Ceritinib plus nivolumab in patients with advanced *ALK*-rearranged non-small-cell lung cancer: results of an open-label, multicenter, phase 1B study

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Title: Ceritinib plus nivolumab in patients with advanced *ALK*-rearranged non-small-cell lung cancer: results of an open-label, multicenter, phase 1B study

Short title: Ceritinib plus nivolumab in *ALK*-rearranged NSCLC

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Myers Squibb and owns stock in Bristol-Myers Squibb and Xcovery. ***VG, OAB, LW, and JWS*** *are employees of Novartis.* ***PC, JB, and YYL*** *are employees and owns stock in Novartis.* ***DSWT*** *reports grants and personal fees (advisory role, consultant, and research funding) from Novartis, grants and personal fees from Boehringer Ingelheim (advisory role and travel), personal fees from MSD, grants and personal fees from Pfizer (research funding and trial), personal fees from Bristol-Myers Squibb, personal fees from Roche, grants from Bayer (research funding), grants and personal fees from AstraZeneca outside the submitted work.*

Abstract

Introduction: Induction of PD-L1 expression due to constitutive oncogenic signaling has been reported in NSCLC models harboring *EML4–ALK* rearrangements. We assessed safety and activity of ceritinib plus nivolumab in these patients.

Methods: In this open-label, phase 1B, multicenter, dose-escalation and expansion study, previously treated (ALK inhibitor [ALKi]/chemotherapy) or treatment-naïve patients with stage IIIB/IV *ALK*-rearranged NSCLC received nivolumab 3 mg/kg intravenously every 2 weeks plus ceritinib (450 mg/300 mg) daily with low-fat meal.

Results: In total, 36 patients were treated (450 mg cohort [n=14]; 300 mg cohort [n=22]). In the 450 mg cohort, four patients experienced DLTs. In the 300 mg cohort, two patients experienced DLTs. Among ALKi-naïve patients, the overall response rate (ORR) was 83% (95% CI 35.9–99.6) in the 450 mg cohort and 60% (95% CI 26.2–87.8) in the 300 mg cohort. Among ALKi-pretreated patients, the ORR was 50% (95% CI 15.7–84.3) in the 450 mg cohort and 25% (5.5–57.2) in the 300 mg cohort. The ORR point estimate was observed to be greater in patients who were positive for PD-L1 as compared to those who were negative for PD-L1 with overlapping CIs (e.g., at a cutoff ≥1% PD-L1, 64% [95% CI 35.1–87.2] patients had confirmed responses as compared to those with negative PD-L1 staining (31% [95% CI 11.0–58.7]). Most frequently reported grade 3/4 adverse events were increased alanine aminotransferase (ALT) (25%), increased gamma-glutamyl transferase (22%), increased amylase (14%), increased lipase (11%), and maculopapular rash (11%). Incidence of all grade rash (grouped term) was 64% in both cohorts; grade 3 rash was reported in 29% and 14% patients in the 450 mg and 300 mg cohorts, respectively; no grade 4 rash was reported.

Conclusion: Ceritinib plus nivolumab has activity; ORR appears to correlate with PD-L1 at baseline. Toxicity, especially rash, is more common than with either single agent.

Key words: Ceritinib, nivolumab, ALK, PD-1, NSCLC

Introduction

Drugs that target oncogenic driver mutations or inhibit immune checkpoints are reshaping management of non-small-cell lung cancer (NSCLC).[1] *ALK* rearrangements are key oncogenic drivers occurring in 3%–7% of patients with NSCLC.[2,3] Ceritinib (Zykadia; Novartis, East Hanover, NJ, USA), a selective oral ALK inhibitor (ALKi), is approved for the treatment of patients with metastatic *ALK*-rearranged NSCLC; both in the first-line setting and patients who progressed on or are intolerant to crizotinib.[4] The most common adverse events (AEs) with ceritinib at 750 mg/day fasted reported in clinical trials were diarrhea, nausea, vomiting, increased alanine aminotransferase (ALT), decreased appetite, increased aspartate aminotransferase (AST), fatigue, and abdominal pain; all reported in >30% patients.[5–9] Recent data from a phase 1 study of ceritinib (ASCEND-8; NCT02299505) showed that the frequency and severity of gastrointestinal toxicities were lower with a starting dose of 450 mg/day under fed condition compared to the dose of 750 mg/day under fasted condition, with less patients requiring dose reduction or interruption, resulting in a higher median relative dose intensity and comparable efficacy.[10,11] Based on the ASCEND-8 data, the 450 mg dose of ceritinib with food was recently approved as the recommended dose in the USA[12] and Europe.[13]

Nivolumab (Opdivo, Bristol-Myers Squibb, NY, USA) is a PD-1 immune checkpoint inhibitor approved by the US Food and Drug Administration (FDA) for metastatic NSCLC progressed during or after platinum-based chemotherapy[14] and approved in Europe for locally advanced or metastatic NSCLC after prior chemotherapy.[15] In two phase 3 trials, an overall survival (OS) benefit was observed

with nivolumab compared to docetaxel regardless of the PD-L1 expression level;[16–18] however, survival was enhanced in patients with nonsquamous NSCLC having higher PD-L1 expression.[16,17] The most frequently reported AEs with nivolumab in clinical trials were fatigue, nausea, decreased appetite, and asthenia.[16,17]

Induction of PD-L1 expression due to constitutive oncogenic signaling has been reported in NSCLC models harboring *EML4–ALK* rearrangements, contributing to immune escape in these models.[19] This preclinical evidence and the demonstrated efficacy of ceritinib monotherapy in *ALK*-rearranged NSCLC and nivolumab monotherapy in stage IIIB/IV NSCLC provided a rationale to evaluate the combination ceritinib plus nivolumab in patients with *ALK*-rearranged NSCLC. This multicenter, phase 1B, dose-finding, proof-of-concept study is the first study assessing the safety and activity of the combination ceritinib plus nivolumab in these patients.

Patients and methods

Study design and participants

In this phase 1B study, patients were recruited from nine centers across eight countries. The study design included a dose-escalation phase, guided by Bayesian Logistic Regression Model (BLRM) with overdose control to determine the maximum-tolerated dose (MTD)/recommended dose for expansion (RDE),[20,21] followed by a two-arm expansion phase, using the RDE of the combination, and enrolling ALKi-treated (one prior treatment with any ALKi except ceritinib) and ALKi-naïve patients. Results from the dose-escalation phase are reported in this article.

Adult patients (age ≥18 years) were eligible if they had histologically or cytologically confirmed stage IIIB/IV *ALK*-rearranged NSCLC with *ALK*-rearrangement determined by the FDA-approved Vysis ALK Break Apart Fluorescent In-Situ Hybridisation Probe Kit (Abbott Molecular Inc, Molecular, Des Plaines, IL, USA) and scoring algorithm (including positivity criteria). If documentation of *ALK* rearrangement was not available, the test to confirm *ALK* rearrangement was performed at a Novartis-designated central laboratory and the result had to be available prior to initiation of ceritinib treatment. PD-L1 expression was not used to determine eligibility. Patients who were treatment-naïve or who had received prior chemotherapy regimens or ALKi for advanced disease were eligible for the dose-escalation phase. Other inclusion criteria included presence of at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, a WHO performance status of 0–1, and adequate organ function and laboratory test results. Patients with asymptomatic or neurologically stable brain metastases (BM) were eligible (Supplementary Table 1).

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation. The study protocol and all amendments were reviewed and approved by the independent ethics committee or institutional review board for each center. All patients provided written informed consent before screening.

Procedures

Eligible patients received ceritinib (at assigned dose levels) once daily with low-fat meal (fed), in continuous 28-day treatment cycles, plus nivolumab 3 mg/kg every 2 weeks (fixed dose). The originally planned dose levels for ceritinib were 450 mg/day fed (starting dose level), 600 mg/day fed, and 300 mg/day fed. In the study, the patients were treated with ceritinib 450 mg/day fed and 300 mg/day fed. Patients continued treatment with ceritinib and/or nivolumab until unacceptable toxicity, death, withdrawal of consent, and/or at the discretion of the investigator. For more information, refer to supplementary appendix.

Outcomes

The primary objective was to determine the MTD and/or RDE of ceritinib plus nivolumab (dose-escalation phase) and to assess the preliminary anti-tumor activity of the ceritinib plus nivolumab combination at the RDE (dose-escalation and dose-expansion phases). The primary endpoints were dose-limiting toxicities (DLTs) in each dose cohort during the first 6 weeks of therapy and overall response rate (ORR, as assessed per RECIST 1.1) by investigator assessment.

Secondary objectives were to assess the safety profile and efficacy based on investigator-assessed duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS). Exploratory objectives included assessment of pharmacokinetics of ceritinib and nivolumab and correlation of clinical efficacy endpoints with baseline PD-L1 expression, and potential resistance biomarkers at the time of disease progression. For more information, refer to supplementary appendix.

Statistical analysis

For dose escalation, a five-parameter BLRM employing the escalation with overdose control (EWOC) principle was used for dose level selection and for determination of the MTD and RDE. Pharmacokinetic parameters for ceritinib were summarized by treatment group using descriptive statistics, including geometric mean and geometric coefficient of variation (CV). For $T_{max,}$ median values were provided. ORR and DCR were estimated and their associated exact binomial 95% confidence intervals (CIs) were reported. PFS and DOR were analyzed using the Kaplan-Meier method; median value with the associated 95% CI was reported.

The data cutoff was August 30, 2017 (except for ceritinib pharmacokinetic data, for which the cutoff was September 9, 2016). We used SAS version 9.4 for analyses. For more information, refer to supplementary appendix.

Results

Between June 11, 2015 and July 11, 2016, 36 patients were treated; of these, 14 patients received ceritinib 450 mg/day fed plus nivolumab 3 mg/kg every 2 weeks and 22 patients received ceritinib 300 mg/day fed plus nivolumab 3 mg/kg every 2 weeks. At data cutoff, 13 patients (five in the 450 mg cohort and eight in the 300 mg cohort) were still on treatment and 23 patients discontinued treatment (Supplementary Fig 1). Seventeen patients discontinued due to disease progression, four due to AEs (cerebrovascular accident [study drug non-related], asthenia [non-related], elevated lipase [study drug related], and increased ALT [study drug related] and increased carcinoembryonic antigen [study drug non-related]) and two patients due to death (both due to disease progression). The median duration of follow-up from treatment start to

cutoff date was 24.6 months (IQR 21.8–25.1) for the 450 mg cohort (25.1 months [24.5–26.1] in the ALKi-naïve and 22.1 months [21.4–24.9] in the ALKi-pretreated patients) and 17.6 months (15.5–20.4) for the 300 mg cohort (19.6 months [15.6–20.6] in the ALKi-naïve and 15.9 months [IQR 14.9–20.1] in the ALKi-pretreated patients).

Baseline patient demographics and disease characteristics are shown in Table 1. The baseline characteristics were similar in patients in the 450 mg and 300 mg cohorts.

The median duration of exposure to study treatment was 47.0 weeks (range 1.0–116.0) for the 450 mg cohort and 37.3 weeks (4.4–91.3) for the 300 mg cohort. Of the 14 patients in the 450 mg cohort, 12 were evaluable for dose-determining analysis. Two patients in each dose level were not evaluable because they did not receive the minimum required 28 days of treatment with ceritinib and/or two complete nivolumab infusions during the first 6 weeks. Four experienced DLTs: pancreatitis in two patients (one grade 2 [asymptomatic] and one grade 3), autoimmune hepatitis in one patient (grade 3), and both lipase (grade 4) and transaminases (grade 3) increased in one patient. Of the 22 patients in the ceritinib 300 mg cohort, 20 patients were evaluable for dose-determining analysis and two experienced DLTs: increased ALT in two patients (both grade 3 with no bilirubin elevation). Both dose levels satisfied BLRM EWOC criteria. The 600 mg/day fed dose was not used because of toxicities noted in the 450 mg fed group.

AEs regardless of study drug relationship in ≥20% of patients (in any cohort) are shown in Table 2. The most frequently reported AE in the overall population (N=36) was diarrhea (69%); only one patient (300 mg cohort) had grade 3/4 diarrhoea. Other

frequently reported AEs (≥30%) in the overall population (N=36) were increased ALT (58%), increased AST (44%), vomiting in 42%, nausea (39%), increased amylase (36%), increased blood creatinine (31%), rash (31%), and rash maculo-papular (31%). The most frequently (>10% of all patients, N=14) reported grade 3/4 AEs in the ceritinib 450 mg cohort were increased ALT, increased amylase, rash, rash maculo-papular, fatigue, gamma-glutamyl transferase (GGT) increased, increased lipase, dyspnea, and increased transaminases (all reported in 14.3% patients). The most frequently (>10% of all patients, N=22) reported grade 3/4 AEs in the 300 mg/day cohort were increased ALT in 32%, increased GGT in 27%, and increased amylase in 14%.

Using pooled terms, rash was a common AE (Table 3). Overall, 64% patients developed rash-related events regardless of study drug relationship, including 19% patients with grade 3/4 rash-related events (Table 3). The proportion of patients with rash-related events was similar in the 450 mg cohort (64%) and the 300 mg cohort (64%). However, the proportion of patients with grade 3/4 rash-related events was 29% in the 450 mg cohort and 14% in the 300 mg cohort. Overall, the incidence of rash was 93% in the Asian patients and 46% in the non-Asian patients (Table 3). A majority of patients (50% in each cohort) experienced the initial onset of rash during first 6 weeks of the treatment; however, it was not considered as a DLT as per study protocol.

Of the overall 36 patients, AEs requiring ceritinib dose change were reported in 12 (33%) patients and AEs leading to dose interruptions (either drug or both) in 29 (81%) patients (Table 4). Based on these safety findings, including DLTs and rash-

related events, the safety committee (investigators and Novartis) decided to investigate an alternative dosing regimen.

The preliminary efficacy of ceritinib plus nivolumab combination by prior ALKi treatment is shown in Table 5. The confirmed ORR (by investigator) in ALKi-naïve patients was 69% (95% CI 41.3–89.0) (one CR and 10 PRs); the ORR was 83% (95% CI 35.9–99.6) in the 450 mg cohort (all PRs) and 60% (95% CI 26.2–87.8) in the 300 mg cohort (one CR and five PRs). The ORR in ALKi-pretreated patients was 35% (95% CI 15.4–59.2); the ORR was 50% (15.7–84.3) in the 450 mg cohort (all PRs) and 25% (5.5–57.2) in the 300 mg cohort (all PRs).

Kaplan-Meier analysis results of median PFS and DOR with low sample sizes need to be interpreted with caution. In the ceritinib 450 mg cohort, the median DOR was 11.2 months (95% CI 3.7–not estimable [NE]) in ALKi-pretreated patients (N=4), whereas it was not reached in ALKi-naïve patients (N=5) (95% CI 3.9–NE), as a high proportion of responders were censored among ALKi-naïve patients (three of five patients [60%]). In the ceritinib 450 mg cohort, the estimated event-free rates at 6 months and 10 months were 80% (four of five responders at risk) (95% CI 20.4–96.9) in ALKi-naïve patients and 75% (three of four responders at risk) (12.8–96.1) in ALKi-pretreated patients. In the ceritinib 300 mg cohort, the median DOR was not reached for both ALKi-naïve (N=5) (95% CI 3.8–NE) and ALKi-pretreated patients (N=3) (95% CI 7.4–NE) due to the high proportion of responders censored: five of six patients (83%) among ALKi-naïve patients and two of three patients (67%) among ALKi-pretreated patients. In the ceritinib 300 mg cohort, the estimated event-free rates at 10 months were 83% (five of six responders at risk) (95% CI 27.3–97.5) in ALKi-naïve patients and

67% (two of three responders at risk) (5.4–94.5) in ALKi-pretreated patients. Due to a high proportion of responders censored, we need to interpret the results with caution. The best percentage change from baseline in target lesions for ALKi-naïve and ALKi-pretreated patients is shown in Supplementary Fig. 2.

Across both cohorts, the median PFS was not reached in ALKi-naïve patients and was 4·6 months (95% CI 2.1–13.6) in ALKi-pretreated patients (Fig. 1), data for each dose level are provided in Table S2; the proportion of patients censored were 10 of 16 patients (62.5%) among ALKi-naïve patients and four of 20 patients (20.0%) among ALKi-pretreated patients. The corresponding estimated PFS rates at 12 months were 67.5% (95% CI 38.4–85.1) and 35.0% (15.7–55.2), respectively.

In the ceritinib 450 mg cohort, the median PFS was 6.4 months (95% CI 0.8–13.7; seven [88%] of eight patients had events) in ALKi-pretreated patients (N=8), whereas it was not reached in ALKi-naïve patients (N=6) (95% CI 1.8–NE; three [50%] of six patients had events) (Table 5), as a high proportion of patients were censored among ALKi-naïve patients (three of six patients [50%]). In the ceritinib 450 mg cohort, the estimated event-free rates at 12 months were 67% (95% CI 19.5–90.4) in ALKi-naïve patients and 38% (8.7–67.4) in ALKi-pretreated patients (Table 5). In the ceritinib 300 mg cohort, the median PFS was 3.7 months (95% CI 1.8–NE; nine [75%] of 12 patients had events) in ALKi-pretreated patients (N=12), whereas it was not reached in ALKi-naïve patients (N=10) (95% CI 1.9–NE; three [30%] of 10 patients had events), as a high proportion of patients were censored among ALKi-naïve patients (seven of ten patients [70%]). In the ceritinib 300 mg cohort, the estimated event-free rates at 12

months were 67% (95% CI 27.2–88.1) in ALKi-naïve patients and 33% (10.3–58.8) in ALKi-pretreated patients.

Among the 15 patients with BM at baseline, six were ALKi-naïve, of which four had a confirmed response (three PR and one CR) and nine were ALKi-pretreated, of which two had a confirmed PR (Supplementary Table 2).

In total, 30 patients had baseline tumor tissue available for PD-L1 staining using the IHC 28-8 pharmDx assay. At each cutoff of PD-L1 expression examined, the ORR point estimate was observed to be greater in patients who were positive for PD-L1 as compared to those who were negative for PD-L1 with overlapping CIs (Supplementary Table 3). For example, at a cutoff ≥1% PD-L1, 64% (95% CI 35.1–87.2) patients had confirmed responses as compared to patients with negative PD-L1 staining (31% [95% CI 11.0–58.7]) (Supplementary Table 3).

Discussion

This study explored the combination of an ALKi (ceritinib) with a PD-1 inhibitor (nivolumab) in patients with *ALK*-rearranged NSCLC. This combination appears to have promising activity, particularly in patients with high PD-L1 expression based on an exploratory analysis; however, the combination was associated with relevant toxicity, principally rash, ALT/AST elevations, and lipase elevations.

Recently a phase 1/2 study (CheckMate 370) evaluated the safety and tolerability of first-line nivolumab plus crizotinib in patients with *ALK*-positive NSCLC. However, of the first 13 patients treated with nivolumab plus crizotinib, five (38%) developed severe

hepatic toxicities leading to the discontinuation of the combination; of these, two patients died.[22]

Other second-generation ALKi are being explored in combination with immunotherapy.[23] Recently, Kim et al presented the data from alectinib plus atezolizumab study[24] in which alectinib was given as run-in from 7 days before combining with atezolizumab. The ORR reported in their study was 86% (18 out of 21 patients) and the median PFS was 21.7 (95% CI: 13.1–NE) months. The incidence of treatment-related AEs with combination was 52% with grade 3 rash reported in 19% patients.[24]

In the current study, four patients in the ceritinib 450 mg fed cohort experienced DLTs among 12 evaluable patients; the 450 mg dose satisfied BLRM EWOC criteria. Further, the incidence of rash was higher than that observed with ceritinib monotherapy (up to 22%)[6,7,9] or nivolumab monotherapy (up to 18%).[16–18] The overall incidence of rash-related events (pooled term) was 64% and was similar in both tested dose levels; however, the incidence of grade 3 rash was higher at the 450 mg dose level (29% vs 14%). Of note, none of the patients reported grade 4 rash. The incidence of all grade rash (pooled term) was higher in Asian (93%, 13 of 14 patients) vs non-Asian patients (45%, 10 of 22 patients); the interpretation of these results is limited due to the small sample size. The mechanism of rash-related events with the combination ceritinib plus nivolumab is unclear. Other frequent grade 3/4 AEs were increased ALT, increased GGT, increased amylase, and increased lipase; however, these AEs were not increased from those known for either agent. The incidence of diarrhea and vomiting in the 450 mg fed cohort was higher than that reported with ceritinib 450 mg fed in the ASCEND-8

study,[11] perhaps due to the fact that nivolumab is also known to be associated with these AEs.[16,17] However, no increased frequency of colitis was observed and these AEs were managed by dose interruption, dose reduction, or supportive concomitant medication. The MTD was not reached and the recommended phase 2 dose was not established. Based on these safety findings, an alternative dosing regimen (Regimen B) is being investigated. In this alternative dosing regimen, ceritinib monotherapy is administered for two cycles before initiation of combination therapy with nivolumab in order to allow for safety observation and ceritinib dose reduction prior to initiation of combination therapy with nivolumab. Thus, the regimen was designed in such a way that ceritinib was given initially as monotherapy, and later nivolumab was added with the rationale that the frequency of toxicity with the original regimen would decrease. The dose of ceritinib used in the alternative regimen was 450 mg fed, as the ceritinib steady-state pharmacokinetics of the 450 mg fed regimen was similar to that of 750 mg fasted (based on ASCEND-8 study);[10] therefore, the efficacy from ceritinib would not be compromised. In the study by Kim et al, alectinib was given as monotherapy during run-in period followed by the combination with atezolizumab; interestingly, in that study, safety of the combination of alectinib and atezolizumab was acceptable.[24] Both explored cohorts have demonstrated preliminary evidence of activity. As expected, the ORR was higher in the ceritinib 450 mg cohort than in the ceritinib 300 mg cohort in both ALKi-naïve and ALKi-pretreated patients. The PD-L1 inhibitor, durvalumab, used as a third-line or later treatment, has shown limited activity (ORR, 12%) in patients with *ALK*-positive NSCLC.[25] In the current study, ORR was observed to be higher in patients with positive PD-L1 staining, suggesting an additive effect by combining ceritinib with

nivolumab; however, due to small sample sizes, these results need to be interpreted with caution. PFS time in previously treated ALK patients was short in this study; however, it has to be noted that 20 of 36 patients (56%) received ≥2 prior antineoplastic regimens and 6 of 36 patients (17%) received ≥2 ALKi.

The ceritinib steady-state pharmacokinetics of the 450 mg fed regimen was similar to that from the 750 mg fasted regimen (historical data).[26] This finding is consistent with the results of the ASCEND-8 study, which demonstrated that ceritinib 450 mg with food, had comparable exposure and efficacy, with improved GI safety compared to ceritinib 750 mg in fasted patients with *ALK*-rearranged NSCLC.[10,11] Nivolumab C_{trough} reached steady state by cycle 8 and remained stable afterwards. Accumulation of C_{trough} from the first dose to steady state was 3.7-fold, consistent with the published values.[27] While some benefit was observed in patients at all PD-L1 levels, greater benefit was found in those with higher PD-L1 positivity. However, given the small sample size and the exploratory nature of this analysis, these results need to be interpreted with caution (Supplementary Table 3). The absence of either detectable ctDNA or baseline *ALK* somatic SNV mutations may be associated with longer PFS; however, these results need to be interpreted with caution.[28] The major limitation of our study include smaller sample size for the exploratory analysis of ORR; future studies with larger number of patients are assessing ALKi in combination with PD-1 inhibitor in ALK-positive NSCLC patients with higher PD-L1 positivity.

Taken together, combining ceritinib with nivolumab has been associated with increase in toxicity including rash (grade ≤3) when administered concomitantly at recommended single-agent doses. Nevertheless, this combination appears to elicit

activity, with exploratory analysis suggesting that high PD-L1 expression may enrich for patients more likely to respond. Identifying subgroups of patients with *ALK*-rearranged NSCLC who may yet benefit from adding an anti-PD1 therapy to ceritinib remains a crucial challenge. Based on these safety findings, an alternative dosing regimen is being investigated in which ceritinib is administered as monotherapy for two cycles before initiation of the combination therapy with nivolumab.

Contributors

MM, ATS, JFV, TJ, GL, GS, YYL, JWS, and DSWT *contributed to study design.* ***MPL, GS, VG, and JWS*** *contributed to study execution.* ***PC*** *contributed to study conduct oversight and data monitoring.* ***EF, FGdB, MM, HHL, ATS, JFV, TJ, GL, MPL, GS, and DSWT*** *recruited patients and contributed to data collection.* ***EF, HHL, ATS, JFV, TJ, GL, MPL, GS, VG, PC, YYL, JWS, and DSWT*** *contributed to data analysis and interpretation.* ***JB*** *contributed to biomarker testing and analysis (PD-L1 and ctDNA) and data interpretation.* ***OAB*** *performed bioinformatics and correlative analysis for the cfDNA sequencing data.* ***LW*** *contributed to planning, conducting, and interpreting statistical analysis.* ***YYL*** *contributed to pharmacokinetic and pharmacodynamics data analysis and interpretation.* ***EF*** *wrote the first draft of the manuscript with the help of a medical writer. All authors provided input for data interpretation, critically revised the content, and approved the final draft of manuscript for publication.*

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Data availability statement

Novartis will not provide access to patient-level data if there is a reasonable likelihood that individual patients could be re-identified. Phase 1 studies, by their nature, present a high risk of patient re-identification; therefore, patient individual results for phase 1 studies cannot be shared. In addition, clinical data, in some cases, have been collected subject to contractual or consent provisions that prohibit transfer to third parties. Such restrictions may preclude granting access under these provisions. Where co-

development agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

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Figure legends

Fig 1. Progression-free survival by prior ALKi status

Abbreviations: ALKi, anaplastic lymphoma kinase inhibitor; CI, confidence interval; NE, not estimable.

***Table 1*: Baseline characteristics**

	Ceritinib 450 mg fed plus nivolumab 3 mg/kg N=14	Ceritinib 300 mg fed plus nivolumab 3 mg/kg N=22
Age		
Median (range), years	56.5 (36.0–78.0)	53.0 (35.0–66.0)
<65, n (%)	10 (71.4)	21 (95.5)
≥65, n (%)	4 (28.6)	1 (4.5)
Sex, n (%)		
Male	8 (57.1)	10 (45.5)
Race, n (%)		
Asian	6 (42.9)	8 (36.4)
Caucasian	8 (57.1)	14 (63.6)
WHO performance status, n (%)		
0	7 (50.0)	7 (31.8)
1	7 (50.0)	15 (68.2)
Smoking history, n (%)		
Never smoker	7 (50.0)	10 (45.5)
Ex-smoker	6 (42.9)	11 (50.0)
Current smoker	1 (7.1)	1 (4.5)
Key metastatic site of cancer, n (%)		
Brain	5 (35.7)	10 (45.5)
Bone	5 (35.7)	9 (40.9)
Liver	3 (21.4)	7 (31.8)
Prior antineoplastic regimens, n (%)		
0	1 (7.1)	3 (13.6)
1	4 (28.6)	8 (36.4)
2	5 (35.7)	5 (22.7)
≥3	4 (28.6)	6 (27.3)
Prior ALKi, n (%)		
0	6 (42.9)	10 (45.5)
1	5 (35.7)	9 (40.9)
2	2 (14.3)	2 (9.1)
3	1 (7.1)	1 (4.5)

Abbreviations: ALKi, ALK inhibitor.

***Table 2*: All-causality adverse events (in ≥10% of patients for grade 1 or 2 and all grade 3 and 4 events)**

Preferred term, n (%)	Ceritinib 450 mg fed plus nivolumab 3 mg/kg N=14			Ceritinib 300 mg fed plus nivolumab 3 mg/kg N=22		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Diarrhoea	12 (85)	0	0	12 (55)	1 (5)	0
ALT increased	6 (43)	2 (14)	0	6 (27)	7 (32)	0
AST increased	6 (43)	1 (7)	0	8 (36)	1 (5)	0
Vomiting	6 (43)	1 (7)	0	7 (32)	1 (5)	0
Nausea	6 (43)	0	0	8 (36)	0	0
Amylase increased	4 (29)	2 (14)	0	4 (18)	3 (14)	0
Blood creatinine increased	3 (21)	0	0	8 (36)	0	0
Rash	4 (29)	2 (14)	0	5 (23)	0	0
Rash maculo-papular	3 (21)	2 (14)	0	4 (18)	2 (9)	0
Fatigue	2 (14)	2 (14)	0	5 (23)	1 (5)	0
Headache	5 (36)	0	0	5 (23)	0	0
Upper respiratory tract infection	5 (36)	0	0	5 (23)	0	0
Back pain	4 (29)	1 (7)	0	3 (14)	1 (5)	0
Cough	4 (29)	0	0	5 (23)	0	0
Decrease appetite	4 (29)	0	0	5 (23)	0	0
GGT increased	1 (7)	2 (14)	0	0	5 (23)	1 (5)
Pyrexia	2 (14)	0	0	6 (27)	1 (5)	0
Blood ALP increased	2 (14)	1 (7)	0	5 (23)	0	0
Lipase increased	1 (7)	0	2 (14)	3 (14)	1 (5)	1 (5)
Pruritus	3 (21)	0	0	5 (23)	0	0
Abdominal pain upper	2 (14)	0	0	5 (23)	0	0
Arthralgia	3 (21)	0	0	4 (18)	0	0
Non-cardiac chest pain	2 (14)	1 (7)	0	3 (14)	0	0
Anaemia	2 (14)	1 (7)	0	2 (9)	0	0
Constipation	0	0	0	5 (23)	0	0
Abdominal Pain	3 (21)	0	0	0	1 (5)	0
Stomatitis	3 (21)	0	0	1 (5)	0	0
Hypophosphataemia	2 (14)	1 (7)	0	0	0	0
Rash macular	2 (14)	1 (7)	0	0	0	0
Hypothyroidism	2 (14)	0	0	1 (5)	0	0
Pericardial effusion	0	0	1 (7)	0	0	0

Dyspepsia	1 (7)	0	0	3 (14)	0	0
Pancreatitis	1 (7)	1 (7)	0	0	0	0
Asthenia	1 (7)	0	0	2 (9)	1 (5)	0
Influenza like illness	0	0	0	4 (18)	0	0
General physical health deterioration	0	0	0	0	1 (5)	0
Autoimmune hepatitis	0	1 (7)	0	0	0	0
Conjunctivitis	0	0	0	3 (14)	0	0
Pneumonia	1 (7)	1 (7)	0	1 (5)	0	0
Nasopharyngitis	2 (14)	0	0	0	0	0
Head injury	1 (7)	0	0	0	1 (5)	0
Blood bilirubin increased	2 (14)	0	0	3 (14)	0	0
Transaminases increased	0	2 (14)	0	0	1 (5)	0
Weight decreased	2 (14)	0	0	1 (5)	0	0
Neutrophil count decreased	2 (14)	0	0	0	0	0
Hepatic enzymes increased	0	1 (7)	0	0	0	0
Hyperglycaemia	1 (7)	1 (7)	0	2 (9)	1 (5)	0
Hypokalaemia	0	0	1 (7)	0	1 (5)	0
Hyperamylasaemia	0	0	0	0	1 (5)	0
Hyponatraemia	0	0	0	0	1 (5)	0
Musculoskeletal pain	1 (7)	0	0	4 (18)	0	0
Neck pain	1 (7)	0	0	3 (14)	0	0
Musculoskeletal chest pain	0	0	0	3 (14)	0	0
Muscular weakness	0	0	0	1 (5)	1 (5)	0
Dizziness	2 (14)	0	0	2 (9)	0	0
Cerebrovascular accident	0	1 (7)	0	0	0	0
Seizure	0	0	0	0	1 (5)	0
Insomnia	2 (14)	0	0	3 (14)	0	0
Anxiety	0	0	0	1 (5)	0	0
Mental status changes	0	1 (7)	0	0	0	0
Renal impairment	0	1 (7)	0	0	0	0
Dyspnoea	0	2 (14)	0	2 (9)	0	0
Pulmonary oedema	0	0	0	0	0	1 (5)
Dry skin	2 (14)	0	0	3 (14)	0	0

Rash papular	2 (14)	0	0	1 (5)	0	0
Drug eruption	1 (7)	0	0	0	1 (5)	0
Xeroderma	0	1 (7)	0	0	0	0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Table 3*: Overview of rash

Rash maximum grade, n (%)	All patients N=36	Dose		Race	
		Ceritinib 450 mg fed plus nivolumab 3 mg/kg N=14	Ceritinib 300 mg fed plus nivolumab 3 mg/kg N=22	Asian N=14	Non-Asian N=22
All grades (all causality)	23 (64)	9 (64)	14 (64)	13 (93)	10 (46)
Grade 3	7 (19)	4 (29)	3 (14)	3 (21)	4 (18)
Grade 2	8 (22)	3 (21)	5 (23)	7 (50)	1 (5)
Grade 1	8 (22)	2 (14)	6 (27)	3 (21)	5 (23)

*Pooled terms: rash maculo-papular, rash, dry skin, rash macular, rash papular, dermatitis acneiform, drug eruption, rash erythematous, rash pruritic, blister, dermatitis, dermatitis allergic, erythema, exfoliative rash, skin exfoliation, xeroderma.

Table 4: Overview of safety

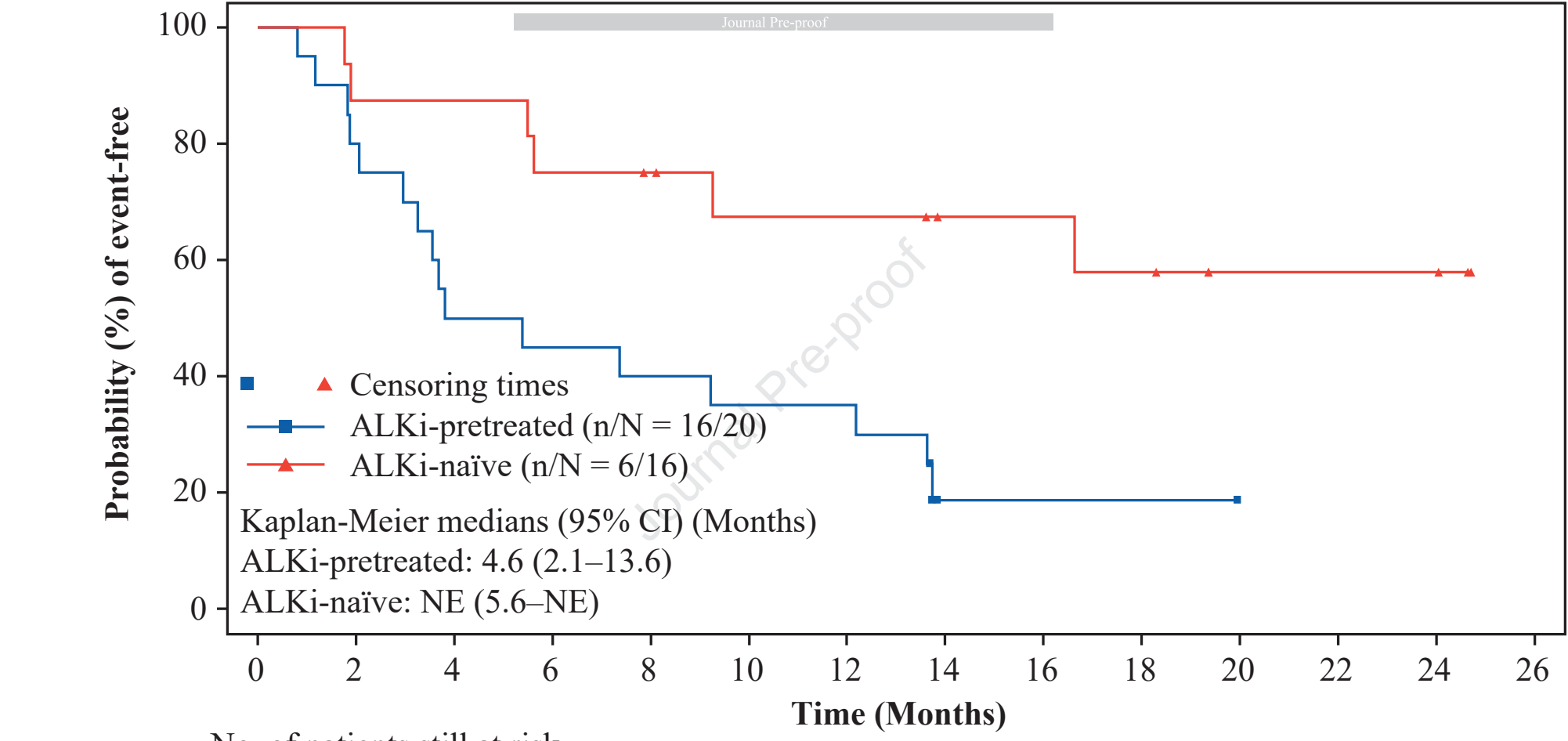
	Ceritinib 450 mg fed plus nivolumab 3 mg/kg N=14	Ceritinib 300 mg fed plus nivolumab 3 mg/kg N=22	Total N=36
Adverse events, n (%)			
All adverse events	14 (100)	22 (100)	36 (100)
Grade 3/4 adverse events	13 (93)	18 (82)	31 (86)
Adverse events (study drug related)	14 (100)	22 (100)	36 (100)
Adverse events requiring ceritinib dose change, n (%)			
All adverse events	3 (21)	9 (41)	12 (33)
Grade 3/4 adverse events	0	3 (14)	3 (8)
Adverse events leading to dose interruptions (either drug or both), n (%)			
All adverse events	13 (93)	16 (73)	29 (81)
Interruption of ceritinib	12 (86)	17 (77)	29 (81)
Interruption of nivolumab	9 (64)	9 (41)	18 (50)
Grade 3/4 adverse events	12 (86)	11 (50)	23 (64)
Adverse events leading to discontinuation (either drug or both), n (%)			
All adverse events	5 (36)	6 (27)	11 (31)
Grade 3/4 adverse events	3 (21)	5 (23)	8 (22)

***Table 5*. Best overall response, duration of response, and progression-free survival by investigator review**

	ALKi-naïve			ALKi-pretreated		
	Ceritinib 450 mg fed plus nivolumab 3 mg/kg N=6	**Ceritinib 300 mg fed plus nivolumab 3 mg/kg N=10**	**Total N=16**	**Ceritinib 450 mg fed plus nivolumab 3 mg/kg N=8**	**Ceritinib 300 mg fed plus nivolumab 3 mg/kg N=12**	**Total N=20**
Overall response rate, n (%) [95% CI]	5 (83) [36–100]	6 (60) [26–88]	11 (69) [41–89]	4 (50) [16–84]	3 (25) [6–57]	7 (35) [15–59]
Complete response, n (%)	-	1 (10)	1 (6)	-	-	-
Partial response, n (%)	5 (83)	5 (50)	10 (63)	4 (50)	3 (25)	7 (35)
Stable disease, n (%)	-	3 (30)	3 (19)	2 (25)	6 (50)	8 (40)
Progressive disease, n (%)	1 (17)	1 (10)	2 (13)	-	3 (25)	3 (15)
Unknown	-	-	-	2 (25)	-	2 (10)
Disease control rate, n (%) [95% CI]	5 (83) [36–100]	9 (90) [56–100]	14 (88) [62–98]	6 (75) [35–97]	9 (75) [43–95]	15 (75) [51–91]
Duration of response, n/N (%)	2/5 (40)	1/6 (17)	3/11 (27)	3/4 (75)	1/3 (33)	4/7 (57)
Median (95% CI) (months)	NE (3.9–NE)	NE (3.8–NE)	NE (3.9–NE)	11.2 (3.7–NE)	NE (7.4–NE)	11.9 (3.7–NE)
Event-free rates, % (95% CI)						
6 months	80 (20–97)	83 (27–98)	82 (45–95)	75 (13–96)	100 (100–100)	86 (33–98)
10 months	80 (20–97)	83 (27–98)	81.8 (45–95)	75 (138–96)	67 (5–95)	71 (26–92)
Progression-free survival, n/N (%)	3/6 (50)	3/10 (30)	6/16 (38)	7/8 (88)	9/12 (75)	16/20 (80)
Median (95% CI) (months)	NE (1.8–NE)	NE (1.9–NE)	NE (5.6–NE)	6.4 (0.8–13.7)	3.7 (1.8–NE)	4.6 (2.1–13.6)
Event-free rates, % (95% CI)						
6 months	67 (20–90)	80 (41–95)	75 (46–90)	50 (15–78)	42 (15–67)	45 (23–65)
8 months	67 (20–90)	80 (41–95)	75 (46–90)	38 (9–67)	42 (15–67)	40 (19–60)

12 months	67 (20–90)	67 (27–88)	68 (38–85)	37.5 (9–67)	33 (10–59)	35 (16–55)

Abbreviations: ALKi, anaplastic lymphoma kinase inhibitor; CI, confidence interval; NE, not estimable.



No. of patients still at risk

ALKi-pretreated	20	16	10	9	8	7	7	1	1	1	0	0	0	0
ALKi-naïve	16	14	14	12	11	9	9	7	7	6	3	3	3	0