Author's response to reviews

Title: A randomized, phase 2 study comparing pemetrexed plus best supportive care versus best supportive care as maintenance therapy after first-line treatment with pemetrexed and cisplatin for advanced, non-squamous, non-small cell lung cancer

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Author's response to reviews: see over
Point-by-Point Responses to Reviewer’s Comments

Title: A randomized, phase 2 study comparing pemetrexed plus best supportive care versus best supportive care as maintenance therapy after first-line treatment with pemetrexed and cisplatin for advanced, non-squamous, non-small cell lung cancer

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Reviewer: Thomas Stinchcombe

Major compulsory revisions

1. **When discussing the overall survival and progression-free survival from first dose of induction therapy it should be emphasized that these are strictly exploratory since the trial was not statistically designed to answer that question and only 51.9% of patients were randomized to the intervention under investigation.**
   Response: We agree on emphasizing that the study was not designed to analyze the survival from the induction phase, and thus the text has been revised to specify these analyses were exploratory throughout the manuscript.

2. **I assume response and disease progression were assessed by the investigator, and this should be included in the study assessments.**
   Response: Yes, you are right. We have revised the text in the Study Assessments section to include this point: ‘Tumor assessments were performed by investigators at each investigative site, per RECIST (version 1.0) requirements [8], at baseline (no more than 4 weeks before the initiation of induction therapy) and every 6 weeks (±1 week) during study therapy’ (in ‘Methods/Study assessments’).

   Since this was not a placebo control trial this assessment was susceptible to bias, and that should be discussed as well
   Response: We agree with you and we hence have acknowledged this limitation in the Discussion section: ‘Another potential limitation that could be worth mentioning is the absence of a placebo arm. The investigator-assessed response and disease progression are normally not precisely measured as OS is (with an exact date of death), and therefore may be subject to assessment bias, particularly in open-label studies such as this one. Obviously, we cannot rule out this possibility. However, as this is a phase II proof of concept study rather than a confirmatory phase III trial, an independent review panel was not used to validate the investigator assessments. The administration of placebos in
oncology studies was reviewed by Chvetzoff and Tannock [12], it was shown to improve symptom control (such as pain and appetite) but did not lead to tumor response. Hence, given that our primary and secondary endpoints were PFS, OS and tumor response rate, we argue that the absence of a placebo would not introduce significant bias to our efficacy outcome measures in this trial' (in 'Discussion section').

3. **The PARAMOUNT trial was published in the Lancet Oncology, and the references 10 and 11 should be changed to reflect the final publication.**

   Response: The PARAMOUNT' final publication in Lancet Oncology was updated as suggested (References # 13 and 14).

   **There was also an early analysis of overall survival included in the publication which should be included in the discussion**

   Response: As we have now the overall survival final results, presented on June 2012 at the 48th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, we have updated this information in the Discussion section: "Patients achieved a median OS of 13.9 months from randomization (16.9 months from start of induction) on the pemetrexed continuation maintenance arm compared to 11.0 months from randomization (14.0 months from start of induction) on the placebo arm [14]" (in 'Discussion section').

4. **In the discussion the authors discuss differences in baseline characteristics of patients enrolled in pemetrexed and BSC arms; stage IV patients (19 in the pemetrexed and 17 in the BSC), male patients (20 in the pemetrexed and 17 in the BSC) as well as response to therapy (partial response 10 in the pemetrexed and 11 in the BSC).**

   Given the small difference in the number of patients and the multiple factors that influence prognosis this discussion is very dubious, and should be eliminated

   Response: We agree and have removed those sentences.

**Minor essential revisions**

1. **This is a minor point, but was there an eligibility criterion for renal function?**

   Response: Yes, there was an eligibility criterion for renal function in the protocol and it was added in this revised version – ‘a calculated creatinine clearance (CrCl) ≥45 mL/min based on the standard Cockcroft and Gault formula and a serum creatinine <1.5 x ULN’ (in ‘Methods section/Patient eligibility’).

2. **I would recommend including the median PFS in the text on page 13 with the hazard ratio**

   Response: In accordance with your suggestion, the numbers were added in the main text – ‘The median PFS time for the maintenance phase for both treatment arms was 3.2 months
(95% confidence interval [CI]: 2.9 to 6.1 for the pemetrexed/BSC arm, 95% CI: 2.2 to 4.3 for the BSC arm). The PFS HR stratified by the best tumor response for induction therapy was 0.76, two-sided 95% CI: 0.42 to 1.37; one-sided p-value=0.1815’ (in ‘Results section/Progression-free survival and overall survival’)

3. **I would suggest including the data from the non-squamous patient population from the trial by Ciuleanu as well as the intent-to-treat since that is the patient population of clinical interest and similar to the patient population enrolled in this trial**

   Response: With regard to the Ciuleanu et al study, we added the following sentences:
   ‘…The primary endpoint of PFS and the secondary endpoint of OS were analyzed by the intention to treat principle. The PFS was statistically significantly longer in the pemetrexed/BSC arm than in the placebo/BSC arm (median PFS: 4.3 vs 2.6 months, respectively; hazard ratio [HR]=0.50, 95% CI: 0.42-0.61, p<0.0001). Overall survival (OS) was also significantly improved for the pemetrexed/BSC arm compared to the placebo/BSC arm (median OS: 13.4 vs 10.6 months, respectively; HR=0.79, 95% CI: 0.65-0.95; p=0.012) [5]’ (in ‘Background section’).

4. **The use of treatment emergent adverse events for reporting the adverse events in both arms is ambiguous since patients in the best supportive care did not receive treatment**

   Response: Per study protocol ‘treatment-emergent adverse events (TEAE)’ were defined as any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment. The TEAEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.’ (in ‘Methods section/Study Assessments’).
Reviewer: Buelent Polat

Major compulsory revisions

1. *Initially n=106 patients were included into this study. Of this 76 patients had no progression after 4 cycles of cisplatin/pemetrexed induction chemotherapy. But only 55 patients were randomized. What happened with the remaining 21 patients who also were eligible for inclusion into the study?*

   Response: We have added a patient disposition’s figure to better explain the destiny of all patients, and the text was also modified.

   Following the induction phase, a total of 80 (75.4%) patients had no disease progression documented. At the moment of randomization for the maintenance phase actually 25 patients were not randomized (received less than 4 induction cycles, n=14; death, n=3; unknown, n=6; patient decision, n=1; non-compliance, n=1), and 55 patients qualified for both requirements (4 cycles of induction chemotherapy and no disease progression documented) (80-25=55)

   – ‘Patient disposition is summarized in Figure 1. A total of 108 patients were screened for the study, of whom 1 did not meet the eligibility criteria and 1 was lost to follow-up. Therefore, 106 patients were enrolled and received at least 1 dose of induction therapy.

   Following the induction phase, a total of 80 (75.4%) patients had no disease progression documented, although 55 patients of them were considered protocol-qualified and were randomized to maintenance treatment with pemetrexed/BSC (n=28) or BSC alone (n=27).’

   (in 'Results section/Patient Disposition')

   – Figure 1. Patient Disposition
Discontinued, n=17 (30.9%)
Reasons for discontinuation:
Death, n=15 (55.6%)
Lost of follow-up, n=2 (7.4%)

Enrolled
N=106

CR/PR/SD/UNK= Complete Response (n=1, 0.9%)/Partial Response (n=26, 24.5%)/Stable Disease (n=49, 46.2%), per RECIST/UNK=unknown (i.e. progression had not been documented, and 1 or more target or nontarget sites had not been assessed [n=4, 3.8%])

Unknown= insufficient data

Abbreviations: AE= adverse event, BSC= best supportive care, Pem= pemetrexed, PD= progressive disease

Minor essential revisions

1. For clarification please consider to give the PFS duration of the both groups in months in the abstract and the main text and not only in table 2
Response: In accordance with your suggestion we added the time of PFS in the Abstract and Results – ‘The median PFS time for the maintenance phase for both arms was 3.2 months (pemetrexed/BSC arm, 95% CI: 2.9 to 6.1; BSC arm, 95% CI: 2.2 to 4.3).’ (in 'Results section/Progression-free survival and overall survival')

2. Please cite the recently published full paper of the PARAMOUNT Study: Lancet Oncology 2012 Mar;13(3) Please consider citing also the article on the according quality of life data of the above mentioned study
Response: The PARAMOUNT final publication in Lancet Oncology was updated as suggested, and its recently known overall survival results were also mentioned. (References # 13 and 14)

3. A further study was recently published by Zhang et al. in a similar setting on maintenance therapy with Gefitinib in Lancet Oncology May 13(5)
Response: Although the INFORM study shared with our study the search of an optimal maintenance therapy, we do not feel encouraged to make reference to this study since we found in it other substantial differences: induction phase with platinum-based doublet chemotherapy, switch maintenance therapy, and east Asian ethnicity.

4. There is a comparable rate of grade 3/4 toxicities in both arms of about 18%. Can you explain why the patients in the BSC arm experienced these?
Response: During the maintenance phase, the percentages of patients with at least one grade 3/4 toxicity were similar in both arms (pemetrexed/BSC, 17.9%; BSC, 18.5%), but just 1 patient with at least 1 grade 3/4 TEAE was considered to be possibly drug related in the BSC arm (anemia)’ (in 'Results section/Safety')

5. On page 17 you state that maybe the patient cohort in your study did not have sufficient access to supportive care. But since your investigational question was comparison of best supportive care against BSC plus pemetrexed you have to assure that the patients have access to supportive treatments
Response: In our study, per protocol, the BSC was given according to local standards and homogeneously between both arms. The comment addressed here tries to open a discussion about a probably worse prognosis of this Arab population compared to patients in more industrialized countries. In order to avoid confusion we clarify the wording of these sentences as following: 'In the current study, the median PFS and OS times for the maintenance phase for the pemetrexed/BSC arm were 3.2 and 12.2 months, respectively, which are substantially shorter than the median PFS and OS times of 4.5 months and 15.5 months observed in the previous phase 3 trial in patients with advanced, non-squamous NSCLC following switch maintenance therapy with pemetrexed [5]. It could be possible this Arab patient population may have less access to health care than patients from more affluent, industrialized countries, and that would favor a relatively poorer prognosis, although these statistical variations could also be explained by the smaller size of the population of the current study.' (in 'Discussion section').

6. On page 12, what is meant by inadequate response? Did 64% of patients have disease progression?
Response: Yes, that is correct, it means disease progression (the words 'inadequate response' were replaced by 'disease progression' throughout all the manuscript).

Discretionary revisions

1. Page 12 line 7: please write randomized instead of 'randomization'
Response: Corrected

2. Page 18 and 19: missing brackets when citing ref. 10 and 11
Response: Corrected
3. Page 15 line 6: please consider not to combine ‘best response’ and ‘progressive disease’ in one sentence since could be confusing
   Response: In order to avoid confusion we changed the sentence to ‘Nine (32.1%) patients in the pemetrexed/BSC arm and 10 (37.0%) patients in the BSC arm showed progressive disease’

4. Please give the p-values or HR in the figure legends
   Response: Added
Reviewer: YoungHak Hak Kim

I wonder whether the authors' statistical assumption using a one-sided alpha of 0.2 is appropriate. Is it too lax to appeal the need for further clinical trials? In fact, the results of both PFS and OS were almost identical between the two arms.

Response: To clarify this concept, we added in Discussion section the following statement: ‘A primary consideration in designing a phase 2 clinical study is to minimize the chance that a truly active agent or regimen is erroneously rejected by keeping the probability of type II error (false-negative) low [11]. We attempted to do this by using a higher type I error rate (alpha=0.2) than would typically be used in a larger phase 3 trial (alpha=0.05).’ *(in 'Discussion section').


Moreover, there’s no new information including toxicity after the publication of PARAMOUNT study

The further conducted confirmatory Phase 3 trial 'PARAMOUNT' (published recently in Lancet Oncology in Mar 2012/ASCO June 2012) confirmed the superior PFS and OS in the pemetrexed arm compared to the placebo arm, and showed an acceptable safety profile. We added the following sentences: ‘The main differences in adverse events reported in the Paramount trial between the two arms were higher grade 3/4 toxicity rates for pemetrexed as follows: fatigue (4.2% vs 0.6%, respectively), anemia (4.5% vs 0.6%), and neutropenia (3.6% vs 0%) [14]. Consistent with the safety results for our study, the safety data from the PARAMOUNT study showed that pemetrexed maintenance therapy was generally well-tolerated [5,14].’ *(in 'Discussion section').

Major compulsory revisions – Results

1. **Patient Disposition:** Five (17.9%) patients in the pemetrexed/BSC arm and 10 (37.0%) patients in the BSC arm fully completed the study.

   **What means fully completed?**

   Response: To better explain the sentence was rephrased as follows: ‘Five (17.9%) patients in the pemetrexed/BSC arm and 10 (37.0%) patients in the BSC arm were alive and progression-free at the end of the study’ (in ‘Discussion section/Results’). Also we added in Methods/Study Treatment: ‘The end of the study was set at 12 months after maintenance phase randomization or 30 days after the end of the maintenance treatment’.

2. **Patient Disposition:** The most common reason for premature study discontinuation in both arms was death (pemetrexed/BSC, 60.7%; BSC, 55.6%), which was predominantly due to the study disease.

   **Does that mean treatment-related death, or else what does that mean?**
Response: It means any death due to non-squamous NSCLC (the words ‘study disease’ were replaced by ‘non-squamous NSCLC’ throughout all the manuscript).

3. **Tumor Response: Therefore, the disease control rate for the induction phase was 71.7% (76/106). Of the 55 patients randomized to the maintenance phase, 7 (25.0%) patients in the pemetrexed/BSC arm and 11 (40.7%) patients in the BSC arm responded to the induction therapy.**

   **There are 21 patients who achieved disease control and were not randomized to the maintenance phase. The reason should be disclosed.**

Response: Please refer to Reviewer 2, first bullet, response number 1
Reviewer: Bryan Schneider

Abstract

1. The median PFS and OS numbers should be stated in the abstract and not use vague terms like 'similar'
   Response: The specific times were added.

Background

1. Would benefit from careful editing with particular focus on English usage and grammar. For example the first sentence ....typically a relatively brief... should be reworded
   Response: The document was edited to improve its quality.
2. Second paragraph, most practicing oncologists would know pemetrexed is not platinum
   Response: The non-platinum adjective was removed.
3. Would expand briefly on why vitamin supplementation is given (to reduce cytopenias)
   Response: According to your suggestion the following sentences were added: ‘Its multiple enzyme inhibitions also account for the potentially adverse effects of pemetrexed, including myelosuppression (mainly transient neutropenia), oral mucositis, diarrhea, and rash/desquamation. It has been found that the hematological and nonhematological toxicities of pemetrexed can be reduced through routine vitamin supplementation (folic acid and vitamin B_{12}), without loss of efficacy [4].’ (in ‘Background section’).
4. Second paragraph ‘.....despite more patients receiving additional systemic anticancer therapy……’ should be removed as this is misleading and clearly reflects bias of the authors. If you consider the maintenance drug to be active 2nd line therapy, then 100% of the study arm received 2nd line therapy whereas only 67% of the control arm received 2nd line therapy. Furthermore, 51% of the study arm received 3rd line therapy with no data on the number of patients in the control arm that received 3rd line therapy (presumably less though)
   Response: Removed

Methods

1. Would specify the 6th edition of the TNM staging system was used
   Response: We specify the 6th edition of the TNM used, in the main text (in ‘Methods section/Patient eligibility’), and as a footnote of Table 1.
2. **Under study treatment, first paragraph, the sentence ‘Randomized patients who discontinued study treatment without progression...’ is unclear**
   Response: Deleted, it was explained better: ‘Following induction therapy, patients who still remained in the study without disease progression were randomized...’ (in 'Methods/Study treatment').

3. **Patients were observed until disease progression?**
   Response: In order to clarify, the end of the study was added: ‘The end of the study was set at 12 months after maintenance phase randomization or 30 days after the end of the maintenance treatment’ (in 'Methods/Study treatment').

**Results**

1. **Under patient disposition: ‘inadequate response’ does this mean they progressed during the therapy?**
   Response: Yes, it means disease progression (the words 'inadequate response' were replaced by 'disease progression' throughout all the manuscript).

2. **Last sentence of the paragraph ‘Fully completed the study’ needs clarification. What defined completion of the study? Disease progression?**
   Response: in Methods/Study treatment was added: ‘The end of the study was set at 12 months after maintenance phase randomization...’

3. **Progression-free and overall survival: These data need to be presented in a clearer fashion that a practicing oncologist will understand. The median PFS for both arms should be presented in this section. The interpretation of the hazard ratio could then be reviewed in the discussion section if the authors want to explain why the HR is potentially meaningful despite no improvement in the median PFS**
   Response: The specific PFS and OS data were added and the interpretation of the HR was deleted from the Results section.

**Safety**

1. **Would avoid vague descriptors like ‘relatively low’**
   Response: We changed it to ‘acceptable safety profile’

2. **Death from AE not related to study drug should be presented in the text. What were the specific AEs?**
   Response: Deaths from AE occurred were added (sudden death and cardiac arrest). The specifics AEs are now explained in Results Section, and also in Table 3.

**Discussion**
1. **PARAMOUNT has been published in full manuscript form. Would update the reference. Lancet Oncol 2012;13:247-55**
   
   Response: The PARAMOUNT final publication in Lancet Oncology was updated as suggested (References # 13 and 14)

2. **Would expand on the clinical relevance of the trial results**
   
   Response: We added the following explanation: ‘The median PFS times for the maintenance phase did not differ between the two treatment arms. Although clinical researcher may be more familiar with median survival in comparing two treatment groups, this single median point comparison could be insufficient. In contrast, the HR estimate based on Cox regression model compares the whole range of survival times across the two groups; hence a more effective measure of survival difference, given the proportional hazard assumption is met. HR has been commonly used to present the primary result of survival data in oncology trials…Recent results of a phase 3 trial provide stronger evidence of the potential benefit of continuation pemetrexed maintenance therapy [13,14]…’

3. **The authors note more men and stage IV patients in the maintenance arm as potential reasons for the modest results. However there were only 2 more stage IV patients and 3 more men compared to the control arm. It this enough to dilute a survival benefit?**
   
   Response: We removed this observation, in accordance with its low number and low impact in the survival conclusion.

4. **A large portion of the patients were never-smokers in both arms (about 40%). This population typically has a good prognosis and could have also diluted a small but meaningful benefit with the maintenance pemetrexed. They typically do better with most therapy compared to the current/former smokers**
   
   Response: We agree with you on the concept that the patients with lung cancer with a light or never-smoking history have a better prognosis than patients who are former or current smokers. But in our study, as we have more patients that were ever smokers (former + current), with no meaningful difference within arms (Former + current smoker patients at baseline in the pemetrexed/BSC arm, n=16 [56%]; BSC arm, n=17 [63%]), the patients’ smoking status seems to add more a negative than a better influence in their prognosis.