Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial


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Study Presentation

This study was partly presented as a Poster Discussion of Metastatic NSCLC session in the 2016 ASCO annual meeting (3–7 June 2016, Chicago, IL, USA).

ClinicalTrials.gov number: NCT01823068

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Background:

Chromosomal rearrangements involving RET, which are found in about 1% of non-small cell lung cancer (NSCLC), define a unique molecular subset. We performed this study to examine the efficacy and safety of vandetanib 300 mg daily in this patient population.

Patients and methods:

This study was a multi-center, open-label, phase II clinical trial. Patients were enrolled if they had metastatic or recurrent NSCLC with a RET rearrangement, which was confirmed by fluorescence in situ hybridization, had progressive disease against platinum-based doublet chemotherapy, and had a performance status of 0–2. The primary endpoint was the objective response rate.

Results:

A total of 18 patients were enrolled in this study between July 2013 and October 2015. Patients were aged 35–71 years; three had a performance status of 2, and the majority were a heavily pretreated population (≥ two different previous chemotherapy regimens in 72% of the patients). Among the 17 evaluable patients, three had a partial response (objective response rate = 18%) and eight had a stable disease (disease control rate = 65%). Among these patients, the partial response or disease stabilization was durable for more than 6 months in eight patients. Vandetanib also showed a progression-free survival of 4.5 months, and an overall survival of 11.6 months during a median follow-up duration of 14 months. The safety profile was comparable with previous studies of vandetanib. Most vandetanib-related adverse events were mild with prevalent hypertension and rash (in >70% of patients). Grade 3 toxicity included hypertension (n = 3), QT prolongation (2), and elevation of aminotransferases (1), and as a consequence the dose was reduced in four patients. There were no adverse events associated with grade 4 or 5 toxicity.

Conclusion:

Vandetanib is moderately active in pretreated patients with advanced NSCLC-harboring RET rearrangements.

Key words: vandetanib, RET rearrangement, non-small cell lung cancer

Introduction

Non-small cell lung cancer (NSCLC) is frequently driven by genomic alterations involving canonical oncogenes including EGF, KRAS, ALK, BRAF, and ROS1 [1]. Cancer cells with these alterations exhibit exquisite dependence on those oncogenic signaling pathways for the maintenance of their malignant phenotype, the inhibition of which could result in a marked tumor response [2].
Specific inhibition of those oncogenes by small molecular inhibitors have shown clinical efficacy and transformed the treatment landscape of NSCLC in the past decade [3, 4].

Genomic rearrangement involving the rearranged during transfection (RET) proto-oncogene in lung cancer was first discovered in a young, never-smoking male patient with adenocarcinoma in 2011 [5]. RET encodes a receptor tyrosine kinase that is essential for the developmental process of several tissue types including the neural crest, kidneys, and germ cells [6]. RET is located near the centromere of chromosome 10q, and most frequently rearranged by pericentromeric inversion resulting in the fusion gene KIF5B – RET [7–9]. Other fusion counterparts have been identified including CCDC6, NCOA4, and TRIM33; all of them have a dimerization domain that could facilitate ligand-independent activation of the RET kinase [10]. RET rearrangements were found in about 1% of NSCLCs and were more frequent in young, never-smoking patients, and most cases were adenocarcinomas [11, 12].

Multiple lines of evidence indicate that RET rearrangements are likely driver oncogenic events in NSCLC. First, they are mutually exclusive to other driver genomic alterations including activating mutations of EGFR and KRAS, and ALK rearrangements [1, 13]. Secondly, functional experiments confirmed that RET rearrangements have transforming activity and confer in vitro and in vivo sensitivity to various RET kinase inhibitors [7–9]. Finally, an early finding of a phase II clinical trial (NCT01639508) indicated the promising activity of cabozantinib, a multi-tyrosine kinase inhibitor that has activity on RET kinase in patients with advanced NSCLC with RET rearrangements [14]. To examine the efficacy of RET kinase inhibition in this population, we performed a proof-of-concept, phase II clinical trial of vandetanib (NCT01823068), a multi-tyrosine kinase inhibitor that has activity on VEGFRs, EGFR, and RET in pretreated patients with advanced NSCLC with RET rearrangements.

Materials and methods

Study design

This study was an investigator-initiated, multi-center, open-label, phase II clinical trial examining the efficacy and safety of vandetanib in a molecularly defined patient population. The primary endpoint was the objective response rate (ORR), and the secondary endpoints were the progression-free survival (PFS), disease control rate (DCR) defined as the combined fraction of stable disease, partial response and complete response, overall survival (OS), and safety. The protocol of this study (supplementary Text 1, available at Annals of Oncology online) was reviewed and approved by all institutional review boards of participating institutions. This study was conducted following the Declaration of Helsinki from the World Medical Association, and all participating patients provided written informed consent. This study was supported by AstraZeneca and Sanofi Genzyme.

Patient eligibility and treatment

Eligible patients had histologically confirmed, metastatic or recurrent NSCLC with a RET rearrangement, and had evidence of objective disease progression based upon platinum-based doublet chemotherapy. Other eligibility criteria included an age of 18 years or older, a performance status of 0 – 2 by the Eastern Cooperative Oncology Group (ECOG) scale, appropriate organ function that was addressed by laboratory studies, and measurable disease that was documented by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients were excluded if they had unstable brain metastasis or spinal cord compression requiring treatment, had major surgery or received chemotherapy within 28 days before the initiation of the study drug, had significant cardiovascular comorbidity or interstitial lung disease, and had a corrected QT interval greater than 480 ms on the screening electrocardiography.

Participating patients received vandetanib 300 mg once daily, and this treatment was continued until objective disease progression, deterioration of the patient’s clinical course, unacceptable toxicity, or death.

Study assessments

Patient screening was performed 2 weeks before the initiation of the study treatment. To enrich patients with RET rearrangements, we recruited patients with negative results from studies examining the presence of other oncogenic drivers, including EGFR mutations and ALK rearrangements. For some patients, the status of the KRAS mutation, BRAF mutation, ROS1 rearrangement, HER2 amplification, and MET amplification were also examined; only patients with negative results from these tests were recruited. At screening, patients underwent molecular testing for a diagnosis of RET rearrangement using their archival tumor tissues. In patients without or insufficient tumor tissue for molecular diagnosis, fresh tumor tissue was obtained by biopsy. RET rearrangements were detected by break-apart fluorescence in situ hybridization (FISH) by a previously described method [15] and further confirmed by immunohistochemistry, RT-PCR, or targeted deep sequencing-based panel assay (CancerSCAN™, Samsung Genome Institute) in cases with available study materials. During screening, patients also underwent 12-lead electrocardiography, chest X-ray, chest computed tomography, and other imaging studies if needed. After initiation of the study treatment, tumor assessment was performed every 8 weeks by the investigators. In patients without disease progression after one year of vandetanib treatment, the tumor assessment was continued every 12 weeks for 1 year, and then every 24 weeks for another 1 year. Adverse events were regularly monitored until 28 days after the final administration of vandetanib. All adverse events were documented in detail by the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Statistical analysis

We used Simon’s optimal two-stage design for phase II clinical trials to calculate the number of patients for this trial [16]. The clinically uninteresting response rate, p0, was set at 0.05, and the sufficiently promising response rate, p1, was set at 0.35. Alpha and beta values were set at 0.05 and 0.10, respectively. If one or more objective responses were observed among the first six evaluable patients, 11 more patients had to be recruited for the study. Vandetanib was considered of interest if three or more objective responses were observed out of 17 evaluable patients. The median durations of PFS, OS and duration of follow-up were calculated with the Kaplan–Meier method, and their 95% confidence intervals were calculated using the log-log transform method. The date of the data cutoff was 1 June 2016.

Results

Patient population and molecular diagnosis

From July 2013 to October 2015, a total of 315 patients with NSCLC without EGFR mutation or ALK rearrangement were recruited for eligibility screening of this study (supplementary Figure 1, available at Annals of Oncology online). A break-apart signal indicating a RET rearrangement was positive for 26 (8.3%)
patients out of 306 patients with valid FISH results. Among them, 18 patients were enrolled in this study (Table 1). The median age was 56 years. A third of the patients were female, and 61% were never smokers. Adenocarcinoma was the predominant histologic type in the study patients (supplementary Figure 2A, available at Annals of Oncology online). Two or more lines of cytotoxic chemotherapy had been performed before the initiation of vandetanib in 72% of the patients. Four patients received an anti-angiogenic agent before the initiation of the study treatment (three with bevacizumab and one with motesanib).

The presence of a RET rearrangement was further validated in 10 out of 18 patients by immunohistochemistry (n = 5), targeted deep sequencing (n = 4), and RT-PCR (n = 4; supplementary Figure 2B–D, available at Annals of Oncology online). Sequencing-based methods provided information on the fusion counterparts in eight patients: five patients had RET fused with KIF5B, two patients with CCDC6, and in one patient with a novel counterpart, MYO5C (structure of this rearrangement is depicted in supplementary Figure 2E, available at Annals of Oncology online).

### Efficacy

Among the 18 patients, 17 were evaluable for their treatment responses. Three (18%) exhibited a partial response (PR), and eight (47%) had a stable disease (SD) for their best responses (Figure 1); these responses were durable for more than 6 months in eight (47%) patients. Immediate disease progression was identified in six (35%) patients. Tumor shrinkage, which was observed in three patients with PR, was moderate representing a 38%, 33%, and 31% decrease in tumor size in each case. The ORR was 18%, and the DCR was 65%.

The median PFS was 4.5 months (Figure 2); three patients were censored because they were on the treatment and undergoing regular follow-up for disease progression at the data cut-off. All other patients whose disease have progressed to vandetanib were related to the progression of extracranial lesions. The median OS was 11.6 months (Figure 2) with a median follow-up of 14 months. The 1-year overall survival rate was 33%, and 10 (56%) out of 18 patients had died at the data cut-off.

Among the eight patients with a known rearrangement counterpart, no objective response was observed among patients with the KIF5B – RET fusion. Two of them presented with SD. Two patients with the CCDC6 – RET fusion showed contrasting responses. Both patients received vandetanib for their second-line treatment after the failure of the platinum-doublet regimens; one patient exhibited a PR; however, the other patient showed a mixed tumor response with stabilized intrathoracic lesions but an early progression of liver metastasis. A patient with MYO5C – RET showed a SD, and the response was durable for 8 months.

### Safety

The toxicity profile of vandetanib in this study was similar to that of previously published clinical trials with a higher incidence of rash (72% versus 42 – 45% in previous studies [17, 18]) and a lower incidence of nausea (6% versus 23 – 33%). Hypertension (n = 16; 89%), rash (n = 13, 72%), diarrhea (n = 8, 44%), and acne (n = 5, 28%) were the most frequent adverse events in the study patients (Table 2). Five patients experienced adverse events of grade 3: hypertension (n = 3, 17%), asymptomatic QTc prolongation in the electrocardiography (n = 2, 11%), and elevated serum level of aminotransferases (n = 1, 6%). Among them, four patients underwent dose modification to 200 mg daily (n = 3) and was further reduced to 100 mg daily (n = 1). A patient had died with rapid deterioration of her general medical condition just four days after the initiation of vandetanib. Her ECOG performance status was 2 at the screening examination but worsened by the time of the vandetanib treatment. This event was likely attributable to disease progression, rather than a drug-related adverse event. No adverse events associated with grade 4 or 5 toxicity were identified.

### Discussion

In this study, vandetanib showed moderate efficacy in pretreated patients with advanced NSCLC with RET rearrangements. Although the pre-specified alternative hypothesis of this study was fulfilled, the ORR of 18% and the PFS of 4.5 months were much lower than what have been reported for small molecular inhibitors in pretreated patients with typical oncogene-driven NSCLCs, such as EGFR inhibitors in EGFR-mutant NSCLCs (ORR = 50 – 73%; PFS = 7 months) [19] and ALK inhibitors in ALK-rearranged NSCLCs (ORR = 65%; PFS = 7.7 months) [4].
The efficacy outcomes of our study is comparable to recent results of another ongoing phase II study of vandetanib with similar design ($n = 17$; ORR = 53%; PFS = 4.7 months) [20] and with a retrospective analysis of a global registry study ($n = 11$ for vandetanib subgroup; ORR = 18%; PFS = 2.9 months) [21] indicating that our study well represents the biology of RET-rearranged advanced NSCLCs. The reason for the low efficacy of vandetanib in RET-rearranged NSCLCs remains unclear. As one possible explanation, vandetanib might be suboptimal for RET inhibition. Previous in vitro experiments indicated that the IC$_{50}$ values of vandetanib for the inhibition of RET kinase were higher than other multi-tyrosine kinase inhibitors including cabozantinib or ponatinib [22, 23]. In fact, a recent result of a phase II study of cabozantinib, which is known to have lower IC$_{50}$ values on RET kinase compared with vandetanib, in patients with RET-rearranged NSCLCs reported an ORR of 28% and a PFS of 7 months.

Figure 1. Treatment responses of the study patients.

(A) Waterfall plot indicates the change in tumor size measured by RECIST version 1.1 for 17 evaluable patients. Dashed line shows a 30% decrease in tumor size. The numbers above the horizontal axis indicates time to progression (in months) in each sample. The counterpart genes of RET rearrangements in available cases and histologic subtypes were described below the plot. ADC, adenocarcinoma; LCC, large cell carcinoma; SqCC, squamous cell carcinoma. (B) Plain chest radiography and computed tomography of a patient reveal that multiple lung masses were decreased in size after 8 weeks of treatment with vandetanib.
The PFS of that study appeared to be greater than what was reported in our study, although the ORR was not as great as what was reported for EGFR or ALK inhibitors in their relevant molecularly defined patient subsets. Furthermore, studies of currently available RET inhibitors commonly raised safety concerns; dose-limiting toxicities related with the VEGFR family and EGFR were prominent in studies using vandetanib (>80% of patients experienced hypertension, and >60% rash; Seto et al. [20] and our study) and cabozantinib (the dose was reduced at least once in 12 out of 20 patients [24]). We think that it is questionable whether the efficacy of vandetanib in this study justifies the safety profile. To address more explicitly whether RET inhibition could be a favorable treatment option for this population, future clinical trials of more specific RET inhibitors under development are awaited.

Table 2. Summary of adverse events attributable to administration of vandetanib

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>16 (89)</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Acne</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Xerosis</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Nail change</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (17)</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Increased AST and ALT</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

We gratefully appreciate J. W. Yun and W.-Y. Park for their assistance in the characterization and validation of MYO5C–RET rearrangement.
Funding
This study was supported by research grants from the Seoul National University Hospital Research Fund (05-2012-0030), which was sponsored by AstraZeneca and Sanofi Genzyme.

Disclosure
SHL has reported personal fees from AstraZeneca, BMS, MSD, Novartis, Pfizer, Roche. KP has reported consultant/advisory relationship to disclose with AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Eli Lilly, Hanmi, Kyowa Hakko Kirin, Novartis, Ono Pharmaceutical and Roche, and has research funding from AstraZeneca. All remaining authors have declared no conflicts of interest.

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