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REVIEW ARTICLE

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Immunotherapy for gastroesophageal cancer

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ABSTRACT

Cancers of the esophagus, esophageal-gastric junction or stomach are one of the most frequently diagnosed cancers in Europe and in the world. They are characterized by a poor clinical prognosis, hence it is necessary to look for new, more effective methods of their treatment. The dynamic development of immunotherapy based on immune checkpoint inhibitors such as antibodies blocking receptor proteins CTLA-4, PD-1 or ligand for the programmed death receptor 1 (PD-L1) has led to a significant improvement in the effects of treatment of many cancers and initiated a number of studies evaluating the effectiveness and safety of immunotherapy in patients diagnosed with upper gastrointestinal cancer. The following paper presents the results of research that have become the basis for significant changes in the treatment strategy of patients with esophageal cell squamous carcinoma (ESCC), esophageal adenocarcinoma (EAC), adenocarcinoma of the esophagogastric junction (GEJ), gastric cancer, which are also reflected in the recommendations of oncological societies (NCCN, ASCO).

Key words: esophageal cell squamous carcinoma (ESCC), esophageal adenocarcinoma (EAC), adenocarcinoma of the esophagogastric junction (GEJ), gastric cancer, immunotherapy, PD-1, CTLA-4, CPS

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Epidemiology and etiology

Esophageal cancer

Esophageal cancer is the eighth most common cancer in the world and the sixth leading cause of cancer-related death [1]. It is diagnosed more commonly in *males* than females (2 to 8 times in different geographical zones) [2]. From a biological point of view, there are at least two different types of esophageal cancer. Esophageal squamous cell carcinoma (ESCC) is a neoplasm that in terms of molecular abnormalities is similar to squamous cell carcinomas of the head and neck region. Esophageal adenocarcinomas (EAC), as well as the *gastro-esophageal* junction (GEJ) cancer molecularly correspond to one of the 4 subtypes of gastric cancer, i.e. the chromosomal instability subtype. ESCC is the most common cancer worldwide although, in developed countries, the EAC rate is growing dynamically [3]. This is due to changing exposure to risk factors. For ESCC, they include low socio-economic status, consumption of tobacco, alcohol, hot drinks and nitrosamines, as well as deficiencies of vitamins C, E, and folic acid [4]. Risk factors for EAC include Barrett's esophagus, gastroesophageal reflux, obesity, and tobacco consumption [5]. Screening guidelines for the early detection of esophageal cancer have not yet been established, and there is a lack of scientific evidence to support their development. Esophageal cancer has a high mortality rate and poor prognosis. The 5-year survival rates do not exceed 20%, and median overall survival (OS) is about 9 months in ESCC

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patients and 11 months in EAC patients [6]. At diagnosis, distant metastases are found in about 40% of patients, and median OS in this group of patients does not exceed half a year. The results of clinical trials published in recent years have become the basis for a paradigm shift in the treatment of esophageal cancer.

Gastroesophageal junction cancer

In recent decades, the incidence of distal gastric cancer (GC) has decreased in Western countries, while the incidence of GEJ adenocarcinoma has clearly increased [7]. In the United States, the incidence of GEJ cancers has been increasing by 4–10% annually since the 1970s [8]. However, this growing trend should be interpreted with caution due to difficulties in obtaining consistent epidemiological data on the occurrence of GEJ cancer, which results from the heterogeneous definition of this cancer. For many years, GEJ cancers were classified as either esophageal or gastric cancers, or even "indeterminate" according to the World Health Organization's International Classification of Oncological Diseases. Despite this distinction in locations, there are still controversies in its definition, and cancers in this location are sometimes referred to as cancers of the lower esophagus or cardia.

In Asian countries, the definition of GEJ is based on the Nishi classification, according to which the GEJ region is defined as an area 2 cm above and below the Z-line. It includes not only adenocarcinoma but also squamous cell carcinoma. In Western countries, the Siewert classification has been widely used, according to which GEJ cancers are considered to be adenocarcinomas with the epicenter located 5 cm above or below the anatomical cardia [9]. The Siewert classification of GEJ adenocarcinomas includes:

— type I: 1–5 cm above the cardia, adenocarcinoma of the distal esophagus (almost the same as esophageal adenocarcinoma); it usually develops on the basis of intestinal metaplasia (Barrett's esophagus) and infiltrates the *gastroesophageal* junction;
— type II: carcinoma of the cardia, whose center is between 1 cm above and 2 cm below the cardia; develops on the basis of cardia epithelium or intestinal metaplasia;
— type III: 2–5 cm below the cardia; subcardial tumor infiltrating the *gastroesophageal* junction [10].

Barrett's esophageal adenocarcinoma is a cancer that typically corresponds to Siewert type II GEJ cancer.

According to the latest 8th edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastases (TNM) classification, neoplasms infiltrating the *gastroesophageal* junction with the epicenter of the tumor located up to 2 cm below the anatomical cardia are staged and treated as esophageal cancers, while in the case of tumor epicenters located below 2 cm, as gastric cancers [11].

Factors that increase the risk of developing GEJ cancer include gastroesophageal reflux disease (GERD), hiatal hernia, obesity, and smoking [12, 13]. Male sex and age are also considered risk factors for GEJ adenocarcinoma although the incidence of the disease in females and males differs between types according to the Siewert classification (male to female ratio was 10.7 in type I, 4.9 in type II, and 2.2 in type III) [14].

The exact definition of GEJ cancers is not only of epidemiological importance. GEJ cancers have a different biology and prognosis than esophageal and gastric cancers. Differentiation also occurs within GEJ cancers; it is known that Siewert II and III cancers have a better prognosis than Siewert I [15]. GEJ cancers are characterized by high aggressiveness, and due to their localization, rapid systemic spread in both the thoracic and abdominal cavities. The disease is usually diagnosed at an advanced stage.

Gastric cancer

Gastric cancer (GC) is the fifth most common cancer in the world and the third leading cause of cancer-related deaths [16]. Men are affected about 2 times more often than women.

Gastric cancer-related morbidity and mortality vary widely by geographic region, but there has been a reduction in incidence worldwide over the last 50 years. These changes are attributed to the increased availability of fresh fruit and vegetables and the reduction in the consumption of pickled vegetables and smoked meat [17]. As many as 90% of GC cases (excluding cardia) can be attributed to *Helicobacter pylori* infections. While advances in the prevention and treatment of *H. pylori* infection have reduced the overall incidence of GC, they have also contributed to an increase in the incidence of cardia carcinoma (approximately a 7-fold increase in recent decades) [18].

A better understanding of the etiology and risk factors may help to reach a consensus on the approach to *H. pylori* infection. Dietary modification, smoking cessation, reducing alcohol consumption, and exercise currently appear to be the most effective ways to prevent GC. Some countries (e.g. Japan, South Korea, Chile, and Venezuela) have introduced population screening programs. Such programs mainly include radiological examinations with contrast and endoscopy [19]. Attempts are also made to determine the pepsinogen serum level or serological tests for *H. pylori*, but this is a subject of controversy, and there is no evidence of the effectiveness of such methods.

People with a family history of GC or patients with invasive lobular breast cancer diagnosed before the age of 50 are recommended to undergo genetic testing for mutations in the *CDH1* gene, encoding E-cadherin, which significantly increases the risk of GC [20].

There are even suggestions that carriers of mutations in the *CDH1* gene should be referred for prophylactic gastrectomy. Lynch syndrome is also associated with increased risk of GC [21].

Determination of PD-L1 expression

Immune checkpoint proteins, especially programmed death-ligand 1 (PD-L1) and programmed death receptor-1 (PD-1), play a key role in regulating the intensity and duration of the immune response, preventing the development of autoimmunity. These proteins also play an important role in the evasion of the anticancer immune response by cancer cells [22]. The interaction of PD-L1 (on the tumor cell) and PD-1 (on the surface of cytotoxic T cells) leads to suppression of T cells. Excessive expression of PD-L1, observed in progression of many cancers, allows escape from immune surveillance. PD-1 or PD-L1 inhibitors can specifically block the interaction of PD-1 and PD-L1 and thereby enhance the host's antitumor immune response and inhibit tumor growth.

PD-L1 expression on tumor cells or antigen-presenting cells is a potential predictor of response to immunotherapy. This expression can be recognized and measured by various available diagnostic techniques, e.g. enzyme-linked immunosorbent assay (PD-L1-ELISA), western blot, and next-generation sequencing (NGS) [23]. Currently, a widely used, practical and economical approach is the determination of PD-L1 expression in the tumor by immunohistochemistry (IHC) [24].

In the pivotal studies with PD-1 or PD-L1 inhibitors, specific drugs were combined with dedicated diagnostic tests, assessing PD-L1 expression on cancer cells, immune cells in the tumor stroma, or both. Several IHC assays are currently available to determine PD-L1 expression. Most of them have been developed as companion diagnostic tests for treatment in clinical trials. The assays use unique antibodies (22C3, 28-8, SP263, SP142) and staining platforms (Dako and Ventana), as well as different scoring methods and different clinical thresholds to determine PD-L1 positive expression [25]. Due to this variability, as well as the high variability of PD-L1 expression in different tumors, some controversy regarding the predictive value of the PD-L1 assay has arisen. In some cancers, a high inter-assay agreement has been shown, which could suggest that they can be used interchangeably, but this is currently not widely recommended. The development of a homogeneous, clinically significant, and reproducible method of PD-L1 assessment is crucial for identifying patients for treatment with PD-1/PD-L1 inhibitors, as it can significantly reduce the cost of diagnosis and shorten turnaround time [26, 27].

Tumor cells that show membrane staining of any intensity are considered PD-L1-positive. In tumor-associated immune cells, both membrane and cytoplasmic staining are considered positive [28].

In studies of patients with non-small cell lung cancer (NSCLC), the IHC 22C3 test was used to calculate the percentage of stained tumor cells (TPS, tumor proportion score) [29]. Tumor-infiltrating immunocompetent cells were not included in these assays. The TPS is calculated based on the number of PD-L1-positive tumor cells divided by the total number of all viable tumor cells multiplied by 100. Determining PD-L1 expression on tumor cells is also referred to as the tumor cell (TC) index, which also means the percentage of PD-L1-positive tumor cells related to all viable tumor cells on the slide [30].

In subsequent studies, in patients with GC and other cancers, TPS/TC turned out to be less effective in identifying treatment responders. Moreover, PD-L1 staining on both tumor cells and stromal immunocompetent cells has been shown to correlate better with treatment response in some cancers. Therefore, a method was developed to assess the expression of PD-L1 on both cell types in one area. This method of assessment was called a combined positive score (CPS) and allows the quantification of cancer and immune cells in one assessment [31]. The total positivity is calculated by the number of PD-L1-positive cells, including cancer cells, lymphocytes, and macrophages divided by the total number of viable cancer cells multiplied by 100. Thus, for the CPS, a score greater than 100 can be obtained.

The third method evaluates PD-L1 expression only in tumor-infiltrating immune cells (IC) — lymphocytes, macrophages, granulocytes, dendritic cells, or plasma cells, as a percentage of the tumor area with PD-L1 positive cells of any intensity. The latter assessment method is not used in the diagnosis of patients with gastrointestinal cancers. The described differences are presented graphically in Figures 1 and 2 [32, 33].

Immunotherapy in the treatment of patients with esophageal, gastroesophageal junction, and gastric cancer

Historically, advanced esophageal and gastric cancers were treated in the same way. For this reason, a diverse population of patients diagnosed with ESCC, EAC, GEJ, and GC was included in clinical trials with immunotherapy. The analysis of the results of these studies is difficult and makes the overall picture of immunological treatment seem extremely complicated. For this reason, it is also not possible to discuss the results of clinical trials for esophageal and gastric cancer immunotherapy

separately. In order to systematize the topic, clinical trials concerning mainly ESCC will be discussed separately. Clinical trials relating to GC but also trials that recruited patients with EAC and GEJ will be described separately.

Immunotherapy in the treatment of esophageal cancer

The CheckMate 648 study included 970 previously untreated patients with locally advanced, recurrent, or metastatic ESCC. Patients, regardless of PD-L1 expression, were randomly assigned to those treatment groups: nivolumab (240 mg every 2 weeks) with chemotherapy (cisplatin 80 mg/m^2 day 1, 5-fluorouracil 800 mg/m^2 day 1–5); nivolumab (3 mg/kg bw every 2 weeks) with ipilimumab (1 mg/kg bw every 6 weeks), or chemotherapy alone in the above scheme. In 49% of patients, PD-L1 expression on cancer cells was ≥ 1% [34].

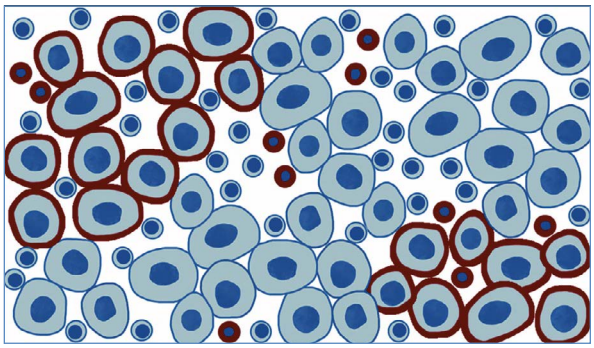

Figure 1. Schematic determination of PD-L1 (*programmed death-ligand* 1) expression on tumor cells (large cells with membrane staining) and tumor-infiltrating immunocompetent cells (small cells with membrane and cytoplasmic staining) [32]

The combination of nivolumab with chemotherapy significantly prolonged median overall survival (OS) compared to chemotherapy alone (13.2 *vs.* 10.7 months) and reduced the risk of death [hazard ratio (HR) = 0.74; 95% confidence interval (CI) 0.58–0.96] in the entire study population. The greatest benefit was achieved in the subgroup of patients with PD-L1 expression ≥ 1% (15.4 *vs.* 9.1 months, respectively, HR = 0.54; 95% CI 0.37–0.80). The use of nivolumab combined with ipilimumab compared to chemotherapy also resulted in significantly longer median OS (12.7 *vs.* 10.7 months) and a reduced risk of death (HR = 0.78; 95% CI 0.62–0.98) in the total population and in the subgroup with PD-L1 expression ≥ 1% (13.7 *vs.* 9.1 months, respectively; HR = 0.64; 95% CI 0.46–0.90). At the same time, immunotherapy alone was associated with a higher risk of primary treatment resistance, early progression, and death [35]. The objective response rate (ORR) was highest in the nivolumab plus chemotherapy subgroup compared to combination immunotherapy and chemotherapy alone (53%, 35%, and 20%, respectively). There was no benefit from immunotherapy in terms of PFS and OS in patients without PD-L1 expression. A retrospective analysis of treatment results based on the CPS index was also performed. The majority of patients (824 of 906) had a CPS ≥ 1. The best results were achieved in the CPS ≥ 10 subgroup. Grade 3 and 4 adverse events were more common in the nivolumab/chemotherapy group compared to chemotherapy and combination immunotherapy (47% *vs.* 36% *vs.* 32%, respectively)

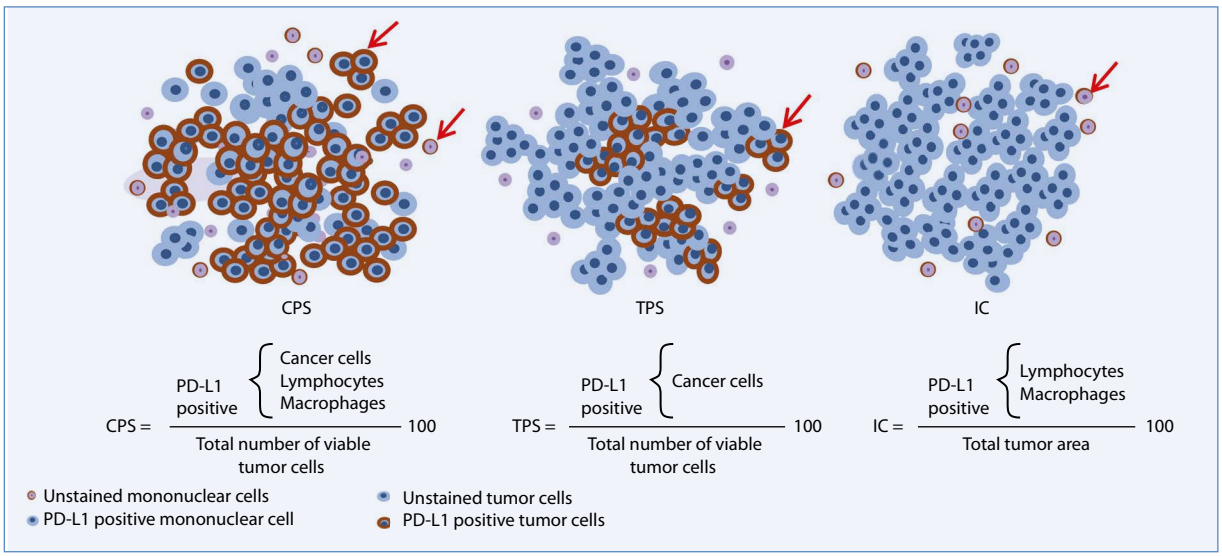

Figure 2. Methods of calculating programmed death-ligand 1 (PD-L1) expression indices — cumulative positive CPS, percentage of stained tumor cells (TPS) and tumor-infiltrating immune cells (IC) [33]; CPS — combined positive score; TPS — tumor proportion score (percentage of stained tumor cells); IC — immune cells (tumor-infiltrating immune cells)

and also were more likely to lead to treatment discontinuation (34% *vs.* 19% *vs.* 8%, respectively). This may be related to the fact that the duration of treatment with nivolumab and chemotherapy was the longest (5.7 *vs.* 3.4 *vs.* 2.8 months, respectively). Based on this study, two combination therapies — nivolumab in combination with ipilimumab and nivolumab in combination with fluoropyrimidine and platinum-based chemotherapy — have been approved by the European Medicines Agency (EMA) for the first-line treatment of patients with advanced, inoperable, relapsed or metastatic ESCC with tumor PD-L1 expression ≥ 1%. It should be mentioned that the US Food and Drug Administration (FDA) registered nivolumab in combination with ipilimumab or chemotherapy for the above-mentioned group of patients, regardless of PD-L1 expression.

Based on the KEYNOTE-590 study, pembrolizumab was registered in the treatment of esophageal cancer [36]. It included 749 previously untreated patients with locally advanced, recurrent, or metastatic esophageal cancer or GEJ (Siewert type 1), with a predominance of ESCC patients (73%). Patients were enrolled regardless of PD-L1 expression and randomly assigned to treatment with pembrolizumab (200 mg every 3 weeks for up to 2 years) with chemotherapy (cis-platinum 80 mg/m^2 day 1, 5-fluorouracil 800 mg/m^2 day 1–5 to 6 cycles) or chemotherapy alone. In 51% of patients, PD-L1 expression in tumor according to the CPS was ≥ 10. The CPS index was not a stratifying factor, however, subgroup analysis based on a CPS ≥ 10 was included in the statistical analysis.

The addition of immunotherapy significantly improved survival rates compared to chemotherapy alone with prolongation of median OS (from 9.8 to 12.4 months, HR = 0.73; 95% CI 0.62–0.83) and PFS (from 5.8 to 6.3 months, HR = 0.65, 95% CI 0.55–0.76). There was also an increase in the ORR (from 29 to 45%). The extension of median OS was driven mainly by ESCC patients (median OS 12.6 *vs.* 9.8 months, HR = 0.73; 95% CI 0.61–0.88), with the greatest benefit in patients with a CPS ≥ 10% (median OS 13.9 *vs.* 8.8 months, HR = 0.57; 95% CI 0.43–0.75). A smaller but significant gain was observed in all patients with a CPS ≥ 10%, regardless of histological type (median OS 13.5 *vs.* 9.4 months, HR = 0.64; 95% CI 0.51–0.80). The benefit of adding immunotherapy was not demonstrated in subgroups of patients with adenocarcinoma (HR = 0.74; 95% CI 0.54–1.02), ESCC with the CPS < 10 (HR = 0.99; 95% CI 0.74 –1.32), and all patients with CPS < 10 (HR = 0.86; 95% CI 0.68–1.10). The incidence of grade 3 and 4 adverse events was similar in both arms (86% in the study arm and 83% in the control arm).

Based on this study, pembrolizumab in combination with platinum-fluoropyrimidine-based chemotherapy has been approved by the EMA and is indicated for the first-line treatment of patients with unresectable or metastatic locally advanced esophageal cancer or human epidermal growth factor receptor 2 (HER-2) negative adenocarcinoma of the gastroesophageal junction, with a CPS ≥ 10. The FDA registered pembrolizumab in combination with chemotherapy for the above-mentioned group of patients, regardless of the CPS.

The effectiveness of immunotherapy in combination with chemotherapy in the first-line palliative treatment of ESCC patients has been confirmed by subsequent clinical trials using other anti-PD-1 molecules. The results of studies with camrelizumab, tislelizumab, sintilimab, and toripalimab in the Asian population were comparable to the results of previously presented studies [37–40]. The effectiveness of combining immunotherapy with platinum and paclitaxel-based chemotherapy has also been confirmed. The results of treatment effectiveness analyses depending on PD-L1 expression prevented unambiguous interpretation.

Immunotherapy can also be used at a later stage of palliative treatment. The phase III KEYNOTE-181 study was conducted in a group of 628 patients with locally advanced, inoperable, or metastatic ESCC (64%), EAC, and GEJ cancers (Siewert type I) regardless of PD-L1 expression (35% of patients had a CPS ≥ 10) with progression after first-line treatment. Patients were randomly assigned to treatment with pembrolizumab (200 mg every 3 weeks for up to 2 years) or single-agent chemotherapy (irinotecan, paclitaxel, or docetaxel) [41]. The result of the study was negative — no advantage of immunotherapy over chemotherapy in terms of OS in the general population was demonstrated. However, median OS was prolonged in an unplanned and retrospective subgroup analysis of ESCC patients with a CPS ≥ 10 (9.3 *vs.* 6.7 months in the chemotherapy group, HR = 0.64; 95% CI 0.46–0.90) with an over 2-fold increase of the 12-month survival rate (43% *vs.* 20%, respectively). The superiority of pembrolizumab was not demonstrated in the subgroup of patients with adenocarcinoma and ESCC with a CPS < 10. Fewer severe adverse events were observed in patients treated with pembrolizumab — 18% *vs.* 41%.

Pembrolizumab has not been registered by the EMA, while the FDA has registered the drug for the second and subsequent treatment lines in patients with advanced or metastatic ESCC with PD-L1 expression (CPS ≥ 10). According to the recommendations of the European Society for Medical Oncology (ESMO), pembrolizumab may be an option in this subgroup of patients if they have not previously received immunotherapy.

In the phase III ATTRACTION-3 study, treatment with nivolumab (240 mg every 2 weeks) was compared with single-agent chemotherapy (docetaxel or paclitaxel) in patients with locally advanced unresectable or metastatic ESCC with progression after at least one treatment line with platinum and fluoropyrimidine. The patients were qualified regardless of PD-L1 expression

(≥ 1% in about half of the patients) [42]. The use of nivolumab was associated with prolonged median OS compared to chemotherapy (10.9 *vs.* 8.4 months, HR = 0.77; 95% CI 0.62–0.96), almost doubling the 3-year survival rate — 15.3% *vs.* 8.7%, and a lower incidence of serious adverse events – 18% *vs.* 63%. PD-L1 expression had no impact on the effectiveness of immunotherapy, and the analysis of the CPS was not presented [43].

Based on these results, nivolumab in monotherapy was registered by the EMA and the FDA for the treatment of patients with advanced unresectable, recurrent, or metastatic ESCC after previous combination chemotherapy based on fluoropyrimidines and platinum.

The first positive results regarding the radical treatment of this disease have also been published, and further prospective clinical trials are ongoing. The result of the CheckMate 577 study showed the effectiveness of nivolumab in the adjuvant treatment of patients with esophageal cancer with residual disease after previous radiochemotherapy [44]. The study included 794 patients with esophageal (60%) or GEJ (40%) cancer; 30% were patients with squamous cell carcinoma. Patients were randomized to treatment with nivolumab (240 mg every 2 weeks for 1 year) or placebo. The primary endpoint of the study was disease-free survival (DFS). The use of nivolumab resulted in a doubling of median DFS (22.4 *vs.* 11 months, HR = 0.69; 95% CI 0.56–0.86). Only 9% of patients did not complete the one-year treatment with immunotherapy due to adverse events. The treatment benefit was independent of histopathology type, tumor location, and PD-L1 expression. Due to the too-short follow-up period and the required number of events not being met, data on OS are missing.

Both the EMA and the FDA have registered nivolumab for the adjuvant treatment in patients with esophageal or gastroesophageal junction cancer, with residual disease, after previous neoadjuvant radiochemotherapy and surgery. A study using immunotherapy after radical radiochemotherapy in patients with squamous cell esophageal cancer is ongoing (KEYNOTE-975, NCT04210115).

Immunotherapy in the treatment of patients with advanced gastric cancer

The clinical effect and safety of nivolumab in the first-line treatment of patients with advanced adenocarcinoma of the upper gastrointestinal tract (GC 69%, GEJ 18%, and EAC 12%) were assessed in the three-arm CheckMate 649 study involving 2031 patients randomly assigned to nivolumab in combination with FOLFOX/XELOX chemotherapy, chemotherapy, or combined immunotherapy with nivolumab and ipilimumab [45]. HER2 overexpression was an exclusion criterion. Patients were eligible for the study regardless of PD-L1 expression, which was the stratifying factor (PD-L1 ≥ 1% *vs*. PD-L1 < 1%). The endpoints included PFS and OS in the subgroup of patients with CPS ≥ 5 (60% of the total study population). The study was positive for both endpoints. The addition of nivolumab to chemotherapy in patients with a CPS ≥ 5 was associated with an increase in median PFS from 6 to 7.7 months (HR = 0.68; 95% CI 0.56–0.81) and median OS from 11.1 to 14 .4 months (HR = 0.70; 95% CI 0.61–0.81). This translated into an increase in the 2-year survival rate from 19% to 31%. In the total patient population, median OS was prolonged from 11.6 to 13.8 months (HR = 0.79; 95% CI 0.71–0.88). However, an unplanned subgroup analysis showed no benefit of adding immunotherapy in the subgroup with a CPS < 5 (median OS 12.4 *vs.* 12.3 months; HR = 0.94; 95% CI 0.79–1.11) and a CPS <10 (median OS 12.4 *vs.* 12.5 months; HR = 0.91; 95% CI 0.78–1.06). Treatment with immunotherapy alone, compared to chemotherapy, did not increase median OS in the total study population or in the subgroup with a CPS ≥ 5. The safety profile of the therapies used did not differ significantly from those known from previous studies. Treatment-related grade 3 or 4 adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) occurred in 60% of patients treated with nivolumab in combination with chemotherapy, 45% of patients receiving chemotherapy alone, and 38% of patients treated with immunotherapy alone, and the treatment discontinuation rate due to AEs was 38%, 26%, and 22%, respectively [46]. Based on this study, the EMA registered nivolumab in combination with chemotherapy based on fluoropyrimidines and platinum derivatives for the first-line treatment in patients with HER-2 negative, advanced or metastatic EAC, GEJ cancer or GC with PD-L1 expression CPS ≥ 5. The FDA approved nivolumab for the same indication regardless of PD-L1 expression.

The effectiveness of the combination of CAPOX/SOX chemotherapy with nivolumab was also assessed in the ATTRACTION-4 study with Asian patients diagnosed with unresectable, advanced, or recurrent, HER2--negative GC, or GEJ cancer [47]. The use of chemoimmunotherapy compared to chemotherapy alone led to an increase in median PFS (10.4 *vs.* 8.3 months; HR = 0.68; 95% CI 0.51–0.90), with no impact on OS. Positive PD-L1 expression was not an inclusion criterion. PD-L1 expression was assessed only on tumor cells, and the TPS did not influence the obtained results. The analysis based on the CPS was not included in the statistical plan of the study. This may suggest that in adenocarcinomas of the upper gastrointestinal tract, the TPS/TC index is less effective than the CPS in identifying patients responding to treatment.

The effect of pembrolizumab in the first-line treatment of patients with advanced GEJ cancer or GC was also evaluated in the KEYNOTE-062 study, in which 763 patients with a CPS ≥ 1 were randomized to pembrolizumab in monotherapy, in combination with

chemotherapy (cisplatin + 5Fu/capecitabine), or chemotherapy alone [48]. The primary endpoint was OS and PFS in patients with a CPS ≥ 1 or a CPS ≥ 10. The use of pembrolizumab alone resulted in comparable median OS in patients with a CPS ≥ 1 (10.6 *vs.* 11.1 months) compared to chemotherapy alone (10.6 *vs.* 11.1 months; HR = 0.91; 95% CI 0.74–1.10) and longer median OS in patients with a CPS ≥ 10 (37% of the total population) (17.4 *vs.* 10.8 months, respectively; HR = 0.69; 95% CI 0.49–0.97). These relations were not analyzed for statistical significance, as the study plan assumed a prior positive effect of chemoimmunotherapy, which was not achieved. The combination of pembrolizumab with chemotherapy compared to chemotherapy alone did not improve median OS in patients with a CPS ≥ 1 (12.5 *vs.* 11.1 months; HR = 0.85; 95% CI 0.70–1.03) nor with a CPS ≥ 10 (12.3 *vs.* 10.8 months; HR = 0.85; 95% CI 0.62–1.17). Interpretation of the results of this study is difficult in the context of the positive result of the CheckMate 649 study, which was conducted in a similar population. The differences may be the result of several factors, including the use of different chemotherapy regimens in these studies, a higher percentage of patients receiving second-line immunotherapy in the KEYNOTE-062 study, and finally, a high percentage of patients with a CPS ≥ 5 (60%) and a CPS ≥ 10 (48.5%) in the CheckMate 649 population compared to the patients with a CPS ≥ 10 in KEYNOTE-062 population (37%). This may indicate some kind of favorable sample selection in the CheckMate 649 study, as the assumptions of the statistical plan of the study based on analyses of similar populations assumed that the percentage (CPS ≥ 5) would be approximately 35%. Finally, the number of patients in the CheckMate 649 study was almost 3-fold higher compared to the KEYNOTE-062 study, which affected the statistical power and allowed the authors to show even small differences in the treatment effect.

Unlike anti-PD1 antibodies, the effectiveness of antibodies directed against the ligand of PD-1 in the treatment of gastric cancer has not been confirmed. In the Javelin Gastric 100 study, maintenance treatment with avelumab after first-line chemotherapy in patients with advanced, inoperable, HER-2 negative GEJ cancer or GC was evaluated [49]. No OS benefit was demonstrated (median OS was 10.4 months for avelumab and 10.9 months for chemotherapy alone) although the 24-month survival rate was higher in the avelumab group (22.1% *vs.* 15.5%). Avelumab used in the third treatment line (Javelin Gastric 300) was also not more effective than chemotherapy of the investigator's choice [50].

Pembrolizumab and nivolumab were also evaluated in subsequent treatment lines. The KEYNOTE-061 study compared pembrolizumab and paclitaxel in patients (n = 395) with advanced GEJ adenocarcinoma and GC, with PD-L1 expression CPS ≥ 1, with disease progression after first-line treatment based on a combination of platinum and fluoropyrimidine [51]. The primary endpoint was overall survival and progression-free survival in PD-L1-positive patients (CPS ≥ 1). The use of pembrolizumab in the subsequent treatment line compared to paclitaxel was associated with a similar ORR (16 *vs.* 14%), significantly shorter median PFS (1.5 *vs.* 4.1 months, respectively; HR = 1.27; 95% CI 1.03–1.57), and no effect on median OS (9.1 *vs.* 8.3 months, respectively; HR = 0.82; 95% CI 0.66–1.03). Post-hoc analyses after 24 months of follow-up showed a significantly longer duration of response in the pembrolizumab arm (19.1 *vs.* 5.2 months for paclitaxel) and a doubling of the 2-year survival rate (19.9% *vs.* 8.5%). The results of the retrospective analysis showed that the greatest clinical benefit was achieved in the subgroups of patients with a CPS ≥ 5 and a CPS ≥ 10. The results of this study did not change clinical practice.

Nivolumab used in the third and subsequent treatment lines in patients with unresectable, recurrent GEJ cancer or GC turned out to be more effective than placebo [52]. In the ATTRACTION-2 randomized study in an Asian population, the ORR was reported only in patients treated with nivolumab (11.2%). The median duration of response was relatively long (9.53 months), resulting in a slight prolongation of median OS compared to placebo (5.26 *vs.* 4.14 months, respectively; HR = 0.63; 95% CI 0.51–0.78). Similar results were obtained with pembrolizumab used in subsequent lines. In the one-arm KEYNOTE-059 study with 259 patients, the ORR was 11.6% with a median duration of response of 8.4 months, with better outcomes in PD-L1 positive patients (15.5% and 16.3 months, respectively) [53].

It is difficult to draw solid conclusions from the results of these two studies. The use of placebo in the control group (ATTRACTION-2) or the lack of a control group (KEYNOTE-059) raises the question of whether immunotherapy would be more effective than classic cytotoxic drugs in this clinical situation. ESMO guidelines do not recommend the use of immunotherapy in subsequent treatment lines in unselected populations.

Microsatellite instability (MSI), a phenotypic reflection of mismatch repair deficiency (dMMR), is found in approximately 10% of gastric cancer patients. dMMR/MSI cancer is found more often in patients with stages I and II and the elderly. In the group of patients over 85 years of age, dMMR/MSI can account for 48% of cases [54–57]. In advanced disease, the percentage of dMMR/MSI tumors is estimated at 3–7%. Retrospective analyses of the previously described clinical trials have shown that this selected group may benefit incomparably more from the use of immunotherapy [54]. In the KEYNOTE-062 study, dMMR/MSI patients (7.3% of the total population) treated with pembrolizumab had a 2-fold higher ORR of 65% compared to 37% in patients treated with chemotherapy alone.

The median duration of response was 21.2 months in this subgroup and median OS was not reached. The 2-year survival rate was 71% for pembrolizumab, 65% for the combination of pembrolizumab with chemotherapy, and 26% for chemotherapy alone [54]. These data suggest that in dMMR/MSI patients, there is no benefit from adding chemotherapy to immune therapy.

In the CheckMate 649 study, despite the disappointing results of treatment with immunotherapy alone (nivolumab with ipilimumab), dMMR/MSI patients (3% of the total population) seem to benefit the most from this therapy. Combination immunotherapy was associated with an ORR of 70% compared with 55% for chemoimmunotherapy. Median OS for the combination of nivolumab and ipilimumab was not reached (HR = 0.28; 95% CI 0.08–0.92) while for the combination of chemotherapy and nivolumab it was 38.7 months and for chemotherapy alone 12.3 months (HR = 0.38; 95% CI 0.17–0.84). The benefit was observed regardless of the CPS value [45].

Immunotherapy in patients with dMMR/MSI GEJ cancer and GC is also active in further treatment lines. The ORR for pembrolizumab was 46% (*vs.* 16% for chemotherapy) in the KEYNOTE-061 study (5.3% of dMMR/MSI patients), and 57.1% in the KEYNOTE-059 study (4% of dMMR/MSI patients). Median PFS and OS in dMMR/MSI patients treated with pembrolizumab were not reached in both studies, and the 12-month survival rates were 71% and 73%, respectively [54]. Pembrolizumab immunotherapy has been registered by the EMA for the treatment of patients with unresectable or metastatic dMMR/MSI GC after failure of at least one treatment line. Treatment with immunotherapy without chemotherapy in patients with dMMR/MSI gastric cancer has not yet been registered as the first-line treatment and is not recommended.

The value of immunotherapy in the earlier stages of MSI/dMMR GC was demonstrated in a phase II study, in which a 12-week neoadjuvant treatment with nivolumab and ipilimumab resulted in pathomorphological complete response in 58.6% of operated patients [55].

New therapeutic options based on combining immune checkpoint inhibitors with targeted therapy

The positive effects of using trastuzumab in the treatment of patients with advanced GC with HER2 overexpression became the basis for the concept of combining anti-HER2 therapy with immunotherapy and chemotherapy. In the KEYNOTE-811 study, a triple combination of trastuzumab with chemotherapy and pembrolizumab/placebo was evaluated. The first interim analyses show a higher ORR (74.4% in the pembrolizumab arm *vs.* 51.9% in the placebo arm), complete remission rate (11.3% *vs.* 3.1%, respectively), and disease control rate (95% *vs.* 89.3%) [58, 59].

The INTEGA study evaluates the effect of combining trastuzumab with nivolumab and ipilimumab in relation to nivolumab combined with trastuzumab and FOLFOX chemotherapy in patients with HER2-positive, advanced GEJ adenocarcinoma and GC [60]. Preliminary data suggest a prolongation of median PFS and OS with chemotherapy compared to the combination of immunotherapy and anti-HER2 treatment (median PFS 10.7 *vs.* 3.2 months, median OS 21.8 *vs.* 16.4 months) [61]. The ongoing (enrollment phase) DESTINY-GASTRIC 03 study is evaluating the role of trastuzumab deruxtecan in patients progressing on trastuzumab (Part 1) or previously untreated with anti-HER2 therapy (Part 2). An interesting concept is also the combination of immune checkpoint inhibitors with ramucirumab, which blocks *Vascular endothelial growth factor receptor 2* (VEGFR2). The effect of such a combination is increasing the expression of PD-L1, increasing the infiltration of the tumor microenvironment by CD8+ T cells, and inhibiting the function of regulatory T lymphocytes responsible for immunosuppressive phenotype [62]. The clinical effect and safety of the combination of ramucirumab and pembrolizumab in the first-line treatment of patients with advanced GEJ adenocarcinoma or GC was assessed in the JVDF study [63]. The primary endpoint was the safety of combination therapy and the secondary endpoints were PFS, OS, and ORR. Median OS in the population of 28 patients included in the study was 14.6 months and was longer in the group of patients expressing PD-L1 (17.3 months in PD-L1 positive patients *vs.* 11.3 months in PD-L1 negative patients). A similar relationship also concerned PFS, whose median in the general population was 5.6 months (8.6 months in PD-L1 positive patients *vs.* 4.3 months in PD-L1 negative patients). Treatment-related grade 3 adverse events according to the CTCAE were reported in 18 patients, with hypertension (14%) and transaminase elevation (11%) being the most common. Importantly, none of the patients had CTCAE grade 4 or 5 complications.

Conclusions

Immunotherapy has significantly changed the treatment strategy for patients with ESCC, EAC, GEJ cancer, and GC. This was reflected in the international expert recommendations of the ESMO and National Comprehensive Cancer Network (NCCN). The number of presented studies and their results show how complicated this topic is and how many aspects still need to be explained. Figures 3 and 4 present the up-to-date knowledge regarding first-line and subsequent-line

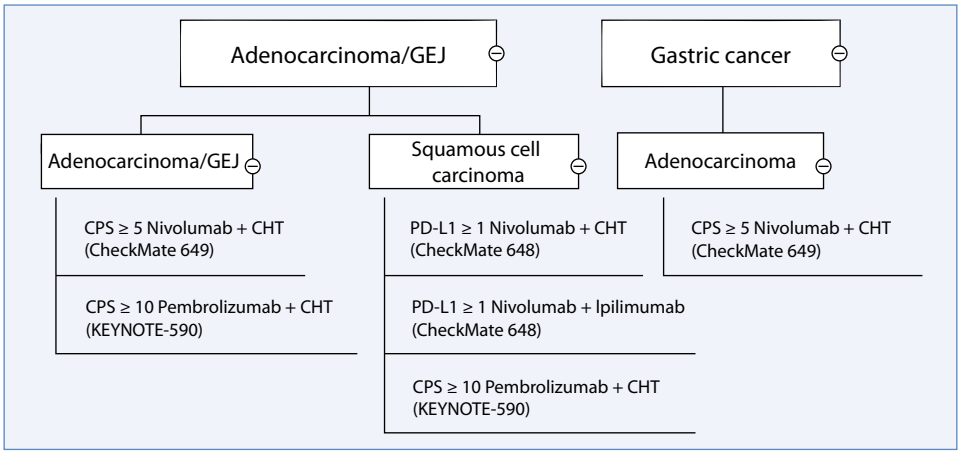

Figure 3. Immunotherapy of esophageal and gastric cancer — the first line of systemic treatment; GEJ — gastroesophageal junction; CPS — combined positive score; CHT — chemotherapy; PD-L1 — programmed death-ligand 1

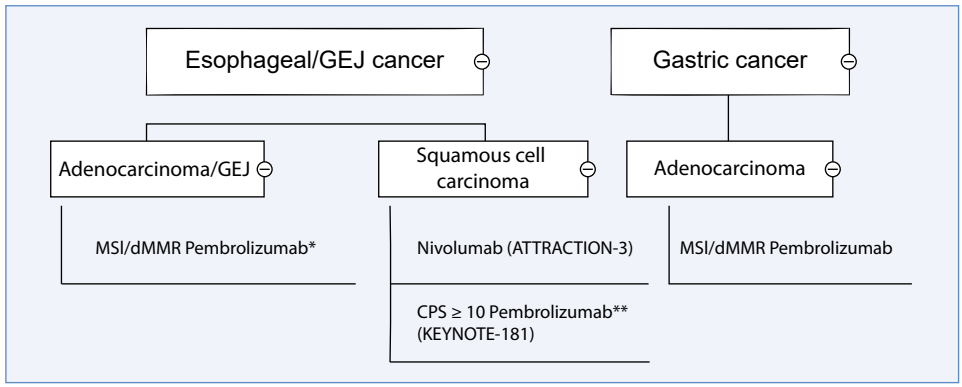

Figure 4. Immunotherapy of esophageal and gastric cancer — the second and subsequent lines of systemic treatment; *No EMA registration, recommended by ESMO; **No EMA registration, recommended by ESMO as an option; GEJ — gastroesophageal junction; MSI — microsatellite instability; dMMR — mismatch repair deficient; CPS — combined positive score.

treatments with immunotherapy of advanced esophageal and gastric cancer based on EMA registered indications and ESMO recommendations. Many interesting studies are still ongoing, which may lead to further changes in the guidelines.

Conflict of interest

M.G.: received remuneration from Merck, Amgen, BMS, MSD, and Servier, unrelated to the article.

B.R.: received remuneration from Merck, Amgen, BMS, MSD, and Servier, unrelated to the article.

M.K., W.R.: declare no conflict of interest.

T.K.: received honoraria from Roche, MSD, and BMS, unrelated to the article.

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