Optimal First-Line Therapy for Metastatic Adenocarcinoma of the Esophagus

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Opinion statement
Treatment strategies for esophageal adenocarcinoma patients continue to advance with the generation of more data from clinical trials that are permitting us to refine the use of immunotherapy in combination with other treatment modalities. While the frontline therapy for metastatic esophageal adenocarcinoma has become more complicated with the approval of combination regimens, it is also yielding better outcomes. These treatment strategies can now be individualized to fit patient circumstances and goals as well as the biomarker profile of their individual tumors leading to an increased likelihood of treatment related remissions and extended median survivals. Comprehensive genomic profiling at diagnosis should now be standard to allow the management team to customize each patient’s treatment plan based on the genetic abnormalities discovered in their tumor. By refining these targeted approaches, we will see decreased toxicities and increased survival.
Introduction

Esophageal carcinoma accounts for 1.1% of all new cancer cases and 2.7% of all the cancer deaths in the USA. The 5-year survival between 2012 and 2018 was 20.6% for all patients with early-stage esophageal cancer and 5.7% for the approximately 40% of patients diagnosed with metastatic disease. Adenocarcinoma (AC) is the predominant histologic subtype in the western hemisphere while squamous cell carcinoma (SCC) predominates in Asian populations [1]. In the USA, AC accounts for two-thirds of diagnoses.

National Comprehensive Cancer Network (NCCN) guidelines reflect principles of systemic therapy and suggest that an individual’s treatment plan must be constructed with attention to their performance status, co-morbidities, and the toxicity profiles of the proposed regimens. For example, doublet regimens are often better tolerated than triplet chemotherapy regimens. The guidelines suggest several possible options rather than favoring a single first line regimen as a standard of care to treat unresectable or metastatic disease. Herein, we review and provide context for recently presented/published studies in frontline metastatic esophageal and gastroesophageal junction (GEJ) ACs based on biomarkers. The complex paradigms for treating this disease are evolving rapidly as we learn how to harness the potential for immunotherapy in combination with other treatments.

Frontline management of metastatic esophageal adenocarcinoma

Until recently clinicians could offer metastatic esophageal and GEJ AC patients palliative treatments to improve quality of life and extend survival without hope for long term survival. With the discovery of effective approaches to harness the patient’s immune system, in rare cases, curative intent therapy for advanced disease has become possible. Chemo-immunotherapy combinations have extended median OS and PFS and are establishing new first-line standards of care for patients with unresectable SCC and subtypes of unresectable esophageal ACs. The Food and Drug Administration (FDA) has approved the use of the PD-1 checkpoint inhibitors, pembrolizumab and nivolumab in combination with chemotherapy, as initial treatment for patients with unresectable esophageal, GEJ, and gastric carcinomas. We review the results of recent frontline trials, most biomarker driven, to illustrate current management controversies. Most data for esophageal AC management are extrapolated from gastric and GEJ studies due to genetic similarities.

Biomarker guided therapy in metastatic esophageal adenocarcinoma

Individualized initial therapy selection depends on three key variables: tumor histology, biomarker status, and the patient’s performance status. Biomarker assessment should include, at a minimum, evaluation of the tumor for programmed cell death ligand-1 (PD-L1) expression, human epidermal growth factor receptor 2 (HER2) overexpression, and deficient mismatch repair (dMMR) (also known as microsatellite instability high [MSI-H]) status. With the advent of multiple FDA-approved testing platforms, decrease in cost, and extension of insurance coverage, multigene panel tests (MGPT) are now both readily available and accessible. An evidence-based analysis by an expert panel convened by ASCO recently recommended that MGPT be performed in patients with solid tumor malignancies who have the potential to benefit from targeted therapies [2]. There has been considerable progress in the frontline management of metastatic esophageal/GEJ ACs and immune checkpoint inhibitors (ICI) have transformed the treatment landscape [3]. We highlight the key therapeutic advances, controversies, and their impact on the prognosis of patients with this aggressive malignancy in the frontline setting.

PD-L1 expression

PD-L1 is expressed on the tumor cell surfaces and, when bound to PD-1, inhibits T cell-mediated anti-tumor effects [4]. ICIs inactivate this pathway and restore the immune system’s anti-tumor effects [5]. PD-L1 expression is a pivotal biomarker for predicting response to immunotherapy in esophageal and gastric malignancies. The combined proportion score (CPS) measures PD-L1 expression on tumor and immune cells. It has become the standard evaluation tool for quantifying PD-L1 expression [6, 7]. The 22c3 pharmDX and 28-8 pharmDx tests are commonly used in clinical practice to detect PD-L1 expression [8, 9•]. Although historical data suggested that these two assays are concordant, recent data found expression rates using the 28-8 assay were double those of the 22C3 assay with only a moderate level of concordance at CPS ≥ 5 [10] (Fig. 1).
The prevalence of PD-L1 expression (CPS > 1) using the 22C3 assay in esophageal/GEJ ACs depends upon tumor location and histology: esophageal AC 18%, esophageal SCC 65%, GEJ AC 14%, and gastric AC 18% [11]. PD-L1 expression, using 28-8 assay, in Checkmate 648 and 649 noted 87% positivity in esophageal SCC and 82% positivity among gastroesophageal ACs. Therefore, PD-L1 expression levels depend upon the assay used. Additionally, high PD-L1 expression correlated with evidence of Epstein Barr virus (EBV) infection, HER2- mutation, and dMMR [9•]. Prevalence of PD-L1 expression is consistent across published studies, in ACs of esophagus, GEJ, and stomach (Table 1). Clinical trials focused on chemo-immunotherapy combinations based on PD-L1 biomarker expression are described below.

A. Chemo-immunotherapy

Combinations of chemotherapy and immunotherapy are promising in patients selected according to tumor CPS and have changed the treatment paradigm in the front-line setting. The CheckMate 649 (CM-649) trial added nivolumab to platinum-based chemotherapy in treatment naïve unresectable esophageal, GEJ, and gastric AC patients [12•]. The primary endpoints were OS and PFS in tumors with PD-L1 CPS ≥ 5. Combination therapy significantly improved median OS (14.4 vs. 11.1 month, \(P < 0.0001\), HR 0.71 CI (0.59–0.86)) in CPS ≥ 5, all randomized patients, and in patients with CPS ≥ 1. Interestingly, 60% of enrolled patients had CPS ≥ 5 in this study, a higher prevalence rate than was reported in previous studies [13–15]. The higher prevalence was possibly attributed to heterogeneity in the enrolled population, in their tumors, or in the testing methodology. Although HER2-positive patients were excluded from this trial, patients with unknown HER2 expression status were enrolled, potentially leading to tumor heterogeneity. In contrast, improvement in median PFS was demonstrated only in CPS ≥ 5 cohort (7.7 vs. 6.0 months, \(P < 0.0001\), HR 0.68 CI (0.56–0.81)). It remains to be seen whether the results hold true for primary unresectable esophageal ACs. Patients with esophageal AC comprised only 13% of the patient population in this study and there was no statistical difference in median OS between the chemotherapy and chemo-immunotherapy groups regardless of CPS status in the subgroup analyses. Nevertheless, these results led to FDA approval and adoption of chemo-immunotherapy with nivolumab in the frontline management of upper gastrointestinal cancers.

The ATTRACTION 4 randomized phase III trial evaluated the efficacy of nivolumab plus platinum-based chemotherapy in a predominantly Asian population
| Study | Checkmate-649 [11] | ATTRACTION 4 [15] | Orient 16 [16*] | Keynote-062 [18*] | Keynote-590 [17*] | Keynote-811 [37] |
|-------|---------------------|-------------------|-----------------|-------------------|-------------------|-------------------|
| Location of Cancer and histology | Gastric/GEJ Adenocarcinoma Gastric/GEJ Adenocarcinoma | Gastric/GEJ | Esophageal Squamous cell and | Adenocarcinoma | adenocarcinoma | Gastric/GEJ |
| Adenocarcinoma | | | | | | |
| Number of patients with positive PD-L1 expression CPS score | CPS ≥ 5 (955/1581, 60.4%) | CPS ≥ 1 (114/724, 15.7%) | CPS ≥ 5 (397/650, 61%) | CPS ≥ 10 (281/763, 36.8%) | CPS ≥ 10 SCC: 283/548, 51.6% Adeno: 100/203 | CPS ≥ 1 (364/434, 83.8%) |
| PD-L1 methodology | 28-8-Dako | 28-8-Dako | NA | 22C3 | 22C3 | 22C3 |
| Anti-PD1 agent | Nivolumab | Nivolumab | Sintilimab | Pembrolizumab | Pembrolizumab | Pembrolizumab |
| Chemotherapy | CapeOX/ FOLFOX | CapeOX | CapeOX | CF/X | CF | CF/ CapeOX + Trastuzumab |
| Primary End point | OS, PFS CPS ≥ 5 | OS, PFS All CPS CPS ≥ 10 | OS CPS ≥ 10 | OS, PFS CPS ≥ 1 | OS, PFS CPS ≥ 10 | OS, PFS All CPS |
| Results | mOS: 14.4 vs. 11.1 mo PFS: 7.7 vs. 6.9 mo | mOS: 17.45 vs. 17.15 mo PFS: 12.9 vs. 8.7 mo | mOS: 18.4 vs. 12.9 | mOS: 10.6 vs. 11.1 mo PFS: 2.0 vs. 6.4 mo | mOS: 11.6 vs. 9.9 mo PFS: 6.3 vs. 5.7 mo | mOS: |
| ORR: 60% vs. 45% | ORR: 57% vs. 48% | ORR: | ORR: | ORR: 15% vs. 37% | ORR: 48% vs. 25% | ORR: 74.4% vs. 51.9% |
with HER2-negative, untreated, unresectable advanced GEJ or gastric AC [16]. Co-primary end points were PFS and OS. While chemo-immunotherapy significantly improved PFS (12.9 vs. 8.7 months, \( P = 0.0003 \), HR 0.73), it did not significantly improve median OS. A higher proportion of patients (\( \sim 27\% \)) in the control arm received immunotherapy post-progression which could have obscured differences in the median OS. Additionally, patients with GEJ AC comprised a small subset (8%) of the entire trial population and nivolumab plus chemotherapy did not significantly prolong PFS (8.34 vs. 5.59 months, HR 0.59 CI (0.29–1.18)) or OS (14.88 vs. 17.15 months, HR 1.0 CI (0.55–1.82)).

Although the CM-649 and ATTRACTION-4 studies share a similar design and stratification factors, there are distinctions that are worth considering that complicate cross trial comparisons. While the CM-649 study included predominantly a non-Asian (76%) population, the latter study included an entirely Asian population. Median OS was prolonged for the first time to greater than 12 months in a Phase III trial in this patient population in both studies. Interestingly, the median OS was further prolonged (>17 months) in ATTRACTION-4 compared to CM-649 and other contemporary studies in the first line setting. This stresses the importance of geographical heterogeneity and population-based differences in the use/tolerability of further lines of therapy between Asian and Western populations on survival outcomes. Illustrative of the different patterns of care that characterize management of patients, 66% of patients cared for by Asia-based practitioners who enrolled in the ATTRACTION-4 study received post-progression therapy compared to 39% of patients in CM-649.

Orient 16 was a phase III randomized double-blind trial that compared the efficacy and safety of capecitabine and oxaliplatin (CapeOX) ± the PD 1 inhibitor Sintilimab in HER2-negative untreated, unresectable locally advanced or metastatic GEJ or gastric AC patients [17]. The primary endpoints were OS in patients with PD-L1 CPS ≥ 5 and OS in all patients. Of 650 patients enrolled in the study, 61% had PD-L1 CPS ≥ 5 and the chemo-immunotherapy combination improved their median OS (18.4 vs. 12.9 months, \( P = 0.0023 \), HR 0.6). Similarly, the combination significantly prolonged median OS and PFS compared to chemotherapy alone (15.2 vs. 12.3 months, \( P = 0.009 \), HR: 0.7) in all randomized patients.

The Keynote 590 study evaluated platinum-based chemotherapy ± pembrolizumab in untreated patients with unresectable, or metastatic AC or SCC of the esophagus or GEJ [18]. Among the 749 enrolled patients, 167 had ACs and 97 of those had CPS ≥ 10. Chemo-immunotherapy significantly prolonged median OS in patients with CPS ≥ 10 (13.5 vs. 9.4 months, \( P < 0.0001 \), HR 0.62 CI (0.49–0.78)) and in all comers (12.4 vs. 9.8 months, \( P < 0.0001 \), HR 0.73 CI (0.62–0.86)). However, a subgroup analysis of patients with adenocarcinomas did not show benefit in median OS with the addition of immunotherapy regardless of CPS score. The study found that the Asian population had better outcomes than the non-Asian population (mOS: 14.0 vs. 10.5 months). Although this study is a positive study, it does not explain the complex impact of anatomy, histopathology, and geography (Asian vs non-Asian) on outcomes.

The KEYNOTE 062 study randomized patients to pembrolizumab alone or platinum-based chemotherapy ± pembrolizumab in patients with HER2 negative, advanced gastric and GEJ cancers [19]. The primary study end points were median OS and PFS in patients (n = 763) with PD-L1 CPS ≥ 1 and CPS ≥ 10. While pembrolizumab was non-inferior to chemotherapy in the CPS > 1 population, neither pembrolizumab nor pembrolizumab plus chemotherapy demonstrated superiority in median OS or PFS over chemotherapy alone in GEJ or gastric AC patients regardless of PD-L1 status.

Differences in the interpretation of the published data by regulatory authorities across the world has led to disparate availability of these agents depending upon where a patient resides. In the USA, the FDA has approved combinations of platinum-based chemotherapy with nivolumab or pembrolizumab for the indication of treating patients with metastatic esophageal AC regardless of the tumor PD-L1 expression. However, in Europe, these combinations with nivolumab or pembrolizumab are approved for use in patients with tumors that have PD-L1 expression ≥ 5 and ≥ 10 respectively. The NCCN guidelines also listed chemo-immunotherapy as category 1 options, like European approvals and does not recommend immunotherapy for patients with tumors with CPS ≤ 1. In our opinion, knowledge of PD-L1 expression is essential, but is not the sole biomarker that should be evaluated, before initiating frontline treatment with checkpoint inhibitors. There is marked intra-patient and intra-tumoral heterogeneity of PD-L1 expression suggesting that PD-L1 expression can vary as a function of the location, the size of the sample tested, and when the sample for testing is procured. When primary tissues tested positive for PD-L1 expression, simultaneously obtained tissue from metastatic lesions tested negative for PD-L1 expression in up to 60% of cases [20]. Knowledge about the anatomical location,
histopathological characteristics, and molecular subtype of tumors, as well as the patient’s race play key roles in determining response to immunotherapy.

B. Immunotherapy

Single agent immunotherapy is currently not FDA approved; however, its use can be considered in certain circumstances in the frontline management of upper GI cancers. Pembrolizumab is a reasonable consideration in asymptomatic elderly or frail patients without bulky disease with tumors that have a CPS $\geq 10$. Pembrolizumab demonstrated non-inferiority to chemotherapy in CPS $\geq 1$ (10.6 vs. 11.1 months, HR 0.91 CI (0.69–1.18)) and in CPS $\geq 10$ cohort (17.4 vs. 10.8 months, HR 0.69 CI (0.49–0.97)) in the Keynote-062 study [19*, 21]. Although the median OS favored pembrolizumab alone in the CPS $\geq 10$ patient population, the study was not powered to test for superiority.

Recently, a cohort analysis of patients treated with immunotherapy doublets compared to chemotherapy from the CM-649 trial has been published. The combination of nivolumab and ipilimumab in patients with CPS $\geq 5$ did not improve median OS compared to chemotherapy alone (11.6 vs. 11.2 months, $P = 0.23$, HR: 0.89 CI (0.71–1.10)). PFS and ORR were also not significantly improved in the doublet immunotherapy cohort compared to the cohort treated with chemotherapy alone. However, more durable responses were demonstrated in both CPS $\geq 5$ (13.2 vs. 6.9 months) and in all randomized patients (13.8 vs. 6.8 months). Further studies on molecular characterization of tumors in addition to PD-L1 to demonstrate its potential to be predictive for doublet immunotherapy benefit are necessary [22].

Maintenance immunotherapy after first-line induction chemotherapy was studied in patients with untreated, locally advanced/metastatic GEJ/gastric carcinomas in Javelin trial [23]. Patients who have not progressed after 12 weeks of chemotherapy were randomized to maintenance avelumab or continued chemotherapy with OS as the primary endpoint. Avelumab did not improve median OS in the overall population and in the pre-specified PD-L1 positive cohort.

C. Chemotherapy backbone

Multiple combinations of chemotherapy agents are listed as first-line treatment options for metastatic or locally advanced esophageal/GEJ AC by the NCCN guidelines. These combinations commonly include a fluoropyrimidine paired with a platinum-based agent. Doublet cytotoxic regimens have generally been preferred over triplet regimens due to better tolerability and similar survival outcomes. A meta-analysis comparing CapeOX and FOLFOX for metastatic colorectal cancer showed no statistical difference regarding OS and overall response rate [24]. There are limited data comparing these regimens in esophageal cancer patients. CapeOX significantly prolonged median OS in patients with stage III gastric cancer in the adjuvant setting compared to FOLFOX. No OS difference was observed between the two regimens in stage I and II gastric cancer patients [25]. The other commonly used and guideline endorsed chemotherapy backbones include cisplatin plus 5-fluorouracil (CF), cisplatin plus capecitabine (CX), and S-1 plus oxaliplatin [16*, 19*, 26]. CF is as effective as oxaliplatin and 5-fluorouracil, while the former regimen has been associated with increased risk of grade 3 or 4 neutropenia, alopecia, renal toxicity, hearing loss, and thromboembolism compared to FOLFOX [27]. Hence, an oxaliplatin based chemotherapy backbone is our preferred regimen in patients with advanced esophageal adenocarcinoma.

Physicians in the CHECKMATE 649, Attraction 4, and Orient 16 trials most commonly opted to use CapeOX [28]. Checkmate 649 allowed physicians to choose CapeOX every 3 weeks or FOLFOX every 2 weeks with or without nivolumab until disease progression or unacceptable toxicity [12*]. The median duration of treatment in the chemotherapy alone group was 4.8 months for FOLFOX and 4.9 months for CapeOX with 45 vs. 40% patients requiring protocol mandated dose reductions or omissions of oxaliplatin due to toxicity. The median duration of nivolumab monotherapy after the patients chemotherapy 7.0 months and 6.8 months. In the Attraction 4 trial, both cohorts received oxaliplatin for a similar amount of time (4.6 and 5.4 months) with similar ability to tolerate nivolumab as monotherapy (5.2 and 6.3 months). Patients in the Orient 16 trial received up to 4.5 months of the CapeOX regimen and were allowed to continue sintilimab or placebo for up to 24 months [17*]. In our opinion, platinum-based chemotherapy can be held after 4 months of chemoinmunotherapy as long as imaging demonstrates response per RECIST criteria since many patient’s tolerance for oxaliplatin declines with cumulative dosing in real world practice.

Microsatellite instability

MSI-H tumors represent up to 5% of esophageal ACs. MSI-H status correlates to an increase in PD-L1 expression and a better prognosis [29]. This is thought to be
due to the increased number of neoantigens present on
the cell surfaces of tumors with the MSI-H phenotype
that in turn attract T lymphocytes. T lymphocytes stim-
ulate PD-L1 expression through interferon-gamma se-
cretion resulting in increased expression of PD-L1 in
affected cells permitting the host’s natural immunity to
recognize and destroy tumor cells.

Immune checkpoint inhibitors (ICI), either as single
agents or combination, have demonstrated significant
efficacy and have improved survival outcomes in pa-
tients with advanced or metastatic solid tumors with
dMMR/MSI-H status. The FDA-approved pembrolizu-
mab for patients with unresectable or metastatic tumors
demonstrating dMMR/MSI-H, regardless of the primary
site, in the second-line or later treatment in 2017. Effic-
cacy data regarding the value of ICI in the front-line
management of patients with unresectable/metastatic
MSI-H esophageal cancers are limited and are extrapo-
lated from subset analyses of completed clinical trials or
from neoadjuvant studies.

In Keynote 062, MSI-H gastric and GE junction cancers
constituted approximately 7% (50/763 patients) of the
study population [19•]. Median OS was not reached with
pembrolizumab compared to chemotherapy (NR vs. 8.5
months, HR 0.29 CI (0.11–0.81) in patients with PD-L1
CPS of ≥ 1. This study is one of the earlier studies that
demonstrated a survival benefit of anti-PD-1 therapy for
MSI-H tumors over chemotherapy in the frontline setting.

Keynote 059 was a global phase-II study that evalu-
ated the efficacy of pembrolizumab in previously treated
GEJ or gastric cancers [21, 30]. Seven out of 174 patients
(4%) with available tissue samples had MSI-H tumors.
Four of the seven patients experienced objective re-
sponses (57% CI(18.4–90%)) and their median OS
was not reached at the time the study was reported.

Keynote 061 compared pembrolizumab to paclitaxel
among the MSI-H gastric and GE junction cancer patients
(15 vs. 12 patients, 4.5% incidence in study population) in
the second-line treatment setting [31]. Pembrolizumab led
to a significantly improved median OS at 28 months of
follow-up (NR vs. 8.1 months, HR 0.42 CI (0.13–1.31)).

The CM-649 trial evaluated 44 patients with MSI-H
tumors and their median OS was significantly improved
(unstratified HR: 0.38 vs. 0.78 for MSS cohort) in this
subset of patients with chemo-immunotherapy com-
pared to chemotherapy alone. Additionally, 34 of the
44 patients had tumors that expressed CPS ≥ 5 and had a
significant increase in median OS compared to CPS ≤ 5
(NR vs. 8.8 months, P = 0.1808, HR 0.33 CI (0.12–
0.87)) [12•]. The nivolumab plus ipilimumab cohort
had only 11 patients with MSI-H status and median OS
(NR vs. 10 months, unstratified HR: 0.28) and objective
response rates (70 vs. 57%) were prolonged compared
to chemotherapy alone respectively.

The NEONIPIGA is a phase II trial that evaluated
neoadjuvant nivolumab and ipilimumab followed by
adjuvant nivolumab in patients with resectable MSI-H
GEJ or gastric cancers. Among the 32 patients included
in the study, 29 patients underwent surgery and patho-
logic complete response (pCR) was the primary end
point of the study [32]. A pCR of approximately 59%
(17/29 patients) supports the feasibility and efficacy of
ICI doublets in the neoadjuvant setting.

ICIs have demonstrated excellent improvement in
outcomes in subsets of MSI-H patients with upper GI
cancers. However, the trials from which these data are
drawn were not powered to draw definitive conclusions
for an MSI-H population and results are all drawn from
subset analyses. Further prospective studies evaluating
the efficacy of either single vs. doublet ICI are para-
mount in cohorts of patients with MSI-H esophageal
and gastric cancers. Although the referenced studies have
included few patients with esophageal adenocarcino-
mas, it is reasonable to extrapolate the data from GEJ
and gastric cancers in real world practice until further
prospective trials are completed.

**Human epidermal growth factor receptor**

Human epidermal growth factor receptor 2 (HER2) is
another targetable biomarker with a prognostic and pre-
dictive impact in patients with locally advanced or me-
tastatic esophageal or gastric carcinomas. It is a trans-
membrane tyrosine kinase receptor and activation of
HER2 initiates an intracellular signal cascade that influ-
ences cellular growth, and proliferation. The prevalence
of HER2 overexpression and/or amplification varies
based on the histological type and location of a malign-
ancy within the upper gastroesophageal tract exhibiting
a slightly higher frequency in GEJ cancers
compared to gastric cancers (32 vs. 21%) [33]. Analyses
of HER2 status should be performed using immunohis-
stochemistry and/or fluorescent in-situ hybridization
(FISH) based on expert panel guidelines [34]. The addi-
tion of trastuzumab, a humanized monoclonal anti-
body against HER2, to chemotherapy-improved ORR
and survival outcomes in HER2-positive advanced gas-
tric or GEJ cancer decade [35]. Lapatinib, an orally ad-
ministered small molecule inhibitor of HER2, was
studied in combination patients and has been the standard of care over the past with chemotherapy in the TyTan trial and did not improve overall survival compared to chemotherapy alone [36].

There is interest in assessing the synergistic effects of HER-2 targeted therapy and immunotherapy as trastuzumab upregulates PD-L1 levels in targeted HER2-overexpressing cancer cells through interferon gamma production [37]. The increased interferon gamma production occurs through the engagement of immune cells with trastuzumab. The clinical implications of this synergistic activity were observed in the KEYNOTE 811 which compared trastuzumab + chemotherapy ± pembrolizumab for patients with unresectable HER2-positive (overexpressed) gastric or GEJ AC [38]. The first interim analysis showed statistically significant and clinically meaningful improvement in ORR (74.4% vs. 51.7%, P < 0.05) and complete response rate (11% vs. 3%) with the addition of pembrolizumab [39]. These findings led to FDA approval of this regimen for management of patients with locally advanced or metastatic esophageal and GEJ carcinomas.

**Considerations during COVID-19 pandemic**

Corona virus 2019 (COVID-19) continues to impact cancer care and outcomes. It is important to limit health care exposure of patients with esophageal ACs and other malignancies and their caregivers with the following strategies:

- Single agent ICI, pembrolizumab can be considered in elderly patients with poor PS and less bulky disease and CPS ≥ 10. One advantage of this regimen is the administration schedule in initially every 3 weeks which transition to every 6 weeks based on patient tolerability.
- Esophageal AC patients with MSI-H tumors can be started on chemo-immunotherapy or single ICI alone based on tumor burden. Patients started on chemo-immunotherapy can be transitioned to single agent immunotherapy based on response assessed by subsequent imaging.
- Consideration of chemotherapy regimens that limit the frequency of patient visits is another strategy. Capecitabine and oxaliplatin based regimens provide both the benefit of visits every 3 weeks and have the additional advantage of oral chemotherapy administration.

**Conclusions and future directions**

Combination chemotherapy and immunotherapy has become the first-line standard of care for patients with unresectable SCC of the esophagus and certain biomarker determined subtypes of unresectable or metastatic esophageal/GEJ AC. The published data need to be interpreted in the context of biomarkers, anatomical location of the tumor, and geographical location of the patient. The activity of ICIs is limited in PD-L1 negative/MSS tumors and novel strategies to augment ICI response are essential. Fewer patients with esophageal ACs have enrolled in clinical trials to date as compared to those with GEJ and gastric ACs. Based on the existing data, patients assigned to receive chemo-immunotherapy have not enjoyed prolonged median OS compared to those enrolled in the control arms of trials in subgroup analyses [13, 19]. Prospective studies that recruit exclusively patients with esophageal ACs are needed to validate the promising findings demonstrated with chemo-immunotherapy.
Table 2. List of ongoing or completed clinical trials using novel therapeutic agents in esophageal and GEJ adenocarcinomas

| Clinical trial identifier | Cancer location | Phase | Study arms | Primary endpoints | Biomarker target | Comments |
|--------------------------|----------------|-------|------------|------------------|------------------|----------|
| NCT03783936 | Esophageal, Gastric | II | Single Arm: mFOLFOX6 + trastuzumab +avelumab | Objective response rate | HER2+ | |
| NCT05152147 | Esophageal, Gastric | III | Arm A: Trastuzumab + CAPOX Arm B: Zanidatamab + CAPOX Arm C: Zanidatamab + Tislelizumab + CAPOX | Overall Survival, Progression-free survival | HER2+, PD-1 | |
| NCT03008278 | Esophageal, Gastric, GEJ | I/II | Single Arm: Olaparib + ramucirumab | I: Dose Escalation II: Objective response rate II: Objective response rate | PARP, VEGFR-2 | |
| NCT04594811 | Esophageal, Gastric, GEJ | II | Single Arm: Nivolumab + NT-I7 | II: Objective response rate | PD-L1 | |
| NCT03281369 | Esophageal, GEJ (gastric cohort) | Ib/II | Arm 1: Atezolizumab + Tiragolumab-Cisplatin+5FU Arm 2: Atezolizumab + Cisplatin+5FU Arm 3: Cisplatin+5FU Arm 4: Atezolizumab + Tiragolumab | Objective response rate, Percentage with adverse events | PD-L1 | TIGIT |
| NCT02689284 | Esophageal, Gastric | II | Single Arm: Margetuximab + Pembrolizumab | Dose Escalation, Objective response rate | HER2+, Trial enrollment completed, awaiting results |
Multiple clinical trials are ongoing for patients with metastatic esophagus and GEJ ACs in the front-line setting (Table 2). These trials are evaluating novel anti-PD-L1, anti-HER2, and anti-TIGIT monoclonal antibodies as monotherapies or in combination with PARP inhibitor, VEGFR2 inhibitor, or chemotherapy. Circulating tumor DNA guided management strategies to help determine the future of treatment continues to focus on targeted combination therapy.

Compliance with Ethical Standards

Conflict of Interest
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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Keynote 590 evaluated platinum based chemotherapy +/- pembrolizumab and noted superiorit in the small subset of patients with esophageal AGs and did not show an OS benefit in the the full analysis cohort. It was also noted that the overall survival was increased in the Asian population as compared to the non-Asian population.

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Keynote 062 showed the non-inferiority of pembrolizumab and platinum based chemotherapy vs chemotherapy and placebo. Superiority criteria were not met but pembrolizumab was non-inferior to chemotherapy.

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