Original Study

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Phase 1b/2 Randomized Study of MEDI-575 in Combination With Carboplatin Plus Paclitaxel Versus Carboplatin Plus Paclitaxel Alone in Adult Patients With Previously Untreated Advanced Non–Small-Cell Lung Cancer

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Abstract

Platelet-derived growth factor receptor blockade was explored as a potential mechanism to improve the efficacy of first-line therapy in patients with advanced non–small-cell lung cancer (NSCLC). In this phase 1b/2 study, therapy with MEDI-575, carboplatin, and paclitaxel (n = 53) did not improve progression-free survival versus carboplatin and paclitaxel alone (n = 46), and resulted in a higher rate of adverse events in patients with treatment-naive advanced NSCLC.

Introduction: Platinum doublet chemotherapy has represented the standard of care in advanced non–small-cell lung cancer for decades. Targeting platelet-derived growth factor receptors (PDGFR) is a potential mechanism to improve the efficacy of first-line therapy. This randomized phase 1b/2 trial investigated the addition of the anti-PDGFRα monoclonal antibody MEDI-575 to first-line carboplatin/paclitaxel (CP) chemotherapy. **Patients and Methods:** The phase 1b component was a dose-escalation study combining MEDI-575 with carboplatin area under the plasma concentration versus time curve 6 and paclitaxel 200 mg/m^2 (CPM), with the end point of identifying a recommended phase 2 dose. The phase 2 component randomized patients to CPM or CP, with primary end point of progression-free survival. Secondary end points included overall survival, overall response rate, and adverse event rates. **Results:** Overall, 99 patients were enrolled and received either CPM (n = 53; 4 phase 1b, 49 phase 2) or CP (n = 46). Demographics were as follows: 63/36 male/female, 78/21 aged ≤ 70/> 70 years; 37/62 squamous/nonsquamous, 42/53 Eastern Cooperative Oncology Group performance status 0/1. The phase 2 portion of the trial did not meet its primary end point: progression-free survival was shorter with CPM (4.6 vs. 5.5 months) than CP. No significant difference was seen in overall response rate (31.7% vs. 22.5%) or median overall survival (10.0 vs. 11.8 months). More serious adverse events were observed in patients receiving CPM (47% vs. 40%); in particular, 9 patients in the CPM group had significant gastrointestinal or respiratory adverse events (including abscess, perforation, and pneumothorax). **Conclusion:** The addition of MEDI-575 to CP chemotherapy as first-line treatment of advanced non–small-cell lung cancer did not improve efficacy and resulted in increased toxicity.

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Introduction

Advanced non–small-cell lung cancer (NSCLC) remains the most common single cause of cancer deaths in the world.[1] For select subgroups with actionable driver mutations or elevated programmed death ligand 1 expression, efficacious and well-tolerated options exist, including combinations of chemotherapy and immune checkpoint inhibitors; however, for those ineligible for targeted therapy, only systemic cytotoxic chemotherapy may offer improvements in overall survival (OS).[2]

Platelet-derived growth factors (PDGFs) are peptide growth factors that stimulate cellular growth, proliferation, and differentiation.[3] They exert their cellular effects through transmembrane receptor tyrosine kinases PDGF receptors (PDGFR)-α and -β. PDGFRα plays an important role in human carcinogenesis, both as a direct target on tumor cells and as a mediator of stromal support for cancer cell growth. Expression of PDGFRα has been observed in multiple solid tumors, including lung cancer.[4]

MEDI-575 is a human immunoglobulin G subclass 2 kappa antibody that selectively binds to PDGFRα.[5] MEDI-575 has demonstrated antitumor activity using preclinical NSCLC tumor models.[5] Furthermore, combination treatment studies demonstrated that treatment of tumor-bearing mice with MEDI-575 plus carboplatin/paclitaxel (CP) chemotherapy was better tolerated and resulted in improved antitumor activity than either regimen alone.[6]

Therefore, the purpose of this study was to investigate the safety and efficacy of the addition of MEDI-575 to CP as first-line treatment for patients with advanced NSCLC.

Patients and Methods

This phase 1b/2, multicenter, open-label study of MEDI-575 evaluated the dose, antitumor activity, safety, and pharmacology (pharmacokinetics [PK], immunogenicity, and biomarkers) of MEDI-575 administered in combination with CP in patients with previously untreated advanced NSCLC. This study had 2 components: dose determination (phase 1b) and randomization (phase 2). This study was conducted in compliance with the principles of the Declaration of Helsinki, and each participating center received ethics board approval before conduct of the study. All patients provided written informed consent before participation.

Treatment

The protocol called for a minimum of 3 and up to 12 patients to be treated as part of the "safety run-in" phase 1b with MEDI-575 25 mg/m^2 in combination with CP (carboplatin dosed to area under the plasma concentration vs. time curve 6 and paclitaxel 200 mg/m^2). Once the recommended phase 2 dose (RP2D) was achieved, the phase 2 trial would seek to enroll 112 additional patients to be randomized 1:1 to CP or CP in combination with MEDI-575 (CPM) at the RP2D. All drugs were administered intravenously once every 21 days for up to 6 cycles. Patients in the CPM arm could continue to receive maintenance MEDI-575 after completing 6 cycles of CPM.

Patients

Adults with treatment-naive advanced NSCLC, good performance status (Eastern Cooperative Oncology Group performance status [ECOG PS], 0-1), adequate organ function, and measurable disease were eligible. Key eligibility criteria are provided in Supplemental Table 1 in the online version. Disease progression was determined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patients were enrolled from centers in North America (NA), the European Union (EU), and Japan. The intent-to-treat populations included all NA/EU patients who entered the phase 1b trial or who were randomized into the phase 2 trial, and all Japanese patients were randomized into the phase 2 trial. Efficacy is reported for the NA/EU cohort randomized into the phase 2 trial. Safety is reported for all patients who received any protocol-defined therapy (phase 1b and phase 2; NA/EU and Japanese cohorts). The NA/EU patients and Japanese patients were considered as separate cohorts.

Study End Points and Statistical Methods

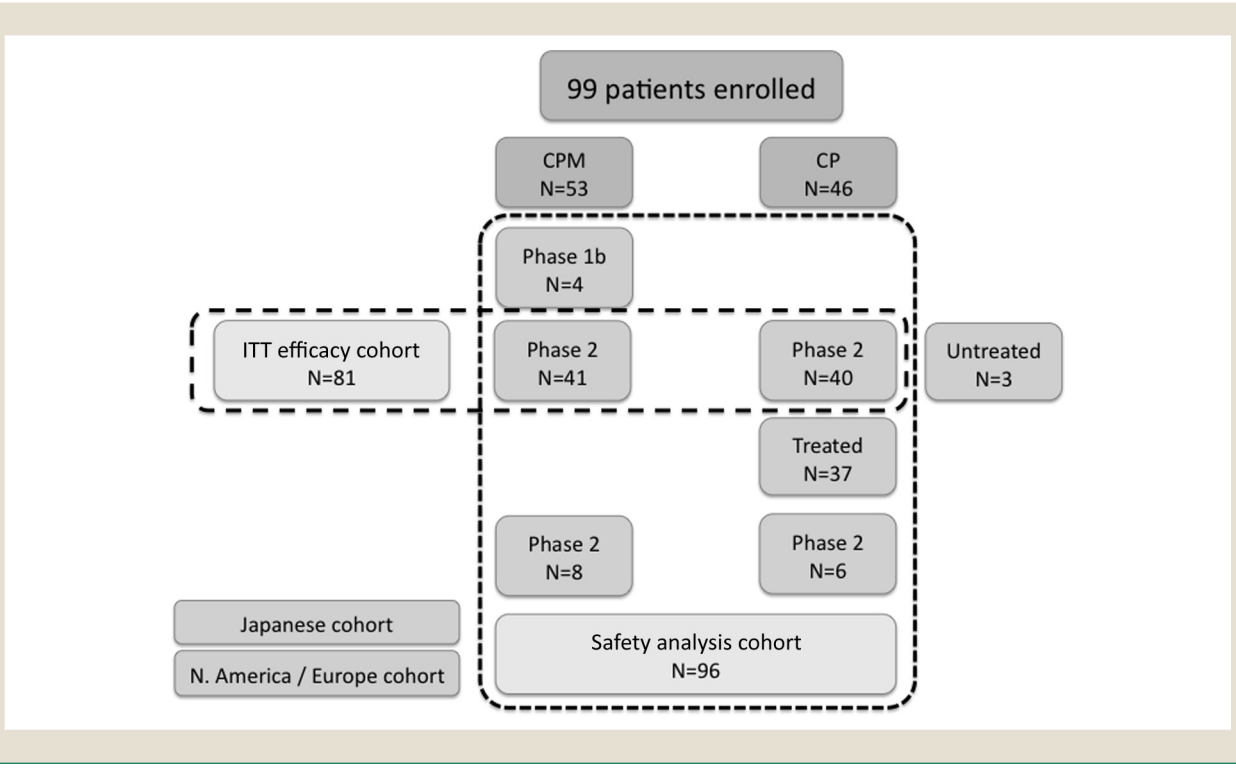
The primary end point of the phase 1b component was to identify the RP2D. The primary end point of the phase 2 component was progression-free survival (PFS). Secondary end points included OS, overall response rate, and safety and tolerability, including adverse events (AEs). In the NA/EU cohort, randomization was stratified according to disease stage (IIIB vs. IV) and by ECOG PS (0 vs. 1). In the Japanese cohort, randomization was not stratified.

PK, immunogenicity, and pharmacodynamic (platelet-derived growth factor [PDGF]-AA ligand) samples were collected at prespecified time points after dose administration; PK and antidrug antibody (ADA) data were collected from the phase 1b and phase 2 CPM groups, and pharmacodynamic data were collected in the phase 1b and phase 2 portions. A competitive electrochemiluminescence PK assay using a Meso Scale Discovery (Meso Scale Diagnostics, Rockville, MD) platform was used for quantitative determination of MEDI-575 in human serum and for the qualitative determination of ADAs against MEDI-575 in human serum. The PK parameters after the first and steady-state doses were estimated using noncompartmental analysis using Phoenix WinNonlin v.6.3 (Certara, Princeton, NJ). A commercial immunoassay kit (Milliplex MAP Human Cytokine/Chemokine Kit; Millipore, Billerica, MA),validated for the measurement of the PDGF-AA protein, and the Luminex xMAP technology platform (Luminex, Austin, TX) were used to quantitate the relative levels of PDGF-AA in plasma.

PDGFRα protein expression was measured using immunohistochemistry on formalin-fixed, paraffin-embedded tissue sections after heat-induced epitope retrieval using commercially available rabbit anti-PDGFRα polyclonal antibody according to the manufacturer's recommendations. Hematoxylin and eosin–stained sections were analyzed for quality and presence of tumor. Immunohistochemical staining was analyzed for staining intensity, localization, and frequency.

PFS in the CP arm was expected to be 4.5 months. The sample size was calculated on the basis of an expected PFS in the CPM arm of 7.5 months, corresponding to a hazard ratio (HR) of 0.60. With a planned 12-month accrual and minimum follow-up of 8 months, an estimated 96 patients for the NA/EU cohort were needed to observe 69 PFS events by the end of the minimum follow-up

Figure 1 Study Flow Diagram for Patient Groups



Abbreviations: CP = carboplatin/paclitaxel chemotherapy; CPM = carboplatin/paclitaxel in combination with MEDI-575.

Table 1 Demographic and Baseline Patient Characteristics

Characteristic	CPM (Phase 1b) (N = 4)	CPM (Phase 2) (N = 49)	CP (N = 46)
Sex			
Male	3	33	27
Female	1	16	19
Age			
≤ 70 years	3	35	41
> 70 years	1	14	5
Histology			
Squamous	1	18	18
Nonsquamous	3	31	28
Stage			
IIIB	2	5	3
IV	2	44	42
ECOG PS[a]			
0	3	17	22
1	1	31	21
2+	0	1	0
Unknown	0	0	3

Abbreviations: CP = carboplatin/paclitaxel chemotherapy; CPM = carboplatin/paclitaxel in combination with MEDI-575; ECOG PS = Eastern Cooperative Oncology Group performance score.
[a]One patient had ECOG PS 0 at enrollment but had ECOG PS 2 before cycle 1, day 1; 3 patients with unknown ECOG PS had ECOG PS 0 or 1 at enrollment, but values were unavailable before cycle 1, day 1.

period. The Kaplan-Meier method was used to evaluate PFS, which was then compared with a 2-sided, stratified log-rank test at the $\alpha = 0.2$ significance level between study arms.

Results

Ninety-nine patients were enrolled between December 2010 and July 2012: 4 in the phase 1b and 95 in the phase 2 trial parts. The NA/EU centers enrolled 85 patients; 14 were enrolled in Japan. In total, 53 patients were randomized to CPM (4 in phase 1b and 49 in phase 2) and 46 patients to CP (Figure 1). The treatment arms were well balanced for sex, ECOG PS, histology, and disease stage (Table 1). More elderly patients were included in the CPM group (28% vs. 11% aged ≥ 70 years).

Of the 99 enrolled patients, 3 received no treatment (all in the CP arm). Among the remaining 96 patients, 53 patients received CPM for a median of 4 cycles, whereas 43 patients in the CP group received a median of 6 cycles. The study was stopped early on the recommendation of the Data Safety Monitoring Committee owing to a lack of efficacy and safety concerns.

Efficacy

Efficacy reports are based on 81 patients randomized to the phase 2 portion from the NA/EU cohort. The overall response rate in the CPM arm was 31.7%, compared to 22.5% in the CP arm ($P = .49$; Table 2). The median time to response was 1.4 months in both groups. Patients in the CPM arm had a shorter PFS of 4.6 months, compared to 5.5 months in the CP arm, representing an HR for progression in the CPM group of 2.20 (95% confidence interval

Table 2 Efficacy Outcomes in ITT Population in Phase 2 Component in North American/European Cohort (N = 81)

Outcome	CPM (N = 41)	CP (N = 40)	Hazard Ratio (95% CI)	*P*
ORR	31.7%	22.5%	NA	.49
PFS, months (95% CI)	4.6 (3.9-5.5)	5.5 (4.7-6.5)	2.205 (1.1-4.5)	.03
DoR, months (95% CI)	4.2 (3.7-5.0)	3.3 (1.3-4.0)	NA	Underpowered to assess
TTP, months (95% CI)	4.6 (3.9-6.4)	6.4 (4.9-10.3)	3.017 (1.2-7.4)	Underpowered to assess
OS, months (95% CI)	10.0 (6.4-11.6)	11.8 (8.2—NC)	1.315 (0.7-2.4)	Underpowered to assess

Abbreviations: CI = confidence interval; CP = carboplatin/paclitaxel chemotherapy; CPM = carboplatin/paclitaxel in combination with MEDI-575; DoR = duration of response; ITT = intent to treat; NA = not available; NC = not calculable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TTP = time to progression.

[CI], 1.1-4.5; $P = .03$). Median OS in the CPM cohort was 10.0 months versus 11.8 months in the CP arm (HR = 1.31; 95% CI, 0.7-2.4). Kaplan-Meier curves for PFS and OS are shown in Figure 2A and B.

In subgroup analysis, when comparing populations with squamous and nonsquamous disease, CPM did not offer a differential benefit in either group. In patients with nonsquamous histology, PFS was 4.4 months in the CPM arm versus 4.8 months in the CP group (HR = 1.9; 95% CI, 0.8-4.6). In patients with disease of squamous histology, PFS was 5.5 months in the CPM arm versus 5.6 months in the CP arm (HR = 1.9; 95% CI, 0.5-7.7 months).

Safety

Safety data were based on all 96 patients who received any study treatment. All 53 CPM patients and 42 of 43 CP patients reported at least one AE (Table 3). Serious AEs (grade 3/4) were more common in patients receiving CPM than CP (47% vs. 39%). The frequency of grade 3/4 AEs leading to discontinuation of study drug was also higher in the CPM than the CP cohort (32% vs. 19%). The most common AEs leading to discontinuation were peripheral neuropathy (3.8% with CPM; 4.7% with CP) and peripheral sensory neuropathy (5.7% with CPM; 2.3% with CP).

Notably, in the CPM group only, 6 patients experienced serious gastrointestinal AEs, including bleeding, abscess, and bowel perforation. Three additional patients in the CPM group had significant respiratory AEs of pneumothorax or abscess. None of these 9 events occurred during phase 1b. Owing to the nature of these AEs in the CPM group, together with the overall risk—benefit analysis, the study was terminated early, based on the Data Safety Monitoring Committee's recommendation.

PDGFRα Expression

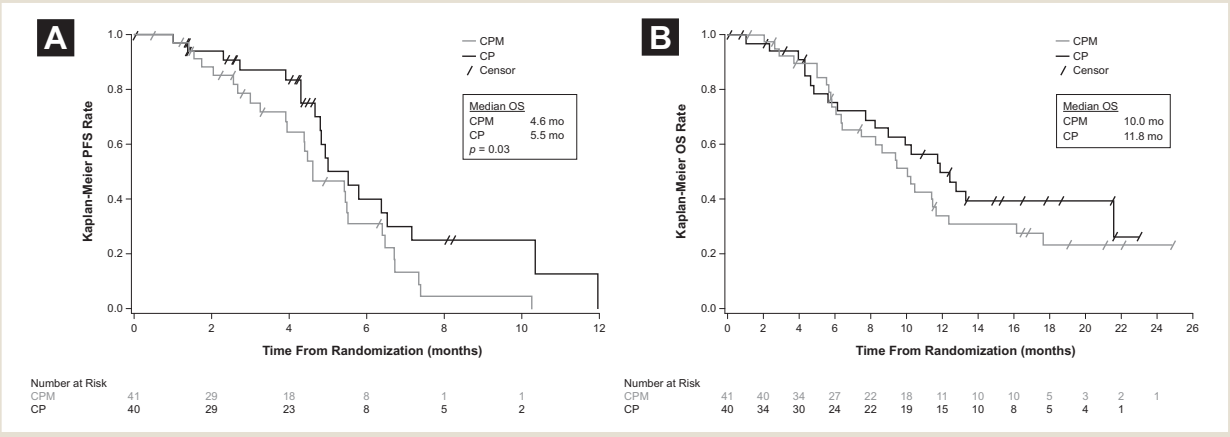
Tumor samples were available for testing from 63 patients (35 CPM and 28 CP). Positive PDGFRα in tumor cells was observed in 9 (14%) of 63 cases and in tumor-associated stromal cells in 29 (46%) of 63 cases. Correlation analysis of response and PDGFRα expression, regardless of localization of staining, was not performed.

PK, Pharmacodynamics, and ADAs

The PK of MEDI-575 declined in a biphasic manner consistent with the receptor-mediated clearance of antibodies after the intravenous dose of 25 mg/kg every 3 weeks. An accumulation in PK exposure of approximately 1.16-fold was observed during the randomized phase 2 portion.

Consistent with the MEDI-575 mechanism of action, an increase in PDGF-AA ligand was observed from baseline to day 63 after MEDI-575 in the phase 2 CPM group, and a decrease in PDGF-AA ligand level was observed from baseline to day 63 in the phase 2 CP group.

Figure 2 PFS (A) and OS (B) in ITT Population. Population Comprised Phase 2 of North American/European Cohort



Abbreviations: CP = carboplatin/paclitaxel chemotherapy; CPM = carboplatin/paclitaxel in combination with MEDI-575; ITT = intent to treat; OS = overall survival; PFS = progression-free survival.

Table 3 Select Adverse Events

Parameter	CPM (N = 53)	CP (N = 43)
AE		
Any AE	53 (100%)	42 (98%)
Any serious AE	25 (47%)	17 (40%)
Serious AE leading to hospitalization	21 (40%)	16 (37%)
Discontinued therapy due to AE	17 (32%)	8 (19%)
Grade 3/4 Nonhematologic Events		
Fatigue	9 (17.0)	2 (4.7)
Peripheral neuropathy	6 (11.3)	1 (2.3)
Dehydration	5 (9.4)	2 (4.7)
Diarrhea	5 (9.4)	1 (2.3)
Decreased appetite	4 (7.5)	2 (4.7)
Hyponatremia	4 (7.5)	1 (2.3)
Hypotension	4 (7.5)	0
Vomiting	2 (3.8)	0
Hypomagnesemia	2 (3.8)	0
Nausea	1 (1.9)	1 (2.3)
Grade 3/4 Hematologic Events		
Neutropenia	10 (18.9)	4 (9.3)
Febrile neutropenia	6 (11.3)	3 (7.0)
Decreased neutrophil count	6 (11.3)	1 (2.3)
Anemia	7 (13.2)	6 (14.0)
Thrombocytopenia	5 (9.4)	0
Other Significant AEs		
Gastrointestinal bleeding	2 (3.8)	0
Diverticular abscess	2 (3.8)	0
Acute diverticulitis	1 (1.9)	0
Colonic perforation	1 (1.9)	0

Includes all treated patients, including for CPM 4 in phase 1b and 49 in phase 2; in CP, 43 in phase 2. Three patients randomized to CP were not treated and were not included in safety analysis.
Abbreviations: AE = adverse event; CP = carboplatin/paclitaxel chemotherapy; CPM = carboplatin/paclitaxel in combination with MEDI-575.

Thirteen patients (26.5%) in the phase 2 CPM group developed ADA-positive samples, and 4 of these patients had their PK impacted by ADAs.

Discussion

We here report a trial with negative findings. It failed to meet the primary end point of improved PFS in patients with NSCLC. Among 99 patients enrolled and 96 treated, the addition of MEDI-575 to standard CP chemotherapy did not improve PFS. Indeed, PFS was statistically significantly superior in the control (CP) arm. Further, there was an excess of toxicity in the CPM arm, so MEDI-575 is not being studied further for lung cancer or other malignancies.

Are there reasons for the failure of the study, and could correlative markers have identified patients more likely to benefit? Certainly the observed response rate was numerically higher in the CPM cohort, but the median number of cycles was lower in this arm. Therefore, it is possible that there may be efficacy to this approach of targeting PDGFR, although MEDI-575 may not be the optimal drug to use because of the higher rates of serious AEs. It should also be noted that this study took place before the availability of immune checkpoint inhibitor therapies.

MEDI-575 has also been investigated in a phase 2 second-line trial of patients with recurrent glioblastoma, with similarly disappointing results. Of 56 enrolled patients, no complete or partial responses were observed.[7] Indeed, in a phase 1 dose-escalation study in Japanese patients with advanced solid tumors (n = 22), among 20 evaluable patients treated with MEDI-575, no complete or partial responses were observed.[8]

In terms of other anti-PDGFR drugs, olaratumab is an anti-PDGFRα monoclonal antibody currently approved in combination with doxorubicin for doxorubicin-sensitive soft-tissue sarcoma.[9] In a randomized phase 2 study of patients with unresectable or metastatic soft-tissue sarcoma, olaratumab plus doxorubicin improved PFS versus doxorubicin alone (6.6 months vs. 4.1 months, respectively) and improved OS duration (26.5 months vs. 14.7 months, respectively).[10] In addition, crenolanib besylate was active in a phase 1 study of patients with gastrointestinal stromal tumors.[11] However, crenolanib has specific activity when the PDGFRα *D842V* mutation is present, with an observed clinical benefit rate of 31%. Mutation screening may result in better patient selection but unfortunately was not a part of the current study.

Conclusion

MEDI-575 treatment did not improve PFS when added to CP chemotherapy in patients with previously untreated advanced NSCLC, and the combination was not well tolerated.

Clinical Practice Points

- PDGFRα is involved in human carcinogenesis, and expression of PDGFRα has been observed in lung cancer.
- MEDI-575, a monoclonal antibody that selectively binds to PDGFRα and inhibits PDGF ligand binding and subsequent downstream signaling, showed antitumor activity in preclinical NSCLC tumor models.
- Findings from this phase 1b/2 study conducted in patients with previously untreated advanced NSCLC showed that MEDI-575 did not improve PFS when added to paclitaxel/carboplatin chemotherapy, and the combination was not well tolerated.
- MEDI-575 is not being studied further for lung cancer or other malignancies; however, research is ongoing with other agents that target PDGFRα.

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Disclosure

P.W.-P. has participated in advisory boards for AstraZeneca. S.G. has participated in advisory boards for AstraZeneca/MedImmune. T.T. has received honoraria and study grants from AstraZeneca KK, Eli Lilly Japan KK, MSD K.K., ONO Pharmaceutical Co, Pfizer Japan, Taiho Pharmaceutical Co, honoraria from Boehringer

Ingelheim Japan, and study grants from Takeda Pharmaceutical Co., Ltd. X.L. and M.D. are employees of MedImmune and own stock in AstraZeneca. G.B. has served as a consultant for Abbvie, Adicet, Amgen, Ariad, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Clovis, Genentech, Merck, Novartis, and Xcovery, and he or his institution has received study grants from Adaptimmune, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Exelixis, Genentech, GlaxoSmithKline, Immatics, Incyte, Kite, MacroGenics, Merck, Novartis, Roche, Torque, and Xcovery.

Supplemental Data

A supplemental table accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.11.012.

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Supplemental Table 1 Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• Aged 18 years or older (20 years or older for subjects in Japanese cohort) at time of screening.	• Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic, or hormone therapy for treatment of cancer.
• Histologically confirmed inoperable stage IIIB or stage IV squamous-cell NSCLC according to American Joint Committee on Cancer Tumor Node Metastases staging system, 7th ed.	• Previous monoclonal antibody treatment specifically directed against PDGF or PDGF receptors.
• Eastern Cooperative Oncology Group performance status of 0 or 1.	• Receipt of any previous systemic anticancer therapies for advanced or metastatic disease including chemotherapy regimens, hormone therapy, TKIs, radiotherapy, investigational agents, or any biological or immunologic-based therapies (including, but not limited to, monoclonal antibody therapy such as bevacizumab).
• Life expectancy of $\geq$ 3 months.	• Previous adjuvant/neoadjuvant radiotherapy or chemotherapy for treatment of previous nonmetastatic disease is allowed provided that 6 months have elapsed from end of such therapies to time of enrollment.
• Prothrombin time elevation grade 2 or less by National Cancer Institute Common Toxicity Criteria for Adverse Events criteria (version 4.0) acceptable for patients receiving anticoagulant therapy.	• New York Heart Association class 2 or higher congestive heart failure.

• Adequate hematologic function, defined as:
  • Hemoglobin level $\geq$ 9 g/dL.
  • Absolute neutrophil count $\geq$ 1500/mm^3.
  • Platelet count $\geq$ 100,000/mm^3.
	• History of myocardial infarction, unstable angina, transient ischemic attack, or stroke within 6 months before enrollment.
	• History of other invasive malignancy within 5 years except for cervical carcinoma-in-situ, nonmelanomatous carcinoma of skin, or ductal carcinoma-in-situ of breast that have been surgically cured.
	• Evidence of active infection requiring use of systemic antimicrobial treatment within 72 hours before initial treatment with MEDI-575.
	• Use of immunosuppressive medication (inhaled and topical corticosteroids are permitted) within 7 days before enrollment.

• Adequate organ function, defined as:
  • Aspartate aminotransferase and alanine aminotransferase $\leq 5\times$ institutional ULN for cases involving liver metastasis, and $\leq 2\times$ institutional ULN for all other cases.
  • Bilirubin level $\leq 1.5\times$ ULN, except in case of patients with documented or suspected Gilbert disease, $\leq 5\times$ ULN.
  • Calculated creatinine clearance $\geq$ 50 mL/min as determined by Cockroft-Gault equation.
	• Systemic immunosuppressive steroid therapy. Patients may receive replacement doses of steroids (defined as $\leq$ 30 mg per day hydrocortisone or equivalent) if receiving a stable dose for $\geq$ 2 weeks before enrollment.
	• History of active HIV or active hepatitis B virus or hepatitis C virus infection.

• Patients must have $\geq$ 1 lesion that is measurable using RECIST v1.1.	
• Normal potassium level at baseline.	
• Normal magnesium level at baseline.	

Known brain metastases was an exclusion criterion until an amendment to the protocol in February 2012.
Abbreviations: NSCLC = non–small-cell lung cancer; PDGF = platelet-derived growth factor; ULN = upper limit of normal; RECIST = Response Evaluation Criteria in Solid Tumors.