April 29, 2019

Fang-Fang Ji
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Dear Dr. Fang-Fang Ji and Reviewers:

Please find enclosed the edited manuscript in Word format (file name 47100-Manuscript File.docx)

Name of Journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 47100

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Title: TYMS/KRAS/BRAF Molecular Profiling Predicts Survival Following Adjuvant Chemotherapy in Colorectal Cancer

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We thank the reviewers and the Science Editor for their thorough and careful review of our manuscript. The manuscript had been revised according to the editorial suggestions you had indicated in the manuscript and the recent edits are listed below:

- The reference numbers were corrected to be superscripted in square brackets at the end of the sentence.
- Article Highlights was written according to the guidelines.
- We provided the decomposable figures, whose separate parts are movable and words can be edited.

All of the revisions to the revised manuscript are highlighted in the updated version of the manuscript.

All required files were signed and provided in a PDF format.

You will find below our replies to the comments of the reviewers, as well as the modifications that were introduced in the revised version of the manuscript.

Comments of Reviewer #1 (Reviewer code: 02731983)

This is a retrospective but valuable work which may enlight further studies. I have some concerns that the survival analyses do not include some important surgical factors such as surgical margins, mesorectum-mesocolon integrity and CRM. As well as tumor and patient-based factors, we know that surgeon and surgical factors have influence on oncologic outcome. Multivariate analysis should have include well-known clinicopathologic and surgical factors. The authors should mention this in the limitations..

Reply to comments: We thank you for pointing out that this important information was missing. We have now added this in the patients and methods section.

Comments of Reviewer #2 (Reviewer code: 03537671)

Dear Authors, I read your study with great interest. The study findings are indeed hypothesis generating. However, for colorectal cancer, to present data without taking mismatch repair deficiency/microsatellite instability, which is

now a very well known factor included even in guidelines to help guide adjuvant chemotherapy would be a very significant limitation. I would encourage the authors to do that since MMR/MSI testing is now recommended universally. Good Wishes.

Reply to comments: We thank you for the kind comments on our manuscript as well as for pointing out the lack of inclusion in this analysis of other important prognostic and predictive markers in the management of colorectal cancer. We have now added this as a limitation. The aim of the study was to investigate the implications of *TYMS* polymorphisms, *KRAS* and *BRAF* mutations in the survival of patients with colorectal cancer treated with adjuvant chemotherapy and we did not include the other markers. As the number of patients included in this analysis is small, such an analysis forms a great idea to be planned as a new research project including larger cohorts and run prospectively.

Comments of Reviewer #3 (Reviewer code: 02441103)

The study found that the group of TYMS polymorphisms 2RG/3RG, 2RG/LOH and 3RC/LOH and the absence of ins/LOH was associated with better prognosis in CRC pts treated with adjuvant chemotherapy while mBRAF was associated with increased risk of death. The limitation is that the levels of TYMS protein expression and activity were not examined. For Fig 1 and Fig 2, the symbols and lines presented are not evident and should be improved.

Reply to comments: Thank you for your kind comments on our manuscript as well as for the detailed assessment of its contents. As noted in the Limitations section, we agree that an important limitation is that TYMS protein expression and activity levels were not examined. Also, we improved the symbols and lines of Fig 1 and Fig 2.

We thank the reviewers for their insightful comments and suggestions to improve our manuscript. We thank the Editor for allowing us the time and opportunity to respond to the reviewers' comments, and look forward to sharing our opinions and research findings with the scientific community through publication in **World Journal of Gastrointestinal Oncology.**

Best regards,

Anastasios Ntavatzikos, MD, PhD student