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Immunotherapeutics and other anticancer agents in the management of advanced gastric cancer

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Advanced gastric cancer (AGC) is characterized by high mortality. The survival is estimated as 14.2 months. The treatment of choice in the early stages of GC is surgery. Due to high potential of malignancy, postoperative chemotherapy is usually administered. Novel methods of treatment involve immunotherapeutic agents (IA). The new therapies seem to be a hopeful perspective for patients with advanced GC. In this review, we present the outcomes of clinical trials in GC treatment with IA and their mechanisms of action. Furthermore, we present the benefits and shortcomings of immunotherapy and describe potential directions for future research.

Key words: advanced gastric cancer, immunotherapeutic agents, monoclonal antibodies, immune checkpoint inhibitors

Introduction

Gastric cancer (GC) is the fifth most common diagnosed malignancy with 1.1 million new cases in 2020 [1]. A surgical procedure is a crucial part of the treatment [2]. Adjuvant chemotherapy is usually administered postoperatively. Advanced gastric cancer (AGC), defined by extensive infiltration of adjacent tissue or metastasis, has a poor prognosis. Currently, chemotherapy plays a key role in AGC management. The median overall survival of AGC is estimated as 14.2 months [3]. Due to the low effectiveness of chemotherapy, immunotherapy is considered as a promising, novel part of AGC treatment. The aim of this paper is to report outcomes of several clinical trials in phase I, II, and III. We have made an attempt to present the mechanisms of action of various IA and provide valuable insights into the clinical implementation of these state-of-the art treatment agents.

Strategy for advanced gastric cancer treatment

For the first line treatment, it is recommended to use a platin agent (e.g. cisplatin) and fluoropyrimidine (e.g. 5-fluorouracil) in human epidermal growth factor receptor 2 (HER2) negative tumor. Cisplatin and oxaliplatin share similar efficacy. However, they differ in terms of adverse events (AE). Cisplatin treatment is associated with renal dysfunction and thromboembolic complications while oxaliplatin may cause neuropathy and diarrhea [4]. In HER2-positive cancer, trastuzumab is added to standard chemotherapy. Trastuzumab is an anti-HER2 monoclonal antibody. It was proven that combined therapy increases overall survival compared to chemotherapy alone in the ToGa trial [5]. In the second line treatment ramucirumab – an anti-vascular endothelial growth factor (VEGFR) monoclonal antibody may be administered. [6]. Third line treatment may be considered in progression of the disease despite prior therapy. Figure 1

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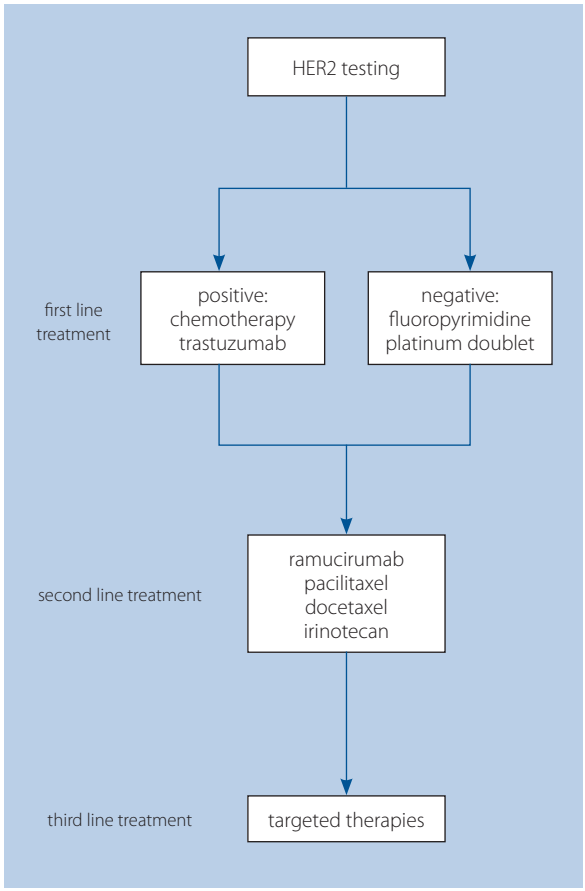
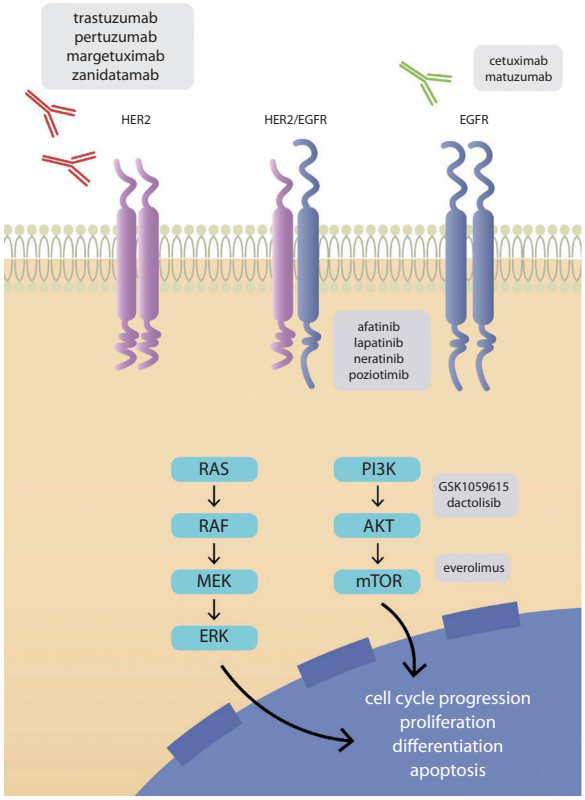


Figure 1. Treatment strategy for advanced gastric cancer according to the National Comprehensive Cancer Network (NCCN)



HER2 – human epidermal growth factor receptor 2; EGFR – epidermal growth factor receptor; ERK – extracellular signal regulated kinase; PI3K – phosphatidylinositol-3--kinase; mTOR – mammalian target of rapamycin

Figure 2. Epidermal growth factor signaling of receptors and target therapies

presents the strategy of AGC treatment based on guidelines of the National Comprehensive Cancer Network (NCCN) [7].

Anti-HER2 inhibitors

HER2 is a member of epidermal growth factor receptors which are tyrosine kinases. HER1, HER3 and HER4 are other members of this group. All receptors have an extracellular domain, transmembrane region and intracellular tyrosine kinase with carboxy--terminal region. While ligands of HER1, 3, and 4 receptors have been identified, ligands of HER2 are still unknown (fig. 2) [8, 9]. HER2 is a proto-oncogene, and its function is to stimulate cell proliferation and inhibit apoptosis. Expression of this tyrosine kinase was found in the gastrointestinal tract, breast, kidney, and heart. Overexpression of HER2 is present in types of breast and GC (range from 4.4% to 53.4%) [10]. To identify HER2 over--expression in GC, immunohistochemistry and fluorescence *in situ* hybridization (FISH) is used. Expression is classified into three groups: negative: 0+/1+; equivocal: 2+ or positive: 3+ [11].

Trastuzumab

It is considered that patients with HER2 overexpression IHC2+ or IHC3+ are eligible to be treated with trastuzumab [12]. It is an IgG1 anti-HER2 monoclonal antibody that binds to the extracellular domain of the receptor and suppresses cancer cells proliferation and survival. Furthermore, trastuzumab indirectly stimulates antibody dependent cellular cytotoxicity (ADCC) [13]. Since trastuzumab was evaluated as safe and efficient in the ToGa trial, several other agent combinations with trastuzumab are currently being assessed. However, it still remains the only target therapy in the first line treatment. Based on the outcomes, the Food and Drug Administration (FDA) has approved trastuzumab in HER2-positive GC. Despite the promising results of the ToGa trial, poorer survival has been observed in routine clinical use of trastuzumab [14]. Xelox is composed of oral capecitabine and intravenous oxaliplatin. This combination is one of the most frequently applied regimens [15]. Two phase II clinical trials evaluated the outcomes of combination XELOX + trastuzumab (tab. I) [16, 17]. Favorable toxicity and promising outcomes were reported (OS 21 *vs.* 13.8 months). A recent phase II study evaluated the efficacy of trastuzumab in combination with docetaxel and capecitabine as a first line treatment. It has shown high efficacy (median overall survival 20.9 months) and safety (absence of major AE other than neutropenia, leukopenia, and hand-foot syndrome). Moreover, tumor shrinkage was observed in most of the patients [18].

Trastuzumab deruxtecan

Trastuzumab deruxtecan (DS-8201) is a novel treatment agent composed of a HER2 monoclonal antibody covalently connec-

Table I. Representation of currently recruiting or ongoing clinical trials with the use of anticancer agents mentioned in this review

ID	Treatment agents	Study design	Number of participants	Treatment line
NCT05152147	zanidatamab/ tislelizumab/ tislelizumab + chemotherapy	phase III	714	first
NCT03929666	zanidatamab + chemotherapy	phase II	362	first
NCT05274048	neratinib + trastuzumab deruxtecan	phase I	18	one prior line of chemotherapy + HER2 directed therapy
NCT04768686	pembrolizumab + FLX475	phase II	90	second and third
NCT04745988	pembrolizumab + lenvatinib	phase II	30	first
NCT03321630	pembrolizumab + lenvatinib	phase II	24	second or further
NCT04249739	pembrolizumab	phase II	93	first
NCT04592211	pembrolizumab + olaparib + pacilitaxel	phase Ib/II	71	second
NCT04882241	pembrolizumab + chemotherapy *vs.* placebo + chemotherapy	phase III	120	first
NCT03488667	pembrolizumab + mFOLFOX	phase II	40	first
NCT04782791	nivolumab + SOX *vs.* nivolumab	phase II	30	first
NCT03784040	nivolumab + OTSGC-A24 *vs.* nivolumab + OTSGC-A24 + ipilimumab	phase Ib	40	–
NCT05111626	nivolumab + bemarituzumab nivolumab + bemarituzumab + mFOLFOX6 *vs.* placebo + nivolumab + mFOSFOX6	part 1: phase Ib part 2: phase III	702	–
NCT03995017	nivolumab + rucaparib + ramucirumab *vs.* rucaparib + ramucirumab	phase I phase II	61	second or third
NCT03443856	nivolumab + ipilimumab *vs.* chemotherapy	phase II	240	second
NCT03979131	avelumab + chemotherapy	phase II	37	–
NCT03966118	avelumab + ramucirumab + pacilitaxel	phase II	59	second
NCT04893252	durvalumab + vactosertib	phase II	55	third
NCT04817826	durvalumab + tremelimumab	phase II	31	first

ted to the topoisomerase I inhibitor. The mechanism of action is based on inhibition of DNA replication. [19]. Shitara K. et al. performed phase I and phase II clinical trials to evaluate the effect of trastuzumab deruxtecan on patients with GC. Both studies proved that conjugate monoclonal antibodies have manageable toxicity and high efficacy. In the latter, the objective response rate in the study group was 43% and 12% in the control group. Furthermore, in both studies tumor shrinkage was observed. The most frequent non-hematopoietic AE were nausea and decreased appetite, while decreased neutrophil count and anemia were the most common hematopoietic AEs [20, 21].

Trastuzumab emtansine

Trastuzumab emtansine (TE) is another novel agent composed of an anti-HER2 antibody and microtubule inhibitor (DM1). After internalization and lysosome destruction, cytotoxin is released and DM1 binds to tubulin which causes apoptotic cell death (fig. 3) [22]. A large randomized control phase II/III trial (GATSBY) assessed the trastuzumab emtansine efficacy in 107 centers. However, there was no improvement of overall survival in patients treated with TE compared to taxane (docetaxel). Possible explanations include primary or acquired resistance of cancer cells (e.g. due to efflux of emtansine) or disruption of binding to the tubulin [23]. Several treatment agents are being developed for cancers resistant to trastuzumab emtansine.

XMT-1522

XMT-1522 is a novel antibody drug conjugate (ADC) composed of an anti-HER2 antibody that binds to different regions of the HER2 epitope (not competing with trastuzumab) and F-

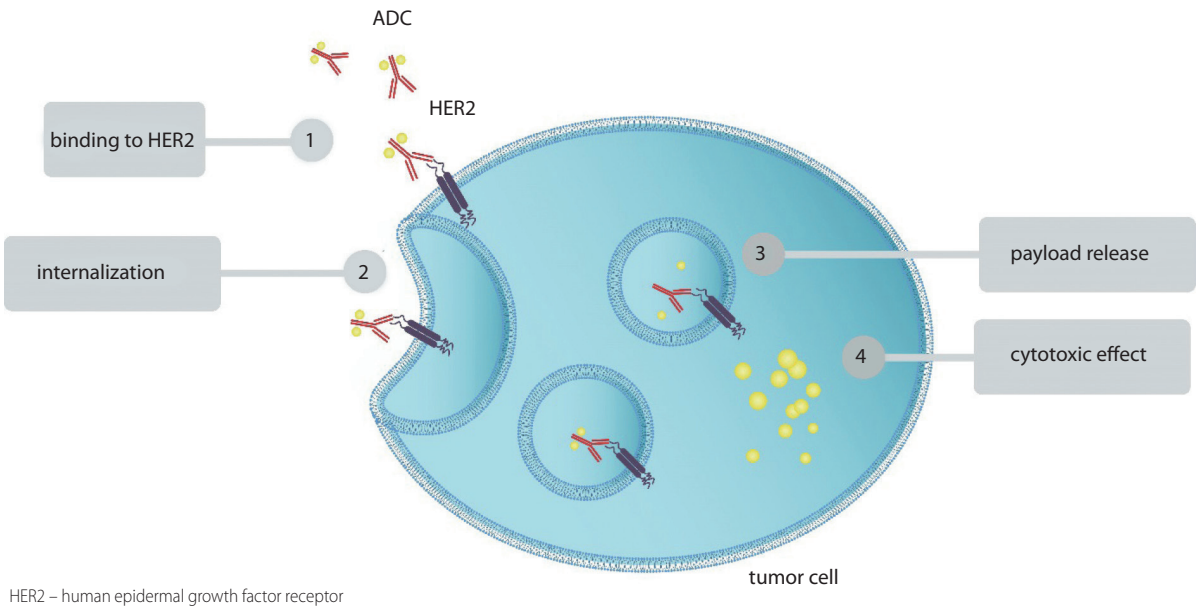


Figure 3. Mechanism of antibody drug conjugate (ADC)

-hydroxypropylamide (AF-HPA) which is an inhibitor of tubulin polymerization. According to the study performed by Le Joncour V. et al., XMT-1522 proves high efficacy against breast and GC cells resistant to TE in mouse xenograft models and *in vitro* [24].

Trastuzumab duocarbazine

Trastuzumab duocarbazine (SYD985) is an ADC agent composed of a monoclonal antibody and duocarmycin payload. It contains DNA binding and alkylating molecules and eventually causes cell death [25]. According to the study with mouse xenograft models, 1 mg/kg SYD985 equals to 5 mg/kg of trastuzumab in antitumor activity [26].

Zanidatamab

Zanidatamab (ZW25) is a novel anti-HER2 bispecific antibody which is considered effective in various types of cancers. It binds to two HER2 epitopes: ECD2 (pertuzumab binding domain) and ECD4 (trastuzumab binding domain) [27]. These novel anti--HER2 antibodies and ADCs should be considered in patients resistant to trastuzumab. Several clinical trials have evaluated the efficacy of zanidatamab in GC (NCT05152147, NCT03929666).

Dactolisib

Dactolisib (BEZ235) is a dual PI3K/ mTOR inhibitor which specifically targets HER2(+) GC cells. It has shown high efficacy in xenograft models compared to trastuzumab. Furthermore, some modest synergy with trastuzumab was observed [28].

Pertuzumab

Pertuzumab is another drug that might be combined with trastuzumab. It is a monoclonal antibody that binds to the ECD2 epitope of HER2. It suppresses heterodimerization of HER2 with other members of epidermal growth factor receptors (HER1, 3, 4). Thus, combined with trastuzumab, efficacy could be increased [29]. In phase III, a randomized, placebo-controlled JACOB trial study group was composed of pertuzumab, trastuzumab, and chemotherapy while the control group included placebo, trastuzumab, and chemotherapy. Progression-free survival was significantly increased in the study group (8.5 *vs.* 7.0; p = 0.0001), while no statistical difference was observed in overall survival (17.5 *vs.* 14.2; p = 0.057). Overall, the most common AE, was diarrhea. Neutropenia was the most frequent grade 3–5 AE [30]. Phase II randomized INNOVATION trial is currently being performed to assess the efficacy of pertuzumab + trastuzumab with chemotherapy *vs.* trastuzumab + chemotherapy *vs.* chemotherapy [31].

Margetuximab

Margetuximab is a novel monoclonal anti-HER2 antibody which is a trastuzumab derivative. It binds to the same domain as trastuzumab. However, its Fc1 region has been engineered to have increased affinity to stimulatory CD16A on NK cells. In addition, it has weaker affinity to suppressing CD32B found on macrophages and NK cells. Thus, it improves the immune identification of cancer cells [32]. Results of the phase Ib–II CP-MGAH22–05 study with the use of margetuximab with pembrolizumab (anti-PD1 antibody) suggest that a new chemotherapy-free treatment strategy might be considered [33]. Currently, the MAHOGANY phase II/III trial is being performed which will evaluate margetuximab + retifanlimab + chemotherapy / no chemotherapy *vs.* margetuximab + tebotelimab + chemotherapy as a first line treatment for GC [34].

Tyrosine kinase inhibitors (TKI)

Tyrosine kinases regulate cell functions and constitute a heterogenous group of proteins. They take part in cell cycle and angiogenesis processes. Abnormal function of tyrosine kinases is associated with neoplastic development. Treatment agents targeting tyrosine kinases are called pan-HER inhibitors.

Afatinib

Afatinib, an inhibitor of receptor tyrosine kinases. Its mechanism is based on suppression of autophosphorylation in EGFR dimer which inhibits the signaling pathway [35]. An *in vitro* study has proven its suppressing mechanism on tyrosine kinases in overexpressed HER2 GC cells. In addition, it is suggested to use afatinib in case of trastuzumab resistance [36]. Afatinib, in combination with cisplatin and 5-fluorouracil, as a first line treatment did not increase efficacy in the phase II clinical trial. However, a favorable safety profile was observed which may replace toxic chemotherapeutic agents [37].

Lapatinib

Lapatinib is another tyrosine kinase inhibitor. It binds to the cytoplasmic ATP-binding site of HER1 and HER2 kinases which inhibits signaling cascades. Dual targeting of lapatinib may overcome resistance to anti-HER2 antibodies and achieve higher efficacy compared to mono-targeting agents [38]. In a phase II randomized placebo-controlled trial (EORTC 40071), the addition of lapatinib to ECF/X (epirubicin, cisplatin, 5-fluorouracil / capecitabine) did not provide any improvement in efficacy [39]. Furthermore, two phase III clinical trials (LOGIC, TyTAN) showed that lapatinib combined with capecitabine, oxaliplatin or pacilitaxel do not increase overall survival [40, 41].

Neratinib

Neratinib is an irreversible pan-HER inhibitor. While it has been approved in the treatment of breast cancer, limited studies evaluated its effect on GC. In GC cell lines study, promising results were obtained. Comprehensive HER inhibition reduced cell proliferation and decreased the invasive character of cancer cells [42].

Poziotinib

Poziotinib (HM781-36B) is another pan-HER inhibitor which achieved promising results in phase I clinical trial in patients with solid organ tumors. The maximal tolerated dose was established as 24 mg/day and 18 mg/day in intermittent or continuous dosing schedule respectively [43]. In a phase I/II clinical trial, poziotinib combined with pacilitaxel and trastuzumab showed good efficacy and beneficial toxicity. Furthermore, 62.5% of patients experienced tumor shrinkage [44].

Programmed cell death 1

PD-1 (CD279), discovered in 1992, is an inhibitor of innate and adaptive immune responses. It is similar in 15% and 20% to CD28 and CTLA4 respectively. PD-1 is located on macrophages, NK cells, B cells, T cells and dendritic cells [45]. PD-L1 (CD274) and PD-L2 (CD273) are ligands of PD-1. PD-L1 is expressed on hematopoietic and non-hematopoietic cells (e.g. heart, muscle, lung, liver) while PD-L2 is mainly expressed on antigen presenting cells (APC) [46]. PD-1 stimulation after binding to PD-L1 leads to T cells' immunological tolerance (fig. 4). This mechanism involves kinases dephosphorylation (SHP2) which inhibits TCR and CD28 signaling [47]. Expression of CD274 was found in various types of tumors. Therefore, tumor cells create an immunosuppressive environment which allows to avoid lysis [48]. Overexpression of PD-L1 in GC cells is associated with several factors such as lymph-node metastasis, depth of infiltration, microsatellite instability, and EBV infection [49]. Furthermore, higher expression of CD274 on macrophages was found in tumors with increased secretion of CXCL8 [50]. However, heterogeneity in PD-L1 expression is observed among different gastric cell lines which might be associated with different genomic mutations (e.g. TP53, SMAD4, KRAS) [51].

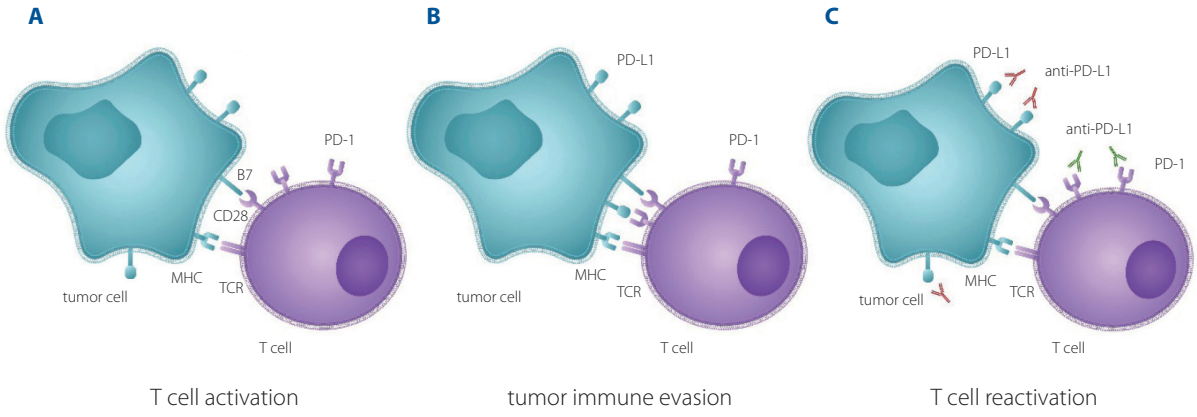


Figure 4. T cell activation after stimulation of TCR and costimulation from CD28 (A). Mechanism of the tumor immune evasion programmed death receptor (PD-1) and programmed death ligand 1 (PD-L1) (B). Introduction of PD-1 and PD-L1 monoclonal antibodies reactivates T cell (C)

Pembrolizumab

Pembrolizumab (MK-3475) is an IgG4 monoclonal antibody which targets PD-1 and inhibits binding to PD-L1 and PD-L2 [52]. In phase II (KEYNOTE 059) trial, pembrolizumab was evaluated as monotherapy in post second line treatment. Therapeutic success of third line chemotherapy treatment is usually marginal. Thus, new agents are required to increase the benefits in case second line treatment fails. Pembrolizumab achieved promising results; 42.6% of enrolled patients experienced tumor size reduction [53]. In KEYNOTE-061, a randomized, phase III trial, pembrolizumab did not improve overall survival compared to pacilitaxel in patients with a PD-L1 combined positive score ≥1. However, it is suggested that pembrolizumab might achieve greater efficacy with patients with increased PD-L1 expression or with better performance status [54]. In 2022, an updated KEYNOTE-061 trial showed that pembrolizumab was associated with an increased 24-month survival rate but did not statistically increase OS compared to pacilitaxel. A benefit was also observed in patients with PD-L1 abundance [55]. In KEYNOTE 062, a phase III randomized controlled trial, pembrolizumab was used as monotherapy and compared to chemotherapy or added to chemotherapy. Results showed that pembrolizumab did not increase median overall survival, but it was non inferior compared to chemotherapy. On the other hand, fewer AE were observed. However, the survival benefit was significant in the case of CPS ≥10 and high microsatellite instability tumors [56]. Promising results were reached in KEYNOTE 659, a phase IIb trial, where pembrolizumab was combined with S-1 and oxaliplatin and used in first line treatment. The objective response rate was 73.9% in PD-L1 CPS >1 and <10 subgroups while 71% in CPS >10 [57]. Currently, KEYNOTE-811, a phase II, randomized, placebo-controlled trial is being performed. It will assess first line treatment efficacy of pembrolizumab, or placebo combined with trastuzumab and chemotherapy in HER2(+) GC [58]. A large phase III clinical trial with 1542 participants (KEYNOTE-859) will evaluate the efficacy of pembrolizumab combined with chemotherapy in HER2-negative GC as first line treatment [59].

Nivolumab

Nivolumab (ONO-4538) is IgG4 monoclonal antibody which targets PD-1. Consequently, PD-1/PD-L1 and PD-1/PD-L2 signaling pathways are blocked [60]. In ATTRACTION-2, a phase III randomized placebo-controlled trial, the efficacy and safety of nivolumab was compared to placebo in patients with at least two previous chemotherapy treatments. Results proved nivolumab prolongs progression-free survival and overall survival (HR 0.60; 0.49–0.75); $p < 0.0001$ and HR 0.63; 0.51–0.78; $p < 0.0001$, respectively) [61]. In ATTRACTION-3, a phase III trial, nivolumab was compared to chemotherapy in second line treatment. The addition of nivolumab was associated with a significant increase of OS (10.9 *vs.* 8.4 months; $p = 0.019$). Furthermore, survival enhancement was achieved regardless of PD-L1 expression [62]. Evaluating the efficacy of nivolumab as a first line treatment was also performed. ATTRACTION-4, a phase II clinical trial, showed high responsive rate in patients treated with nivolumab with S1 and oxaliplatin, as well as in patients with nivolumab, capecitabine, and oxaliplatin (66.7% and 70.6% respectively) [63]. A recent phase III clinical trial with 724 patients did not improve OS in HER negative GC compared to chemotherapy. On the other hand, an improvement in progression-free survival was identified [64].

Avelumab

Avelumab is an IgG1 antibody which binds to PD-L1 and removes the suppression of T cells. There are several ongoing clinical trials evaluating avelumab as a first, second or perioperative treatment agent [65]. In JAVELIN Gastric 300, a phase III, randomized trial (third line avelumab *vs.* chemotherapy), avelumab did not increase progression-free survival or overall survival. However, fewer AE were observed in the avelumab group compared to chemotherapy [66]. In JAVELIN Gastric 100, another phase III randomized clinical trial, avelumab did not show superiority in OS compared to chemotherapy in patients previously treated with chemotherapy. However, this treatment agent may be potentially successful in patients with higher expression of PD-L1. In addition, in this trial fewer grade 3 AE were observed as well (12.8% *vs.* 32.8% in the chemotherapy group) [67].

Durvalumab

Durvalumab is another anti-PD-L1 monoclonal antibody. Currently, monotherapy is used to treat unresectable stage III lung cancer. However, durvalumab has shown activity towards hepatocellular and GC as well [68]. In a phase Ib/IIb clinical trial, the efficacy of darvalumab was assessed as monotherapy or combined with tremelimumab (anti-CTLA-4). Response rates were low in all approaches. However, a combination of two treatment agents resulted in a 1-year survival rate [69]. Recently, PRODIGE 59-DURIGAST, a phase II study has begun. It will evaluate FOLFIRI with durvalumab and tremelimumab as a second line treatment in AGC [70]. MATTERHORN III is another study evaluating durvalumab compared to chemotherapy in resectable GC [71].

Chimeric antigen receptor

The application of chimeric antigen receptors (CAR) is a mechanism used to allow T cells to recognize tumor-specific antigens. Host's lymphocytes are modified using viral vectors and, after the introduction of CAR, are reinfused to the circulatory system. This would allow them to destroy cancer cells (fig. 5). The next generation of CARs have costimulatory domains or secrete cytokines that are able to remodel tumor environments, such as interleukin-12 (fourth generation – TRUCKs) [72]. Its presence in tumor tissue increases the activity of CD8+ cells, prolongs expansion of T cells, and suppresses exhaustion and apoptosis

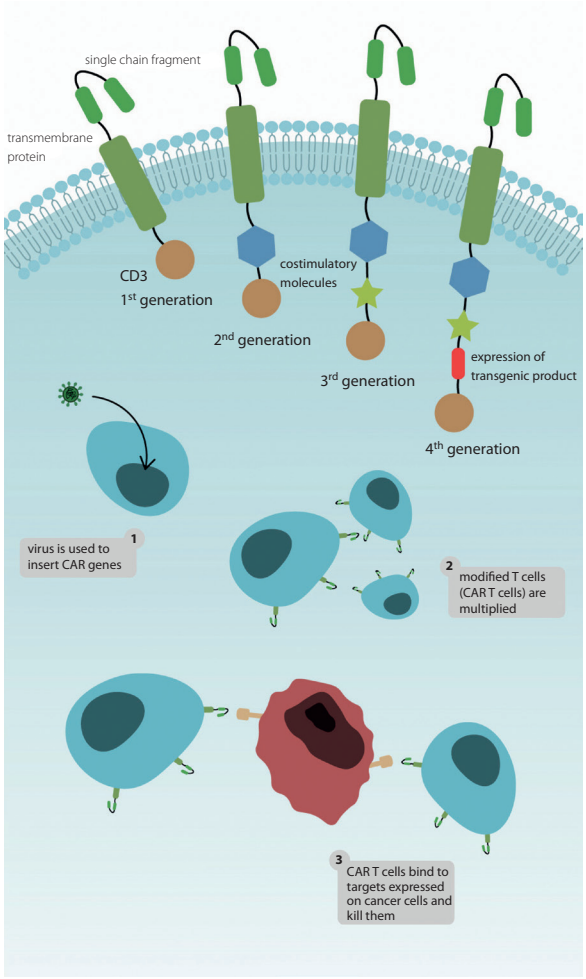


Figure 5. Chimeric antigen therapy (CAR) generations and antitumor mechanism

of immune cells. Additionally, IL-12 enhances NK cells and macrophages infiltration to targeted tissue [73]. CAR T cells treatment is associated with specific AE. Firstly, those might be associated with cells expressing certain antigens recognized by CARs – on--target effects. B cell aplasia is an example of AE which might develop after the introduction of CARs that recognize B cell antigens – CD19 or CD20. However, such AE can be reversed by suppressing the infusion of modified T cells or by eliminating target cells if the treatment is directed towards solid organ cancers [74]. One of the most frequent off-target AE is cytokine release syndrome (CRS). Cytokines from CAR T cells or the host's immune cells might induce CRS. Symptoms usually involve high fever, tachycardia, headache or malaise among others [75]. Several CAR T cells were developed to assess the potential treatment of GC. For instance, antitumor activity of CAR recognizing CLDN18.2, an isoform of claudin-18 which has been considered as potential target, was evaluated. *In vitro* and *in vivo* trials have proven that modified T cells could lyse GC cells that express CLDN18.2 [76].

Challenges and future directions

Ongoing clinical trials including the mentioned agents are listed in table I. Despite the extensive benefits of immunotherapy, resistance to HER2 and PD-1 inhibitors is a significant barrier which needs to be addressed. Mechanisms of resistance are unclear and not fully understood. Elimination of those obstacles would make GC cells more potent for therapy. A recent study by Sampera A. et al. found that HER2 resistance is associated with enhanced activity of two signal pathways (Pi3K/mTOR and MAPK/ERK) along with elevated expression of other members of the HER family. Pan-HER inhibitors effectively reversed trastuzumab resistance [77]. Normal epithelial cell-specific-1 (NES1) is one of the genes considered as responsible for inducing resistance to HER2 inhibitors. Overexpression of NES1 and activation of Pi3K/mTOR pathway has been found in resistant cells. Combining trastuzumab and PI3K/mTOR inhibitor could reduce resistance and block tumor growth [78]. The coiled-coin protein named GSE1 and human epidermal growth factor receptor-2 (ERBB2) have also been linked with trastuzumab resistance and greater risk of metastasis [79, 80]. Wang D.S. et al. suggest that noninvasive analysis of circulating tumor DNA (ctDNA) can demonstrate intrinsic or acquired resistance and offer personalized treatment [81]. Furthermore, anti-HER2 treatment agents induce expression of certain genes, such as HAS2 and SHB which could be used as predictive markers for trastuzumab response [82].

Microsatellites are repeated sequences of nucleotides which compose 3% of the human genome [83]. A mismatch repair system takes part in correcting errors which occurred during division of cell and DNA replication. Defects of this system can result in multiple mutations in microsatellites [84]. Microsatellite instability (MSI) has been linked with various neoplasms, including GC. The MSI phenotype is associated with expression of abundant neoantigens which stimulates an immunological response. Moreover, expression of PD-L1 has been identified in MSI tumor cells which makes it susceptible to ICI [85]. The clinical benefit of pembrolizumab has been demonstrated in metastatic MSI tumors [86]. The NCT04817826 clinical trial (INFINITY) will evaluate the efficacy of tremelimumab and durvalumab in the treatment of MSI GC. Wang Y.L. et al. have confirmed that MSI GC showed higher PD-1/PD-L1 expression compared to microsatellite stable (MSS) tumors [87]. GC can be additionally classified using the status of the Epstein-Barr virus (EBV). EBV is associated with the development of various neoplasms including GC, nasopharyngeal carcinoma or lymphomas. It is considered that 2–20% of all GC cases are EBV positive [88]. The Epstein-Barr virus(+) GC is associated with higher expression of PD-1L compared to EBV(–) cells [89]. Several clinical trials are being performed to evaluate the efficacy of pembrolizumab in EBV(+) GC (NCT03257163, NCT05166577). Therefore, MSI and EBV(+) can be considered as beneficial markers in ICI treatment. MicroRNAs (miRNA) are other significant regulators of cancer genes which has been related to treatment resistance. Phosphatase and tensin homologue (PTEN) counteracts PI3K pathway. MiRNA-221/222 and miRNA-214 target PTEN and promote GC invasion [90].

Activity of miR-105-5 has been correlated with reduced expression of PD-L1 [91]. Circular RNA (circRNA) are covalently closed RNA fragments generated by back-splicing. Features of circRNA are not fully understood but they take part in gene transcription and interact with proteins. Furthermore, circRNA has been associated with cancer progression [92]. CircDLG1 has been identified in PD-1 resistant GC and enhanced invasion and immune evasion of cancer cells [93].

Despite recent advances in immunotherapy, multiple mechanisms of immune evasion remain unknown. Future studies should concentrate on overcoming resistance to known and tested treatment agents, such as trastuzumab or pembrolizumab. Trials with anti-HER2 agents combined with PI3K/mTOR inhibitors should be performed. Furthermore, it is necessary to identify potential targets in MSS and EBV(–) GC. Better understanding of miRNA and circRNA could reveal novel possibilities and treatment options. Additionally, novel potential targets are being evaluated: membrane mucin MUC17 (NCT04117958); methyl methanesulfonate and ultraviolet-sensitive gene 81 (MUS81) [94] or claudin 18.2 (CLDN18.2) [95].

Conclusions

Outcomes of many clinical trials are highly hopeful. The majority of the mentioned trials show the benefits of combination IA with chemotherapy compared to chemotherapy alone. Additionally, immunotherapy may constitute or support drugs in part of first, second or third line treatment. Adverse effects are related to treatment strategy and depend on whether they are in combination with chemotherapy. However, IA seem to be safer than chemotherapeutic agents. The achieved results from the clinical trials are promising enough to consider implementing immunotherapy in AGC management. Nevertheless, further studies toward evaluating the mechanisms of resistance to anti-HER2 antibodies and ICI are needed. In certain cases, a combination of treatment agents with various mechanisms of action may overcome resistance.

Conflict of interest: none declared

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