

October 2019

Reviewer's code: 02929648  
Good paper.

ANSWER: We thank the reviewer for his/her positive comments.

Reviewer's code: 00209021

The authors undertook a review concerning current concepts in ameloblastoma-targeted therapies in BRAF V600E mutation. They should be congratulated for this high quality review. The manuscript is well-written with adequate reference to the current medical literature in the field. The content of the text is satisfactory enough and the figures and table iare informative. The review can be published for educational purposes especially for clinicians in the field.

ANSWER: We thank the reviewer for his/her positive comments.

Dear Jie Wang  
Science Editor

I re-submit a systematic review for publication in *World Journal of Clinical Oncology*, titled "Current concepts in ameloblastoma targeted therapies in BRAF V600E mutation: systematic review" (Manuscript ID 47669).The paper was coauthored by Rogelio González-González, Sandra López-Verdín, Jesús Lavallo-Carrasco, Nelly Molina-Frechero, Mario Isiordia-Espinoza, Ramón G Carreón-Burciaga and Ronell Bologna-Molina.

In this second revision of the systematic review, we perform all the suggestions and correctios made by the Science Editor, hoping that these were resolved as was indicated.

The corrections are highlighted in red colour and also are included in the main text and cover letter, as well as the files are attached in the present submission.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. **There are no conflicts of interest to declare.**

Thank you for your consideration. I look forward to hearing from you.

Sincerely,  
Ronell Bologna-Molina



## **AUTHORS REPLY**

**1.5 SUPPORTIVE FOUNDATIONS.** You need to provide the grant application form(s) or certificate of funding agency for every grant, or we will delete the part of "Supported by...".

A. We decided to delete this section due the support given to this study was not established in a document, thus, we do not have the corresponding certificate.

**Supportive foundation acknowledgment.**

A. As well as the prior observation, we decided to delete this paragraph due we do not have the certificate of the funding agency.

**1.6 PRISMA 2009 Checklist.**

We reviewed the current paragraph and we made a minimal grammatical correction.

**1.7 Correspondence to.** Telephone and fax numbers should consist of +, country number, district number and telephone or fax number; for example, +86-10-85381892.

A. The telephone and fax number have been added.

**1.9 Keywords.** Please don't include abbreviations in the key words.

The terms BRAF and BRAF V600E were not abbreviated due they are well defined concepts in the biological and medical literature. The current proteins can be found in the data base MeSH (Medical Subject Heading), which is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed. Furthermore, the definition of each term was already included in the abstract section, specifically in the background.

**Audio core tip.**

A. The audio is already attached, and it accomplishes the requirements indicated by the editor. The features of this file are the following:

- Length: 41 seconds.
- File Format: mp3.
- Bits velocity: 320 kpbs.
- Sampling rate: 48 kHz.
- File size: 1.58 MB.

**Article Highlights.**

### ***Research background***

Ameloblastomas are benign tumors that arise from the odontogenic epithelium whose behavior is defined as aggressive, infiltrative, recurrent, with aesthetic implications and rarely propense to local and distant metastases. Recently *BRAF V600E* gene mutation has been reported in ameloblastomas. Thus, targeted therapies against this mutation have been evaluated as an alternative treatment. In this study, a systematic review was performed in order to evaluate the frequent mutation of *BRAF* and another associated mutations, as well as targeted therapies against them.

### ***Research motivation***

Performing a systematic review allows to know the reports of frequent mutations in ameloblastomas and alternative treatments against them, as well as evaluate therapeutic response.

### ***Research objectives***

The aim of this study was to evaluate the presence of *BRAF V600E* mutation and another related mutations in ameloblastomas and provide information about the role of the mutations in the behavior of ameloblastomas, as well as targeted therapies reported.

### ***Research methods***

A literature research was carried out between January 1st 2009-2019 in order to perform a systematic review, of which 19 articles with relevant content regarding *BRAF* and its mutations in ameloblastomas were included, as well as targeted therapies against them..

### ***Research results***

A total of 624 ameloblastomas were evaluated, in which *BRAF V600E* was the most frequent mutation. Of the total of the included articles (19), four case reports registered targeted therapies against *BRAF V600E*.

### *Research conclusion*

In the current study, the most frequent mutation was BRAF V600E, which interestingly was frequently associated to other mutations that conferred more aggressiveness with recurrence and metastases. Regarding anatomic location, it is suggested that associated mutations to *BRAF V600E* are more common in the mandible. Targeted therapies against this mutation represented a significant outcome in patients that presented these types of tumors. Since this is the first systematic review developed about this subject, it could be suggested that the use of targeted therapies as adjuvant to surgical treatment may offer important outcome in the clinical evolution and the follow up, specially in recurrent, metastatic and malignant ameloblastic tumors.

### *Research prospective*

The information obtained in this review demonstrates the current implementation of targeted therapies against BRAF V600E mutation in ameloblastic tumors.

### **References. Please check and confirm that there are no repeated references!**

A. We have already verified that there are not repeated references in this section and in the main text as well.

**Please add PubMed citation numbers (PMID NOT PMCID) and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.**

A. The references have been verified. The references number 18 and 28 were corrected adding PMID and DOI.

18. **Pereira NB**, Pereira KM, Coura BP, Diniz MG, de Castro WH, Gomes CC, Gomez RS. BRAFV600E mutation in the diagnosis of unicystic ameloblastoma. J Oral Pathol Med 2016; **45**(10): 780-785. [PMID:27084044 DOI:[10.1111/jop.12443](https://doi.org/10.1111/jop.12443)]

28. **Tan S**, Pollack JR, Kaplan MJ, Colevas AD, West RB. BRAF inhibitor treatment of primary BRAF-mutant ameloblastoma with pathologic assessment of response. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016; **122**(1): e5-7. [PMID:27209484 DOI:[10.1016/j.oooo.2015.12.016](https://doi.org/10.1016/j.oooo.2015.12.016)]

**Figures. Regarding the figures:**

**Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.**

A. The figures were modified according to the indicated requirements. All the figures were included in different PowerPoint files as was asked. The “\*” symbols were substituted by letters “a” and “b” in figure 2. In the figure 3 the text “BRAF WT= BRAF Wild-type.” was added at the legend of the figure.

B. Figure 1 was included in a PowerPoint file.

**Tables. Please provide the decomposable TABLE, whose parts are movable and words can be edited.**

**Please don't include any \*, #, †, §, ‡, ¥, @....in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters.**

**Please don't include abbreviations in the title of the figure/table.**

**Please explain all the abbreviations in the figure/table legends: full name (abbreviation).**

**Please explain all the abbreviations of each figure/table under each piece of figure/table legends.**

A. The editable files are already included in different Word files. Moreover, superscript numbers were used in the table 1. Regarding abbreviations, we attached the explanation in the background; the proteins and genes are included in MeSH. Some mutations are not defined due they have been recently described in ameloblastomas. In the table 1 the text “BRAF WT= BRAF Wild-type.” was added at the legend of the figure.