

Answering Reviewers

Reviewer: 1

Comments:

This manuscript is an invited minireview about the immunotherapy in small cell lung cancer. It contains clinically important up-to-date information. I recommend publishing. The article needs some small corrections; first correction should be made in pp#4; the word “natural” should be added before IFN-a such as “Group B received chemotherapy + natural IFN-a”, and second correction should be made as “the OS was 13.0 months with Durvalumab plus platinum+etoposide and 10.3 months with platinum+etoposide” in the Durvalumab section in pp#10 & 11.

1. the word “natural” should be added before IFN-a such as “Group B received chemotherapy + natural IFN-a”

Thank you for your comments. We have revised it as your request. Please see yellow highlight on Page3,Line13.

2. second correction should be made as “the OS was 13.0 months with Durvalumab plus platinum+etoposide and 10.3 months with platinum+etoposide” in the Durvalumab section in pp#10 & 11.

Thank you for your comments. We have revised it as your request. Please see yellow highlight on Page 9, Line 11-12.

Reviewer:2

Comments:

The authors have done a very good job in reviewing the recent clinical studies of immunotherapy for small cell lung cancer. There are only a few essential minor things which need to be taken care of before publication. Minor Issues: 1. Page 4 (Under IL-2 section): “cytotoxic T cells do not enter the immune microenvironment”. You really mean “tumor microenvironment”? 2. Page 4, Under “Vaccines” section. Chemotherapy may be immunoinhibitory or immunostimulatory, depending on: (1). Type of chemotherapeutic agents. Some agents induce immunogenic cell death, and therefore they are immunostimulatory while others are inhibitory. (2). The dose used. Usually higher doses kill immune cells and thus immunoinhibitory. 3. Page 5, line 9 from the bottom. In “For example, expression of tumor-infiltrating lymphocytes (TILs) in SCLC is...”, it seems that the word” expression” is an error. 4. Page 6, under “CTLA-4”. One of the major functions of CTLA-5 inhibitors is to inhibit regulatory T cells. Please add 1-2 sentences of discussion and cite 1-2 relevant papers here. 5. Ref #20. The one cited is just an abstract. The full paper has been published now: Carvajal-Hausdorf D, Altan M, Velcheti V, Gettinger SN, Herbst RS, Rimm DL, Schalper KA. Expression and clinical significance of PD-L1, B7-H3, B7-H4 and TILs in human small cell lung Cancer (SCLC). J Immunother Cancer. 2019 Mar 8;7(1):65.

doi: 10.1186/s40425-019-0540-1. [PMID: 30850021] Please update.

1. “cytotoxic T cells do not enter the immune microenvironment”. You really mean “tumor microenvironment”?

Thank you for your comments. We have revised it as your request. Please see: Please see yellow highlight on Page 3, Line 30-31

2. Chemotherapy may be immunoinhibitory or immunostimulatory, depending on: (1). Type of chemotherapeutic agents. Some agents induce immunogenic cell death, and therefore they are immunostimulatory while others are inhibitory. (2). The dose used. Usually higher doses kill immune cells and thus immunoinhibitory.

Thank you for your comments. We have revised it as your request. We have deleted the sentence “which was contrary to the general belief that the immune function decreases after chemotherapy” to avoid ambiguity.

3. In “For example, expression of tumor-infiltrating lymphocytes (TILs) in SCLC is...”, it seems that the word “expression” is an error.

Thank you for your comments. We have revised it as your request. We have deleted the word “expression”. Please see yellow highlight on Page 5, Line 2.

4. One of the major functions of CTLA-5 inhibitors is to inhibit regulatory T cells. Please add 1-2 sentences of discussion and cite 1-2 relevant papers here.

Thank you for your comments. We have added a paragraph under CTLA-4 section. Please see yellow highlight on Page 5, Line 7-11.

5. Ref #20. The one cited is just an abstract. The full paper has been published now: Carvajal-Hausdorf D, Altan M, Velcheti V, Gettinger SN, Herbst RS, Rimm DL, Schalper KA. Expression and clinical significance of PD-L1, B7-H3, B7-H4 and TILs in human small cell lung Cancer (SCLC). JImmunother Cancer. 2019 Mar 8;7(1):65. doi: 10.1186/s40425-019-0540-1. [PMID: 30850021] Please update.

Thank you for your comments. We have revised it as your request. Please see yellow highlight on Page 14, Line 5-8.

Reviewer:3

Comments:

This manuscript is well written, seems conducted by experienced medical researcher and practitioner. I have no objection to the contents and subject of manuscript. but I have two minor revisions for perfection: 1) although the contents are fine, some tables or figures which can summarize information of which authors want to emphasize are

necessary. 2) two key components of treatment of SCLC is systemic and radiation therapy, as authors also suggested. But no radiotherapy content is found. I recommend to add a small section about the recent RT indication for SCLC, or ongoing studies regarding combination of immunotherapy and radiotherapy. (probably latter will be nicer)

1. although the contents are fine, some tables or figures which can summarize information of which authors want to emphasize are necessary.

Thank you for your comments. We have added a table to summarize several important studies about the ICIs. Please see yellow highlight on Page 10, Line 21-22 and Page 20.

2. two key components of treatment of SCLC is systemic and radiation therapy, as authors also suggested. But no radiotherapy content is found. I recommend to add a small section about the recent RT indication for SCLC, or ongoing studies regarding combination of immunotherapy and radiotherapy. (probably latter will be nicer)

Thank you for your comments. We have revised it as your request. We have added a section "ICIs combined with radiotherapy" and Reference 44. Please see yellow highlight on Page 9, Line 18-28 and Reference 44.