Evdoxia Hatjiharissi, M.D., Ph.D.

Consultant Hematologist, Director

Division of Hematology, 1st Department of Internal Medicine

Aristotle University of Thessaloniki (AUTH)

AHEPA General Hospital, S. Kiriakidi St. 1, 54 636

Thessaloniki, Greece

Phone: +30-2313-303218, +306956204304, Fax : +30-2310-994638

E-mail: ehatjiharissi@gmail.com

Lian-Sheng Ma, Science Editor, Company Editor-in-Chief, Editorial Office

**Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-399-1568

**E-mail:** l.s.ma@wjgnet.com

Thessaloniki, 27 June 2021

**Re: Manuscript "Primary Gastric non-Hodgkin Lymphomas: recent advances regarding disease pathogenesis and treatment''**

Dear Editor,

Thank you for sending us the reviewers' comments. We have included a point-by-point analysis of the concerns raised by the reviewers. Please find attached our revised manuscript highlighting the amendments made (in bold).

We would be glad if you now reconsider our revised manuscript for publication in your reputable Journal. We thank you very much for your kind consideration.

Sincerely yours,

Evdoxia Hatjiharissi, M.D., Ph.D.

# Answers to Comments

We particularly wish to thank the Reviewers for their encouragement in our paper and for their constructive comments. We agree with these well-aimed comments and we fully answer and comply with them, taking them very seriously into account. We also thank the Reviewers for the positive comments they made for our work.

## Reviewer #1:

### Reviewer 1 – Q1

The Reviewer states: 'In the molecular pathogenesis, please check the spell of immune-pirivileged in the fifth row.'

### Answer – Q1

The word "pirivileged" has been replaced with the correct form ''privileged'', as the Reviewer suggested.

### Reviewer 1 – Q2

The Reviewer states: 'In my opinion, authors should add references as a review.'

### Answer – Q2

We have added 8 more references as a Review (Aleman BMP et al 2010, Paydas S 2015, Kuo SH et al 2012, Olszewska-Szopa M 2019, Kuo SH et al 2014, Aviles A et al 2004, Cuccurullo R et al 2014, Kang HJ et al 2020) according to the Reviewer's suggestion.

### Reviewer 1 – Q3

The Reviewer very correctly states: 'It is difficult for reviewer to point out the problem in the absence of line number.'

### Answer – Q3

We agree and we have placed line numbers through the whole manuscript in order to facilitate the corrections, as the Reviewer suggested.

### Reviewer 1 – Q4

The Reviewer very correctly states: 'An additional list of acronyms is more readable'.

**Answer – Q4**

We agree and a full list of abbreviations/acronyms has now been added, according to the Reviewer's suggestion.

**Reviewer 1 – Q5**

The Reviewer points out: 'Insufficient evidence is listed to support immunochemotherapy (R-CHOP) is the optimal treatment for patients with DLBCL PGLs'.

**Answer – Q5**

A Novel Table comparing R-CHOP vs CHOP providing more information for patients with DLBCL PGLs has now been added as the Reviewer suggested. The Table summarizes the main findings of the conducted retrospective studies until today. Indeed, there is lack of a head to head comparison between CHOP and R-CHOP in PGLs.

Previously, we retrospectively evaluated the trends in clinical presentation, management and outcome among 165 consecutive patients with a biopsy-proven primary gastric DLBCL who were seen in the years 1980-2017. The study cohort was divided into two subgroups based on the era of treatment (CHOP vs R-CHOP, before and after the initiation of rituximab). A better outcome after immunochemotherapy (R-CHOP) was observed comparatively (see Prior Presentation section).

Now that a longer follow-up of the patients has been achieved, we still have the same conclusion that a better outcome has been noted for the R-CHOP patient cohort, like in the past (see Prior Presentation). However, there are individual variations of the results in terms of the OS and freedom from progression (FFP) time intervals, which will be analyzed accordingly (manuscript under preparation within the next few months).

Moreover, in the 'Scientific Gaps' session we have pointed out that: 'Today, immunochemotherapy with R-CHOP is the most acceptable option for treating gastric DLBCL, as for nodal DLBCL. R-CHOP was established as a standard approach for DLBCL patients,

when in the study of patients aged 60-80 years, the rate of complete response (CR) was significantly higher in the group that received R-CHOP vs CHOP[60].'

**Reviewer 1 – Q6**

The Reviewer very correctly states: 'In the part of clinical studies, I don't understand what authors expressed in the first paragraph.'

**Answer – Q6**

The first paragraph has been removed and extensively re-written in a more explanatory way, in order to be easier understood, as the Reviewer pointed. It now has the following structure: 'The optimal treatment for DLBCL PGLs is not clear, since prospective clinical studies are missing. In the past, a spectrum of treatment approaches was applied ranging from gastrectomy or radiotherapy alone to chemotherapy (CHOP) or the combination of chemotherapy plus radiotherapy and surgery. *Wang YG et al* compared surgery over conservative treatment in a retrospective study. Conservative treatment in this study included chemotherapy (CHOP) or radiotherapy alone, chemotherapy plus radiotherapy or H-p I eradication (HPE). The authors found superiority of surgery alone in comparison with conservative treatment in the DLBCL type regarding prognosis, but not in the MALT type[16]. Nowadays, the role of surgical resection has been minimized, even in cases of extreme intestinal obstruction, since immunochemotherapy can induce rapid and complete resolution of large obstructing tumor masses. Gastrectomy is restricted to the management of major complications including perforation or hemorrhage of DLBCL PGLs.'

**Reviewer #2:**

**Reviewer 2 – Q1**

The Reviewer states: 'Benefit of CHOP vs R-CHOP therapy and checkpoint inhibitors can be given in a table so that it will be easy for the readers to understand.'

**Answer – Q1**

A Table comparing R-CHOP vs CHOP regarding the existing retrospective studies has now been added, as the Reviewer suggested. There are no data in the literature (no studies either retrospective or prospective have been conducted), regarding checkpoint inhibitors (CIs) at the level of comparison between CIs vs R-CHOP or CHOP for primary gastric lymphomas.

**Reviewer 2 – Q2**

The Reviewer reports: 'Role of radiation in primary gastric DLBCL and gastric MALToma not mentioned at all.'

**Answer – Q2**

We agree with the well-aimed comment of the Reviewer and we have added the following paragraph at the session of the manuscript entitled 'Comparison Among Clinical Studies / Treatment' addressing this issue. 'Regarding the role of radiotherapy, more data is available for patients with gastric MALT lymphoma or early stage gastric lymphoma. When there is an unsatisfactory response to HPE, recurrence after HPE or in MALT cases negative for H-p I, gastric radiotherapy of the entire stomach plus irradiation of the pathological and the perigastric lymph nodes (30-40Gy, 15-20 fractions) have been proposed. However, it is less clear whether radiotherapy should be applied or not in cases of DLBCL PGLs. It looks as though that involved-field radiotherapy has a role especially for patients with a DLBCL PGL of advanced stage who achieve a partial remission (PR) after immunochemotherapy (R-CHOP). R-CHOP plus additional local treatment for gastric lesions (e.g. consolidative radiotherapy or surgical resection) has also been recommended. The other side of the coin has been described as well, as several studies found that in the era of immunochemotherapy (R-CHOP), radiotherapy does not improve OS. The side effects of radiotherapy should always be taken into account in clinical decision making.'

## Reviewer #3:

**Reviewer 3 – Q1**

The Reviewer very correctly reports: 'H. pylori eradication has already been established for gastric MALT lymphoma, but do you think it is also effective for DLBCL? Only one line is mentioned in this paper with one article as a reference, but I wanted you to comment a little deeper (The below paper also reported the effectiveness of H. pylori eradication for gastric DLBCL). Paydas S. Helicobacter pylori eradication in gastric diffuse large B cell lymphoma. World J Gastroenterol. 2015 Apr 7;21(13):3773-6. doi: 10.3748/wjg.v21.i13.3773. PMID: 25852262. Even recently, there have been reports of successes and failures, and it seems that opinions are divided, so please tell us your thoughts.'

**Answer – Q1**

We agree and we have extensively covered this question in 3 novel pragraphs in the part of our manuscript entitled 'Comparison Among Clinical Studies / Treatment', at the end of this section. We provide both sides of the coin regarding HPE in patients with DLBCL PGLs. We have also moved a paragraph explaining the role of HPE in gastric MALT lymphomas (which is the gold standard) from the 'Molecular pathogenesis' section to the 'Comparison Among Clinical Studies / Treatment' section, as it fits better there. Our personal opinion is that HPE should not be applied as monotherapy, even in early stage of H-p l-positive DLBCL PGLs. We have also included the suggested paper to our References list, because it is very up to the point.

**Reviewer 3 – Q2**

The Reviewer points out: 'The authors have selected the necessary articles suitable for discussing recent advances in the pathogenesis and treatment and explained them from their own perspective. Gastric DLBCL is a heterogeneous disease that is actually difficult to review and I would like to pay tribute to the authors who compiled this educational review article. Finally, I highly appreciate this paper, and I hope that this article will be accepted with only a few revisions.'

**Answer – Q2**

We thank the Reviewer for the positive comment of our work.

**Science Editor:**

The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. Please provide the authors' contributions. 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.

**Answer**

All requested documents, author contributions, original figure documents with PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the Editor have now been provided, according to the Science Editor's suggestions.

**Language Quality:**

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

**Answer**

All minor language issues based on the peer review report have been resolved. A native-English speaker, experienced in medical English writing has edited the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format and general readability, like the Editor suggested.