nature portfolio

Peer Review File

Toripalimab plus chemotherapy and radiotherapy for treatment-naive advanced esophageal squamous cell carcinoma: A single-arm phase 2 trial

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author): with expertise in ESCC, therapy

This phase II trial investigated the efficacy and safety of the combination of radiotherapy and chemoimmunotherapy in patients with stage IV ESCC. The results indicated that the addition of radiotherapy to first-line chemoimmunotherapy is effective with a manageable safety profile. Moreover, potential biomarkers were also investigated. Overall, this study could bring some novel information to the field of advanced esophageal cancer.

Some comments:

1. In the abstract, the prescription dose is 50-50.4 Gy, however, it is 45-50.4 Gy in the Methods section. Please check it.
2. In this study, patients received toripalimab for a maximum of 1 year or until disease progression or evidence of intolerable toxicity. Since eligible patients were advanced ESCC, why is the toripalimab not used for a maximum of 2 years or until tumor progression?
3. Please explain why this trial included patients with stage IVA. For these patients (n=6), neoadjuvant CRT or definitive CRT should be the standard of care.
4. The timing of radiotherapy for metastatic lesions is not clear.
5. Exploratory endpoints included the relationship between clinical outcomes with biomarkers in blood (soluble PD-L1 and cytokines). The results section did not present the findings of soluble PD-L1.

Reviewer #2 (Remarks to the Author): with expertise in ESCC, therapy

This study presents the first prospective evaluation of the safety and efficacy of radiotherapy combined with chemo-immunotherapy in previously untreated advanced esophageal squamous cell carcinoma (ESCC) patients. The results showed that patients who completed the full course of radio-chemotherapy had a median progression-free survival (PFS) of 12.8 months, which was higher than in previous studies. This combination treatment also demonstrated manageable safety. Furthermore, the tumor microenvironment and peripheral cytokines were found to be predictive of treatment response. Although this study provides valuable information for the field of advanced esophageal cancer, the sample size is too limited to draw definitive conclusions.

Major comments:

1. The expected median PFS in the study was 12 months, and the final result for patients who completed radiotherapy was 12.8 months, meeting the endpoint. However, the mPFS in the intention-to-treat (ITT) population was only 9.8 months. Various circumstances, including disease progression and treatment side effects, may prevent the administration of radiotherapy following chemotherapy and immunotherapy in advanced esophageal cancer, as observed in this study. Consequently, using the PFS of patients who completed radiotherapy to assess this combined treatment modality may be inappropriate, and the results of the ITT population may be more accurate.

2. In this study, 27 (81.8%) patients had oligometastases, of which 12 were in distant organs and 15 in non-regional lymph nodes, and 6 patients (18.2%) had only regional lymph node metastases (cTanyN3M0). The concept of regional lymph nodes is not clearly defined in the article. It is mentioned in the protocol the distant (non-regional) lymph nodes included supraclavicular and retroperitoneal lymph nodes. However, in some statuses, the supraclavicular and retroperitoneal lymph nodes should be considered as regional lymph nodes, and radiotherapy with radical dose should be indispensable for such local advanced disease.

The radiation dose of primary lesion was mentioned in abstract 50–50.4 Gy in 25–28 fractions, but 45–50.4 Gy in other parts in the article. A dose of 45Gy may not be sufficient for controlling the primary lesion. The rationale for selecting this dose should be elucidated, and comprehensive descriptions of various radiation doses and their therapeutic effects in different sites are warranted.

This study investigated biomarkers; however, the statistical power of p-values between subgroups is limited due to the small sample size.

In this study toripalimab was used for up to 1 year, however, in previous studies immunotherapy maintained for 2 years in patients with advanced esophageal cancer. At present, there is not enough evidence to support that the addition of radiotherapy can reduce the maintenance of immunotherapy.

Reviewer #3 (Remarks to the Author): with expertise in biostatistics, clinical trial study design

The statistical analysis employed in this simple single-arm phase II trial appears largely appropriate. However, several minor comments and questions need addressing before advancing this report.

Some statistical analysis methods are solely described in Figure legends but should be included in the 'Statistical Analyses' section.

Line 130: "Intent-to-Treament" should read as "Intent-to-Treat."

Line 180 (and potentially elsewhere): Due to the extensive number of statistical tests conducted, caution should be exercised in drawing positive conclusions from somewhat large p-values. Consider multiplicity adjustment.

Line 182 (and potentially elsewhere): Refrain from concluding "similar" when statistical significance was not attained. Instead, describe the finding as "no difference was found" (attributable to small sample size or excessive data variation).

Table 1: Consider reporting the interquartile range alongside (or in lieu of) the range for Age.

Line 612: "Kaplan-Meier" refers to an estimator, not an analysis. Please rectify this.

Figure 2B is exemplary.

Consider adding confidence bands to the Kaplan-Meier curves where doing so would add valuable information, unless overlapping bands obscure the information.

For box plots, contemplate transforming the y-axis when outliers are present and the bulk of the data are compressed. Retain the original scale (e.g., 0, 2000, 4000, 6000) in the log-transformed figure.

Figure 7B: Consider log-transformation for enhanced clarity when outliers are present. Additionally, consider also plotting the differences.

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Authors’response

Reviewer #1

Thank you for your encouragement and insightful comments.

	Reviewer's comments	Authors' responses or change made	Page number
1	In the abstract, the prescription dose is 50-50.4 Gy, however, it is 45-50.4 Gy in the Methods section. Please check it.	Thank you for your meticulous observation. In the Methods section, we cited the prescribed dose range (45–50.4 Gy) as specified in the study protocol. However, all patients received doses ranging from 50–50.4 Gy, with no patient receiving less than 50 Gy. We have corrected this discrepancy in the Methods section.	Line 344, Line 349 on page 16
2	In this study, patients received toripalimab for a maximum of 1 year or until disease progression or evidence of intolerable toxicity. Since eligible patients were advanced ESCC, why is the toripalimab not used for a maximum of 2 years or until tumor progression?	Thank you for your insightful question. Although most clinical studies on advanced solid tumors recommend a maintenance period of 2 years for anti-PD-1 drugs, current research does not provide definitive evidence on the optimal duration of immune checkpoint inhibitors (ICIs). Previous studies have shown that patients with advanced melanoma who discontinued anti-PD-1 treatment after 1 year exhibited durable anti-tumor responses and a low risk of recurrence during long-term follow-up.[1,2] Additionally, a real-world multicentre observational study involving 1,011 Indian patients also demonstrated that short-course ICI treatment was comparable to standard treatment in terms of efficacy and safety.[3] Therefore, the optimal duration of ICIs in advanced cancers warrants further exploration. At the start of our study in early 2021, following the publication of results from the Phase III KEYNOTE-590 and ESCORT-1st clinical trials, the median progression-free survival (PFS) and 1-year PFS rates were 6.3 months and 24%, and 6.9 months and 23%, respectively (1-year PFS rates estimated from Kaplan−Meier curves). This clearly indicated that approximately 80% of patients experienced disease progression or death	Lines 220-225 on page 10 and 11

within 1 year and were unable to complete the 2-year immunotherapy maintenance. Furthermore, a 2-year immunotherapy maintenance period could result in greater adverse effects for patients who do not respond to the treatment.

Moreover, our study is a Phase II exploratory trial, where the primary strategy was to add radiotherapy to all lesions on top of systemic treatment, potentially reducing the risk of progression in primary and metastatic lesions during maintenance immunotherapy. Therefore, it is worth exploring whether the duration of immunotherapy maintenance could be shortened due to this treatment strategy. Time-limited ICI therapy may potentially reduce the adverse effects associated with long-term drug treatment and the associated financial burden for patients. In the discussion section of the manuscript, we have added some details regarding this issue.

Currently, two Phase II clinical trials[4,5] are exploring treatment regimens for advanced esophageal cancer that combine radiotherapy with immunotherapy and chemotherapy, considering a maintenance duration of 1 year. The outcomes of these exploratory studies will provide more evidence to determine the optimal duration of immunotherapy for advanced esophageal cancer.

3 Please explain why this trial included patients with stage IVA. For these patients (n=6), neoadjuvant CRT or definitive CRT should be the standard of care.

Thank you for your comment. The six patients classified as stage IVA had extensive primary lesions with multiple nodal metastases and significant extranodal extension. Following multidisciplinary team (MDT) discussions, they were deemed unsuitable for curative concurrent chemoradiotherapy. The appropriate treatment options considered were chemotherapy combined with immunotherapy, or participation in clinical

		trials. We have included PET-CT images of a typical case from these patients to demonstrate this point at the end of the response letter for your reference (Figure 1).	
4	The timing of radiotherapy for metastatic lesions is not clear.	Thank you for your comment. Currently, there is a lack of guidelines and consensus on the optimal timing of radiotherapy for distant metastatic lesions. Among the enrolled patients, 15 had oligometastatic non-regional lymph nodes. For these patients, we considered including both the metastatic lymph nodes and the primary lesion in a single radiotherapy plan for concurrent treatment. For the remaining patients with distant organ metastases, we planned to administer sequential radiotherapy to the metastatic sites as soon as the primary esophageal lesion treatment was completed.	
5	Exploratory endpoints included the relationship between clinical outcomes with biomarkers in blood (soluble PD-L1 and cytokines). The results section did not present the findings of soluble PD-L1.	Thank you for your comment. In the methods section of our manuscript, we outlined the analysis of several exploratory endpoints, including the relationship between clinical outcomes and the types of immune cells in the tumor microenvironment, as well as biomarkers in peripheral blood (such as circulating tumor DNA, next-generation sequencing, and soluble PD-L1). Secondary endpoints included the 2-year overall survival and health-related quality of life (HRQoL). As data collection and analysis for these specific endpoints are still ongoing, we plan to publish these results in future. Modifications regarding this description have been included in the "Follow-up and Outcomes" section of the revised manuscript.	Lines 382-383 on page 18

Reviewer #2

Thank you for your encouragement and professional comments and suggestions.

	Reviewer's comments	Authors' responses or change made	Page number
1	The expected median PFS in the study was 12 months, and the final result for patients who completed radiotherapy was 12.8 months, meeting the endpoint. However, the mPFS in the intention-to-treat (ITT) population was only 9.8 months. Various circumstances, including disease progression and treatment side effects, may prevent the administration of radiotherapy following chemotherapy and immunotherapy in advanced esophageal cancer, as observed in this study. Consequently, using the PFS of patients who completed radiotherapy to assess this combined treatment modality may be inappropriate, and the results of the ITT population may be more accurate.	Thank you for your valuable feedback. We agree with your assessment and appreciate your insights. Based on the Editor's suggestion, we have revised the abstract to meet the journal's requirements. In the revised abstract, we have specifically focused on the data from the intention-to-treat (ITT) population. Although the median progression-free survival (mPFS) for the ITT population was only 9.8 months, this still represents a positive improvement in PFS when compared to the 5.7–7.3 months reported in existing literature.	Lines 44-64 on page 3
2	In this study, 27 (81.8%) patients had oligometastases, of which 12 were in distant organs and 15 in non-regional lymph nodes, and 6 patients (18.2%) had only regional lymph node metastases (cTanyN3M0). The concept of regional lymph nodes is not clearly defined in the article. It is mentioned in the protocol that the distant (non-regional) lymph nodes include supraclavicular and retroperitoneal lymph nodes. However, in some statuses, the supraclavicular and	Thank you for your comment. In our manuscript, we included in the Methods section that we used the 8th edition of the American Joint Committee on Cancer (AJCC) staging system,[6] which clearly defines regional lymph nodes for esophageal cancer, including 1R/1L/2R/2L/4R/4L/7/8U/8M/8L/9R/9L/15/16/17/18/19/20. Supraclavicular and retroperitoneal lymph nodes (lymph nodes below the celiac trunk) are considered distant metastatic sites, not regional lymph nodes for esophageal cancer. Therefore, according to the 8th edition AJCC staging system for	Lines 351-352 on page 16 Supplementary 2, Supplementary Methods, S2

	retroperitoneal lymph nodes should be considered as regional lymph nodes, and radiotherapy with radical dose should be indispensable for such locally advanced disease.	esophageal cancer we used, we still classify supraclavicular and retroperitoneal lymph nodes as distant (non-regional) lymph nodes. We accept your suggestion and have provided a detailed definition of the concept of regional lymph nodes in our study in Supplementary 2. We also agree with your viewpoint that aggressive, even radical, treatment may be beneficial for patients with oligometastatic disease, a point that is thoroughly discussed in the Discussion section of the paper.	
3	The radiation dose of primary lesion was mentioned in abstract 50–50.4 Gy in 25–28 fractions, but 45–50.4 Gy in other parts in the article. A dose of 45Gy may not be sufficient for controlling the primary lesion. The rationale for selecting this dose should be elucidated, and comprehensive descriptions of various radiation doses and their therapeutic effects in different sites are warranted.	Thank you for your careful observation. In the Methods section, we cited the prescribed dose range (45–50.4 Gy) specified in the study protocol, as it was anticipated that some patients might not tolerate radiation doses of 50 Gy or higher during the design phase of the study. However, in practice, all patients received doses ranging from 50–50.4 Gy. We have corrected this discrepancy in the Methods section of the revised manuscript.	Line 344, Line 349 on page 16
4	This study investigated biomarkers; however, the statistical power of p-values between subgroups is limited due to the small sample size.	Thank you for your comment. This shortcoming of the study has been acknowledged in the limitations section of our manuscript. Given the exploratory nature of this study, the sample size was small, and no adjustments were made for multiple comparisons or multiplicity. We have included a description of the adjustment for multiplicity in the "Statistical Analyses" section as follows: "Because of the exploratory nature of this clinical study, no adjustments were made for multiple comparisons." . In the section "Biomarkers for Treatment Response and Outcomes," we have adopted a more cautious interpretation of the results, with corresponding modifications. The explorations of biomarkers in the current Phase II study are very	Lines 440-441 on page 20 Lines 166-174, Lines 184-190 on page 8-9

		preliminary, aimed at identifying some differential trends and selecting potential predictive markers of value. Our ongoing Phase III clinical trial has expanded the sample size to 100 participants, allowing us to focus more on these biomarkers. With the increased sample size, we expect to obtain more statistically significant data.	
5	In this study toripalimab was used for up to 1 year, however, in previous studies immunotherapy maintained for 2 years in patients with advanced esophageal cancer. At present, there is not enough evidence to support that the addition of radiotherapy can reduce the maintenance of immunotherapy.	Many thanks for your helpful suggestion. Although most clinical studies on advanced solid tumors recommend a maintenance period of 2 years for anti-PD-1 drugs, current research does not provide definitive evidence on the optimal duration of immune checkpoint inhibitors (ICIs). Previous studies have shown that patients with advanced melanoma who discontinued anti-PD-1 treatment after 1 year exhibited durable anti-tumor responses and a low risk of recurrence during long-term follow-up.[1,2] Additionally, a real-world multicentre observational study involving 1,011 Indian patients also demonstrated that short-course ICI treatment was comparable to standard treatment in terms of efficacy and safety.[3] Therefore, the optimal duration of ICIs in advanced cancers warrants further exploration. At the start of our study in early 2021, following the publication of results from the Phase III KEYNOTE-590 and ESCORT-1st clinical trials, the median progression-free survival (PFS) and 1-year PFS rates were 6.3 months and 24%, and 6.9 months and 23%, respectively (1-year PFS rates estimated from Kaplan−Meier curves). This clearly indicated that approximately 80% of patients experienced disease progression or death within 1 year and were unable to complete the 2-year immunotherapy maintenance. Furthermore, a 2-year immunotherapy maintenance period could result in greater adverse effects for patients who do not respond to	Lines 220-225 on page 10 and 11

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Moreover, our study is a Phase II exploratory trial, where the primary strategy was to add radiotherapy to all lesions on top of systemic treatment, potentially reducing the risk of progression in primary and metastatic lesions during maintenance immunotherapy. Therefore, it is worth exploring whether the duration of immunotherapy maintenance could be shortened due to this treatment strategy. Time-limited ICI therapy may potentially reduce the adverse effects associated with long-term drug treatment and the associated financial burden for patients. In the discussion section of the manuscript, we have added some details regarding this issue.

Currently, two Phase II clinical trials[4,5] are exploring treatment regimens for advanced esophageal cancer that combine radiotherapy with immunotherapy and chemotherapy, considering a maintenance duration of 1 year. The outcomes of these exploratory studies will provide more evidence to determine the optimal duration of immunotherapy for advanced esophageal cancer.

Reviewer #3

Thank you for your encouragement and professional comments and suggestions.

	Reviewer's comments	Authors' responses or change made	Page number
1	Some statistical analysis methods are solely described in Figure legends but should be included in the 'Statistical Analyses' section.	Thank you for your comment. We have revised the section on 'Statistical Analyses', incorporating all statistical methods employed, including those previously only described in the Figure legends.	Lines 433-442 on page 20
2	Line 130: "Intent-to-Treament" should read as "Intent-to-Treat."	Thank you for the correction. We have made the corresponding change in the revised manuscript.	Lines 134 on page 7
3	Line 180 (and potentially elsewhere): Due to the extensive number of statistical tests conducted, caution should be exercised in drawing positive conclusions from somewhat large p-values. Consider multiplicity adjustment.	Thank you for your comment on adjustment for multiplicity. It is crucial to consider multiplicity adjustments in clinical trials. Given the exploratory nature of this study and the small sample size, no adjustments were made for multiple comparisons or multiplicity. We have included a description of the adjustment for multiplicity in the "Statistical Analyses" section as follows: "Because of the exploratory nature of this clinical study, no adjustments were made for multiple comparisons.". However, according to your suggestion, we have added the results of the multiplicity adjustment at the end of the response letter for your reference. (Table 1. Multiple testing p values obtained using Benjimini-Hochberg method).	Lines 440-441 on page 20
4	Line 182 (and potentially elsewhere): Refrain from concluding "similar" when statistical significance was not attained. Instead, describe the finding as "no difference was found" (attributable to small sample size or excessive data variation).	Thank you for your comment. In the section "Biomarkers for Treatment Response and Outcomes," we have revised our description of the results accordingly.	Lines 162-194 on page 8-9
5	Table 1: Consider reporting the interquartile range alongside (or in lieu of) the range for Age.	Thank you for your suggestion. We have updated Table 1 according to your recommendation.	Lines 633 on page 30, Table 1

6	Line 612: "Kaplan-Meier" refers to an estimator, not an analysis. Please rectify this.	Thank you for pointing this out. We have revised the text from "Kaplan–Meier survival analysis" to "Kaplan–Meier estimates of survival.".	Lines 645 on page 34, Fig. 3
7	Figure 2B is exemplary. Consider adding confidence bands to the Kaplan-Meier curves where doing so would add valuable information, unless overlapping bands obscure the information.	Thank you for your suggestion. Based on your recommendation, we have modified the figures to include confidence bands on the Kaplan–Meier curves.	Fig. 3
8	For box plots, contemplate transforming the y-axis when outliers are present and the bulk of the data are compressed. Retain the original scale (e.g., 0, 2000, 4000, 6000) in the log-transformed figure.	Thank you for your suggestion. We have made modifications to the figures accordingly. For Fig. 4 and Supplementary Fig. 1, we used a log10 transformation on the y-axis, but retained the original scale for labeling (e.g., 0, 2000, 4000, 6000). For Fig. 5, and Supplementary Figs. 1 and 2, we applied a square root transformation on the y-axis, yet the labels still reflect the original values.	Fig. 4, Fig. 5, Supplementary Figs. 1 and 2
9	Figure 7B: Consider log-transformation for enhanced clarity when outliers are present. Additionally, consider also plotting the differences.	Thank you for your suggestion. We have made modifications to the figures accordingly.	Supplementary Fig. 2

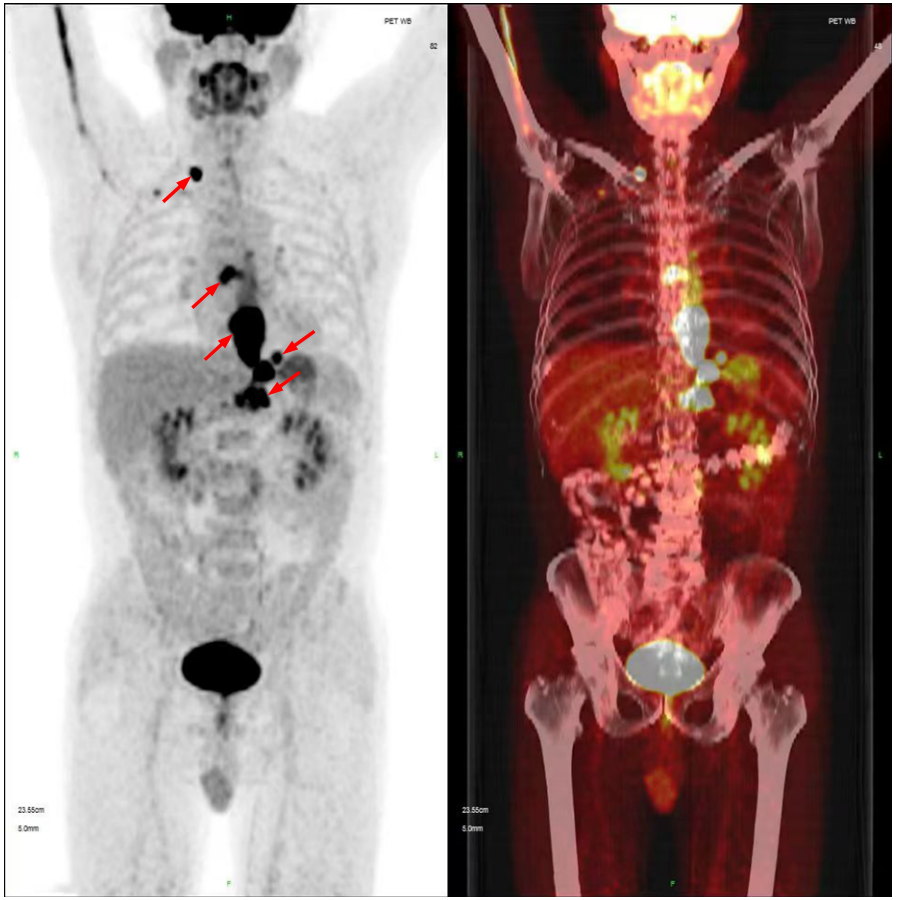

Figure 1. The ^{FDG} PET-CT scans showed the baseline disease status, indicating multiple lymph node metastases (1R/7/16/17/18/19/20) with enlarged and fused lymph nodes. Red arrows indicate the locations of tumor distribution.The patient was staged as cT4N3M0. After multidisciplinary discussion, it was concluded that there were no indications for radical surgery or definitive chemoradiotherapy.

Table 1. Multiple testing p values obtained using Benjimini-Hochberg method

Differences of cytokines at baseline between PR and SD		
Variables	**Original p Value**	**Benjimini-Hochberg Adjusted p Value**
BaseLine IL2	0.370	0.503
BaseLine IL4	0.310	0.503
BaseLine IL6	0.300	0.503
BaseLine IL10	0.076	0.503
BaseLine IL17	0.640	0.304
BaseLine IL37	0.440	0.640
BaseLine TNF	0.390	0.503
BaseLine IFN	0.063	0.304
Differences of cytokines at on-treatment between PR and SD		
Variables	**Original p Value**	**Benjimini-Hochberg Adjusted p Value**
onTreat IL2	0.500	0.640
onTreat IL4	0.390	0.640
onTreat IL6	1.000	1.000
onTreat IL10	0.480	0.640
onTreat IL17	0.560	0.640
onTreat IL37	0.310	0.640
onTreat TNF	0.190	0.640
onTreat IFN	0.026	0.208

Reference

1. Pokorny R, McPherson JP, Haaland B, Grossmann KF, Luckett C, Voorhies BN, et al. Real-world experience with elective discontinuation of pd-1 inhibitors at 1 year in patients with metastatic melanoma. J Immunother Cancer (2021) 9(1): e001781. doi: 10.1136/jitc-2020-001781

2. Gibney GT, Zaemes J, Shand S, Shah NJ, Swoboda D, Gardner K, et al. Pet/Ct scan and biopsy-driven approach for safe anti-Pd-1 therapy discontinuation in patients with advanced melanoma. J Immunother Cancer (2021) 9(10):e002955. doi: 10.1136/jitc-2021-002955

3. Abraham G, Noronha V, Rajappa S, Agarwal A, Batra U, Somani N, et al. The clinical utility and safety of short-course immune checkpoint inhibitors in multiple tumours-a real-world multicentric study from India. Int J Cancer (2022) 150(6):1045–52. doi: 10.1002/ijc.33868

4. Study of PD-1 antibody combined with chemoradiotherapy in oligometastatic esophageal cancer. Identifier: NCT04821765. https://ClinicalTrials.gov/show/NCT04821765, (2020).

5. Phase II clinical study for Sintilimab (IBI308) in the maintenance therapy after second-line chemoradiotherapy for local and/or regional recurrent esophageal squamous cell cancer patients. Identifier: ChiCTR1900027161. https://www.chictr.org.cn/showproj.html?proj=45230.

6. Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the Esophagus and Esophagogastric Junction: An Eighth Edition Staging Primer. J Thorac Oncol. 2017;12(1):36-42. doi:10.1016/j.jtho.2016.10.016

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

My comments have been addressed in the revisions.

Reviewer #2 (Remarks to the Author):

Thank you for the response from the author. However, the authors have not provided a satisfactory explanation for issues such as small sample sizes and the duration of immunotherapy cycles in the experimental design. PFS does not match the predetermined values, suggesting potential issues in sample size calculation and statistical analysis. The use of short immunotherapy maintenance cycles in the experimental design could negatively impact overall survival. The manuscript still contains uncertainties, making it challenging to replicate and generalize the conclusions.

Reviewer #3 (Remarks to the Author):

Thank you very much for thoroughly addressing all my previous concerns and questions. I do not have any additional concern

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POINT-BY-POINT RESPONSES TO THE COMMENTS OF REVIEWERS

Reviewer #1 (Remarks to the Author):
My comments have been addressed in the revisions.

Response: We appreciate the reviewer's high-quality comments that have helped improve the quality of this manuscript.

Reviewer #2 (Remarks to the Author):

Thank you for the response from the author. However, the authors have not provided a satisfactory explanation for issues such as small sample sizes and the duration of immunotherapy cycles in the experimental design. PFS does not match the predetermined values, suggesting potential issues in sample size calculation and statistical analysis. The use of short immunotherapy maintenance cycles in the experimental design could negatively impact overall survival. The manuscript still contains uncertainties, making it challenging to replicate and generalize the conclusions.

Response: We appreciate the reviewer's insightful comments. We understand the concerns you have raised. Regarding the first issue of sample size, our study's sample size was based on strict statistical assumptions. According to the previous KEYNOTE 590 study, the median PFS for first-line immunotherapy combined with chemotherapy in patients with advanced esophageal squamous cell carcinoma was 6.3 months. In our previous clinical practice, we found that adding radiotherapy to tumor lesions based on standard chemotherapy combined with immunotherapy can prolong patient survival. On May 25, 2022, we published online case reports of two typical patients[1]. Therefore, we made the following statistical assumptions in this study: We expect the PFS in this study to reach 12.0 months. With an enrollment period of 12 months and a follow-up period of 12 months, and considering a 20% dropout rate, this study plans to enroll 32 patients. We aim to perform a final analysis of PFS upon observing 16 PFS events, which would provide an 80% power to detect a significant improvement in PFS in the experimental group compared to historical controls, at a two-sided significance level of 0.05. Due to the exploratory nature of this study, the sample size is relatively small, which we have explained in the limitations section of the manuscript. As we have already initiated a Phase III randomized controlled trial based on this Phase II study, the calculated sample size for the Phase III study is 100 cases. This will expand the sample size and make the upcoming study results more valuable.

Regarding the second issue of the duration of immunotherapy maintenance, we have detailed the rationale for choosing a 1-year immunotherapy maintenance period in our previous response letter. We still believe that the duration of immunotherapy maintenance in advanced esophageal cancer is worth exploring. Considering that the median PFS for patients with advanced esophageal cancer is between 5 to 8 months, this indicates that most patients do not have the opportunity to complete a 2-year immunotherapy maintenance period. We need new clinical studies to further explore this issue, especially after adding local radiotherapy.

Reviewer #3 (Remarks to the Author):

Thank you very much for thoroughly addressing all my previous concerns and questions. I do not have any additional concerns.

Response: We appreciate the reviewer's recognition. The previous comments have helped us better report the results of this study, for which we are deeply grateful.

Reference

1. Wu L, Liu J, Liang L, et al. "Sandwich Therapy"-Immunotherapy Plus Concurrent Chemoradiotherapy for Advanced Esophagogastric Junction Carcinoma: Report of Two Cases and Literature Review. Front Oncol. 2022;12:794153. Published 2022 May 25. doi:10.3389/fonc.2022.794153