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Phase III study (MONET1) of motesanib plus carboplatin/paclitaxel in patients with advanced nonsquamous nonsmall-cell lung cancer (NSCLC): Asian subgroup analysis

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Abstract

Background This preplanned subset analysis of the phase III MONET1 study aimed to determine whether motesanib combined with carboplatin/paclitaxel (C/P) would result in improved overall survival (OS) versus chemotherapy alone, in a subset of Asian patients with nonsquamous nonsmall-cell lung cancer (NSCLC).

Patients and methods Patients with nonsquamous NSCLC (stage IIIB/IV or recurrent) and no prior systemic therapy for advanced disease were randomized to IV carboplatin (AUC, 6 mg/ml min) and paclitaxel (200 mg/m²) for up to six 3-week cycles, plus either oral motesanib 125 mg q.d. or placebo. Primary end point was OS; secondary end points included progression-free survival (PFS), objective response rate (ORR), and safety.

Results Two hundred twenty-seven Asian patients from MONET1 were included in this descriptive analysis. Median OS was 20.9 months in the motesanib plus C/P arm and 14.5 months in the placebo plus C/P arm ($P = 0.0223$); median PFS was 7.0 and 5.3 months, respectively, ($P = 0.0004$); and ORR was 62% and 27%, respectively, ($P < 0.0001$). Grade ≥ 3 adverse events were more common in the motesanib plus C/P arm versus placebo plus C/P (79% versus 61%).

Conclusion In this preplanned subset analysis of Asian patients with nonsquamous NSCLC, motesanib plus C/P significantly improved OS, PFS, and ORR versus placebo plus C/P.

Clinical trial number NCT00460317.

Key words

Asia, carboplatin, motesanib, NSCLC, paclitaxel

Introduction

The incidence of lung cancer is high (and increasing) in Asia [1], with an estimated age-standardized incidence of 22.3 per 100 000 [2]. Nonsmall-cell lung cancer (NSCLC) accounts for 80%–85% of all cases of lung cancer [3].

Cigarette smoking is estimated to cause 85%–90% of lung cancers in the USA [4]. In large parts of Asia, the associated hazards and peak of smoking-related deaths may not be fully realized for at least two decades [5].

Currently, platinum-based doublet combination chemotherapy is the first-line treatment of choice for NSCLC; however, the prognosis for patients with advanced NSCLC is poor with a median overall survival (OS) of 8–11 months [3]. Bevacizumab, a targeted antiangiogenic agent, in combination with carboplatin/paclitaxel (C/P) significantly improved OS versus chemotherapy alone in patients with recurrent or advanced NSCLC [6]. Multitargeted antiangiogenic agents may provide advantages over agents with single targets [7].

Motesanib is a highly selective, oral small-molecule multikinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2, -3, platelet-derived growth factor receptor (PDGFR), and Kit [8]. Motesanib has demonstrated antitumor activity as monotherapy in advanced solid tumors [9, 10]. In a phase II study in advanced nonsquamous NSCLC, motesanib plus C/P was estimated to be as efficacious as bevacizumab plus C/P [11].

However, in the phase III MONET1 study, OS was not significantly improved with motesanib plus C/P compared with C/P alone in patients with advanced nonsquamous NSCLC, or in a subset of patients with adenocarcinoma [12]. In a retrospective population-based study of NSCLC in the USA, Asian ethnicity was found to be an independent favorable prognostic factor for OS in NSCLC regardless of smoking status [13].

The objectives of the present study were to assess OS, progression-free survival (PFS), and adverse events (AEs) in an exploratory subgroup analysis of Asian patients with advanced nonsquamous NSCLC who received motesanib plus C/P in the MONET1 study, compared with placebo plus C/P.

materials and methods

study design

MONET1 was an international, double-blind, placebo-controlled, randomized phase III study to evaluate the efficacy and tolerability of motesanib when administered with C/P. Full details of the methodology have been previously reported [12]. In brief, patients received carboplatin (AUC, 6 mg/ml min) and paclitaxel (200 mg/m²) on day 1 of each 3-week cycle up to six cycles and were randomized 1:1 to also receive oral motesanib 125 mg q.d. (arm A) or placebo (arm B). Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent.

The primary end point was OS; secondary end points included PFS, overall response rate (ORR), and the incidence of AEs.

patients

Patients aged ≥ 18 years with histologically confirmed unresectable stage IIIB NSCLC with pericardial or pleural effusion or stage IV/recurrent nonsquamous NSCLC were eligible for inclusion. Other inclusion criteria included measurable or nonmeasurable disease by modified Response Evaluation Criteria in Solid Tumors (RECIST) [14]; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and life expectancy ≥ 3 months. Key exclusion criteria included symptomatic or untreated central nervous system metastases. Study procedures were approved by an independent ethics committee/institutional review board at each study site, and all patients provided written informed consent.

assessments

Tumor assessments were made via computed tomography (CT) or magnetic resonance imaging scans (assessed per modified RECIST v1.0). AEs were graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0.

statistical analysis

For the present exploratory subanalysis, the Asian subset included patients enrolled in East Asia; Japan, Korea, Philippines, Hong Kong, Taiwan, or Singapore. Non-Asian patients were those enrolled in the European Union, US, Canada, Australia, South America, Turkey, Ukraine, India, Israel, or Russia.

P-values are descriptive only due to the exploratory nature of this subanalysis. The full analysis set (all randomized patients) was used for all efficacy analyses. For OS and PFS, arms A and B were compared using a two-sided stratified log-rank test; stratified Cox proportional hazards model was used to define HR. For ORR, the treatment arms were compared using the stratified Cochran–Mantel–Haenszel test. The safety analysis set (all randomized patients who received at least one dose of motesanib) was used for all analyses of safety.

results

This analysis included 227 Asian patients with nonsquamous NSCLC who were randomized to receive motesanib ($n = 110$; arm A) or placebo ($n = 117$; arm B) in addition to C/P (Table 1). Approximately 50% of patients ($n = 106$) were Japanese (arm A: $n = 55$; arm B: $n = 51$); and almost 90% ($n = 198$) had adenocarcinoma. Baseline demographics and disease characteristics of the Asian patients were compared with the total population treated in the MONET1 study ($N = 1090$). A higher percentage of Asian patients were never smokers compared with the overall population.

Table 1.

Baseline demographics and disease characteristics

Efficacy and safety analyses of the Asian patients were compared with non-Asian patients ($n = 863$). At the time of analysis, 139 patients had died and 88 continued on study. Asian and non-Asian patients received a median of 164 and 106 days of motesanib, respectively, versus 125 and 126 days of placebo. In Asian patients, median daily dose of motesanib was 121.6 mg compared with 125.0 mg in the non-Asian population. Median follow-up was 63 weeks.

survival outcomes

In Asian patients, treatment with motesanib plus C/P was associated with improved OS (median 20.9 versus 14.5 months [$P = 0.0223$]; Figure 1A) and PFS (7.0 versus 5.3 months [$P = 0.0004$]; Figure 1C) compared with placebo plus C/P. No difference between arms was observed in non-Asian patients for OS (Figure 1B) or PFS (Figure 1D).

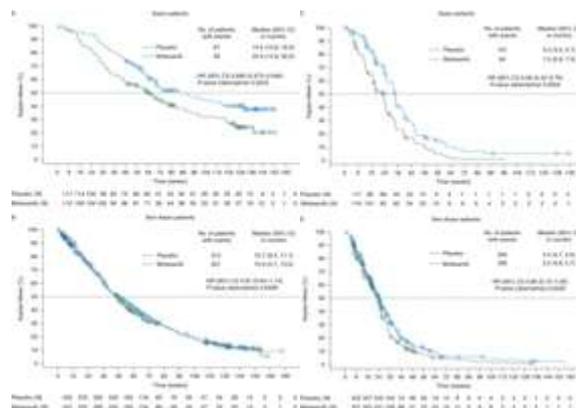


Figure 1.

Overall (A and B) and progression-free (C and D) survival.

response

All 227 Asian patients were assessable for response by modified RECIST (Table 2). In Asian patients, the ORR was 62% for motesanib plus C/P and 27% for placebo plus C/P ($P < 0.0001$). The difference in ORR between treatment arms was more evident in Asian than non-Asian patients.

Median duration of response among responders in the Asian population was 5.8 months for motesanib plus C/P and 4.4 months for placebo plus C/P.

Table 2.

Overall response by RECIST

adverse events

The safety analysis included 222 Asian patients compared with 850 non-Asian patients (Table 3). Motesanib/placebo-related AEs were more common in the Asian subgroup, compared with the non-Asian subgroup. Motesanib treatment was discontinued due to AEs in 26% of Asian and 32% of non-Asian patients. The frequency of motesanib/placebo-related serious AEs appeared similar between the Asian and non-Asian patients; however, more treatment-emergent grade 5 AEs were reported in the non-Asian patients compared with the Asian patients.

Table 3.

Safety overview in Asian and non-Asian patients

The most common treatment-emergent AEs in the Asian subgroup are shown in Table 4. Neutropenia (44% versus 28%), hypertension (51% versus 9%), thrombocytopenia (21% versus 15%), diarrhea (63% versus 33%), and vomiting (38% versus 30%) occurred more frequently in the motesanib plus C/P group compared with the placebo plus C/P group. In addition, 9% of patients in the motesanib group had gallbladder-related AEs (cholecystitis, cholecystitis acute, gallbladder enlargement, gallbladder edema) compared with 2% in the placebo group. Hypothyroidism was observed in 6% of patients receiving motesanib plus C/P versus <1% in those receiving placebo plus C/P. There was a low incidence of bleeding/thrombosis events, and no difference was observed between the two treatment arms.

Table 4.

Treatment-emergent AEs (any grade) in Asian patients ($\geq 10\%$ in either arm)

discussion

This subset analysis of MONET1 found that in Asian patients with advanced nonsquamous NSCLC, motesanib plus C/P treatment was associated with increased OS ($P < 0.05$), PFS ($P < 0.001$), and ORR ($P < 0.0001$) compared with C/P alone, whereas in the non-Asian subgroup there were no significant differences in OS and PFS, and a substantially smaller increase in ORR ($P = 0.0033$).

The reason for the differential effect of motesanib in the Asian subpopulation is unclear; however, a number of factors may be involved. There is evidence of epidemiologic, etiologic, and pharmacogenomic differences between Asian and Caucasian lung cancer patients [15], which may affect the impact of motesanib added to C/P. A higher rate of epidermal growth factor receptor (EGFR) mutations was found in Asian compared with Caucasian or non-Asian populations [15], and EGFR mutations have been associated with better outcomes following treatment with EGFR tyrosine kinase inhibitors, such as gefitinib [16]. Additionally, there is known interaction between the EGFR and VEGFR signaling pathways in NSCLC [17] with EGFR regulating VEGF production. Of the VEGF pathway inhibitors, currently bevacizumab plus C/P is the only combination to have demonstrated an OS benefit [6]. A subgroup analysis of bevacizumab plus chemotherapy in Asian patients suggested improved outcomes with addition of bevacizumab [18].

A differential rate of EGFR mutation in Asian versus non-Asian patients may have had an effect on the impact of motesanib in MONET1; however, EGFR mutational status was not determined and, therefore, no analyses were carried out that took this factor into account.

Similar results were observed in a recent phase III study of sunitinib plus erlotinib versus placebo plus erlotinib in patients with refractory NSCLC [19]. In the overall study population, OS and PFS were not improved in patients who received combination therapy compared with those who received erlotinib alone whereas an exploratory subgroup analysis in patients with Asian ethnicity showed significantly improved OS and lower PFS [19]. EGFR mutational status was not established in the majority of patients, and thus analyses were not presented to determine whether this factor was associated with the differential efficacy seen in Asian patients.

Another factor possibly affecting the findings from our subset analysis is the differential effectiveness of C/P seen in patients with advanced NSCLC in Japan and the USA, which may be associated with pharmacogenomic differences between these populations affecting paclitaxel disposition and DNA repair [20]. PFS and OS were longer, but rates of neutropenia were significantly higher with C/P in Japanese versus American patients, possibly associated with specific genetic differences between populations. Notably, the addition of motesanib to C/P has been associated with a moderate increase in paclitaxel exposure [21]. Enhancement of this effect due to specific pharmacogenomic factors in Asian patients may have contributed to differential activity and toxicity related to paclitaxel exposure in the present analysis.

Asian [13] and specifically Japanese [22] and Korean [23] ethnicity are independent favorable prognostic factors for OS compared with white/Caucasian ethnicity in patients with NSCLC. Associated with the pharmacogenetic and pharmacodynamic differences discussed above, there are differences in treatment guidelines for NSCLC between Asian and Western countries [15]. Based on market share, the most commonly used first-line regimen for advanced NSCLC in Japan is C/P, followed by gefitinib [15]; in Korea, the authors' experience suggests that gemcitabine/cisplatin is more widely used than C/P [24, 25]. Thus, the findings of this analysis, showing an association with improved outcomes with the addition of motesanib to C/P, may be of particular importance. The findings from other studies and analyses in Asian patients provide support for the activity and tolerability of angiogenesis inhibitors in combination with chemotherapy for first-line NSCLC [26–28].

Duration of motesanib treatment was longer (and continued for longer than placebo) in Asian than in non-Asian patients in MONET1. Motesanib plus C/P may be better tolerated by Asian versus non-Asian patients, supported by the higher rate of treatment discontinuations due to AEs in the latter population. Alternatively, responding patients may have stayed on therapy for longer as a consequence of the observed responses. The incidence of any-grade and grade ≥ 3 motesanib-related AEs appeared higher among Asian patients in the motesanib plus C/P arm, associated with this longer duration of therapy. In contrast, the rate of grade 5 AEs in the motesanib arm appeared higher in non-Asian patients, although this finding was also seen in the placebo arm.

A number of AEs were observed more frequently in the motesanib versus placebo arm, including hypertension, neutropenia, diarrhea, nausea, rash, and gallbladder-related AEs, consistent with previous studies of motesanib, and other angiogenesis inhibitors for NSCLC [11, 21, 27, 28]. There did not appear to be any excess of drug-related mortality in Asian patients versus non-Asian patients. Bleeding complications were low compared with those observed in a previous study of motesanib in NSCLC [11] and were consistent with studies of other angiogenesis inhibitors [26, 27]. In addition, bleeding was not increased in the motesanib plus C/P arm compared with placebo plus C/P.

In summary, in this exploratory subset analysis of Asian patients with nonsquamous NSCLC, treatment with motesanib plus C/P was associated with improved OS, PFS, and ORR compared

with placebo plus C/P. A phase III study in Asian patients is ongoing to confirm these findings (JPRN-JapicCTI-121887).

funding

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disclosure

KP is a consultant/has an advisory role for Amgen, Inc. KK (Taiho, Lilly, AstraZeneca, Daiichi-Sankyo) and GS (Lilly, AstraZeneca, Roche Diagnostics) have received honoraria. YI has received research funding from Amgen, Inc. and Takeda Bio Development Center Ltd. BY and YJH are employees and shareholders of Amgen, Inc. All remaining authors have declared no conflicts of interest.

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