Does nivolumab combined with fluorouracil-based chemotherapy produce higher objective response rate than other immunochemotherapy regimes in metastatic esophageal cancer?

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In regard to Gao et al.

To the Editor: We read with interest the systematic review and network meta-analysis by Gao et al.[1] comparing the efficacy and safety of first-line immunotherapy, immunochemotherapy, chemotherapy, and targeted therapy for advanced and metastatic esophageal cancer. Since immune checkpoint inhibitors (ICIs) combined with either fluorouracil + cisplatin (fluorouracil-based chemotherapy, FbCT) and paclitaxel + cisplatin (fluorouracil-free chemotherapy, FfCT) have become the standard first-line treatment for metastatic esophageal squamous cell carcinoma (ESCC),[2–6] this is a topical article exploring the optimal drug combination in cases where randomized controlled trials (RCTs) directly comparing various drugs, including cytotoxic and immunotherapeutic drugs, for metastatic ESCC patients, are lacking. In contrast to other meta-analysis,[7] this review by Gao et al. reports that Nivolumab + FbCT shows a significant advantage in objective response rate (ORR) compared to three other immunochemotherapy regimes (nivolumab + FbCT vs. camrelizumab + FbCT, OR 4.04; nivolumab + FbCT vs. camrelizumab + FfCT), OR 2.83; nivolumab + FbCT vs. toripalimab + FfCT, OR 2.47).

These contrary results may be attributable to the incomplete trial data, thus potentially leading to inaccurate classification based on the chemotherapy regimens. The RATIONALE-306 trial, as reported in the 2022 ESMO conference,[8] involved randomizing patients in a 1:1 ratio to receive either tislelizumab or placebo combined with investigator-selected chemotherapy (fluoropyrimidine [capecitabine or 5-fluorouracil] and platinum [cisplatin or oxaliplatin] or paclitaxel and platinum). The final report of the RATIONALE-306 trial had shown that 178 of 324 patients (54.9%) received tislelizumab combined with paclitaxel + platinum, while 146 of 324 patients (45.1%) received tislelizumab combined with FbCT (fluoropyrimidine + platinum).[9] Unfortunately, this trial was misclassified to the tislelizumab + FbCT group. Furthermore, ORIENT-15 trial also has 6.1% of patients (20/327) receiving sintilimab combined with FbCT (5-fluorouracil + cisplatin). Therefore, a further sensitive analysis, subgroup analysis or updated analysis might be more appropriate.

In addition, significant concern for ORR exists in this article. Fig. 4B could not be found in the main text. A total of 7 studies (CheckMate 648, KEYNOTE-590, ESCORT-1st, RATIONALE-306, ORIENT-15, JUPITER-06 and ASCO e16084)[2–6,9,10] exploring the treatment efficacy of ICIs + chemotherapy was included in this analysis, and results from ASTRUM-007 trial studying the benefits of serplulimab combined with FbCT (5-fluorouracil + cisplatin) in PD-L1-positive ESCC were recently reported.[11] Detailed ORRs from different trials were shown in Table 1. In ESCC patients, the ORR of nivolumab + FbCT was 47.4%, while ORRs of other combinations of ICIs + FfCT (camrelizumab + FfCT, Sintilimab + FfCT, toripalimab + FfCT) ranged from 66.1 to 79.2%. In addition, although the KEYNOTE-590 trial didn't reported the ORR of ESCC patients, subgroup analysis showed that 38 of 67 Japanese ESCC patients (56.7%) receiving pembrolizumab + FbCT achieved objective response.[12] The network meta-analysis conducted by Gao et al.[1] showed that patients receiving nivolumab/pembrolizumab + FbCT had higher OR rates than patients receiving other ICIs combinations. However, among all these trials, the ORRs of ICIs + FfCT were numerically higher than those of ICIs + FbCT both in the whole patients and in the ESCC patients.

Although the author discussed the potential reasons for the different ORRs between different ICIs combinations, we advise exercising caution when interpreting the study by Gao et al. due to the presence of unbalanced patient samples and potential

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Study	Intervention	ORR in all patients	ORR in ESCC patients
CheckMate 648	Nivolumab + fluorouracil + cisplatin	NA	47.4% (152/321)
	Nivolumab + ipilimumab	NA	27.7% (90/325)
	fluorouracil + cisplatin	NA	26.9% (87/324)
ESCORT-1st	Camrelizumab + paclitaxel + cisplatin	NA	72.1% (215/298)
	paclitaxel + cisplatin	NA	62.1% (185/298)
ORIENT-15	Sintilimab + paclitaxel/fluorouracil + cisplatin	NA	66.1% (216/327)
	Paclitaxel/fluorouracil + cisplatin	NA	45.5% (151/332)
JUPITER-06	Toripalimab + paclitaxel + cisplatin	NA	69.3% (178/257)
	paclitaxel + cisplatin	NA	52.1% (134/257)
ASCO e16084	Camrelizumab + fluorouracil + platinum	NA	55.6% (5/9)
	Camrelizumab + taxol + platinum	NA	79.2% (19/24)
ASTRUM-007	Serplulimab + 5-fluorouracil + cisplatin	NA	57.6% (212/368)
	5-fluorouracil + cisplatin	NA	42.1% (77/183)
KEYNOTE-590	Pembrolizumab + 5-fluorouracil + cisplatin	45.0% (168/373)	56.8% (42/74)[a]
	5-fluorouracil + cisplatin	29.3% (110/376)	38.8% (26/67)[a]
RATIONALE-306	Tislelizumab + platinum + paclitaxel/fluoropyrimidine	NA	63.5% (207/326)
	platinum + paclitaxel/fluoropyrimidine	NA	42.4% (137/323)

[a]ORRs in Japanese patients from KEYNOTE-590; NA, not available.

Table 1: **ORRs of chemotherapy ± ICIs in the first-line treatment of esophageal cancer from different trials.**

misclassifications which may have contributed to conclusions contrary to those of other reports.

Contributors

Ying Li and Yong Chen are principally conceived of this Letter. Lin Shen and Xudong Yin reviewed the literature, obtained the collected data. Zixuan Chen drew up the table. Ying Li wrote the manuscript draft and Yong Chen revised the manuscript critically.

Declaration of interests

The author declare no conflicts of interest.

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