

## Special Article - Esophageal Cancer

# Immune Therapy in Esophageal Cancer: A Rationale and Current Status

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## Introduction

Esophageal cancer carries a poor prognosis within the United States and worldwide, with adenocarcinoma (EA) prevailing in the U.S. and the West as it is etiologically tied to rising obesity rates, associated acid reflux, and Barrett esophagus. However, the number afflicted with squamous cell carcinoma (ESCC) throughout the world is far greater than adenocarcinoma. ESCC is most prevalent in the Far East, including Japan and China, as well as in South Africa, Turkey, and Iran as it is etiologically tied to tobacco use, diets low in fresh fruit and vegetables, chemical preservatives in food, and exposure to the human papillomavirus (HPV) [1]. Surgical resection remains the gold standard of treatment for early tumors, but the addition of chemotherapy and radiation therapy has proven necessary for the control and enhanced survival of those presenting with locally advanced disease. While systemic cytotoxic chemotherapy is the chief option for the palliation of metastatic disease, immune checkpoint inhibitor therapy has emerged as a promising new therapeutic option as it has for several other malignancies. The theoretical basis for testing immune checkpoint inhibitor therapy for those with esophageal cancer rests with the tumor's association with mutagenic toxins and its increased mutational burden. Herein we review current results and ongoing studies seeking improved outcomes in patients with esophageal cancer treated with immune therapy.

## Esophageal Cancer

Esophageal cancer represents one percent of all new cancer diagnoses in the United States but carries a dismal average survival rate of less than 20 percent at 5 years [2]. An estimated 16,980 cases were diagnosed in the U.S. in 2015, with an estimated 15,590 patients expected to die from this disease [2]. Worldwide, approximately 455,800 cases are diagnosed each year, with 400,200 deaths per year representing the 6<sup>th</sup> most common cause of cancer death [3]. In spite of advances in combining chemotherapy, radiation therapy, and surgery, the 5-year overall survival rate ranges from 4.2% for those presenting with distant metastases at diagnosis to 40.4% for those presenting with locally advanced cancer at diagnosis [4].

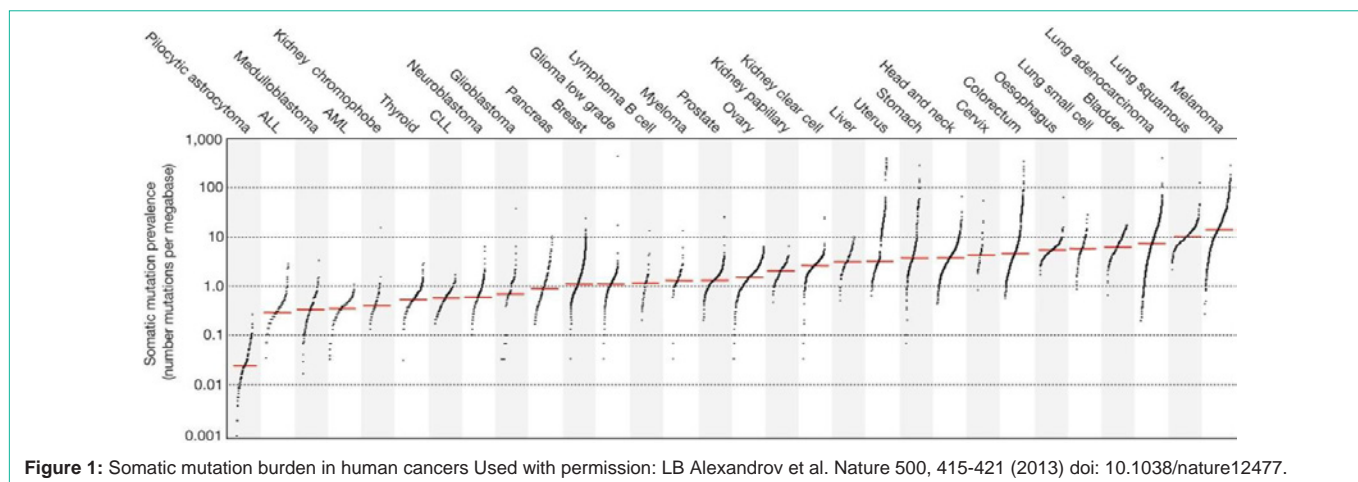
Histologically, esophageal cancer can be divided into adenocarcinoma (EA) and squamous cell carcinoma (ESCC). These differ in etiology, precursor lesions, molecular properties, and epidemiology. While the incidence of EA has surpassed that of ESCC in the U.S., ESCCs represent 80 percent of esophageal cancer cases worldwide [5]. In spite of these statistics, clinical trials and the treatment guidelines they helped establish have not distinguished between patients with the two different histologies. Specifically, clinical trials based in the U.S. largely reflect the performance of patients with EA, leaving ESCC an understudied disease [1].

## Current Standard of Care for Esophageal Cancer

Multiple randomized controlled trials and meta-analyses have demonstrated survival benefit for patients with EA and ESCC treated with neoadjuvant chemoradiation [6]. The current standard of care for both EA and ESCC was established after publication in 2012 of the chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS), in which patients with both histologies were treated with weekly carboplatin AUC 2 and paclitaxel 50 mg/m<sup>2</sup> administered concurrently with 41.4 Gy external-beam radiation prior to surgery versus surgery alone [7]. At initial publication, after a median follow-up of 45.4 months, the median overall survival (OS) was 49.4 months in the chemoradiotherapy-surgery group versus 24 months in the group undergoing surgery alone (P=0.003); notably, patients with ESCC had not yet reached a median OS [7]. Subsequently, at a median follow-up of 84 months, patients treated with neoadjuvant chemoradiotherapy followed by surgery still showed significant benefit in median progression-free survival (PFS) and OS as compared to those undergoing surgery alone [8]. Furthermore, among the patients treated neoadjuvantly, those with ESCC experienced near doubling of PFS and OS [8]. It is worth noting, however, that in spite of these significant gains, only 41% of the patients originally enrolled in the chemoradiotherapy plus surgery group were still alive at this median follow-up period of 7 years [8].

Even before the establishment of neoadjuvant chemoradiotherapy and surgery as the new standard of care for patients with esophageal cancer, studies explored the benefit of surgery in patients who achieved a complete pathologic response to neoadjuvant chemo radiotherapy. RTOG 85-01, a randomized trial comparing chemoradiotherapy to radiotherapy alone, without subsequent surgery, showed a 21% 5-year OS in patients with ESCC and a 27% 5-year combined OS for EAs and ESCCs [9,10]. The degree of pathologic response to neoadjuvant chemoradiotherapy was then shown to correlate with survival [11]. Subsequently, two randomized trials compared definitive chemoradiation to chemoradiation followed by surgery in patients with ESCC [12,13].

Neither trial showed an overall survival advantage for the addition



**Figure 1:** Somatic mutation burden in human cancers Used with permission: LB Alexandrov et al. Nature 500, 415-421 (2013) doi: 10.1038/nature12477.

of surgery to chemoradiation, although surgery was associated with a lower rate of local progression at 2 years [12]. Ultimately, these studies support the currently accepted practice of treating ESCC patients with definitive chemoradiation and foregoing surgery for patients who demonstrate a clinical complete response (cCR) by endoscopic clearance and 18F-fluorodeoxyglucose (FDG)-PET scan resolution of all FDG-avid areas.

Taken together, the above data underscore the need for novel local and systemic treatment modalities to improve upon the progress achieved with current chemoradiation for those with locally advanced esophageal cancer. The overarching goal, as with most neoadjuvant therapy, is to achieve a complete clinical response that can be translated into a complete pathologic response with attendant improved survival.

## Immune Checkpoint Blockade and PD-L1 Expression in Esophageal Cancer

By evolving from a series of mutations arising in healthy cells, often as a result of extrinsic toxic insults, some cancers can be characterized as being “foreign” to their hosts. More specifically, they escape immune editing, a process by which tumors find a way to overcome their host’s natural immune defenses [14-16]. Most of these tumors have been shown to carry a relatively high mutational burden, thus presenting a larger variety of novel antigens to the immune system [15]. The classic example of a tumor with a high mutational burden that has demonstrated the property of overcoming immune editing is melanoma. Cancers that do not appear “foreign” to their host use immune editing to bypass the host’s immune defenses, and tumor growth proceeds largely unimpeded as a result of immune tolerance toward cancer cells [16].

The immune system’s attack against foreign antigens is highly regulated by stimulatory and inhibitory mechanisms that evolved to prevent overly destructive immune responses to pathogen invasion. Cancer cells exploit immune checkpoints to avoid recognition [17,18]. To date, two inhibitory receptors, programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4), have been successfully employed in the clinic for therapeutic inhibition that releases the breaks on immune attack against tumor cells. PD-1 and CTLA-4 are expressed on tumor-infiltrating lymphocytes (TILs) in

the tumor microenvironment, while PD-L1 and PD-L2 are expressed on the surface of tumor cells [19-21]. Monoclonal antibodies against PD-1 (nivolumab and pembrolizumab) and its ligand, PD-L1 (atezolizumab), as well as against CTLA-4 (ipilimumab) are currently selectively approved in the treatment of melanoma, small cell and non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma, Hodgkin lymphoma, and head and neck squamous cell carcinoma. These tumors generally feature high numbers of somatic mutations and neoantigens, which may be recognized as “foreign” to their host (Figure 1). In general, these are the tumors that have been associated with better clinical outcomes following PD-1 blockade [15,22]. Therefore, we can hypothesize that esophageal cancer and ESCC in particular, ranking high among mutation-bearing tumors, would also present promising targets for immune checkpoint inhibitors [15,23].

However, a clear biomarker for response to immune checkpoint blockade remains elusive. Many of the tumors that bear a high somatic mutation burden can be recognized by pathologists as having a high tumor lymphocytic infiltration, which also correlates with better clinical outcomes [24,25]. Absolute numbers and relative proportions of different lymphocyte subtypes affect prognostic value [26].

Additionally, several tumor types have been analyzed to determine the reliability of PD-L1 as a predictive biomarker for response to anti-PD-1 therapy [27,28]. Among these, studies in gastric and GEJ adenocarcinoma, as well as one study of patients with EA yielded a mixed set of outcomes, mostly associating PD-L1 expression with a poor prognosis [29-38]. Furthermore, EA was found to express PD-L1 at lower rates than gastric adenocarcinoma and to preferentially express PD-L2 over PD-L1 [31,38]. Over-expression of PD-L1 and associated poor prognosis may also support the pursuit of checkpoint blockade in esophageal cancer [27]. While high expression of PD-L1 has been used as a criterion for treatment with the PD-1 inhibitor pembrolizumab, its role as a predictive biomarker for all tumors has yet to be established [27,39].

## Immune Checkpoint Inhibitor Therapy in Esophageal Cancer

Although reports testing ipilimumab and tremelimumab, both CTLA-4 inhibitors, for patients with gastroesophageal cancers were disappointing, more recent trials testing the PD-L1 inhibitor

**Table 1:** Active Clinical Trials for Immune Therapy in Gastric and Gastroesophageal Junction Adenocarcinoma and Esophageal Adenocarcinoma and Squamous Cell Carcinoma.

Trail Name	ClinicalTrials.gov Identifier	Description	Status
<b>Immune Checkpoint Inhibitors</b>			
KEYNOTE-062	NCT 02494583	A randomized phase III trial of <b>pembrolizumab</b> alone and in combination with cisplatin and fluorouracil versus cisplatin and fluorouracil alone for treatment –naïve patients with advanced gastric and GEJ adenocarcinoma	Recruiting
KEYNOTE-061	NCT 02370498	A phase III trial of <b>pembrolizumab</b> versus paclitaxel for patients with advanced gastric and GEJ adenocarcinoma who progressed after platinum and fluoropyrimidine-based chemotherapy	Active Not recruiting
KEYNOTE-059	NCT 02335411	A phase III trial of <b>pembrolizumab</b> alone and in combination with cisplatin+5- fluorouracil in patients with recurrent or metastatic gastric or GEJ adenocarcinoma	Active Not recruiting
-	NCT 02642809	A pilot study combining <b>pembrolizumab</b> with locally delivered radiation therapy for the initial treatment of metastatic esophageal cancers	Recruiting
<b>Adoptive T-Cell Therapy</b>			
-	NCT 02457650	A phase I trial of T-cell receptor transduced T-cells targeting NY-ESO-1 in metastatic malignancies, including esophageal cancer, that express NY-ESO-1	Recruiting

pembrolizumab and the PD-1 inhibitor nivolumab have shown encouraging results [40-42].

An abstract presented at the 2016 ASCO Gastrointestinal Cancers Symposium described results of a Japanese phase II trial that evaluated treatment with nivolumab alone in 65 patients with ESCC who had progressed on up to 4 previous lines of therapy [43]. The investigators reported 1 complete response and 10 partial responses for a total response rate of 17.2% in addition to a 25% rate of stable disease [43]. Median OS was 12.1 months [43].

KEYNOTE-028, a multicohort phase Ib trial assessing the safety and efficacy of anti-PD-1 therapy with pembrolizumab in patients with PD-L1-positive advanced solid tumors included patients with advanced EA (26%) and ESCC (74%) [44]. Results for this cohort, also presented at the 2016 ASCO Gastrointestinal Cancers Symposium, showed an overall response rate (ORR) of 30.4%, with 13% of patients showing stable disease, 30.4% PFS at 6 months, 21.7% PFS at 12 months, and a median duration of response of 40 weeks [44].

KEYNOTE-012, another phase Ib trial assessing the effect of pembrolizumab in patients with PD-L1-positive recurrent or metastatic adenocarcinoma of the stomach or GEJ suggested activity in this group of patients: 22% showed a partial response and 14% showed stable disease [42]. Tumor site (gastric versus GEJ) was not specified for the patients who responded [42].

Preliminary results of the CheckMate-032 trial assessing the effect of anti-PD-1 therapy with nivolumab alone or in combination with anti-CTLA-4 treatment with ipilimumab in patients with advanced or metastatic gastric, esophageal, or GEJ cancer who had progressed on chemotherapy showed a 16% overall response rate, including 2 patients with a CR [45]. We anticipate further breakdown of the data by tumor type in the forthcoming full report from this trial [45].

Several studies are ongoing for immune checkpoint therapy alone or in combination with immunotherapy in patients with GEJ or esophageal cancer (Table 1) [42].

## Radiation Therapy and Immune Checkpoint Blockade

The abscopal effect describes, in patients treated locally with radiation therapy, the subsequent response of unirradiated tumor sites [46,47]. Although the abscopal effect has been appreciated for decades, its mechanism has only recently been elucidated. By

releasing tumor-associated antigens, radiation has been described as inducing a vaccine-like effect by priming the adaptive immune system [46,47]. An abscopal response was observed in a patient advanced melanoma previously treated with ipilimumab, who subsequently received palliative radiation to a painful metastatic site [48]. This patient's tumor expressed NY-ESO-1, an antigen expressed in normal testicular germ cells and placenta, as well as in selected malignant tissues, including advanced melanomas and ESCC [48-50]. Significant regression was observed in tumors outside the radiation field [48]. Immune analyses revealed an increase in NY-ESO-1-specific antibody responses and in the proportion of NY-ESO-1-specific CD4+ T cells that expressed inducible co-stimulator (ICOS), a marker of T cell activation [48]. A second patient with melanoma treated with ipilimumab also experienced a similar abscopal response following radiation, with a corresponding increase in the antibody response against the cancer-testis antigen MAGE-A3 [51]. These studies offer rationale for exploring the effects of combining immune therapy with standard of care chemoradiotherapy for patients with esophageal cancer.

## Ongoing Trials and Possibilities for the Future

### Adoptive T-Cell therapy

An alternate form of immunotherapy, primarily developed in melanoma, isolates and expands antigen-specific T-cells from among tumor-infiltrating lymphocytes, subsequently transferring the T-cells back to lymphodepleted patients [52]. Adoptive T-cell therapy has proven effective in patients with metastatic melanoma and synovial sarcoma, particularly with T-cells specific to cancer testis antigen NY-ESO-1 [53-55]. The expansion of adoptive T-cell therapy to esophageal cancer among other malignancies is under active investigation. NCT02457650 is a Phase I trial currently recruiting patients with a number of different malignancies expressing NY-ESO-1, including EA and ESCC, to therapy with T-cell receptor-transduced T cells targeting NY-ESO-1 (Table 1).

### Combining immune checkpoint inhibition with radiation therapy in esophageal cancer

To our knowledge, a single active trial is available at this time for combined immune therapy and radiation therapy. NCT02642809 is a pilot study for the combination of anti-PD-1 therapy with pembrolizumab with locally delivered radiation therapy in the

form of brachytherapy in patients with treatment-naïve metastatic esophageal cancers (Table 1).

Most patients with esophageal cancer present with locally advanced tumors without clinical evidence of metastatic disease. Therefore, most patients are treated with chemotherapy and radiation prior to surgery with the goal of significant down staging prior to surgery or chemotherapy and radiation as definitive therapy, especially for those with ESCC. Our group has developed a protocol to test the safety of the PD-1 inhibitor nivolumab, given initially alone and then with radiation and carboplatin and paclitaxel for patients with ESCC. Our goal is to move PD-1 therapy from the palliative setting into the curative setting for patients with ESCC.

## Conclusion

Monotherapy with immune checkpoint inhibitors has shown promising response rates in early clinical trials for patients with esophageal, as well as gastric and gastroesophageal junction tumors. However, larger randomized trials for patients with esophageal adenocarcinoma and squamous cell carcinoma are needed to corroborate current results. Additionally, we hypothesize that multimodality therapy combining current standard chemoradiotherapy and immune therapy may help improve upon the positive results seen thus far.

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