Advancements in Immune Checkpoint Inhibitors for Oesophageal Squamous Cell Carcinoma: Current Status and Future Perspectives

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Oesophageal cancer is the eighth most prevalent malignancy globally, with oesophageal squamous cell carcinoma (ESCC) constituting 85% of documented cases. It is also the sixth leading cause of cancer-related death. We review two studies recently presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium 2024 that assessed the role of chemotherapy plus immunotherapy in ESCC. The SKYSCRAPER-08 trial evaluated the impact on overall survival (OS) of tiragolumab and atezolizumab combined with cisplatin and paclitaxel in the first-line recurrent/metastatic setting. There was a statistically significant increase in OS compared with placebo plus chemotherapy. In the setting of curative intent, the ESCORT-NEO trial investigated neoadjuvant therapy for resectable, locally advanced ESCC by comparing chemotherapy alone with chemotherapy plus camrelizumab. It met the co-primary endpoint of higher pathological complete response. Both studies underscore the emerging role of immune checkpoint inhibitors in the management of ESCC, both in advanced and neoadjuvant settings. These offer possible practice-changing findings that will improve patient outcomes and serve as a backbone for future immunotherapy studies in ESCC.

Oesophageal cancer is the eighth most commonly diagnosed cancer and is the sixth leading cause of cancer death worldwide.[1,2] Worldwide, around 604,100 new instances of oesophageal cancer were recorded in 2020, leading to approximately 544,100 deaths. This translates to a standardized incidence rate of 6.3 per 100,000 people and a mortality rate of 5.6 per 100,000. The majority of cases, about 85%, were oesophageal squamous cell carcinomas (ESCCs), totalling approximately 512,500 cases. Notably, men experienced incidence and mortality rates approximately two to three times higher than those of women. There were significant disparities in incidence and mortality rates across different regions globally, with Eastern Asia and Southern and Eastern Africa, where ESCC is the most common histology, exhibiting the highest rates. Projections suggest that if these rates remain constant, the year 2040 could see approximately 957,000 new cases of oesophageal cancer, comprising 806,000 ESCC cases.[3]

Immune checkpoint inhibitors (ICIs) represent a promising therapeutic avenue in the context of ESCC, a malignancy typified by its aggressive behaviour and unfavourable prognosis. These agents act by modulating crucial regulatory pathways of the immune system, notably targeting programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4). By inhibiting these checkpoints, ICIs aim to reinvigorate the host immune response against malignant cells, promoting tumour recognition and destruction.

However, the tumour microenvironment (TME) plays a complex role in shaping the immune landscape in ESCC. The TME is characterized by a diverse array of immune cells, stromal components and extracellular matrix elements that can either facilitate or hinder effective antitumour immunity. For instance, the presence of immunosuppressive cells, such as regulatory T cells and myeloid-derived suppressor cells, can inhibit the activity of effector T cells, thereby compromising the efficacy of ICIs.[4] Additionally, tumour-associated macrophages can adopt a pro-tumourigenic phenotype, further exacerbating immune evasion.[5]

Recent studies have highlighted the importance of the TME in predicting response to ICI therapy. For example, high levels of tumour-infiltrating lymphocytes and a high tumour mutational burden (TMB) have been correlated with improved outcomes in patients receiving ICIs.[6] Furthermore, the TME may also secrete various cytokines and chemokines that modulate immune cell infiltration and function, creating a hostile environment for effective antitumour immunity.[7] Ongoing research aims to optimize patient selection, identify predictive biomarkers and explore novel

combination strategies that enhance the immunogenicity of tumours and modify the TME to maximize the therapeutic potential of ICIs in ESCC management.

Two recent clinical trials presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium 2024 (ASCO GI 2024) demonstrated promising results, advocating for the incorporation of novel immunotherapeutic agents alongside conventional chemotherapy in the management of locally advanced and metastatic ESCC, as well as in neoadjuvant therapy for resectable ESCC.

The SKYSCRAPER-08 trial (A Study of Atezolizumab Plus Tiragolumab in Combination with Paclitaxel and Cisplatin Compared with Paclitaxel and Cisplatin as First-line Treatment in Participants with Unresectable Locally Advanced, Unresectable Recurrent, or Metastatic Esophageal Carcinoma; ClinicalTrials.gov identifier: NCT04540211) evaluated the efficacy and safety of first-line treatment with tiragolumab (anti-T-cell immunoreceptor with immunoglobulin and ITIM [immunoreceptor tyrosine-based inhibitory motif] domains [TIGIT] antibody) plus atezolizumab (anti-programmed death ligand-1 [PD-L1] antibody) in combination with chemotherapy compared with placebo plus chemotherapy. This was in an Asian population with unresectable locally advanced, unresectable recurrent or metastatic ESCC.[8]

The ESCORT-NEO trial (Chemotherapy Plus Camrelizumab Versus Chemotherapy Alone as Neoadjuvant Treatment for Resectable Esophageal Squamous Cell Carcinoma: A Multi-center, Randomized Phase III Trial; Chinese Clinical Trial Register identifier: ChiCTR2000040034) investigated chemotherapy, with or without camrelizumab (anti-PD-1 antibody), in the neoadjuvant setting for resectable ESCC.[9]

In this narrative review, our objective is to comprehensively analyse the current clinical landscape regarding the role of ICIs in managing locally advanced/metastatic and resectable ESCC. Additionally, we will evaluate the underlying rationale, outcomes, conclusions and critical assessment of the above studies that incorporate two emerging immunotherapy targets into existing standard-of-care regimens.

Locally advanced/metastatic oesophageal squamous cell carcinoma
Current role of immune checkpoint inhibitor in standard of care
The CheckMate 648 (A Study to Evaluate Efficacy in Subjects with Esophageal Cancer Treated with Nivolumab and Ipilimumab or Nivolumab Combined with Fluorouracil Plus Cisplatin Versus Fluorouracil Plus Cisplatin; ClinicalTrials.gov identifier: NCT03143153) and KEYNOTE 590 (Pembrolizumab Plus Chemotherapy Versus Chemotherapy Alone for First-line Treatment of Advanced Oesophageal Cancer: A Randomised, Placebo-controlled, Phase 3 Study; ClinicalTrials.gov identifier: NCT03189719) studies established the standard of care in the frontline setting for recurrent metastatic ESCC, which consists of chemotherapy combined with PD-L1 axis inhibitors or PD-L1 plus CTLA-4.[10,11]

CheckMate 648 evaluated the efficacy and safety of the ICIs nivolumab (a PD-1 inhibitor) and ipilimumab (a CTLA-4 inhibitor), either together or in combination with chemotherapy.[10] Nine hundred and seventy previously untreated adults with unresectable advanced, recurrent or metastatic ESCC were randomized into three arms: nivolumab plus chemotherapy (fluorouracil and cisplatin), nivolumab plus ipilimumab or chemotherapy alone. The primary endpoints were overall survival (OS) and progression-free survival (PFS).

After a minimum of 13 months of follow-up, there was a significant improvement in median OS for both nivolumab plus chemotherapy (hazard ratio [HR] 0.74; 99.1% confidence interval [CI], 0.58–0.96); p=0.002) and nivolumab plus ipilimumab (HR 0.78; 98.2% CI, 0.62–0.98; p=0.01) compared with chemotherapy alone. These benefits were observed in patients with tumour-cell PD-L1 expression of 1% or greater, as well as in the overall population. The safety profiles of the nivolumab-containing regimens were consistent with those of the individual components, although grade 3 or 4 treatment-related adverse events (TRAEs) were more common with nivolumab plus chemotherapy (seen in 47% of the patients) than with the other two regimens (32% in nivolumab plus ipilimumab and 36% in chemotherapy alone).

The KEYNOTE 590 study investigated the efficacy of pembrolizumab (a PD-1 inhibitor) in combination with chemotherapy as a first-line treatment for patients with metastatic or unresectable recurrent ESCC or oesophageal adenocarcinoma.[11] This randomized, double-blind, phase III trial enrolled 749 patients to receive either pembrolizumab plus chemotherapy (cisplatin and fluorouracil) or placebo plus chemotherapy. Seventy-three per cent of the patients (n=548) had ESCC. The primary endpoints were OS and PFS in patients with ESCC. At the first interim analysis, after a median follow-up of 22.6 months, pembrolizumab plus chemotherapy significantly improved OS (HR 0.73; 95% CI, 0.60–0.88; p=0.0006) and PFS (HR=0.65; 95% CI, 0.54–0.78; p<0.0001), establishing this approach as a first-line standard of care. In the updated analysis, after a median follow-up of 59 months, pembrolizumab plus chemotherapy led to a significant improvement in OS, with a median OS of 12.3 versus 9.8 months with chemotherapy alone (HR 0.72; 95% CI, 0.62–0.84) in the intention-to-treat population. Significant benefits were seen in the patient subsets with ESCC (n=584, HR 0.71; 95% CI, 0.60–0.85), those with a combined positive score (CPS) of ≥10 (n=383, HR 0.64; 95% CI, 0.52–0.80) and those with ESCC and a CPS of ≥10 (n=286, HR 0.60; 95% CI, 0.46–0.76).[12]

Novel immune checkpoint inhibitor: Tiragolumab
The monoclonal antibody tiragolumab exerts its therapeutic effects through a distinct mechanism of action by primarily targeting TIGIT, an inhibitory immune checkpoint receptor.[13,14] It is mainly expressed on memory T cells, T regulatory cells and natural killer cells.[15,16] By binding to TIGIT, tiragolumab disrupts its interaction with its ligands, including the poliovirus receptor and its isoforms, nectin-2 and nectin-3, thereby impeding downstream inhibitory signalling pathways.[17] This blockade facilitates the activation and proliferation of effector T cells within the TME. Furthermore, tiragolumab administration enhances antigen-presenting cell function and augments dendritic cell maturation, thereby promoting a robust antitumour immune response.[13] Preclinical studies demonstrated the synergistic potential of tiragolumab in combination with other immunotherapeutic agents, such as PD-1/PD-L1 inhibitors, further highlighting its role as a promising therapeutic modality in oncology.[18]

The GO30103 trial (Safety and Pharmacokinetics [PK] of Escalating Doses of Tiragolumab as a Single Agent and in Combination with Atezolizumab and/or Other Anti-cancer Therapies in Locally Advanced or Metastatic Tumors; ClinicalTrials.gov identifier: NCT02794571) assessed the safety and antitumour activity of tiragolumab dose escalation, either alone (phase Ia; n=24) or in combination with fixed-dose atezolizumab (phase Ib; n=49), in patients with advanced solid tumours.[19] Tiragolumab combined with atezolizumab was well tolerated, with no dose-limiting toxicities observed. The most frequent TRAEs were fatigue and pruritus, primarily of grade 1 or 2 severity. The recommended phase II dose of

tiragolumab with atezolizumab was 600 mg administered intravenously every 3 weeks. While phase Ia showed a confirmed objective response rate (ORR) of 0%, phase Ib demonstrated antitumour activity in 6% of patients overall, with the combination of tiragolumab plus atezolizumab showing a confirmed ORR of 46% in non-small-cell lung cancer and 28% in oesophageal cancer cohorts.

A subsequent phase Ib trial by Wainberg et al. (LBA-5 Phase Ib Study of the Anti-TIGIT Antibody Tiragolumab in Combination with Atezolizumab in Patients with Metastatic Esophageal Cancer) assessed the efficacy and safety of tiragolumab combined with atezolizumab in patients with oesophageal cancer (13 ESCC). The study enrolled 21 participants, with 33% of the cohort being Asian. Among the patients, 67% experienced grades 3–4 adverse events, with only one being deemed related to treatment. The predominant adverse events included rash (38%), anaemia (24%) and hepatitis (24%). The confirmed ORR was 28%, with a median duration of response lasting 15.3 months.[20] These data supported the development of the SKYSCRAPER-08 trial.

SKYSCRAPER-08 trial
The SKYSCRAPER-08 trial investigated the efficacy and safety of tiragolumab plus atezolizumab in combination with chemotherapy, compared with placebo plus chemotherapy, as first-line treatment in an Asian population with recurrent/metastatic ESCC. Patients (n=451) received either tiragolumab and atezolizumab plus chemotherapy (cisplatin and paclitaxel) or chemotherapy alone for six cycles, followed by maintenance therapy until loss of clinical benefit or unacceptable toxicity. In the final analysis, as of 13 February 2023, the median OS was 15.7 months for the tiragolumab plus atezolizumab group compared with 11.1 months for the placebo plus chemotherapy group (HR 0.70; 95% CI, 0.55–0.88; p=0.0024).[8]

TRAEs occurred in 98.2% of patients in both arms, with grade 3/4 TRAEs reported in 59.6% of the tiragolumab plus atezolizumab plus chemotherapy group and 56.4% of the placebo plus chemotherapy group. Grade 5 TRAEs were observed in a relatively small percentage of patients (2.6%) in the tiragolumab plus atezolizumab plus chemotherapy group and 0.9% in the placebo plus chemotherapy group. Key immune-related adverse events (irAEs) observed in the experimental combination group included immune-related rash (38.6%), immune-mediated hepatitis (35.1%), immune-mediated hypothyroidism (17.5%), infusion-related reactions (17.5%) and immune-related pneumonitis (7.5%).[8]

SKYSCRAPER-08: Discussion
The study met the primary endpoints of statistically significant and clinically meaningful improvements in both PFS and OS for the tiragolumab plus atezolizumab plus chemotherapy regimen. Subgroup analyses, including the PD-L1 status, showed consistent benefits, and the safety profile was consistent with the known risks associated with the individual treatments. Most of the irAEs were of lower severity (grade 1 or 2) and, per researchers, were effectively managed with standard interventions. Grade 5 adverse events were rare but present, highlighting the need for vigilant monitoring and management of severe reactions.

This study did not include a cohort of tiragolumab plus chemotherapy, so isolating the effects of tiragolumab without atezolizumab is not possible. However, the MORPHEUS-EC trial (A Study of Multiple Immunotherapy-based Treatment Combinations in Patients with Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Cancer or Esophageal Cancer; ClinicalTrials.gov identifier: NCT03281369) did evaluate this, where 152 patients with untreated,

locally advanced, unresectable or metastatic ESCC were randomized to three groups: chemotherapy alone, atezolizumab plus chemotherapy and tiragolumab plus atezolizumab plus chemotherapy with a median follow-up of 8.7, 11.4 and 10.9 months, respectively.[21] Interim analysis as of 14 March 2023 showed ORRs of 47.8, 53.8 and 67.7%, while median PFS durations were 4.1, 6.8 and 6.9 months, respectively. A numerical improvement in OS was observed with tiragolumab plus atezolizumab plus chemotherapy (16 months; 95% CI, 11.3–21.7) compared with atezolizumab plus chemotherapy (13.1 months; 95% CI, 12.2–16.3) and chemotherapy alone (9.9 months; 95% CI, 7.6–23.2). Adverse events of special interest (AESIs) were observed in 39 (62.9%) patients receiving tiragolumab, 38 (58.5%) patients receiving atezolizumab and 9 (39.1%) patients in the control group. The most frequent AESIs (>5%) were immune-mediated and similar to SKYSCRAPER-08. irAEs such as rash, hepatitis, hypothyroidism and pneumonitis were observed but with different incidence rates. Higher rates of grade 4/5 adverse events were noted in the tiragolumab plus atezolizumab group, leading to a higher discontinuation rate due to adverse events in this group. Grades 1 and 2 irAEs were also predominant but included a wider range of symptoms due to the multiple treatment arms.[21]

In the MORPHEUS-EC trial, the limited follow-up duration and the small patient cohort preclude drawing definitive conclusions regarding OS. At this stage, the data support the preliminary efficacy of the tiragolumab and atezolizumab combination. However, it is important to note that the addition of tiragolumab to atezolizumab may enhance therapeutic efficacy, while the administration of atezolizumab alone could potentially be sufficient in certain cases.

Approaches to resectable oesophageal squamous cell carcinoma
Neoadjuvant chemotherapy in oesophageal squamous cell carcinoma
The standard of care for treatments for locally advanced ESCC (National Comprehensive Cancer Network v3/2024) includes neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy and definitive chemoradiotherapy.[22–25] Two randomized studies support the use of preoperative chemotherapy for resectable ESCC. Boonstra et al. investigated preoperative cisplatin and etoposide versus surgery alone. In this trial, 169 patients with ESCC participated, with 85 patients receiving preoperative chemotherapy (CS group) and 84 undergoing immediate surgery (S group). Initial results, reported in 1997, demonstrated improved OS in the CS group.[26] Updated results in 2011 showed a median OS of 16 months in the CS group versus 12 months in the S group, with 2-year survival rates of 42 and 30% and 5-year survival rates of 26 and 17%, respectively. An intention-to-treat analysis revealed a significant OS benefit for the CS group (p=0.03), along with improved disease-free survival (p=0.02). No difference in failure pattern was observed between the two groups, leading to the conclusion that preoperative chemotherapy with the cisplatin and etoposide combination significantly enhances OS in patients with ESCC.[26]

In the JCOG 9907 trial (A Randomized Trial of Postoperative Adjuvant Chemotherapy with Cisplatin and 5-fluorouracil Versus Neoadjuvant Chemotherapy for Clinical Stage II/III Squamous Cell Carcinoma of the Thoracic Esophagus), 330 patients were randomized to surgery followed by chemotherapy (group 1) or chemotherapy followed by surgery (group 2).[27] There was a 5-year OS of 43% in group 1 and 55% in group 2, with preoperative chemotherapy showing a significant survival benefit (HR 0.73; 95% CI, 0.54–0.99; p=0.04) over surgery followed by chemotherapy.

These findings also support the use of neoadjuvant chemotherapy with cisplatin plus 5-fluorouracil for resectable ESCC.[27]

Subsequently, the JCOG1109 NExT trial (A Randomized Controlled Phase III Trial Comparing Two Chemotherapy Regimen and Chemoradiotherapy Regimen as Neoadjuvant Treatment for Locally Advanced Esophageal Cancer; UMIN000009482) compared three neoadjuvant chemotherapy regimens – cisplatin/5-fluorouracil (CF), docetaxel/cisplatin/5-fluorouracil (DCF) and CF with radiation (CF-RT) followed by surgery – in patients with locally advanced ESCC.[28] After a median follow-up of 3 years, the trial demonstrated a significant improvement in OS with the DCF regimen (72.1%) compared with CF (62.6%), with p=0.006. Neoadjuvant doublet chemotherapy plus radiotherapy did not show a significant improvement in survival compared with doublet chemotherapy. By stratified Cox regression analysis for OS, HR (95% CI) was 0.68 (0.50–0.92) for CF versus DCF and 0.84 (0.63–1.12) for CF versus CF-RT.[28]

Neoadjuvant chemo-immunotherapy in resectable oesophageal squamous cell carcinoma: Camrelizumab

The ESCORT-1st trial (Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-free Survival in Patients with Advanced or Metastatic Esophageal Squamous Cell Carcinoma; ClinicalTrials.gov identifier: NCT03691090) investigated the efficacy and safety of camrelizumab, an anti-PD-1 antibody, in combination with chemotherapy (six cycles of paclitaxel and cisplatin every 3 weeks) as a first-line treatment for advanced or metastatic ESCC.[29] This randomized, double-blind, placebo-controlled, multicentre, phase III trial randomized 596 untreated patients in a 1:1 ratio to camrelizumab plus chemotherapy or placebo plus chemotherapy. The median OS was 15.3 months in the camrelizumab-chemotherapy group compared with 12.0 months in the placebo-chemotherapy group, with an HR of 0.70 (95% CI, 0.56–0.88; one-sided p=0.0010). The median PFS was 6.9 months in the camrelizumab-chemotherapy group compared with 5.6 months in the placebo-chemotherapy group, with an HR of 0.56 (95% CI, 0.46–0.68; one-sided p<0.0001). TRAEs of grade 3 or higher were observed in 63.4% of patients in the camrelizumab-chemotherapy group and 67.7% in the placebo-chemotherapy group, with treatment-related deaths reported in 3.0 and 3.7% of patients, respectively. Camrelizumab plus chemotherapy significantly improved both OS and PFS in patients with advanced or metastatic ESCC compared with chemotherapy alone.[29]

To investigate this combination in the curative setting, Liu et al. carried out a single-arm, phase II study to investigate the safety and efficacy of camrelizumab plus chemotherapy in locally advanced, resectable ESCC, with pathological complete response (pCR) as the primary endpoint.[30] Fifty-five out of the 60 enrolled patients (91.7%) completed two cycles of camrelizumab plus nab-paclitaxel and carboplatin before surgery. In this study, 51 patients underwent surgery with a high R0 resection rate (98.0%). pCR was achieved in 39.2% (20 patients), while 9.8% (5 patients) had a complete response in the primary tumour but residual disease in lymph nodes. TRAEs affected 96.7% (58 patients), primarily leucocytopenia (86.7%). Grade 3 or worse adverse events occurred in 56.7% (34 patients), with one patient experiencing a grade 5 event. Notably, there were no in-hospital or postoperative 30- and 90-day mortalities.[30] These findings supported the feasibility of camrelizumab with chemotherapy as neoadjuvant therapy for locally advanced ESCC.

ESCORT-NEO trial

The recent phase III ESCORT-NEO trial assessed the efficacy and safety of neoadjuvant camrelizumab plus chemotherapy followed by adjuvant camrelizumab compared with neoadjuvant chemotherapy alone in patients with resectable locally advanced ESCC.[9] This multicentre, randomized, open-label, phase III study enrolled 391 patients into three groups: (A) camrelizumab, albumin-bound paclitaxel and cisplatin; (B) camrelizumab, paclitaxel and cisplatin; and (C) paclitaxel and cisplatin. Co-primary endpoints were the pCR rate and event-free survival (EFS). Data from the pCR rate were presented at the ASCO GI 2024.

The planned two cycles of neoadjuvant therapy were completed by 128 (97.0%), 125 (96.2%) and 122 (94.6%) patients from groups A, B and C, respectively, and 114 (86.4%), 116 (89.2%) and 103 (79.8%) patients underwent surgery. The primary endpoints were the pCR rate and EFS. There was a higher pCR rate in groups A and B compared with group C (28.0 and 15.4% versus 4.7%, respectively), with major pathological response rates of 59.1, 36.2 and 20.9%. Surgical outcomes indicated a high R0 resection rate across all groups (99.1, 95.7 and 92.2%), with manageable rates of postoperative complications (34.2, 38.8 and 32.0%). During neoadjuvant treatment, the incidence rates of grade 3 TRAEs were 34.1, 28.5 and 28.8%.[9]

Neoadjuvant camrelizumab plus chemotherapy demonstrated superior pCR rates and a tolerable safety profile compared with neoadjuvant chemotherapy alone in resectable ESCC. It also highlighted the feasibility of neoadjuvant camrelizumab plus chemotherapy, demonstrated by a high completion rate of neoadjuvant therapy and surgical procedures. The incidence of grade 3 or higher TRAEs during neoadjuvant treatment was manageable across all groups, indicating an acceptable safety profile for this combination therapy approach.[9]

The underlying mechanisms contributing to the higher pCR rates observed in the nab-paclitaxel arm compared with conventional paclitaxel in this study remain elusive. Furthermore, the results of the second co-primary endpoint, EFS, are unavailable, and there is no established correlation between pCR rate and EFS/OS in these patients with ESCC. Zhang et al. conducted a prospective, multicentre observational study of 255 patients with ESCC at 13 tertiary hospitals in Southeast China who received at least one dose of camrelizumab-containing neoadjuvant therapy.[31] Of these, 169 patients (66.3%) underwent surgery, with 36 (21.3%) achieving pCR. The median OS in the study was not yet reached, and the estimated 1-year OS rate was 87.8% (95% CI, 82.5–91.5).

These results on the use of neoadjuvant camrelizumab and chemotherapy for ESCC must be interpreted within the broader context of other neoadjuvant treatment modalities. In the NEOCRTEC5010 trial (Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus: A Phase III Multicenter, Randomized, Open-label Clinical Trial; ClinicalTrials.gov identifier: NCT01216527), Yang et al. evaluated neoadjuvant chemoradiotherapy followed by surgery in patients with ESCC, reporting a notably higher pCR rate of 43.2% after a median follow-up of over 50 months.[32] This extended follow-up allowed for a comprehensive analysis of long-term outcomes, including survival and recurrence rates. In contrast, long-term data for the neoadjuvant camrelizumab-chemotherapy regimen are currently lacking.

The JCOG1109 NExT trial further contributes to this discussion, demonstrating that triplet neoadjuvant chemotherapy with DCF significantly improved OS over the doublet regimen of CF. Moreover, neoadjuvant doublet chemotherapy plus radiotherapy did not show a significant OS benefit compared with doublet chemotherapy alone for locally advanced ESCC.[28] These findings underscore the need to explore future strategies to optimize perioperative treatment for ESCC,

including evaluating the efficacy of neoadjuvant chemoradiotherapy, triplet chemotherapy (such as DCF) and neoadjuvant chemotherapy combined with ICIs in terms of survival and disease control. Trials should focus on directly comparing these multimodal treatment strategies to identify the most effective approach. Additionally, expanding the use of combination ICI regimens, such as nivolumab–ipilimumab and durvalumab–tremelimumab, presents another avenue for future research, as these regimens are currently approved only for perioperative management of ESCC cases with microsatellite instability-high tumours.

Conclusion

In conclusion, moving forward, there is a pressing need to identify novel therapeutic targets for ESCC, which warrants close collaboration with efforts made in preclinical research and early-phase drug development. Exploring combination therapies involving anti-TIGIT and PD-L1 inhibitors, akin to the approach adopted in the CheckMate 648 trial with nivolumab and ipilimumab, holds promise for potentially yielding clinical benefits with reduced toxicity in the recurrent metastatic ESCC setting. Additionally, future research should focus on optimizing patient selection for combination therapies by using biomarkers such as TMB or PD-L1 expression to enhance treatment personalization. The long-term efficacy and safety of these regimens must be rigorously assessed through extended follow-up studies to determine their sustainability over time. Furthermore, evaluating the feasibility and clinical efficacy of incorporating ICIs into neoadjuvant radiotherapy regimens for locally advanced ESCC could yield substantial improvements in treatment outcomes. Such research should include a thorough exploration of immune modulation effects within the TME, which could result in synergistic therapeutic responses. These efforts will be crucial in advancing the field towards more personalized, effective and durable treatment strategies for ESCC. ❑

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