Phase II study of erlotinib plus tivantinib (ARQ 197) in patients with locally advanced or metastatic EGFR mutation-positive non-small-cell lung cancer just after progression on EGFR-TKI, gefitinib or erlotinib

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ABSTRACT
Background: Patients with epidermal growth factor receptor (EGFR) activation mutation-positive non-small-cell lung cancer (NSCLC) respond well to EGFR tyrosine kinase inhibitors (EGFR-TKIs), but eventually become resistant in most cases. The hepatocyte growth factor/c-Met (HGF/c-Met) pathway is reported as a poor prognostic factor in various cancers. As c-Met is involved in EGFR-TKI resistance, a c-Met inhibitor and EGFR-TKI combination may reverse the resistance. This study evaluated the efficacy and safety of a c-Met selective inhibitor, tivantinib (ARQ 197), in combination with erlotinib, in Japanese EGFR mutation-positive patients with NSCLC who progressed while on EGFR-TKIs.

Methods: This study enrolled 45 patients with NSCLC with acquired resistance to EGFR-TKIs, who were orally administered a daily combination of tivantinib/erlotinib. The primary end point was the overall response rate (ORR) and secondary end points included disease control rate, progression-free survival (PFS) and overall survival (OS). The patients underwent a mandatory second biopsy just after progression on EGFR-TKIs. The predictive biomarkers were extensively analysed using tumour and blood samples.

Results: The ORR was 6.7% (95% CI 1.4% to 18.3%), and the lower limit of 95% CI did not exceed the target of 5%. The median PFS (mPFS) and median OS (mOS) were 2.7 months (95% CI 1.4 to 4.2) and 18.0 months (95% CI 13.4 to 22.2), respectively. Both were longer in c-Met high patients (c-Met high vs low: mPFS 4.1 vs 1.4 months; mOS 20.7 vs 13.9 months). Partial response was observed in three patients, all of whom were c-Met and HGF high. The common adverse events and their frequencies were similar to those known to occur with tivantinib or erlotinib alone.

Key questions
What is already known about this subject?
▸ Patients with epidermal growth factor receptor (EGFR) activation mutation-positive non-small-cell lung cancer (NSCLC) respond well to EGFR tyrosine kinase inhibitors (EGFR-TKIs), but eventually become resistant in most cases. The hepatocyte growth factor/c-Met (HGF/c-Met) pathway is reported as a poor prognostic factor in various cancers. As c-Met is involved in EGFR-TKI resistance, a c-Met inhibitor and EGFR-TKI combination may reverse the resistance.

What does this study add?
▸ This is the first study to evaluate the efficacy and safety of a c-Met selective inhibitor, tivantinib (ARQ 197), in combination with erlotinib, in Japanese EGFR mutation-positive patients with NSCLC who progressed while on EGFR-TKIs, and to necessitate a second biopsy just after progression on EGFR-TKIs. The primary end point (objective response rate) did not achieve the target level (ie, the lower limit of 95% CI exceeding the 5% threshold).
▸ Partial response was observed in three patients, all of whom were c-Met and HGF high expression by immunohistochemistry.
▸ Median progression-free survival (mPFS) and median overall survival (mOS) of c-Met high patients were longer than those of c-Met low patients, and, similarly, mPFS and mOS of HGF high patients were longer than those of HGF low patients.
**INTRODUCTION**

In Asia, lung cancer is the most frequent malignant tumour in males and the second most frequent in females. About 85% of lung cancer is classified into non-small-cell lung cancer (NSCLC), and activating epidermal growth factor receptor (EGFR) mutation is present in 32% of Asian and 85% of lung cancer is classified in Caucasians and 15% in non-Asian patients with NSCLC. EGFR tyrosine kinase inhibitors (EGFR-TKIs) showed significant clinical benefit as a first-line treatment in patients with advanced or metastatic NSCLC with activating EGFR mutation. However, most of those responders eventually become resistant. Secondary mutation of EGFR (T790M), conversion to small-cell lung cancer and activated hepatocyte growth factor/c-Met (HGF/c-Met) signalling have been reported as the mechanisms of acquired EGFR-TKI resistance. A non-clinical study reported that acquired EGFR-TKI resistance was reversed by the combination of a c-Met inhibitor and gefitinib in an EGFR-TKI-resistant lung cancer cell line with c-Met amplification.

Activation of HGF/c-Met signalling due to overexpression of HGF/c-Met is reported to be involved in tumour infiltration and metastasis, and is identified as a poor prognosis factor in NSCLC. Tivantinib (ARQ 197) is an oral, non-ATP competitive, low-molecular weight selective c-Met inhibitor. The primary metabolic enzyme of tivantinib, CYP2C19, is known for the gene polymorphism associated with loss of function. The frequency of homozygotes with CYP2C19 loss-of-function polymorphism (poor metabolisers (PMs)) is about 3% in Caucasians and 15–20% in Asians. A previous Japanese phase I study showed a recommended tivantinib dose of 240 mg twice daily in PMs, and 360 mg twice daily in the other patients (extensive metabolisers (EMs)) with or without erlotinib, an EGFR-TKI, in patients with NSCLC (ARQ 197–0071, ARQ 197–003 and ARQ 197–005 studies).

The clinical efficacy of the tivantinib/erlotinib combination in EGFR-TKI-naive NSCLC has been evaluated by comparing it with the placebo/erlotinib combination in three randomised phase II/III trials: ARQ 197–209 study (n=167 from the USA/European Union (EU)), MARQUEE study (n=1048 from the USA/EU) and ATTENTION study (n=307 from Asia, only EGFR mutation-negative patients were enrolled). The primary end point of the ARQ 197–209 study was progression-free survival (PFS) and that for the other two studies was overall survival (OS). These studies showed an extension of PFS, with the p value in ARQ 197–209, MARQUEE and ATTENTION studies as 0.038 (HR 0.68), 0.001 (HR 0.74) and 0.019 (HR 0.719), respectively. The MARQUEE study also showed an extension of OS in high c-Met patients (HR 0.70; p=0.03). However, the percentage of EGFR mutation-positive patients in the ARQ 197–209, MARQUEE and ATTENTION studies was merely 10.2%, 10.4% and 0%, respectively. Therefore, clinical profiles including efficacy and safety of the tivantinib/erlotinib combination in EGFR mutation-positive patients have hardly been examined yet.

This is the first phase II study to evaluate the efficacy of the tivantinib/erlotinib combination in EGFR mutation-positive patients who are resistant to previous EGFR-TKI treatment. Tumour biopsy just after progression on EGFR-TKIs was mandatory for study entry to explore predictive biomarkers of efficacy of the tivantinib/erlotinib combination.

**PATIENTS AND METHODS**

**Study design**

This study was a phase II, single-arm, open-label, 10-centre study with a target sample size of 40 (ARQ 197–007 study; NCT01580735). Patients with EGFR mutation-positive advanced or metastatic NSCLC, just after gefitinib or erlotinib treatment, were enrolled to receive the tivantinib/erlotinib combination. Only gefitinib and erlotinib were approved as EGFR-TKIs at the time of this study. Prior platinum-based regimen was allowed. Tivantinib was provided by Kyowa Hakko Kirin Co, Ltd. Tivantinib was administered at 360 mg twice daily to CYP2C19 EMs and 240 mg twice daily to PMs, during or immediately after meals. Erlotinib 150 mg four times a day was given on an empty stomach, ≥2 hours after meals, regardless of prior treatment. The primary study end points were objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and safety. Tumour response was also evaluated by an independent review committee.
Predictive biomarkers of antitumour activity were exploratory end points. Tissue samples with confirmed tumour cells were collected in the period between progression on EGFR-TKIs and study registration. The pretreatment tumour tissues were assayed for c-Met by immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH), HGF by IHC (SRL, Inc, Tokyo) and extensive lung cancer gene mutation analysis LungCarta (MassARRAY, Agena Bioscience, California, USA). BioPlex test (BioRad, California, USA) and soluble c-Met concentration analysis (Immunno-Biological Laboratories Co, Ltd, Gunma, Japan) were performed on blood samples at screening and 2 weeks after the start of the tivantinib/erlotinib combination. Details of the analyses are described in online supplementary Data.

This study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice (GCP). The Institutional Review Boards in all hospitals approved this study, and all patients gave written consent to participate in the study.

**Inclusion/exclusion criteria.** The main inclusion criteria included: age ≥20 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤1; stage IIIB or IV NSCLC at the time of registration; EGFR mutation-positive (exon 19 deletion mutation and/or exon 21 L858R point mutation) before informed consent; history of receiving at least one prior regimen of systemic chemotherapy; history of only one regimen of either gefitinib or erlotinib monotherapy immediately before this study and disease progression following the prior EGFR-TKI monotherapy.

**Patient evaluation.** The baseline evaluation included vital signs, haematological tests, blood biochemistry tests, ECG, CYP2C19 polymorphism analysis and tumour measurement. Vital signs and haematological/blood biochemistry tests were performed every week in the first 4 weeks and every 2 weeks thereafter. ECG and tumour measurement were performed every 6 weeks. Tumour measurement was evaluated based on Response Evaluation Criteria in Solid Tumor (RECIST) V1.1. Adverse events (AEs) were evaluated based on Common Terminology Criteria for Adverse Events (CTCAE) V4.0.

**Statistical analysis.** The statistical analysis in this study was prospectively defined in the protocol. ORR, the primary end point, with its 95% CI, was estimated. ORR in the tivantinib/erlotinib combination was assumed to be 20% based on the 16.7% ORR reported in the phase II ARQ 197–209 study. The target level of ORR was the lower limit of the 95% CI exceeding 5% threshold of ORR, based on the response rate of docetaxel, which is commonly used after EGFR-TKI failure. Under these assumptions, efficacy could be evaluated in 40 patients at a power of 80%.

PFS and OS, the secondary end points, were estimated by the Kaplan-Meier method. The patients who received poststudy treatment before PD or death confirmation and those with no PD or death confirmation were censored for PFS on the day of non-PD confirmation, and data of patients whose deaths had not been confirmed were censored for OS on the day of the most recent survival confirmation.

**RESULTS.** Forty-five patients were registered between June 2012 and February 2013. Data were cut-off in September 2015. The patient characteristics are shown in table 1. The proportion of females, adenocarcinoma and non-smokers was high, and amplified c-Met (FISH) was low (6.7%).

All registered patients were included in the efficacy analysis. As shown in table 2, none of the 45 patients achieved complete response as the best overall response, while 3 patients achieved partial response (PR). ORR was 6.7% (95% CI 1.4% to 18.3%), which did not achieve the target level (ie, the lower limit of 95% CI exceeding the 5% threshold). Twenty-two patients showed stable disease (SD), and DCR was 48.9% (95% CI 33.7% to 64.2%). Median PFS (mPFS) and median OS (mOS) were 2.7 months (95% CI 1.4 to 4.2) and 18.0 months (95% CI 13.4 to 22.2), respectively.

All the registered patients were included in the safety analysis. Drug-related AEs occurred in 41 of 45 patients (91.1%). Table 3 shows drug-related AEs that occurred at a frequency of ≥5%. The most frequent drug-related AEs were dermatitis acniform, decreased appetite and stomatitis, and those events were all grade ≤2 except for grade 3 decreased appetite (2.2%). Anaemia in eight patients (17.8%), and decreased neutrophil count and white cell count in five patients each (11.1%) were observed as haematotoxicity, typical AE of tivantinib, and approximately half of these haematotoxicities were grade ≥3. All grade ≥3 haematotoxicities, except one case of anaemia, occurred within a month of starting the tivantinib/erlotinib combination. These haematotoxicities resolved in all the patients following the study-treatment interruption and granulocyte colony-stimulating factor (G-CSF) therapy. Interstitial lung disease (ILD), possibly related to the study drugs, occurred in two patients (4.4%). One patient developed grade 3 ILD 92 days after starting the combination. The event resolved with steroid pulse therapy. The other patient developed concurrent lung infection and ILD 124 days after starting the combination. Although these events improved initially with study-treatment interruption, and antimicrobial agent and steroid pulse therapy, the patient died of ILD 137 days after starting the combination.

This study also investigates the correlation between c-Met status and antitumour activities. Immunostaining showed the same incidence (48.9%) of high and low expression of c-Met (table 1). All three patients who achieved PR were c-Met high. Of the 22 c-Met high
| Patient characteristics                                      | Overall N=45 | EM N=36 | PM N=9 |
|--------------------------------------------------------------|--------------|---------|--------|
| **Gender**                                                  |              |         |        |
| Female                                                      | 28 (62.2%)   | 19 (52.8%) | 9 (100.0%) |
| Male                                                        | 17 (37.8%)   | 17 (47.2%) | 0      |
| **Age (years)**                                             | 65.2 (35–85) | 65.2 (41–85) | 65.1 (35–79) |
| **CYP2C19 phenotype**                                       |              |         |        |
| EM                                                          | 36 (80.0%)   | 36 (100.0%) | 0      |
| PM                                                          | 9 (20.0%)    | 0        | 9 (100.0%) |
| **EGFR mutation status (possibly duplicated)**              |              |         |        |
| Exon19 deletions                                            | 23           | 21      | 2      |
| L858R                                                       | 22           | 15      | 7      |
| **Tumour histology**                                        |              |         |        |
| Adenocarcinoma                                              | 44 (97.8%)   | 35 (97.2%) | 9 (100.0%) |
| Large cell carcinoma                                        | 1 (2.2%)     | 1 (2.8%) | 0      |
| **Number of prior chemotherapies**                          |              |         |        |
| 1                                                           | 33 (73.3%)   | 27 (75.0%) | 6 (66.7%) |
| 2                                                           | 10 (22.2%)   | 8 (22.2%) | 2 (22.2%) |
| 3                                                           | 2 (4.4%)     | 1 (2.8%) | 1 (11.1%) |
| **Smoking history**                                         |              |         |        |
| Current                                                     | 0            | 0       | 0      |
| Previous                                                    | 19 (42.2%)   | 17 (47.2%) | 2 (22.2%) |
| Never                                                       | 26 (57.8%)   | 19 (52.8%) | 7 (77.8%) |
| **Prior surgeries**                                         |              |         |        |
| Yes                                                         | 8 (17.8%)    | 5 (13.9%) | 3 (33.3%) |
| No                                                          | 37 (82.2%)   | 31 (86.1%) | 6 (66.7%) |
| **Prior radiotherapies**                                    |              |         |        |
| Yes                                                         | 19 (42.2%)   | 16 (44.4%) | 3 (33.3%) |
| No                                                          | 26 (57.8%)   | 20 (55.6%) | 6 (66.7%) |
| **ECOG PS (baseline)**                                      |              |         |        |
| 0                                                           | 22 (48.9%)   | 16 (44.4%) | 6 (66.7%) |
| 1                                                           | 23 (51.1%)   | 20 (55.6%) | 3 (33.3%) |
| **Recent prior chemotherapy regimen (except for maintenance/adjuvant)** | | | |
| ERL                                                         | 9 (20.0%)    | 9 (25.0%) | 0      |
| GEF                                                         | 36 (80.0%)   | 27 (75.0%) | 9 (100.0%) |
| **Best overall response to recent prior chemotherapy (except for maintenance/adjuvant)** | | | |
| CR                                                          | 1 (2.2%)     | 1 (2.8%) | 0      |
| PR                                                          | 32 (71.1%)   | 25 (69.4%) | 7 (77.8%) |
| SD                                                          | 11 (24.4%)   | 9 (25.0%) | 2 (22.2%) |
| NE                                                          | 1 (2.2%)     | 1 (2.8%) | 0      |
| **Met status**                                              |              |         |        |
| High                                                        | 22 (48.9%)   | 17 (47.2%) | 5 (55.6%) |
| Low                                                         | 22 (48.9%)   | 18 (50.0%) | 4 (44.4%) |
| Unknown                                                     | 1 (2.2%)     | 1 (2.8%) | 0      |
| **Met (FISH) status**                                       |              |         |        |
| Amplified                                                   | 3 (6.7%)     | 3 (8.3%) | 0      |
| Normal                                                      | 25 (55.6%)   | 22 (61.1%) | 3 (33.3%) |
| Unknown                                                     | 17 (37.8%)   | 11 (30.6%) | 6 (66.7%) |
| **HGF status**                                              |              |         |        |
| High                                                        | 32 (71.1%)   | 26 (72.2%) | 6 (66.7%) |
| Low                                                         | 13 (28.9%)   | 10 (27.8%) | 3 (33.3%) |

Met status:
- High: 50% or more tumour cells with moderate or strong (2+ or 3+) staining intensity by IHC.
- Low: other than ‘Met status high’ or ‘unknown’.
- Unknown: ‘missing data’ or reported as ‘reference value’.

Met (FISH) status:
- High: defined as gene copy number ≥4.
- Low: other than ‘Met (FISH) status high’ or ‘unknown’.
- Unknown: ‘missing data’ or reported as ‘reference value’.

HGF status:
- High: H-score of ≥200 by IHC.
- Low: H-score of <200 by IHC.

CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EM, extensive metabolisers; ERL, erlotinib; FISH, fluorescence in situ hybridisation; GEF, gefitinib; HGF, hepatocyte growth factor; IHC, immunohistochemistry; NE, not evaluable; PM, poor metabolisers; PR, partial response; PS, performance status; SD, stable disease.
patients, ORR and DCR were 13.6% (95% CI 2.9% to 34.9%) and 54.5% (95% CI 32.2% to 75.6%), respectively. As shown in figure 1A, B, mPFS and mOS were longer in c-Met high patients; mPFS was 4.1 months (95% CI 1.4 to 7.0) in c-Met high and 1.4 months (95% CI 1.4 to 4.2) in c-Met low, while mOS was 20.7 months (95% CI 13.6 to 27.3) in HGF high and 13.9 months (95% CI 8.2 to 27.3) in c-Met low patients.

The correlation between expression level of HGF, the only known c-Met ligand, and antitumour activities, was also evaluated. As shown in table 1, there were 32 HGF high patients and 13 HGF low patients. All three patients who achieved PR were HGF high. Of the 32 HGF high patients, ORR and DCR were 9.4% (95% CI 2.0% to 25.0) and 56.3% (95% CI 37.7% to 73.6%), respectively. As shown in figure 1C, D, mPFS and mOS were longer in HGF high; mPFS was 2.8 months (95% CI 1.4 to 4.2) in HGF high and 1.4 months (95% CI 0.7 to 5.5) in HGF low, while mOS was 18.2 months (95% CI 13.6 to 27.3) in HGF high and 12.4 months (95% CI 2.8 to 28.8) in HGF low patients.

To explore predictive biomarkers of tivantinib, an extensive lung cancer gene mutation analysis LungCarta of 26 genes known to contribute to tumour progression was performed in tumour samples collected from all patients after confirmation of PD on the previous EGFR-TKI treatment (see online supplementary table S1). At least one gene mutation was found in 43 of 45 patients. Of these 43 patients, 41 had exon 19 deletion mutation and/or exon 21 L858R point mutation, as expected from the target patient population for this study. T790M mutation was found in half of the patients, and this result was consistent with the known proportion of EGFR-TKI-resistant mutations. Other than these mutations, mutation of STK11, a tumour suppressor and an upregulator of AMP-activated protein kinase, was found.

| Table 2: Tumour response |
|--------------------------|
| Overall                  |
| N                        | 45 |

| Best overall response   |          |
|-------------------------|----------|
| CR                      | 0        |
| PR                      | 3        |
| SD                      | 19       |
| Non-CR/non-PD           | 0        |
| PD                      | 21       |
| NE                      | 2        |
| Response                | 3        |
| ORR (%) (95% CI)        | 6.7 (1.4 to 18.3) |
| Disease control         | 22       |
| DCR (%) (95% CI)        | 48.9 (33.7 to 64.2) |

CR, complete response; DCR, disease control rate; disease control, CR/PR/SD, DCR: disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; response, CR/PR, ORR: objective response rate; SD, stable disease.

| Table 3: Summary of drug-related treatment emergent AEs stratified by worst grade (MedDRA/J) |
|---------------------------------------------------------------|
| AE PT                                                        |
| N (Per cent)        | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---------------------|---------|---------|---------|---------|---------|
| At least one TEAE   | 41      | 91.1    | 14      | 15      | 9       | 2       | 1       | 12      | 26.7    |
| Dermatitis acneform | 24      | 53.3    | 15      | 9       | 0       | 0       | 0       | 0       |         |
| Decreased appetite  | 14      | 31.1    | 8       | 5       | 1       | 0       | 0       | 1       | 2.2     |
| Stomatitis          | 13      | 28.9    | 11      | 2       | 0       | 0       | 0       | 0       |         |
| Diarrhoea           | 12      | 26.7    | 9       | 3       | 0       | 0       | 0       | 0       |         |
| Dry skin            | 10      | 22.2    | 9       | 1       | 0       | 0       | 0       | 0       |         |
| Anaemia             | 8       | 17.8    | 0       | 4       | 4       | 0       | 0       | 4       | 8.9     |
| Malaise             | 8       | 17.8    | 4       | 3       | 1       | 0       | 0       | 1       | 2.2     |
| Paronychia          | 7       | 15.6    | 5       | 2       | 0       | 0       | 0       | 0       |         |
| Fatigue             | 6       | 13.3    | 4       | 1       | 1       | 0       | 0       | 1       | 2.2     |
| Alanine aminotransferase increased | 6 | 13.3 | 6 | 0 | 0 | 0 | 0 | 0 |         |
| Weight decreased    | 6       | 13.3    | 1       | 5       | 0       | 0       | 0       | 0       |         |
| Dysgeusia           | 6       | 13.3    | 4       | 2       | 0       | 0       | 0       | 0       |         |
| Nausea              | 5       | 11.1    | 5       | 0       | 0       | 0       | 0       | 0       |         |
| Neutrophil count decreased | 5   | 11.1    | 0       | 2       | 1       | 2       | 0       | 3       | 6.7     |
| White cell count decreased | 5 | 11.1   | 0       | 2       | 2       | 1       | 0       | 3       | 6.7     |
| Pruritus            | 5       | 11.1    | 5       | 0       | 0       | 0       | 0       | 0       |         |
| Aspartate aminotransferase increased | 4 | 8.9 | 4 | 0 | 0 | 0 | 0 | 0 |         |
| Hypertension        | 4       | 8.9     | 0       | 4       | 0       | 0       | 0       | 0       |         |
| Abdominal pain      | 3       | 6.7     | 3       | 0       | 0       | 0       | 0       | 0       |         |
| Vomiting            | 3       | 6.7     | 3       | 0       | 0       | 0       | 0       | 0       |         |
| Nasopharyngitis     | 3       | 6.7     | 2       | 1       | 0       | 0       | 0       | 0       |         |
| Blood bilirubin increased | 3 | 6.7 | 1 | 2 | 0 | 0 | 0 | 0 |         |
| Lymphocyte count decreased | 3 | 6.7 | 0 | 1 | 2 | 0 | 0 | 2 | 4.4     |

AE, adverse event; MedDRA/J, Medical Dictionary for Regulatory Activities/Japanese version; PT, preferred term; TEAE, treatment emergent AE.
in seven patients,21 TP53 (another tumour suppressor) in four patients,21 and of PIK3CA and MET (N375S) in one patient each. However, no apparent correlation was observed between the presence of these mutations and antitumour activities of the tivantinib/erlotinib combination.

Soluble c-Met concentrations seemed to associate with longer PFS and OS (see online supplementary figure S1), but did not vary much among patients as a predictive biomarker (see online supplementary table S2). On the other hand, there was no particular trend between the efficacy and concentration of nine types of protein (angiopoietin-2, follistatin, G-CSF, HGF, interleukin-8, leptin, platelet derived growth factor-BB, platelet endothelial cell adhesion molecule-1 and vascular endothelial growth factor), which were measured using the human angiogenesis panel BioPlex (see online supplementary table S3).

DISCUSSION
This study was the first clinical trial of tivantinib in EGFR mutation-positive patients with NSCLC resistant to EGFR-TKIs. Although the primary end point was not met for the target level (ie, lower limit of ORR 95% CI did not exceed 5%), preplanned biomarker tests revealed several important findings.

Our biomarker analysis demonstrated that PFS and OS were longer in c-Met high and HGF high patients (figure 1), and all three PR patients were diagnosed as both c-Met and HGF high. This indicates that the tivantinib/erlotinib combination presents superior efficacy in EGFR-resistant patients with high expression of c-Met high or HGF high, both reported as poor prognostic factors.8–11 Interestingly, similar superior efficacy in a poor prognosis population (ie, c-Met high and/or HGF high) was observed in previous phase III studies testing the tivantinib/erlotinib combination, even though those studies enrolled patients with NSCLC with backgrounds different from this study. The MARQUEE study enrolled EGFR-TKI-naïve Caucasian patients including about 10% EGFR mutation-positive patients, and resulted in longer OS in c-Met high; HR was 0.70 (95% CI 0.49 to 1.01, vs placebo) in c-Met high, and 0.90 (95% CI 0.64 to 1.26, vs placebo) in c-Met low.16 Similarly, the ATTENTION study that enrolled EGFR-TKI-naïve Asian patients, all of whom were EGFR mutation-negative, showed longer OS in HGF high patients; HR was 0.541 (95% CI 0.303 to 0.964, vs placebo) in HGF high, and 0.949 (95% CI 0.523 to 1.720, vs placebo) in HGF low.17 Considered together, these data suggest that activated HGF/c-Met signalling could be an independent predictive biomarker for selecting patients with NSCLC who may respond to tivantinib and, furthermore, tivantinib might have some potential as a single agent particularly for NSCLC with activated HGF/c-Met signalling, regardless
of EGFR activation or inhibition. In fact, PR was reported in 2 of 25 patients with NSCLC in a phase I study on the safety of tivantinib as a single agent,\textsuperscript{13} and this may encourage further studies to evaluate the efficacy of tivantinib as a single agent.

Tumour samples of all patients just after progression following EGFR-TKIs were collected to perform an extensive lung cancer gene mutation analysis LungCarta on 26 genes known to contribute to tumour progression. Exon 19 deletion mutation, exon 21 L858R point mutation and T790M mutation comprised almost all the other mutations found in this study. Thus, no mutation that could possibly be used as a predictive biomarker for the tivantinib/erlotinib combination was suggested in this study. The frequency of c-Met exon 14 skipping, which has been reported in recent studies,\textsuperscript{22} was not covered by the LungCarta panel we used.

Regarding c-Met copy number, Engelman et al\textsuperscript{7} reported the involvement of amplified c-Met for the resistance mechanism to EGFR-TKIs in EGFR mutation-positive NSCLC. In this study, only three patients (6.7%) had amplified c-Met (FISH), and the best overall response was one SD and two PD. Owing to the small sample size of this population, tivantinib did not show a clear reversal of acquired EGFR-TKI resistance related to the amplified c-Met.

The common AEs and their frequencies reported in this study were similar to those known for tivantinib and erlotinib monotherapy.\textsuperscript{13–17} Therefore, the tivantinib/erlotinib combination may be expected to be generally tolerable for EGFR mutation-positive patients with NSCLC previously treated with EGFR-TKIs. The incidence of ILD in this study was 4.4% (2/45 patients), which was comparable to that (4.3%; 429/9909) reported in patients treated with erlotinib alone in the phase IV POLARSTAR study (postmarketing surveillance conducted in Japan).\textsuperscript{24} However, the risk of ILD with the tivantinib/erlotinib combination was not completely ruled out because the sample size in this study was small. The Asian phase III ATTENTION study implied an increased risk of ILD in patients with NSCLC treated with the tivantinib/erlotinib combination.\textsuperscript{17} Further safety evaluation and selection of patients likely to respond is necessary to develop the tivantinib/erlotinib combination for patients with NSCLC resistant to EGFR-TKIs.

Although this study did not prove clinical benefit of tivantinib in patients with acquired resistance to EGFR-TKIs, activated HGF/c-Met signalling, which is reported as a poor prognostic factor in NSCLC,\textsuperscript{5,11} may define a patient subset associated with longer survival by treatment using the tivantinib/erlotinib combination. It will be interesting to evaluate the efficacy of tivantinib alone in patients with activated HGF/c-Met signalling in the future.

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