# Supplemental data

Supplemental Data 1.doc

**Table S1.** Demographics and Baseline Characteristics. Reprinted with permission from Kim DW et al, Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase–Positive Non–Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial, Journal of Clinical Oncology, Volume 35 (Issue 22), Pages 2490-2498. © 2017 by American Society of Clinical Oncology.1

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Arm A****90 mg Once Daily****n=112** | **Arm B****90 mg 🡪****180 mg Once Dailya****n=110** | **Total****N=222** |
| Median age, years (range) | 50.5 (18–82) | 56.5 (20–81) | 54.0 (18–82) |
| Gender, female, n (%) | 62 (55) | 64 (58) | 126 (57) |
| Race, n (%) |  |  |  |
| White | 72 (64) | 76 (69) | 148 (67) |
| Asian | 39 (35) | 30 (27) | 69 (31) |
| Other | 1 (1) | 4 (4) | 5 (2) |
| ECOG performance status, n (%) |  |  |  |
| 0 | 34 (30) | 45 (41) | 79 (36) |
| 1 | 71 (63) | 56 (51) | 127 (57) |
| 2 | 7 (6) | 9 (8) | 16 (7) |
| Smoking history, n (%) |  |  |  |
| Never | 71 (63) | 63 (57) | 134 (60) |
| Former | 34 (30) | 43 (39) | 77 (35) |
| Current | 6 (5) | 4 (4) | 10 (5) |
| Unknown | 1 (1) | 0 | 1 (<1) |
| Histology, n (%) |  |  |  |
| Adenocarcinoma | 107 (96) | 108 (98) | 215 (97) |
| Adenosquamous carcinoma | 1 (1) | 0 | 1 (<1) |
| Squamous | 2 (2) | 1 (1) | 3 (1) |
| Large cell | 1 (1) | 1 (1) | 2 (1) |
| Mucoepidermoid carcinoma | 1 (1) | 0 | 1 (<1) |
| Baseline brain metastases,b n (%) | 80 (71) | 74 (67) | 154 (69) |
| Prior chemotherapy, n (%) | 83 (74) | 81 (74) | 164 (74) |
| Best response to prior crizotinib,b n (%) |  |  |  |
| CR or PR | 71 (63) | 73 (66) | 144 (65) |
| SD | 28 (25) | 21 (19) | 49 (22) |
| PD | 8 (7) | 6 (5) | 14 (6) |
| Unknown | 5 (4) | 10 (9) | 15 (7) |
| Median cumulative duration of prior crizotinib regimens, months (range) | 11.3 (1–59) | 13.2 (1–72) | 12.6 (1–72) |
| Location of target lesions, n (%) of lesions |  |  |  |
| Total | n=247 | n=204 | n=451 |
| Extracranial | 209 (85) | 172 (84) | 381 (84) |
| Intracranial | 38 (15) | 32 (16) | 70 (16) |
| ≥1 baseline CNS target lesion, n (%) of patients |  |  |  |
| No | 84 (75) | 87 (79) | 171 (77) |
| Yes  | 28 (25) | 23 (21) | 51 (23) |

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PR, partial response; SD, stable disease.

a180 mg once daily with 7-day lead-in at 90 mg.

bAs assessed by the investigator.

Reference

1. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J Clin Oncol.* 2017;35(22):2490-2498.

**Table S2.** Multivariable Analysesa of PFS and OS in Patients With ≥1 Evaluable Response Assessment.

|  |  |
| --- | --- |
|  | **Hazard Ratio (95% CI)** |
|  | **PFS**  |  |
|  | **Investigator Assessed** | **IRC Assessed**  | **OSb** |
| **Best target lesion shrinkage** |
|  None | Reference | Reference | Reference |
|  1–25% | 0.53 (0.27–1.04) | 0.19 (0.04–0.93) | 0.55 (0.25–1.22) |
|  26–50% | 0.47 (0.25–0.89) | 0.08(0.02–0.39) | 0.38 (0.17–0.84) |
|  51–75% | 0.43 (0.22–0.83) | 0.07(0.01–0.33) | 0.42 (0.19–0.95) |
|  76–100% | 0.31 (0.16–0.62) | 0.09(0.02–0.43) | 0.33 (0.14–0.77) |
| **Treatment arm** |
| Arm A (90 mg once daily) | Reference | Reference | Reference |
| Arm B (90 mg → 180 mg once daily)c | 0.76 (0.54–1.07) | 0.81 (0.55–1.18) | 0.73 (0.46–1.15) |
| **Baseline ECOG performance status** |
|  0–1 | Reference | Reference | Reference |
|  2 | 1.81 (0.94–3.48) | 1.54(0.71–3.35) | 2.01 (0.93–4.33) |
| **Smoking status** |  |  |  |
|  Never/unknown | Reference | Reference | Reference |
|  Current/former | 1.46 (1.02–2.08) | 0.97 (0.64–1.46) | 1.02 (0.63–1.65) |

Abbreviations: OS, overall survival; PFS, progression-free survival.

aCox proportional hazards regression model.

bShrinkage categories based on investigator-assessed shrinkage.

c180 mg once daily with 7-day lead-in at 90 mg.

**Table S3.** Adverse Events Leading to Dose Reduction in ≥2 Patients Overall

|  | **Arm Aa****90 mg Once Daily****n=109** | **Arm B****90 mg 🡪****180 mg Once Dailyb****n=110** |
| --- | --- | --- |
| **Patients with ≥1 AE leading to dose reduction, n (%)**  | 8 (7.3) | 32 (29.1) |
| Blood creatine phosphokinase increased | 2 (1.8) | 7 (6.4) |
| Rash | 1 (0.9) | 3 (2.7) |
| Lipase increased | 1 (0.9) | 2 (1.8) |
| Decreased appetite | 0 | 2 (1.8) |
| Electrocardiogram QT prolonged | 0 | 2 (1.8) |
| Hyponatremia | 0 | 2 (1.8) |
| Nausea | 0 | 2 (1.8) |
| Pneumonitis | 0 | 2 (1.8) |
| Amylase increased | 1 (0.9) | 1 (0.9) |
| Cough | 1 (0.9) | 1 (0.9) |
| Hypertension | 1 (0.9) | 1 (0.9) |

aFor arm A, dose modification was required for any grade 3 or 4 nonhematologic toxicity, including laboratory abnormalities.

* Grade 3: For 90 mg once daily dose, hold until event is grade 1 or lower, or has returned to baseline. Resume at 90 mg once daily or 60 mg once daily (at investigator’s discretion). For recurrence at 90 mg once daily, hold until event is grade 1 or lower, or has returned to baseline, and resume treatment at 60 mg once daily. When the current dose is 60 mg once daily, consider discontinuing treatment.
* Grade 4: For 90 mg once-daily dose, hold until event is grade 1 or lower, or has returned to baseline. Resume treatment at 60 mg once daily or discontinue (at investigator’s discretion). When the current dose is 60 mg once daily, consider discontinuing treatment.

bFor arm B, dose modification was required for grade 2 events lasting longer than 3 days or any grades 3 or 4 nonhematologic toxicity, including laboratory abnormalities.

* For 90 mg once daily dose (previous to dose escalation):
	+ Grade 2 (>3 days) and grade 3: Hold until event is grade 1 or lower, or has returned to baseline. Resume at 90 mg once daily (at investigator’s discretion).
	+ Grade 4: Hold until event is grade 1 or lower, or has returned to baseline. Resume treatment at 60 mg once daily or discontinue (at investigator’s discretion).
* After dose escalation:
	+ Grade 3: When the dose is 180 mg once daily, hold until event is grade 1 or lower, or has returned to baseline and then resume at 180 mg once daily or 120 mg once daily (at investigator’s discretion). When the current dose is 120 mg once daily, hold until event is grade 1 or lower, or has returned to baseline and resume at 90 mg once daily after recovery. When the current dose is 90 mg once daily, hold until event is grade 1 or lower, or has returned to baseline and resume at 60 mg once daily after recovery, or discontinue (at investigator’s discretion). When the current dose is 60 mg once daily, consider discontinuing treatment.
	+ Grade 4: When the current dose is 180 mg once daily, hold until event is grade 1 or lower, or has returned to baseline; resume at 120 mg once daily, or discontinue (at investigator’s discretion) When the current dose is 120 mg once daily, hold until event is grade 1 or lower, or has returned to baseline. Resume at 90 mg once daily, or discontinue (at investigator’s discretion). When the current dose is 90 mg once daily, hold until event is grade 1 or lower, or has returned to baseline and resume at 60 mg once daily after recovery, or discontinue (at investigator’s discretion). When the current dose is 60 mg once daily, consider discontinuing treatment.