

## Responses to Reviewers' comments

**Manuscript No: 75416**

**Revised Title: Necessity of neutrophil-to-lymphocyte ratio monitoring for hypothyroidism using nivolumab in patients with cancer**

Dear Editor:

We are grateful for the opportunity to submit a revised version of the manuscript. We are indebted to the Reviewers for the time dedicated to improving its quality. The point-by-point responses are provided below. We hope that all issues are addressed adequately.

Yours sincerely,

Yusuke Nakazawa, on behalf co-authors.

### *Reviewer #2*

This manuscript evaluated the effect of NLR fluctuations during nivolumab treatment on the incidence and onset period of hypothyroid. Results showed patients with hypothyroidism had a significantly lower NLR at the treatment initiation, and the incidence of hypothyroidism was higher among those with NLR <5. Patients with persistently low NLR (<3.5) developed hypothyroidism earlier. And concluded that low NLR at the treatment initiation increases the incidence of treatment-induced hypothyroidism and its persistence may be a risk factor for the early onset of hypothyroidism. These findings provide an easy available parameter to predict the development of hypothyroidism during nivolumab treatment. Limitations included: The reason for patient to discontinue nivolumab and whether it was related to hypothyroidism need to be discussed in the manuscript.

#### **Response:**

Thank you for your excellent review and thoughtful comments. We appreciate your time and opinion and have addressed your queries in the manuscript and discussed them below.

In this study, no patients discontinued nivolumab due to hypothyroidism. In patients who developed hypothyroidism, the reasons for discontinuing nivolumab during the observation period were progression of disease in 9 patients and irAEs in 2 patients (pneumonitis and rashes). In patients without hypothyroidism, the reasons for discontinuing nivolumab during the observation period were progression of disease in

51 patients and irAEs in 10 patients (pneumonitis in four patients; rashes in two patients; and myocarditis, colitis, eosinophilia, and hypophysitis each in one patient). We have added the text on page 11, lines 8–16.

**Reviewer #3**

This article mainly investigates the effect of NLR fluctuation on the incidence and onset period of hypothyroidism during nivolumab treatment. The manuscript is well written, however, there are still some concerns about this review.

**Response:**

We want to thank Reviewer #3 for the excellent and constructive comments to improve our manuscript. Considering your recommendations, the text was carefully edited. We have separated the topics for a more readable response.

1. In part “INTRODUCTION”, I suggest that the introduction about nivolumab should be more detailed.

**Response:**

We have added the mechanism of action and indications for nivolumab in the “INTRODUCTION” section. We have added the text on page 6, lines 2–10.

2. In this study, the follow-up period is up to the 12th administration, is the interval between two consecutive treatments the same? How long?

**Response:**

In this study, nivolumab was administered primarily at 2-week intervals, but it was temporarily administered at 3-week intervals when the hospital was closed or requested by the patient. We have added the text on page 9, lines 21–23.

3. The included patients discontinued treatment after receiving <6, 6–11, or ≥12 nivolumab administrations. Why are patients discontinued nivolumab treatment? Are there some relevant criteria or indications?

**Response:**

The decision to discontinue treatment in this study was made by the clinician depending on the progression of disease or the development of severe irAE. The reasons for discontinuing nivolumab in patients who administered nivolumab <6 times were progression of disease in 34 patients and development of severe irAEs in six patients (pneumonitis: two patients, rashes: one patient, myocarditis: one patient, hypophysitis: one patient, and eosinophilia: one patient). The reasons for discontinuing nivolumab in patients who administered nivolumab 6–11 times were progression of disease in 26 patients and irAEs in six patients (pneumonitis: three patients, rashes: two patients, and colitis: one patient). We have added the text on page 8, lines 3–5; page 10, lines 8–12; and

page 10, lines 15–18.
4. In part “Statistics”, are continuous variables tested for normality? I think it is necessary to declare.
<b>Response:</b> The distribution of continuous variables in this study was evaluated using the Shapiro–Wilk test. Based on the distribution of the data, continuous variables were statistically analyzed using the Student’s <i>t</i> -test or Mann–Whitney’s U-test. We have added the text on page 9, lines 4–7.
5. In Table1, it is normative that the data of the same variable keep the same decimal places (eg. P value). Additionally, the layout of Table1 should be improved, for example, “median” and “(min-max)” should be inputted in one table cell.
<b>Response:</b> We thank the reviewer for the helpful suggestion. We have improved the content of Table 1 for easier understanding.

#### 4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

<b>Response:</b> The paper has been revised and edited by an experienced scientific editor who has improved the grammar and stylistic expression of the paper. We have attached a new
--

language editing certificate.
-------------------------------

## 5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/ definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

The basic rules on abbreviations are provided here:

(1) Title: Abbreviations are not permitted. Please spell out any abbreviation in the title.
---

<b>Response:</b>
------------------

We have corrected the title to include the term “cancer” as pointed out by the Editor-in-chief.
---

(2) Running title: Abbreviations are permitted. Also, please shorten the running title to no more than 6 words.
---

<b>Response:</b>
------------------

We confirmed that no correction is needed.
--

(3) Abstract: Abbreviations must be defined upon first appearance in the Abstract. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori).
---

<b>Response:</b>
------------------

We confirmed that no correction is needed.
--

(4) Key Words: Abbreviations must be defined upon first appearance in the Key Words.
--

<b>Response:</b>
------------------

We confirmed that no correction is needed.
--

(5) Core Tip: Abbreviations must be defined upon first appearance in the Core Tip. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori)
--

<b>Response:</b>
------------------

We have defined the abbreviation NLR in the “Core tip” section.
---

(6) Main Text: Abbreviations must be defined upon first appearance in the Main Text. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori).
---

<b>Response:</b>
------------------

We confirmed that no correction is needed.
--

(7) Article Highlights: Abbreviations must be defined upon first appearance in the Article Highlights. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori).
---

<b>Response:</b>
------------------

We have added the “Article Highlights” section on page 14, line 22, to page 16, line 6.
---

(8) Figures: Abbreviations are not allowed in the Figure title. For the Figure Legend text, abbreviations are allowed but must be defined upon first appearance in the text. Example 1: A: Hepatocellular carcinoma (HCC) biopsy sample; B: HCC-adjacent tissue sample. For any abbreviation that appears in the Figure itself but is not included in the Figure Legend textual description, it will be defined (separated by semicolons) at the end of the figure legend. Example 2: BMI: Body mass index; US: Ultrasound.

**Response:**

We have replaced the abbreviation "NLR" in the title of the figure to "neutrophil-to-lymphocyte ratio."

(9) Tables: Abbreviations are not allowed in the Table title. For the Table itself, please verify all abbreviations used in tables are defined (separated by semicolons) directly underneath the table. Example 1: BMI: Body mass index; US: Ultrasound.

**Response:**

We confirmed that no correction is needed.

## 6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

**(1) Science editor:**

A Retrospective Study was conducted to investigate whether continuously monitoring NLRs during nivolumab treatment is useful for predicting the incidence and onset period of hypothyroidism. This study found that low NLR at the treatment initiation increases the incidence of treatment-induced hypothyroidism.(2) This is an interesting study. However, the question raised by the reviewers should be addressed. (3) The methods used are correct. (4) The results can be obtained with those methods. (5) The interpretation of the results and the conclusions is suitable. (6) The findings of this article have a certain experimental basis for future prospective clinical trials.(7) Please refer to [www.wjgnet.com/bpg/GerInfo/287](http://www.wjgnet.com/bpg/GerInfo/287) for requirements in the journal's Guidelines for manuscript type and related ethics and relevant documents. Some documents are missed.

Please refer to [www.wjgnet.com/bpg/GerInfo/287](http://www.wjgnet.com/bpg/GerInfo/287) for requirements in the journal's Guidelines for manuscript type and related ethics and relevant documents. Some documents are missed.

**Response:**

We have confirmed that some documents regarding the disclosure of conflicts of interest are missing. We have attached the ICMJE Form, which states the conflict of interest for each author.

**(2) Company editor-in-chief:**

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

**Revision :**

We confirmed that no correction is needed.

The author(s) must include the keyword "Cancer" in the manuscript title.

**Revision :**

We have revised the title to include the term "cancer," as per the suggestion.

Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

**Revision :**

Figures are submitted in PowerPoint format.

In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper).

<p><b>Revision :</b></p> <p>All figures are original.</p>
<p>If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.</p>
<p><b>Revision :</b></p> <p>Copyright information has been added in PowerPoint figures.</p>
<p>Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.</p>
<p><b>Revision :</b></p> <p>Tables have been formatted accordingly.</p>

## 7 STEPS FOR SUBMITTING THE REVISED MANUSCRIPT

<p><b>Step 1: Author Information</b></p> <p>Please click and download the Format for authorship, institution, and corresponding author guidelines, and further check if the authors names and institutions meet the requirements of the journal.</p>
<p><b>Response:</b></p> <p>We confirmed that no correction is needed.</p>
<p><b>Step 2: Manuscript Information</b></p> <p>Please check if the manuscript information is correct.</p>
<p><b>Response:</b></p> <p>We confirmed that no correction is needed.</p>
<p><b>Step 3: Abstract, Main Text, and Acknowledgements</b></p> <p>(3) Requirements for Article Highlights: If your manuscript is an Original Study (Basic Study or Clinical Study), Meta-Analysis, or Systemic Review, the "Article Highlights" section is required. Detailed writing requirements for the "Article Highlights" can be found in the Guidelines and Requirements for Manuscript Revision.</p>
<p><b>Response:</b></p>

We have added the “Article Highlights” section on page 14, line 22 to page 16, line 6.

**Step 4: References**

Reminder: It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

**Revision:**

We have corrected the “References” section as per your indication.