

*Editor-in-Chief*

*World Journal of Clinical Oncology*

*09 Feb 2022*

*Dear Editor-in-Chief,*

**Re:** Our manuscript No. **82293** entitled “**Immune Microenvironment of Medulloblastoma: The Association between its Molecular Subgroups and Potential Targeted Immunotherapeutic Receptors**”

We would like to thank you and the reviewers for your valuable time in reviewing our MS. Below are our responses to the comments raised by the reviewers (item-by-item).

## **Reviewer# 1:**

### **1. Title**

It's okay.

**Reply to the comment:** Acknowledged

### **2. Abstract**

Fine, but it gives too general information, an abstract need to be well summarized with detailed information. Authors need to be specific by giving percentage when reporting outcomes information and not by giving general information like high, low, reduced or increased. Example 1<sup>st</sup> paragraph line 4; “Nevertheless, the recurrence rate remains high”, high by exactly what percent? The same applied to line 16 and 17.

**Reply to the comment:** All statements have been edited either by changing the statement content or by adding a percentage. Check for example Line 49 and 59

### **3. Key Words**

Yes, but I think the word “review” should appear as one of the keywords

**Reply to the comment:** Added

#### 4. Introduction

Well written but.

-Consider my suggestions from number 2.

**Reply to the comment:** Acknowledged and done for most of the important statements.

- Under title; Current therapeutic approach, It is true that the treatment modality is Surgery followed by chemoradiotherapy and lastly chemotherapy, but is there any room of delaying radiotherapy by giving adjuvant chemotherapy 1<sup>st</sup> to pediatric below 2 years? (Find literatures about this and comment). Under the same title can you mention on radiotherapy and chemotherapy doses as per risk stratification? Because treatment algorithm depends on risk stratification

**Reply to the comment:** In reference (27) and (28) as well as reference (18) *Rutkowski et al* explained that radiotherapy given for age less than 3 years may increase risk of cognitive dysfunction. Therefore, the radiotherapy should be deferred in this age group. We added this statement. **Check line 160-161.** I believe this paper is not for dose-related risk stratification.

#### 5. Illustrations and tables.

Ok

**Reply to the comment:** Acknowledged

#### 6. References

Ok

**Reply to the comment:** Acknowledged

### Reviewer# 2:

This paper covers very interesting topics. Contents are generally well written except for some points. English writing needs much improvement. After improvements in the contents and English, this paper can be very useful. Specific comments are below. This review still lacks important factors. In a new short section, the author should discuss environmental, dietary, reproductive, and life habit factors which influence microbiome and immune system, and response to therapy. The authors should discuss these points, influence of those factors on cellular metabolism, tumor

biology, and clinical outcome. These factors may influence molecular pathology and response to therapy in each patient differentially. Several studies shown gut microbiome influence response to immunotherapy in various tumor types. There are also influences of germline genetic variations on immunity and cancer. Gene-by-environment interactions should be discussed. In those lines, research on diet, environment, lifestyle, reproductive factors should be integrated with analyses of personalized molecular biomarkers in tumor - that is needed for research on cancers including pediatric cancers and brain tumors. The authors should discuss molecular pathological epidemiology research that can investigate those factors in relation to molecular pathologies, and clinical outcomes. Molecular pathological epidemiology research can be a promising direction and has been discussed in the literature, eg, Ann Rev Pathol 2019, Gut 2022.

**Reply to the comment:** The formation of medulloblastoma during embryological development is old theory and has been already elucidated in the literature. There were no papers in the literature discussed about the maternal factors for the development of medulloblastoma however, we added a brief discussion about the embryological growth of medulloblastoma particularly the part of rhombic lip failure. Check **the line 100-110**.