25th May 2016

Professor Jing Yu

Science Editor

World Journal of Gastroenterology

Dear Professor Yu,

RE: Resubmission of revised Manuscript 26090

We thank the editorial staff at *World Journal of Gastroenterology* for the opportunity to resubmit this manuscript in its revised form. Please find below a detailed list of changes and comments to address the reviewers concerns. The text within the manuscript has been modified using the track changes function to reflect these changes. We feel that these changes have improved the content and clarity of the article.

Reviewer 1

1. Some undifferentiated-type (diffuse type) adenocarcinomas, which are not related to H. pylori infection, may not show the inflammatory cell infiltration. Please indicate the expression of tumor-associated antigen in those cases if the authors have the information.

Diffuse type adenocarcinomas account for the majority of the samples in the TCGA GS subtype. Based on the findings of the TCGA study this subtype did not have a significant immune signature and therefore are unlikely to benefit from existing immunotherapies. These are very briefly discussed on paragraph 2 page 4 and paragraph 2 page 14. We have inserted additional text to clarify this.

2. The authors showed the frequencies of GCs with MSI (22%) and EBV associated GC (9%) in page 3. Please clarify those references.

We have included appropriate references (Now page 4)

3. As the authors described, GC is histologically, molecularly and immunologically heterogeneous. Are the frequency of MSI and progression free survival (PFS) different between intestinal and diffuse type GC or among four molecular phenotypes?

The MSI high subtype comprises in its entirety one of the 4 molecular subtypes and almost all samples within this group are of intestinal type (now clarified on page 4. At this stage outcome data associated with the TCGA study is immature and therefore we do not have data for PFS however the ACRG study found that the MSI subtype showed the best prognosis and the lowest frequency of recurrence (Cristescu et al 2015). This is described and referenced on page 10.

4. If possible, the relationship between molecular phenotype and histology or cancer staging should be discussed.

MSI and EBV subtypes have high immune signature and are predominantly of the intestinal subtype. CIN are also predominantly intestinal (p4) but are associated with TP53 mutations and copy number alterations (p14). The GS subtype are predominantly diffuse and are characterized by aneuploidy (p14). At this stage we are not aware of any literature that describes a relationship between immune status and cancer stage.

Reviewer 2

No changes suggested

We thank the reviewers for their suggested revisions.

We feel that that the *World Journal of Gastroenterology* readership would be very interested in a review of current literature surrounding the topic of immunology as a way to target specific subtypes of gastric cancer.

Yours Sincerely,

Associate Professor Alex Boussioutas MBBS, PhD, FRACP