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Original Research

Nazartinib for treatment-naive *EGFR*-mutant non-small cell lung cancer: Results of a phase 2, single-arm, open-label study



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1. Introduction

First- and second-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are effective first-line treatments for advanced non-small cell lung cancer (NSCLC) with EGFR-activating mutations. However, $\sim 50\%$ -60% of patients develop resistance due to secondary EGFR gatekeeper Thr790Met (T790M) mutations [1-7]. Third-generation EGFR-TKIs were designed as irreversible inhibitors with selectivity for both EGFR-activating and T790Mresistance mutations. These drugs selectively inhibit mutated EGFR while sparing wild-type, thereby potentially reducing off-target toxicities [3,8-10]. In 2018, the third-generation EGFR-TKI osimertinib received FDA approval in the first-line setting for patients with metastatic EGFR-mutant (Leu858Arg [L858R] or exon 19 deletions [ex19del]) NSCLC, based on the findings from the phase 3 FLAURA trial [11,12].

Nazartinib is a novel, third-generation EGFR-TKI [9]. In phase 1 of this study, nazartinib demonstrated antitumor activity and manageable safety in patients with *EGFR*-mutant (varying *EGFR* alterations, with or without the T790M mutation) advanced NSCLC who received \leq 3 prior lines of systemic therapy (NCT02108964) [13]. In phase 1, 7 dose-limiting toxicities (DLTs) were observed in 6 (3%) patients who received 150 mg, 225 mg, or 350 mg nazartinib once

daily [13]; 2 of 73 patients receiving the 150-mg dose experienced DLTs (1 maculopapular rash and 1 pneumonitis) [13]. The maximum tolerated dose was not met, and the recommended phase 2 dose (RP2D) was declared as 150 mg once daily tablets [13]. The RP2D for nazartinib capsules was also selected as 150 mg once daily based on the available safety, pharmacokinetics (PK), efficacy data, and Bayesian logistic regression model recommendation. Herein, we report the phase 2 results of first-line nazartinib.

2. Methods

2.1. Study design, patients, and treatment

The design of this phase 1/2 trial has been described previously [13]. In phase 2, treatment-naive patients (aged \geq 18 years) with stage IIIB/IV *EGFR*-mutant NSCLC and an Eastern Cooperative Oncology Group performance status of \leq 1 were enrolled from 12 centers in Asia, USA, Canada, and Europe. They were required to have locally documented *EGFR* L858R and/or ex19del mutations, or other rare activating mutations (eg, L861Q, G719A/S/C, S768I), which confer sensitivity to first- and second-generation EGFR-TKIs. Patients with neurologically stable and controlled brain metastases were also permitted. Other key eligibility criteria are presented in Supplemental Methods. Nazartinib (tablet and/or capsule) was administered orally at the RP2D of 150 mg once daily [13] on a continuous 28-day dosing schedule.

The study was undertaken in accordance with the Declaration of Helsinki revised edition, the International Council for Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, and local ethical and legal requirements. Study approval was obtained from ethics committees of all centers according to national laws. All patients provided written informed consent.

2.2. Outcomes

The primary endpoint was Blinded Independent Review Committee (BIRC)-assessed overall response rate (ORR) per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Secondary endpoints included: safety; tolerability (dose interruptions and reductions); investigator-assessed ORR per RECIST v1.1; BIRC- and investigator-assessed duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and time to response (TTR) per RECIST v1.1; overall survival (OS); and the PK of nazartinib and its metabolite LMI258. Exploratory endpoints included: outcome correlated with targeted sequencing of a cancer-associated gene panel in archival/newly acquired biopsy or plasma sample and subsequent paired newly acquired biopsy or plasma sample, where available, on treatment and at end of treatment (EOT); and the relationship between nazartinib plasma concentration and the corrected OT interval by Fridericia (QTcF).

2.3. Study assessments

Imaging data were centrally collected and read by the BIRC based on RECIST v1.1. Tumor response was assessed locally and centrally based on RECIST v1.1. Baseline imaging assessments were performed within 28 days prior to the first dose of nazartinib, following which imaging assessments for response evaluation were performed every 8 weeks (\pm 7 days) by computed tomography/magnetic resonance imaging (CT/MRI) until disease progression, death, loss to follow-up, or withdrawal of consent. Brain CT/MRI was mandated at baseline and every 8 weeks (\pm 7 days) for patients with baseline brain lesions. Other study assessments are presented in Supplemental Methods.

2.4. Statistical analyses

Efficacy and safety were assessed in the full analysis set and safety set, respectively, which comprised all patients who received ≥ 1 dose of nazartinib. The primary analysis was conducted when all enrolled patients had completed ≥ 6 cycles of treatment or had discontinued prior to that time for any reason. The ORR and DCR were estimated based on the exact binomial distribution. The DOR, TTR, PFS, and OS were described using Kaplan-Meier methods. The Clopper-Pearson method and the log-log transformation approach were used to calculate confidence intervals (CIs) for binary outcomes (ORR, DCR) and CIs for Kaplan-Meier-estimated medians, respectively [13]. The statistical methods for the PK analyses are presented in Supplemental Methods.

3. Results

3.1. Patients

Overall, 45 patients received ≥ 1 dose of nazartinib and were included in the efficacy and safety analyses. The median study follow-up time from enrollment to data cutoff (November 1, 2019) was 30 months (range: 25–34) in all patients and in those with baseline brain metastases. At data cutoff, treatment was ongoing in 19 patients (42%), and 26 (58%) had discontinued treatment primarily due to progressive disease (PD; n = 19, 42%; Table S1). The baseline characteristics are presented in Table 1. Of note, 19 patients (42%) had baseline brain metastases, a known adverse prognostic factor.

3.2. Overall efficacy

The BIRC-assessed ORR was 69% (95% CI, 53-82) and the DCR was 91% (95% CI, 79-98; Table 2). Majority experienced a reduction in the size of target lesions (Fig. 1). The median TTR was 4 months (95%) CI, 2–6). The median DOR was 25 months (95% CI, 14-not estimable [NE]; Table 2). The median followup time for PFS and OS was 17 months (range: (0-33) and 25 months (range: (0-33)) per BIRC. The median PFS was 18 months (95% CI, 15-NE; Table 2). Investigator-assessed efficacy was consistent with that reported by BIRC and is presented in Table S2 and Fig. S1. The median OS was NE (95% CI, 23-NE). There were 15 (33%) events, and the 33-month OS rate was 56% (95% CI, 33-74; Table 2). Kaplan-Meier curves for DOR, PFS, and OS are presented in Fig. S2.

3.3. Patients with brain metastases per RECIST v1.1

Of the 19 patients with brain metastases at baseline, data from 18 patients with ≥ 1 postbaseline evaluable assessment were used. Of these, 2 had received prior brain radiotherapy in a palliative setting; the time between end of brain radiotherapy and start of nazartinib treatment was 25 days in one patient and 18 days in the other patient.

3.4. Whole-body efficacy by brain metastases at baseline

In patients with baseline brain metastases (n = 18), BIRC-assessed whole-body ORR was 67% (95% CI, 41-87). The median DOR was 15 months (95% CI, 9-25; Table 2). The median TTR was 4 months (95% CI, 2-7). The median duration of follow-up for PFS was 14 months (range: 2-33). The median PFS was 17 months (95% CI, 11-21; Table 2). Investigator-assessed whole-body efficacy by baseline brain metastases is presented in Table S2.

3.5. Analysis of brain lesions by brain metastases at baseline

Per BIRC assessment, 17 of 18 patients had brain metastases as non-target lesions and 1 had brain metastases as target lesions; lesions were absent/normalized in 9 of 17 patients (53%) with brain non-target lesions, and none had worsening lesions. Of 27 patients without baseline brain metastases, only 2 developed new brain metastases postbaseline (Table S3). Investigator analysis of brain lesions is presented in Table S3.

3.6. Safety

The median duration of exposure to nazartinib was 24 months (range: 0–34). The median relative dose intensity was 99% (range: 50–100). Table 3 lists the most frequent adverse events (AEs; all-causality; $\geq 10\%$ of patients, any grade) as well as the corresponding proportion of patients with grade 1, grade 2, and grade 3/4 AEs. Any grade maculopapular rash (n = 17, 38%) was more common than dermatitis acneiform (n = 10, 22%). Any grade dry skin and paronychia were reported in 5 patients (11%) each (Table 3). The most frequent grade 3/4 AEs (all-causality) were maculopapular rash (n = 5, 11%; all were grade 3), increased lipase (n = 5, 11%; 1 was grade 4), and hypokalemia (n = 3, 7%; all were grade 3). Treatment-related AEs are presented in Supplemental Results.

The AEs leading to discontinuation (all grade 3), reported in 3 patients (7%), were fungal pneumonia (n = 1; also fatal), pancreatic carcinoma and bile duct obstruction (n = 1), and maculopapular rash (n = 1); treatment-related). Any-grade and grade 3/4 serious AEs (SAEs; all-causality) were reported in 18 (40%) and 14 patients (31%), respectively. Treatment-related SAEs were grade 1 hepatitis B reactivation and grade 2 pneumonitis (n = 1, 2% each). The patient with hepatitis B reactivation was not receiving any antiviral prophylaxis. No cases of hepatitis B reactivation were reported after the protocol amendment with the introduction of guidelines for HBV, HCV testing, assessment, follow-up, and prophylaxis. There were 6 (13%) on-treatment deaths, 5 due to the underlying disease and 1 due to fungal pneumonia (not treatment-related).

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Demographics and baselii	ne characteristics.
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Characteristic		All patients $N = 45$
Median age (range), in years		64 (28-83)
Sex, n (%)	Female	27 (60)
	Male	18 (40)
Race, n (%)	Asian	28 (62)
	Caucasian	17 (38)
ECOG PS, n (%)	0	19 (42)
	1	26 (58)
Smoking history, n (%)	Never smoked	30 (67)
	Former smoker	13 (29)
	Current smoker	2 (4)
Tumor histology/cytology,	Adenocarcinoma	43 (96)
n (%)	Large-cell carcinoma	1 (2)
	Other	1 (2)
Stage at time of entry, n (%)	IIIB	1 (2)
	IV	44 (98)
Number of metastatic	1	8 (18)
sites, n (%)	2	10 (22)
	3	9 (20)
	≥ 4	18 (40)
Sites of metastases, n (%)	Brain	19 (42)
	Bone	20 (44)
	Liver	5 (11)
EGFR mutation, n (%)	EX19DEL only	25 (56)
	L858R only	18 (40)
	T790M + EX19DEL	1 (2)
	+ G719S/A/C	
	EX19DEL + L858R	1 (2)
Prior therapy, n (%)	Non-biopsy surgery	6 (13)
	Radiotherapy	9 (20)
	Chemotherapy	2 (4)
	Adjuvant setting	1 (2)
	Therapeutic setting	1 (2)

ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor.

Maculopapular/macular/papular rash type led to dose interruptions in 3 patients (7%) and dose adjustments in 4 patients (9%); 16 patients (36%) took medication/therapy for this rash type. The AEs in this rash type were recovered/resolved in 14 patients (31%), recovering/resolving in 5 (11%), and not recovered/ resolved in 9 patients (20%). The median time to first occurrence of maculopapular/macular/papular rash type was 5 weeks (range: 1–87).

None of the patients reported an increase in QTcF > 60 ms or new QTcF > 500 ms. Six of 43 patients (14%) reported new QTcF > 450 to \leq 480 ms, and 2 of 45 (4%) reported new QTcF > 480 to \leq 500 ms (Table S4). Data on cardiac disorders and eye disorders are presented in Supplemental Results.

3.7. Pharmacokinetics

The steady state PK parameters of nazartinib are presented in Table S5. The PK at the RP2D of 150 mg once daily was consistent with that reported in phase 1 of this study [13]. Nazartinib reached peak plasma concentration at 3 h following oral administration. At steady

Efficacy parameter	Brain metastases present	Brain metastases absent	All patients
• •	$N = 18^{a}$	N = 27	N = 45
BOR, n (%)			
CR	0	2 (7)	2 (4)
PR	12 (67)	17 (63)	29 (64)
SD	6 (33)	4 (15)	10 (22)
PD	0	2 (7)	2 (4)
Unknown ^b	0	2 (7)	2 (4)
ORR, n (%) (95% CI)	12 (67) (41-87)	19 (70) (50-86)	31 (69) (53-82)
DCR, n (%) (95% CI)	18 (100) (82-100)	23 (85) (66-96)	41 (91) (79-98)
DOR			
Median (95% CI), months	15 (9-25)	NE (15–NE)	25 (14-NE)
PFS			
Median (95% CI), months	17 (11–21)	NE (15–NE)	18 (15-NE)
OS			
Median (95% CI), months	_	_	NE (23-NE)
OS rate, % (95% CI) at:			
12 months	_	_	90 (76-96)
24 months	_	_	65 (49-78)
33 months	_	_	56 (33-74)
36 months	-	_	NE

Table 2BIRC-assessed whole-body efficacy and OS.

BIRC, Blinded Independent Review Committee; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

ORR: CR + PR

DCR: CR + PR + SD

^a Of the 19 patients with brain metastases at baseline, data from 18 patients with \geq 1 postbaseline evaluable assessment were used.

^b No valid postbaseline assessment.

state, the geometric mean accumulation ratio was 1.65. The exposure of the active metabolite LMI258 was below 15% of the parent exposure at steady state. A PK comparison was conducted between the capsule and tablet formulations at 150 mg and 100 mg at single dose and steady state using data from phase 1 of this study, and the exposures of nazartinib were comparable (Table S6). The relationship between nazartinib plasma concentration and QTcF change from baseline was described with a linear mixed-effect model using time-

matched PK and ECG data from this study. At the steady-state mean nazartinib C_{max} with the 150-mg dose (833 ng/mL), the estimated mean QTcF change from baseline was 6.3 ms (90% CI, 4.71–7.79; Table S7, Fig. S3).

3.8. Biomarker analyses

Twenty baseline tumor samples underwent nextgeneration sequencing (NGS) using a comprehensive



Fig. 1. Best percentage change from baseline in sum of longest lesion diameters per BIRC assessment in all patients. BIRC, Blinded Independent Review Committee; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease. n: number of patients with a baseline and ≥ 1 postbaseline assessment of target lesions based on BIRC assessment. *Patient discontinued treatment. Percentage changes from baseline > 100% are set to 100%. The dashed line refers to the RECIST v1.1 criteria for PR defined as $\geq 30\%$ decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

Adverse events regardless of causality in > 10% of patients (any grade).

Table 3

Preferred terms	All patients $(N = 45)$				
	Grade 1 n (%)	Grade 2 n (%)	Grade 3/4 n (%)	Any grade ^a n (%)	
Number of patients with ≥ 1 event	43 (96)	37 (82)	29 (64)	44 (98)	
Diarrhea	21 (47)	4 (9)	1 (2)	21 (47)	
Maculopapular rash	15 (33)	3 (7)	5 (11)	17 (38)	
Pyrexia	11 (24)	2 (4)	1 (2)	13 (29)	
Cough	8 (18)	4 (9)	0	12 (27)	
Stomatitis	12 (27)	0	1 (2)	12 (27)	
Decreased appetite	6 (13)	6 (13)	0	11 (24)	
Pruritus	9 (20)	4 (9)	0	11 (24)	
Dermatitis acneiform	10 (22)	4 (9)	0	10 (22)	
Hypertension	2 (4)	7 (16)	1 (2)	8 (18)	
Headache	7 (16)	2 (4)	0	7 (16)	
Nausea	7 (16)	0	0	7 (16)	
Rash	7 (16)	1 (2)	0	7 (16)	
Constipation	6 (13)	0	0	6 (13)	
Increased lipase	2 (4)	3 (7)	5 (11)	6 (13)	
Nasopharyngitis	5 (11)	3 (7)	0	6 (13)	
Upper respiratory tract infection	2 (4)	4 (9)	0	6 (13)	
Upper abdominal pain	5 (11)	0	0	5 (11)	
Alopecia	5 (11)	0	0	5 (11)	
Increased amylase	3 (7)	1 (2)	2 (4)	5 (11)	
Anemia	3 (7)	2 (4)	1 (2)	5 (11)	
Back pain	3 (7)	1 (2)	1 (2)	5 (11)	
Dry skin	5 (11)	1 (2)	0	5 (11)	
Fatigue	5 (11)	0	1 (2)	5 (11)	
Peripheral edema	5 (11)	0	0	5 (11)	
Paronychia	3 (7)	2 (4)	0	5 (11)	
Urinary tract infection	3 (7)	2 (4)	0	5 (11)	
Vomiting	4 (9)	1 (2)	0	5 (11)	

AE, adverse event; CTCAE v4.03, Common Terminology Criteria for Adverse Events version 4.03; MedDRA v22.1, Medical Dictionary for Regulatory Activities version 22.1.

Adverse events by preferred terms are listed.

MedDRA v22.1, CTCAE v4.03.

^a A patient with multiple severity grades for an AE is only counted under the maximum grade.

cancer-related gene panel, and *EGFR*-activating mutation(s) were confirmed in all 20 patients. One sample was removed due to 0% tumor content in the sequenced tissue. The most frequently observed concurrent alterations (\geq 5 patients) were in *TP53* (n = 11; 10 singlenucleotide variants [SNVs] and 1 insertion/deletion [indel]), *AKT3* (n = 5; 1 amplification and 4 indels), and *CSF1R* (n = 5; all SNVs). In patients with a concurrent *TP53* alteration (n = 11), the best overall responses (BORs) were 1 complete response (CR), 6 partial responses (PRs), 2 stable disease (SD), and 2 PD. In those without a concurrent *TP53* alteration (n = 9), the BORs were 1 CR, 5 PRs, 2 SD, and 1 unknown (Fig. 2).

Of 6 patients who had results from both tissue and plasma NGS at baseline, concordance of *EGFR*-activating mutations was observed in 4 patients (the remaining 2 patients had insufficient circulating tumor DNA [ctDNA]).

Matched baseline, on-treatment (cycle 3 day 1 [C3D1]), and EOT plasma samples from 12 patients were assessed by NGS. At baseline, ctDNA was not detected in 3 of the 12 patients, while ctDNA including *EGFR*-activating mutations were detected in the remaining 9. Five patients with detectable *EGFR*-acti-

vating mutations at baseline also had samples available at C3D1 for analysis. Of these C3D1 samples, none had detectable ctDNA. Among 10 patients with available samples at EOT, ctDNA was undetectable in 7; of the remaining 3, the same *EGFR*-activating mutations from baseline re-emerged in 2, while there was insufficient ctDNA at baseline compared with EOT in the other (Table S8, Fig. S4). No variants were identified at EOT in association with previously reported mechanisms of acquired resistance to EGFR-TKIs [14,15] (Table S9).

4. Discussion

First-line nazartinib demonstrated efficacy in patients with stage IIIB/IV *EGFR*-mutant NSCLC despite a high proportion of patients with baseline brain metastases. Per BIRC assessment, 69% of patients achieved an overall response and 91% showed disease control. Responses were durable, with a median DOR of 25 months. The median PFS was 18 months. After a median follow-up time of 25 months, the median OS was not reached, with 56% of patients alive at 33 months.

CNS recurrence is a frequent complication in patients with EGFR-mutant NSCLC, with a 2-year estimated risk of CNS progression of ~15%-20% while on treatment with EGFR-TKIs [16-19]. Since the presence of brain metastases is associated with a poor prognosis and impaired quality of life, control of CNS progression is an important consideration for these patients [17,20,21]. In this study, nazartinib showed clinically meaningful antitumor activity in the brain. Brain lesions were absent/normalized in 53% of patients with brain non-target lesions. Of the 27 patients without baseline brain metastases, only 2 developed new brain metastases postbaseline, which is suggestive of a protective effect of nazartinib against brain metastases. In the phase 3 FLAURA trial, which evaluated first-line osimertinib in EGFR-mutant (ex19del or L858R) advanced NSCLC, CNS progression was reported in 7 of 226 patients (3%) with no known or treated CNS metastases at study entry in the osimertinib group [12,22].

The phase 1/2 AURA study evaluated first-line osimertinib 80 mg once daily administered to patients with locally advanced/metastatic *EGFR*-mutant NSCLC (N = 30) [23]. Noting the limitations of cross-trial comparisons, the ORR observed with nazartinib was comparable to that reported for osimertinib (69% versus 67% [95% CI, 47–83]), with a median DOR of 25 months versus 19.3 months (95% CI, 12.2–24.7), respectively [23]. The median PFS was 18 months versus 22.1 months (95% CI, 13.7–30.2) for nazartinib and osimertinib, respectively [23].

Nazartinib had a manageable safety profile, including with respect to AEs that are usually associated with wild-type EGFR inhibition [13]. The most common AEs were largely similar to those reported previously [12,13,23,24]. Maculopapular/macular/papular rash was the most common rash type reported in this study, which presented during the first 2 months of treatment; events within this rash type responded to medication and were resolved or resolving at the time of data cutoff in a majority. Maculopapular rash, which is characteristic of nazartinib, is generally different from the known EGFR-TKI acneiform rash and is usually acute and self-limiting [13]. Of note, nazartinib did not show potential to cause clinically relevant QTcF prolongation at the steady-state mean C_{max} with the 150-mg dose; the upper bounds of the 90% CI for the predicted change at this concentration level was 7.79 ms, which was below the 10-ms threshold as indicated as relevant in the ICH E14 [25]. In the FLAURA trial, ECG QT prolongation events were reported in 28 patients (10%) in the osimertinib group [24]. In a concentration-QTc analysis conducted using AURA2 study data, a linear relationship was observed between osimertinib concentration and $\Delta QTcF$ [26]. The predicted mean (upper 90% CI)



Fig. 2. Progression-free survival and response according to the presence of genetic alterations assessed with next-generation sequencing. amp, amplification; CR, complete response; del, deletion; DOR, duration of response; indel, insertion/deletion; PD, progressive disease; PR, partial response; SD, stable disease; snv, single nucleotide variant; UNK, unknown.

 $\Delta QTcF$ was 14.2 (15.8) ms at the steady-state maximum osimertinib concentration for an 80-mg once-daily dose [26]. The results from our study do not reveal nazartinib to have significant proarrhythmic potential; however, these observations warrant further investigation.

The *TP53* co-alteration frequency reported in this study was largely consistent with that reported in prior studies ($\sim 50\%-60\%$) in *EGFR*-mutant NSCLC [13,27]. Results from phase 1 of this study suggested a possible association between *TP53* mutations in tumors and a lower response rate to nazartinib [13]. However, in this preliminary analysis from phase 2, there was no observable correlation between any concurrent genetic alterations and BOR, likely due to a small sample size. A formal statistical analysis was not conducted to test this correlation. Among 5 patients with *EGFR*-activating mutations detected at baseline who also had samples analyzed at C3D1, none had persistent ctDNA at this time point, which suggested successful clearance of ctDNA.

In conclusion, first-line nazartinib is a promising third-generation EGFR-TKI for patients with advanced *EGFR*-mutant NSCLC, including those with baseline brain metastases. Furthermore, the results from the concentration-QTcF analysis suggest that nazartinib did not impact cardiac rhythm conduction. These findings support further clinical development of nazartinib as a single agent and in combination with other anticancer therapies to circumvent acquired resistance to EGFR-TKIs.

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Role of funder

The study was designed by the sponsor and study investigators. Data were collected by investigators and analyzed by the sponsor. All authors, including those employed by the funder, were involved in data interpretation. The sponsor had a role in the study design, as well as collection, analysis, and interpretation of data in collaboration with the study investigators. The sponsor also collaborated with the investigators to write the report.

Data sharing statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel based on the scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on http://www.clinicalstudydatarequest.com/.

Meeting presentation

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Author contributions statement

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Conflict of interest statement

The authors declare the following financial interests/ personal relationships that may be considered as potential competing interests: Dr. Tan reports consulting or advisory role for Novartis, Merck, Loxo, AstraZeneca, Roche, Pfizer, Amgen, and Janssen; travel, accommodation, and expenses from Pfizer, Boehringer Ingelheim, and Roche; honoraria from Bristol-Myers Squibb, Takeda, Novartis, Roche, and Pfizer; and research funding (institution) from Novartis, GlaxoSmithKline, Amgen, and AstraZeneca. Dr. S-W Kim reports advisory role for AstraZeneca, Amgen, Boehringer Ingelheim, Eli Lilly, and Novartis; research funding from AstraZeneca and Novartis; and honoraria from Boehringer Ingelheim. Dr. Ponce Aix reports consulting or advisory role for Bristol-Myers Squibb, Merck, and Roche; speakers' bureau for Bristol-Myers Squibb, Merck, and Roche; and travel, accommodations, expenses from AstraZeneca, Merck, and Roche. Dr. Sequist reports consulting or advisory role for AstraZeneca, Genentech/Roche, Janssen Oncology, and Takeda; and research funding (institution) from Astra-Zeneca, Blueprint Medicines, Boehringer Ingelheim, Genentech, Guardant Health, Johnson & Johnson, Loxo, Merck, Merrimack, Novartis, and Pfizer. Dr. Smit reports consulting or advisory role (institution) for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Merck KGaA. MSD Oncology. Novartis. Roche/Genentech. Seattle Genetics, and Takeda; and research funding (institution) from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Roche/Genentech. Dr. Yang reports personal fees (advisory board) from AstraZeneca, Boehringer Ingelheim, Roche, Novartis, Bristol-Myers Squibb, Ono Pharmaceuticals, Takeda, Eli Lilly, Pfizer, MSD, Merck, Amgen, Yuhan, and Daiichi Sankyo; grants to conduct investigator initiated study from AstraZeneca; and institutional fees (advisory board) from Amgen, Boehringer Ingelheim, Takeda, Eli Lilly, Pfizer, MSD, Merck, Bayer, Yuhan, Daiichi Sankyo, Janssen, and GlaxoSmithKline. Dr. Hida reports honoraria from AstraZeneca, Bristol-Myers Squibb, Chugai Pharma, Clovis Oncology, Kissei Pharmaceutical, Eli Lilly, MSD, Nippon Boehringer Ingelheim, Novartis, Ono Pharmaceutical, Pfizer, and Taiho Pharmaceutical; and research funding (institution) from Abbvie, Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Chugai Pharma, Clovis

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Appendix A. Supplementary data

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