

Peer Review File

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Comment 1: Page 3 – Lines 115-117 – It is not necessary to report findings in the introduction. I would delete this sentence and add a sentence indicating that principal component analysis was carried out to identify symptom and cytokine clusters, followed by an exploration of associations between identified symptom and cytokine clusters.

Reply 1: We have made the changes as suggested.

Changes in the text:

Added, page 6 line 117-119: **Principal component analysis was carried out to identify symptom and cytokine clusters, followed by an exploration of associations between identified symptom and cytokine clusters.**

Removed: Original lines page 6 115-117: A pro inflammatory cytokine cluster was found to correlate with a physical functioning symptom cluster and a gastro-intestinal-fatigue symptom cluster.

Comment 2: Page 4 – Statistical analysis – Given the number of comparisons made (15 for symptoms and 20 for cytokine levels – Tables 4 and 6) between baseline and week 4, you should consider correcting the p-value that would be considered significant (e.g. Bonferroni correction). In addition, please state the p-value that is considered significant (e.g. $p < 0.05$).

Reply 2: We have corrected the p-value using Bonferroni correction. This resulted in no significant changes for neither symptoms nor cytokines at the two timepoints. This is however not the focus of the paper and does not affect the major findings.

Changes in the text:

Page 9, line 174-176: We clarified that Bonferroni correction was use by adding this information in the text.

Page 12 line 232-238:

Removed: Constipation was, however, significantly improved. Only minor differences were observed through analyzing individual factors over time. A significant increase in the symptom scale was observed for question 1 (short walk), 2 (fatigue), 4 (shortness of breath) and 13 (tenseness), whereas lower symptom scores were observed for question 10 (constipation) (see Table 4).

New text, line 232-234: ... , **whereas constipation was improved, although no statistical significance was seen using paired t-test with Bonferroni correction.**

Table 4: Significance stars were removed, table head was extended clarifying level of significance: **The p -value for each pair is reported, significance level is $p < 0.003$ according to Bonferroni correction analyzing 15 parameters.**

Table 6: Significance stars were removed, table head was extended as for table 4: **Significance, p , referring to significance using Wilcoxon signed-rank test. Bonferroni corrected p -value based on 20 cytokines gives significant difference if $p < 0.0025$.**

Comment 3: Page 5 – Correlation of Cluster – What statistical test was used to evaluate the association between symptom and cytokine clusters? Based on your reporting of and “R” value in Table 8, I believe you used simple linear regression. Is this correct? Please specify the statistical test used.

Reply 3: Yes, we used linear correlation, calculating Pearson correlation coefficient, r . This has been clarified in Materials and Methods, and we have also changed R to be the more correct “ r ” instead.

Changes in the text:

Added in line 219: **Linear correlation was performed calculating the Pearson correlation coefficient, r .**

R replaced for r in line 261,262,264 and Table 8.

Comment 4: Pages 13 and 14 - Table 3 – The table does not provide the breakdown of cancer types for week 4. Since the number of patients included in the baseline and week 4 analysis differ, the types of cancer diagnoses would also be expected to differ. Please include the types of cancer for patients included in the week 4 analysis.

Reply 4: We have added information about cancer types at week 4.

Changes in the text: See table 3, number of cancer types at week 4 has been added.

Comment 5: Pages 13 and 14 - Table 3 – There is a discrepancy in the number of patients with metastases (94) and the number of metastatic sites (location) listed (51). I would expect there to be more metastatic sites than patients, since it would not be unusual for patients to have more than one metastatic site. Additionally the number with no metastases (67) is not consistent with the number of patients with metastases (94) and the total number of patients accrued to the study (110). If there were 94 patients with metastases then there should only be 16 patients without metastases. Please check your numbers and confirm reported number of patients with metastases and number of metastatic sites.

Reply 5: We are grateful for the observant comment, data for liver, lung, skeletal and abdominal metastases are missing in table 3. This has now been added for both timepoints.

Changes in the text: See table 3, number of patients with liver, lung, skeletal and abdomen metastases are described.

Comment 6: Page 15 – Table 4 – Please see above comment re: multiple comparisons and need for a correction of the p-value considered to be significant. In addition, you have several p-values marked with an asterisk, presumably identifying those p-values as < 0.05 . However, there is no footnote to the table to define what the asterisk means. Please add a footnote to clarify.

Reply 6: We have performed the requested alterations, see reply 2 for details.

Comment 7: Page 18 – Table 6 - Please see above comment re: multiple comparisons and need for a correction of the p-value considered to be significant. In addition, you have several p-values marked with an asterisk, presumably identifying those p-values as < 0.05 . However, there is no footnote to the table to define what the asterisk means. Please add a footnote to clarify.

Reply 7: We have performed the requested alterations, see reply 2 for details.

Comment 8: Page 18 – Table 6 – I interpret the four columns under the heading “Mean \pm SD (pg/ml)” to be “mean” columns 1 and 3 and “ \pm SD” columns 2 and 4. To make it easier for the reader I would suggest collapsing columns 1 and 2 and 3 and 4 respectively so that the Mean \pm SD are all in the same cell (e.g. for IL-10, Baseline 1.59 ± 1.80 and 4 weeks 1.3 ± 1.38)

Reply 8: We have changed both Table 4 and Table 6 as suggested.

Changes in the text: See Table 4 and 6.

Comment 9: Miscellaneous – Consider adding box plot figure(s) of individual patient cytokine values. This/these would demonstrate the variability in the levels and aid the reader in interpreting the robustness of the cytokine clusters identified and their association with symptom clusters.

Reply 9: We have previously chosen not to add a figure of the cytokines to limit the size of the manuscript. We understand the intent, and our suggestion is to add a figure of individual cytokine values

as scatter plots in supplementary material. If the reviewer and/or editor prefer to add the figure in the manuscript we have no objection and will assist in the changes required.

Changes in the text: line 254: **and supplementary figure 1.**

Supplementary figure 1 added in the submission.

While preparing the figure we noticed a typing error in table 6 for IL-17F: the cytokine levels has been corrected to 66.79 in baseline and 44.77 at 4w.