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PEER-REVIEW REPORT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 77104

Title: Real-life multi-center retrospective analysis on nivolumab in difficult-to-treat patients with advanced hepatocellular carcinoma

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03372482
Position: Editorial Board
Academic degree: MD, PhD

Professional title: Academic Research, Assistant Professor, Associate Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: Belgium

Manuscript submission date: 2022-04-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-04-15 20:28

Reviewer performed review: 2022-04-15 20:43

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This study evaluates the real-world effectiveness of nivolumab monotherapy in patients with advanced HCC, not eligible for other treatment. METHODS: they conducted a retrospective, multicentric study, including 29 patients with advanced HCC from 3 Belgian tertiary hospitals. All patients had had prior chemotherapy or were intolerant or ineligible for treatments. All study subjects received nivolumab 3mg/kg in monotherapy, administered once every two weeks intravenously. Treatment continued until disease progression, severe adverse events, or death. Data were retrieved from patients' medical records. The outcome parameters radiological response according to RECIST criteria, the biological response through the evolution of the alpha-fetoprotein (AFP) level, and clinical response considering both the Child-Pugh score and the World Health Organization Performance Status (WHO-PS) were reported. A safety profile was also reported. Statistical analysis was performed using SPSS Statistics 27 statistical software package. RESULTS: The radiological overall response rate (ORR) to nivolumab monotherapy was 24,1%, with a complete response rate of 13.9% and a disease control rate of 44.8%. The biological overall response rate was 20.7%. Radiological and biological response were significantly associated both with each other ($P < 0.001$) and with overall survival ($P < 0,005$ for radiological response and $P < 0,001$ for biological response). Overall survival was 14.5 months (+/- 2.1), and progression-free survival was 10.9 months (+/- 2.3). Seventy-eight % of patients remained clinically stable with a WHO performance status of 0 or 1 after 4 months of therapy. No significant association between the etiology of the liver disease and the response to nivolumab could be detected. Grade 3 adverse events occurred in 17.2% of patients, none had grade 4

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adverse events. CONCLUSION: Nivolumab monotherapy is a good treatment choice in frail patients with HCC who are ineligible for the standard of care or other validated systemic treatments. In General: it's a good paper and the subject of the manuscript is applicable and useful. Title: the title properly explain the purpose and objective of the article Abstract: abstract contains an appropriate summary for the article, language used in the abstract is easy to read and understand, there are no suggestions for improvement. Introduction: authors do provide adequate background on the topic and reason for this article and describe what the authors hoped to achieve. Results: the results are presented clearly, the authors provide accurate research results, there is sufficient evidence for each result. Conclusion: in general: Good and the research provides sample data for the authors to make their conclusion. Grammar: Need Some revision. (Check The Paper Comments). Finally, this was an appealing article, in its current state it adds much new insightful information to the field.

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Reviewer's code: 03646555

Position: Peer Reviewer

Academic degree: FRACP, MBBS

Professional title: Attending Doctor, Lecturer, Staff Physician

Reviewer's Country/Territory: Australia

Author's Country/Territory: Belgium

Manuscript submission date: 2022-04-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-04-28 23:32

Reviewer performed review: 2022-04-29 13:29

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SPECIFIC COMMENTS TO AUTHORS

1. There is a confusing lack of definition of response outcomes in the abstract. It is not made clear to the casual reader what the differences is between "disease control rate"/ "complete response rate"/ "radiological overall response rate". Furthermore, "biological overall response rate" is not defined. I suggest the abstract would be best if the authors just presented only radiological overall response rate (with a definition) and biological overall response rate (with a definition). 2. It should be stated in the abstract, and in the relevant section of the manuscript, than no patients ceased nivolumab due to adverse events. 3a. I do not think it is important to state in the abstract that "no association between the etiology of the liver disease and the response to nivolumab could be detected"- it is not clinically very relevant. 3b. Furthermore, there is no quantitative analysis presented in the main text of the manuscript (in the section around line 410) as to how the authors analysed the association between the etiology of the liver disease and the response to nivolumab. What response criteria was used in such an analysis? Which statistical methods were used? How did the authors group different etiologies into categories (e.g. were HBV, HCV, Ethyl, NAFLD, other, all separate categories)? A sentence such as "Furthermore, the sentence "In the group of patients with progressive disease under nivolumab the origin of cirrhosis was heterogeneous and equally distributed" is inadequate, it does not constitute any statistical proof of the lack of association between liver disease aetiology and nivolumab response. 3c. Furthermore, there is significant inconsistency throughout the manuscript regarding whether the authors are looking at etiology of liver disease in the whole cohort, or only those with cirrhosis. In table 1, the authors do not actually present etiology of liver disease, but

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"origin cirrhosis", which fails to describe the aetiology of liver disease in any non-cirrhotic patients (perhaps some of them were non-cirrhotic viral hep B patients who are still prone to HCC?). Furthermore the section in line 410 is labelled "etiology of cirrhosis". However it is implied in the abstract and in lines 411 to 415 that statistical analysis comparing aetiology with response was performed using all patients (e.g. possibly including such non-cirrhotic hep B patients), not just cirrhotics. But then the sentence "In the group of patients with progressive disease under nivolumab the origin of cirrhosis was heterogeneous and equally distributed" implies that only patients with cirrhosis were being analysed. 4a. In this same section from line 410, the authors also state "and 5 of the 7 patients with a good treatment response (71.4%) had no underlying cirrhosis at baseline". It is unclear what the definition of "a good treatment response" is here. 4b. Furthermore, this sentence does not belong in this section. It implies that the authors are also analysing the effect of the presence of cirrhosis, not aetiology, in regards to response rates. 4c. Finally, neither this sentence, nor the sentences in line 506 to 509, provide any statistical analysis about the association between the presence/absence of cirrhosis and response rates. "71.4%" is just a single proportion. It has absolutely no statistical power to assert that there is "higher chance of response to therapy when there is no underlying cirrhosis". It would be just as erroneous to say that "A majority of those with a good treatment response were male, suggesting a higher chance of response to therapy with male gender". 5. In line 200, a citation should be given for the BCLC staging system (I suggest Reig et al, BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update, Journal of Hepatology 2022 vol. 76 j 681–693). 6. Similarly citations should be included for the up-to-7 criteria (to make it more clear for casual readers who may not have advanced familiarity with HCC staging systems). 7. The supplementary data table requires a legend for all its abbreviations. 8. The definition of biologic response (a >25% increase

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of the AFP blood level) should be in the methods section, not the results. 9. At line 341, the significant Breslow coefficient of 10.27 should have a p value as well. 10a. The lines from 272 to 275 are very confusing as they present larger composite rates (DCR and ORR) on either side of the smaller subcategory response rates, mislabel the ORR as simply "response rate", and fail to define the DCR. I suggest the authors state "4 patients (13.9%) showed a complete response, 3 patients (10.3%) a partial response and 6 patients (20.7%) showed stable disease following nivolumab therapy. As a consequence, the overall response rate (defined as complete or partial response) was 24.1% . The disease control rate (DCR, defined as complete or partial response or stable disease) was 44.8%." 10b. The bar graph figure 1 should therefore also have the percentages included, and also have labelled brackets on the right hand side indicating which bars are included in the ORR, and which bars are included the DCR. 11a. Similarly, lines 290- 291 do not define what constitute the biological response rate and biological disease control rate, and definitions should be included. Furthermore, the biological response rate should be named "overall biological response rate" to be consistent with the abstract. 11b. The bar graph figure 3 should therefore also have the percentages included, and also have labelled brackets on the right hand side indicating which bars are included in the overall biological response rate, and which bars are included the biological disease control rate. Furthermore, the bar labelled "response (decrease of 25% from baseline)" should be relabelled as "Decrease (decrease of 25% from baseline)" so as to not add extra confusion, when the word "response" is already being used in the overall biological response rate. 12. In the section "WHO performance status", the authors present pie graphs at 2 and 4 months. However these are not adequate to reflect the assertion that "a subgroup of patients responds well to nivolumab, also clinically, while another subgroup does not respond" because they do not quantify the proportions of patients who improved and the proportions who worsened. Furthermore, interpretation of these

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pie graphs is impossible because the total patient numbers at 0, 2 and 4 months were different due to censorship. I think the authors should firstly state the total numbers at 0, 2 and 4 months. Then they should presenting quantitative numbers about patient subgroups who worsened, who improved, who stayed the same. Finally, they could (optionally) present the data in a different non-pie-chart format, such as a scatterplot with multiple lines e.g.(https://community.jmp.com/t5/Discussions/How-to-make-a-line-graph-containing-multiple-lines/td-p/70247) showing each patient's linear progress through each stage, noting when patients are censored. 13. The similar criticisms in point 12 above apply for the analysis of the Child-Pugh score- again, simply presenting the Child Pugh proportions at 0, 2 and 4 months does not give an accurate picture of some patients worsening and some patients improving. 14. In line 441, the sentence "6 of 29 patients (20,7%) showed an impressively good and sustained response to nivolumab monotherapy" does not define what response is being used here- is it overall radiological response?

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's code: 03372482
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Academic Research, Assistant Professor, Associate Professor
Reviewer's Country/Territory: Egypt
Author's Country/Territory: Belgium

Manuscript submission date: 2022-04-15

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Reviewer accepted review: 2022-07-04 07:25

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Peer-reviewer	Peer-Review: [ ] Anonymous [Y] Onymous

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applicable and useful. Title: the title properly explains the purpose and objective of the article Abstract: abstract contains an appropriate summary for the article, the language used in the abstract is easy to read and understand, and there are no suggestions for improvement. Introduction: authors do provide adequate background on the topic and reason for this article and describe what the authors hoped to achieve. Results: the results are presented clearly, the authors provide accurate research results, and there is sufficient evidence for each result. Conclusion: in general: Good and the research provides sample data for the authors to make their conclusion. Finally, this was an appealing article, in its current state it adds much new insightful information to the field. Therefore, I accept that paper to be published in your journal