Supplementary appendix

Supplementary Table S1: Comparison of study designs in ASCEND-4 and PROFILE 1014

	ASCEND-4[1]	PROFILE 1014[2]
Study design	• Open-label, randomized, controlled, multi-center, phase III study	• Open-label, randomized, controlled, multi-center, phase III study
Geographic distribution	• 31 countries	• 31 countries
Clinical trials identifier	NCT01828099	NCT01154140
Data cut-off date	June 24, 2016	November 30, 2013
Intervention and dosing information	• Oral ceritinib (750 mg) once daily in fasting condition • Chemotherapy by intravenous infusion in 21-day cycles: - Pemetrexed (500 mg/m^2 of body-surface area) plus cisplatin (75 mg/m^2) for 4 cycles OR - Pemetrexed (500 mg/m^2 of body-surface area) plus carboplatin (target area under the curve of 5 to 6 mg per milliliter per minute) for 4 cycles	• Oral crizotinib (250 mg) twice daily without regard to meals • Chemotherapy by intravenous infusion in 21-day cycles: - Pemetrexed (500 mg/m^2 of body-surface area) plus cisplatin (75 mg/m^2) for a maximum of 6 cycles OR - Pemetrexed (500 mg/m^2 of body-surface area) plus carboplatin (target area under the curve of 5 to 6 mg per milliliter per minute) for a maximum of 6 cycles
Sample size	• Ceritinib: N = 189 • Chemotherapy: N = 187 (12 patients were randomized to pemetrexed and carboplatin but did not receive treatment) - Pemetrexed and cisplatin: N = 87 (47% of chemo arm) - Pemetrexed and carboplatin: N = 100 (53% of chemo arm)	• Crizotinib: N = 172 (1 patient was not treated) • Chemotherapy: N = 171 (2 patients did not receive treatment) - Pemetrexed and cisplatin: N = 91 (53% of chemo arm) - Pemetrexed and carboplatin: N = 78 (46% of chemo arm)
Treatment continuation	• Treatment continued until BIRC-confirmed RECIST-defined progressive disease (PD), unacceptable toxicity, pregnancy, start of a new anticancer therapy, treatment discontinuation at the discretion of the patient or investigator, loss to follow-up, death, or study termination by sponsor • Patients were allowed to continue treatment as assigned beyond BIRC-confirmed RECIST-defined PD at the discretion of the investigator if perceived to be experiencing clinical benefit • Patients randomized to chemotherapy arm, without progressive disease, received pemetrexed maintenance after 4 cycles of chemotherapy treatment	• Treatment continued until RECIST-defined progression of disease as determined by the independent radiology review, unacceptable toxicity, death or consent withdrawal • Patients were allowed to continue treatment as assigned beyond RECIST-defined progression, as determined by independent radiology review, at the discretion of the investigator if perceived to be experiencing clinical benefit • After 6 cycles of chemotherapy, patients randomized to chemotherapy arm remained in the trial with no additional treatment (i.e., maintenance therapy was not permitted) and with ongoing tumor assessments until RECIST-defined progression by the independent radiology review

	ASCEND-4[1]	PROFILE 1014[2]
Inclusion criteria	• Patients aged 18 years or older • Histologically or cytologically confirmed diagnosis of non-squamous NSCLC • Positive for an *ALK* rearrangement as assessed by the Ventana Immunohistochemistry (IHC) test performed at Novartis designated central laboratories • Patients with newly diagnosed stage IIIB (locally advanced; not a candidate for definitive multimodality therapy) or stage IV (metastatic) NSCLC or with relapsed locally advanced or metastatic NSCLC • Patients with ≥1 measurable lesion as defined by RECIST 1.1 (previously irradiated site lesion may only be counted if there is clear sign of progression since the irradiation) • No prior systemic anti-cancer therapy (e.g. cytotoxic drugs, monoclonal antibody therapy, crizotinib or other *ALK* inhibitors, or other targeted therapies, either experimental or not), with exception of neo-adjuvant or adjuvant therapy • Patients with central nervous system (CNS) metastases were allowed if neurologically stable with no requirement for increasing doses of steroids within the 2 weeks prior to screening	• Patients aged 18 years or older (an upper age limit of 65 years old in India) • Histologically or cytologically confirmed diagnosis of non-squamous NSCLC • Positive for an *ALK* rearrangement as determined centrally with the use of a Vysis *ALK* Break Apart FISH Probe Kit [Abbott Molecular] • Patients with locally advanced not suitable for local treatment, recurrent, or metastatic NSCLC with no prior systemic treatment for locally advanced or metastatic disease • Tumors must have measurable disease as per RECIST (version 1.1) • No prior systemic treatment for locally advanced or metastatic disease with exception for prior adjuvant chemotherapy for Stage I-III or combined modality chemotherapy-radiation for locally advanced disease allowed if completed > 12 months prior to randomization • Patients with brain metastases were allowed if treated and neurologically stable with no ongoing requirement for corticosteroids, e.g. dexamethasone, for ≥2 weeks and not taking CYP3A4 inhibitors, inducers, or substrates
Major exclusion criteria	• Hypersensitivity to any of the excipients of ceritinib • Severe hypersensitivity to platinum containing drugs, pemetrexed or any known excipients	• Current treatment on another therapeutic clinical trial • Prior therapy directly targeting *ALK* • Prior malignancy (other than current NSCLC); pregnancy or breastfeeding; severe acute or chronic medical or psychiatric conditions • Use of CYP3A4 inhibitors, inducers, or substrates
Tumor response measure	• RECIST 1.1 based on investigator and BIRC assessment	• RECIST 1.1 confirmed by independent radiologic review
Assessment/visit schedule	• Tumor assessments were performed at baseline and >5 weeks after start of treatment (unless disease progression was determined by investigator within 7 weeks or death occurred)	• Tumor assessments were performed at screening and every 6 weeks from the date of randomization (with exception of bone and brain scans that are to be performed every 12 weeks unless metastases were present at baseline) until progression of disease determined by the independent radiologist. The tumor assessments after progression were performed every 12 weeks

	ASCEND-4[1]	PROFILE 1014[2]
Cross-over	• Patients randomized to the chemotherapy arm were allowed to cross over to enter the extension treatment phase to receive ceritinib therapy after BIRC-confirmed RECIST-defined PD was documented - 80 (42.8%) patients randomized to chemotherapy arm crossed over to receive ceritinib	• Patients randomized to the chemotherapy who had RECIST-defined progression of disease as determined by independent radiology review were allowed to cross-over to receive crizotinib, provided they met screening eligibility criteria for safety relevant to crizotinib therapy - 120 (70%) patients randomized to chemotherapy arm crossed over to receive crizotinib - 21 (12%) patients randomized to crizotinib arm subsequently received platinum-based chemotherapy (the timing of this cross-over is unclear)

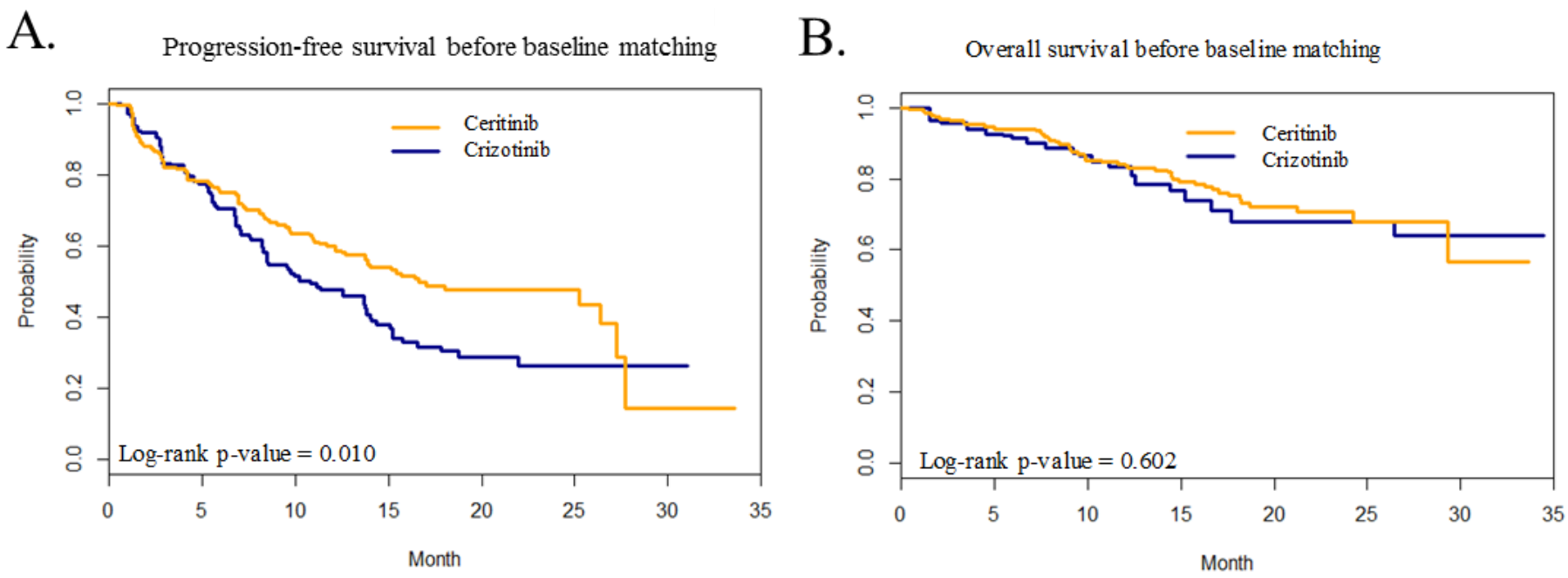
Abbreviations: *ALK*: Anaplastic Lymphoma Kinase; BIRC: Blinded Independent Review Committee; FISH: Fluorescence in Situ Hybridization; IHC: Immunohistochemistry; OS: Overall Survival; PFS: Progression-Free Survival; RECIST: Response Evaluation Criteria in Solid Tumors.

Sources:

[1] Soria JC, Tan DS, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017;389(10072):917-29.

[2] Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371(23):2167-77.

Supplementary Figure S1: PFS and OS for ceritinib and crizotinib before matching (primary analysis)



Supplementary Table S2: Comparison of efficacy outcomes before and after matching (sensitivity analysis)

	Before Matching			After Matching		
	Ceritinib N = 189	**Crizotinib (from ALEX) N = 151**	**Difference (Ceritinib vs. Crizotinib)**	**Ceritinib N = 189**	**Crizotinib (from ALEX) N = 151**	**Difference (Ceritinib vs. Crizotinib)**
PFS						
Median (months), 95% CI	16.6 (12.7, 27.2)	10.4 (7.6, 14.5)	Log-rank *p-value* = 0.012*	16.6 (5.9, 27.7)	10.4 (7.6, 14.5)	Log-rank *p-value* = 0.016*
HR (ceritinib vs. crizotinib)[1], 95% CI			0.68 (0.51, 0.92), *p-value* = 0.012*			0.69 (0.50, 0.94) *p-value* = 0.020*
OS						
Median (months)	NR	NR	Log-rank *p-value* = 0.574	NR	NR	Log-rank *p-value* = 0.416
HR (ceritinib vs. crizotinib)[1], 95% CI			0.88 (0.58, 1.35) *p-value* = 0.570			0.83 (0.53, 1.31) *p-value* = 0.430

Notes:

* P-values < 0.05 were considered significant; CI = confidence interval; HR = hazard ratio; NR = not reached; OS = overall survival; PFS = progression-free survival

1. The proportional hazards assumption was not rejected.

Supplementary Figure S2: Histogram of weights applied to the ASCEND-4 patients (primary analysis)