Dear members of the Editorial Office
Dear reviewers

Thank you very much for considering our study for acceptance to the World Journal of Hepatology, we are very honored.
We would also like to thank you for revising our manuscript so closely and for all of your useful remarks to upgrade the quality of our study. We studied them carefully one by one and adjusted our manuscript according to all of your comments.

We reconsidered the strengths and weaknesses of our study. Our main strengths are the following:

1. We enrolled patients with advanced HCC who were ineligible for standard of care or other validated systemic treatments, because of intolerability, contra-indications or progressive disease under prior systemic therapy. We included patients with impaired liver function and poor performance status, a population that is usually not included in RCT's.
2. Given the recent fast evolutions in the systemic treatment of advanced HCC nowadays, this study is very topical.
3. Furthermore, we showed notably better results than reported in literature. Hence nivolumab monotherapy should be considered as a valuable treatment option in selected patients otherwise not eligible for systemic treatment.
4. This article provides interesting information as a starting point for further research, eg. on patient selection per treatment strategy.

The major limitation of this study would be the retrospective nature of the study, and the rather small patient population.

We first read the entire peer-review report carefully, in order to gain a complete understanding of its content. Then, we tried our best to revise the manuscript according to the peer-reviewers' comments and suggestions. Please find our responses and revision below.

Reviewer 1

Comment 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).
Response: Thank you for noticing. We agree with your proposal. Radiological overall response is defined as complete or partial response according to the iRECIST and mRECIST criteria and biological overall response rate is defined as a decrease of > 25% in AFP blood level.
Revision: We adjusted in the abstract, page 5, lines 134-137

Comment 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.
Response: Thank you, we agree this is a very relevant addition.
Revision: We added it in the abstract (page 6, line 143) and in the full-text (page 15, line 430)

Comment 3:
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 "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.
Response:

3a: We agree that it is not clinically relevant that we found "no association between the etiology of the liver disease and the response to nivolumab", we shouldn't state that in the abstract. As suggested we removed it from our abstract (page 6).

3b: This is a very relevant and true remark, thank you.
The statistical analysis used was the Chi-Square Test, Pearson correlation was -0.308 with p-value 0.111. The response criterium that was used was the radiological response. 'HBV cirrhosis', 'HCV cirrhosis', 'Ethyl cirrhosis', 'NAFLD cirrhosis' , 'other cirrhosis' and 'no cirrhosis' were all separate categories.

3c: We admit that this analysis wasn't set up correctly, and we would like to thank you for pointing this out to us. We intended to look at the etiology of cirrhosis, not at

the etiology of liver disease. We realize that we made a poor choice of subgroups here and we should have excluded the subgroup 'no cirrhosis' from our analysis. We will revise this and clear this mistake out, we will also clarify it in the full-text and rule out all inconsistency, as to eliminate any possibility for misinterpretation (page 15).

However we want to emphasize that we didn't intend to prove any causality whatsoever, we did no multivariate analysis with adjustment for confounders, we never had the intention to do that, given the small numbers of patients per subgroup and the lack of power, which makes it impossible to draw conclusions. This was a side analysis in our study, absolutely not a major finding and not the message we want to give. We only intended to check if there happened to be a correlation in our population (without making assumptions about causality). But we realize that the analysis we initially made is not clinically relevant given the small numbers of patients and above all the incorrect choice of subgroups.

We performed a new and correct analysis, investigating the correlation between viral VS non-viral disease and treatment response to nivolumab, as we believe this would be more clinically relevant.
For your information, in our study cohort there were no patients in the non-cirrhosis group with an underlying viral disease (HBV or HCV). In our entire study cohort there were 4 patients with HBV and 2 patients with HCV, and all 6 had cirrhosis. Anyhow, even in our new analysis, which is set up correctly, comparing the response in viral liver disease vs non-viral liver disease, there are too little data for a powered analysis and it is impossible to draw conclusions. We clearly stated this in the text, to make the reader aware of this (page 15).

We also agree that the sentence "In the group of patients with progressive disease under nivolumab the origin of cirrhosis was heterogeneous and equally distributed" is inadequate, and that it indeed does not constitute any statistical proof. It was merely an observation from out data. As not to create confusion about this, we removed this from our text. We will revise this section and clarify this in the text so the reader cannot be misled.

Revison: Page 15, lines 432-443.

"Correlation between viral vs. nonviral etiology of liver disease and response to nivolumab

Previous studies[15] suggested a more favorable outcome in certain etiologies of underlying liver disease (e.g., viral-mediated) because of improved antiviral immune responses and reduction of viral load after ICI therapy.
In our study cohort, we could not detect an association between a viral versus a nonviral etiology of liver disease and the radiological response to nivolumab (Pearson correlation was -0.330 with p value 0.086). However, it is important to note that this finding is of limited

relevance given the small patient numbers (only 6 patients had an underlying viral liver disease) and hence the lack of power for a robust statistical analysis; therefore, it is impossible to draw conclusions based on this small amount of data."

TABLE 1 VIRAL VS NON-VIRAL LIVER DISEASE AND RESPONSE TO NIVOLUMAB

Radiological response	Non-viral liver disease	Viral disease	Total
Progressive disease	10	5	15
Stable disease	5	1	6
Partial response	3	0	3
Complete response	4	0	4
Total	22	6	28

Legend: The numbers represent the patient count.

Comment 4:

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"

4a: The reviewer is right, we didn't define 'a good treatment response' here. With a good treatment response we meant radiological partial or complete response. There were 7 patients with radiological partial or complete response, of whom 5 had no cirrhosis.

4b: For our response to this we refer to our response to Comment 3; thanks to the reviewer we realize that this analysis wasn't set up correctly, evidently we should have left the subgroup of patients with 'no cirrhosis' out of our analysis of the etiology of cirrhosis.

4c: The reviewer is right that 71.4% is just a single proportion without statistical power to assert that there is a higher chance of response to therapy when there is no underlying cirrhosis. It was merely an observation from our data, but there is no causality and it is not interpretable thus we removed it from our discussion, page 18.

Comment 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)
Response: Thank you, this is indeed a valuable citation, to inform the casual reader.
Revision: Citation added, page 8, line 223. Reference nr11 (page 23).

Comment 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).
Response: We agree, we added the citation. Thank you.
Revision: Mazzaferro et al (2009) cited, page 10, line 279. Reference nr13 (page 23).

Comment 7: The supplementary data table requires a legend for all its abbreviations.
Response: Indeed, this was lacking. Thank you.
Revision: Legend added to supplementary data table, page 33-34, lines 776-780.

Comment 8: The definition of biologic response (a >25% increase of the AFP blood level) should be in the methods section, not the results.
Response: We rearranged this, so the definitions of biological response and progression are clear in the Methods section and the Results section can be alleviated from these definitions.
Revision: Adjusted in the full-text, page 9, lines 244-247.

Comment 9: At line 341, the significant Breslow coefficient of 10.27 should have a p value as well.
Response: This is true, we added the P-value.
Revision: P-value was 0.016, added in the full-text, page 13, line 366-367.

Comment 10: 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.

Response: Thank you very much for this suggestion, we agree that it is more clear like that. We also re-edited the figure according to your suggestions and we agree that it is an improvement.
Revision:
10a : Adjusted in the text, page 11, lines 306-310.
10b: Adjusted figure, Page 25.

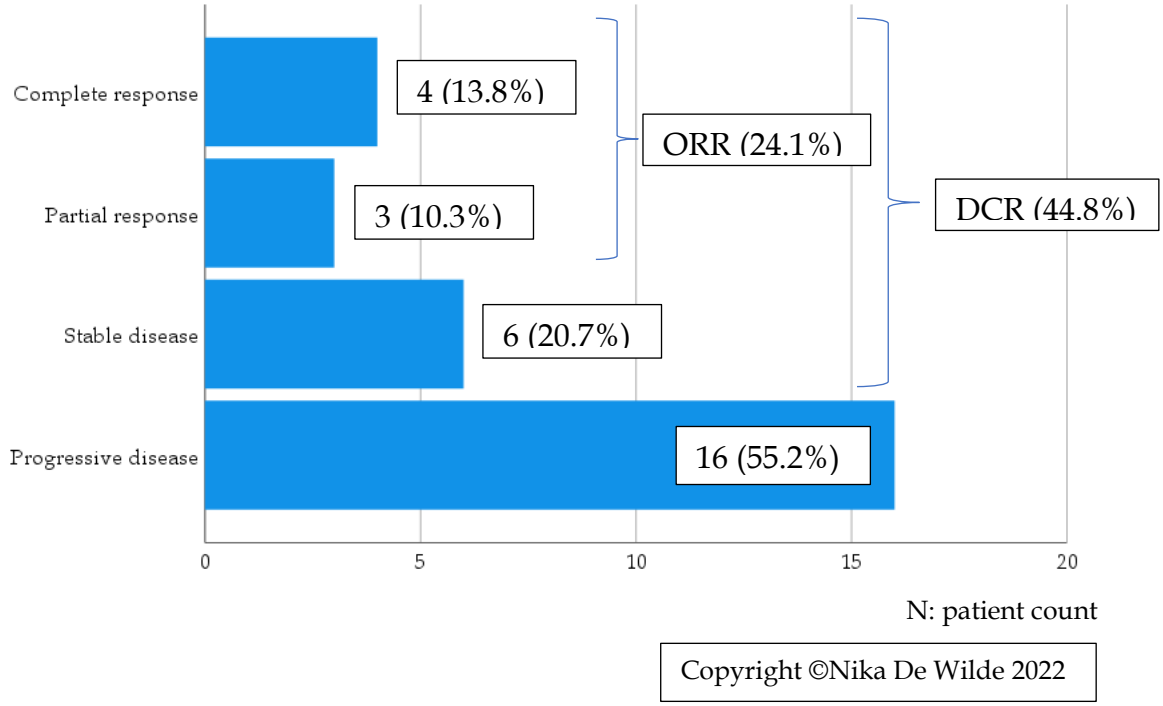


FIGURE 1 RADIOLOGICAL RESPONSE CATEGORIES BY MRECIST AND IRECIST

Legend: Figure 1 showing the number (and %) of patients per radiological response category. ORR: overall response rate, DCR: disease control rate.

Comment 11: 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.

Response: Again, thank you very much for this suggestion, we agree and adjusted this according to your suggestions.
Revision:
11a: Adjusted in the text, page 11-12, lines 321-324.
11b: Adjusted figure, Page 26.

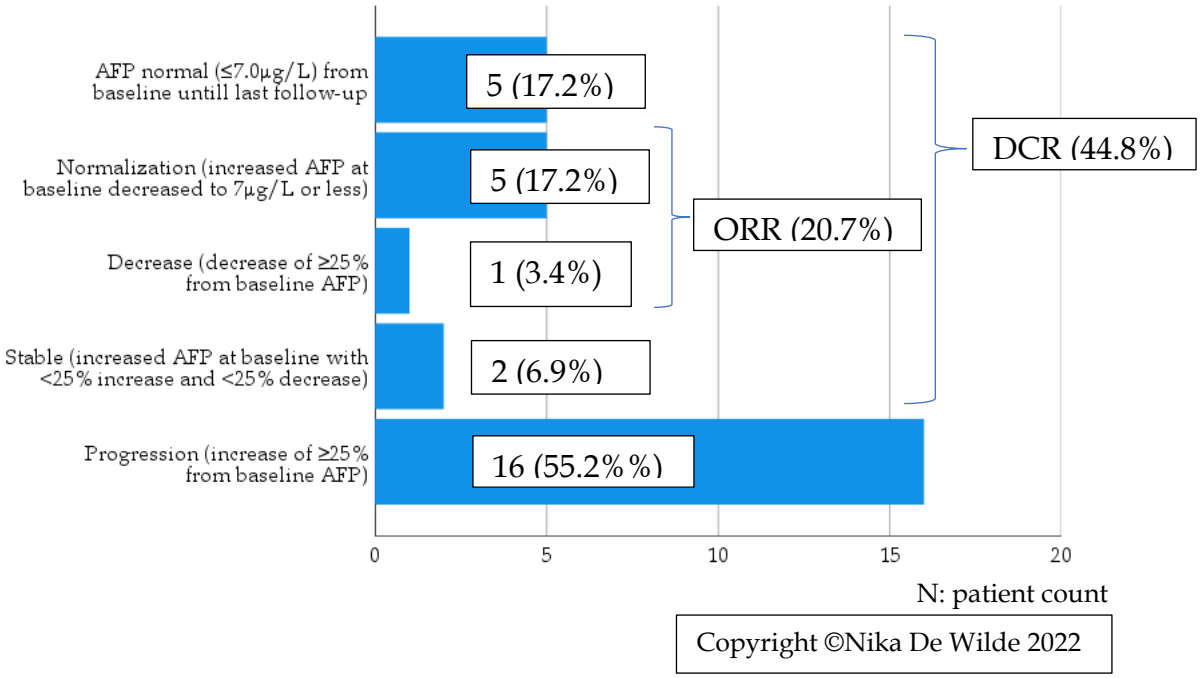


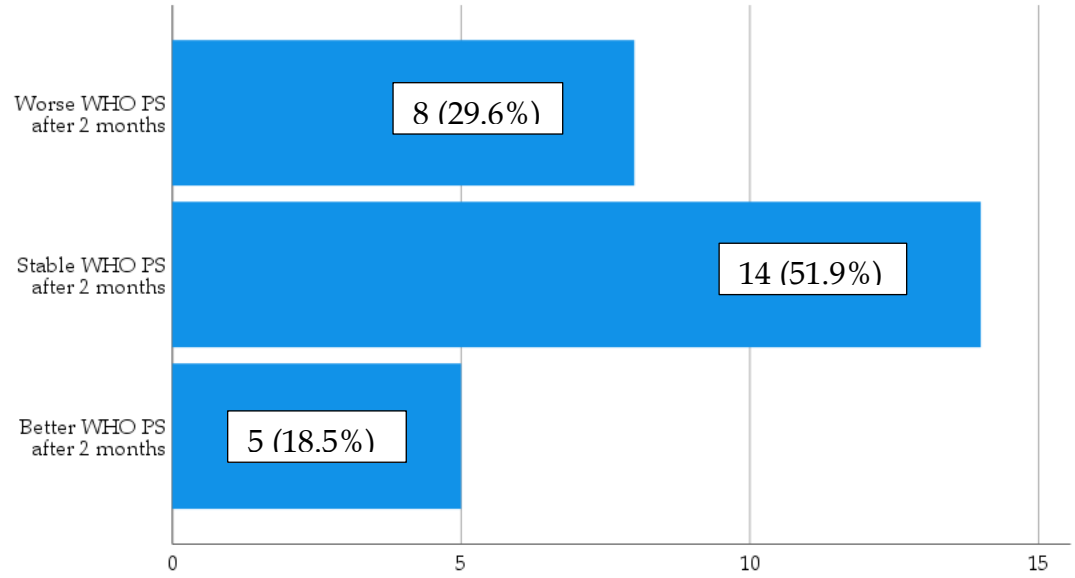
FIGURE 2 BIOLOGICAL (AFP) RESPONSE CATEGORIES

Legend: Figure 2 showing the number (and %) of patients per biological response category. AFP: alpha-fetoprotein, ORR: overall response rate, DCR: disease control rate.

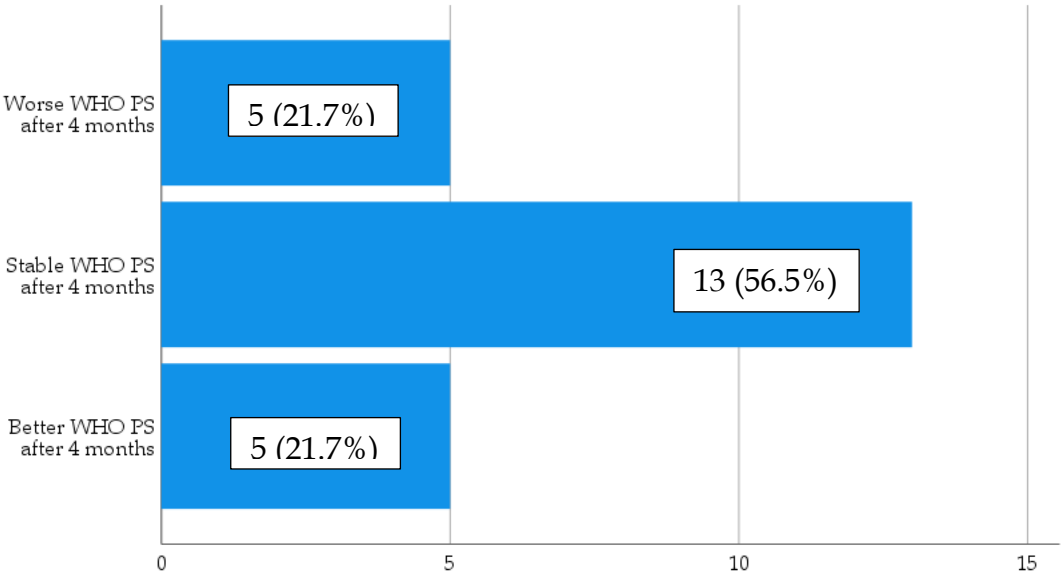
Comment 12: In the section "WHO performance status", the authors present pie graphs at 2 and 4 months. However these are not adequate to reflect the assertion that "a subgroup of patients responds well to nivolumab, also clinically, while another subgroup does not respond" because they do not quantify the proportions of patients who improved and the proportions who worsened. Furthermore, interpretation of these 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.

Response: Thank you, we understand your point and we see that the evolution of WHO PS indeed is more relevant than just the absolute numbers of the different categories (WHO PS 0,1,2,3 and 4) in different moments in time. We made a table presenting the quantitative numbers about patient subgroups who worsened, who improved and who stayed the same; with respective percentages. We didn't present

this data as a scatterplot with multiple lines because it wouldn't be a clear overview given the limited categories on the y-axis (only 4 levels: WHO PS 0,1,2 and 3), so it wouldn't be possible to differentiate the lines from each other or to show an evolution over time visually.
For this reason we opted for another visual representation through a bar chart.
Revision: Adjusted in the text, page 14, lines 391-406. We added a graph (page 29) and a table (page 31).



A



B

FIGURE 3 EVOLUTION OF THE WHO PS AFTER 2 MONTHS (A) AND 4 MONTHS (B) OF TREATMENT, COMPARED TO BASELINE

Legend: Figure 5 showing the proportion of patients with an improved, a stable, and a worse WHO PS after 2 months (A) and after 4 months (B) compared to baseline. WHO PS: World Health Organisation Performance Status.

TABLE 2 EVOLUTION OF WHO PERFOMANCE STATUS

WHO PS	2 months	4 months
Worse PS	8 (29.6%)	5 (21.7%)
Stable PS	14 (51.9%)	13 (56.5%)
Better PS	5 (18.5%)	5 (21.7%)
Total	27 (100%)	23 (100%)
Death	2	6

Legend: WHO PS: World Health Organisation Performance Status.

Comment 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.

Response: Thank you, same response as to Comment 12. We made a table presenting the quantitative numbers about patient subgroups who worsened, who improved and who stayed the same, with respective percentages.
Revision: We adjusted the text (page 14-15, lines 411-424)) and made a new table (page 32).

TABLE 3 EVOLUTION OF CHILD-PUGH SCORE

Child Pugh score	2 months	4 months
Worse CP	9 (36%)	7 (33.3%)
Stable CP	15 (60%)	12 (57.1%)
Better CP	1 (4%)	2 (9.5%)
Total	25 (100%)	21 (100%)
Death	2	6
Missing	2	2

Legend: CP: Child-Pugh Score.

Comment 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?

Response: Thank you, we clarified this in the text.
Revision: Adjusted in the text, page 16, line 463.

Reviewer 2

Comment: 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.

Response: Thank you very much for your positive feedback and for your language polishing throughout the entire manuscript. We have incorporated all of your corrections, and we had our manuscript revised for language editing by American Journal Experts.

Editorial office:

(1) Science editor:

This study evaluates the real-world effectiveness of nivolumab monotherapy in patients with advanced HCC, not eligible for other treatment. The study adds novel insight to the current literature. However, the overall presentation needs a major overhaul in order to meet publication standards.
Language Quality: Grade C (A great deal of language polishing)
Scientific Quality: Grade C (Good)

Response: Thank you very much for considering our study for acceptance to the World Journal of Hepatology. We attempted to make the manuscript one uniform whole, we re-edited the figures and re-arranged the lay-out of the tables according to the guidelines of the WJoH.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision

by Authors. However, the quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Respons: Thank you very much for considering our study for acceptance to the World Journal of Hepatology.
We provided the English Language Certificate issued by a professional English language editing company.

We provided a separate document with all the original figures (cfr infra).
The figures were generated and edited in SPSS, but we managed to delete as much text as possible and re-edited them in Microsoft office.
Figures 1 and 2 are replaced by the original SPSS figures, re-edited in Microsoft Office Word. Figures 3 and 4 were generated by SPSS and then edited in software program Paint. It was for us unfortunately impossible to re-edit them in Microsoft Office because more software tools were required to edit and merge the graphs to the desired figures. We did however also provide the original SPSS figures, unedited an un-merged. Figure 5 was replaced on the advice of the reviewer, with identical lay-out as Figure 1 and 2. Copyright information was added to all the figures.
If there is anything else we can do, we would be glad to hear it.

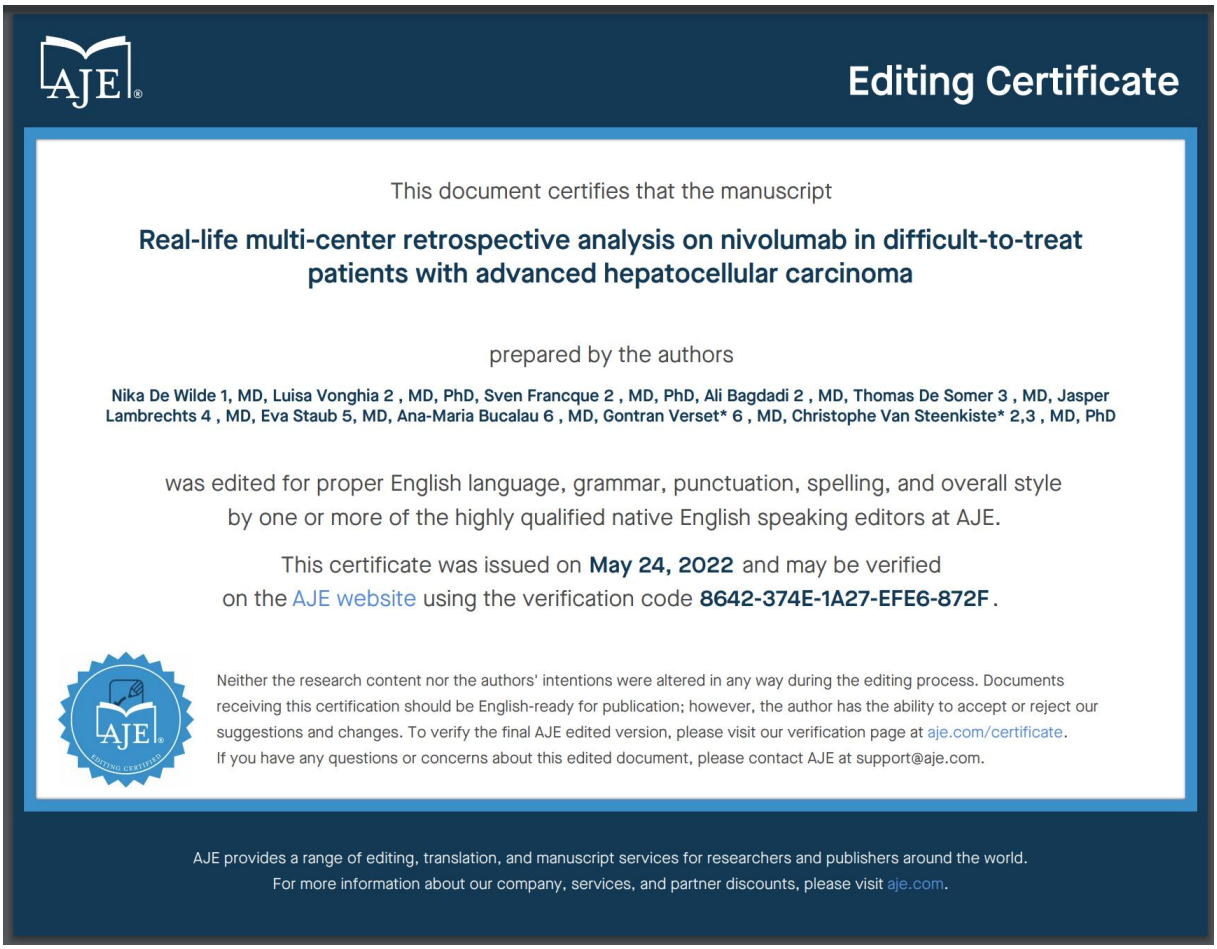
We also provided a separate document with the tables (cfr. infra). The tables all have the same lay-out according to the guidelines of the WJoH, they are editable and reprocessable in Microsoft Office.

Please contact us in case of any questions of concerns.

Sincerely,

Nika De Wilde
MD, Ghent University, Belgium

Language editing certificate



AJE

Editing Certificate

This document certifies that the manuscript

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

prepared by the authors

Nika De Wilde 1, MD, Luisa Vonghia 2 , MD, PhD, Sven Francque 2 , MD, PhD, Ali Bagdadi 2 , MD, Thomas De Somer 3 , MD, Jasper Lambrechts 4 , MD, Eva Staub 5, MD, Ana-Maria Bucalau 6 , MD, Gontran Verset* 6 , MD, Christophe Van Steenkiste* 2,3 , MD, PhD

was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at AJE.

This certificate was issued on **May 24, 2022** and may be verified on the AJE website using the verification code **8642-374E-1A27-EFE6-872F**.

Neither the research content nor the authors' intentions were altered in any way during the editing process. Documents receiving this certification should be English-ready for publication; however, the author has the ability to accept or reject our suggestions and changes. To verify the final AJE edited version, please visit our verification page at aje.com/certificate. If you have any questions or concerns about this edited document, please contact AJE at support@aje.com.

AJE provides a range of editing, translation, and manuscript services for researchers and publishers around the world. For more information about our company, services, and partner discounts, please visit aje.com.

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

Original figures

The figures were generated and edited in SPSS, but we managed to delete as much text as possible and re-edited them in Word Microsoft Office. The little text that was obligatory generated in SPSS was put in letter type 'Book Antiqua' as requested by the Author Guidelines.

Original figure 1, generated in SPSS and edited in Microsoft Office by the authors

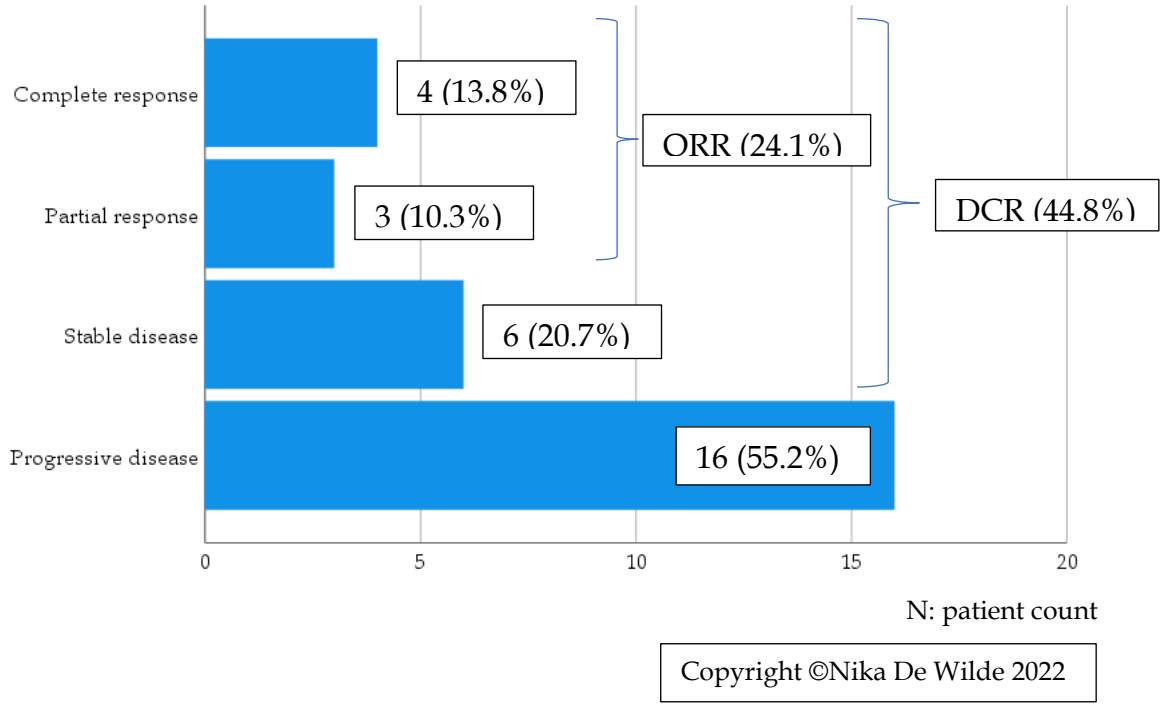


FIGURE 4 RADIOLOGICAL RESPONSE CATEGORIES BY MRECIST AND IRECIST

Legend: Figure 1 showing the number (and %) of patients per radiological response category. ORR: overall response rate, DCR: disease control rate.

Original figure 2, generated in SPSS and edited in Microsoft Office by the authors

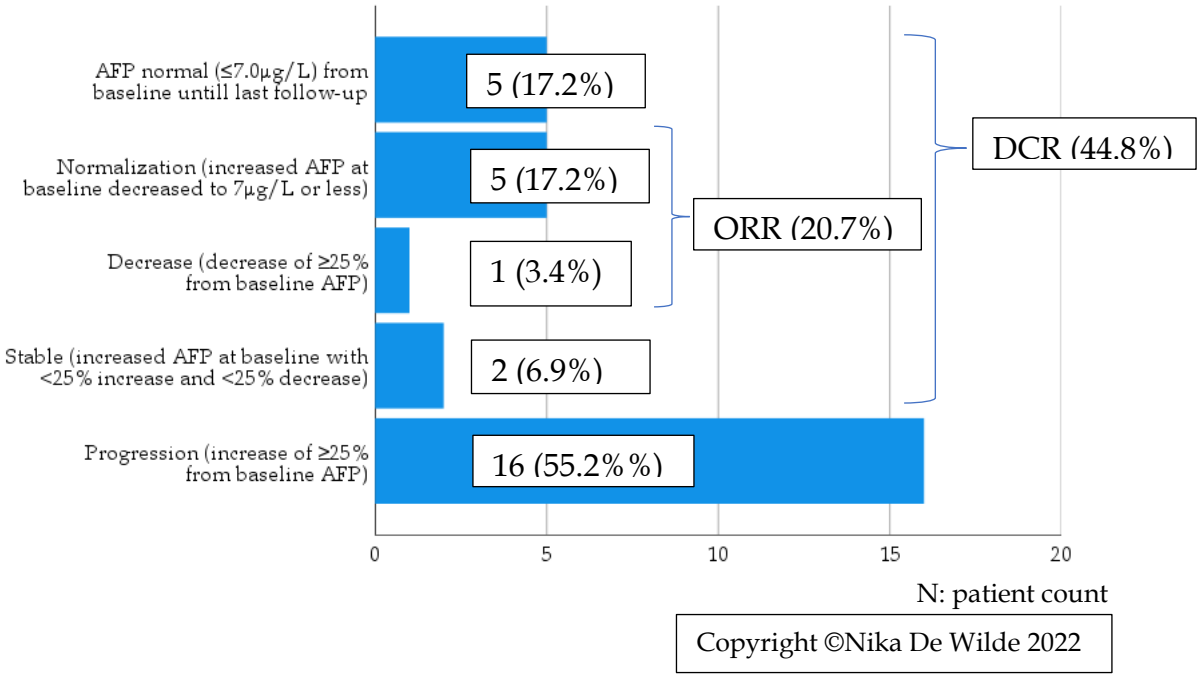


FIGURE 5 BIOLOGICAL (AFP) RESPONSE CATEGORIES

Legend: Figure 2 showing the number (and %) of patients per biological response category. AFP: alpha-fetoprotein, ORR: overall response rate, DCR: disease control rate.

Figure 3, generated in SPSS and merged and edited by the Authors in Paint

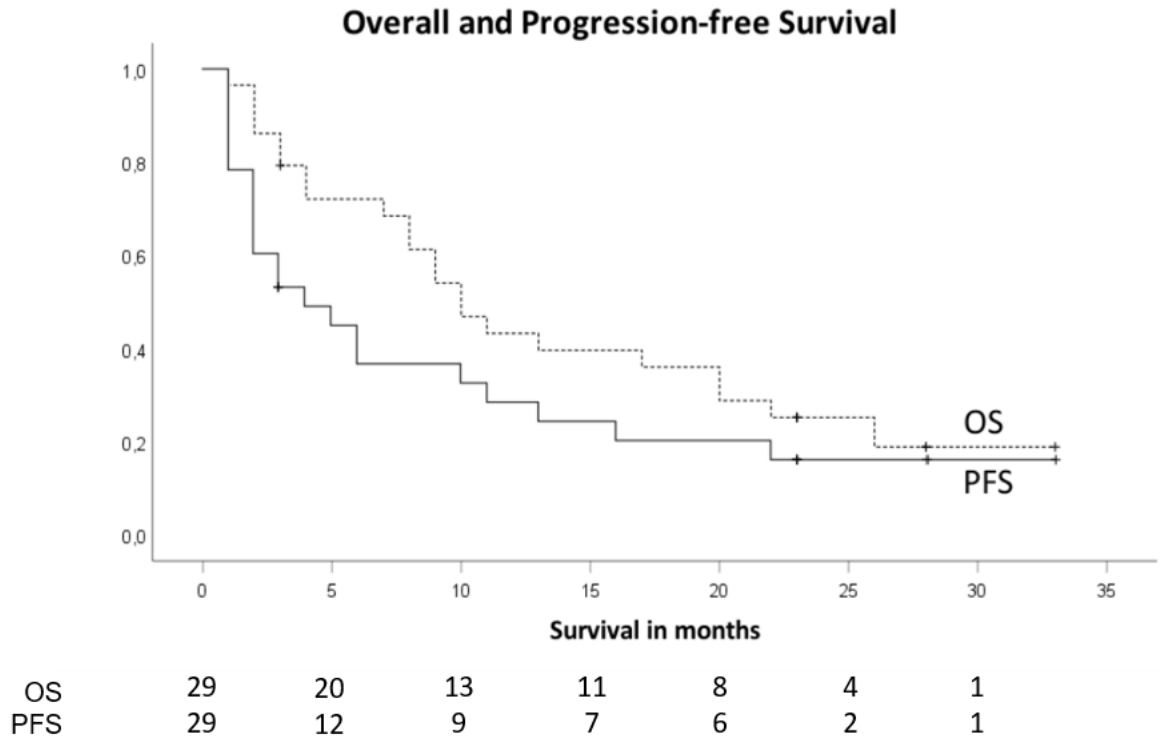
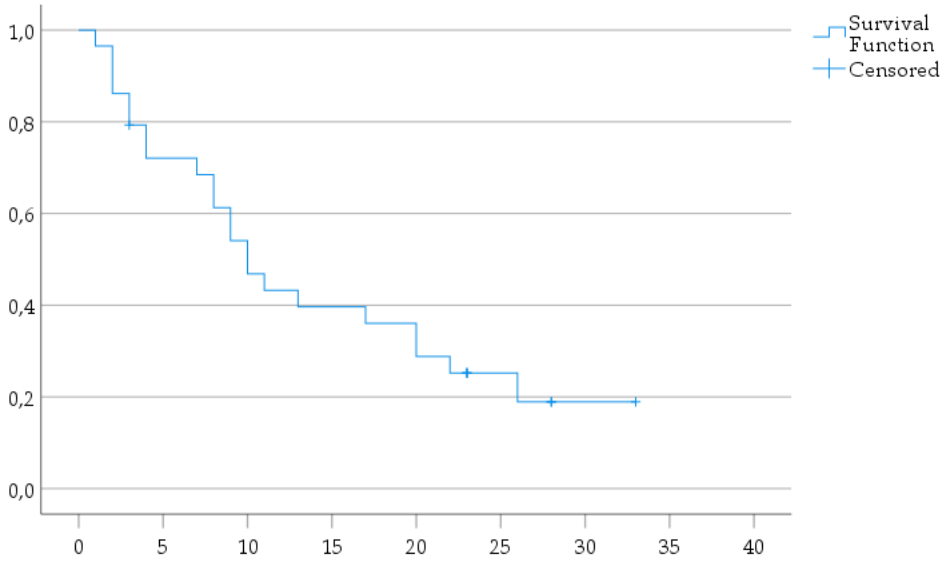


FIGURE 6 OVERALL AND PROGRESSION-FREE SURVIVAL

Legend: The graph shows the Kaplan-Meier survival curves for overall and progression-free survival. Below the graph the number of patients still alive at that time is depicted. OS: overall survival; PFS: progression-free survival.

Original Figures composing Figure 3, generated in SPSS

Overall survival since start of nivolumab:



Progression-free survival since start nivolumab:

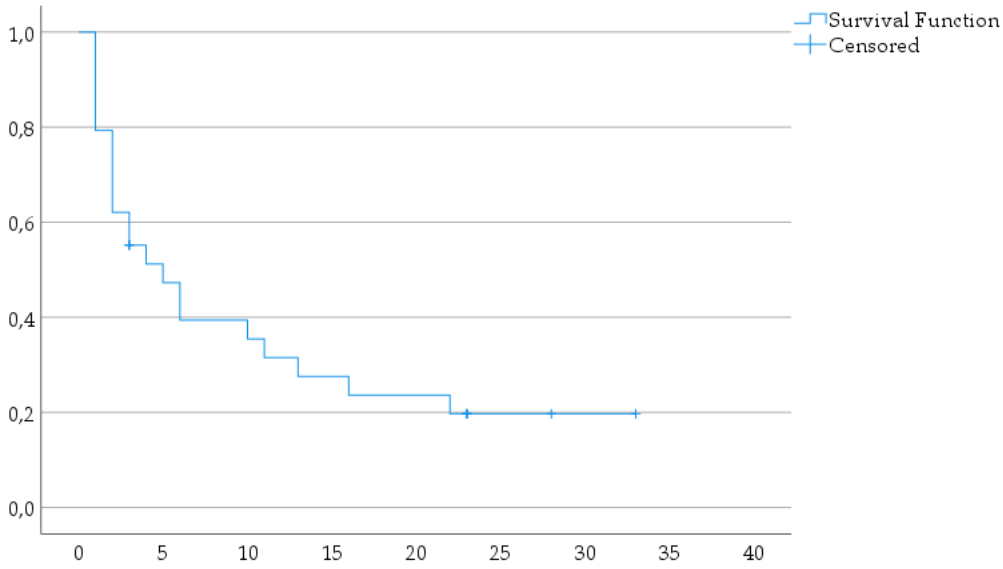
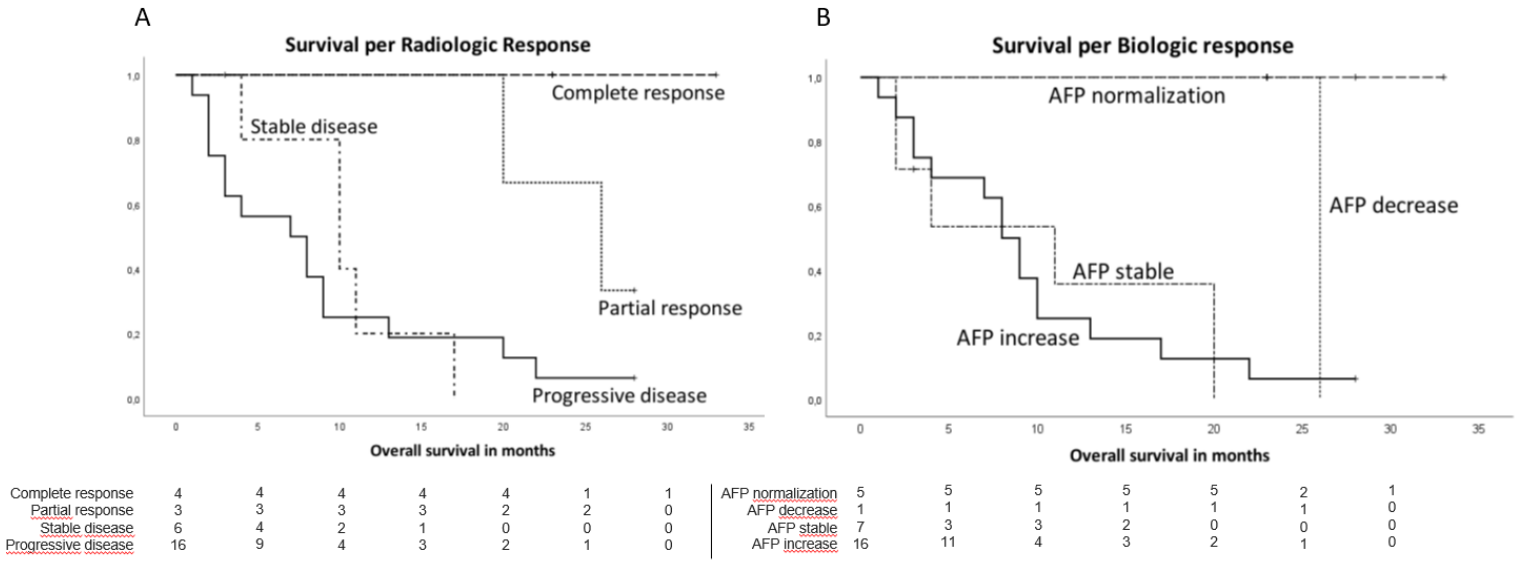


Figure 4, generated in SPSS and merged and edited by the Authors in Paint



Complete response	4	4	4	4	4	1	1
Partial response	3	3	3	3	2	2	0
Stable disease	6	4	2	1	0	0	0
Progressive disease	16	9	4	3	2	1	0

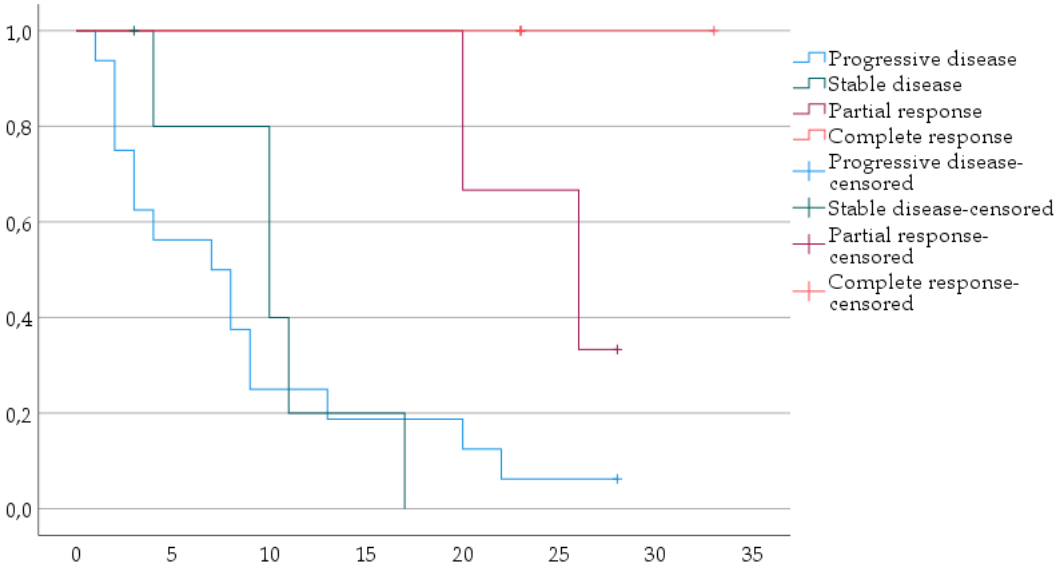
AFP normalization	5	5	5	5	5	2	1
AFP decrease	1	1	1	1	1	1	0
AFP stable	7	3	3	2	0	0	0
AFP increase	16	11	4	3	2	1	0

FIGURE 7 SURVIVAL PER RADIOLOGICAL (A) AND BIOLOGICAL (B) RESPONSE

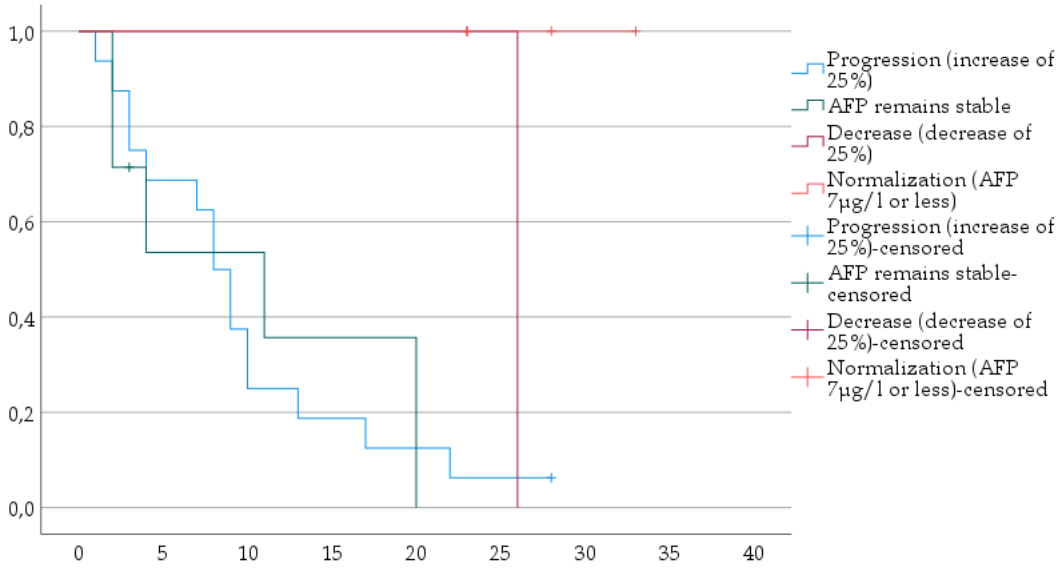
Legend: The graph shows the Kaplan-Meier survival curves for each category of radiological (A) and biological (B) response. Below the graph the number of patients still alive at that time is depicted. AFP: alpha-fetoprotein; AFP decrease: AFP decrease without normalization.

Original figures composing Figure 4, generated in SPSS

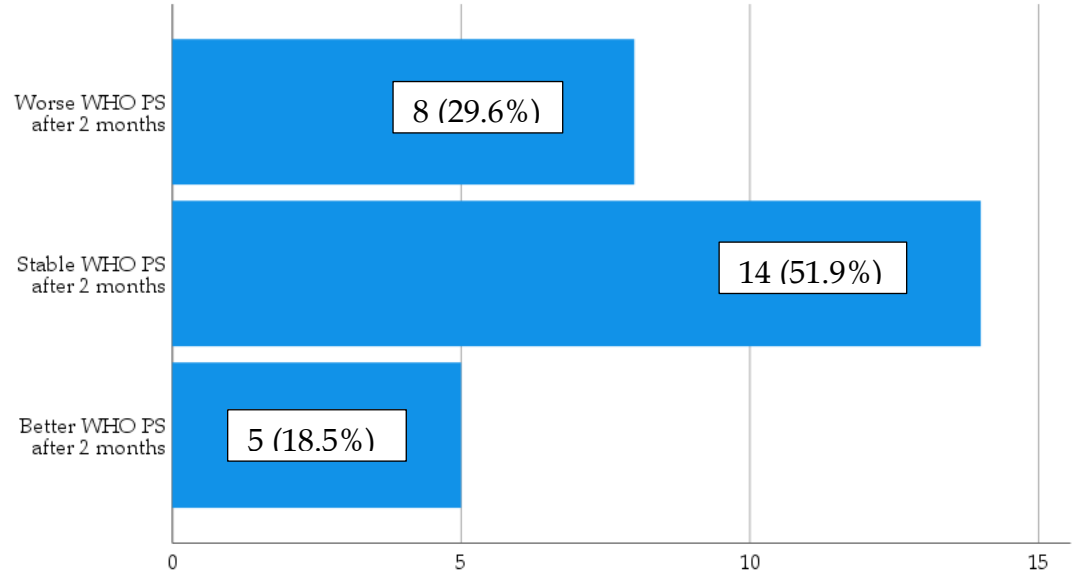
A Survival per radiological response



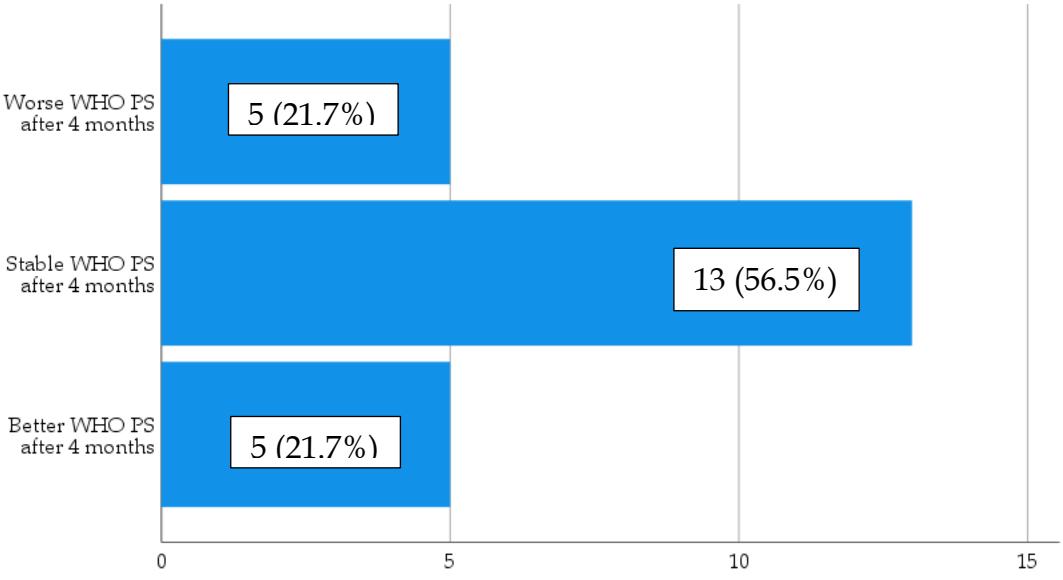
B Survival per biological response



Original figure 5, generated in SPSS and edited in Microsoft Office by the authors



A



B

FIGURE 8 EVOLUTION OF THE WHO PS AFTER 2 MONTHS (A) AND 4 MONTHS (B) OF TREATMENT, COMPARED TO BASELINE

Legend: Figure 5 showing the proportion of patients with an improved, a stable, and a worse WHO PS after 2 months (A) and after 4 months (B) compared to baseline.

WHO PS: World Health Organisation Performance Status.

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

Nika De Wilde et al.

Tables according to the guidelines of World Journal of Hepatology

Characteristic	Case Subjects (N = 29)
Sex	
Male (n)	21
Female (n)	8
Age at diagnosis (years, mean(SEM))	69.1 (2.1)
BMI (kg/m², mean (SEM))	26.6 (1.0)
BCLC stage (n)	
BCLB B	1
BCLB C	28
HCC characteristics (n)	
Bilobar	18/28

TABLE 4 PATIENT CHARACTERISTICS

Multifocal	15/26
Vascular invasion	8/29
UP-TO-7-Criteria	16/29
Metastasis (n)	
No metastases	16
1 meta location	8
2 meta locations	3
4 meta locations	2
AFP at baseline (ng/ml, mean (SEM))	4375.6 (2566.6)
Cirrhosis (n)	
No Cirrhosis	10
Child-Pugh A	10
Child-Pugh B	8
Unknown	1
Origin cirrhosis (n)	
HBV	4
HCV	2
Ethyl	7
NAFLD	3
Other	2
Missing	1
WHO performance status (n)	
0	5
1	21
2	3
Previous treatment (n) (= Resection, radiofrequency ablation, transarterial radioembolization, transarterial chemoembolization, selective internal radiation therapy, sorafenib, capecitabine, GEMOX, doxorubicine, FOLFOX, regorafenib, cabozantinib)	
Yes	27
No	2

Legend: SEM: standard error of the mean; BMI: body mass index; BCLC: Barcelona Clinic Liver Cancer; HCC: hepatocellular cancer; AFP: alpha-fetoprotein; HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: nonalcoholic fatty liver disease.

TABLE 5 SURVIVAL PER RADIOLOGIC RESPONSE CATEGORY

Radiological response	Total N	Overall survival (months +- SEM)	N of deaths (%)	N alive at study closure (%)
Progressive disease	16	8.8 (+- 2.0)	15 (93.7%)	1 (6.3%)
Stable disease	6	10.4 (+- 2.1)	5 (83.3%)	1 (16.7%)
Partial response	3	Not assessable	2 (66.7%)	1 (33.3%)
Complete response	4	Not assessable	0 (0%)	4 (100%)
Overall	29	14.5 (+-2.1)	22 (75.9%)	7 (24.1%)

Legend: Not assessable: patients were alive at study closure.

TABLE 6 SURVIVAL PER BIOLOGICAL RESPONSE CATEGORY

Biological (AFP) response	Total N	Overall survival (months +- SEM)	N of deaths (%)	N alive at study closure (%)
Increase ≥25%	16	9.6 (+-1.8)	15 (93.7%)	1 (6.3%)
Stable	2	2	2 (100%)	0 (0%)
Decrease ≥25% without normalization	1	26	1 (100%)	0 (0%)
Normalization of AFP (<7µg/l)	5	Not assessable	0 (0%)	5 (100%)
AFP remains negative	5	13.8 (+-3.9)	4 (80%)	1 (20%)
Overall	29	14.5 (+-2.1)	22 (75.9%)	7 (24.1%)

Legend: Not assessable: patients were alive at study closure.

TABLE 7 EVOLUTION OF WHO PERFOMANCE STATUS

WHO PS	2 months	4 months
Worse PS	8 (29.6%)	5 (21.7%)
Stable PS	14 (51.9%)	13 (56.5%)
Better PS	5 (18.5%)	5 (21.7%)
Total	27 (100%)	23 (100%)
Death	2	6

Legend: WHO PS: World Health Organisation Performance Status.

TABLE 8 EVOLUTION OF CHILD-PUGH SCORE

Child Pugh score	2 months	4 months
Worse CP	9 (36%)	7 (33.3%)
Stable CP	15 (60%)	12 (57.1%)
Better CP	1 (4%)	2 (9.5%)
Total	25 (100%)	21 (100%)
Death	2	6
Missing	2	2

Legend: CP: Child-Pugh Score.

TABLE 9 VIRAL VS NON-VIRAL LIVER DISEASE AND RESPONSE TO NIVOLUMAB

Radiological response	Non-viral liver disease	Viral disease	Total
Progressive disease	10	5	15
Stable disease	5	1	6
Partial response	3	0	3
Complete response	4	0	4
Total	22	6	28

Legend: The numbers represent the patient count.