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Treatment Landscape and Emerging Therapies in Oesophageal Cancer: Interviews with Two Key Opinion Leaders

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Interview Summary

For this article, the EMJ conducted interviews in February 2022 with two key opinion leaders (KOL), Zachary Wilmer Reichenbach, who works in the Department of Gastroenterology, Section of Medicine, and Center for Substance Abuse Research (CSAR), Lewis Katz School of Medicine, Philadelphia, Pennsylvania, USA, and Elizabeth Smyth, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK, both of whom have a wealth of experience and expertise in managing oesophageal cancer, to gain their perspectives on the treatment landscape. The experts gave valuable insights into several pertinent issues in oesophageal cancer treatment and discussed significant recent developments in the field.

This article discusses the current challenges in the diagnosis and treatment of oesophageal cancer and treatment strategies for this disease. The rationale behind immunotherapy for oesophageal cancer treatment is discussed and emerging molecules are explored.

INTRODUCTION

Oesophageal cancer ranks seventh in terms of incidence and is the sixth leading cause of cancer-related morbidity worldwide, with more than 604,000 new cases and 544,000 deaths reported globally in 2020.[1-3] With a few exceptions for rare subtypes, oesophageal cancers are classified histologically into oesophageal squamous cell carcinoma (ESCC) or oesophageal adenocarcinoma (EAC), which have varying geographical and racial distribution, and differ in location (ESCC in the upper and mid-oesophagus; EAC in the lower oesophagus at the junction with the stomach).[4,5]

ESCC is associated with low socioeconomic status and alcohol and tobacco use,[6] and is globally predominant (70–90% of oesophageal cancers);[7] however, it is most common in East Asia and becoming less common in Western countries. In contrast, EAC (5% of oesophageal cancers)[7] is the most common histological subtype in Western countries, correlating with an increasing incidence of obesity, gastro-oesophageal reflux disease, and Barrett's oesophagus.[4] Oesophageal cancer is a male-dominant aggressive malignancy, with patient survival corresponding to clinical stage.[8] The 5-year survival rate for oesophageal cancer is 19.9% and for metastatic disease is 5.2%.[9] Although chemotherapy regimens increase long-term survival, the overall survival (OS) of patients with advanced (locally advanced or metastatic) oesophageal cancer remains dismal.[3,10,11]

CURRENT CHALLENGES IN THE DIAGNOSIS AND TREATMENT OF OESOPHAGEAL CANCER

Smyth explained that there are no screening programmes for oesophageal cancer in non-Asian countries and there is a lack of early clinical symptoms in patients with this disease;[6] therefore, oesophageal cancer is often diagnosed at an advanced stage (Stage III or IV), when patients present with symptoms such as dysphagia. According to Smyth, only 30–40% of patients with this aggressive disease are eligible for curative treatment, and long-term survival is poor (approximately 1 year for most patients).

Reichenbach recognised that there are currently many challenges in oesophageal cancer, including a lack of early detection, incomplete understanding of the pathogenesis, insidious presentation, heterogenous symptoms, and low patient awareness of symptoms. Reichenbach pointed out that there is screening for Barrett's oesophagus (histologically-defined lesions that often precede EAC); however, this screening is suboptimal as many cases are currently missed.[12] The racial disparity associated with oesophageal cancer is another significant challenge, with disproportionately higher incidence rates and lower survival rates for Black patients compared with White patients with ESCC.[13,14] There is also a disproportionate occurrence of EAC in White compared with Black patients.[13]

Further challenges in oesophageal cancer, outlined by Reichenbach, include poor social status (particularly for ESCC) because this impacts when patients are diagnosed (impoverished patients lack access to care) and their nutritional status is probably poor. Also, dysphagia does not develop until the lumen is <13 mm, at which point the patient cannot eat, is losing weight, and often develops iron deficiency. Patients may have undertaken compensatory mechanisms, such as modifying their diet to include soups, yoghurts, smoothies, and purées as they can no longer eat solids, thus potentially delaying seeking medical help.

CURRENT TREATMENT STRATEGIES FOR OESOPHAGEAL CANCER

Reichenbach considered that chemotherapy containing a platinum and a fluoropyrimidine agent has been the hallmark treatment for oesophageal cancer for a long time. However, now this field is in a dynamic state, with new pharmaceutical agents such as programmed cell death protein 1 (PD-1) inhibitors on the market, and renewed interest in chemotherapy regimens like folinic acid plus fluorouracil plus oxaliplatin and folinic acid plus fluorouracil plus irinotecan. The treatment paradigm for patients depends on disease stage at diagnosis. Early-stage cancers may be amenable to endoscopic resection or dissection and more invasive surgery may be curative if there are minimal metastases.

Smyth explained that locally advanced ESCC and EAC differ in terms of biomarkers and sensitivity to treatment. Patients with locally advanced ESCC may be cured using chemoradiotherapy and do not necessarily need surgery, whereas patients with locally advanced EAC always need surgery. In contrast, treatment is similar for metastatic ESCC and EAC: both can be treated with chemotherapy plus immunotherapy, depending on the biomarkers. Smyth described how, until recently, the only treatment for ESCC was chemotherapy, and for EAC was chemotherapy with additional trastuzumab for patients with *HER2*+ disease (approximately 20% of patients). The last 2–3 years has seen the emergence of immunotherapy as monotherapy in later stages of disease, and in combination with chemotherapy in the first-line advanced setting, and this is extending OS.

Current treatment strategies in the European Union (EU) are below. The KOLs remarked that they expect appropriate updates to guidelines to consider new standards of care for oesophageal cancer.

FIRST-LINE TREATMENT FOR OESOPHAGEAL SQUAMOUS CELL CARCINOMA

Smyth explained that there are two first-line options for locally advanced (i.e., non-metastatic) ESCC: neoadjuvant chemoradiotherapy followed by surgery; and definitive chemoradiotherapy (i.e., no surgery),[15] and that a fair proportion of patients are cured using the second option. In contrast, in patients with advanced (metastatic) ESCC, chemotherapy plus immunotherapy is an option.

Data from Keynote 590[16] support the use of chemotherapy plus immunotherapy in ESCC in patients who have tumours that express programmed death-ligand 1 (PD-L1) and have combined positive score (CPS; the ratio of PD-L1 staining tumour cells, macrophages and lymphocytes relative to all tumour cells) ≥10. At the first interim analysis (median follow-up: 22.6 months) in Keynote 590, pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy for OS in patients with ESCC and CPS ≥10 (median: 13.9 versus 8.8 months; hazard ratio [HR]: 0.57; 95% confidence interval [CI]: 0.43–0.75; p<0.0001). Smyth clarified that patients who do not have tumours that express PD-L1 and CPS ≥10 do not benefit from chemotherapy plus immunotherapy and are not treated in this way.

The recently published CheckMate 648[17] in patients with ESCC showed that chemotherapy plus the monoclonal antibody nivolumab significantly improved OS compared with chemotherapy alone in patients with tumour proportion score (TPS; the proportion of tumour cells that stain positive for PD-L1) ≥1 or CPS ≥1. At a minimum 13-month follow-up, OS was significantly longer with nivolumab plus chemotherapy than with chemotherapy alone in TPS ≥1 patients (median: 15.4 versus 9.1 months; HR: 0.54; 99.5% CI: 0.37–0.80; p<0.001) and in the overall population (median: 13.2 versus 10.7 months; HR: 0.74; 99.1% CI: 0.58–0.96; p=0.002).[17]

Smyth described that nivolumab plus ipilimumab (and no chemotherapy) in CheckMate 648[17] also significantly improved OS compared with chemotherapy alone in patients with TPS ≥1 (median: 13.7 versus 9.1 months; HR: 0.64; 98.6% CI: 0.46–0.90; p=0.001) and in the overall population (median: 12.7 versus 10.7 months; HR: 0.78; 98.2% CI: 0.62–0.98; p=0.01). Smyth noted the lower response rates in this non-chemotherapy cohort, and that some patients showed early progression, so it is not clear which patients will benefit from an immunotherapy-only approach.

Smyth summarised that immune checkpoint inhibitor plus chemotherapy is established as standard of care in first-line advanced (metastatic) disease. There is a licence for pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥10.[18] In addition, there is a positive Committee for Medicinal Products for Human Use (CHMP) opinion recommending approval for nivolumab plus ipilimumab for first-line treatment of patients with unresectable advanced, recurrent, or metastatic ESCC with tumour cell PD-L1 expression ≥1%.[19]

SECOND-LINE TREATMENT FOR OESOPHAGEAL SQUAMOUS CELL CARCINOMA

In second-line clinical studies, only those patients with ESCC who were not treated with immunotherapy in first-line were eligible for this treatment in second-line. In the KEYNOTE-181 trial,[20,21] pembrolizumab demonstrated a survival benefit compared with conventional chemotherapy in patients with CPS ≥10 (median: 9.3 versus 6.7 months; HR: 0.69; 95% CI: 0.52–0.93; p=0.0074). Smyth also noted that second-line immunotherapy studies, such as ATTRACTION-3,[22] for patients who are immunotherapy-naïve also showed that nivolumab is superior to chemotherapy in terms of OS (median: 10.9 versus 8.4 months; HR: 0.77; 95% CI: 0.62–0.96; p=0.019) and this treatment is not biomarker selective.

Therefore, second-line treatment with immune checkpoint inhibitor monotherapy in patients with ESCC who have not received immunotherapy in first-line is now standard of care.

FIRST-LINE TREATMENT FOR OESOPHAGEAL ADENOCARCINOMA

Smyth remarked that EAC is biologically the same as gastric cancer; therefore, a gastric cancer paradigm is followed for the management of EAC. The licences for EAC are based on Keynote 590[16] (chemotherapy plus pembrolizumab in patients with PD-L1 CPS ≥10), although Smyth noted this trial was underpowered for EAC, and CheckMate 649,[23] a global trial in patients with EAC, gastro-oesophageal junction adenocarcinoma or gastric cancer (regardless of PD-L1 expression) randomised to nivolumab plus chemotherapy, nivolumab plus ipilimumab, or chemotherapy alone.

The primary endpoints in CheckMate 649 were OS or progression-free survival in patients with CPS ≥5.[23] Nivolumab plus chemotherapy resulted in significant improvements in OS (HR: 0.71; 98.4% CI: 0.59–0.86; p<0.0001) and progression-free survival (HR: 0.68; 98% CI: 0.56–0.81; p<0.0001) versus chemotherapy alone in patients with CPS ≥5 (minimum follow-up: 12.1 months).[23]

Therefore, the EU licences for EAC are pembrolizumab in patients with PD-L1 CPS ≥10 and nivolumab in patients with PD-L1 CPS ≥5.

LATER LINES FOR OESOPHAGEAL ADENOCARCINOMA

Smyth pointed out that there is no licensed second-line immunotherapy for EAC as clinical trials conducted in this area so far have not been positive. In third-line, patients with chemorefractory gastro-oesophageal adenocarcinoma may receive nivolumab, based on the results from ATTRACTION-2.[24,25]

Smyth pointed out that ESCC is slightly more sensitive to immunotherapy than EAC, with better response rates to monotherapy, and bigger improvements in OS in combination with chemotherapy.

THE ADJUVANT SETTING

Smyth explained that patients with resectable ESCC or EAC, who receive neoadjuvant chemoradiotherapy followed by surgery (known as trimodality therapy) and do not have a complete response in their pathological resection specimen (i.e., tumour cells are present), have a high risk of disease recurrence. Traditionally, no further treatment was given after surgery; however, the very promising results for nivolumab in a curative adjuvant setting in CheckMate 577[26] have challenged this approach. In this study, patients with ESCC or EAC who received trimodality therapy and had non-pathological complete response were randomised to nivolumab or placebo for a year.[26] Disease-free survival (the primary endpoint) for the placebo group was 11.0 months (95% CI: 8.3–14.3), which shows how poor the prognosis is for patients in whom chemoradiotherapy is unsuccessful; however, disease-free survival was doubled in the nivolumab group to 22.4 months (95% CI: 16.6–34.0). Smyth emphasised that nivolumab did not impact negatively on quality of life, in contrast to oesophagectomy, which has a huge quality of life impact as patients are unable to eat, lose weight, and feel very weak following surgery.

Smyth summarised that adjuvant nivolumab after trimodality therapy in high-risk patients is a new standard of care, and that biomarker selection is not used for this approach because stratification using TPS in CheckMate 577[26] showed no differences. Greater benefit is seen in patients with ESCC compared with EAC; however, this approach is valid for both types of oesophageal cancer.

HOLISTIC APPROACH

Reichenbach advocated a holistic approach to establish whether the patient can withstand surgery or chemoradiotherapy and to identify predictors of poor survival outcome such as Eastern Cooperative Oncology Group/World Health Organization Performance Status (ECOG/WHO PS) of 2, >3 metastatic sites, and time to progression of <6 months, all of which indicate a more aggressive disease course. He added that the treatment chosen depends on disease stage, tumour status, patient status (can they eat or swallow?); patient preference (do they feel they can tolerate the potential side effects?); and, in some countries, which treatments are available according to the patient's health insurance. Further considerations include optimising nutritional status, and whether there is an early need for a percutaneous gastroscopy tube or oesophageal stenting.

IMMUNOTHERAPY FOR OESOPHAGEAL CANCER

The Rationale Behind Using Immunotherapy for Oesophageal Cancer

Reichenbach disclosed that oesophageal cancer is a "particularly stubborn" cancer, where conventional treatments have fallen short in terms of controlling disease, preventing metastases and prolonging survival, and that the rationale for this cancer is the same as for every cancer in that "we need to do something better." He regarded immunotherapy as an exciting area in which the body can be primed to use its natural defences to kill cancer cells. As noted by Weadick et al.,[27] the presence of tumour-infiltrating lymphocytes in oesophageal cancer indicates an endogenous immune response, which is potentially amplifiable by immune checkpoint inhibition. Reichenbach commented on the tremendous growth in the field of oesophageal cancer in recent years and considered the PD-1 inhibitors to be a huge asset and were changing the landscape for oesophageal cancer.

The rationale according to Smyth for administering immunotherapy to patients with oesophageal cancer is based on three important factors: adding immunotherapy to chemotherapy deepens the response to chemotherapy and improves response rate; utilising immunotherapy improves OS; and administering immunotherapy as monotherapy is associated with decreased toxicity compared with chemotherapy.

Ongoing Immunotherapy Research

Both KOLs highlighted that trials for other PD-1 inhibitors have demonstrated similar results to the licensed PD-1 inhibitors. For example, tislelizumab in the Phase III study RATIONALE 302 (NCT03430843)[28,29] showed statistically significant and clinically meaningful improvement in OS (2.3 months), a higher and longer response, and a 30% reduction in the risk of death (HR: 0.70; 95% CI: 0.57–0.85; p=0.0001) compared with chemotherapy in patients with advanced or metastatic ESCC, who had disease progression during or after first-line systemic therapy. Tislelizumab plus chemotherapy also demonstrated durable responses with manageable tolerability in patients with advanced ESCC in a Phase II study.[30]

From a basic science perspective, Reichenbach considered tislelizumab to be a "very smart approach" because it is specifically engineered to minimise binding to the Fc γ receptor on macrophages, thereby limiting antibody-dependent phagocytosis,[30] which means the antibodies remain for longer and have potentially more effect.

Smyth defined that there are many different ongoing trials, including the RATIONALE 311 (NCT03957590)[31,32] investigating tislelizumab plus chemoradiotherapy, that are integrating immunotherapy into definitive chemoradiotherapy treatment approaches, and it is quite likely that these will be effective in the future. She reiterated that ESCC is much

more common in Asian patients than other populations, and there are several Asia-only trials with emerging PD-1 inhibitors, including camrelizumab,[33,34] toripalimab,[35] and sintilimab[36] that have produced effective results, including consistent improvements in OS. Smyth acknowledged that global trials are needed for global populations but the huge population of patients with ESCC in Asia merits these Asia-only trials and the use of these drugs in Asia.

Safety Profiles of PD-1 Inhibitors

Reichenbach indicated that the safety profile of PD-1 inhibitors is better than for chemotherapy; however, adding PD-1 inhibitors to chemotherapy in the first-line setting may lead to an incremental increase in toxicity. He noted that PD-1 inhibitors can be associated with severe side effects such as pneumonitis, hepatitis, and colitis; however, these effects are rare.[37]

Smyth acknowledged that there is clear evidence from clinical trials, including ATTRACTION-3,[22] that anti-PD-1 monotherapy in the second-line setting is more tolerable than chemotherapy; however, a slight increase in side effects should be expected upon the addition of PD-1 inhibitors to chemotherapy in first-line. Nonetheless, there are few significant (≥Grade 3) immune-related side effects, few patient discontinue treatment, and the risk of treatment-associated death is low. Smyth suggested that there is a need to learn how to manage the toxicity of PD-1 inhibitors plus chemotherapy but generally this treatment combination is tolerable for patients.

Immunotherapy Treatment Considerations

For Reichenbach, the main considerations in selecting immunotherapy for patients with oesophageal cancer are efficacy, safety, and evaluation to see whether the patient is strong enough to survive the potential side effects (e.g., establish whether they are predisposed to certain side effects because of poor hepatic function or underlying inflammatory bowel disease). He suggested that the order of treatment application may matter. As chemotherapy may deplete the T cell population, the response to a subsequent PD-1 inhibitor may not be as robust as if the inhibitor were administered before the chemotherapy.

Reichenbach stated that the data support the use of immunotherapy in oesophageal cancer and this therapy should probably be used early on rather than waiting for progression or metastases to occur.

How patients with oesophageal cancer are chosen for immunotherapy depends on the setting, Smyth emphasised. In the EU, immunotherapy is administered first-line to patients based on their PD-L1 status, with CPS or TPS used depending on the molecule being utilised. In contrast, in the USA, PD-L1 status is not required for selection of patients for first-line immunotherapy. Selection for second-line immunotherapy is not based on PD-L1 status in the EU or USA.

Smyth recommended the following treatment algorithm for the EU for first-line: check PD-L1 status, then patients with positive PD-L1 receive chemotherapy plus immunotherapy and those with negative status receive chemotherapy alone. There is no evidence that patients with positive PD-L1 status who received chemotherapy plus immunotherapy in first-line will benefit from immunotherapy in second-line, so these patients receive chemotherapy in second-line. Patients who did not receive immunotherapy in first-line (approximately 50% of patients) may benefit from immunotherapy in second-line.

The KOLs noted that the criteria for immunotherapy monotherapy are the same as for chemotherapy. Patients with high-volume or rapidly progressing disease are less likely to benefit, and expectations of treatment need to be realistic. In particular, the results of the second-line study ATTRACTION-3[22] in patients with advanced ESCC indicated that patients with high-volume or rapidly progressing disease may benefit more from chemotherapy than from immunotherapy; however, Smyth noted these are considerations rather than hard criteria for selecting patients.

How Do PD-1 Inhibitors Fit into the Clinical Picture for Oesophageal Cancer?

According to Reichenbach, PD-1 inhibitors are rewriting the clinical picture for oesophageal cancer and, although they are currently a novelty,

with perhaps some hesitancy surrounding their use, they are likely to be increasingly used as clinicians become familiar with these drugs.

Smyth considered that there are several emergent PD-1 inhibitors, all of which have demonstrated comparable efficacy to the established PD-1 inhibitors nivolumab and pembrolizumab. She pointed out that although the efficacy and toxicity of these emergent PD-1 inhibitors is very much a class effect, regulatory approvals may differ according to the patient populations studied.

EMERGING MOLECULES AND FUTURE RESEARCH IN OESOPHAGEAL CANCER

Smyth pointed out that research in oesophageal cancer is now being directed towards the second generation of immune checkpoint inhibitors, with targets including T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT),[38-40] T cell immunoglobulin and mucin-containing molecule 3,[41,42] and lymphocyte-activation gene 3.[43] She predicted that the most important next generation target will be TIGIT, which is expressed frequently in ESCC and less often in EAC. Adding anti-TIGIT antibodies (tiragolumab) to anti-PD-L1 (atezolizumab) has shown promising clinical efficacy in non-small cell lung cancer,[44] and Smyth thought that TIGIT was likely to be the next "hot molecule" in ESCC.

Reichenbach discussed the research interest in monoclonal antibodies for treatment of oesophageal cancer. For example, ramucirumab, which targets and binds vascular endothelial growth factor receptor-2, has been shown to improve survival outcomes in combination with paclitaxel.[45,46] Reichenbach then turned his attention to basic science and the renewed interest in microRNA[47] research, stating that microRNA signatures may become available for early detection of disease or use in a treatment paradigm. For example, increased expression of miR-196a in oesophageal cancer cells was found to be associated with decreased *UHRF2* and *TET2* expression, with knockdown of miR-196a or *UHRF2* overexpression, suppressing oesophageal cancer cell proliferation and migration.[48] Further research shows that addition of skimmianine, a natural fluoroquinolone alkaloid with anti-inflammatory properties, to cultured ESCC cells blocked activation of *ERK1/2*, which are necessary for tumourigenesis and progression.[49]

Reichenbach also alluded to the considerable research interest in the potential role of the gut microbiome in oesophageal cancer,[50] including how bacterial signatures in the oesophagus and oral pharynx change with development and progression of oesophageal cancer; however, whether these changes are causative, or a consequence of the cancer is unknown.

Racial disparities are the subject of future research for Reichenbach and collaborators, who will sample oesophageal tissue and use single-cell RNA sequencing to assess at a molecular level the basis of these differences in incidence and presentation of disease.

FUTURE PROSPECTS AND CONCLUSIONS

Reichenbach concluded that he expects nivolumab and pembrolizumab to gain a larger foothold in the oesophageal cancer arena, and that tislelizumab will also become a significant treatment option provided there continues to be good data from clinical practice. He could also foresee a move towards more personalised medicine and research into small molecule inhibitors. Reichenbach proposed: "With such an aggressive disease, we need big bold ideas, innovative approaches, and new treatments [...] and should forge ahead and find the treatments of tomorrow."

Smyth expressed excitement that for advanced oesophageal cancer there will be integration of new compounds, which will hopefully add to the efficacy seen with established PD-1 inhibitors. She remarked that for earlier stage cancers, the addition of immune checkpoint inhibitors to chemoradiotherapy is more likely to be associated with pathological complete responses and durable remissions. Smyth highlighted the importance of neoadjuvant treatment in oesophageal cancer and concluded that she would like to see an organ-sparing approach evolve for patients with ESCC, through improving the response rate to chemoradiotherapy, and that to avoid

oesophagectomy, which is a life-changing surgery, would be “an excellent result.”

References

1. Sung H et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
2. International Agency for Research on Cancer (IARC). Oesophageal fact sheet, 2020. 2020. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/6-Oesophagus-fact-sheet.pdf. Last accessed: 28 February 2022.
3. Yamamoto S, Kato K. Immuno-oncology for esophageal cancer. Future Oncol. 2020;16(32):2673-81.
4. Abbas G, Krasna M. Overview of esophageal cancer. Ann Cardiothorac Surg. 2017;6(2):131-6.
5. He S et al. Advances and challenges in the treatment of oesophageal cancer. Acta Pharm Sin B. 2021;11(11):3379-92.
6. Huang FL, Yu SJ. Oesophageal cancer: risk factors, genetic association, and treatment. Asian J Surg. 2018;41(3):210-5.
7. Panda SK et al. Persistent cough: an unexpected diagnosis. J Family Med Prim Care. 2020;9(5):2548-51.
8. Qiu MJ et al. Prognostic evaluation of oesophageal cancer patients with stages I–III. Aging (Albany NY). 2020;12(14):14736-53.
9. National Cancer Institute. Cancer stat facts: oesophageal cancer. Available at: https://seer.cancer.gov/statfacts/html/esoph.html. Last accessed: 28 February 2022.
10. Teixeira Farinha H et al. Immunotherapy for oesophageal cancer: state-of-the-art in 2021. Cancers (Basel). 2022;14(3):554.
11. Njei B et al. Trends in oesophageal cancer survival in United States adults from 1973 to 2009: a SEER database analysis. J Gastroenterol Hepatol. 2016;31(6):1141-6.
12. Yusuf A, Fitzgerald RC. Screening for Barrett's oesophagus: are we ready for it? Curr Treat Options Gastroenterol. 2021:1-16.
13. Chen Z et al. Incidence and survival differences in esophageal cancer among ethnic groups in the United States. Oncotarget. 2017;8(29):47037-51.
14. Okereke IC et al. Disparities in esophageal cancer care based on race: a National Cancer Database analysis. Dis Esophagus. 2021;DOI:10.1093/dote/doab083.
15. Stahl M, Budach W. Definitive chemoradiotherapy. J Thorac Dis. 2017;9(Suppl 8):S792-8.
16. Sun JM et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet. 2021;398(10302):759-71. Erratum in: Lancet. 2021;398(10314):1874.
17. Doki Y et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. N Engl J Med. 2022;386(5):449-62.
18. Merck Sharp & Dohme B.V. KEYTRUDA. Summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf. Last accessed: 30 March 2022.
19. Bristol Myers Squibb. Bristol Myers Squibb receives positive CHMP opinion recommending approval for Opdivo (nivolumab) plus Yervoy (ipilimumab) for first-line treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma. 2022. Available at: https://news.bms.com/news/details/2022/Bristol-Myers-Squibb-Receives-Positive-CHMP-Opinion-Recommending-Approval-for-Opdivo-nivolumab-plus-Yervoy-ipilimumab-for-First-Line-Treatment-of-Patients-with-Unresectable-Advanced-Recurrent-or-Metastatic-Esophageal-Squamous-Cell-Carcinoma/default.aspxhttps://news.bms.com/news/corporate-financial/2022/Bristol-Myers-Squibb-Receives-Positive-CHMP-Opinion-Recommending-Approval-for-Opdivo-nivolumab-plus-Yervoy-ipilimumab-for-First-Line-Treatment-of-Patients-with-Unresectable-Advanced-Recurrent-or-Metastatic-Oesophageal-Squamous-Cell-Carcinoma/default.aspx. Last accessed: 9 June 2022.
20. Kojima T et al. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced oesophageal cancer. J Clin Oncol. 2020;38(35):4138-48.
21. Cao Y et al. Pembrolizumab versus chemotherapy for patients with oesophageal squamous cell carcinoma enrolled in the randomized KEYNOTE-181 trial in Asia. ESMO Open. 2021;7(1):100341.
22. Kato K et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(11):1506-17. Erratum in: Lancet Oncol. 2019;20(11):e613.
23. Janjigian YY et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398(10294):27-40.
24. Kang YK et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10111):2461-71.
25. Chen LT et al. A phase 3 study of nivolumab in previously treated advanced gastric or gastroesophageal junction cancer (ATTRACTION-2): 2-year update data. Gastric Cancer. 2020;23(3):510-9.
26. Kelly RJ et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med. 2021;384(13):1191-203.
27. Weadick CS et al. Recent advances in immune-based approaches for the treatment of esophagogastric cancer. Expert Opin Emerg Drugs. 2022;27(1):1-13.
28. Shen L et al. RATIONALE 302: randomized, phase 3 study of

tislelizumab versus chemotherapy as second-line treatment for advanced unresectable/metastatic oesophageal squamous cell carcinoma. ePoster Presentation 4012 at 2021 ASCO Annual Meeting. J Clin Oncol. 2021;39(Suppl 15):4012.

29. BeiGene. A randomized, controlled, open-label, global phase 3 study comparing the efficacy of the anti-PD-1 antibody tislelizumab (BGB-A317) versus chemotherapy as second line treatment in patients with advanced unresectable/metastatic oesophageal squamous cell carcinoma. NCT03430843. https://clinicaltrials.gov/ct2/show/NCT03430843.
30. Xu J et al. Tislelizumab plus chemotherapy as first-line treatment for advanced oesophageal squamous cell carcinoma and gastric/gastroesophageal junction adenocarcinoma. Clin Cancer Res. 2020;26(17):4542-50.
31. Yu R et al. RATIONALE 311: tislelizumab plus concurrent chemoradiotherapy for localized esophageal squamous cell carcinoma. Future Oncol. 2021;17(31):4081-9.
32. BeiGene. A phase 3, randomized, double-blind, placebo-controlled study of tislelizumab (BGB-A317) versus placebo in combination with concurrent chemoradiotherapy in patients with localized oesophageal squamous cell carcinoma. NCT03957590. https://clinicaltrials.gov/ct2/show/NCT03957590.
33. Luo H et al. Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic oesophageal squamous cell carcinoma: the ESCORT-1st randomized clinical trial. JAMA. 2021;326(10):916-25.
34. Yang W et al. Neoadjuvant programmed cell death 1 blockade combined with chemotherapy for resectable oesophageal squamous cell carcinoma. J Immunother Cancer. 2022;10(1):e003497.
35. Xing W et al. The sequence of chemotherapy and toripalimab might influence the efficacy of neoadjuvant chemoimmunotherapy in locally advanced oesophageal squamous cell cancer-a phase II study. Front Immunol 2021;12:772450.
36. Xu J et al. Clinical and biomarker analyses of sintilimab versus chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma: a randomized, open-label phase 2 study (ORIENT-2). Nat Commun. 2022;13(1):857.
37. Wang DY et al. Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. JAMA Oncol. 2018;4(12):1721-8. Erratum in: JAMA Oncol. 2018;4(12):1792.
38. Wang P et al. Increased coexpression of PD-L1 and TIM3/TIGIT is associated with poor overall survival of patients with esophageal squamous cell carcinoma. J Immunother Cancer. 2021;9(10):e002836.
39. Harjunpää H, Guillerey C. TIGIT as an emerging immune checkpoint. Clin Exp Immunol. 2020;200(2):108-19.
40. No authors listed. Tiragolumab impresses in multiple trials. Cancer Discov. 2020;10(8):1086-7.
41. Dixon KO et al. TIM-3 restrains anti-tumour immunity by regulating inflammasome activation. Nature. 2021;595(7865):101-6.
42. Cui SJ et al. TIM-3 polymorphism is involved in the progression of oesophageal squamous cell carcinoma by regulating gene expression. Environ Mol Mutagen. 2021;62(4):273-83.
43. Ruffo E et al. Lymphocyte-activation gene 3 (LAG3): the next immune checkpoint receptor. Semin Immunol. 2019;42:101305.
44. Yeo J et al. TIGIT/CD226 axis regulates anti-tumor immunity. Pharmaceuticals (Basel). 2021;14(3):200.
45. Xu RH et al. Efficacy and safety of weekly paclitaxel with or without ramucirumab as second-line therapy for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma (RAINBOW-Asia): a randomised, multicentre, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol. 2021;6(12):1015-24.
46. Abdel-Rahman O et al. Outcomes of ramucirumab plus paclitaxel among patients with previously treated metastatic gastric/lower oesophageal cancer: a real-world study. Am J Clin Oncol. 2021;44(4):158-61.
47. Lu TX, Rothenberg ME. MicroRNA. J Allergy Clin Immunol. 2018;141(4):1202-7.
48. Hu CM et al. MiR-196a promotes the proliferation and migration of oesophageal cancer via the UHRF2/TET2 axis. Mol Cell Biochem. 2022;477(2):537-47.
49. Liu Y et al. Skimmianine as a novel therapeutic agent suppresses proliferation and migration of human oesophageal squamous cell carcinoma via blocking the activation of ERK1/2. Neoplasma. 2022:69(3):571-82.
50. Dan W et al. Human microbiota in oesophageal adenocarcinoma: Pathogenesis, diagnosis, prognosis and therapeutic implications. Front Microbiol. 2022;12:791274.