

Revolutionizing Esophageal Squamous Cell Carcinoma Treatment: Immunotherapy Breakthroughs

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ABSTRACT

The advent of immunotherapy has significantly transformed the treatment paradigm for esophageal carcinoma. The adjuvant therapy study CheckMate-577 showcased the PD-1 inhibitor nivolumab's improved disease-free survival (DFS). In first-line treatment, combining PD-1 inhibitor pembrolizumab with chemotherapy (KEYNOTE-590) yielded heightened overall survival (OS) in PD-L1 positive squamous cell carcinoma patients with a combined positive score (CPS \geq 10). Furthermore, nivolumab, whether with ipilimumab or chemotherapy (CheckMate 648), exhibited superior OS compared to chemotherapy alone. Two impactful clinical trials have notably positioned immunotherapy as the forefront for early-stage treatment in advanced esophageal cancer. These trials, delving into immune checkpoint inhibitors, disclosed prolonged progression-free survival compared to conventional treatments, with one trial revealing an overall survival improvement. While ongoing, these findings prompt experts in esophageal cancer to envision potential establishment of new standard treatment protocols for this historically challenging cancer type. On March 22, 2021, FDA approval was granted for pembrolizumab (Keytruda) combined with chemotherapy for specific esophageal or gastroesophageal cancer patients ineligible for surgery, traditional chemotherapy, or radiation. This regulatory decision rested upon insights from the KEYNOTE-590 trial, detailed in the Cancer Currents report. This review seeks to synthesize these trials, integrating them into prevailing treatment strategies, possibly introducing early immunotherapy for advanced esophageal cancer.

Keywords: Immunotherapy; Pembrolizumab; Esophageal cancer; Adenocarcinoma

Introduction

Esophageal cancer is one of the deadliest disease with the universal health burden over 60,000 new cases which gets reported annually¹. Esophageal cancer is divided in two subtypes squamous cell cancer (ESCC) mainly in the proximal part of esophagus and Adenocarcinoma mostly in the distal part. Squamous subtype of esophageal cancer comprises 90% of all carcinomas and remaining 10% is adenocarcinoma. There is

also one third subtype small cell carcinoma which is very rare and have not much studied in depth. In this particular literature review we are going to emphasize on esophageal squamous cell cancer.

Current clinical trials have shown very promising results of immunotherapy in the early treatment of advanced ESCC. Two large trials have demonstrated that immune checkpoint inhibitors have extended the duration, that individuals with advanced

esophageal cancer lived without their cancer progressing when compared to standard treatments². In one of these studies, patients who received a checkpoint inhibitor not only experienced extended progression-free survival but also lived longer overall. These promising results indicate that immunotherapy may indeed become a crucial component of early treatment for specific individuals with advanced esophageal cancer.

Before the advent of checkpoint inhibition in ESCC treatment, the standard approaches were neoadjuvant radiochemotherapy along with surgery for localized cases. Definitive chemoradiation for those cases where surgery was not an option but systemic chemotherapy for advanced metastatic disease³. As per CROSS trial, which is referenced in^{3,4} patients with locally advanced resectable ESCC underwent preoperative treatment which involves five weekly cycles of carboplatin and paclitaxel along with concurrent radiotherapy (totaling 41.4 Gy in 23 fractions) followed by surgery. The study revealed that the neoadjuvant chemoradiotherapy approach led to a substantial 10- year overall survival benefit, demonstrating a notable 13% increase in survival. This likely suggests that the treatment approach had a significant positive impact on long-term survival in patients with ESCC^{3,4}.

Following the failure of a palliative first-line treatment for squamous cell carcinoma, there is a lack of randomized trials that definitively establish the benefits of chemotherapy compared to best supportive care (BSC). In such cases, when patients have a good performance status, common chemotherapy options often include irinotecan, paclitaxel or docetaxel. These treatments are frequently utilized in the absence of concrete evidence from randomized trials^{5,6}.

The introduction of immune checkpoint inhibitors (ICIs) has had a huge impact on the treatment approach for ESCC. These inhibitors have significantly altered the treatment regimen. Key components in this immunotherapeutic approach involve the programmed death receptor 1 (PD-1) and its ligand (PD-L1), which play an important role in regulating the immune response against cancer cells. This mechanism has led to a transition in the way ESCC has been managed. When cytotoxic T-cells bind to cancer cells through their PD-1 receptor interacting with its ligand, PD-L1, on the surface of cancer cells, it enables those cancer cells to evade the anti-tumor immune response. This interaction acts as a mechanism by which cancer cells can suppress the immune system's ability to target and destroy them, contributing to the progression of the tumor. Immune checkpoint inhibitors work by blocking this interaction, thereby restoring the immune response and enhancing the body's ability to combat cancer cells⁷.

Certainly, based on the background this narrative review's main objectives are overview of immunotherapy in ESCC which aims to present the current landscape of immunotherapy, role of ICIs and their utilization in treatment and how to include them at different stages of cancers and also significance of promising biomarkers in ESCC immunotherapy which can be essential for patient selection and treatment response prediction.

Overview of Immune Checkpoint Inhibitors

The immune system has built-in safeguards to prevent it from attacking healthy cells. Checkpoint proteins act as switches that regulate immune responses. Cancer cells can manipulate these switches to evade immune attacks. Immune checkpoint inhibitor drugs target these proteins, potentially restoring the immune system's ability to target and combat esophageal cancer cells.

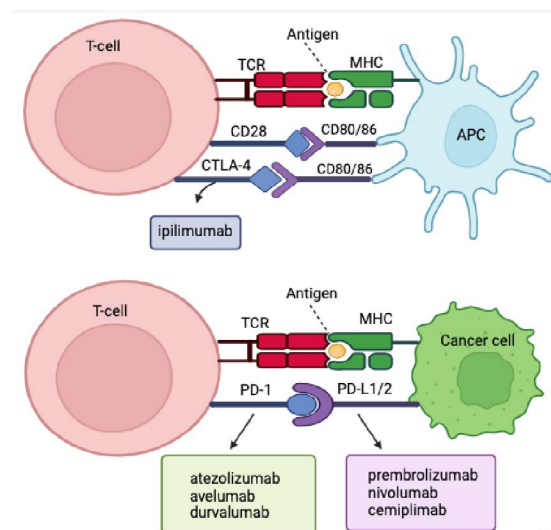


Figure 1: The Function of Immune Checkpoint Inhibitors in Cancer Treatment.

PD-1 Inhibitors

Pembrolizumab (Keytruda) and nivolumab (Opdivo) are medications that specifically target PD-1, a protein found on T cells, a component of the immune system. PD-1 usually serves to prevent T cells from attacking healthy cells. By inhibiting PD-1, these drugs enhance the immune system's ability to target and combat cancer cells. This mechanism can lead to tumor shrinkage or a reduction in their growth rate^{7,8}.

Pembrolizumab is employed in the treatment of certain advanced esophageal or gastroesophageal junction (GEJ) cancers, particularly when standard treatments like surgery and chemoradiation are not viable options. Depending on the specific circumstances, Pembrolizumab may be administered as a standalone treatment or in combination with chemotherapy. Nivolumab has several applications in the treatment of esophageal and gastroesophageal junction (GEJ) cancers:

- For individuals who underwent chemotherapy and radiation (chemoradiation) before surgery and have residual cancer following surgery.
- As a standalone treatment for advanced squamous cell cancer of the esophagus, often after attempting chemotherapy.
- In combination with chemotherapy as the initial treatment for advanced squamous cell cancer of the esophagus, potentially extending survival for some patients.
- In combination with chemotherapy for those with advanced adenocarcinoma of the esophagus or advanced cancer of the gastroesophageal junction (GEJ).

CTLA-4 Inhibitor

Ipilimumab (Yervoy) is an immunotherapy drug that enhances the immune response by targeting a different protein, CTLA-4, found on T cells. This protein typically regulates T cell activity. It is used in combination with nivolumab as the primary treatment for advanced squamous cell cancer of the esophagus that is inoperable or has spread to other areas of the body⁶.

Genetic Signatures for Immunotherapy

In cases of metastatic ESCC where the prognosis is often poor due to its aggressive nature of the disease, selecting the best treatment approach is of utmost importance. This decision involves creating a well-defined and evidence-based plan for

therapy to ensure that patients receive the most effective and individualized treatment options. So the outcomes of significant clinical trials indicate that there exists a subset of patients referred to as “responders” who experience greater benefits from immunotherapy. These individuals demonstrate a more favorable response to immunotherapeutic treatments compared to others. Conversely, these trials have also revealed that there is a group of patients for whom immunotherapy does not provide any discernible benefits. Indeed, in these patients, the application of ICIs may potentially exacerbate their medical condition. Several factors contribute to this, including the extended time it takes for some patients to respond to immunotherapy and the possibility of hyper progression, a phenomenon where the disease progresses even more rapidly during treatment^{9,10}.

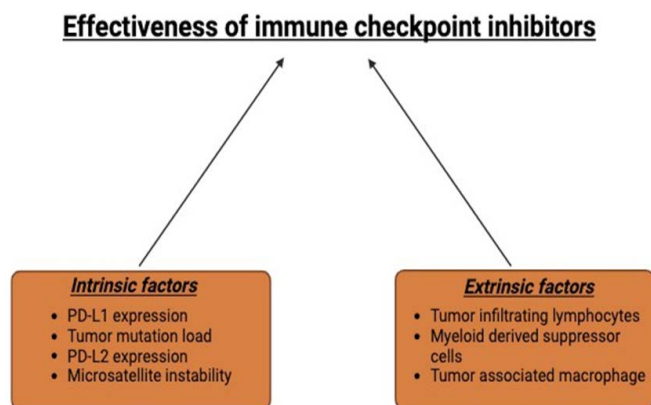


Figure 2: Effectiveness of immune checkpoint inhibitors.

Hence, research has been focused on exploring predictive and prognostic molecular biomarkers in recent years. These markers are essential for identifying suitable candidates for immunotherapy^{11,12}.

In the context of immunotherapy, the expression of PD-L1 is a significant factor. Nevertheless, landmark trials in this area have demonstrated substantial variation in how PD-L1 is assessed, scored, and the threshold values used. This lack of standardization has resulted in inconsistencies in its evaluation. In this context, a systematic review and meta-analysis by Leone AG et al. has been published. This review encompassed data from 5,257 patients who participated in ten randomized controlled trials involving immunotherapy for advanced Esophageal Squamous Cell Carcinoma (ESCC)¹³. In this analysis, the use of immunotherapy demonstrated improved survival outcomes (Hazard Ratio: 0.71), and this effect was consistent across different regions (Asian versus non-Asian) and treatment lines (first-line versus subsequent lines). Additionally, immunotherapy led to enhancements in Progression-Free Survival (PFS) and Objective Response Rate (ORR) with Hazard Ratio (HR) of 0.78 and an odds ratio of 1.5, respectively.

ESCC Represents a Distinct Medical Condition.

The KEYNOTE-590 trial, which compared pembrolizumab plus chemotherapy to chemotherapy alone, significantly influenced clinical practice. However, a challenge emerged from including both (ESCC) and esophageal or Siewert type I Gastroesophageal Junction (GEJ) adenocarcinomas in the same trial, with ESCC accounting for 73% of the patients. Given its strong association with DNA damage from smoking and alcohol, ESCC displays heightened sensitivity to immunotherapy compared to gastroesophageal adenocarcinomas, highlighting the need to consider ESCC as a distinct and separate disease¹⁴.

The initial results show improved median Overall Survival (OS) in various groups. Patients with Esophageal Squamous Cell Carcinoma (ESCC) and a Programmed Death-Ligand 1 (PD-L1) Combined Positive Score (CPS) of 10% or higher exhibited notably increased OS by 13.9 months as compared to 8.8 months.

Similarly, the overall ESCC patient group also experienced enhanced OS by 12.6 months as compared to 9.8 months. This positive trend extended to all patients with a PD-L1 CPS of 10% or higher which is 13.5 months as compared to 9.4 months and the entire study population is 12.4 months as compared to 9.8 months. However, in an exploratory analysis, patients with a PD-L1 CPS less than 10% did not experience a significant improvement in median OS when pembrolizumab was added to chemotherapy showed 10.5 months as compared to 10.6 months¹⁴.

Data from the CheckMate 648 trial, presented at the 2021 ASCO Annual Meeting, suggests that Nivolumab and Ipilimumab are potential first-line treatments for advanced (ESCC). The trial included three arms: chemotherapy alone, Nivolumab with chemotherapy, and Nivolumab with Ipilimumab. Both Nivolumab and chemotherapy and Nivolumab and Ipilimumab showed improved Overall Survival (OS) compared to chemotherapy, especially in patients with a Programmed Death-Ligand 1 Combined Positive Score (PD-L1 CPS) of 1% or higher and in all patients in the study. These innovative combinations were generally well-tolerated, with Nivolumab and chemotherapy showing slightly more toxicity than chemotherapy alone. Thus the drawback of this study was its lack of blinding¹⁵.

Adjuvant Immunotherapy Enhances Disease-Free Survival

The standard treatment for esophageal and gastroesophageal junction (GEJ) cancer has been trimodality therapy, which involves neoadjuvant chemoradiation followed by surgery. Despite this approach, recurrence rates have been notably high, especially for individuals with remaining pathologic disease. The lack of validated adjuvant therapies led to ongoing surveillance as the standard of care.

CheckMate-577, a phase III trial, was the first to demonstrate a significant survival benefit in the adjuvant setting. Updated findings presented at the ESMO 2021 Congress and subsequently published in The New England Journal of Medicine confirm that adjuvant nivolumab continues to enhance disease-free survival compared to a placebo (median, 22.4 vs. 10.4 months)¹⁶. As a result, the FDA approved nivolumab in May 2021 for patients with fully removed ESCC or (GEJ) cancer who still have some remaining disease after neoadjuvant chemoradiotherapy. Nivolumab was safe and, importantly, didn't negatively affect the patients' quality of life⁸. It's very much uncertain whether these findings can apply to patients who have received perioperative chemotherapy, like the FLOT regimen, commonly used in the treatment of (GEJ) cancer in certain centers. For those patients who faces disease recurrence shortly after adjuvant nivolumab, the optimal treatment approach remains uncertain. However, a reasonable strategy involves providing chemoimmunotherapy to patients who experiences relapse of more than 6 months after completing adjuvant therapy and using chemotherapy alone for those with disease recurrence during or within 6 months of time.

Future Directions

In the past couple of years, significant progress has been

made in the field of gastroesophageal cancers, yet there remains a substantial demand for further advancements. Likely, there is a pressing need for improved biomarkers to accurately identify the patients who truly gain benefits from immunotherapy. Recent understanding suggests that gastroesophageal cancers differ from melanoma, indicating the existence of potentially more effective immune checkpoints that should be the focus of targeted therapies. There is a promising lineup of agents in development that target immune checkpoints like CD40, CD73, and many more. It is hoped that one of these will lead to the next significant breakthrough in the field. While we wait for a major breakthrough, it's important to recognize the value of adjuvant therapy in treating gastroesophageal cancer and the accomplishment of surpassing a 1-year survival rate in metastatic cases.

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