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Review Article

Advances in immunotherapy for metastatic esophageal cancer

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ABSTRACT

Conventionally, the treatment of metastatic esophageal carcinomas with cytotoxic chemotherapy has yielded very poor results. Recently, the incorporation of immune checkpoint inhibitors into the treatment landscape has produced promised results. This review highlights the landmark trials conducted in this area and brings out the relevant results which have changed or are likely to change the clinical practices among the oncologists.

Keywords: Esophageal carcinoma, Immune checkpoint inhibitors, PD-L1, Chemotherapy, Metastatic

INTRODUCTION

Cancers of the esophagus (EC), including esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), are among the most fatal cancers in the world. ESCC, being more common in Southeast Asian and African regions, is very aggressive and occurs in the middle or upper one-third of the esophagus. EAC, more common in European and North American regions, usually occurs in the lower third of the esophagus and originates from glandular lining near the stomach. EC is the 8th most common cause of cancer worldwide and 6th most common cause of cancer mortality.[1] Half of EC cases present at an advanced stage. Conventionally, systemic chemotherapy (CT) has been the mainstay of treatment in such cases, yielding a median survival of only around 12 months. Recently, immune checkpoint inhibitors (ICIs) have been extensively studied for the treatment of advanced EC. Several phase III trials have demonstrated benefits in response and survival as compared to CT along with a manageable safety profile in advanced EC.[2] There are more data on esophagogastric junction (EGJC) or gastric cancers rather than on isolated EC. Limited literature on EC urged us to write this review.

RATIONALE OF ICIs

The immune system of human body is a complex interaction between cells and biochemical signals that orchestrate the detection and damage from external antigens, while avoiding autoimmune damage. Cancer cells are not foreign cells; hence, they are not so easily detected by immune cells. As per newly proposed "cancer-immunity cycle" model, dead cancer cells emit antigens recognizable by antigen-presenting cells. This leads to the recruitment of CD 4 and CD 8+T-cells at the tumor sites. Cancer cells manipulate signals to escape from immune surveillance. By overcoming this, the immune system can be used as a potential weapon against cancer. This

forms the rationale of ICIs, where we use either agonists of stimulatory receptors or antagonists of inhibitory signals to immune cells. Nonetheless, as of now, only a subset of EC patients benefit from ICIs. Biomarker research is underway, to select the potential patients most likely to benefit from therapy and spare others from side effects (e.g., inflammation of skin, intestines, endocrine system, and liver) and failure of treatment.[3]

ROLE OF BIOMARKER TESTING

Any targeted therapy, including ICIs, does not equally benefit all patients. Hence, predictive biomarkers are needed to select potential patients most likely to benefit from these agents. Key biomarkers proposed for ICIs in EC include microsatellite instability (MSI) and programmed death-ligand 1 (PD-L1) expression.[4] Four subtypes of esophagogastric cancers can be distinguished at the molecular level: Tumors with chromosomal instability (50%), MSI-high (MSI-H) tumors (22%), Epstein–Barr virus-positive (8%), and genomically stable tumors (20%).[5] PD-L1 is the ligand that blocks the programmed death receptor 1 (PD-1), leading to immune tolerance. PD-L1 testing is available by various immunohistochemistry (IHC) methods, and rates of positivity in clinical trials are reported as tumor proportion score (TPS) only or as combined positive score (CPS) for the tumor cells, lymphocytes, and macrophages. The CPS appears to be a better as it looks at many cells constituting tumor microenvironment. In patients with EC undergoing ICIs treatment, testing for a mutation or DNA MMR deficiency is routinely checked. A high MSI is a surrogate marker of MMR deficiency and it results from failure of repair to mismatched nucleotides during DNA replication. Thus, a higher tumor mutational burden (TMB) results in increased neoantigens load. Testing can be done by IHC, by polymerase chain reaction, or by next-generation sequencing (NGS). MSI is seen in <1% of ECs.[6] A high TMB, recently defined as the presence of 10 or more mutations per megabase detected by NGS, is another potential biomarker of ICIs benefit.[7] Other potential biomarkers of response to ICIs include detection of the Epstein–Barr virus, in which tumors can lead to enhanced expression of both PD-L1 and PD-L2,[8] and other germline and somatic mutations that may increase the TMB including mutations in POLE.[9]

ICIs IN FIRST LINE

The results of three recent positive Phase 3 trials have established a new standard-of-care practice for the use of ICIs in combination with first-line (1L) CT in EGJC. Results of these trials are outlined in [Table 1]. These trials have demonstrated remarkable accomplishment of a benchmark overall survival (OS) exceeding 12 months for the 1st time in this disease.

In 1L EAC

The KEYNOTE-059 trial, in locally advanced or metastatic EGJCs adenocarcinomas, showed that treatment with pembrolizumab alone in 1L setting achieves an ORR of 26% with an OS rate of 63.6% after 1 year (40.1% after 2 years) in 31 patients having PD-L1-positive cancers.[10] This approach was further tested in KEYNOTE-062 study. First results demonstrated that single-agent pembrolizumab was not inferior compared to CT in terms of OS in PD-L1-positive cancers (CPS ≥1). In CPS ≥10 cancers, pembrolizumab showed an improvement in OS compared to CT alone (17.4 vs. 10.8 months; HR 0.69).[11] KEYNOTE-062 was an open-label, randomized Phase 3 study with three treatment arms, 1L CT (capecitabine or infusional 5-fluorouracil [5-FU] plus cisplatin) with or without pembrolizumab, and CT or pembrolizumab alone, in patients with gastric or EGJC and a CPS of ≥1%. Of the 763 patients studied, 66% had gastric primary cancers and were administered capecitabine/cisplatin. This trial could not demonstrate superiority for a co-primary endpoint of OS using pembrolizumab along with CT versus CT in all patients (12.5 vs. 11.1 months; HR, 0.85; $P = 0.05$) or in those with a CPS of at least 10% (12.3 vs. 10.8 months; HR, 0.85; $P = 0.16$). Nevertheless, non-inferiority analysis, with an hazard ratio (HR) of 1.2, showed that pembrolizumab was non-inferior to CT for OS (10.6 vs. 11.1 months). More patients died with single-agent pembrolizumab initially and the median PFS was low (median, 2.0 vs. 6.4 months) as compared to single-agent CT. In MSI-H subset (6.6%), both the pembrolizumab arms achieved better OS versus CT alone, independently of CPS. Although pembrolizumab failed to improve OS when added to first-line CT in this trial, the results for MSI-H cancers favor pembrolizumab in front line for MSI high cancers with or without CT.[12]

In the randomized, open-label CheckMate 649 trial, 1581 patients who had gastric or EGJC received 1L nivolumab with or without oxaliplatin-based CT. Less than one-third had cancers of the esophagus and EGJC. OS and PFS were studied as co-primary endpoints in the 60% of patients having CPS ≥5%. Nivolumab improved OS (14.4 vs. 11.1 months; HR, 0.71; $P < 0.001$) and PFS (7.7 vs. 6.0 months; HR, 0.68). Nivolumab also improved OS in the patients with a CPS of ≥1% (HR, 0.77) and all patients (HR, 0.80). However, OS was not improved in the subgroup of patients with a CPS of < 1% and the subgroup with a CPS of < 5% (HR, 0.92 and 0.94, respectively). RR improved with the addition of nivolumab in the patients with a CPS of ≥5% (from 45% to 60%), and the duration of response (DoR) improved from 7.0 to 9.5 months. Nivolumab produced better RR irrespective of the CPS.[13] On the basis of CheckMate 649, the FDA approved on April 16, 2021, nivolumab in combination with fluoropyrimidine- and platinum-containing CT for advanced

Table 1: Major trials on 1L use of immune checkpoint inhibitors.

Trial (phase)	Cancer type	Number of pts	Treatment arms	PFS (m)	OS (m)
KEYNOTE-062 (3)	Gastric/GEJ cancer	763 (CPS≥1%)	Chemotherapy ± pembrolizumab Pembrolizumab versus chemotherapy	-	12.5 versus 11.1 10.6 versus 11.0
JAVELIN Gastric 100 (3)	Gastric/GEJ cancer	749	Avelumab versus chemotherapy maintenance	-	10.4 versus 10.9
CheckMate 649 (3)	Gastric/GEJ cancer	925 (CPS≥5%) 1581 (all patients)	Nivolumab+FOLFOX versus FOLFOX	7.7 versus 6.0 (CPS≥5%)	14.4 versus 11.1 (CPS≥5%)* 13.6 versus 11.6 (all pts)*
ATTRACTION-4 (3)	Gastric/GEJ cancer	724	Nivolumab versus placebo+chemotherapy	10.5 versus 8.3*	17.5 versus 17.2
KEYNOTE-590 (3)	Esophageal/GEJ adenocarcinoma and squamous cell cancer	383 (CPS>10%) 740 (all patients)	Pembrolizumab versus placebo+chemotherapy	7.5 versus 5.5 (CPS>10%)* 6.3 versus 5.8 (all pts)*	13.9 versus 8.8 (CPS>10%)* 12.4 versus 9.8 (all pts)*
CheckMate 648 (3)	Esophageal squamous cell cancer	970 (49% TPS>1%)	Nivolumab+Chemotherapy Nivolumab+Ipilimumab Chemotherapy	-	15.4* 13.7* 9.1 (TPS>1%)
ESCORT-1 (3)	Esophageal squamous cell cancer	596	Camrelizumab versus placebo+chemotherapy	6.9 versus 5.6*	15.3 versus 12.0*

*Statistically significant. CPS: Combined positivity score, FOLFOX: Leucovorin, 5-fluorouracil, and oxaliplatin, GEJ: Gastroesophageal junction, m: Months, OS: Overall survival, pts: Patients, RR: Response rate, TPS: Tumor proportion score

or metastatic gastric cancer, gastroesophageal (GEJ) junction cancer, and esophageal adenocarcinoma.[14]

An Asian trial, ATTRACTION-4 trial, provides additional evidence for a benefit of the addition of nivolumab to CT in the 1L setting. In this randomized Phase 3 trial of 724 patients with gastric or EGJC, nivolumab or placebo was combined with oxaliplatin-based CT. ICI-CT combination was superior to CT alone in the primary endpoint of PFS (10.5 vs. 8.3 months; HR, 0.68; $P < 0.0007$) and resulted in a higher RR (57.5% vs. 47.8%) and DoR (12.9 vs. 8.7 months). However, OS with nivolumab and OS with placebo were similar (17.5 vs. 17.2 months). The absence of a survival benefit may be attributable to the high percentage of patients in the CT -alone arm who subsequently received an ICI (27%). In this trial, the effect of CPS status was not addressed.[15]

In 1L ESCC

KEYNOTE-590 is the trial fetching approval of pembrolizumab in metastatic ESCC. This placebo-controlled, double-blind, randomized Phase 3 trial recruited 740 patients, three-fourth of whom had ESCC, and half were Asians. In comparison with placebo, pembrolizumab produced superior OS in patients with a CPS of ≥10% (13.9 vs. 8.8 months; HR, 0.57), in patients with ESCC who had a CPS of ≥10% (13.5 vs. 9.4 months; HR, 0.62), in all patients with ESCC (12.6 vs. 9.8 months; HR, 0.72), and in all patients treated (12.4 vs. 9.8 months; HR, 0.73). Survival benefits were seen in patients with ESCC (HR, 0.72) and EAC (HR, 0.74), but the benefit was smaller in patients with a CPS score of <10% (HR, 0.86) than in patients with a CPS of at least 10% (HR, 0.62). In addition, pembrolizumab improved PFS in all subgroups in comparison with placebo. In pembrolizumab arm, the RR was higher (45.0% vs. 29.3%) and the DoR was significantly longer (8.3 vs. 6.0 months) in all patients treated. On the basis of these results, pembrolizumab is now approved in combination with 1L CT in esophageal and GEJ squamous cell cancer and adenocarcinoma.[16] Further, among all randomized patients, the 24-month OS rate was 28% in the pembrolizumab arm compared with 16% in CT arm. The study showed that there was no significant improvement in OS among some specific subgroups, including patients in non-Asian regions, patients diagnosed with adenocarcinoma, and patients with CPS of <10. However, significant improvement in PFS was found for patients with EAC and patients in non-Asian regions.[17] Although OS was not significantly improved for patients with esophageal adenocarcinoma in the KEYNOTE-590 study, interpretation of subgroup data is not warranted because such analyses would have been limited by the small sample size. The significant effect of pembrolizumab on PFS for EAC found in the KEYNOTE-590 study is supported by data from the CheckMate 649 study, which enrolled patients with

gastric cancer, including a subgroup of patients with EC or EGJC (30% were adenocarcinoma type in CheckMate 649 vs. 26% in KEYNOTE-590). The CheckMate 649 study found that nivolumab plus CT significantly improved OS among all randomized patients.[18]

CheckMate 648, an open-label Phase 3 trial in patients with metastatic ESCC, compared 5-FU/cisplatin CT alone, CT plus nivolumab, and a non-CT regimen of nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg (Nivo/Ipi). This trial, the largest ever conducted in ESCC, treated 970 patients. Half (49%) had a PD-L1 TPS of ≥1%, which defined the primary endpoint analysis population. Among the patients with a TPS of ≥1%, OS with nivolumab plus CT was superior to OS with CT alone (15.4 vs. 9.1 months; HR, 0.54; $P < 0.0001$), and Nivo/Ipi was also superior to CT (13.7 vs. 9.1 months; HR, 0.64; $P = 0.001$). PFS in the group with a TPS of ≥1% was better with CT and nivolumab than with CT alone (HR, 0.65; $P = 0.0032$) but the values were similar in a comparison of CT with Nivo/Ipi (HR, 1.02). RR was also higher in the group with a TPS of ≥1% in a comparison of nivolumab and CT with CT alone (53% vs. 20%) and a comparison of Nivo/Ipi with CT alone (35% vs. 20%). In all patients treated, regardless of TPS, OS with nivolumab plus CT was superior to OS with CT alone (13.2 vs. 10.7 months; HR, 0.74), and OS with Nivo/Ipi was also superior to OS with CT alone (12.8 vs. 10.7 months; HR, 0.78). The DoR was longer in the nivolumab arms, with the longest median DoR observed for Nivo/Ipi (11.8 months in the TPS >1% group and 11.1 months in all patients). In the group with a TPS of <1%, however, no survival superiority over CT was seen for nivolumab plus CT or for Nivo/Ipi (HR, 0.96 and 0.96, respectively); superiority was seen only in the TPS-positive patients. Future regulatory approval is likely for the addition of nivolumab to first-line CT and for the non-CT option of Nivo/Ipi in ESCC.[19]

Another trial in ESCC has been reported from China. ESCORT-1, a double-blind, placebo-controlled, randomized Phase 3 trial of the anti-PD-1 antibody camrelizumab (another anti-PD-1 ICI of Chinese origin), evaluated cisplatin and paclitaxel CT with and without the addition of camrelizumab in 596 patients, of whom 56% were PD-L1 positive (>1%). OS was longer with the addition of camrelizumab to CT than with CT alone (15.3 vs. 12.0 months; HR, 0.70; $P = 0.0010$), as was PFS (6.9 vs. 5.6 months; HR, 0.56; $P < 0.0001$). Survival was superior in both PD-L1-negative (HR, 0.79) and PD-L1-positive patients (HR, 0.59), and the RR was higher with camrelizumab (72.1% vs. 62.1%). The addition of camrelizumab to 1L CT in ESCC will likely be approved in China.[20]

ICIs IN SECOND LINE

In EAC

In the second-line (2L) setting, monotherapy with pembrolizumab was not inferior compared to CT in terms of OS in PD-L1-positive tumors (CPS ≥1). In CPS ≥10 tumors, the pembrolizumab group showed an OS of 17.4 months versus 10.8 months in the CT group.[21] In the CheckMate-032 study, the ORR was higher in PD-L1-positive tumors (27 vs. 12%) in Western patients[22] [Table 2].

In ESCC

There are promising results for the use of anti-PD-1/anti-PD-L1 antibodies in ESCC [Table 2]. The KEYNOTE-181 trial, of pembrolizumab versus investigator's choice CT (paclitaxel, docetaxel, or irinotecan) in the 2L for advanced or metastatic ESCC and EAC, showed that pembrolizumab was superior to CT regarding OS in the CPS ≥10 arm. The 12-month OS rate was 43% in this arm compared to 20% in the control arm.[23] In patients with unresectable advanced or recurrent esophageal cancer (refractory or intolerant to fluoropyrimidine plus platinum), the ATTRACTION-3 study showed a significant improvement in median OS with nivolumab (10.9 months) versus CT (8.4 months) (HR 0.77, $P = 0.019$).[24] Camrelizumab has been approved for the 2L treatment of advanced ESCC in China. In a trial, up to the cutoff point of the ESCORT clinical trial data, the median OS was 8.3 months (95% CI 6.8–9.7) in the camrelizumab group and was 6.2 months (95% CI 5.7–6.9) in the CT group (stratified log-rank $P = 0.001$). The median PFS was 1.9 months (95% CI 1.9–2.4) in the camrelizumab group and was 1.9 months (95% CI 1.9–2.1) for those treated with docetaxel or irinotecan CT [Table 2].[25]

In a recent meta-analysis on ICI in ESCC comprising seven clinical trials encompassing 1733 patients, Gu *et al.* demonstrated that ICIs as 2L or further were associated with an increased chance of the objective RR (relative risk: 1.82, 95% confidence interval: 0.82–4.04; $P = 0.002$) and median OS (HR: 0.75, 95% CI: 0.67–0.85; $P < 0.001$) compared with CT in locally advanced or metastatic ESCC. Moreover, ICI was associated with significant improvement in median OS (HR: 0.61, 95% CI: 0.48–0.77, $P < 0.001$) compared with CT in the PD-L1-positive population. However, ICIs were also effective in all patients independent of PD-L1 expression. The most common Grade ≥3 treatment-related adverse events (TRAEs) were anemia, asthenia, rash, fatigue, anorexia, diarrhea, pneumonia, neutropenia, and vomiting. Patients receiving ICIs had a decreased risk of TRAEs (relative risk: 0.82, 95% CI: 0.62–1.08; $P < 0.001$) and Grade ≥3 TRAEs (RR: 0.50, 95% CI: 0.42–0.60; $P < 0.001$) compared with those undergoing CT.[26]

IO IN SUBSEQUENT LINES

The large Phase 2 expansion cohort of the KEYNOTE-059 trial reported results for pembrolizumab in 259 patients with gastric or EGJ adenocarcinoma. This international

Table 2: Major trials on immune checkpoint inhibitors in≥2L therapy.

Trial (phase)	Cancer type	Number of pts	Treatment arms	PFS (ms)	OS (ms)
KEYNOTE-059 (2)	Gastric/GEJ cancer	259	Pembrolizumab	-	5.6
ATTRACTION-2 (3)	Gastric/GEJ cancer	493	Nivolumab versus placebo	-	5.3 versus 4.1
JAVELIN Gastric 300 (3)	Gastric/GEJ cancer	371	Avelumab versus paclitaxel or irinotecan	1.4 versus 2.7	4.6 versus 5.0
KEYNOTE-061 (3)	Gastric/GEJ cancer	395 (PD-L1+)	Pembrolizumab versus paclitaxel	1.5 versus 4.1	9.1 versus 8.3
KEYNOTE-181 (3)	Esophageal/GEJ adenocarcinoma or squamous cancer	222 (CPS≥10%)	Pembrolizumab versus paclitaxel, docetaxel, or irinotecan	-	9.3 versus 6.7*
ATTRACTION-3 (3)	Esophageal squamous cancer	419	Nivolumab versus paclitaxel or docetaxel	-	10.9 versus 8.4*

*Statistically significant. GEJ: Gastroesophageal junction, m: Months, OS: Overall survival, pts: Patients, PD-L1+: Programmed death-ligand 1 positive, RR: Response rate

multicenter trial enrolled equal proportions of patients with gastric (48.3%) and EGJ cancers (51.4%). Half of the patients had received 2 prior regimens (51.7%), and half had received ≥3 regimens (48.3%). A total of 24.3% were human epidermal growth factor receptor 2 (HER2)positive, 57% had a CPS of at least 1%, and a small minority had MSI-H tumors (4.0% with tissue available for testing). The RR in all patients, which was the primary endpoint, was 11.6%, and it was superior in PD-L1-positive patients (15.5%) versus PD-L1-negative patients (6.4%). In addition, the DoR was superior in PD-L1-positive patients versus PD-L1-negative patients (16.3 vs. 6.9 months). The RR was 57.1% in MSI-H patients. In the KEYNOTE-059 trial, pembrolizumab in the 3L setting (or later) in non-Asian patients showed RR of 12% with a median OS of 5.6 months.[27] The effect of nivolumab monotherapy in esophagogastric cancer refractory to or intolerant of ≥2 previous CT regimens is comparable to that of pembrolizumab, but the impact of PD-L1 expression on efficacy is contradictory. In the ATTRACTION-2 study, nivolumab monotherapy increased the 12-month OS in an Asian collective to 27 versus 11% with placebo (HR0.63, $P < 0.0001$), independently of the PD-L1 status, Lauren classification, and localization of the tumor.[28]

JAVELIN Gastric 300 was a negative trial in patients with previously treated advanced disease. In this open-label Phase 3 trial, 371 patients with previously treated gastric or GEJ adenocarcinoma received avelumab or physician's choice of CT with either paclitaxel or irinotecan. PD-L1 positivity, defined as a TPS of ≥1%, was present in 26.8% of the 317 patients tested. Superiority for OS, the primary endpoint, was not achieved with avelumab (4.6 months) versus CT (5.0 months; HR, 1.1; $P = 0.81$). PFS and the RR favored CT (2.7 months, 4.3%) over avelumab (1.4 months, 2.2%). No difference in survival outcome was observed as a function of PD-L1 status or the CT administered. However, the control arm of this trial received active therapy as compared nivolumab trial and Phase 2 expansion cohort data for pembrolizumab where control arms received placebo or no therapy [Table 2].[29]

IO+CHEMO+HER2

Recent advances, including the inclusion of trastuzumab in the 1L treatment of metastatic HER2-positive disease and the inclusion of ramucirumab in 2L treatment, have now been surpassed by the advent of ICIs.[8] Another trial, leading to regulatory approval of 1L ICI in esophagogastric cancer, was KEYNOTE-811. This randomized, placebo-controlled Phase 3 trial evaluated trastuzumab CT with or without pembrolizumab in HER2-positive esophagogastric cancer. In a planned interim analysis of the first 264 patients treated, most were HER2 positive, with an IHC score of 3+ (79–82%) and a CPS of at least 1% (85–88%). The RR was significantly higher with pembrolizumab (74.4%) than with placebo (51.9%; $P = 0.0001$), as was the complete RR (11% vs. 3%). Based on these interim results, the combination of pembrolizumab with 1L CT in HER2-positive esophagogastric cancer was granted accelerated approval.[30]

FDA APPROVALS

(a) Based on CheckMate 649, the FDA approved on April 16, 2021, nivolumab (Opdivo, Bristol-Myers Squibb Company) in combination with fluoropyrimidine- and platinum-containing CT for 1L treatment of advanced or metastatic gastric cancer, GEJ junction cancer, and esophageal adenocarcinoma.[14]

(b) On March 22, 2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck Sharp, and Dohme Corp.) in combination with platinum- and fluoropyrimidine-based CT for patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1–5 cm above the GEJ junction) carcinoma who are not candidates for surgical resection or definitive chemoradiation. On the basis of the KEYNOTE-590 study, in March 2021, the FDA approved a combined CT and pembrolizumab treatment protocol for primary inoperable or metastatic esophageal and gastroesophageal junction cancers, which is not reliant on PD-L1 expression or histological type.[31]
(c) On June 10, 2020, the Food and Drug Administration approved nivolumab (OPDIVO, Bristol-Myers Squibb Co.) for patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.[32]
(d) On July 30, 2019, the Food and Drug Administration approved pembrolizumab (KEYTRUDA, Merck) for patients with recurrent, locally advanced, or metastatic, ESCC whose tumors express PD-L1 (CPS ≥ 10), as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.[33]
(e) On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck and Co.) for adult and pediatric patients with unresectable or metastatic, MSI-H, or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This is the FDA's first tissue/site-agnostic approval.[34]
(f) On June 16, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck and Co., Inc.) for the treatment of adult and pediatric patients with unresectable or metastatic TMB-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[35]

FUTURE PERSPECTIVES

Looking at the wide applicability of ICIs in EC, their requirement is likely to rise further. More specific, reliable, economical, and easily reproducible biomarkers are needed for cost-effective and safe use of ICIs. In a resource-constrained setting like India, efforts are needed to reduce the cost of these drugs to benefit a maximum number of patients. Based on the results of a study from China, camrelizumab is a cost-effective option compared with docetaxel or irinotecan CT in patients with advanced ESCC as 2L therapy from the perspective of Chinese society. Although the price of nivolumab in China is lower than that in several other countries, camrelizumab still has a 68.35% lower price than nivolumab.[4] A high degree of response that is durable is seen in most patients, and the initially approved indication for the later-line use of these agents in MSI-H esophagogastric cancers will likely be changed to include earlier-line therapy.[4]

CONCLUSION

The incorporation of ICIs in therapeutic landscape of EC has brought a new ray of hope. The three pivotal positive trials have brought the use of ICIs in first-line setting in combination with CT. Nivolumab added to 1L CT in gastric and GEJ adenocarcinoma is now the treatment of choice. Pembrolizumab with 1L CT is new standard therapy in esophageal and GEJ adenocarcinoma and squamous cancer. In addition, in HER2-positive esophagogastric adenocarcinoma, pembrolizumab added to trastuzumab and CT is now the gold standard. The judicious use of ICIs in the light of available biomarkers at various treatment levels may enable an astute oncologist to provide significantly better results to the cancer patients.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

Author Dr. HS Darling is on the Editorial Board of the journal.

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