Lazertinib in patients with *EGFR* mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1–2 study

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Summary

Background Patients with *EGFR*-mutated non-small-cell lung cancer (NSCLC) given EGFR tyrosine kinase inhibitors (TKIs) inevitably become resistant to first-generation or second-generation drugs. We assessed the safety, tolerability, pharmacokinetics, and activity of lazertinib—an irreversible, third-generation, mutant-selective, EGFR TKI—in patients with advanced NSCLC progressing after EGFR TKI therapy.

Methods This first-in-human, open-label, multicentre, phase 1–2 study had three parts: dose escalation, dose expansion, and dose extension; here, we report results on dose escalation and dose expansion. The study was done in 14 hospitals in Korea. Eligible patients were aged 20 years or older and had advanced NSCLC harbouring an activating *EGFR* mutation and progressing after first-generation or second-generation EGFR TKI treatment, a defined tumour T790M mutation status, an Eastern Cooperative Oncology Group performance status of 0–1, at least one measurable extracranial lesion, defined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and adequate organ function. Patients were enrolled to seven dose-escalation cohorts according to a rolling six design; five cohorts were expanded. Patients were given oral lazertinib 20 mg, 40 mg, 80 mg, 120 mg, 160 mg, 240 mg, or 320 mg once daily continuously in 21-day cycles. Primary endpoints were safety and tolerability and secondary endpoints included objective response in evaluable patients. This study is registered with ClinicalTrials.gov, NCT03046992, and the phase 2 extension study is ongoing.

Findings Between Feb 15, 2017, and May 28, 2018, 127 patients were enrolled into the dose escalation group (n=38) and dose expansion group (n=89). No dose-limiting toxicities occurred. There was no dose-dependent increase in adverse events. The most commonly reported adverse events were grade 1–2 rash or acne (in 38 [30%] of 127 patients) and pruritus (in 34 [27%]). Grade 3 or grade 4 adverse events occurred in 20 (16%) patients, with the most common being grade 3 pneumonia (four [3%]). Treatment-related grade 3 or 4 adverse events occurred in four (3%) patients; treatment-related serious adverse events were reported in six patients (5%). There were no adverse events with an outcome of death and no treatment-related deaths. The proportion of patients achieving an objective response by independent central review assessment was 69 (54%; 95% CI 46–63) of 127.

Interpretation Lazertinib had a tolerable safety profile and showed promosing clinical activity in patients with NSCLC progressing on or after EGFR TKI therapy. Our findings provide a rationale for further clinical investigations.

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Introduction

Patients with *EGFR*-mutated non-small-cell lung cancer (NSCLC) given EGFR tyrosine kinase inhibitors (TKIs) inevitably become resistant to first-generation or second-generation drugs.[1,2] The most common mechanism of acquired resistance involves an exon 20 point mutation leading to a threonine to methionine substitution at amino acid position 790 (T790M) of EGFR.[3] The recognition of this mechanism provided a rationale for the development of third-generation EGFR TKIs with activity against T790M-positive tumours. One such drug is osimertinib, which is approved for patients with metastatic *EGFR* T790M-positive NSCLC that has progressed on or after EGFR TKI therapy.[4]

Lazertinib (YH25448) is an oral, highly potent, irreversible, third-generation, mutant-selective, and wild-type-sparing EGFR TKI, with half maximal inhibitory concentration (IC_{50}) values of 2 nM for L858R/T790M double mutant EGFR compared with 76 nM for wild-type EGFR.[5] Using in vitro and in vivo experimental models, Yun and colleagues[6] compared the antitumour activity and toxicity profiles of lazertinib and osimertinib.

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Research in context

Evidence before this study

We searched PubMed using the terms "NSCLC", "EGFRm+", "T790M", and "third generation" with no time restriction, for reports published in English. This search revealed several published clinical studies of third-generation EGFR tyrosine kinase inhibitors (TKIs) in patients with *EGFR*-mutated non-small-cell lung cancer (NSCLC) who had acquired resistance either to first-generation or second-generation EGFR TKIs. Most studies showed that the third-generation TKI therapies were specifically designed to target T790M, an EGFR TKI-resistance mutation, more selectively than the wild-type form. Most third-generation EGFR TKIs, except osimertinib, have shown various issues with regard to their safety and activity in initial clinical trials, and their development has subsequently ceased. By contrast, osimertinib has been established as a standard treatment in patients with metastatic *EGFR* T790M-positive NSCLC that has progressed on or after EGFR TKI therapy through a confirmatory clinical trial, AURA3. In pre-clinical testing, lazertinib has shown higher activity, especially for brain metastasis, and better selectivity for T790M-mutant *EGFR*, than osimertinib. Therefore, this first-in-human study was designed to assess the safety, tolerability, pharmacokinetics, and preliminary activity of lazertinib in patients with *EGFR*-mutant NSCLC who progressed on or after previous TKI treatments.

Added value of this study

Our study shows that lazertinib was generally well tolerated and active in most patients previously treated with EGFR TKIs whose tumors harboured *EGFR* T790M mutations. We also confirmed the predicted intracranial activity of lazertinib.

Implications of all the available evidence

Our data show that lazertinib is a promising new EGFR TKI for the treatment of patients with *EGFR*-mutant NSCLC with acquired resistance to previous EGFR TKI treatments, with a possible role in the treatment of patients with brain metastases. Although the ongoing dose extension part of this study will further explore the activity and safety of lazertinib in patients with NSCLC, additional clinical studies involving single drug and combination therapy are clearly warranted.

In these analyses, lazertinib had higher selectivity against various mutant EGFRs, including T790M, and less activity against wild-type EGFR than did osimertinib, suggesting that lazertinib might have fewer off-target side-effects than osimertinib. Additionally, in a murine brain metastasis model,[6] lazertinib more efficiently inhibited intracranial tumour growth than did osimertinib, showing that it might be more effective in treating lung cancer brain metastases. In-vivo dose-escalation assays[6] suggested that at high doses, lazertinib was less likely to induce skin toxicity than was osimertinib. These preclinical data suggested that lazertinib might be clinically more effective and better tolerated than osimertinib, providing a rationale for the clinical development of this drug.

The aim of our first-in-human, phase 1–2 study, in which we enrolled patients with advanced NSCLC harbouring activating mutations of *EGFR* that had progressed after EGFR TKI therapy, was to explore the safety, antitumour activity, and pharmacokinetics of lazertinib. There were three planned parts to the study: the dose escalation part, the dose expansion part (in which only patients with tumour T790M mutations were enrolled), and a phase 2 dose extension part, which is ongoing.

Methods

Study design and participants

We did a first-in-human, open-label, phase 1–2 study at 14 hospitals in Korea (appendix p 1). Only the dose escalation and dose expansion parts of the trial are reported here; the phase 2 dose extension part, which will provide data for the activity and safety profiles of lazertinib 240 mg in larger cohorts of patients, is ongoing and will be reported when completed. Eligible patients were aged 20 years or older with a histologically or cytologically confirmed diagnosis of NSCLC, which was locally advanced or metastatic and harboured an activating *EGFR* mutation (L858R, exon 19 deletion, G719X, or L861Q).[7] Other inclusion criteria included an Eastern Cooperative Oncology Group performance status 0–1 with no deterioration over the previous 2 weeks, a minimum life expectancy of 3 months, and at least one measurable extracranial lesion, defined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[8] Patients had to have previously received a first-generation or second-generation EGFR TKI and had disease progression despite treatment (regardless of progression site). Disease progression was ascertained by investigators using radiological documentation. Patients could have received intervening therapy between their last EGFR TKI treatment and study enrolment. For the dose escalation part of the study, central confirmation of tumour T790M mutation status was required; for the dose expansion part, tumours had to be T790M-positive. In each case, T790M status was to be determined according to a sample taken after progression.

Exclusion criteria included treatment with an investigational product within 30 days, an EGFR TKI within 8 days (or within five half-lives, whichever period was longer), cytotoxic chemotherapy or other anticancer drugs within 14 days, major surgery within 4 weeks, radiotherapy with a wide field within 4 weeks, or radiotherapy within a limited field within 1 week, of the first dose of study treatment. Patients were excluded if they were receiving (or were unable to stop 1 week before

See Online for appendix

the first study dose) medications or herbal supplements known to be inhibitors or inducers of CYP3A4, or if they had been treated with EGFR TKIs targeting the T790M resistance mutation. Further exclusion criteria included symptomatic spinal cord compression, brain metastases that were symptomatic or required emergency treatment (eg, steroids for at least 2 weeks before the start of the study), intracranial haemorrhage that was symptomatic or required treatment, CNS complications that required urgent neurosurgical intervention (eg, resection or shunt placement), leptomeningeal metastasis before the start of the study, medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis that required steroid treatment, any evidence of clinically active interstitial lung disease, or cardiovascular disease, as defined by a history of symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment, a history of myocardial infarction or unstable angina within 6 months of the start of the study, or left ventricular ejection fraction of less than 50%. Clinical laboratory exclusion criteria included mean resting corrected QT interval (QTc) more than 470 ms obtained from three electrocardiograms; any clinically important abnormalities in rhythm, conduction, or morphology of a resting electrocardiogram; any factors that increased the risk of QTc prolongation or risk of arrhythmic events, and inadequate organ function (absolute neutrophil count $<1{\cdot}5\times10^9$ cells/L; platelet count $<100\times10^9$ cells/L; haemoglobin <90 g/L; alanine aminotransferase or aspartate aminotransferase $>2{\cdot}5\times$the upper limit of normal [ULN] if no demonstrable liver metastases, or $>5{\cdot}0\times$ULN in presence of liver metastases; total bilirubin $>1{\cdot}5\times$ULN if no liver metastases, or $>3{\cdot}0\times$ULN in the presence of documented Gilbert's syndrome [unconjugated hyperbilirubinemia] or liver metastasis; serum creatinine $>1{\cdot}5\times$ULN concurrent with creatinine clearance less than 50 mL/min as measured by the centre's standard method [eg, Cockcroft and Gault equation]; unexplained inadequate liver function; troponin I test result confirmed by the central laboratory as exceeding the ULN).

The protocol (available in the appendix) was approved by the institutional review boards or ethics committees of all participating centres. The study was done in accordance with the protocol, the principles expressed in the Declaration of Helsinki, and applicable regulatory requirements. Site investigators were not to implement any deviation or changes to the protocol without review and documented approval from the institutional review board of an amendment, except if the changes were necessary to eliminate an immediate hazard to the study participants, and the sponsor was to be informed of any change. All patients, or their legally acceptable representative in situations in which consent could not be given by patients, provided written informed consent before any study-specific procedures were done.

Procedures

Tumour *EGFR* mutation status was determined centrally using a cobas EGFR mutation test (version 2; Roche, Basel, Switzerland).

In the dose escalation part of the study, three to six patients were enrolled per dose level of lazertinib (20 mg, 40 mg, 80 mg, 120 mg, 160 mg, 240 mg, or 320 mg) according to a rolling six design which allows for accrual of two to six patients concurrently onto a dose level based on the number of patients currently enrolled and evaluable, the number who have a dose-limiting toxicity, and the number still at risk of developing a dose-limiting toxicity (appendix p 8).[9] The starting dose of lazertinib was 20 mg, based on nonclinical pharmacokinetic and pharmacodynamic studies, as well as repeat-dose toxicology studies in rats and dogs (unpublished). The starting dose of lazertinib 20 mg daily was increased by 100% increments up to 80 mg. Thereafter, subsequent dose escalation levels were determined by the safety review committee after consideration of available safety and pharmacokinetic data. Dose escalation proceeded according to the occurrence of dose-limiting toxicity, until the maximum tolerated dose was reached. The maximum tolerated dose was defined as the dose level immediately below that at which two or more of three to six patients experienced a dose-limiting toxicity. Dose-limiting toxicity was assessed from the first dose of study treatment (day 1, cycle 0) to the last dose of study treatment in cycle 1 (day 21) and was defined as an event assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that, despite optimal therapeutic intervention, met any of the following criteria: grade 4 haematological toxicity lasting for more than 4 days; febrile neutropenia; any grade 3 or worse non-haematological toxicity including QTc prolongation (>500 ms or 60 ms above baseline); any other toxicity that worsened from baseline, was clinically significant or unacceptable, and was judged to be a dose-limiting toxicity by a safety review committee; any adverse event leading to permanent discontinuation of treatment; and any adverse event resulting in a disruption of the dosing schedule by more than 14 days. Alopecia of any grade and isolated laboratory changes without clinical sequelae or significance were not deemed dose-limiting toxicities. Toxicity from cycle 2 and beyond was to be taken into account by the safety review committee in determining dose escalation.

Lazertinib was given orally as tablets, to patients in a fasted state, once daily, and continuously in 21-day cycles until documented evidence of disease progression, unacceptable toxicity, noncompliance, withdrawal of consent, or investigator decision. Conditions for dose modification and treatment discontinuation in the event of toxicity were protocol-specified. If a patient had a grade 3 or worse or unacceptable adverse event, including dose-limiting toxicity not attributable to the disease,

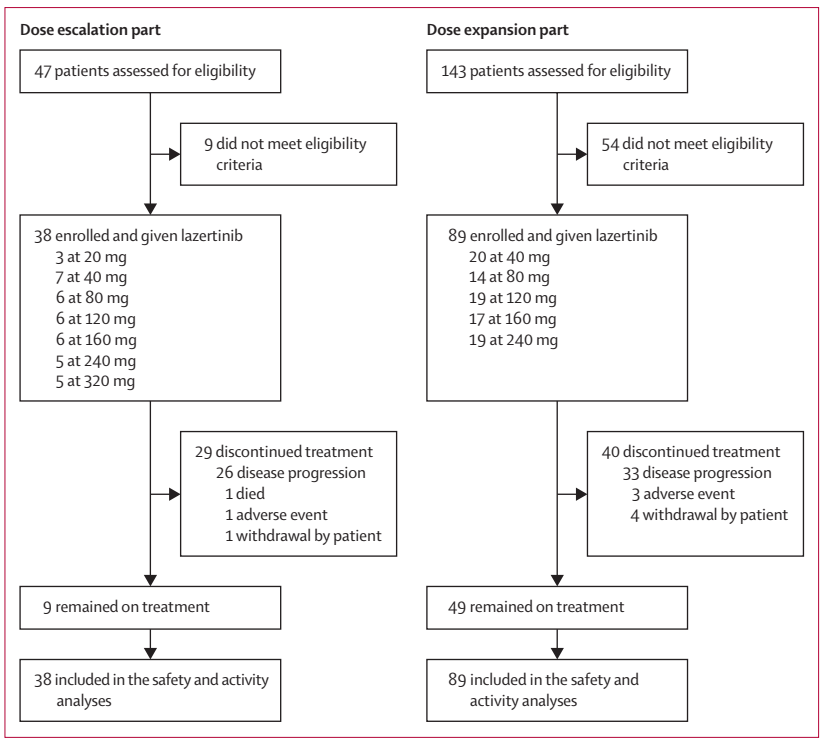

Figure 1: **Trial profile**

dosing was interrupted and supportive therapy was administered, in accordance with local practice. If the toxicity did not resolve to grade 2 or better after 21 days, then the patient was withdrawn from the study. If patients experienced corneal ulceration or interstitial lung disease, they were not permitted to restart lazertinib treatment. Other conditions for discontinuation included patients' decision; adverse events; severe non-compliance with the protocol; disease progression as per RECIST (version 1.1); opinion of the investigator that the patient was no longer receiving clinical benefit; incorrect initiation of treatment in relation to compliance with eligibility criteria; and pregnancy.

In the dose expansion part, additional patients with T790M-positive tumours were enrolled to selected dose levels, provided that the maximum tolerated dose had not been reached.

In the dose escalation and dose expansion parts of the study, blood and urine samples for laboratory safety assessments were taken at protocol-specified timepoints (appendix pp 81–83). Blood samples for pharmacokinetic assessments were collected in both the dose escalation and dose expansion parts of the study (appendix p 85). To allow for pharmacokinetic assessment of single and multiple doses, patients initially received a single dose on day 1 cycle 0, then once daily continuous dosing was initiated after a 7-day washout period (patient visit window of two days) in the dose escalation part. In the dose expansion part, patients received once daily continuous doses from day 1 cycle 1 without a single dose on day 1 cycle 0. Pharmacokinetic parameters assessed for lazertinib were area under the plasma concentration-time curve from zero to the time of the last quantitative concentration (AUC_t), maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), and apparent terminal elimination half-life ($t_{1/2}$) after single dose administration; AUC during the dosing interval at steady state (AUC_{ss}), C_{max} at steady state ($C_{max,ss}$), time to reach $C_{max,ss}$ ($T_{max,ss}$), trough plasma concentration on day 15 of cycle 1 (C_{D15}), metabolic ratio (ratio of YH26334 [the main metabolite of lazertinib] to lazertinib based on AUC at steady state; MR_{ss}), and accumulation ratio based on AUC (R_{ac}) after multiple dose administration.

Adverse events were monitored throughout the study, from informed consent until 28 days after study treatment was discontinued, and were graded according to the Common Terminology Criteria for Adverse Events (version 4.0). Response was assessed by CT or MRI by investigators and independent central review according to RECIST (version 1.1), at baseline and then at every two cycles (patient visit window of 7 days) after the start of multiple once daily dosing. CNS surveillance (CT or MRI) was done only in patients with brain lesions at baseline, according to the same schedule. A measurable brain metastasis was defined as an intracranial brain lesion that had progressed or not responded to previous radiotherapy that could be accurately measured by MRI at baseline as being at least 10 mm in the longest diameter and that was suitable for accurate repeated measurements.

Outcomes

For the dose escalation and dose expansion parts of this study, the primary endpoints were safety and tolerability. Secondary endpoints were the proportion of patients with an objective response (confirmed complete or partial response), duration of response (defined as the time from the date of the first documented response, provided it was subsequently confirmed, until the date of documented progression or death from any cause), the proportion of patients with disease control (confirmed complete or partial response and stable disease), tumour shrinkage, and pharmacokinetics of lazertinib. For the dose expansion part of the study, secondary endpoints also included progression-free survival (defined as the time from the start of once daily continuous dosing to the time of disease progression or death from any cause in the absence of progression); overall survival (the time from the start of once daily continuous dosing to the time of death from any cause), which will be reported elsewhere; and for patients with brain metastases, the proportion of patients with an intracranial objective response, duration of intracranial response, and intracranial progression-free survival (defined as the time from the start of multiple once daily dosing to the time of intracranial disease progression or death from any cause, which was assessed in evaluable patients with brain metastases at baseline).

Statistical analysis

No formal power calculations were done. Enrolment of approximately 30 patients was anticipated in the dose escalation part, with the final number dependent on the occurrence of dose-limiting toxicity. In the dose expansion part, approximately 20 additional patients per dose cohort were to be enrolled, which was deemed to be a sufficient number of patients to provide a preliminary assessment of antitumour activity. The safety review committee was allowed to halt enrolment on the basis of emerging safety data. For activity and safety endpoints, data from patients in the dose-escalation and dose-expansion cohorts were pooled. The safety analysis population for the assessment of the primary endpoints included all patients who were given at least one dose of lazertinib. The activity analysis population included all patients in the safety analysis population who had a baseline RECIST 1.1 assessment. Activity analyses related to brain metastases were done for all patients in the activity analysis population who had a measurable or non-measurable intracranial lesion at baseline. The pharmacokinetics analysis population included all patients who had at least one measurable lazertinib concentration collected after a dose was given. All protocol deviations that occurred during pharmacokinetic evaluation were considered for their severity and effect on pharmacokinetics. Response assessments done by investigators served as sensitivity analyses. No formal interim analyses were planned. Subgroup analyses of activity according to T790M mutation status, and in patients with brain metastases at baseline, were pre-specified in the protocol. The assessment of activity in patient subgroups defined by lazertinib grouped dose level was a post hoc analysis. Time to event endpoints were assessed, and associated medians and 95% CIs were calculated, using the Kaplan-Meier method.[10]

Non-compartmental parameter calculation and statistical analysis for pharmacokinetics were done using Phoenix WinNonlin (version 8.1; Certara, NJ, USA). Other statistical analyses were done with SAS 9.4.

This trial is registered with ClinicalTrials.gov, NCT03046992.

Role of the funding source

The study was designed by representatives of the sponsor in conjunction with the lead investigators (BCC and M-JA). The sponsor collected the study data and analysed and interpreted these data in collaboration with the authors. The sponsor commissioned and funded medical writing services to support the drafting of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Feb 15, 2017, and May 28, 2018, 127 patients were enrolled and received at least one dose of lazertinib (figure 1). Baseline characteristics of patients given lazertinib are summarised in table 1. The data cutoff for this analysis was Nov 26, 2018, at which time 58 (46%) of 127 patients remained on treatment, and patients had received a median of 13 cycles (IQR 7–19) of treatment. The median duration of treatment was 9·7 months (IQR 5·6–12·6). The median follow-up period for progression-free survival was 11·0 months (IQR 8·1–15·0).

In the dose escalation part, 38 patients were enrolled into dose level cohorts up to 320 mg (appendix p 8).

	Dose escalation (n=38)	Dose expansion (n=89)
Age, years	60 (54–67)	63 (57–71)
Sex		
Male	13 (34%)	38 (43%)
Female	25 (66%)	51 (57%)
ECOG performance status		
0	14 (37%)	21 (24%)
1	24 (63%)	68 (76%)
Tumour histology		
Adenocarcinoma	37 (97%)	88 (99%)
Other	1 (3%)	1 (1%)
EGFR mutation status*		
Exon 19 deletion	21 (55%)	55 (62%)
L858R	13 (34%)	34 (38%)
Other	1 (3%)	0
None detected	3 (8%)	0
EGFR T790M status*		
Positive	19 (50%)	89 (100%)
Negative	19 (50%)	0
Brain metastasis		
Yes	11 (29%)	37 (42%)
No	27 (71%)	52 (58%)
AJCC stage†		
IIIB	2 (5%)	1 (1%)
IV	36 (95%)	88 (99%)
Previous lines of systemic therapy	2 (1–3)	1 (1–2)
Number of previous EGFR TKIs	1 (1–1)	1 (1–1)
Previous treatment‡		
Gefitinib	26 (68%)	58 (65%)
Erlotinib	9 (24%)	20 (22%)
Afatinib	4 (11%)	18 (20%)
Immediate previous EGFR TKI		
Yes	21 (55%)	72 (81%)
<30 days	11 (29%)	49 (55%)
≥30 days	10 (26%)	23 (26%)
No	17 (45%)	17 (19%)
Time from last EGFR TKI (months)	1·8 (0·8–6·3)	1·0 (0·6–2·0)

Data are median (IQR) or n (%), unless otherwise stated. AJCC=American Joint Committee on Cancer. ECOG=Eastern Cooperative Oncology Group. TKI=tyrosine kinase inhibitor. *As tested in a central laboratory. †Seventh edition. ‡Patients may have had more than one previous treatment.

Table 1: **Baseline characteristics**

	20 mg (n=3)			40 mg (n=27)			80 mg (n=20)			120 mg (n=25)			160 mg (n=23)			240 mg (n=24)			320 mg (n=5)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Rash or acne*	1 (33%)	0	0	7 (26%)	0	0	2 (10%)	0	0	10 (40%)	0	0	8 (35%)	0	0	8 (33%)	0	0	2 (40%)	0	0
Pruritus	0	0	0	5 (19%)	0	0	4 (20%)	0	0	6 (24%)	0	0	8 (35%)	0	0	10 (42%)	0	0	1 (20%)	0	0
Constipation	1 (33%)	0	0	5 (19%)	0	0	7 (35%)	0	0	6 (24%)	0	0	3 (13%)	0	0	3 (13%)	0	0	1 (20%)	0	0
Decreased appetite	1 (33%)	0	0	4 (15%)	0	0	3 (15%)	0	0	2 (8%)	0	0	6 (26%)	0	0	6 (25%)	0	0	2 (40%)	0	0
Diarrhoea	0	0	0	4 (15%)	0	0	0	0	0	3 (12%)	0	0	5 (22%)	0	0	5 (21%)	0	0	1 (20%)	0	0
Nausea	1 (33%)	0	0	2 (7%)	1 (4%)	0	2 (10%)	0	0	3 (12%)	1 (4%)	0	2 (9%)	0	0	4 (17%)	0	0	1 (20%)	0	0
Paraesthesia	1 (33%)	0	0	1 (4%)	0	0	2 (10%)	0	0	3 (12%)	0	0	1 (4%)	0	0	6 (25%)	0	0	0	0	0
Headache	1 (33%)	0	0	2 (7%)	0	0	2 (10%)	0	0	3 (12%)	0	0	0	0	0	5 (21%)	0	0	0	0	0
Nasopharyngitis	0	0	0	4 (15%)	0	0	4 (20%)	0	0	4 (16%)	0	0	1 (4%)	0	0	0	0	0	0	0	0
Vomiting	1 (33%)	0	0	1 (4%)	0	0	1 (5%)	0	0	4 (16%)	1 (4%)	0	1 (4%)	0	0	0	1 (4%)	0	0	0	0
Dyspnoea	1 (33%)	0	0	1 (4%)	0	0	1 (5%)	0	0	1 (4%)	0	0	2 (9%)	1 (4%)	0	1 (4%)	0	0	1 (20%)	0	0
Pneumonia	0	0	0	1 (4%)	0	0	1 (5%)	1 (5%)	0	2 (8%)	1 (4%)	0	0	1 (4%)	0	0	0	0	1 (20%)	1 (20%)	0
Anaemia	0	0	0	0	0	0	1 (5%)	0	0	0	0	0	3 (13%)	1 (4%)	0	2 (8%)	1 (4%)	0	0	0	0
Asthenia	0	0	0	1 (4%)	0	0	4 (20%)	0	0	0	1 (4%)	0	2 (9%)	0	0	0	0	0	0	0	0
Back pain	0	0	0	2 (7%)	1 (4%)	0	1 (5%)	0	0	2 (8%)	0	0	1 (4%)	0	0	1 (4%)	0	0	0	0	0
Platelet count decreased	0	0	0	0	0	0	1 (5%)	0	0	1 (4%)	0	0	2 (9%)	1 (4%)	0	0	0	0	0	0	0
Neutrophil count decreased	0	0	0	0	0	0	2 (10%)	0	0	1 (4%)	0	0	0	0	1 (4%)	0	0	0	0	0	0
Hypertension	0	0	0	1 (4%)	0	0	0	0	0	0	1 (4%)	0	0	1 (4%)	0	0	0	0	0	0	0
Pneumothorax	0	0	0	2 (7%)	0	0	0	0	0	0	1 (4%)	0	0	0	0	0	0	0	0	0	0
Pulmonary embolism	0	0	0	0	0	0	0	0	0	0	1 (4%)	0	0	0	0	1 (4%)	1 (4%)	0	0	0	0
Cataract	0	0	0	0	0	0	0	0	0	0	2 (8%)	0	0	0	0	0	0	0	0	0	0
Enterocolitis	0	0	0	0	1 (4%)	0	0	0	0	1 (4%)	0	0	0	0	0	0	0	0	0	0	0
Hyponatraemia	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (9%)	0	0	0	0	0	0	0
Pneumonitis	0	0	0	1 (4%)	0	0	0	0	0	0	0	0	0	0	0	0	1 (4%)	0	0	0	0
Acute kidney injury	0	0	0	0	0	0	0	0	0	0	1 (4%)	0	0	0	0	0	0	0	0	0	0
Cancer pain	0	0	0	0	0	0	0	1 (5%)	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypokalaemia	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (4%)	0	0	0	0	0	0	0
Hypophagia	0	0	0	0	0	0	0	0	0	0	1 (4%)	0	0	0	0	0	0	0	0	0	0
Myocardial infarction	0	0	0	0	0	0	0	0	0	0	1 (4%)	0	0	0	0	0	0	0	0	0	0
Neurogenic tumour	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (4%)	0	0	0	0

Data are n (%). Treatment-emergent grade 1 or 2 adverse events occurring in 10% or more of patients and all grade 3 and 4 events are presented. No deaths due to adverse events were observed. Patients with two or more incidences of particular adverse events are counted only once for the maximum grade. *Composite category, including preferred terms: rash, rash erythematous, rash macular, rash maculo-papular, rash papular, erythema, folliculitis, and dermatitis acneiform.

Table 2: **Treatment-emergent adverse events in the dose escalation and dose expansion groups**

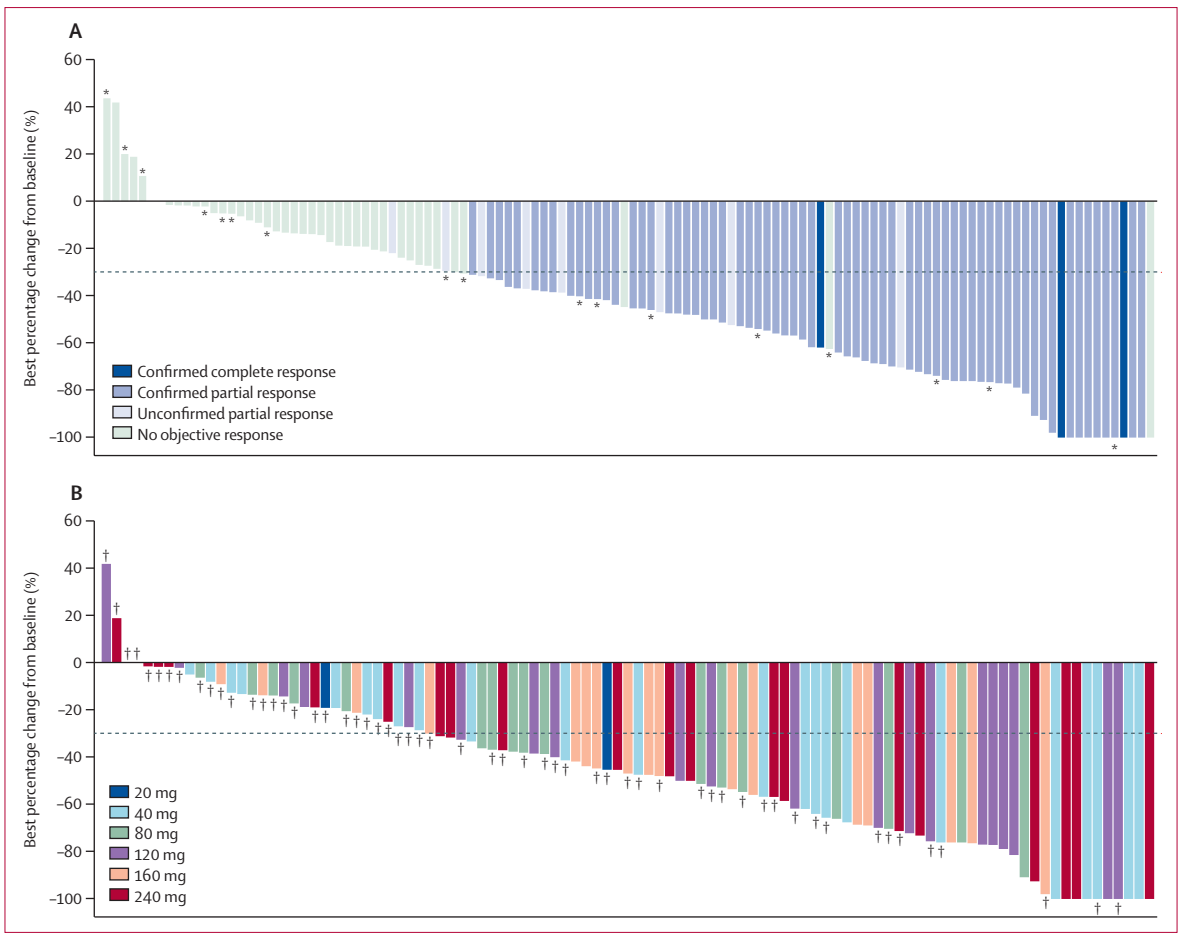

Figure 2: **Waterfall plots of maximal change in size of target lesions**
Plots shows the best percentage change from baseline in the sum of diameters of target lesions according to independent central review. Patients were excluded if they did not have target lesions at baseline or if more than a third (33%) of their target lesions had not been assessed after baseline. (A) Bars are coloured according to response status for patients in the overall population. (B) Bars are colour coded according to dose level for patients with T790M-positive tumours. *T790M-negative based on central testing. †Discontinuation or disease progression.

No dose-limiting toxicities occurred in any of the cohorts. Consequently, the maximum tolerated dose was not reached. The 20 mg starting dose was considered unlikely to be pharmacologically active and an expansion cohort was therefore not planned at this dose. Dose expansion cohorts were subsequently opened for the five doses between 40 mg and 240 mg; 89 patients were enrolled. On the basis of the dose–response relationship for activity, and the safety data, the safety review committee elected not to open the dose expansion cohort of lazertinib for 320 mg.

Adverse event incidence is summarised in table 2 and the appendix (pp 2–4). Adverse events of any grade were reported in 119 (94%) of 127 patients. The most commonly reported adverse events were grade 1–2 rash or acne (38 [30%] of 127 patients) and pruritus (34 [27%]). In relation to adverse events of special interest, two (2%) patients had grade 1 QT interval prolongation and two (2%) patients had pneumonitis (one patient had grade 2 and one grade 3). Grade 3 or grade 4 adverse events occurred in 20 (16%) patients, with the most common being grade 3 pneumonia (four [3%]). There were no adverse events with an outcome of death. Grade 3 events were deemed to be treatment-related in four (3%) patients: enterocolitis (one patient); myocardial infarction (one patient); acute kidney injury, vomiting, nausea, and hypophagia (one patient); and pneumonitis (one patient). There was no clear evidence of a dose-dependent increase in the incidence of adverse events (table 2; appendix p 2). Serious adverse events were reported in 21 (17%) patients; these were assessed as treatment-related in six (5%) patients (appendix p 4). Adverse events led to dose reductions in seven (6%) patients and dose interruption in 15 (12%) patients (appendix p 2). Four (3%) patients discontinued treatment due to adverse events (pneumonitis [n=2], gallbladder cancer [n=1], and nausea [n=1]; appendix p 2). No lazertinib-related deaths occurred. Five patients (4%) (one patient in the 40 mg cohort, two patients in the 80 mg cohort, and two patients in the 160 mg cohort)

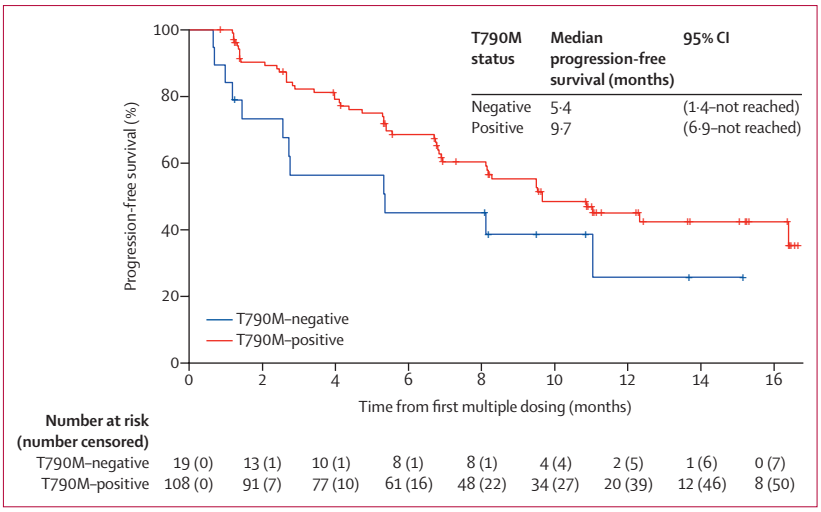

Figure 3: **Progression-free survival by T790M status according to independent central review**

died because of progressive disease and one patient (1%) in the 160mg cohort died because of cardiac arrest. Apart from the two (2%) patients with pneumonitis, no other patients had adverse events classified as interstitial lung disease. Responses generally occurred quickly (appendix p 6).

127 patients were evaluable for response; of those, 108 had a tumour that harboured a T790M mutation, and 19 were T790M-negative. 69 (54%, 95% CI 46–63) patients had an objective response by independent central review assessment, including 66 (52%) with confirmed partial responses and 3 (2%) with confirmed complete responses (figure 2A). 41 (32%) of 127 patients had stable disease. 110 (87%, 95% CI 81–93) patients had disease control. Responses were documented for patients across all doses (appendix p 5). According to investigator assessment, 76 (60%, 95% CI 51–68) patients had an objective response and 114 (90%, 84–95) patients had disease control.

Subgroup analysis showed that 62 (57%, 95% CI 48–67) of 108 patients with T790M-positive tumours and seven (37%, 15–58) of 19 patients with T790M-negative tumours had an objective response by independent central review assessment (figure 2B; appendix p 6). According to investigator assessment, 69 (64%, 95% CI 55–73) of 108 patients with T790M-positive tumours and seven (37%, 15–58) of 19 patients with T790M-negative tumours had an objective response.

18 (out of 127) patients had measurable brain metastases (15 patients had T790M-positive tumours and three patients had T790M-negative tumours). Of those, eight (44%, 95% CI 22–69) had an objective intracranial response by independent central review assessment (appendix p 9).

Duration of response according to dose level is summarised in the appendix p 10. The median duration of response in the overall population was 15·2 months (95% CI 8·6–15·2) and the median progression-free survival was 9·5 months (6·9–16·4) according to independent central review assessment (63 [50%] of 127 patients had a progression event). Subgroup analysis showed that median progression-free survival was longer in patients with T790M-positive tumours (51 [47%] of 108 patients had a progression event) than in patients with T790M-negative tumours (12 [63%] of 19 patients had a progression event; figure 3). In a post-hoc analysis, in 62 patients with T790M-positive tumours who received doses of 120 mg or above, 37 (60%, 95% CI 47–72) patients had an objective response and median progression-free survival was 12·3 months (8·3–not reached; 25 [40%] patients had a progression event) according to independent central review assessment. By contrast, post-hoc analysis showed that in 46 patients with T790M-positive tumours who received doses of 80 mg or lower, 25 (54%, 95% CI 40–69) had an objective response and median progression-free survival was 6·9 months (5·3–16·4; 26 [57%] patients had a progression event). According to investigator assessment, median progression-free survival was 8·1 months (95% CI 6·7–11·0; 76 [60%] of 127 patients had a progression event) in all patients, 9·5 months (6·8–12·4; 60 [56%] of 108 patients had a progression event) in patients with T790M-positive tumours, and 5·4 months (1·2–11·0; 16 [84%] of 19 patients had a progression event) in patients with T790M-negative tumours. In evaluable patients with brain metastases, the median intracranial progression-free survival, according to independent central review assessment, was not reached (95% CI not reached; 11 [23%] of 48 patients had a progression event; appendix p 11). 62 (49%) of 127 patients had disease progression during the study. The pattern of progression at CNS and non-CNS sites is summarised in appendix p 7.

Pharmacokinetic parameters after single and multiple dose administration of lazertinib are summarised in table 3, and mean plasma concentration–time profiles are shown in appendix p 12. Median times to reach maximum plasma concentration after a single dose and at steady state after multiple doses (T_{max} and $T_{max,ss}$) were 2–4 h post-dose across all dose levels. Plasma concentrations of lazertinib appeared to decrease multi-exponentially at all single dose levels, with a mean terminal half-life of 64·72 h after a single dose of 240 mg. Steady state was achieved by 15 days after first-dosing, and the mean accumulation ratio was 2–3 after 22 days of dosing. Maximum plasma concentrations (C_{max} and $C_{max,ss}$) increased in a dose proportional manner over the dose range of 20–320 mg, whereas AUC_t and AUC_{ss} increased in a slightly more than dose-proportional manner (table 3). The systemic exposure of YH26334 at steady state was 2–4% of that of lazertinib, which was similar across all doses (ie, with a similar ratio across all doses).

According to the observed C_{trough} levels at steady state (table 3), we expected that a lazertinib dose of 160 mg or higher would be necessary to achieve sufficient and

	20 mg	40 mg	80 mg	120 mg	160 mg	240 mg	320 mg
Single administration	n=3	n=6	n=6	n=6	n=6	n=4	n=5
AUC_t, h x ng/mL	188·73 (47·92)	676·05 (39·09)	1930·98 (32·65)	2817·78 (26·21)	3520·26 (29·17)	5264·63 (34·46)	5799·86 (27·72)
C_{max}, ng/mL	16·29 (59·45)	43·46 (50·78)	119·01 (37·77)	203·99 (41·12)	179·49 (33·94)	434·05 (28·96)	325·00 (47·97)
T_{max}, h	1·97 (1·97–4·00)	2·03 (2·02–4·00)	2·04 (1·00–6·03)	2·05 (1·02–5·95)	4·09 (2·03–10·17)	1·99 (1·98–4·00)	2·00 (1·93–2·17)
$t_{1/2}$, h	17·54 (47·52)	58·81 (50·69)	79·59 (29·31)	68·46 (30·83)	59·9 (24·7)	64·72 (32·82)	100·72 (80·92)
Multiple administration	n=3	n=24	n=19	n=23	n=15	n=20	n=4
AUC_{ss}, h x ng/mL	347·17 (58·82)	925·45 (40·46)	2429·81 (45·23)	3144·77 (42·64)	4813·65 (34·44)	6541·42 (49·34)	7880·21 (23·16)
$C_{max,ss}$, ng/mL	31·75 (71·18)	74·69 (46·39)	186·70 (50·05)	252·25 (46·12)	361·06 (41·73)	517·15 (43·01)	614·24 (32·69)
$T_{max,ss}$, h	2·03 (1·05–3·97)	2·04 (1·03–10·08)	2·07 (1·00–8·00)	2·05 (0·97–6·07)	2·08 (1·05–8·03)	2·08 (1·92–6·17)	3·09 (2·03–8·13)
C_{D15}, ng/mL*	7·14 (50·93)	20·93 (52·87)	52·78 (55·95)	83·49 (76·12)	154·65 (66·64)	155·99 (52·65)	181·75 (47·51)
MR_{ss}	0·028 (32·627)	0·034 (48·181)	0·026 (37·931)	0·035 (37·416)	0·027 (30·990)	0·020 (33·924)	0·020 (36·430)
R_{ac}†	2·32 (21·98)	1·95 (33·87)	3·28 (31·48)	1·83 (24·71)	2·55 (23·72)	2·36 (32·16)	2·98 (42·29)

Data represent the arithmetic mean (percentage coefficient of variation) except for T_{max} and $T_{max,ss}$, which are the median (range). AUC=area under the plasma concentration–time curve. C_{max}=maximum plasma concentration. T_{max}=time to reach C_{max}. $t_{1/2}$=apparent terminal elimination half-life. C_{D15}=trough plasma concentration on day 15 of cycle 1. MR_{ss}=metabolic ratio (YH26334/lazertinib) based on AUC at steady state. R_{ac}=accumulation ratio based on AUC. *n=3, 25, 18, 24, 21, 23 ,and 4 for 20, 40, 80, 120, 240, and 320 mg, respectively. †n=3, 4, 6, 6, 4, 3, and 4 for 20, 40, 80, 120, 240, and 320 mg, respectively.

Table 3: **Pharmacokinetic parameters of lazertinib after single administration and once daily continuous dosing for 22 days**

consistent target inhibition for a potent and durable response. Considering all available data, a dose level of 240 mg once daily was selected for further evaluation in the ongoing dose extension part of the study, on the basis of the dose–response relationship for activity, and safety.

Discussion

In our phase 1–2, open-label trial, we showed that lazertinib was generally well tolerated, with no dose-limiting toxicities observed up to the highest dose tested, and no apparent dose-dependent increases in the incidence of treatment-emergent adverse events. Consistent with the EGFR wild-type-sparing activity of lazertinib, adverse events commonly associated with EGFR inhibitors, such as skin toxicity (rash or acne) and diarrhoea were confined to grade 1–2 and were reported in fewer than a third of patients.

Lazertinib showed promising antitumour activity across multiple doses in patients with tumours harbouring activating *EGFR* mutations and T790M resistance mutations. Responses tended to be rapid and durable. Because only a small number of patients with T790M-negative tumours were included in our study, we could not fully assess the activity of lazertinib in this subgroup.

CNS metastases are common in patients with *EGFR*-mutated NSCLC, being detectable in approximately 25% of patients at the time of diagnosis of advanced disease, and in an increasing proportion of such patients in the period after diagnosis.[11] The intracranial responses seen in our study in patients with measurable brain metastases confirm the preclinical animal model data suggesting that lazertinib can effectively penetrate the blood–brain barrier.[6] In the future, given the favourable safety profile of lazertinib and absence of dose-limiting toxicities observed in our study, investigation of higher dose concentrations for the treatment of patients with brain metastases might be warranted.

Systemic exposures of lazertinib increased in a near dose-proportional manner after both single and multiple doses of 20–320 mg. Steady state of lazertinib was achieved after 15 days of dosing, as expected given the long half-life. In patients who received doses of 120 mg or higher, mean trough plasma concentrations of lazertinib on day 15 of cycle 1 exceeded the IC_{50} value for downregulation of EGFR phosphorylation in H1975 (T790M/L858R) cells in pre-clinical studies (unpublished). In line with this finding, lazertinib showed durable responses in patients with T790M-positive tumours at doses of 120 mg or higher.

The main limitation of our trial was that it was a single-arm study done in a single Asian country. Therefore, careful consideration should be given when extrapolating the safety and activity data of lazertinib to wider populations.

In addition to the currently approved drug, osimertinib, several other third-generation EGFR TKIs that are in clinical development have shown some degree of activity in patients with T790M-positive NSCLC, including rociletinib, nazartinib, olmutinib, naquotinib, mavelertinib, ASP8273, and avitinib. However, clinical development of some of these drugs has been halted because of safety concerns or low levels of activity.[12,13] In relation to the currently approved third-generation drug, osimertinib, objective responses in the phase 1–2 AURA study[14] were reported in 61% (78 of 127) of patients, and the median progression-free survival was 9·6 months (95% CI 8·3–not reached) in patients with T790M-positive tumours, which is similar to the antitumour activity for lazertinib achieved in our study. The most common adverse events in the AURA study were diarrhoea (118 [47%] of 253 patients) and rash (102 [40%] of 253 patients), which were grade 3 or worse in 2% and 1% of patients, respectively. Overall,

across all dose levels, 32% of patients had grade 3 or worse adverse events (*vs* 16% in our study), which were related to study treatment in 13% of patients (*vs* 3% in our study). One patient in the AURA study died because of pneumonia, which was reported as possibly drug related. Six (2%) cases of potential pneumonitis-like events were also reported, all of which resulted in drug discontinuation, and 11 (4%) patients had an adverse event of prolongation of the corrected QT interval, with none of these events resulting in dose reduction or discontinuation of osimertinib. Similarly, in our study, two (2%) of 127 patients developed pneumonitis and two (2%) developed grade 1 QT interval prolongation. Bearing in mind the caveats associated with cross-trial comparisons, the apparently favourable toxicity profile of lazertinib over osimertinib might be an advantage in future trials of combination therapy in this setting.

In conclusion, our results show that lazertinib is well tolerated, with responses frequently observed in patients with NSCLC harbouring both activating *EGFR* mutations and *EGFR* T790M TKI resistance mutations. Intracranial responses were also frequently seen, indicating effective blood–brain barrier penetration. Lazertinib has a potential therapeutic role in the treatment of NSCLC harbouring *EGFR* T790M mutations, either alone or in combination with other drugs.

Contributors

M-JA, J-YH, KHL, S-WK, D-WK, J-HK, SK, and BCC contributed to study design. M-JA, J-YH, KHL, S-WK, D-WK, Y-GL, EKC, J-HK, G-WL, J-SL, YJM, J-SK, SSL, HRK, MHH, JSA, J-MS, HTK, DHL, and BCC contributed to patient recruitment and the collection and interpretation of study data. SK contributed to the analysis and interpretation of study data. All authors approved the final version for submission.

Declaration of interests

M-JA reports grants from AstraZeneca and Bristol-Myers Squibb outside the submitted work; and personal fees from AstraZeneca, Lilly, MSD, Takeda, Ono Pharmaceutical, and Alpha Pharmaceutical, outside the submitted work. KHL reports personal fees from Bristol-Myers Squibb, MSD, and AstraZeneca, outside the submitted work. S-WK reports grants and personal fees from AstraZeneca, Lilly, and Boehringer Ingelheim, outside the submitted work. D-WK reports grants from Yuhan Corporation during the conduct of the study, and from Alpha Biopharma, AstraZeneca/MedImmune, Hanmi, Janssen, Merus, Mirati Therapeutics, MSD, Novartis, Ono Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, and Xcovery, outside the submitted work; HRK reports personal fees from AstraZeneca, Roche, and Boehringer Ingelheim, outside the submitted work. JSA reports personal fees from AstraZeneca, Boeringer Ingelheim, BMS-Ono, Menarini, Janssen, MSD, Roche, Samsung Bioepis, Pfizer, and Eisai, outside the submitted work. J-MS reports personal fees from AstraZeneca, Dakeda, Boehringer Ingelheim, outside the submitted work; and grants from AstraZeneca, outside the submitted work. DHL reports personal fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, CJ Healthcare, Eli Lilly, ChongKeunDang, Janssen, Merck, MSD, Mundipharma, Novartis, Ono, Pfizer, Roche, Samyang Biopharm, ST Cube, Abbvie, Takeda, and Genexine, outside the submitted work. SK is a salaried employee of Yuhan. BCC reports personal fees for speakers bureau from Novartis; personal fees for advisory boards from Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, Bristol-Myers Squibb, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, and MSD; ownership or stock interest in relation to TheraCanVac Inc, honoraria from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, and MSD; research grant support and contracts from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, and MSD; personal fees for royalty and intellectual property/patent from Champions Oncology; and personal fees for consultancy from Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, Bristol-Myers Squibb, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, and MSD, outside the submitted work. All other authors declare no competing interests.

Data sharing

De-identified participant data will be made available when all trial primary and secondary endpoints have been assessed. Any requests for trial data and supporting material (data dictionary and statistical analysis plan) will be reviewed by the trial management group in the first instance. Only requests that have a methodologically sound proposal and whose proposed use of the data has been approved by the independent trial steering committee will be considered. Proposals should be directed to the corresponding author in the first instance; to gain access, data requestors will need to sign a data access agreement.

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