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First-line onartuzumab plus erlotinib treatment for patients with MET-positive and *EGFR* mutation-positive non-small-cell lung cancer

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ABSTRACT

Introduction: The phase II JO28638 study evaluated first-line onartuzumab plus erlotinib in patients with MET-positive advanced, metastatic, or post-operative recurrent non-small-cell lung cancer (NSCLC) with *epidermal growth factor receptor* (*EGFR*) mutations. The study was stopped following termination of the global METLung study (OAM4971g), which showed lack of efficacy in the onartuzumab/erlotinib arm. We present immature efficacy and safety data from JO28638.

Materials and Methods: Chemotherapy-naïve patients aged ≥ 20 years were enrolled. Patients received onartuzumab (15 mg/kg every 3 weeks) plus erlotinib (150 mg once daily) until progression or unacceptable toxicity. The co-primary endpoints were investigator (INV)-assessed progression-free survival (PFS) and safety. Secondary endpoints: overall response rate (ORR), disease control rate (DCR), overall survival (OS), duration of response (DOR), and pharmacokinetics. Exploratory biomarker analyses were also conducted.

Results: 61 patients received treatment. Median age was 67 years and most patients had stage IV NSCLC (71%), MET-IHC score 2 (87%), and exon 19 deletion *EGFR* mutation (53%). Median PFS (INV) was 8.5 months (95% confidence interval [CI] 6.8–12.4); median OS was 15.6 months (95% CI 15.6–not evaluable); ORR was 68.9% (95% CI 55.7–80.1); median DOR was not reached; DCR was 88.5% (95% CI 77.8–95.3). Pharmacokinetics were similar to previous studies. All patients experienced an adverse event (AE); 26 patients discontinued treatment due to AEs; no grade 5 AEs were reported. No significant correlation was found between biomarkers and efficacy outcomes.

Conclusion: The results presented are inconclusive due to the early termination of the study.

Introduction

The MET transmembrane receptor tyrosine kinase plays a role in embryonic development and wound healing, and is activated by the hepatocyte growth factor (HGF) ligand [1]. Autocrine HGF production, amplification of the *MET* gene, and MET overexpression can all result in aberrant MET signaling [2–5], which is thought to be an oncogenic factor in several malignancies, including lung cancer [5]. In non-small-

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATA, anti-therapeutic antibody; CI, confidence interval; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; HR, hazard ratio; IHC, immunohistochemistry; INV, investigator; NE, not evaluable; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; TKI, tyrosine kinase inhibitor

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cell lung cancer (NSCLC) specifically, MET overexpression is associated with reduced overall survival (OS) and an increased risk of death following resection [6].

Signaling through the epidermal growth factor receptor (EGFR) mediates cell proliferation, angiogenesis, and apoptosis [7]. MET and EGFR are often co-expressed and co-activated [8]. MET is known to upregulate the expression of EGFR ligands, and is associated with acquired and intrinsic resistance to EGFR tyrosine kinase inhibitors (TKIs) [9–12]. In addition, *MET* gene amplification occurs in lung cancers with acquired resistance to EGFR TKIs, which further demonstrates the synergy between MET and EGFR signaling [8,10]. In the presence of HGF, tumor cells harboring an *EGFR*-activating mutation are insensitive to erlotinib. However, following treatment with a combination of erlotinib plus onartuzumab, the tumors' sensitivity to erlotinib is restored [13].

The EGFR TKI, erlotinib, is approved as first-line treatment for *EGFR* mutation-positive NSCLC, and as second-line treatment for recurrent *EGFR*-positive or wild-type NSCLC [14,15]. In the phase III European EURTAC study of first-line erlotinib versus standard chemotherapy for *EGFR*-mutation positive NSCLC (NCT00446225), patients who received erlotinib had significantly longer progression-free survival (PFS) than those who received chemotherapy (hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.25–0.54, $P < .0001$; median 9.7 months [95% CI 8.4–12.3] vs. 5.2 months [95% CI 4.5–5.8]) [15]. However, resistance to EGFR inhibitors, such as erlotinib, frequently occurs [16].

Onartuzumab is a recombinant, humanized, one-armed anti-MET monoclonal antibody, which binds to MET without resulting in its dimerization and activation [1]. In the phase II study of onartuzumab plus erlotinib in patients with advanced NSCLC, those with MET-positive NSCLC had significantly improved PFS (HR 0.53 [95% CI 0.28–0.99], $P = .04$; median 2.9 months vs. 1.5 months) and OS (HR 0.37 [95% CI 0.19–0.72] $P = .002$; median 12.6 months vs. 3.8 months) with onartuzumab plus erlotinib compared with patients who received erlotinib alone [17].

The global phase III METLung study (OAM4971g) determined the efficacy and safety of onartuzumab plus erlotinib versus erlotinib alone in patients with locally advanced or metastatic NSCLC, whose disease had progressed following treatment with platinum-based chemotherapy [18]. The study was terminated early on the recommendation of an independent data monitoring committee, as no improvement in clinical outcomes was observed with the addition of onartuzumab. OS was numerically longer with erlotinib alone compared with onartuzumab plus erlotinib, HR 1.27 (95% CI 0.98–1.65, $P = .067$; median 9.1 months vs. 6.8 months), and median PFS was 2.7 months with onartuzumab plus erlotinib compared with 2.6 months with erlotinib alone (HR 0.99, 95% CI 0.81–1.20, $P = .92$). Patients who received onartuzumab plus erlotinib had a similar overall response rate (ORR; 8.4%) compared with those who received erlotinib alone (9.6%) [18].

The phase II JO28638 study (JapicCTI-132077) evaluated the efficacy and safety of onartuzumab plus erlotinib as first-line therapy in patients with MET-positive advanced, metastatic, or post-operative recurrent NSCLC harboring *EGFR* mutations (exon 19/L858R). The study was initiated after the phase III METLung study, and was stopped following the early termination of the METLung study due to lack of efficacy in the onartuzumab plus erlotinib arm. Here we present the immature efficacy and safety results of the phase II JO28638 study, which is of clinical significance as it is the first phase II study in patients with MET-positive NSCLC with *EGFR* mutations.

Materials and methods

Study design

JO28638 was an open-label, multicenter, single-arm study of onartuzumab plus erlotinib as first-line therapy in patients with MET-positive, *EGFR* mutation-positive NSCLC. Patients received onartuzumab (15 mg/kg intravenous infusion every 3 weeks) plus erlotinib (150 mg once daily orally) until disease progression or unacceptable toxicity. The planned study period was February 2013 to December 2015. The study was undertaken in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines, and written informed consent was obtained from all patients.

Eligibility criteria

The main inclusion criteria were: histologically or cytologically confirmed stage IIIB or IV MET-positive (confirmed by central immunohistochemical [IHC] staining) and *EGFR* mutation-positive (exon 19 deletion or L858R mutation in exon 21 confirmed by polymerase chain reaction [PCR]-based mutation test) NSCLC prior to enrollment; chemotherapy-naïve (including molecular-targeted agents; neoadjuvant and adjuvant chemotherapy were permitted if final treatment was conducted ≥ 6 months before enrollment and no molecular-targeted agents were used); Eastern Cooperative Oncology Group performance status of 0 or 1; measurable lesions according to Response Evaluation Criteria in Solid Tumors version 1.1; aged ≥ 20 years; and life expectancy of ≥ 12 weeks from time of informed consent.

Key exclusion criteria were: central nervous system metastases with symptoms or requiring treatment; prior radiation to the thorax; pregnancy or lactation; any gastrointestinal disorder that may affect absorption of oral medications and known hypersensitivity to any components of the study drug formulations.

Study endpoints

The co-primary endpoints were investigator-assessed PFS and safety (adverse events [AEs]). Secondary endpoints included: ORR, disease control rate (DCR; complete responses plus partial responses plus stable disease), OS, duration of response (DOR), pharmacokinetics, and anti-therapeutic antibody (ATA) testing. Exploratory biomarker analyses (including serum HGF, HGF mRNA in tumor tissue, number of *MET* gene copies in tumor tissue, and so on) were also conducted.

Statistical analyses

The planned sample size was 60 patients, based on the assumption that at least one AE with a true occurrence rate of ≥ 4.9% could be detected with a probability of ≥ 95%. The emphasis of the efficacy analysis was on estimation of the magnitude of PFS. Supplementary Table 1 shows the probability of the 95% lower confidence limit of

Table 1
Patient Demographics.

Characteristics	Onartuzumab + erlotinib ($n = 61$)
Gender, *n* (%)	
Male	26 (43)
Female	35 (57)
Median age, years	67.0
ECOG PS, *n* (%)	
0	31 (51)
1	30 (49)
Stage, *n* (%)	
IIIB	2 (3)
IV	43 (71)
Recurrent	16 (26)
MET-IHC score, *n* (%)	
2	53 (87)
3	8 (13)
EGFR mutation, *n* (%)	
Exon 19 deletion	32 (53)
Exon 21 L858R mutation	29 (48)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; *EGFR* = epidermal growth factor receptor; IHC = immunohistochemistry.

median PFS being higher than the PFS threshold, based on a simulation.

Median PFS, OS, and DOR were estimated using the Kaplan–Meier method and 95% CIs were calculated using Greenwood's formula. The CIs of ORR and DCR were calculated using the Clopper–Pearson method. AEs were graded using Common Terminology Criteria for Adverse Events v4.03 and coded using the Medical Dictionary for Regulatory Activities.

EGFR testing

Prior to enrollment, patients were tested to confirm if their NSCLC was *EGFR* mutation-positive using a high-sensitivity PCR-based test on their tumor tissue or cells. Patients with exon 19 deletions, or the L858R mutation in exon 21, were included in this study; those found to have the T790M mutation in exon 20 were excluded.

MET immunohistochemistry

The rabbit anti-MET monoclonal antibody SP44 (Ventana Medical Systems, Inc., Arizona, USA) was used for MET-IHC testing, which was carried out at LSI Medience Corporation (Tokyo, Japan). Tumors were classified as either positive (score of 2 or 3) or negative (score of 1 or 0) for MET, based on the following scoring criteria: score 3 was defined as ≥ 50% tumor cells with membrane and/or cytoplasmic staining with strong intensity; score 2 was defined as ≥ 50% tumor cells with membrane and/or cytoplasmic staining with moderate or higher intensity but < 50% tumor cells with strong intensity; score 1 was defined as ≥ 50% tumor cells with membrane and/or cytoplasmic staining with weak or higher intensity but < 50% tumor cells with moderate or higher intensity; and score 0 was defined as samples with no staining, or with < 50% tumor cells with membrane and/or cytoplasmic staining (any combination of staining intensities was permitted).

MET gene amplification

MET DNA Probe and Chromosome 7 DIG Probe (Ventana Medical Systems, Inc., Arizona, USA) were used for the *MET* gene amplification assay, which was carried out at LSI Medience Corporation (Tokyo, Japan). *MET* gene amplification was determined as high (total number of *MET* genes in 20 tumor cells ≥ 90) or low (total number of *MET* genes in 20 tumor cells < 90).

Exploratory biomarker analyses

The HGF mRNA assay was performed at LSI Medience Corporation. Testing for 11 gene mutations (*PIK3CA, AKT1, KRAS, NRAS, BRAF, EGFR, FGFR3, FLT3, HRAS, KIT,* and *MET*) was carried out at Genentech, Inc. (California, USA). The HGF assay was carried out at Tandem Labs, Inc. (California, USA). Plasma secretion factor assays (VEGF-A, VEGF-C, PDGF-C, sFLT-1, VEGF-R2, VEGF-R3, FGFb, PLGF, E-selectin, ICAM-1, amphiregulin, EGF, TGF-α, sHER-2, TNF-α, MCP-1, IL-6, IL-8, and IL-10) were carried out MicroCoat Biotechnologie GmbH (Bernried, Germany). The plasma *EGFR* mutation assay was carried at Chugai Research Institute for Medical Science, Inc. (Kanagawa, Japan). All testing was performed according to pre-defined protocols.

Pharmacokinetics

The serum onartuzumab and ATA assays were carried out at Covance BioAnalytical Services LLC (Virginia, USA) according to pre-defined protocols.

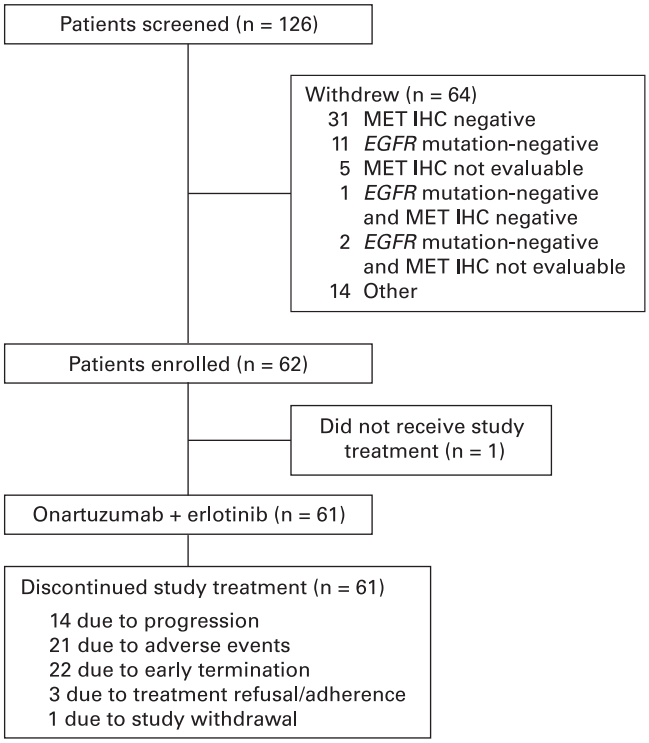

Fig. 1. Study Cohort Attrition.

Results

Patient demographics

A total of 126 patients provided consent for the study, of whom 112 (89%) had *EGFR* mutation-positive NSCLC and 102 had MET-IHC results available. Of these patients, 71 had confirmed MET-positive tumors (70%). After exclusion criteria were applied, 62 patients were enrolled across 22 centers in Japan and 61 patients received treatment (Fig. 1). The median patient age was 67 years and most patients were female (57%) with stage IV NSCLC (71%; Table 1). The majority of patients had a MET-IHC score of 2 (87%) and an exon 19 deletion *EGFR* mutation (53%; Table 1).

Efficacy

Due to the early termination of the study, only immature efficacy results are presented. The median duration of OS follow-up was 10.6 months (range 0.9–15.8 months). Median PFS by investigator was 8.5 months (95% CI 6.8–12.4; Fig. 2). Median OS was 15.6 months (95% CI 15.6–not evaluable [NE]; Fig. 3). ORR (all partial responses) was 68.9% (95% CI 55.7–80.1). Median DOR was not reached (range 1.3–9.7 months). DCR was 88.5% (95% CI 77.8–95.3).

Pharmacokinetics

Pharmacokinetic parameters were similar to those previously reported in the phase I Japanese study of onartuzumab plus erlotinib [19]. Steady state was achieved with at least 4 doses of onartuzumab.

Exploratory biomarker analyses

ORR and PFS were analyzed according to MET-IHC score 2 (n = 53) or 3 (n = 8). ORR was 66.0% (95% CI 51.7–78.5) in patients with MET-IHC score 2, and 87.5% (95% CI 47.3–99.7) in those with MET-IHC score 3. PFS was numerically longer in patients with a MET-IHC score of

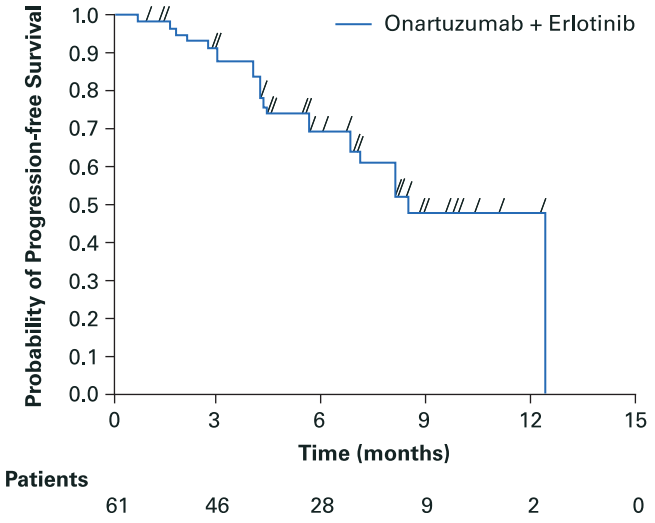

Fig. 2. Progression-free Survival by Investigator. / = Censored.

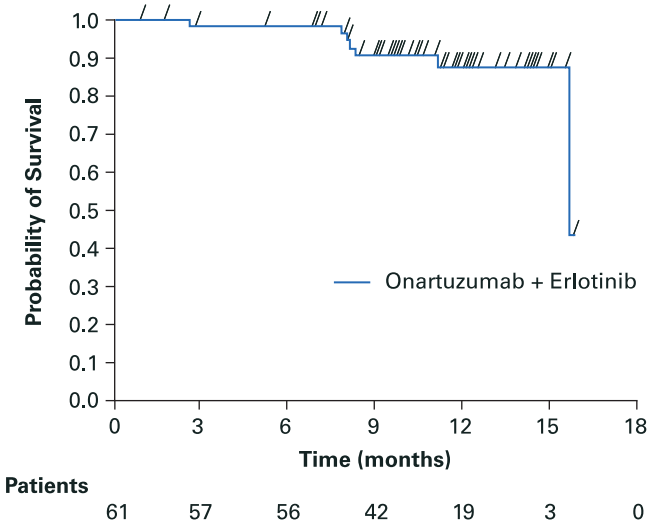

Fig. 3. Overall Survival. / = Censored.

2 compared with patients with a score of 3 (median 8.5 months [95% CI 7.1–12.4] vs. 4.4 months [95% CI 0.7–NE], respectively) (Fig. 4A). ORR and PFS were also assessed according to high (n = 11) and low (n = 45) *MET* amplification. ORR in patients with low *MET* gene amplification was 68.9% (95% CI 53.4–81.8) and in high *MET* gene amplification was 72.7% (95% CI 39.0–94.0). Median PFS was numerically longer for patients with low versus high *MET* gene amplification (12.4 months [95% CI 7.1–12.4] vs. 8.1 months [95% CI 4.0–NE], respectively) (Fig. 4B).

Serum HGF was increased after treatment. This result was also seen previously in the phase I onartuzumab study [19]. There was no meaningful correlation found between the following biomarkers and efficacy outcomes (plasma proteins: VEGF-A, VEGF-C, PDGF-C, sFLT-1, VEGF-R2, VEGF-R3, FGFb, PLGF, E-selectin, ICAM-1, amphiregulin, EGF, TGF-α, sHER-2, TNF-α, MCP-1, IL-6, IL-8, IL-10, and HGF; tissue mHGF). Out of 41 tissue samples, *K-RAS* gene mutation (G12D) was detected in 1 patient (2.4%), and *MET* gene mutation (N375S) was detected in 2 patients (4.9%).

EGFR mutations in plasma were detected by digital PCR. At screening, deletion 19 mutation in plasma was detected in 62.5% (n = 20/32) of patients who had deletion 19 mutation in tumor tissue; L858R mutation in plasma was detected in 27.6% (n = 8/29) of patients who had L858R mutation in tumor tissue; and T790M mutation

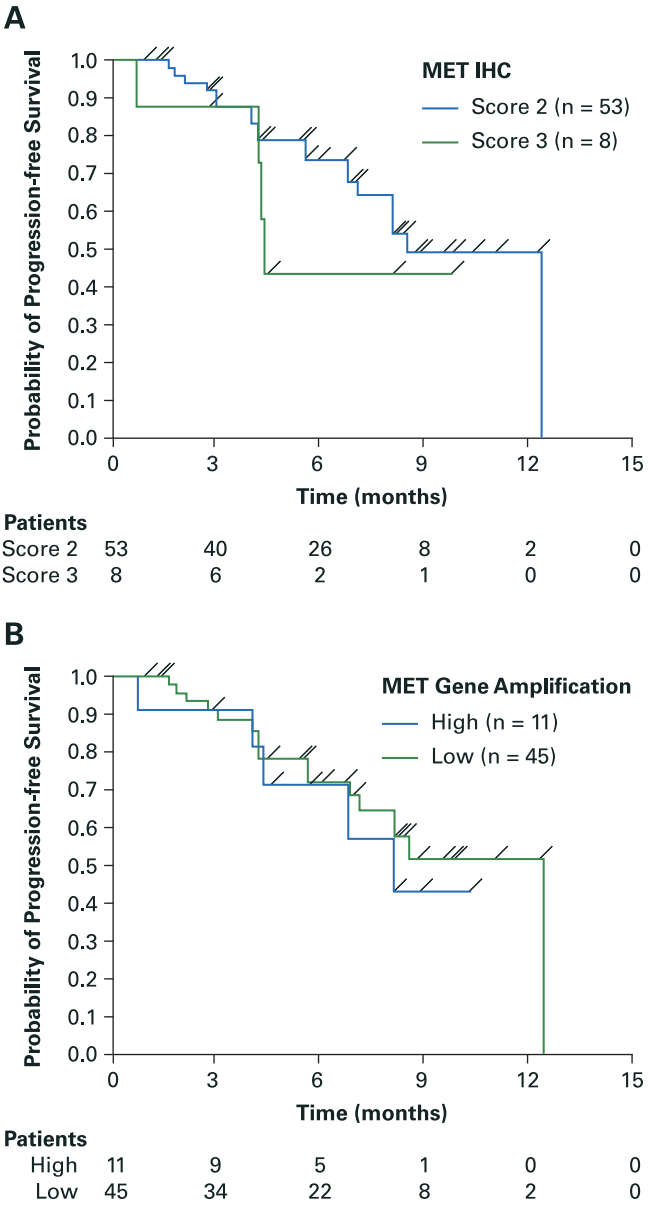

Fig. 4. Progression-free Survival of (A) MET-IHC 2 Versus 3, and (B) *MET* gene Amplification High Versus Low. Abbreviation: IHC = immunohistochemistry. / = Censored.

was detected in 3.3% (n = 2/61) of patients. T790M mutation was detected in 25% (n = 6/24) of patients who experienced progression. In 1 patient who had an L858R mutation detected in plasma prior to enrollment, a deletion 19 mutation and not an L858R mutation was detected in plasma at screening.

Safety

All patients experienced at least one AE. The most common grade 3–4 AEs were acneiform eruption (15%), rash (13%), and paronychia (10%; Table 2). There were four reports (6.6%) of interstitial lung disease. A total of 26 (43%) patients discontinued study treatment due to AEs, including peripheral edema (n = 5), appetite loss (n = 4), and acneiform eruption (n = 4). In total, 39 (63.9%) patients required dose modifications due to AEs, mostly acneiform eruption (n = 10) or rash (n = 10). There were no reported grade 5 AEs. A positive ATA result was detected in 2 patients at screening. However, the ATA results for these patients were negative in tests conducted post-treatment. No cases

Table 2
Adverse Events with a Frequency of ≥ 10%.

Patients, %	Onartuzumab + erlotinib (n = 61)	
	All grades	Grade 3–4
Paronychia	75	10
Acneiform eruption	67	15
Stomatitis	66	0
Diarrhea	62	2
Xerosis cutis	59	3
Peripheral edema	49	2
Hypoalbuminemia	44	8
Pruritus	43	0
Rash	34	13
Appetite loss	33	3
Nausea	28	0
ALT increased	23	5
AST increased	16	0
Malaise	16	0
Weight loss	15	3
Constipation	15	0
Dysgeusia	15	0
Liver dysfunction	13	3
Alopecia	13	0
Dry eyes	12	0
Conjunctivitis	12	0
Nasopharyngitis	12	0
Insomnia	12	0
Vomiting	12	0

Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase.

were reported of a negative ATA result at screening that became positive after treatment.

Discussion

The phase II JO28638 study evaluated the efficacy and safety of onartuzumab plus erlotinib in patients with *EGFR* mutation-positive and MET-positive NSCLC across 22 centers in Japan. Due to the lack of efficacy shown with onartuzumab plus erlotinib in the global phase III METLung study [18], the JO28638 study was terminated early. It is therefore difficult to draw definitive conclusions on the immature efficacy and safety results presented here. However, the data presented are clinically interesting because this was the first phase II study of the first-line treatment of MET-positive NSCLC harboring *EGFR* mutations.

Although previous studies of erlotinib plus onartuzumab in patients with recurrent NSCLC have reported no improvement in efficacy (median PFS 2.7 months and median OS 6.8 months with erlotinib plus onartuzumab in the global METLung study [18]), it is not known whether MET status affects the efficacy of EGFR TKIs such as erlotinib in NSCLC with *EGFR*-activating mutations. The efficacy outcomes reported here for the JO28638 study appear to be similar to those reported in previous studies conducted in Japan of first-line erlotinib monotherapy in patients with *EGFR* mutation-positive NSCLC. The phase II single-arm JO22903 study of erlotinib reported a median PFS of 11.8 months (95% CI 9.7–15.3) and an ORR of 78% (n = 102) [20]. The phase II randomized JO25567 study, which compared erlotinib alone versus erlotinib plus bevacizumab, reported a median PFS of 9.7 months (95% CI 5.7–11.1) in the erlotinib monotherapy arm and an ORR of 64% (95% CI 52–74) [21]. One possible reason for the similar efficacy observed between this study and previous studies is that MET overexpression is a passenger alteration in NSCLC with *EGFR*-activating mutations [18].

The exploratory analysis of PFS by MET-IHC score and *MET* gene amplification showed that patients with a MET-IHC score of 2 and lower *MET* gene amplification had longer PFS than those with a MET-IHC score of 3 and high levels of gene amplification. However, both of these exploratory analyses involved small patient numbers (only 8 patients with IHC score 3 and 11 patients with high *MET* amplification), and therefore the CIs are wide and overlapping in these subgroups. Furthermore, interpretation of these data is limited due to the single-arm study design.

The most common grade 3–4 AEs were as expected (acneiform eruption, rash, and paronychia). These are similar to the most common AEs in the phase III METLung study (rash, dermatitis acneiform, and diarrhea) [18]. In total, 34% (n = 21/61) of patients who received erlotinib plus onartuzumab discontinued treatment due to AEs, which was a higher rate than in the METLung study (8.0%) [18], possibly due to the longer treatment duration in this study compared with METLung (median 6.2 months vs. 2.0 months, respectively).

The exploratory biomarker analyses did not yield positive results; no predictive tissue biomarkers were found, including MET-IHC, *MET* gene amplification, and HGF mRNA. *EGFR* mutations in plasma were detected by digital PCR. However, the sensitivity was lower than existing reports [20], so it may be difficult to draw conclusions from these data.

Limitations of this analysis to consider when reviewing these data include the single-arm, non-randomized nature of the study, its small enrollment size, and the insufficient follow-up period for PFS and OS. Strengths of the study include the robust testing of tumor samples for MET in NSCLC with *EGFR*-activating mutations and the wide array of potential biomarkers tested.

The phase II/III trials conducted with onartuzumab described here did not demonstrate efficacy benefits in patients with NSCLC. However, the phase II study did not include patients with EGFR TKI-resistant disease caused by the MET signaling pathway, and it is possible that this treatment would be efficacious in this population. It has been suggested that ongoing trials of selective MET inhibitors in patients with EGFR TKI-resistant NSCLC by the MET pathway could determine whether MET inhibition may play a role in the treatment of NSCLC, although they are TKI inhibitors [22]. In addition, considering MET status in patients with NSCLC from both the METLung study and this study, combining an anti-MET antibody with a cytotoxic agent may be a viable treatment option for MET-overexpressed tumors. This is currently being investigated in the ongoing phase I/Ib ABBV-399 study (NCT02099058).

Conclusions

The results presented here are immature due to early termination of the study; therefore, it is difficult to draw definitive conclusions regarding the efficacy and safety of onartuzumab plus erlotinib in patients with NSCLC. Exploratory biomarker analyses did not yield any meaningful results. These results, together with those of the global METLung study, suggest that the combination of onartuzumab plus erlotinib is not a suitable treatment for patients with NSCLC.

Conflict of interest disclosures

Kazuma Kishi has participated in speaker bureaus for Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, Boehringer Ingelheim, Taiho, Kyorin, Shionogi, MSD, and AstraZeneca, has received research support from Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, Boehringer Ingelheim, Taiho, Eli-Lilly, Teijin, Dainippon, Kyorin, Shionogi, MSD, Sankyo, Asahi Kasei, and Fujifilm, and has acted in a consulting role for Ono Pharmaceutical Co., Ltd and Boehringer Ingelheim. Hiroshi Sakai has participated in speaker bureaus for Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Bristol-Myers Squibb, Eli Lilly Japan K.K., AstraZeneca, Merck KGaA, and MSD, has received research support from Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Bristol-Myers Squibb, Eli Lilly Japan K.K., AstraZeneca, Merck KGaA, and MSD, and has acted in a consulting role for Ono Pharmaceutical Co., Ltd. Takashi Seto has

participated in speaker bureaus for Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd, Daiichi Sankyo, Eli Lilly Japan, Kissei Pharmaceutical, Kyowa Hakko Kirin, Mochida Pharmaceutical, MSD, Nippon Boehringer Ingelheim Co., Ltd, Nippon Kayaku, Ono Pharmaceutical Co., Ltd, Pfizer Japan, Roche Singapore, Sanofi, Showa Yakuhin Kako, Taiho Pharmaceutical Co., Ltd, Takeda Pharmaceutical, and YakultHonsha, and has received research support from Astellas Pharma, AstraZeneca, Bayer Yakuhin, Chugai Pharmaceutical Co., Ltd, Daiichi Sankyo, Eisai, Eli Lilly Japan, Kissei Pharmaceutical, Merck Serono, MSD, Nippon Boehringer Ingelheim Co., Ltd, Novartis Pharma, Pfizer Japan, Verastem, and YakultHonsha. Toshiyuki Kozuki has received research support from Chugai Pharmaceutical Co., Ltd, AstraZeneca, Lilly, Pfizer, Ono Pharmaceutical Co., Ltd, Bristol-Myers Squibb, and Merck Serono, and has received honoraria from Chugai Pharmaceutical Co., Ltd, AstraZeneca, Lilly, Pfizer, Ono Pharmaceutical Co., Ltd, Bristol-Myers Squibb, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim Co., Ltd, Nippon Kayaku, Taiho Pharmaceutical Co., Ltd, and MSD. Makoto Nishio has received honoraria from Ono Pharmaceutical Co., Ltd, Bristol-Myers Squibb, Pfizer, Chugai Pharmaceutical Co., Ltd, Eli Lilly, Taiho Pharmaceutical Co., Ltd, AstraZeneca, Boehringer Ingelheim, MSD, and Novartis, has acted in a consulting role for Novartis, Daiichi Sankyo Healthcare, Taiho Pharmaceutical Co., Ltd, Bristol-Myers Squibb, Boehringer Ingelheim, Ono Pharmaceutical Co., Ltd, Eli Lilly, Chugai Pharmaceutical Co., Ltd, AstraZeneca, Merck Serono, MSD, and Pfizer, and has received research support from MSD, Novartis, Ono Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Bristol-Myers Squibb, Taiho Pharmaceutical Co., Ltd, Eli Lilly, AstraZeneca, Pfizer, and Astellas. Fumio Imamura has participated in speaker bureaus for Chugai Pharmaceutical Co., Ltd, AstraZeneca, Boehringer Ingelheim, Lilly, Pfizer, Novartis, Taiho Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, Bristol-Myers Squibb, and MSD, and has received research support from Chugai Pharmaceutical Co., Ltd, AstraZeneca, Boehringer Ingelheim, Lilly, Pfizer, Novartis, Taiho Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, Bristol-Myers Squibb, and MSD. Hiroshi Nokihara has received research support from Merck Serono, Pfizer, Taiho Pharmaceutical Co., Ltd, Eisai Pharmaceutical Co., Ltd, Eli Lilly, Novartis, Daiichi Sankyo, GlaxoSmithKline, Quintiles, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, and Ono Pharmaceutical Co., Ltd, and has received honoraria from Taiho Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Ono Pharmaceutical Co., Ltd, Sanofi, and Bristol-Myers Squibb. Miyako Satouchi has received research report from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan, Merck, Novartis, Ono Pharmaceutical Co., Ltd, and Pfizer Japan, and has other relationships with AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan, Merck, Novartis, Ono Pharmaceutical Co., Ltd, Pfizer Japan, and Taiho Pharmaceutical Co., Ltd. Shintaro Nakagawa is an employee of Chugai Pharmaceutical Co., Ltd. Takashi Tahata is an employee of and a stock owner at Chugai Pharmaceutical Co., Ltd. Kazuhiko Nakagawa has participated in speaker bureaus for Astellas Pharma Inc., Ono Pharmaceutical Co., Ltd, AstraZeneca, K.K./Nippon Boehringer Ingelheim Co., Ltd, Novartis Pharma K.K., Bristol-Myers Squibb, Pfizer Japan Inc., Kissei Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, Eli Lilly Japan K.K., Taiho Pharmaceutical Co., Ltd, MSD K.K., AYUMI Pharmaceutical Corporation, EPS Holdings Inc., Kyowa Hakko Kirin Co., Ltd, Showa Yakuhin Kako Co., Ltd, Sym Bio Pharmaceuticals Ltd, Nichi-Iko Pharmaceutical Co., Ltd, and Clinical Trial Co., Ltd, and has received research support from GlaxoSmithKline K.K., Yakult Honsha Co., Ltd, AstraZeneca K.K., PAREXEL International Corp, Kyowa Hakko Kirin Co., Ltd, Otsuka Pharmaceutical Co., Ltd, Pfizer Japan Inc., Astellas Pharma Inc., AbbVie Inc., AC MEDICAL INC., Novartis Pharma K.K., Taiho Pharmaceutical Co., Ltd, Nippon Boehringer Ingelheim Co., Ltd, Merck Serono Co., Ltd, Daiichi Sankyo Co., Ltd, EPS Associates Co., Ltd, Eli Lilly Japan K.K., Quintiles Inc., MSD K.K., Japan Clinical Research Operations, Quintiles Inc., Eisai Co., Ltd, Ono Pharmaceutical Co., Ltd, PPD-SNBL K.K., Bristol-Myers Squibb, Takeda Pharmaceutical Co., Ltd, EPS International Co., Ltd, Covance Inc., Chugai Pharmaceutical Co., Ltd, inVentiv Health Japan, ICON Japan K.K., GRITSONE ONCOLOGY Inc., A2 Healthcare Corp., Novartis Pharma K.K., EP-CRSU Co., Ltd, and Linical Co., Ltd, and has acted in a consulting role for Astellas Pharma Inc., Eli Lilly Japan K.K., and Ono Pharmaceutical Co., Ltd.

Clinical practice points

- The EGFR TKI, erlotinib, is approved as first-line treatment for *EGFR* mutation-positive non-small-cell lung cancer (NSCLC), and as second-line treatment for recurrent NSCLC. Onartuzumab is a recombinant, humanized, one-armed anti-MET monoclonal antibody, which binds to MET without resulting in its dimerization and activation. Onartuzumab plus erlotinib was expected to be effective in NSCLC with activating *EGFR* mutations.
- The phase II JO28638 study evaluated the efficacy and safety of first-line onartuzumab plus erlotinib in patients with MET-positive advanced, metastatic, or post-operative recurrent NSCLC with *EGFR* mutations (exon 19/L858R). This study was initiated after the phase III global METLung study (OAM4971g) and was stopped following the early termination of METLung. Here, we present the immature efficacy and safety results of the phase II JO28638 study.
- The efficacy outcomes reported here are similar to those reported in previous studies conducted in Japan of first-line erlotinib monotherapy in patients with *EGFR* mutation-positive NSCLC. This is consistent with the METLung study. The safety results are aligned with those in the global population, although more patients discontinued treatment due to adverse events than in the METLung study. These differences may be due to the longer treatment duration in JO28638.
- The results are inconclusive due to early study termination. It is therefore difficult to draw definitive conclusions regarding the efficacy and safety of onartuzumab plus erlotinib in patients with NSCLC with *EGFR*-activating mutations. Together with the METLung study results, these data suggest that onartuzumab plus erlotinib is not suitable for the treatment of MET-positive, *EGFR* mutation-positive NSCLC.

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Supplementary materials

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