Author’s response to reviews

Title: A phase I/II study of weekly nab-paclitaxel plus cisplatin in chemotherapy-naïve patients with advanced non-small-cell lung cancer

Authors:
Yoshihiro Hattori (hattori@hp.pref.hyogo.jp)
Yuko Kono (kono119@hp.pref.hyogo.jp)
Shoichi Itoh (sho1.itoh@hp.pref.hyogo.jp)
Takako Inoue (okuyama-ta@mc.pref.osaka.jp)
Yoshiko Urata (urata@hp.pref.hyogo.jp)
Yoshitaka Kawa (ohayoubird@gmail.com)
Rie Tohnai (tohnair@hyogo-cc.jp)
Toru Kumagai (kumagai-to@mc.pref.osaka.jp)
Kazumi Nishino (nisino-ka@mc.pref.osaka.jp)
Ryuji Uozumi (uozumi@kuhp.kyoto-u.ac.jp)
Satoshi Morita (smorita@kuhp.kyoto-u.ac.jp)
Shunichi Negoro (negoro@takarazuka-cst.jp)
Fumio Imamura (imamura-fu@mc.pref.osaka.jp)
Miyako Satouchi (satouchi@hp.pref.hyogo.jp)

Version: 1 Date: 05 Jan 2020

Author’s response to reviews:
Response to Reviewers

Reviewers’ comments:
Giorgio Scagliotti (Reviewer 1): The results of this phase 1/2 trial showed promising activity and acceptable tolerability for the combination of cisplatin plus nab-paclitaxel in chemo-naïve advanced NSCLC patients, requiring further investigation in larger randomized studies.

The article requires major revisions to be suitable for publication:

- In the background: current treatment scenario of advanced NSCLC should be further detailed, including treatment options recommended according to molecular status, PD-L1 expression and histological subtype;

We revised it.
(Background section, line 82-91, page 5)

- At page 7, line 18-25, the comparator arm should be specified;

We added the comparator arm.
(Background section, line 104, page 6)

- The efficacy results of CA031 study trial have been reported at beginning of background while safety at the end: I suggest to report the overall results only once, better at the end;

Thank you for the suggestion. They are reported together at the end.
(Background section, line 129-131, page 8)

- At page 9, line 18-21, the sentence is not clear: do you mean…is supposed to be associated with an improved toxicity profile…? please check and rephrase this sentence.

We revised it.
- Along with molecular alterations, it would be interesting to know also PD-L1 expression status, since patients with PD-L1>50% should be candidate to first-line pembrolizumab.

Thank you for the comments. Because our study started in 2013, it was not mandatory to evaluate PD-L1 expression status from the start of our study. For this reason, PD-L1 expression status was not determined, and thus, it is difficult to analyze data related to PD-L1.

- Furthermore of platinum-pemetrexed is recommended as best upfront regimen in adenocarcinoma patients, representing about half of your study population. Please explain about that.

It is well known that platinum-pemetrexed is one of the best regimens in adenocarcinoma patients. On the other hand, in a subset analysis of the CA031 trial, it was reported (Satouchi M, et al. Lung Cancer. 2013 Jul;81(1):97-101.) that weekly nab-paclitaxel plus carboplatin was effective in Japanese patients (including approximately 80% adenocarcinoma patients). The study was designed to assess nab-paclitaxel as a weekly regimen, which may be an alternative to platinum-pemetrexed in some cases.

- It would be useful providing specific subgroups of stage IV (M1a, M1b, or M1c) according to the 8th TNM version, since it may have relevant prognostic implications, with impact on final OS results.

Thank you for the suggestion. We have performed an analysis, but given the small number of patients, it was difficult to determine the impact on prognosis using our data.
MST (months) (95% CI)
M1a (n=7) 27.7 (12.0 to NE)
M1b (n=6) 7.5 (2.5 to 28.8)
M1c (n=5) NE

- Even if are very few patients it could be interesting evaluating any potential survival differences according to the histological subtype. Furthermore the OS results should be discussed in light of Pemetrexed manteinance data, representing current standard in non-squamous NSCLC.

Thank you for the suggestion. We analyzed the data by histological subtype. Additionally, a comparison of pemetrexed with maintenance treatment was added.

(Results section, line 248-250, page 15)
(Discussion section, line 280-283, page 17)

MST (months) (95% CI)
Non-Sq (n=15) 24.2 (6.3 to NE)
Sq (n=7) 19.8 (6.7 to NE)

- More relevant hematological and non-hematological toxicity rates should be reported in the results section, as well as a brief comment on 30% grade &gt;3 neutropenia, in the discussion.

We revised these points.

(Results section, line 254-258, page 15-16)
(Discussion section, line 290-293, page 18)
- The subgroup analysis of KEYNOTE-407 trial could be discussed, showing that the type of taxane (60.1% of patients in the study received paclitaxel, while 39.9% nab-paclitaxel) did not significantly influence efficacy and safety of immuno-chemotherapy combination, with an interesting trend toward a longer survival and an increased incidence of grade ≥3 AEs in favour of nab-paclitaxel.

Thank you for the comments. We added grade ≥3 AEs, as above. In addition, we added the IMpower130 trial.

(Discussion section, line 305-307, page 19)

- English language revision is recommended

Thank you for the suggestion. English proofreading was performed.

Vittorio Gebbia (Reviewer 2): The authors report a phase I-II aimed to evaluate the efficacy and safety of nab-paclitaxel plus cisplatin in chemotherapy-naïve patients with advanced NSCLC without any actionable mutation drivers.

Overall the paper is concise and well written.

Methodology is correct but further details should be reported concerning the statistical design of the phase II phase of the study.

We added comments regarding these points.

(Methods section, line 217-225, page 13-14)

Moreover authors should comment which is the innovative data of this work since the combination of nab-paclitaxel and platinum salts has been largely reported in medical literature.

Phase II study of nab-paclitaxel + carboplatin for patients with non-small-cell lung cancer and interstitial lung disease.

Kenmotsu H1, Yoh K2, Mori K3, Ono A1, Baba T4, Fujiwara Y5, Yamaguchi O6, Ko R7, Okamoto H8, Yamamoto N9, Ninomiya T10, Ogura T4, Kato T11.


Health-Related Quality of Life With Carboplatin-Paclitaxel or nab-Paclitaxel With or Without Pembrolizumab in Patients With Metastatic Squamous Non-Small-Cell Lung Cancer.

Mazieres J1, Kowalski D2, Luft A3, Vicente D4, Tafreshi A5, Gümüş M6, Laktionov K7, Hermes B8, Cicin I9, Rodríguez-Cid J10, Wilson J11, Kato T12,

Ramlau R13, Novello S14, Reddy S15, Kopp HG16, Piperdi B17, Li X17, Burke T17, Paz-Ares L18.

Thank you for the comments. We added information regarding these points.

(Discussion section, line 304, page 18)

(Discussion section, line 307-311, page 19)

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (BMC_WRITING_RESOURCES_URL http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.

Thank you for the suggestion. English proofreading was performed.