disease status. Safety was assessed by the occurrence of any DLTs and by the incidence, type, and severity of AEs, including serious adverse events (SAEs) and AEs of special interest, which were graded according to the National Cancer Institute Common Terminology Criteria for AEs (v4.0) and encoded using the Medical Dictionary for Regulatory Activities (v22.0). Changes in vital signs, physical findings, and clinical laboratory results during and following administration of alectinib were also recorded.

Statistical analyses

No formal anti-tumour activity or PK analysis was performed due to early closure of the cohort. Tumour assessment data for the intent-to-treat population were provided descriptively. Safety analyses were performed on the safety-evaluable population and included all patients who received at least one dose of study drug.

Results

Patient disposition and demographics

Between 1 September 2017 and 27 February 2019, 40 out of 3787 screened patients were identified as *RET* fusion-

positive (prevalence: 1.06%); eight of these patients were enrolled into the Phase I dose-escalation part of BFAST Cohort B (*RET* fusion-positive) and received alectinib at a dose of 900 mg BID. Patients had a median age of 62.5 years, and all had stage IV lung adenocarcinoma; five patients (62.5%) had CNS disease at baseline. Most patients were white, never smokers, and had a baseline ECOG PS of 1 (Table 1). The most common *RET* fusion partner was *KIF5B* (87.5%). No patients were enrolled into the Phase II dose expansion.

Safety

At the data cut-off date (27 February 2019), mean treatment duration was 3.9 months (range: 0–8 months) with a mean number of doses of 224. Overall, the safety profile was in line with what has previously been reported in Phase III studies of alectinib (600 mg BID), and no new safety signals were observed [15–17]. All eight patients experienced at least one AE, including six (75.0%) who reported AEs potentially related to treatment (Table 2). Seven patients (87.5%) had Grade ≥ 3 AEs, and none of the Grade ≥ 3 AEs were experienced by more than one patient (Table 2). The most common AEs of any grade occurring in more than one patient were constipation (5 patients, 62.5%) and dyspnoea (four patients, 50.0%) (Table 3).

One DLT of death (unknown cause) occurred among the six DLT-evaluable patients; this was recorded as a Grade five event and was considered by the investigator to be related to study treatment and the underlying disease. The patient died at home, and there was insufficient information available to the investigator to rule out the possibility that study treatment contributed to the event. Serious adverse events occurred in five patients (62.5%) (Table 2) and were considered related to study treatment in two patients (25.0%). The serious adverse events included death (nature of the event not known), general physical health deterioration, pneumonia, blood creatine phosphokinase increase, major depression, and dyspnoea (resulting in death).

Adverse events leading to withdrawal of alectinib were reported in three patients (37.5%; death [nature of the event not known], general physical health deterioration, and dyspnoea), and four patients (50.0%) experienced AEs requiring dose modification of alectinib (blood bilirubin increased, blood creatine phosphokinase increased, vomiting, hypokalaemia, major depression, and rhabdomyolysis) (Table 2). Three patients who had AEs that may have been related to treatment required dose modification or interruption (Table 2). A total of four patients died (all cause), including three before the first tumour assessment. Causes of death were clinical progression, worsening dyspnoea and/or respiratory failure due to NSCLC, unknown death at home, and unknown death after PD in long-term follow-up. At the time of data cut-off, six patients had discontinued the study, five due to PD and one due to an AE. There were no AEs of special interest reported with alectinib.

Pharmacokinetics

A total of 54 PK samples were collected from the eight patients. Due to the limited number of patients with a full evaluable PK profile, no formal PK analysis was performed.

Table 1. Baseline demographics and clinical characteristics of the Blood First Assay Screening Trial Cohort B patients

Parameters		Alectinib 900 mg BID (*N* = 8)
Age (years)	Median (range)	62.5 (40.0–70.0)
Sex		
Male		3 (37.5)
Female		5 (62.5)
Race		
American Indian/Alaska Native		1 (12.5)
Asian		1 (12.5)
White		6 (75.0)
ECOG PS		
0		1 (12.5)
1		6 (75.0)
2		1 (12.5)
Smoking status		
Past		1 (12.5)
Never		7 (87.5)
Disease stage	IV	8 (100.0)
SLD by investigator	Median (range)	76 (33.8–140.0)
Histology	Adenocarcinoma	8 (100.0)
CNS metastases		
Present		5 (62.5)
Absent		3 (37.5)
Fusion partner		
KIF5B		7 (87.5)
CCDC6		1 (12.5)

BFAST – Blood First Assay Screening Trial, BID – twice daily, CNS – central nervous system, ECOG PS – Eastern Cooperative Oncology Group performance status, SLD – sum of the longest diameter
Data are presented as n (%) unless otherwise specified.

Table 2. Summary of adverse events in the Blood First Assay Screening Trial Cohort B patients

Patients who experienced any of the following	Alectinib 900 mg BID (*N* = 8)
AE, all-cause	8 (100.0)
Grade 3–5	7 (87.5)
Grade 5	2 (25.0)
Leading to withdrawal from treatment	3 (37.5)
Leading to dose modification/interruption	4 (50.0)
Treatment-related AE	6 (75.0)
Leading to withdrawal from treatment	1 (12.5)
Leading to dose modification/interruption	3 (37.5)
SAE	5 (62.5)
Leading to withdrawal from treatment	3 (37.5)
Leading to dose modification/interruption	2 (25.0)
Related to treatment	2 (25.0)

AE – adverse event, BFAST – Blood First Assay Screening Trial, BID – twice daily, SAE – serious adverse events
Data are presented as n (%).

Table 3. Adverse events experienced by at least two patients

Patients who experienced any of the following	Alectinib 900 mg BID (*n* = 8)
Constipation	5 (62.5)
Dyspnoea	4 (50.0)
Fatigue	3 (37.5)
Headache	3 (37.5)
Diarrhoea	2 (25.0)
Blood bilirubin increased	2 (25.0)
Blood creatine phosphokinase increased	2 (25.0)
Hypokalaemia	2 (25.0)
Pruritus	2 (25.0)
Myalgia	2 (25.0)
Anaemia	2 (25.0)
Insomnia	2 (25.0)

AE – adverse event, BID – twice daily
Data are presented as n (%).

Anti-tumour activity

Confirmed best overall response (by investigator) in the five evaluable patients was stable disease (SD) in four patients and PD in one patient (Table 4). The three remaining patients died before their first tumour assessment. Two of the four patients with confirmed SD were reported to have an unconfirmed partial response.

Discussion

In patients with *RET* fusion-positive NSCLC, the limited anti-tumour activity observed with alectinib in this study does not justify further evaluation of this agent in this setting, where the selective RET inhibitors pralsetinib and selpercatinib have demonstrated greater clinical benefit than alectinib [18]. Four of the five evaluable patients experienced confirmed SD, including two patients with unconfirmed partial responses. The anti-tumour activity of alectinib was generally consistent with prior studies using doses of 450–900 mg BID in patients with *RET*-rearranged NSCLC [19, 20]. Preliminary anti-tumour activity was reported with alectinib administered at 600 mg BID (*n* = 3) or increased to 900 mg BID due to CNS relapse (*n* = 1) in a case series of four patients with advanced *RET*-rearranged NSCLC, three of whom had received prior RET inhibitors [20]. In a single-arm, open-label Phase I/II trial of alectinib dosed at 450 or 600 mg BID in 25 RET inhibitor-naïve Japanese patients with *RET*-rearranged NSCLC, one patient (4%) achieved an objective response and 13 (52%) had disease control at 8 weeks [19].

Blood-based NGS may offer a viable alternative to tissue-based testing in patients with advanced NSCLC, overcoming some of the challenges in obtaining tumour samples, because approximately 30% of patients with advanced or metastatic NSCLC lack sufficient tissue for comprehensive biomarker testing [21–24]. The Blood First Assay Screening Trial is the first trial to use prospective blood-based NGS as the sole method of identifying patients with NSCLC with actionable genetic alterations, and data from the BFAST *ALK*-positive and *ROS1*-positive cohorts support the clinical applicability of blood-based NGS to inform clinical decisions [6, 8]. The prevalence of *RET* fusion-positive NSCLC identified in this study using blood-based NGS (1.06%) is in alignment with the 1–2% *RET* fusion-positive prevalence reported elsewhere [25], and suggests that blood-based and tissue-based biomarker analyses yield similar detection rates.

In BFAST Cohort B, enrolment to the Phase I dose-escalation stage was closed prematurely based on limited clinical activity with 900 mg BID alectinib in patients with advanced *RET* fusion-positive NSCLC. Neither further dose escalation nor the Phase II dose expansion were initiated at the discretion of the sponsor, due to the evolving treatment landscape for patients with advanced *RET* fusion-positive NSCLC at the time. Given the low rate of DLTs in patients treated with alectinib 900 mg BID, escalation to 1200 mg BID could have occurred had the study continued. The 900 mg BID dose of alectinib is higher than the recommended dose of 600 mg BID for the treatment of patients with advanced *ALK*-positive NSCLC [3, 4].

The nature of the reported AEs in BFAST Cohort B was in line with the safety profile of alectinib observed in previous Phase III studies at the 600 mg BID dose [15–17]. Although the number of patients in BFAST Cohort B was very low, the incidence of Grade ≥ 3 AEs and SAEs (87.5% and 62.5%, respectively) was higher than that recorded for patients with *ALK*-positive NSCLC receiving alectinib 600 mg BID in the Phase III ALEX (52% and 39%, respectively) [15] or ALESIA studies (29% and 15%, respectively) [17]. his may be due to the higher peak concentrations and exposure levels of alectinib at the 900 mg BID dose relative to the 600 mg BID dose reported in an earlier Phase I dose-finding study [26], or it may indicate a relatively high tumour burden in our population of patients, most of whom had CNS metastases at presentation. Overall, no new safety signals emerged during this study.

Table 4. Best overall response and duration of response in the individual Blood First Assay Screening Trial Cohort B patients

Patient	Confirmed best overall response*	Unconfirmed best overall response*	Maximum SLD change from baseline (%)	DoR* (months)
1	SD	PR	–44.67	1.9
2	PD	PD	+53.85	–
3	SD	SD	–7.45	–
4	SD	PR	–43.83	1.8
5	SD	SD	–22.84	–

BFAST – Blood First Assay Screening Trial, DoR – duration of response, PD – progressive disease, PR – partial response, SD – stable disease, SLD – sum of longest diameter
** Investigator-assessed*

Summary points

- The multi-cohort BFAST is exploring the anti-tumour activity of targeted therapies or immunotherapy in patients with advanced/metastatic NSCLC using blood-based NGS as the sole method of identifying patients with actionable genetic alterations.
- Alectinib 600 mg twice daily is approved for patients with advanced/metastatic *ALK*-positive NSCLC, but a higher alectinib dose may be required for the treatment of advanced *RET* fusion-positive NSCLC as the IC_{50} of alectinib for *RET* is greater than that for *ALK*.
- The Blood First Assay Screening Trial Cohort B (*RET* fusion-positive), comprising Phase I dose escalation and Phase II dose expansion, was closed prematurely at the discretion of the sponsor due to emerging data from other RET inhibitors; eight patients received alectinib 900 mg BID in Phase I prior to cohort closure.
- Among five efficacy-evaluable patients, confirmed investigator-assessed best overall response was SD in four patients (two of whom had an unconfirmed partial response) and PD in one patient.
- One DLT (death due to unknown cause) occurred and was considered related to alectinib and the underlying disease.
- Serious adverse events were reported in five patients (62.5%), which were considered related to alectinib in two patients (25.0%), and included death, general physical health deterioration, pneumonia, blood creatine phosphokinase increase, major depression, and dyspnoea (resulting in death).
- Treatment-related AEs occurred in six patients (75.0%), three of whom required dose modification or interruption of alectinib.
- No formal PK analysis was performed due to the limited number of evaluable patients.

Conclusions

Despite the early termination of BFAST Cohort B, alectinib 900 mg BID showed limited activity in patients with advanced *RET* fusion-positive NSCLC and no new safety signals were observed. However, as the clinical activity of alectinib was lower than that demonstrated with other RET inhibitors, further evaluation of alectinib in this patient population is not warranted. The limited data collection precludes any definitive conclusions regarding the benefit-risk profile of alectinib in this patient population.

Acknowledgements

Third-party medical writing assistance, under the direction of the authors, was provided by Joanne Bowes, PhD, and Stefan Amisten, PhD, of Ashfield MedComms, an Inizio Company, and was funded by F. Hoffmann-La Roche, Ltd.

Financial disclosure

This study was funded by F. Hoffmann-La Roche, Ltd.

Competing interest disclosure

R.D: Advisory/consultancy fees from F. Hoffmann-La Roche, Ltd, Foundation Medicine, Pfizer, AstraZeneca, Novartis, Merck Sharp & Dohme, Karyopharm, and Boehringer Ingelheim. Honoraria from F. Hoffmann-La Roche, Ltd, AstraZeneca, and Amgen. Participated in data safety monitoring boards/advisory boards for F. Hoffmann-La Roche, Ltd, AstraZeneca, Amgen, and Merck Sharp & Dohme.

N.P: Advisor and honorarium from, and research with, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Foundation Medicine, Gaurdant Health, Merck, MSD, Novartis, NovellusDx, Pfizer, Roche, and Takeda. IP held for Volatile Organic Compounds for Detecting Cell Dysplasia and Genetic Alterations Associated With Lung Cancer; WO/2012/023138.

T.M: Received fees for serving on advisory boards and consulting, and speakers fees and institutional grants and research support from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, and Pfizer. Fees for serving on advisory boards and consulting and speakers fees from ACEA Pharma, Amgen, Boehringer Ingelheim, Daiichi Sankyo, Fishawack Facilitate, Ltd., Eli Lilly, OrigiMed Co. Ltd., Sanofi-Aventis; owns stock and has received fees for serving on advisory boards and board of directors/leadership roles from HutchMed; institutional grants and research support and fees for serving on advisory boards and consulting from Merck Serono and SFJ Pharmaceutical Ltd.; fees for serving on advisory boards, board of directors/leadership roles and consulting from Lunit, Inc.; fees for serving on advisory boards and for consulting from AbbVie, Berry-Oncology, Blueprint Medicines Corporation, C4 Therapeutics, CStone Pharmaceuticals, Curio Science, Eisai, Gilead Sciences, Inc., Gritstone Oncology, Inc., Guardant Health, Hengrui Therapeutics Inc., IQVIA, Janssen, Ignyta, Inc., Incyte Corporation, Inivata, Loxo Oncology Inc., Mirati Therapeutics Inc., Puma Biotechnology Inc., Vertex Pharmaceuticals, Yuhan Corporation; speakers fees and fees for consulting from Alpha Biopharma Co., Ltd., Amoy Diagnostics Co., Ltd., AstraZeneca (before 1 January 2019), BeiGene; fees for serving on advisory boards and institutional grants and research support from AstraZeneca, GI Therapeutics, Inc., Takeda; institutional grants and research support from Roche, XCovery; speakers fees from Daz Group, InMed Medical Communication, Janssen, Liangyihui Network Technology Co., Ltd., Lucence Health Inc., MD Health Brazil, Medscape LLC, Merck Pharmaceuticals HK Ltd., P. Permanyer SL, PeerVoice, Physicians' Education Resource, PrIME Oncology, Research to Practice, Roche Pharmaceuticals/Diagnostic/Foundation Medicine, Shanghai BeBirds Translation and Consulting Co., Ltd., Taiho, Takeda Oncology, touchIME; fees for consulting from Elevation Oncology, MoreHealth, Qiming Development (HK) Ltd., Roche Pharmaceuticals, Takeda Pharmaceuticals HK Ltd.; fees for serving on advisory boards for Roche/Genentech and Virtus Medical Group; fees for a board of directors/leadership role with AstraZeneca PLC; discloses serving on advisory boards (uncompensated) for geneDecode Co., Ltd.; owns stock from Act Genomics-Sanomics Group and Aurora Tele-Oncology Ltd.; declares uncompensated board of directors/leadership roles with the American Society of Clinical Oncology, Asian Thoracic Oncology Research Group, Chinese Lung Cancer Research Foundation Limited, Chinese Society of Clinical Oncology, Hong Kong Cancer

Fund, Hong Kong Cancer Therapy Society, International Association for the Study of Lung Cancer (ending 30 April 2019), St. Stephen's College and Preparatory School.

S.P: Received institutional support for consulting or advising from AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer Ingelheim, Bristol Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, eCancer, Eli Lilly, Elsevier, Foundation Medicine, Illumina, Imedex, IQVIA, Incyte, Janssen, Medscape, Merck Sharp & Dohme, Merck Serono, Merrimack, Novartis, Oncology Education, PharmaMar, Phosplatin Therapeutics, PER, Pfizer, PRIME, Regeneron, RMEI, Roche/Genentech, RTP, Sanofi, Seattle Genetics and Takeda; institutional fees for speaking at company-sponsored public events for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, eCancer, Eli Lilly, Illumina, Imedex, Medscape, Merck Sharp & Dohme, Novartis, PER, Pfizer, Prime, Roche/Genentech, RTP, Sanofi and Takeda; and institutional grants and research support for the conduct of clinical trials from Amgen, AstraZeneca, Biodesix, Boehringer Ingelheim, Bristol Myers Squibb, Clovis, GlaxoSmithKline, Illumina, Eli Lilly, Merck Sharp & Dohme, Merck Serono, Mirati Therapeutics Inc., Novartis, Pfizer, Phosplatin Therapeutics, and Roche/Genentech.

S.P.A: Nothing to disclose.

J.A: Received consulting fees from F. Hoffmann-La Roche, Ltd, AstraZeneca, Takeda, and Pfizer; honorarium from F. Hoffmann-La Roche, Ltd, AstraZeneca, Takeda; and meetings and/or travel support from F. Hoffmann-La Roche, Ltd, AstraZeneca, and MSD.

B.D.V: Nothing to disclose.

M.M: Employment at Syneos Health and works as a Study Statistician in FSP model for F. Hoffmann-La Roche, Ltd on a full-time basis.

V.B: Roche employee and shareholder. Breath Analysis of Pulmonary Nodules. US20130150261 A1; Apparatus for treating a target site of a body; WO/2015/059646.

S.M.S: Genentech employee and Roche shareholder.

E.S: Genentech employee and Roche shareholder.

T.R: Roche employee and shareholder.

M.S.M: Genentech employee and Roche shareholder.

S.M.G: Received fees for consulting from Genentech/Roche, Takeda, AstraZeneca, Pfizer, Daiichi Sankyo and Eli Lilly; served on an independent data monitoring committee for AstraZeneca.

Ethical conduct of research

Institutional Review Board approval was obtained for the study.

Prior presentation

Data from this study were previously presented at the 2020 Virtual World Conference on Lung Cancer (WCLC20), part of the International Association for the Study of Lung Cancer (IASLC), 28–31 January 2020. Clinical trial registration: NCT03178552.

Data sharing statement

Given the small study population, the decision to share the patient-level data needs to be handled on a case-by-case basis to determine if the clinical data can be adequately anonymized to give an acceptably low risk of patient re-identification.

Qualified researchers may submit an enquiry through the data request platform, Vivli, https://vivli.org/ourmember/roche/; however this does not guarantee that the data can be shared. For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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Address for correspondence

Rafal Dziadziuszko
Department of Oncology and Radiotherapy
and Early Clinical Trials Centre
Medical University of Gdańsk
Gdańsk, Poland
Phone: +48 58 584 6269
e-mail: rafald@gumed.edu.pl

Submitted: 06.11.2023
Accepted: 06.01.2024