Clinical outcome for EML4-ALK-positive patients with advanced non-small-cell lung cancer treated with first-line platinum-based chemotherapy

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Received 16 February 2012; revised 19 March 2012; accepted 20 March 2012

Background: The EML4-ALK fusion oncogene represents a recently identified molecular target in a subset of patients with non-small-cell lung cancer (NSCLC). Limited data have been available, however, on the outcome of first-line platinum-based chemotherapy in patients with EML4-ALK-positive advanced NSCLC who have not been treated with an ALK kinase inhibitor.

Patients and methods: The efficacy of platinum-based chemotherapy was compared between patients with advanced nonsquamous NSCLC who harbor EML4-ALK and those who harbor EGFR mutations and those with neither molecular abnormality.

Results: Among 200 patients with advanced nonsquamous NSCLC, 18 (9.0%) were positive for EML4-ALK, 31 (15.5%) harbored EGFR mutations, and 151 (75.5%) were wild type for both abnormalities. Platinum-based combination chemotherapy showed similar efficiencies in the EML4-ALK, EGFR mutation, and wild-type cohorts in terms of response rate and progression-free survival, and overall survival in the EML4-ALK cohort closely resembled that in the wild-type cohort. Within the EML4-ALK cohort, patients with variants 1 or 3 of the fusion gene were predominant and did not appear to differ in their sensitivity to the platinum-based regimens.

Conclusion: Patients with EML4-ALK-positive advanced NSCLC manifest an aggressive clinical course similar to that of those with wild-type tumors if the effective targeted therapy is not instituted.

Key words: anaplastic lymphoma kinase, epidermal growth factor receptor, non-small-cell lung cancer, platinum-based chemotherapy

Introduction

Recent insight into the molecular basis of lung cancer has led to changes in the treatment of this disease. The identification of somatic mutations in the epidermal growth factor receptor (EGFR) gene in a subset of patients with non-small-cell lung cancer (NSCLC) has thus led to the treatment of such patients with EGFR tyrosine kinase inhibitors (TKIs) and a consequent superior response rate, prolonged progression-free survival (PFS), and improved quality of life compared with those achieved with cytotoxic chemotherapy [1, 2]. Fusion of the anaplastic lymphoma kinase (ALK) gene and the echinoderm microtubule-associated protein-like 4 gene (EML4) in NSCLC was also identified in 2007 [3]. The EML4-ALK fusion gene is generated by an inv(2)(p21p23) chromosomal translocation, and it shows oncogenic activity in a mouse model [4]. Several EML4-ALK fusion variants have been identified to date, with the most frequent being variants 1 and 3 [3, 5–8], and between 3% and 13% of lung tumors have been found to harbor EML4-ALK fusions [3, 9, 10]. Preclinical and clinical studies have shown that cancer cells harboring EML4-ALK or other ALK aberrations are highly sensitive to ALK inhibition. In a recent phase I clinical trial, crizotinib (PF-02341066), an inhibitor of the tyrosine kinase activity of both ALK and the proto-oncoprotein MET, showed marked antitumor activity in NSCLC patients with ALK abnormalities, with an objective response rate of 61% and median PFS of 10 months [11].

Limited data have been available, however, regarding overall survival (OS) of patients with EML4-ALK-positive advanced NSCLC who have not been treated with ALK kinase inhibitors. Although several studies have evaluated the efficacy of cytotoxic chemotherapy based on the molecular profile of the disease, classified as EML4-ALK positive, EGFR mutation positive, or wild type for both types of genetic abnormality [10, 12–15], it has remained unclear whether EML4-ALK is an effective prognostic factor [13–15]. Further studies are thus warranted to determine the impact of EML4-ALK on the survival of patients treated with cytotoxic chemotherapy.
In the present study, a large series of patients with advanced nonsquamous NSCLC not previously treated with an ALK inhibitor was screened for EML4-ALK by analysis of formalin-fixed paraffin-embedded (FFPE) tissue specimens obtained by lung biopsy. We evaluated the efficacy of platinum-based chemotherapy according to the molecular profile of the tumors, which were classified as positive for EML4-ALK, positive for EGFR mutation, or wild type for both types of genetic abnormality. In addition, we undertook an exploratory analysis of the efficacy of platinum-based chemotherapy according to the specific variant of EML4-ALK detected.

patients and methods

patients

The present study recruited consecutive patients with advanced nonsquamous NSCLC who were treated with first-line platinum-based combination chemotherapy at Kinki University Hospital between February 2003 and October 2011. Patients met all the following criteria: a histological diagnosis of nonsquamous NSCLC with at least one measurable lesion; a clinical stage of IIIIB or IV; an Eastern Cooperative Oncology Group performance status of 0 or 1; and availability of both complete clinical information and FFPE tissue blocks suitable for genetic analysis of EML4-ALK and EGFR. The choice of first-line chemotherapy regimen was made by the treating physician. Patients who received an EGFR-TKI as first-line treatment or those who received an ALK inhibitor such as crizotinib in any line were excluded from the study. Tumor response was examined by computed tomography and was evaluated according to the RECIST version 1.1. The study protocol was approved by the local institutional review board with the conditions that tissue samples be processed anonymously and analyzed only for somatic mutations (not for germ line mutations) and that the study be disclosed publicly, according to the Ethical Guidelines for Human Genome Research published by the Ministry of Education, Culture, Sports, Science, and Technology, the Ministry of Health, Labor, and Welfare, and the Ministry of Economy, Trade, and Industry of Japan. The present study also conforms to the provisions of the Declaration of Helsinki.

detection of EML4-ALK variants and nucleotide sequencing

Total RNA was extracted from FFPE tissue with the use of an RNeasy FFPE Kit (Qiagen, Valencia, CA) and was subjected to reverse transcription with the use of a High Capacity complementary DNA (cDNA) Reverse Transcription Kit (Applied Biosystems, Foster City, CA). The resulting cDNAs for EML4-ALK fusions (variants 1, 2, 3a, 3b, 4, 5a, 5b, 6, and 7) were detected with the Mass ARRAY iPLEX platform (Sequenom, San Diego, CA), which involves a three-step process consisting of the PCR, single-base primer extension, and separation of the products on a matrix-loaded silicon chip by MALDI–TOF (matrix-assisted laser desorption-ionization–time of flight) mass spectrometry [16]. Data analysis was performed with MassARRAY Typer software version 4.0 (Sequenom). PCR products were subcloned into the TOPO TA pcR2.1 vector (Invitrogen, San Diego, CA) and sequenced with an automated sequencer (ABI Prism 3100 Genetic Analyzer; Applied Biosystems) with the use of M13 universal primers. EGFR mutations that confer sensitivity to EGFR-TKIs were identified either by the Scorpion amplified refractory mutation system or by the PCR-Invader method (BML, Tokyo, Japan).

statistical analysis

Analyzed variables include age, sex, smoking history, tumor histology, clinical stage, and molecular abnormality. Differences in demographic characteristics and treatment response between two subgroups were evaluated with the two-sided Fisher’s exact test; Student’s t-test was performed to compare continuous variables between two subgroups. PFS was calculated from the date of chemotherapy initiation either to the date of progression or death without demonstrated disease progression or to the date of last contact. OS was calculated from the date of chemotherapy initiation to the date of death from any cause or to the date of last contact. The probability of survival as a function of time was estimated with the Kaplan–Meier method, and the difference in survival between subgroups of patients was evaluated with the log-rank test. The hazard ratio (HR) for two subgroups of patients was estimated by proportional hazards regression with a 95% confidence interval (CI). A P value of <0.05 was considered statistically significant. All statistical analysis was performed with GraphPad Prism software (version 5.0; GraphPad Software, San Diego, CA).

results

patient characteristics

We analyzed tumor specimens from 200 of 290 consecutive patients with advanced nonsquamous NSCLC who were treated with first-line platinum-based chemotherapy during the study period. The remaining 90 patients were excluded because there was no or insufficient tumor tissue available for genetic analysis. The baseline characteristics of the 200 enrolled patients are summarized in Table 1. They included 127 (64%) men, 84 (42%) never or light smokers, 178 (89%) individuals with adenocarcinoma, and 163 (82%) patients with disease of stage IV, with the median age of the entire group being 63 years (range, 29–81). The patients were divided into three groups on the basis of the molecular subtype of NSCLC: EML4-ALK positive (n = 18), EGFR mutation positive (n = 31), and wild type (n = 151). Among the 31 patients with EGFR mutations, 15 individuals (48%) had a deletion in exon 19 and 14 individuals (45%) had a point mutation (L858R or L861Q) in exon 21; 18 patients (58%) were treated during the first half of the study period (from 2003 to 2007) and 13 patients (42%) during the second half (from 2007 to 2011). Patients in the wild-type subgroup harbored neither EGFR mutations nor EML4-ALK. One patient harboring both EML4-ALK and an EGFR mutation was classified as EML4-ALK positive. The 18 (9.0%) patients positive for EML4-ALK were significantly younger (median age, 46 years) than were the EGFR mutation-positive patients (median age, 63 years; P < 0.001) or the wild-type patients (median age, 64 years; P < 0.001). There were no significant differences among the three subgroups with respect to sex, smoking history, tumor histology, or disease stage.

efficacy of platinum-based combination chemotherapy according to molecular subtype of NSCLC

We evaluated the efficacy of platinum-based chemotherapy according to the molecular profile of NSCLC. Several chemotherapy regimens were implemented in the study population (supplemental Table S1, available at Annals of Oncology online). The patients were divided into the following subgroups based on the molecular subtype of NSCLC: EML4-ALK positive, EML4-ALK negative, and wild type.
The EML4-ALK-positive cohort included 7 (39%) individuals treated with platinum plus pemetrexed, compared with 4 (13%, P = 0.072) and 25 (17%, P = 0.049) such individuals in the EGFR mutation-positive and wild-type cohorts, respectively. Among the entire study population, 20 (10%) individuals received bevacizumab together with platinum-based doublet chemotherapy [2 (11%), 1 (3%), and 17 (11%) patients in the EML4-ALK, EGFR-mutation, and wild-type subgroups, respectively]. Cisplatin was administered in 7 (39%), 12 (39%), and 26 (17%) patients in the EML4-ALK, EGFR-mutation, and wild-type cohorts, respectively.

All patients were assessable for treatment outcome (Table 2). No significant difference in overall response rate was apparent among the three arms (44%, 45%, and 39% for the EML4-ALK, EGFR-mutation, and wild-type subgroups, respectively). PFS also did not differ significantly between patients with EML4-ALK [median, 6.5 months (95% CI 2.4–10.6)] and either those with EGFR mutations [median, 6.0 months (95% CI 5.2–6.8); HR, 0.78 (95% CI 0.42–1.48); P = 0.452] or those with neither type of molecular abnormality [median, 4.3 months (95% CI 3.4–5.2); HR, 0.82 (95% CI 0.49–1.36); P = 0.437] (Figure 1A).

### Table 1. Patient characteristics according to genetic status of NSCLC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 200)</th>
<th>EML4-ALK+ (n = 18)</th>
<th>EML4-ALK− (n = 182)</th>
<th>P</th>
<th>EML4-ALK+ versus EGFR mutation+</th>
<th>EML4-ALK+ versus wild type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median 63</td>
<td>46</td>
<td>63</td>
<td>44–75</td>
<td>64</td>
<td>35–81</td>
</tr>
<tr>
<td>Range 29–81</td>
<td>29–69</td>
<td>64–75</td>
<td>35–81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male 127 (64%)</td>
<td>9 (50%)</td>
<td>12 (39%)</td>
<td>106 (70%)</td>
<td>0.553</td>
<td>0.108</td>
</tr>
<tr>
<td></td>
<td>Female 73 (37%)</td>
<td>9 (50%)</td>
<td>19 (61%)</td>
<td>45 (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never 65 (33%)</td>
<td>6 (33%)</td>
<td>16 (52%)</td>
<td>43 (28%)</td>
<td>0.559*</td>
<td>0.125*</td>
</tr>
<tr>
<td></td>
<td>Light smoker 19 (10%)</td>
<td>4 (22%)</td>
<td>4 (13%)</td>
<td>11 (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smoker 116 (58%)</td>
<td>8 (44%)</td>
<td>11 (35%)</td>
<td>97 (64%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Adenocarcinoma 178 (89%)</td>
<td>16 (89%)</td>
<td>30 (97%)</td>
<td>132 (87%)</td>
<td>0.546**</td>
<td>1.000**</td>
</tr>
<tr>
<td></td>
<td>Large cell 6 (3%)</td>
<td>1 (6%)</td>
<td>1 (3%)</td>
<td>4 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adenosquamous 2 (1%)</td>
<td>1 (6%)</td>
<td>0</td>
<td>1 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NOS 14 (7%)</td>
<td>0</td>
<td>0</td>
<td>14 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>IIIB 37 (19%)</td>
<td>4 (22%)</td>
<td>5 (16%)</td>
<td>28 (19%)</td>
<td>0.708</td>
<td>0.751</td>
</tr>
<tr>
<td></td>
<td>IV 163 (82%)</td>
<td>14 (78%)</td>
<td>26 (84%)</td>
<td>123 (81%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P value calculated by binary comparison (never or light smokers versus smokers). **P value calculated by binary comparison (adenocarcinoma versus nonadenocarcinoma). NSCLC, non-small-cell lung cancer; NOS, not otherwise specified.

### Table 2. Efficacy of first-line platinum-based treatment based on genetic status of NSCLC

<table>
<thead>
<tr>
<th>Response</th>
<th>EML4-ALK+ (n = 18)</th>
<th>EML4-ALK− (n = 182)</th>
<th>P</th>
<th>EML4-ALK+ versus EGFR mutation+</th>
<th>EML4-ALK+ versus wild type</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR 1 (6%)</td>
<td>0</td>
<td>1 (1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR 7 (39%)</td>
<td>14 (45%)</td>
<td>58 (38%)</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD 6 (33%)</td>
<td>13 (42%)</td>
<td>52 (34%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD 4 (22%)</td>
<td>4 (13%)</td>
<td>40 (26%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR 8 (44%)</td>
<td>14 (45%)</td>
<td>59 (39%)</td>
<td>0.800</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NSCLC, non-small-cell lung cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate.

**OncoLogy online**. The EML4-ALK-positive cohort included 7 (39%) individuals treated with platinum plus pemetrexed, compared with 4 (13%, P = 0.072) and 25 (17%, P = 0.049) such individuals in the EGFR mutation-positive and wild-type cohorts, respectively. Among the entire study population, 20 (10%) individuals received bevacizumab together with platinum-based doublet chemotherapy [2 (11%), 1 (3%), and 17 (11%) patients in the EML4-ALK, EGFR-mutation, and wild-type subgroups, respectively]. Cisplatin was administered in 7 (39%), 12 (39%), and 26 (17%) patients in the EML4-ALK, EGFR-mutation, and wild-type cohorts, respectively.

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**survival outcome of EML4-ALK-positive patients**

After a median follow-up of 10.8 months (range, 0.6–75.3) from the start of platinum-based treatment, 91 patients were still alive at last contact. Kaplan–Meier curves for OS of the three cohorts are shown in Figure 1B. EML4-ALK-positive patients had an OS similar to that of wild-type patients [median OS, 15.7 months (95% CI 6.2–25.3) versus 15.2
months (95% CI 11.6–18.7), respectively; HR, 0.83 (95% CI 0.42–1.63); \( P = 0.591 \). The OS of EGFR mutation-positive patients [median, 24.8 months (95% CI 14.1–35.5)] tended to be longer than that of the EML4-ALK-positive cohort, but this difference was not statistically significant [HR, 0.47 (95% CI 0.17–1.27); \( P = 0.135 \)]. The OS of EGFR mutation-positive patients was significantly greater than that of wild-type patients [HR, 0.56 (95% CI 0.36–0.89); \( P = 0.013 \)].

**Comparison of PFS between patients with different EML4-ALK variants**

The genomic breakpoint in the 18 patients with EML4-ALK was verified by cloning and sequencing. Eight of these tumors (44%) were found to harbor EML4-ALK variant 1, two (11%) had variant 2, and eight (44%) had variant 3 (Figure 2A). To compare the efficacy of platinum-based chemotherapy between patients with different EML4-ALK variants, we determined PFS for those with variant 1 and those with variant 3 (Figure 2B). Waterfall plot analysis showed that the median PFS was similar in both groups (4.8 and 4.3 months for variants 1 and 3, respectively). However, platinum-based combination chemotherapy showed long-term efficacy in two patients with variant 1; one patient received four cycles of chemotherapy with pemetrexed and carboplatin followed by maintenance pemetrexed therapy for 19.3 months until disease progression, whereas the other patient received six cycles of chemotherapy with carboplatin and S-1 and showed no evidence of disease progression for 60.9 months.

**Discussion**

Our present study population comprised 200 patients with advanced nonsquamous NSCLC who were treated with first-line platinum-based chemotherapy and for whom sufficient tissue was available in paraffin blocks for genetic analysis of
EML4-ALK and EGFR. For detection of EML4-ALK transcripts, we applied reverse transcription and the MassARRAY system, which is based on PCR and MALDI-TOF mass spectrometry and which shows a high degree of concordance with fluorescence in situ hybridization [16]. The frequency of EML4-ALK in our present study (9.0%) is consistent with that reported in previous studies [3, 9, 10]. The frequency of EGFR mutations in our study (15.5%) is lower than that previously determined for Asian patients with nonsquamous NSCLC [17]; the reason for this difference is that EGFR mutation-positive patients who received first-line treatment with EGFR-TKIs were excluded from our analysis, with EGFR-TKIs now being a treatment option for chemotherapy-naive EGFR mutation-positive patients on the basis of recent phase III trials comparing EGFR-TKIs with platinum-based chemotherapy [1, 2]. We observed that the demographics of EML4-ALK-positive patients differed from those of fusion-negative patients. Consistent with previous studies, we found that EML4-ALK-positive patients were significantly younger than EGFR mutation-positive or wild-type patients [10, 12, 18, 19]. The proportion of never and light smokers was found not to differ significantly according to EML4-ALK status, although the proportion tended to be higher in EML4-ALK-positive patients than in wild-type patients (P = 0.125).

Crizotinib, the first clinically available TKI that targets ALK, has shown pronounced single-agent activity in patients with EML4-ALK-positive NSCLC [11]. The sensitivity of such patients to platinum-based combination chemotherapy relative to that of patients whose tumors are negative for EML4-ALK has remained unclear, however. Two retrospective studies have investigated whether the tumor molecular profile affects sensitivity to platinum-based combination chemotherapy in advanced NSCLC [10, 12]. These studies did not detect a significant difference in response rate or PFS among patients who were EML4-ALK positive, EGFR mutation positive, or wild type, although the cytotoxic drug partnered with the platinum agent was not specified. Consistent with these findings, we have now shown that patients in the EML4-ALK, EGFR-mutation, and wild-type cohorts exhibited similar sensitivity to platinum-based combination chemotherapy in terms of response rate and PFS. These results suggest that sensitivity to platinum-based chemotherapy is not influenced by EML4-ALK status in patients with advanced NSCLC.

Limited data are available regarding OS of patients with EML4-ALK-positive advanced NSCLC who have not been treated with an ALK kinase inhibitor. Altavilla et al. [14] found that, among 40 patients treated with cisplatin and pemetrexed as first-line combination chemotherapy, the median OS was 17 months for EML4-ALK-positive patients (n = 8) compared with 11 months for EML4-ALK-negative patients (n = 32). Wu et al. [15] showed that, among patients wild type for EGFR who received either monotherapy or platinum-doublet chemotherapy, those positive for EML4-ALK had a superior OS (14.7 months) compared with those negative for the fusion gene (10.3 months). In contrast to these findings, a recent study showed that the OS of crizotinib-naive, EML4-ALK-positive patients with advanced NSCLC did not differ significantly from that of wild-type patients, although details regarding the first-line chemotherapy, given either as a platinum-based doublet or as a single agent, are unclear [13]. These apparent discrepancies may be explained by an unbalanced distribution of platinum-doublet chemotherapy between EML4-ALK-positive and -negative subgroups. Given that platinum-based chemotherapy yields a substantial survival advantage in patients with advanced NSCLC [20], we assessed OS according to the tumor molecular profile in selected NSCLC patients who were offered treatment with platinum-based combination chemotherapy. Furthermore, given that EML4-ALK-positive patients who received an ALK inhibitor such as crizotinib in any line were excluded from our study, the EML4-ALK-positive cohort represents the natural history of advanced NSCLC positive for the fusion gene in the absence of effective targeted therapy. We found that OS in the EML4-ALK cohort closely resembled that in the wild-type cohort (15.7 versus 15.2 months, respectively). Favorable outcomes achieved in the wild-type cohort are likely related to the fact that 104 of 151 patients (69%) received subsequent treatment, including 19 (13%) patients treated with an EGFR-TKI. In the EGFR mutation-positive cohort, most (84%) patients received an EGFR-TKI as second-line or later chemotherapy. EGFR-TKIs have been found to yield a substantial clinical benefit in terms of OS, even when the drug is administered as second-line or later chemotherapy [21, 22]. A trend toward an OS advantage in the EGFR mutation-positive cohort (24.8 months) compared with the EML4-ALK and wild-type cohorts is likely attributable to the difference in the availability of EGFR-TKI treatment among the three groups. These results indicate that, in the absence of treatment with ALK inhibitors, EML4-ALK status does not have prognostic value in patients with advanced nonsquamous NSCLC.

Although various break and fusion points within the EML4 locus give rise to different isoforms of EML4-ALK, it is unclear whether there are any differences in the therapeutic response of patients harboring the different variants that might warrant more specific knowledge of EML4-ALK status [3, 5–9]. We applied the MassARRAY system for screening of EML4-ALK; this system is able to distinguish between the different EML4-ALK variants with the use of only a small amount of FFPE tissue. The two most common variants (variants 1 and 3a/b) were identified in 89% of EML4-ALK-positive tumors in the present study. Although our exploratory analysis of PFS suggested that treatment efficacy was similar in patients harboring variant 1 and those with variant 3, two patients with variant 1 showed a long-term response to platinum-based combination chemotherapy. These observations warrant confirmation in a prospective study as well as exploration of any biological differences between variants 1 and 3.

In conclusion, our results suggest that EML4-ALK status does not affect the sensitivity of patients with advanced NSCLC to platinum-based combination chemotherapy. A randomized phase III study comparing crizotinib with platinum-doublet chemotherapy as the first-line treatment for NSCLC patients harboring EML4-ALK is ongoing; patients assigned to platinum-based chemotherapy can crossover to crizotinib treatment when progressive disease is documented. It will therefore be difficult to obtain OS data for crizotinib-
naive patients with EML4-ALK who are treated with first-line platinum-based chemotherapy in a prospective cohort study. Our present study has shown that EML4-ALK-positive patients with advanced NSCLC manifest an aggressive clinical course similar to that of patients with wild-type tumors if the effective targeted therapy is not instituted. Our findings thus underline the importance of the development of ALK inhibitors for this molecularly defined population of NSCLC patients.

**funding**

This study was not supported by a sponsor or funding agency.

**disclosure**

The authors have declared no conflicts of interest.

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