Peer Review File

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Response to Reviewer A

This report summarized the latest and interesting findings of DLL3-targeted CAR-T therapy against SCLC. This report is intriguing; however, the current study does not meet the publishing criteria in this journal. Therefore, I raised several points to improve the content of the report.

Major Query:

Comment 1) There is a discrepancy between Cell-based immunotherapy and the Model in Table 1. For example, Liu et al. report on CAR-NK cells, but the model refers to CAR-T cells. I am not able to check all the references at my institution. The authors should recheck all the articles and clinical trials to make Table 1 more complete. Without this work, this paper should not be accepted.

Response: Thank you for the valuable input. The discrepancies were corrected. We presented two separate tables. Table 1 focuses on bispecific and trispecific T-cell engagers that target DLL3, which harness T-cell immune responses. Table 2 focuses on cell-based therapies that target DLL3 both in clinical and pre-clinical studies.

> Changes in the text: We revised the paragraph to properly introduce BiTEs (see page 3, line 34), and Table 1 is now only focused on BiTEs (see page 11, line 185).

Comment 2) Ref 17 in table1 focused on both AMG119 and AMG757. Why did the authors describe the AMG119 only? Moreover, the research content could not be checked in Pubmed because it was just an abstract of the meeting. Is the paper necessary in the table?

Response: Thank you. Conference abstract citations (reference numbers 8, 9 and 17) were deleted. Instead, we focused on clinical trials using DLL3-targeted CAR T-cells (AMG119), AMG757, which is a BiTE that targets DLL3, and HPN328, which is a trispecific T-cell engager.

Minor Query:
Comment 3) ES-SCLC should be spelled out at first.

Response: Thank you. We spelled out ES-SCLC both in the text and in the table.

> Changes in the text: We spelled out ES-SCLC (see page 4, line 62), and we avoid its abbreviation in Table 2 (see page 12, line 190).

Comment 4) In Table 1, the authors should state clearly whether it is CAR T cells or CAR NK cells.

Response: Thank you for your suggestion. We corrected that information in the Table.

Changes in the text: Cell-based immunotherapies targeting DLL3 are in Table 2 (see page 12, line 190), and the discrepancies were corrected.

Comment 5) Abbreviations in Table 1 should be explained.

Response: Thank you. Abbreviations are explained beneath the tables.

Changes in the text: We have added abbreviation explanation beneath Tables 1 (see page 11, line 187-188) and 2 (see page 12, line 192-193).

Comment 6) References should be explained in detail. Authors should not make statements that mislead readers into misunderstanding published papers or conference abstracts.

Response: Thank you for your comment. The references that were mentioned only in the table are now described in the text as well, and references coming from conference abstracts were deleted; instead, we focused on published papers and clinical trials targeting DLL3.

Changes in the text: After describing the main findings in BiTE therapies, we described some of their handicaps (see page 4, line 51-53) and explained the CAR-NK study in more detail by adding a new paragraph (see page 4, line 57-64).

We highly appreciate the reviewer's time in reviewing and providing additional feedback to improve our manuscript.

Response to Reviewer B

Comment 1) DLL3-targeted CAR T cells provide new strategy for small cell lung cancer patients. We hope to see more data.

Response: Thank you.

We highly appreciate the reviewer's time in reviewing our revised manuscript.

Response to Reviewer C

Comments:
Comment 1) The authors should better report the advantages and disadvantages of the different pre-clinical models used to study efficacy and safety of DLL3-targeted CAR T-cell therapy

Response: Thank you for the valuable input. We added some of the disadvantages and advantages of the pre-clinical studies to the text.

Changes in the text: We added text about advantages and disadvantages (see page 4, line 51-54, line 54-56, and line 57-64).

Comment 2) The commentary would benefit from a conclusion statement resuming the most important findings on DLL3-targeted CAR T-cell therapy in small cell lung cancer

Response: We added a conclusion based on the findings in pre-clinical models where we emphasized that the safety and efficacy of DLL3-targeted CAR T-cell therapy has been proven in orthotopic, metastatic and flank-tumor models.

> Changes in the text: We added a new paragraph that summarizes DLL3-targeted CAR T-cell therapies in small cell lung cancer (see page 6, line 106-109).

We highly appreciate the reviewer's time in reviewing our revised manuscript.