Response to Reviewer 1 Comments

Manuscript ID: cancers-540782, entitled: Platelets as key factors in hepatocellular carcinoma Hepatocellular Cancer Treatment (Authors: Natasa Pavlovic, Bhavna Rani, Pär Gerwins, Femke Heindryckx), attempted to update the field through their perspective of platelets-mediated chronic inflammation specifically regulated by the hepatic microenvironment. They singled out that potential effect and therapeutic value of platelets in the disease progression, which is of great interest. They offer their insight onto the effects of platelets on the haemostatic microenvironment in liver cirrhosis and cancer, which branch out a new path to therapeutic mechanisms by which they can act on platelets to synthesize, express, and release many bioactive molecules whose functions go beyond mediating haemostasis, leading to HSC and HCC. The clarity should be enhanced by addressing seven specifics below.

**Point 1:** Page 2, Lines 56-59: “Tumor cells are also known to activate the coagulation cascade by secreting thrombin and tissue factor, which results in a meshwork of platelets and fibrin that shields the tumor cells, allowing them to escape immune-surveillance and successfully invade distant sites [15].” Can they be specific in the liver?

**Response 1**
We have found one very recent paper suggesting that this occurs in the liver (published by Zhuang et al, 2019). However, because this escape mechanism is less established in the field of HCC, we have removed the statement from the introduction and added it to the section “the effect of platelets on HCC proliferation and metastasis”. We now clarify that most findings are made in melanoma and breast cancer models; and included a reference to the above-mentioned paper of Zhuang et al to support a similar effect in liver cancer.

**Point 2:** Page 2, Fig 1 “bidirectional signaling between these factors that results in creating a tumor growth” – some narratives should be provided with citations to illustrate how pro-tumor signaling (pro-macrophages) transitions to anti-tumor signaling. Pro-tumor macrophages to NK cells: either using the arrow or blunt end line (choose a symbol for illustration of inhibitory effect); do not use current dual functions of the symbol. The illustration is of confusing: HCC converts to endothelia? HCC converts to HSC? Vice versa? How did that occur? If they mean platelet-mediated activation of the endothelium or HSC, they need to clarify by changing the illustrative scheme.

**Response 2**
We agree that the original image was confusing and have updated it. The figure now contains blunt end lines for inhibitory effects and all “regular” arrows show platelet-mediated activation of the different cell types, with the relevant factors presented next to the lines of the arrow. There are no arrows that represent transition from one cell type into another, so we hope that this solves the confusion. The figure caption has been updated to contain more information about the effect of platelets on the different cell types.
Point 3: Page 8, Fig. 2: How did that work? Single-agent? Dual agents? Multiple agents? How could they orchestrate multiple agents? Side-effects? Any specific to liver cancer?

Response 3
Figure 2 has been updated and the caption has been altered, so it contains a short overview of the drugs that were used as single of dual agents in (pre-)clinical trials for HCC.

Point 4: Page 8, Lines 337-361: they need to mark some text messages (molecules) on Fig. 2, which regulate HSC or HCC.

Response 4:
We updated the figure so that it briefly summarizes how targeting platelet activation would affect the different cell types in the tumor and stromal compartments. The specific molecules that influence the tumor and stromal cells, were added to figure 1. We also updated the text, so that the parts that mention drugs and their binding sites, refers back to the figure.

Point 5: Page 9, line 388: “multifactorial signaling pathways, a large portion of which are yet to be fully understood” - they highlighted platelets effects, but they need to speculate in depth on how to turn the multifactorial agents to the potent mediators in HCC and other chronic liver diseases, which is expected from the reader.

Response 5:
We have rephrased the conclusions, so that we shortly mention how platelets affect the different cells in the stroma and that tumor-stroma interactions are an important driver of hepatocarcinogenesis.

Point 6: Page 9, Lines 396-7: “while the association between blood platelet count and disease outcome remains a controversial topic.” – Why? Clinic reports? What bench marks do they come up to count part such a scheme?

Response 6:
We have rephrased the conclusions to clarify this statement. What we meant was, that both thrombocytopenia and thrombocytosis is seen clinically in HCC-patients and that there have been conflicting reports on their respective prognostic value.

Point 7: Grammar errors and choice of style should be observed with standard English. E.g., Page 2, Fig.1 “bidirectional signaling between these factors that results in creating a tumor growth” – “result” is preferred as with “that” upfront “factors” - style.

Response 7:
We carefully went through the manuscript to correct grammatical errors and spelling mistakes. We have also updated the style in several parts and removed repetitive use of words.