Supplementary Appendix

Methods

Procedures

A low-fat meal (food) defined as approximately 100–500 calories and 1.5–15 g of fat was used in this study given the modest difference in AUC_{inf} between the light snack, low-fat meal, and high-fat meal.[1,2] The starting dose of ceritinib (450 mg/day fed) was based on the efficacy and safety of ceritinib at the approved dose of 750 mg/day fasted, as well as data from an adult healthy volunteer food-effect study.[1] A model-based clinical trial simulation using a population pharmacokinetic model predicted that steady-state exposure of ceritinib at 450 mg with daily low-fat meal would be within 20% of ceritinib exposure at 750 mg fasted. Further, it has been reported that food intake may improve the gastrointestinal tolerability of ceritinib. In a phase 1, randomized, food-effect study (ASCEND-8 trial), ceritinib administered at 450 mg with food had similar steady-state exposure and a more favorable GI safety profile than ceritinib given at 750 mg fasted.[2]

Nivolumab administered at 3 mg/kg every 2 weeks is the approved dose (by US Food and Drug Administration) and schedule and has been safely combined with erlotinib,[3] as well as with platinum-based doublet chemotherapy.[4]

Treatment beyond disease progression was allowed if, in the opinion of the investigator, continued treatment provided clinical benefit. No dose reductions were allowed for nivolumab. Dose reduction for ceritinib (in 150 mg decrements) to a minimum of 150 mg/day was allowed. In the event of dose reductions, re-escalation was not permitted. At baseline, magnetic resonance imaging (MRI) or computed tomography

(CT) scans of the chest and abdomen were done in all patients, whereas MRI or CT scans of the brain were done only for patients with BM at study entry. During treatment, tumor response was assessed every 8 weeks until cycle 13 and subsequently every 12 weeks until progression of disease.

Outcomes

A dose-limiting toxicity (DLT) was defined as any of the following treatment-related AEs (using National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03) occurring during the first 6 weeks of combination treatment: grade 4 bilirubin elevation, grade 4 creatinine elevation, grade 2–4 pneumonitis, grade 4 QT prolongation, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than three times upper normal limit with total bilirubin greater than three times the upper normal limit in the absence of cholestasis or hemolysis, grade 3 nivolumab select AEs (gastrointestinal, renal, pulmonary, hepatic, endocrinopathy, skin, and neurological) that does not resolve to Grade 1 or less within 28 days of AE onset. The following was not defined as a DLT: grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumour) grade 3 rash, grade 3 nivolumab select AE that resolves to grade 1 or less within 28 days of AE onset, or a transient (resolving within 6 hours of onset) grade 3 infusion-related AE. DLTs did not necessarily lead to treatment discontinuation. Overall response rate (ORR) data was reported separately by prior ALK inhibitor (ALKi) status (post hoc analysis) and for patients with BM at baseline per RECIST 1.1.

Ceritinib pharmacokinetic parameters were determined using non-compartmental methods using Phoenix WinNonlin version 6.4 (Pharsight, Mountain View, CA, USA).

The following pharmacokinetic parameters of ceritinib were calculated: area under the concentration–time curve from time 0 to 24 hours ($AUC_{0–24h}$), maximum concentration (C_{max}), and time at Cmax (T_{max}) at cycle 2 day 1. Nivolumab trough concentrations (C_{trough}) were also reported. All AEs were recorded and graded according to the NCI CTCAE version 4.03. All patients were followed up for AEs for 30 days after the last dose of study treatment, and for 100 days after the last dose of nivolumab. Assessments of laboratory parameters, and physical examination were done at baseline and days 1, 8, and 15 of cycle 1; days 1 and 15 of cycle 2; and days 1 and 15 of subsequent cycles until end of treatment. Assessments were also done at the end of study or time of withdrawal. For characterization of potential changes in immune biomarkers, patients were requested to provide a new biopsy between cycle 2 day 15 to cycle 3 day 15. PD-L1 protein expression, determined by Tumor Proportion Score was performed on formalin-fixed, paraffin-embedded tissue, using the Agilent PD-L1 IHC 28-8 pharmDx assay at Mosaic Laboratories. Next-generation sequencing (NGS) was performed at Novartis on ethylenediaminetetraacetic acid plasma. Somatic mutation and ALK rearrangements were obtained from circulating free DNA (cfDNA) using NGDx informatics pipelines. Due to the low mutation burden typically observed in ALK-rearranged NSCLC, samples with ALK rearrangements or ALK somatic single nucleotide variants (SNVs) detected from cell-free DNA were considered circulating tumor DNA (ctDNA) positive. A power >80% for SNV detection from cfDNA was determined for all samples included in the analysis.

Statistical analysis

In the dose-escalation phase, approximately six patients were planned initially at the starting dose levels of ceritinib and nivolumab. Cohorts of approximately six evaluable patients were planned, including at least six patients at the MTD/RDE level. Multiple cohorts were to be sequentially enrolled at the same dose level. Additional cohorts of patients were to be enrolled at any dose level below the estimated MTD/RDE for further evaluation of safety and pharmacokinetic parameters as required. Based on clinical observations from the initial 36 patients treated with the combination therapy, the current regimen (Regimen A) was not further explored. After protocol amendment and incorporation of alternative regimen, the total sample size for the dose-escalation phase was planned to be approximately 56 patients, with 36 patients enrolled in Regimen A and approximately 20 patients on alternative regimen (Regimen B; described in Discussion section). No dose escalation was planned for Regimen B. Results for Regimen B are not reported in this manuscript. During the expansion phase, approximately 30 patients were planned to be treated (approximately 15 patients in ALKi-pretreated and ALKi-naïve arms), resulting in 96% and 79% probability of detecting an AE with a true rate of 10% and 5%, respectively.

The Bayesian approach requires the specification of prior distributions for model parameters, including single-agent parameters (α1, β1) for ceritinib and (α2, β2) for nivolumab, and the interaction parameter (η). Prior distributions for the single-agent activity of each compound were derived using the meta-analytic-predictive (MAP; Neuenschwander 2010) approach based on single-agent DLT data.[5]

Derivation of prior distribution of these parameters was as below:

Prior derivation for ceritinib parameters (log(α1), log(β1)):

A mixture prior was used for single-agent parameters (α1, β1) for ceritinib, which had two bivariate normal components:

1. MAP component: Obtained from dose-DLT data from the study [CLDK378X2101] using the MAP approach

2. Weakly informative component: Reflecting the potential of higher toxicity by single-agent ceritinib and allowing for considerable prior uncertainty

Mixture prior:

To obtain the mixture prior, 95% weight was assigned to the MAP component and 5% to the weakly informative component

Prior derivation for nivolumab parameters (log(α2), log(β2)):

The toxicity profile of nivolumab was investigated in several studies, and the 3 mg/kg dose once every 2 weeks was evaluated in ongoing studies in patients with non-small-cell lung cancer (NSCLC). Bivariate normal prior for the single-agent nivolumab model parameters (log(α2), log(β2)) were based on DLT and safety data from the study [003], a phase 1b dose-escalation study in previously treated patients with various solid tumors, including patients with NSCLC who were treated with single-agent nivolumab.

Prior for interaction parameter η12:

A normal prior distribution for the interaction parameter η12 was derived to reflect the current uncertainty about the toxicity profile of the combination of ceritinib and nivolumab.

The MTD was defined as the highest drug dosage not expected to cause DLT in more than 35% of the treated patients in the first 6 weeks of combination treatment.

Dose recommendation was based on Bayesian posterior summaries, including the mean, median, standard deviation, 95% credible interval, and the probability that the true DLT rate for each dose lied in one of the following categories: [0,16%) under-dosing, [16%,35%) targeted toxicity, and ≥35% excessive toxicity.

A five-parameter BLRM employing the EWOC principle[5,6] was used during the dose-escalation phase for dose level selection and for determination of the MTD and RDE. This model predicts the MTD by updating estimates of the probability of observing a DLT at each dose level in the study as patient information becomes available. Typically, the estimated MTD is a tested dose that has the largest posterior probability of the DLT rate lying between 16% and 35% (target toxicity). Additionally, the use of the EWOC principle limits the risk of exposing patients in the next cohort to an unsafe dose by ensuring the posterior probability of the DLT rate exceeding 35% at any dose is capped at 25%. The final recommended MTD and/or RDE for the combination of ceritinib and nivolumab was to be based on the recommendation from the BLRM, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at the tested doses. Even if an MTD was reached, a lower RDE might have still been selected taking into account the estimation of the MTD as well as the available information on lower grade AEs, AEs at later cycles, pharmacokinetics, and efficacy data. If during the dose-escalation phase an MTD cannot be established after the evaluation of all planned dose levels, then an RDE was to be determined after the evaluation of all available safety, pharmacokinetics, and efficacy data. This decision was made at the dose-decision meeting or teleconference at the time the dose for the RDE was decided.

Patients who received at least one dose of ceritinib and nivolumab in the dose escalation phase of the study and who either met the minimum exposure criteria (a minimum of 28 days of treatment with ceritinib at the assigned dose level and two complete nivolumab infusions during the first 6 weeks after starting combination therapy) and had sufficient safety evaluations or had experienced a DLT during the first 6 weeks of combination therapy were evaluated for the determination of the MTD and/or RDE (dose-determining set). All patients who received at least one dose of either study drug were assessed for safety and efficacy. The pharmacokinetic analysis set was defined separately for ceritinib and nivolumab and consisted of all patients who received at least one dose of corresponding study drug and who had evaluable pharmacokinetic data.

Results

Safety

Serious AEs (SAEs) were reported in 10 (71%) of 14 patients in the 450 mg cohort and 11 (50%) of 22 patients in the 300 mg cohort. Treatment-related SAEs were reported in seven (50%) of 14 patients in the 450 mg cohort (most common events were pancreatitis [n=2] and transaminases increased [n=2]) and three (14%) of 22 patients in the 300 mg cohort (most common event was ALT increased [n=2]). AEs leading to treatment discontinuation were reported in five (36%) of 14 patients in the 450 mg cohort and six (27%) of 22 patients in the 300 mg cohort. Four patients in the 450 mg cohort discontinued due to drug-related toxicity (AST increased [n=1], fatigue [n=1], rash [n=1], and rash maculo-papular [n=1]), whereas five patients in the 300 mg cohort discontinued due to drug-related toxicity (ALT increased [n=2], lipase increased [n=1],

GGT increased [n=1], and amylase increased [n=1]). Deaths were reported in five (36%) of 14 patients in the 450 mg cohort (study indication [n=4] and cerebrovascular accident [n=1]) and 10 (46%) of 22 patients in the 300 mg cohort (study indication [n=9] and pulmonary edema [n=1]); none of these were treatment related.

Pharmacokinetics

The pharmacokinetics of ceritinib increased approximately dose proportionally (Supplementary Fig. 2), with steady-state $AUC_{0–24h}$ and C_{max} of the 300 mg cohort approximately 70%–75% that of the 450 mg cohort. An evaluation of nivolumab C_{trough} suggests that by cycle 8 day 1, steady-state of nivolumab had been reached (Supplementary Table 4).

Efficacy

Biomarker data

Thirty-three patients had baseline plasma samples evaluable for NGS. ctDNA was detected in 55% patients. Somatic SNVs in ALK were detected in 24% patients; of these, seven patients had SNVs at baseline. All eight patients had received prior ALKi treatment. Patients with baseline *ALK* somatic SNV mutations in ctDNA (six of seven patients were ALKi-pretreated, primarily crizotinib) had shorter median PFS (3.1 months [95% CI 0.8–3.8]; 100% patients had events) compared to patients without ALK somatic SNVs (four of 10 patients were ALKi-pretreated) in their ctDNA (12.9 months [1.2–NE]; 60% patients had events) (Supplementary Fig. 4); the proportion of patients censored were 40% among patients without ALK somatic SNVs in their ctDNA and 53% among patients without detectable ctDNA at baseline. However, this needs to be interpreted with caution due to the small sample size.

References

1. Lau YY, Gu W, Lin T, et al: Effects of meal type on the oral bioavailability of the ALK inhibitor ceritinib in healthy adult subjects. *J Clin Pharmacol*. 2016;56:559-66.
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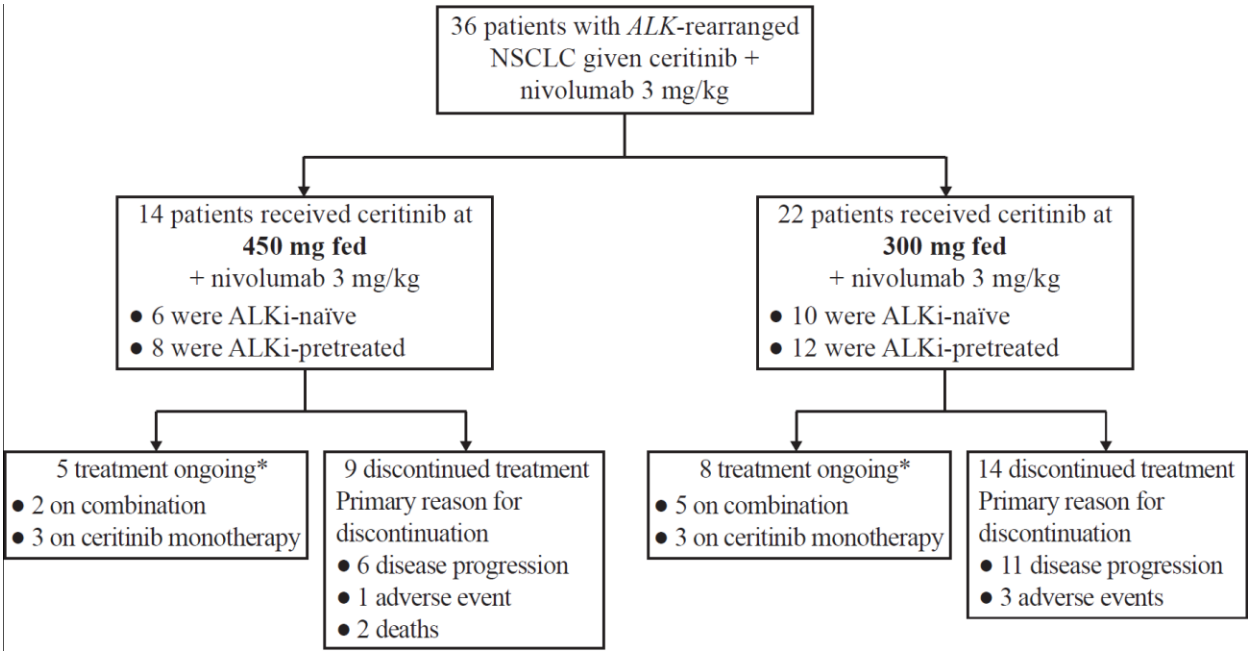
5. Neuenschwander B, Capkun-Niggli G, Branson M, et al: Summarizing historical information on controls in clinical trials. *Clin Trials*. 2010;7:5-18.
6. Babb J, Rogatko A, Zacks S: Cancer phase I clinical trials: efficient dose escalation with overdose control. *Stat Med*. 1998;17:1103-1120.

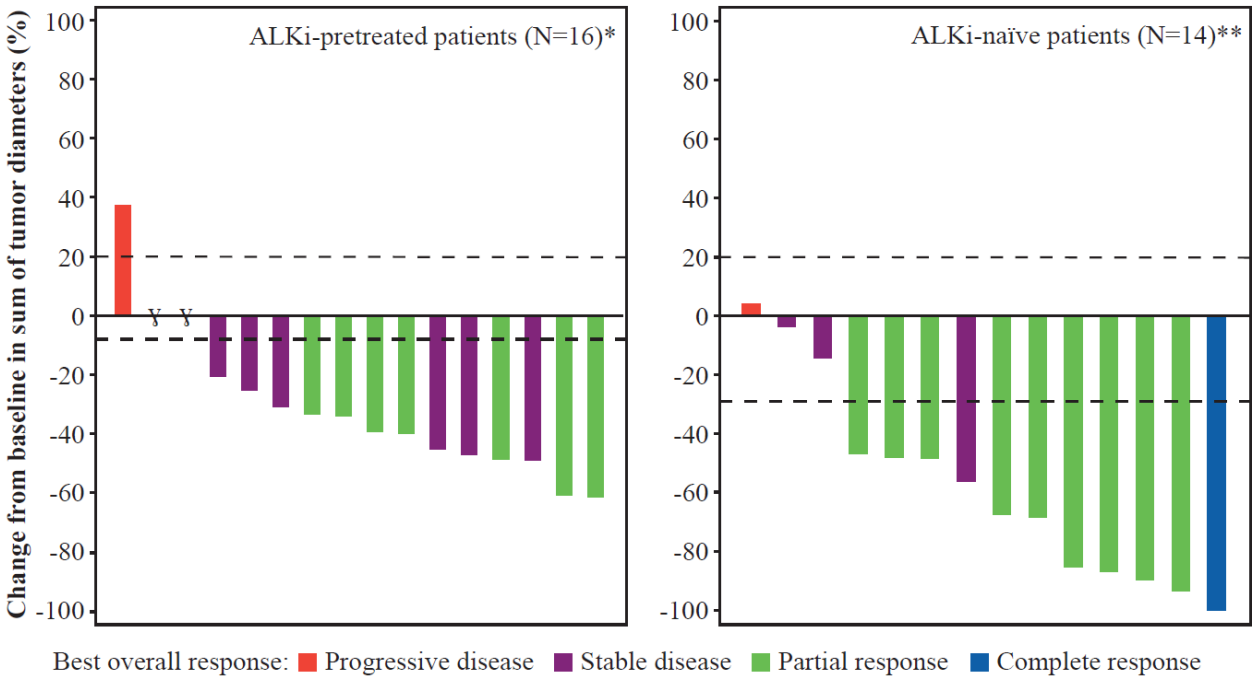
Supplementary Fig 1. Trial profile



*At data cutoff (August 30, 2017). One patient in the 300 mg cohort discontinued due to adverse event (increased carcinoembryonic antigen); the carcinoembryonic antigen was described as an adverse event but should have been categorized as disease progression. None of the deaths were study drug related.

Abbreviations: ALKi, ALK inhibitor; NSCLC, non-small cell lung cancer.

Supplementary Fig 2. Best percentage change from baseline in target lesions by prior ALKi status



*Patients with measurable baseline disease and at least one valid post-baseline assessment (best percentage change from baseline: <0 [81.3%, n=13]; >0 [6.3%, n=1]; 0 [12.5%, n=2]).

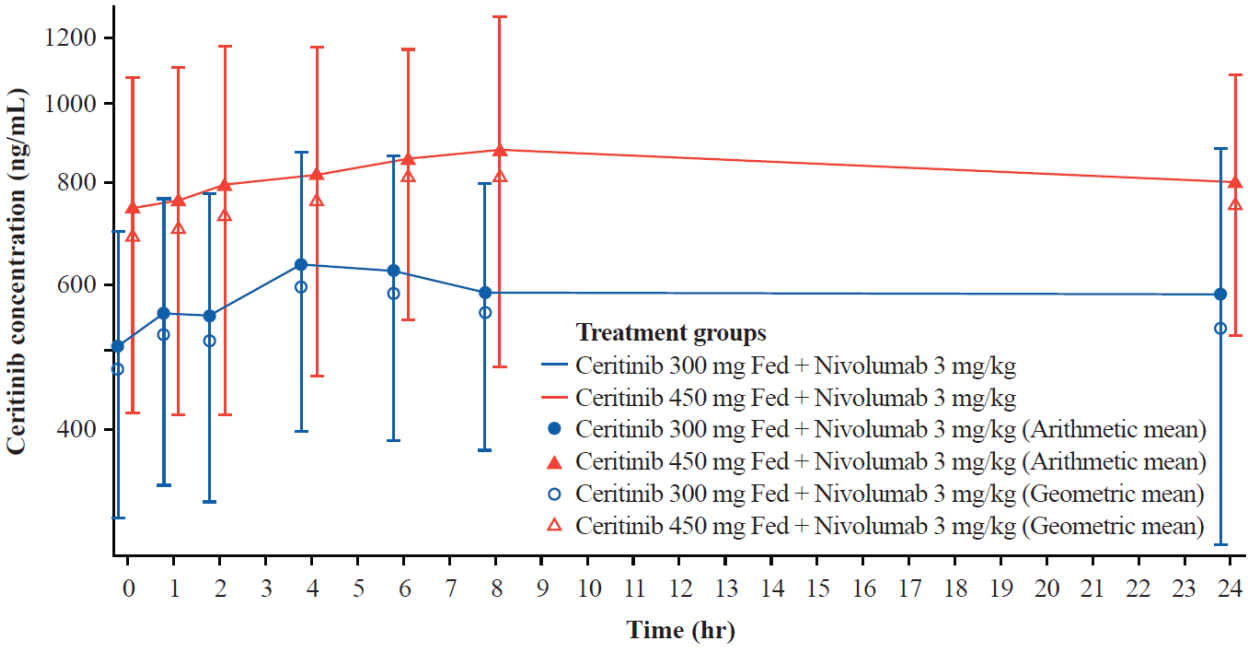
**Patients with measurable baseline disease and at least one valid post-baseline assessment (best percentage change from baseline: <0 [92.9%, n=13]; >0 [7.1%, n=1]).

[Y]Best percentage change from baseline=0.

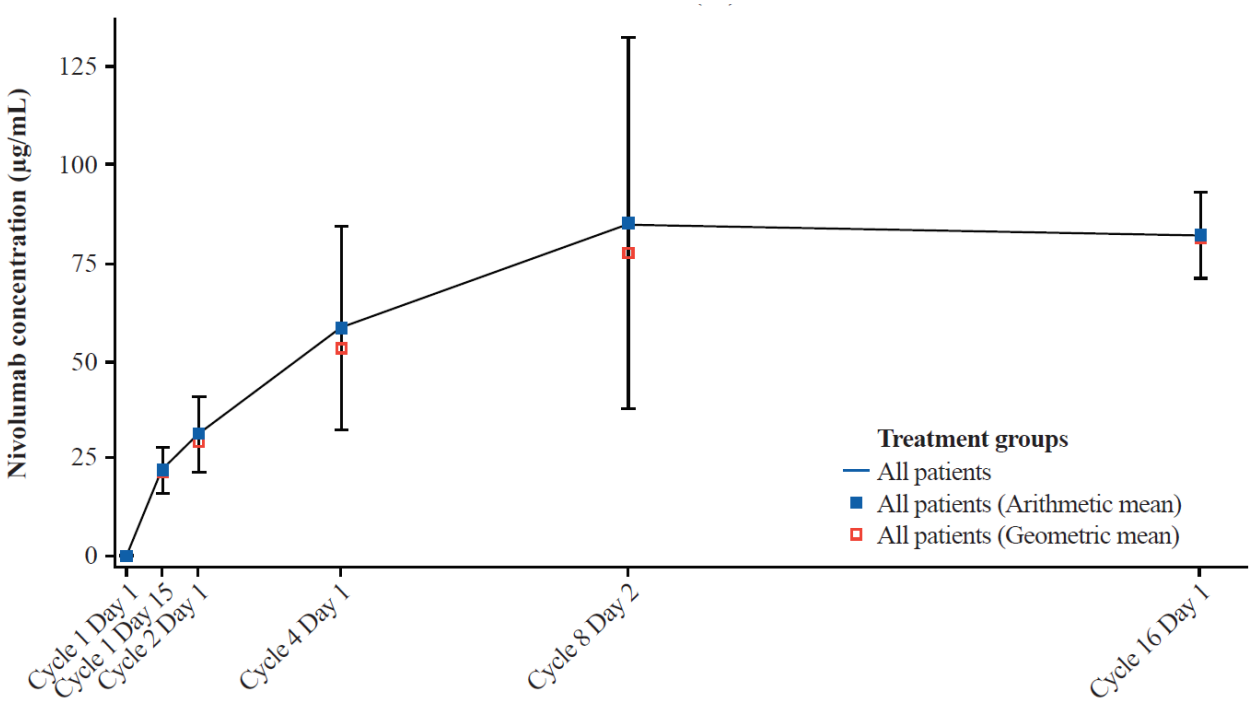
Abbreviation: ALKi, anaplastic lymphoma kinase inhibitor.

Supplementary Fig 3. Pharmacokinetics of ceritinib and nivolumab

A. Geometric mean and arithmetic mean concentration-time profile of ceritinib (cycle 2 day 1)

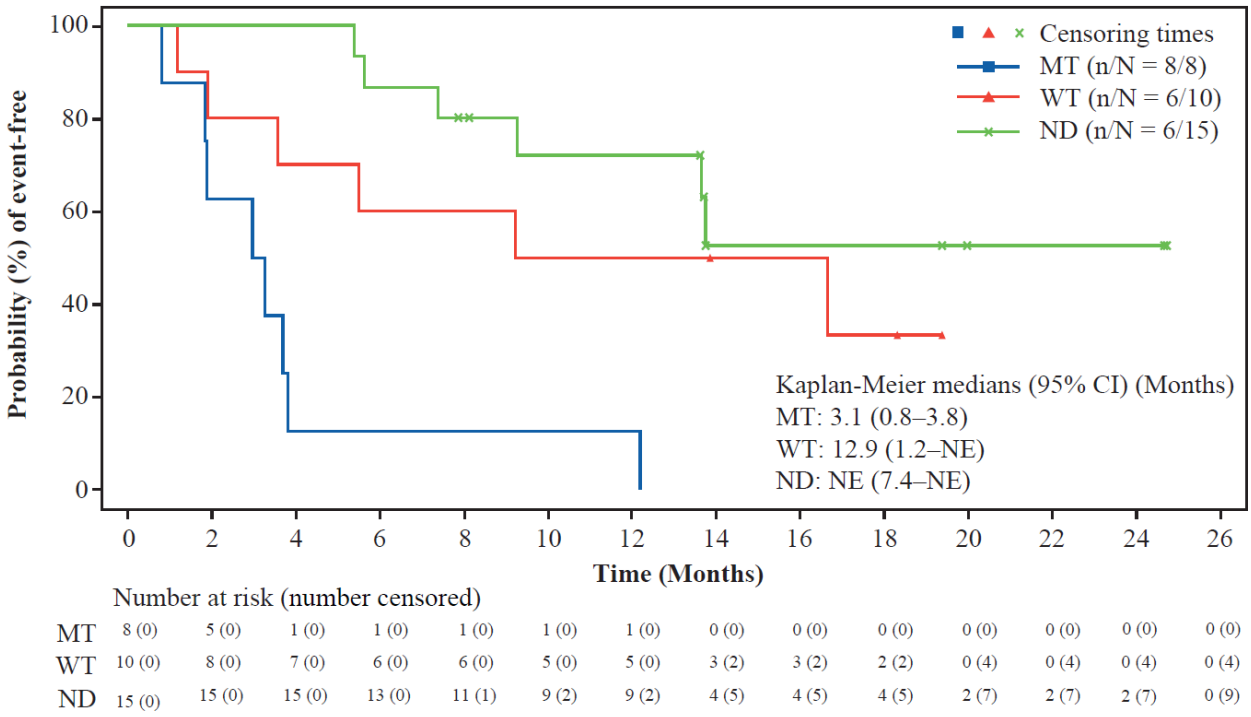


B. Geometric mean and arithmetic mean (SD) trough concentration-time profile of nivolumab



Abbreviation: SD, standard deviation.

Supplementary Fig S4. Progression-free survival by ALK mutation status at baseline



MT group includes patients with ALK SNVs at baseline, WT group includes patients with detectable ctDNA but no SNV mutation in ALK at baseline, and ND group includes patients with no detectable ctDNA at baseline.

Abbreviations: ALK, anaplastic lymphoma kinase. CI, confidence interval; ctDNA, circulating tumor DNA; MT, mutation; ND, not detected; NE, not estimable; SNV, single nucleotide variant; WT, wild type.

Supplementary Tables

Supplementary Table 1. Inclusion/exclusion criteria for the enrolment of patients

Inclusion criteria
Histologically or cytologically confirmed diagnosis of NSCLC carrying an *ALK* rearrangement as determined by the FDA-approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria). If the 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.
Stage IIIB or IV NSCLC or relapsed locally advanced or metastatic NSCLC. Patients with stage IIIB NSCLC must not be candidates for definitive multimodality therapy according to standard guidelines and practices or must defer or decline other approved therapies with proven clinical benefit for stage IIIB NSCLC.
Presence of at least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.
Patients with clinically and neurologically stable CNS metastases who have not required increasing doses of steroids or stable doses of >10-mg daily prednisone equivalent within 2 weeks prior to study entry to manage the CNS symptoms.
Age 18 years or older at the time of informed consent.
In the expansion phase, patients must have received prior treatment according to the following: • <u>Arm 1: ALK inhibitor-treated</u> – ALK inhibitor: yes (one prior treatment with any ALK inhibitor except ceritinib allowed) – Chemotherapy: 0 or 1 prior courses • <u>Arm 2: ALK inhibitor-naïve</u> – ALK inhibitor: no – Chemotherapy: 0 or 1 prior courses Eligible patients received no more than one chemotherapy regimen for advanced disease, except for neo-adjuvant or adjuvant therapy (excluding regimens containing an ALK inhibitor). • Neo-adjuvant or adjuvant therapy (excluding regimens containing an ALK inhibitor) was not considered as a prior chemotherapy regimen unless relapse had occurred less than 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.

- Patients who had received prior chemotherapy other ALK inhibitors, biologic therapy, or other investigational agents must have recovered from all toxicities related to prior anticancer therapies to grade ≤1 (NCI CTCAE v 4.03). However, patients with grade ≤2 peripheral neuropathy or any grade of alopecia, fatigue, nail changes, or skin changes were allowed to enter the study.
- Patients treated with chemotherapy, biological therapy, or other investigational agents must have discontinued the treatment at least 2 weeks (14 days) prior to starting the study drug. If the last chemotherapy contained nitrosourea or mitomycin C, the treatment must have been discontinued at least 6 weeks prior to starting the study drug.
- Patients previously treated with an ALK inhibitor (such as crizotinib) must have discontinued the ALK inhibitor at least 1 week (7 days) prior to the first dose of the study drug.

Patients with the following laboratory values at the screening visit:

- Absolute neutrophil count ≥1.5 × 10^9/L
- White blood cells ≥2.0 × 10^9/L
- Platelets ≥100 × 10^9/L
- Hemoglobin ≥9 g/dL
- Serum creatinine ≥1.5 mg/dL and /or calculated creatinine clearance (using Cockcroft-Gault formula) ≥50 mL/min
- Total bilirubin ≥1.5 × ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin ≥3.0 × ULN or direct bilirubin ≤1.5 × ULN
- AST ≤3 × ULN
- ALT ≤3 × ULN
- ALP ≤5.0 × ULN
- Serum amylase ≤2 × ULN or pancreatic amylase ≤1.5 × ULN
- Serum lipase ≤ULN
- Fasting plasma glucose ≤200 mg/dL (≤11.1 mmol/L)

- Patients with the following laboratory values within normal limits or corrected to within normal limits using supplements during screening:
- Potassium
- Magnesium
- Phosphorus
- Total calcium (corrected for serum albumin)

Patients with a WHO performance status 0–1.

Patients with an ability to understand and provide signed informed consent.
Patients with a willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
Exclusion criteria
Patients with known hypersensitivity to any of the excipients of ceritinib (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide, and magnesium stearate).
Patients with a history of allergy or hypersensitivity to excipients of nivolumab (mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and water for injection).
History of severe hypersensitivity reactions to other monoclonal antibodies.
Prior therapy with anti-PD-1 and/or anti-PD-L1 agents.
History of carcinomatous meningitis.
Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years (except completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type).
Patients requiring emergent use of systemic steroids or emergent surgery and/or radiotherapy.
Patients with an active, known, or suspected autoimmune disease.
Patients with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
Patients with a condition requiring chronic systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days before the first dose of the study treatment. Patients taking inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent were permitted to enroll in the absence of any active autoimmune disease.
Known history of testing positive for human immunodeficiency virus or known acquired immunodeficiency syndrome.
Any positive test for hepatitis B virus or hepatitis C virus, indicating acute or chronic infection. Hepatitis B and C testing needs to be performed within 28 days prior to the first dose.
Patients unable or unwilling to swallow tablets or capsules.
Clinically significant, uncontrolled heart disease and/or a recent cardiac event (within 6 months) such as: • Unstable angina within 6 months prior to screening • Myocardial infarction within 6 months prior to screening

• History of documented congestive heart failure (New York Heart Association functional classification III–IV) • Uncontrolled hypertension defined by a systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg, with or without antihypertensive medication • Initiation or adjustment of antihypertensive medication(s) was allowed prior to screening • Ventricular arrhythmias; supraventricular and nodal arrhythmias not controlled with medication • Other cardiac arrhythmia not controlled with medication • Corrected QT (QTcF) >470 ms using Fridericia's correction on the screening ECG (as mean of triplicate ECGs)
History of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (ie, pneumonitis affecting activities of daily living or requiring therapeutic intervention).
Patients with other severe, acute, or chronic medical conditions, including uncontrolled diabetes mellitus, psychiatric conditions, or laboratory abnormalities, that in the opinion of the investigator, may increase the risk associated with study participation or interfere with the interpretation of study results.
Patients with impairment of GI function or GI disease that may significantly alter the absorption of ceritinib (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, or malabsorption syndrome).
Patients receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with ceritinib and for the duration of the study: • Strong inhibitors or strong inducers of CYP3A4/5 • Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5 and/or CYP2C9 • Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes
Patients treated with warfarin sodium (Coumadin®).
Patients who received unstable or increasing doses of corticosteroids. If patients were on corticosteroids for endocrine deficiencies (eg, adrenal replacement) or tumour-associated symptoms (non-CNS), the dose must have been stabilized (or decreased) for at least 5 days before the first dose of the study treatment.
Patients treated with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before the first dose of the study treatment, and for the duration of the study. Patients on

non–enzyme-inducing anticonvulsants were eligible.
Patients who had received thoracic radiotherapy to lung fields ≤4 weeks prior to starting the study treatment or patients who had not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), patients who had received radiotherapy ≤2 weeks prior to starting the study treatment or had not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤2 weeks prior to starting study treatment was allowed.
Patients who had undergone a major surgery (eg, intrathoracic, intra-abdominal, or intrapelvic) within 4 weeks prior to starting the study treatment or had not recovered from the side effects of such procedures. Video-assisted thoracic surgery and mediastinoscopy were not counted as major surgeries, and patients who had undergone either of these surgeries could receive the study treatment ≥1 week after these procedures.
Patients with regular alcohol intake exceeding 1 drink/day on a daily basis within 3 days prior to the days of blood sample collection for pharmacokinetic assessment.
Patients who consumed grapefruits, pomegranates, star fruits, Seville orange, or products containing the juice of each within 3 days prior to the days of blood sample collection for pharmacokinetic assessment.
Pregnant or nursing (lactating) women.
Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during dosing and for 23 weeks after stopping medication.
Sexually active men had to use a condom during intercourse while taking the study treatment and for 31 weeks after stopping the study treatment. Male patients were not to father a child for 31 weeks after the last dose of the study treatment. A condom was required to be used also by vasectomized men to prevent delivery of the drug via seminal fluid.
History of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.

Abbreviations: ALK, anaplastic lymphoma kinase; ALP, alkaline phosphatase; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; CNS, central nervous system; CYP, cytochrome P450; ECG, electrocardiogram; FDA, Food and Drug Administration; FISH, fluorescence in situ hybridization; GI, gastrointestinal; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small-cell lung cancer; PD-1,

programmed cell death protein-1; PD-L1, programmed cell death ligand-1; QTcF, corrected QT interval by Fredericia; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal; WHO, World Health Organization.

Supplementary Table 2. Best overall response in patients with brain metastases at baseline by investigator review

Ceritinib 450 mg fed plus nivolumab 3 mg/kg		
	ALKi-naïve N=2	**ALKi-pretreated N=3**
Partial response	2 (100%)	1 (33.3%)
Duration of response (months)	22.3+, 21.9+	18.0+
Progression-free survival (months)	24.0+, 24.7+	19.9+
Ceritinib 300 mg fed plus nivolumab 3 mg/kg		
	ALKi-naïve N=4	**ALKi-pretreated N=6**
Complete response	1 (25%)	
Partial response	1 (25%)	1 (17%)
Duration of response (months)	17.5*+, 3.8	7.4
Progression-free survival (months)	19.4+, 5.6	9.2

+Denotes that the patients are ongoing.

*This patient had complete response.

Supplementary Table 3. Best overall response by PD-L1 status

PD-L1 expression	Number of patients	Response rate, n (%) [95% CI]		
		ALKi-naïve patients N=13	ALKi-pretreated patients N=17	All patients N=30
<1%	16	3 (43) [10–82]	2 (22) [3–60]	5 (31) [11–59]
≥1%	14	5 (83) [36–100]	4 (50) [16–84]	9 (64) [35–87]
<5%	19	4 (44) [14–79]	2 (20) [3–56]	6 (32) [13–57]
≥5%	11	4 (100) [40–100]	4 (57) [18–90]	8 (73) [39–94]
<10%	23	5 (50) [19–81]	4 (31) [9–61]	9 (39) [20–62]
≥10%	7	3 (100) [29–100]	2 (50) [7–93]	5 (71) [29–96]

Abbreviations: ALKi, anaplastic lymphoma kinase inhibitor; CI, confidence interval; PD-L1, programmed cell death ligand-1.

Supplementary Table 4. Pharmacokinetics of ceritinib

	Ceritinib 450 mg fed plus nivolumab 3 mg/kg N=13	**Ceritinib 300 mg fed plus nivolumab 3 mg/kg N=21**
Steady-state pharmacokinetics		
AUC_{0-24h} (ng•h/mL)		
Geometric mean (Geo-CV%)	19100 (40.6) n=8	13600 (37.3) n=16
C_{max} (ng/mL)		
Geometric mean (Geo-CV%)	879 (38.1) n=9	660 (38.7) n=17
T_{max} (h)		
Median	7	6

Abbreviations: AUC_{0-24h}, area under the plasma concentration-time curve from time 0 to 24 hours; C_{max}, maximum (peak) plasma drug concentration; T_{max}, time to reach maximum (peak) plasma concentration following drug administration.