Reviewer #1

The authors propose a timely, comprehensive and balanced overview of the use of ICI, EBRT and their combination in HCC. I have only minor comments:

1- In the introduction, the authors stated: "The surgical removal of tumors and elimination of cancerous cells by chemotherapy or radiotherapy are no longer the best options, but rather, the reinvigoration of the antitumor immunity that is suppressed or exhausted in the tumor microenvironment (TME) is now more appealing." Surgery and radiotherapy are still the main curative treatment of solid tumors. Please amend.

Opinion) Thank you for your comment. As your recommendation, we have changed the sentence as "Although surgical removal or elimination of tumor cells by chemotherapy or radiotherapy is still a mainstay treatment, the reinvigoration of the antitumor immunity in the tumor microenvironment (TME) is gaining growing attention.".

2- In the ICI section, the authors stated: "The efficacy and safety of combination treatment with PD-1 and CTLA-4 inhibitors in patients with HCC have been proven in phase I/II trials" I would recommend rephrasing that: while safety can be proven in phase I/II, efficacy should be proven in phase 3. Please cite the recent press release about the Phase 3 Keynote 240 of pembrolizumab ; please cite the waiting of the Checkmate-459 with nivolumab.

Opinion) Thank you for your advice. As your recommendation, we have rephrased the sentences as follow with the appropriate citations; "Another phase 2 trial (KEYNOTE-224) investigating the efficacy of pembrolizumab in patients with advanced HCC who had been previously treated with sorafenib. In this trial, the objective response rate was 17% and 12-month progression-free survival and overall survival were 28% and 54%, respectively. While safety of combination treatment with PD-1 and CTLA-4 inhibitors could be proven in phase I/II, efficacy should be proven in phase III. CheckMate-459 (NCT02576509) trial is an ongoing phase III trial to evaluate the role of nivolumab in frontline setting for advanced HCC. Another ongoing phase III trial, Keynote-240 trial (NCT02702401), is to investigate the benefit of pembrolizumab in previously treated advanced HCC. Most recently, Merck released update on Keynote-240 study. They announced that the patients who have been treated with pembrolizumab had superior OS than those treated with placebo, but the superiority failed to reach pre-specified statistical significance (HR=0.78 [95% CI, 0.611-0.998]; p=0.0238). Although they failed to meet primary endpoints, favorable OS in pembrolizumab-treated group suggests that more evidence are needed to confirm the role of this drug. The final result from Keynote-240 and other ongoing trials are awaited. "

We have added the KEYNOTE-224, another important clinical study of pembrolizumab in patients with advanced HCC who had been previously treated with sorafenib.

3- EBRT in HCC section: ref 45 is inadequately quoted: the BCLC does not support use of EBRT. The

only reference to radiation therapy in the paper referenced in 45 is "Arterial embol isation without chemotherapy, external radiotherapy, and radioembolisation have shown antitumour activity, but survival benefit has not been proven." Please amend, stating that the BCLC does not include EBRT as a main treatment modality for HCC. You could also present more recent recommendation (EASL, but certainly interestingly to your topic asian guidelines).

Opinion) Thank you for your comment. As your advice, BCLC guideline does not recommend to use EBRT and the previous references were not appropriate. Instead, we have mentioned the practice guidelines of EBRT in HCC in Asia area as follows with proper citations; "As a result, EBRT has been utilized increasingly and practice guidelines of EBRT in HCC have been presented especially in Asian area".

4- The authors partially discuss the potential study of SIRT. I would be interested that the authors give some insight about the difference in radiobiology between EBRT and SIRT. In the fractionation section, the authors clearly showed the accumulating evidence for more immunogenic effect of hypofractionation. SIRT is rather an hyperfracionation.

Opinion) Thank you for your comment. Unfortunately, in our knowledge, there is no study investigating the difference in radiobiology between EBRT and SIRT in the perspective of the immunogenic effect. Because SIRT can deliver very high dose radiation in a certain time duration, It is regarded to be similar with high dose EBRT with single fraction. However, recent study showed immunogenic effect of SIRT itself in the clinical setting. Therefore, we have added the results of the study shortly in the PRECLINICAL DATA AND ONGOING TRIALS FOR HCC **section as follows;** "An analysis of tumor-infiltrating leukocytes isolated from patients with HCC after ^{90}Y radioemboliztion revealed SIRT resulted in higher tumor infiltration of $CD8^+$ T cells, and $CD8^+$ and/or $CD56^+$ natural-killer cells and higher expression of tumor necrosis factor-α on both the CD8 and CD4 T cells and antigen-presenting cells in peripheral blood. These implied that SIRT with ^{90}Y enabled the activation of both local and systemic immune and potential of synergy by combination with ICI. There are needs for clinical data regarding the iRT.".

Reviewer #2

This is an interesting manuscript concerning role of radiation therapy on immunotherapy for hepatocellular carcinoma. Therefore, this manuscript will add to growing body of literature on the use of Immunotherapy and radiation therapy in the treatment of HCC. There are a few issues in the manuscript that need to be addressed prior to publication, and I recommend making the following clarifications before publishing this paper. Nevertheless, it should be published. 1. Hope the authors can provide more clinical data concerning the benefit of concurrent ICI and radiation therapy in clinical

practice, as this can make this prospective treatment more convincing.

Opinion) Thank you for your kind comment. Unfortunately, in our knowledge, there is no published data regarding the benefit of concurrent ICI and EBRT for HCC in clinical setting. Instead, we supplement the immunogenic effect of SIRT which is widely utilized irradiation modality in the on-going clinical trials as follow; "An analysis of tumor-infiltrating leukocytes isolated from patients with HCC after ^{90}Y radioemboliztion revealed SIRT resulted in higher tumor infiltration of $CD8^+$ T cells, and $CD8^+$ and/or $CD56^+$ natural-killer cells and higher expression of tumor necrosis factor-α on both the CD8 and CD4 T cells and antigen-presenting cells in peripheral blood. These implied that SIRT with ^{90}Y enabled the activation of both local and systemic immune and potential of synergy by combination with ICI. There are needs for clinical data regarding the iRT.".