PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of first-line osimertinib treatment and post-progression patterns of care in patients with epidermal growth factor receptor activating mutation-positive advanced non-small-cell lung cancer (Reiwa study): study protocol of a multicenter, real-world observational study
AUTHORS	Watanabe, Kageaki; Yoh, Kiyotaka; Hosomi, Yukio; Usui, Kazuhiro; Naka, Go; Kishi, Kazuma; Uemura, Kohei; Ohashi, Yasuo; Kunitoh, Hideo

VERSION 1 – REVIEW

REVIEWER	Scagliotti, Giorgio University of Torino, Department of Oncology
REVIEW RETURNED	04-Feb-2021

GENERAL COMMENTS	I acknowledge Watanabe and colleagues for their manuscript "Efficacy and safety of first-line osimertinib treatment and post-progression patterns of care in patients with epidermal growth factor receptor activating mutation-positive advanced non-small-cell lung cancer (Reiwa study): design and rationale of a multicenter, real-world observational study". This real-life protocol is expected to enhance the knowledge about the efficacy of first-line osimertinib in patients with NSCLC and activating EGFR mutations treated in daily clinical practice. Moreover, insights on patterns of disease progression would be of interest. However, the Authors should clarify some issues about the present protocol: - In the introduction, the Authors report that "[…] osimertinib has been shown to provide a significantly longer progression-free survival (PFS) and overall survival (OS) than the first-generation EGFR TKI[…]". However, the difference in OS was not statistically significant as the interval confidence reached one [hazard ratio for death, 0.80; 95.05% CI, 0.64 to 1.00; P = 0.046]. - In the "participants" section the Authors should clarify the definition of recurrent NSCLC, as some recurrences may be treated with local treatments only; - The Authors should discuss the rationale of including uncommon EGFR activating mutations, as these patients were not originally included in FLAURA study - I have some concerns about the inclusion of patients who received investigational agents (such as those receiving alternating regimens, which are not standard of care). Adding such patients would greatly increase the population heterogeneity; moreover, the inclusion in the second study group of patients treated with combination therapies including osimertinib may not be appropriate especially when analysing safety;

	- In the end-point section, the Authors should better explain B1 progression pattern, as it is not clear; - As the study end-points are all related to first-line osimertinib treatment, it is not clear why the study includes also patients treated with other TKIs or with osimertinib in combination with other agents.

REVIEWER	Wu, Yi-long Guangdong Acad Med Sci, Guangdong Lung Cancer Institute
REVIEW RETURNED	25-Feb-2021

GENERAL COMMENTS	Watanabe et al reported a protocol of design and rationale of a multicenter real word study on efficacy and safety of first-line osimertinib treatment and post-progression patterns for advanced NSCLC. In general osimertinib has became a standard of care for advanced EGFR mutant NSCLC. It is necessary to understand how to treat patients when they were failure to osimertinib measured by imaging. The goal of this protocol is very clear and rational. 1. Post-progression patterns and treatment suggestions for EGFR TKIs have been recommended by NCCN guideline and first time suggested by Dr. Yang (Lung Cancer 2013 Jan;79(1):33-9）. I suggest that these need to be as study background in the introduction session. 2. For the real word study how to control bias especial how to measure PFS is critical and great challenge. Authors should discuss these. 3. How many variables will be study?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Giorgio Scagliotti, University of Torino

Comments to the Author:
I acknowledge Watanabe and colleagues for their manuscript “Efficacy and safety of first-line osimertinib treatment and post-progression patterns of care in patients with epidermal growth factor receptor activating mutation-positive advanced non-small-cell lung cancer (Reiwa study): design and rationale of a multicenter, real-world observational study”. This real-life protocol is expected to enhance the knowledge about the efficacy of first-line osimertinib in patients with NSCLC and activating EGFR mutations treated in daily clinical practice. Moreover, insights on patterns of disease progression would be of interest.
However, the Authors should clarify some issues about the present protocol:

- In the introduction, the Authors report that “[…] osimertinib has been shown to provide a significantly longer progression-free survival (PFS) and overall survival (OS) than the first-generation EGFR TKI[…]”. However, the difference in OS was not statistically significant as the interval confidence reached one [hazard ratio for death, 0.80; 95.05% CI, 0.64 to 1.00; P = 0.046].

Response: As the reviewer pointed out, the difference in OS between osimertinib and first-generation EGFR-TKI reached an interval confidence level of 1, which was not statistically significant. We have clarified this in the text (p6, 124).

- In the “participants” section the Authors should clarify the definition of recurrent NSCLC, as some recurrences may be treated with local treatments only;

Response: The definition of recurrent NSCLC is in the protocol as patients who cannot be treated with local treatments alone and require systemic chemotherapy with EGFR-TKIs. We clearly stated in the "Participants" section (p9, lines 195–197).

- The Authors should discuss the rationale of including uncommon EGFR activating mutations, as these patients were not originally included in FLAURA study

Response: As the reviewer noted, patients with uncommon EGFR activating mutations were not originally included in the FLAURA study. Our study is a real-world observational study of the efficacy and safety of first-line osimertinib treatment and post-progression patterns of care in patients with EGFR activating mutation-positive advanced NSCLC. Osimertinib treatment in patients with uncommon EGFR activating mutations has been reported from Korea (Jang Ho Cho, et al. J Clin Oncol. 2020;38:488–495), but the results were from 36 patients and the data were not sufficient. Therefore, the data on Osimertinib treatment in patients with uncommon EGFR activating mutations were exploratory confirmed by secondary endpoint 12. The evaluation of the efficacy of first-line osimertinib treatment including PFS, OS and response rate were conducted for common EGFR activating mutations as in the FLAURA study. The above was clearly stated in the end point section (p14, lines 304–306).

- I have some concerns about the inclusion of patients who received investigational agents (such as those receiving alternating regimens, which are not standard of care). Adding such patients would greatly increase the population heterogeneity; moreover, the inclusion in the second study group of patients treated with combination therapies including osimertinib may not be appropriate especially when analysing safety;

Response: The efficacy, safety, pattern of exacerbations and post-exacerbation treatment of osimertinib will be studied over time only in patients who have started treatment with osimertinib alone. Patients on combination therapy will be enrolled only and will not be studied for the efficacy and safety of osimertinib. Patients on alternating therapy will be subject to follow-up. As the reviewer pointed out, we think there is a concern about increasing heterogeneity, but we have included a wide range of patients in the study because we thought that osimertinib would be used in various ways in the real world. The points raised by the reviewer will be considered during the analysis. Please refer to the Research proced/span>ures section.

- In the end-point section, the Authors should better explain B1 progression pattern, as it is not clear;

Response: The B1 exacerbation pattern refers to patients who have no subjective symptoms when treatment with osimertinib results in PD on RECIST, and there is no decreased PS or major organ threatening conditions as defined in B3. This pattern is applied when a patient has PD on RECIST due to the appearance of a new lesion or the enlargement of a target or non-target lesion, but the appearance or enlargement of the lesion is asymptomatic and the patient has no symptoms. The above information has been clearly added to the end point section (p12, lines 269–272).

- As the study end-points are all related to first-line osimertinib treatment, it is not clear why the study includes also patients treated with other TKIs or with osimertinib in combination with other agents.

Response: As the reviewer pointed out, all of the end-points relate to the first-line treatment with osimertinib. In general, osimertinib has become a standard of care for patients with advanced EGFR-TKI-naive NSCLC. On the other hand, the combination of EGFR-TKI with Bev or EGFR-TKI with chemotherapy, in addition to single agent osimertinib, has also been described as useful in the Japanese guidelines (Hiroaki Akamatsu et al. Int J Clin Oncol. 2019 24:731-770). In this situation, we decided to find out only the frequency of treatments other than single-agent osimertinib as first-line chemotherapy for EGFR mutation-positive NSCLC in the real world. Patients who have received EGFR-TKIs other than osimertinib or combination therapy with osimertinib and other agents will be enrolled only, and data on the course of treatment will not be collected. Therefore, these patients will not be included in the end-point analysis.

Reviewer: 2
Dr. Yi-long Wu, Guangdong Acad Med Sci

Comments to the Author:
Watanabe et al reported a protocol of design and rationale of a multicenter real word study on efficacy and safety of first-line osimertinib treatment and post-progression patterns for advanced NSCLC. In general osimertinib has became a standard of care for advanced EGFR mutant NSCLC. It is necessary to understand how to treat patients when they were failure to osimertinib measured by imaging. The goal of this protocol is very clear and rational.

1. Post-progression patterns and treatment suggestions for EGFR TKIs have been recommended by NCCN guideline and first time suggested by Dr. Yang (Lung Cancer 2013 Jan;79(1):33-9. I suggest that these need to be as study background in the introduction session.

Response: We have reviewed the paper suggested by the reviewer. The paper is very important and we have included it in the study background of the introduction session (p7, lines 150–152).

2. For the real world study, how to control bias, especially how to measure PFS is critical and a great challenge. Authors should discuss these.

Response: As the reviewer pointed out, we also think that it is very important to control for bias in the real-world trial. In this study, PFS is defined in the endpoint section (p12, lines 255–256), but this would be PFS in a situation where the timing of evaluation is not uniform. We will also clearly state bias as a limitation in the paper presenting the results of this study.

3. How many variables will be studied?

Response: Variables to be included in the analysis as patient background factors are EGFR mutation subtype, age, gender, performance status, smoking history, and primary disease (clinical stage, histology, metastatic organ) (p15, lines 331–334). Patients who receive osimertinib as their first EGFR-TKI treatment will be studied for the endpoints listed in the end point section. This study's primary endpoint is co-primary endpoint. First primary endpoint is the PFS of osimertinib, and another primary endpoint is the percentage of patients who show a pattern of progression when RECIST PD occurs with osimertinib treatment. In addition to the above, we will also investigate 14 secondary end points. Please refer to the end point section.