Author's response to reviews

Title: Pemetrexed for advanced non-small cell lung cancer patients with interstitial lung disease

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Author's response to reviews: see over
Dear, editor and reviewers,

Thank you very much for your generous and helpful comments about our paper. We are resubmitting a revised version of our manuscript entitled, “Pemetrexed for advanced non-small cell lung cancer patients with interstitial lung disease”. We have carefully revised our manuscript according to your comments. We have highlighted our revisions by using a red font in the manuscript.

#Reviewer 1’s comments

**Major compulsory revisions:**

**Patients and Methods:**

Line 12: “interstitial shadow on a chest CT” is not a diagnostic or scientific term. The authors should use recognized terms to describe radiological findings in the study patients.

A) We added the sentence below, and used recognized term to describe “interstitial shadow on a chest CT”. The sentence “Interstitial shadows were defined as reticular shadow, ground glass opacity, honeycombing, and traction bronchiectasis.” was added in “Patient selection” section. (page8, line14-16)

**Discussion:**

Page 17, limitations of the study: The reviewer agrees with the authors that a retrospective analysis of pemetrexed-associated pulmonary toxicity is an adequate tool to assess this issue, it should be stated here that the low number of patients suffering from ILD (n=25) does not allow to make definite conclusions about clinical endpoints such as PFS and OS (and in comparison with patients not suffering from ILD).

A) We added this limitation in the end of “Discussion” section and changed the sentences as follows;

Although the retrospective analysis of pemetrexed-associated pulmonary toxicity is one of the reasonable tools to assess this issue, the small number of patients suffering from ILD also does not allow to make definite conclusions about clinical endpoints such as PFS and OS. (page19, line17-21)

Conclusions:

It is not well understood why patients with IIPs are opposed to patients without ILD, as IIP is a subgroup of patients with ILD (IIP, UIP); this makes the final statements not very clear. In the final statement, the authors say that the risk of pulmonary toxicity is
particularly elevated in patients with a UIP pattern, but this – again – is somewhat at
odds with the previous statement that pulmonary toxicity is higher for pts with IIP
compared to those without ILD. The authors should try to make the Conclusion’s
Sections very clear to the reader.

A) Thank you for your comment. We changed from supplemental figure 1 to figure 1.
Firstly, we would like to investigate the frequency of pulmonary toxicity in the patients
with IIPs and treated with pemetrexed. To compare the frequency of pulmonary toxicity,
we thought the patients without ILD is more suitable control than the patients without
IIPs (the patients without ILD plus the patients with radiation pneumonitis/ CVD-IP).
Moreover, the number of the patients with radiation pneumonitis/ CVD-IP is very small.
That is why we excluded the patients with radiation pneumonitis/ CVD-IP from this
analysis. From the result shown in Table 3, despite no statistically significant difference,
the risk of pulmonary toxicity might be greater for NSCLC patients with UIP pattern on
chest CT than those with non-UIP pattern. So, we changed the sentence in “Conclusion”
section. “The risk of pulmonary toxicity is greater for NSCLC patients discovered to
have a UIP pattern on chest CT findings” was changed to “the risk of pulmonary
toxicity might be higher for NSCLC patients with UIP pattern than non-UIP pattern on
pretreatment chest CT.” (page20, line5-7)

Minor essential revisions:

Abstract:
The authors should explain/write-out the abbreviations (IIP, UIP) in the abstract.
A) We explain/ write out the abbreviations, IIPs (Idiopathic interstitial pneumonia) and
UIP (Usual interstitial pneumonia). (page3, line 10 and 16)

Background:
Line 5 ff: Can the authors also give some numbers about the frequency of ILD in
patients diagnosed with NSCLC? Could the authors mention potential inter-ethnic
differences in the frequency of ILD between Asians and Caucasians (and other
ethnicities), and how this could affect their study results.
A) It has been reported that the prevalence of IPF in the United States and Japan were
estimated to be 14.0 to 42.7 and 3.44 per 100,000 people, respectively. It is unknown
whether the prevalence of IPF and prevalence of lung cancer in IPF patients are
influenced by ethnic, geographic or cultural factors or not, because there are no reports
on direct comparison of incidence and prevalence rate between Caucasian and Japanese.
We added these sentences in “Background” section. (page5, line 12-19)
The authors are encouraged to give a short overview on the major causes of ILD (ex IIP).

A) ILD consists of disorders of known causes as well as disorders of unknown cause. IIPs are most frequent disease in ILD. Then, ILDs except for IIPs contain many heterogeneous diseases like collagen vascular disease related interstitial pneumonia, sarcoidosis, pneumoconiosis, radiation pneumonitis and drug related lung injury. We added these sentences in “Background” section. (page5, line4-8)

Are there similar data for the higher occurrence of chemo-associated pulmonary toxicity in patients with ILD for Caucasians or other non-Asian patient cohorts, or is this rather specific for Asian patients?

A) In the treatment with any anti-cancer agents for Caucasian and non-Asian, it has been reported that the incidence of pulmonary toxicity is about 0.1-1.0% in patients with NSCLC. In most of reports, chemo-associated pulmonary toxicity was not evaluated and compared between patients with ILD and those without ILD. There are no reports on chemo-associated pulmonary toxicity in Caucasian and non-Asian patients with ILD.

End of Introduction: Is there any rationale or hypothesis for why chemo-associated pulmonary toxicity is more frequent in Asian compared to Caucasian patients?
A) It is thought that this ethnic difference may be explained by genetically. However, so far, there is no clear scientific evidence which reveal this difference. We added these sentences in the end of “Background” section. (page6, line11 to page7, line1)

Patients and Methods:
Treatment methods, line 13: Standard dose for folic acid is 1mg daily; is there a particular reason the authors use 350ug of folic acid in their patients?
A) I’m sorry that we missed the dose of folic acid. We usually used 500µg of folic acid according to the report of Hanna N, et al. (J Clin Oncol 2004, 22: 1589) and Ohe Y, et al. (Clin Cancer Res 2008, 14: 4206). We changed the dose of folic acid and added the references in the end of “Treatment method” section. (page9, line15)

Statistical method, Line 13: It remains unclear which „differences in PFS and OS“ were analyzed (between patients experiencing pulmonary toxicity and those not experiencing pulmonary toxicity?).
A) The differences in PFS and OS between IIPs group and non-ILD group were analyzed using the log-rank test. We added “between IIPs group and non-ILD group” in the middle of the sentence. (page10, line18)

Results:
Line 8: Please be careful with abbreviations (HC, honeycombing), better write out.
A) We removed the abbreviations, HC and TB. Instead, we spelled out honeycombing (page 8 line17, 19 and page12 line7, 9) and traction bronchiectasis (page8 line17 and page12 line17).

Line 16: 12% of pts had activating EGFR mutations. Why did these patients receive first-line platinum-based chemo instead of an EGFR inhibitor?
A) In Japan, usually, the NSCLC patients with ILD were not treated with EGFR-TKI due to the high incidence of pulmonary toxicity. Therefore, 12% of patients didn’t receive EGFR-TKI for first line treatment.

Efficacy and survival: Although disease control rate differed between groups, clinical outcome (PFS, OS) did not differ; therefore, and as of the very small number of patients, the authors’s first reporting should be that treatment response and outcome is not relevantly different between the two groups.
A) Thank you for your comments. We changed the order of the sentences. First, we wrote the sentences; “Treatment response and outcome is not relevantly different between the two groups.” Then, we describe in order of response rate, PFS, OS, and disease control rate. (page13, line 2-16)

Discussion:
Page 16, line 9: abbreviation DTX (docetaxel?)
A) We spelled out docetaxel followed by the abbreviation, DTX. (page6, line 15-16)


#Reviewer 2’s comments

**Minor essential revisions**

Introduction. I suggest to report the data about the ILD induced by EGFR TKIs specially in Asian population.

A) Thank you for your comments. We added the description of pulmonary toxicity induced by EGFR-TKI in Japanese compared with Caucasian in “Introduction” section as follow; it has been reported that the incidence of pulmonary toxicity in Japanese patients (2%) is higher than in USA patients (0.3%) in treatment of gefitinib for NSCLC patients by FDA. (page6, line11-13)

2. Introduction. It could be of interest to report the incidence of ILD in Asian compared to Caucasian population and its relation with the antiblastic agents.

A) It has been reported that incidence of PEM-induced pulmonary toxicity is about 0.8% (2 cases in 265 total patients) in Caucasian and 3.5% (4 cases in 116 total patients) in Japanese. The incidence of DTX-induced pulmonary toxicity is about 2.1% (6 cases in 276 total patients) in Caucasian and 4.6% (18 cases in 392 total patients) in Japanese. And it has been reported that the incidence of bleomycin-induced lung injury was 0.66% in Japan and 0.01% in global cases. These rates in Japanese are higher than in Caucasian or other Asian. However, there are no reports on direct comparison of pulmonary toxicity induced by cytotoxic agents among Japanese, other Asian and Caucasian. We describe these sentences in “Background” section. (page6, line13 to page7, line1 and page7, line8-12)

3. Pulmonary toxicity. It is important to define the pulmonary toxicity in particular which pulmonary toxicity and which grade because in the CTCAE there are many pulmonary toxicity with different impact on the quality of life of the patients.

A) We defined pneumonitis, pulmonary fibrosis and adult respiratory distress syndrome in CTCAE terms as pulmonary toxicity, and added this definition in “Evaluation of response and toxicity” section. (page10, line3-7)

4. The use of pemetrexed in this retrospective analysis is from second-line. For this reason the population is too heterogeneous with different risk of ILD induced by previous treatments. A medium/high percentage of patients received probably an EGFR TKI in first (mutated patients) or in second/third-line (wild-type patients), these information should be taken into account in the interpretation of the results and discussed in the article.
A) Thank you for your comments. In terms of overall survival (OS), we have already described “OS in the non-ILD group tended to be longer than in the IIPs group. One possible explanation for this is that more patients had a sensitive EGFR mutation in the non-ILDs group than in the IIPs groups.”

In terms of adverse events including pulmonary toxicity, we evaluated adverse events until 4 weeks after the completion of chemotherapy. Pulmonary toxicity did not occur during 4 weeks after pemetrexed treatment with EGFR-TKI. Pulmonary toxicity also did not occurred during 2 weeks after cessation of pre-treatment EGFR-TKI. Therefore, we suppose PEM-induced pulmonary toxicity was not affected by EGFR-TKI treatment in our research. These descriptions were added in “Evaluation of response and toxicity” section and “Discussion” section. (page18, line9-14)

5. Every statistical consideration is biased by the small number of patients included in this study and every conclusion should be taken with caution.

A) We completely agree with your comment, and added this limitation of this study in “Discussion” section as follows; the sample size of this study is too small. It is not easy to collect data on a large number of patients with between NSCLC and ILD and received with PEM. Therefore, it is difficult to reach a definitive conclusion. (page19, line17-21)