

# Study on Efficacy and Safety of Low-Dose Apatinib Combined with Camrelizumab and SOX Regimen as First-Line Treatment of Locally Advanced and Unresectable Gastric/Gastroesophageal Junction Cancer: A Protocol for an Open-Label, Dose Escalation and Extension Phase Ib Clinical Trial

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**Background:** The standard treatment for advanced gastric/gastroesophageal junction cancer (AGC/GEJC) is palliative chemotherapy combined with targeted therapy. The SOX regimen (S-1 plus oxaliplatin) is recommended as neoadjuvant or palliative first-line chemotherapy in Asian patients. Apatinib, an oral VEGFR tyrosine kinase inhibitor, is associated with additional survival benefit as third- or subsequent-line therapy. However, the median overall survival time of AGC/GEJC is only 8–11 months in the West and 13–17 months in East Asia/Japan, even with the application of anti-angiogenic agents. Hence, the multimodal and individual management of patients is challenging standards to improve prognosis, including the preferential use of low-dose anti-angiogenic drugs and immunotherapy, as well as the application of multi-disciplinary treatment (MDT)-directed conversion therapy.

**Methods/Design:** This single-center study was designed to combine low-dose apatinib with camrelizumab plus the SOX regimen in diagnosed potentially resectable and initially unresectable AGC/GEJC. This a prospective, open-label, single-arm, dose escalation and extension phase Ib clinical trial, conducted in Jiangsu Province Hospital, beginning from June 2020. All patients will first receive this combined regimen (3 weeks/cycle) for at most eight cycles, then apatinib and camrelizumab in maintenance therapy until disease progression, intolerable toxicity, death, a maximum 2 years of treatment or discontinuation for any reason. Follow-up and evaluation will be carried out regularly. If surgery is allowed by MDT discussions, oral apatinib will be discontinued during the last preoperative cycle. The primary endpoints are the objective response rate and maximum tolerated dose according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria (version 1.1) and the Common Terminology Criteria for Adverse Events (CTCAE) criteria (version 5.0).

**Discussion:** This study will assess the response and side effects of AGC/GEJC patients in the use of low-dose apatinib combined with camrelizumab and the SOX regimen, and this combined therapy is expected to be a feasible and optimized first-line treatment option. In addition, this study will provide robust evidence and novel ideas for conversion therapy.

**Trial Registration:** ChiCTR.gov.cn: ChiCTR2000034109.

**Keywords:** clinical trial, AGC/GEJC, low-dose apatinib, camrelizumab, SOX regimen, protocol

## Background

As a highly malignant and lethal tumor,<sup>1</sup> advanced gastric/gastroesophageal junction cancer (AGC/GEJC) is a major healthcare problem across the world. Surgery is considered the most effective treatment for gastric cancer. However, only 50–60% of patients are considered appropriate for radical surgery, while those who do not have the chance of surgery usually have a rather poor prognosis.<sup>2,3</sup> Currently, the standard treatment for AGC/GEJC is palliative chemotherapy combined with targeted therapy. Combination chemotherapy with S-1 plus oxaliplatin (SOX) for metastatic gastric cancer has shown potent efficacy with acceptable toxicity<sup>4–6</sup> and has been recommended as neoadjuvant or palliative first-line chemotherapy in Asian patients.<sup>7,8</sup> In the field of targeted therapy, apatinib is an oral VEGFR tyrosine kinase inhibitor, which is associated with additional survival benefit as third- or subsequent-line therapy.<sup>9</sup> However, the median overall survival (OS) time of AGC/GEJC is only 8–11 months in the West and 13–17 months in East Asia/Japan, even with the application of anti-angiogenic agents.<sup>10,11</sup>

With the ongoing development of immunotherapy, immune checkpoint blockade and low-dose anti-angiogenic agents have shown promising antitumor efficacy and interactive effects.<sup>12–18</sup> Immune checkpoint blockade, represented by anti-programmed death-1 (PD-1) antibodies and antibodies to its ligand (PD-L1), has been approved for use in microsatellite instability (MSI)-high and DNA mismatch repair deficient (dMMR) phenotype of AGC/GEJC as second- or subsequent-line therapy, or as third-line therapy for PD-L1-positive AGC/GEJC, yet with limited monotherapy efficacy.<sup>12–16</sup> T-cell infiltration, visceral metastases, tumor burden and diverse degrees of systemic immune suppression are shown to be different in early, middle and advanced stages of cancer. Hence, more and more clinical trials are attempting to investigate whether the front-line or preoperative use of immune checkpoint blockade helps to potentiate the anti-tumor effect of immunotherapy.<sup>19–21</sup> Unlike chemoradiotherapy, the advancing use of immunotherapy aims to enhance systemic immunity against tumor antigens, eliminating micro-metastases that would otherwise be the source of relapse.<sup>22</sup> Besides, the favorable effects of anti-angiogenic agents are thought to play a role in immunomodulation when administered at a lower dose, not merely to reduce the blood supply to tumor cells.<sup>17,18,23</sup> Of importance, such multimodal and individual management is

challenging standards to improve prognosis. Apart from the innovative treatments mentioned above, perioperative chemotherapy and conversion therapy have also become hot topics in the clinical treatment of locally advanced or unresectable gastric/gastroesophageal junction cancer. Furthermore, their significance in practice has been shown in some related clinical trials.<sup>24,25</sup> Preoperative chemotherapy can not only effectively reduce the clinical stage of the tumor and improve the rate of surgical resection, but also eliminate the vascular residual survival of tumor cells and micro-metastases, reduce the rate of post-operative recurrence and improve patient prognosis.

Based on the above application prospects, we prospectively designed a treatment plan for locally advanced and unresectable gastric/gastroesophageal junction cancer. The main objective of this study is to investigate the impact of first-line use of low-dose apatinib (Jiangsu Hengrui Medicine Co., Ltd, Lianyungang City, Jiangsu Province, China) combined with camrelizumab (Jiangsu Hengrui Medicine Co., Ltd, Lianyungang City, Jiangsu Province, China) and SOX regimen (Jiangsu Hengrui Medicine Co., Ltd, Lianyungang City, Jiangsu Province, China) on the clinical safety, feasibility and prognosis, and this combined therapy is expected to achieve a tolerable and significant curative effect, and even lead to access to surgical conversion with a sufficient pathological response. On the other hand, screening therapeutic-related biomarkers and further enriching the preferential targeted population to improve response rates are potential goals.

## Patients and Methods

### Recruitment and Allocation

Patients who have a diagnosed, potentially resectable AGC/GEJC, including local progression or oligometastases (cohort 1), and patients with unresectable tumors with widespread metastases (cohort 2), will be recruited. Each patient will give their written informed consent prior to enrolment.

Eligibility criteria include age 18–75 years, males or females (non-pregnant and non-lactating females), histologically and/or cytologically proven AGC/GEJC with HER2-negative or unknown HER2 status, treatment-naïve or relapsed more than 6 months after the last post-operative chemotherapy using platinum/fluorouracil with no more than level 2 toxicities, clinical stage IV and assessed as being potentially resectable or unresectable by multidisciplinary discussion (MDT), Eastern

Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate bone marrow, hepatic and renal functions. Moreover, patients with at least one measurable lesion (in accordance with the Response Evaluation Criteria In Solid Tumors [RECIST] criteria [version 1.1]) are eligible. The main exclusion criteria are a potential gastrointestinal bleeding tendency and/or coagulation disorders, uncontrolled blood pressure and prior cardiac dysfunction, and a history of immunodeficiency or other severe autoimmune disease. Patients with a history of prior or concurrent malignancies (except for skin basal cell carcinoma, in situ carcinoma of the cervix or stage I lung/colorectal cancer), central nervous system metastasis or pleural/peritoneal effusion requiring clinical intervention are also excluded. Further details are available in the [Supplementary Data](#).

## Trial Design

This study was designed as a prospective, open-label, single-arm, dose escalation and extension phase Ib clinical trial (registered at ChiCTR.gov.cn: ChiCTR2000034109) conducted in Jiangsu Province Hospital beginning from June 2020. All patients will first receive this combined regimen (3 weeks/cycle) for at most eight cycles, then apatinib and camrelizumab in maintenance therapy until disease progression, intolerable toxicity, death, a maximum 2 years of treatment or discontinuation for any reason. Follow-up and evaluation will be carried out regularly. If surgery is allowed by MDT discussions, oral apatinib will be discontinued during the last preoperative cycle.

The primary endpoints are the objective response rate (ORR) and maximum tolerated dose (MTD) according to RECIST v1.1 criteria and the Common Terminology Criteria for Adverse Events (CTCAE) criteria (version 5.0). The secondary study endpoints include progression-free survival time (PFS), total survival time (OS), disease control rate (DCR), duration of remission (DOR) and adverse events (AEs). R0/R1 resection rate, perioperative safety and the main pathological remission rate (MPR) will be evaluated in patients undergoing conversion surgery. The exploratory endpoints include changes in specific T-cell subsets, vascular normalization structure and functional indices, autophagy-related genes (*Beclin-1*, *P53* and *Klotho* genes, and LC3 protein), PI3K/Akt/mTOR and AMPK/mTOR signaling pathways, tumor microenvironment (TME) and host immune system

response biomarkers (PD-L1, CD8<sup>+</sup> TILs, etc.) and regulators (non-coding RNA).

## Intervention and Assessment

There are two cohorts (called “cohort 1” and “cohort 2”), and a total of about 42 patients with locally advanced or unresectable gastric/gastroesophageal junction cancer will be recruited. The trial consists of two parts: the dose escalation and extension phases. Owing to the lack of evidence-based data from previous clinical studies, the dose escalation phase is converted into three dose gradients (group 1: apatinib 250 mg, po, qod + camrelizumab 200 mg, iv, d1 + oxaliplatin 100 mg/m<sup>2</sup>, iv, d1+ S-1 40 mg, po, bid, d1–14; group 2: apatinib 250 mg, po, qod + camrelizumab 200 mg, iv, d1 + oxaliplatin 130 mg/m<sup>2</sup>, iv, d1 + S-1 40 mg, po, bid, d1–14; group 3: apatinib 250 mg, po, qd + camrelizumab 200 mg, iv, d1 + oxaliplatin 130 mg/m<sup>2</sup>, iv, d1 + S-1 40 mg, po, bid, d1–14) for at most eight cycles to identify the MTD and recommended dose for the second phase. In consideration of immunomodulation and the vascular normalization effect of anti-angiogenesis drugs,<sup>23,26,27</sup> oral apatinib will be given 10 days (±3 days) before the use of camrelizumab and the SOX regimen during the first cycle. Moreover, the dosage of apatinib and oxaliplatin will be escalated if ≤1 patient per cohort experiences dose-limiting toxicity (DLT) within the first 28 days of treatment. DLT is defined as any grade 4 hematological toxicity or any grade 3 or greater non-hematological toxicity that occurs within the first 21 days of treatment, or any drug toxicity that causes a delay of ≥21 days in treatment. If two patients experience DLT, the prior dose is considered the MTD. Once the MTD is established, additional patients will be enrolled at that level in the dose expansion phase and only use apatinib and camrelizumab in maintenance therapy until disease progression, intolerable toxicity, death, a maximum 2 years of treatment or discontinuation for any reason. The study flowchart is shown in [Supplementary Materials Figure 1](#).

The findings of follow-up examinations, including routine blood, liver and kidney function tests, electrolytes, thyroid function, tumor markers (carcinoembryonic antigen [CEA], carbohydrate antigen 199 [CA199], CA125, CA724, CA242, and alpha-fetoprotein [AFP]), hepatitis, human immunodeficiency virus, syphilis, blood coagulation, routine physical examination and any AEs before each cycle of treatment, should be recorded on the case report form (CRF) in detail. When an AE occurs, the

investigators should decide whether to stop the trial according to the severity assessed by CTCAE v5.0 criteria, and the corresponding treatment should be given in time. Thoracoabdominal enhanced computed tomography (CT) or magnetic resonance imaging (MRI) will be executed every 6 weeks ( $\pm 7$  days) for the first 4 months during treatment (the time is calculated in calendar days, and is not affected by drug withdrawal), and every 12 weeks ( $\pm 7$  days) thereafter (excluding legal holidays). For patients with MDT-directed conversion therapy, its preoperative combined therapy is used for at most eight cycles, and oral apatinib will be discontinued during the last preoperative cycle. Postoperative adjuvant therapy will be decided based on pathological reports and surgical results according to the Chinese Society of Clinical Oncology guideline version 2020. Information on the surgical process, surgical pathology and perioperative complications will be recorded.

## Data Collection and Management

The clinical researchers will collect baseline data such as age, sex, body mass index and complications, after written informed consent has been provided. As well as the laboratory indices and imaging examinations mentioned above (see “Intervention and Assessment”), blood and tissue samples obtained from patients will be collected for flow cytometry analysis, immune microenvironment tests and gene sequencing.

All relevant patient information will be recorded in the CRF in a timely and accurate manner by trained and independent clinical research coordinators. If there are any mistakes in the CRF, the investigator will correct them in time. All data will be acquired only by researchers who have signed a confidential disclosure agreement. Significantly, any collected information that could be used to disclose an individual's identity will not be released without consent in this clinical study, except in special and legally permitted circumstances. The ethics committee of Pukou Branch Hospital of Jiangsu Province Hospital will be responsible for ensuring that the rights and well-being of patients are protected, and for maintaining compliance with the approved protocol, data collection, statistical analysis and anonymity in publications.

## Statistical Analysis

A sample size of at least 42 patients in total is planned and the study will be carried out in two phases. The null hypothesis is that the true response rate is 0.5 and the

alternative hypothesis is that the true response rate is 0.7. In the dose escalation phase ( $n \geq 3$  per dosage group), a total of nine patients will be recruited. If there are five or fewer responses among these patients, the study will be stopped early. Otherwise, an additional 33 patients will be enrolled in the dose extension phase, resulting in a total sample size of 42. If there are 29 or more responses among these 42 patients, we can reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.05 and yields a power of 0.8.

Classification variables will be analyzed by the chi-squared test, Fisher's exact test, Wilcoxon rank sum test or Cochran–Mantel–Haenszel (CMH) chi-squared test; continuous variables according with the normal distribution will be compared by the *t*-test, and those according with the non-normal distribution by the Wilcoxon rank sum test and Wilcoxon signed rank sum test. The Kaplan–Meier method and the log-rank test will be used to generate survival curves and compare the differences, respectively. The hazard ratio and 95% confidence interval will be calculated with the Cox regression model. A two-sided test is used in the hypothesis test, and the test statistics with their corresponding *P* values are given such that  $P \leq 0.05$  will be considered to indicate statistical significance and  $P \leq 0.01$  deemed as highly statistically significant. Data analysis will be performed using SPSS<sup>®</sup> software package version 22.0 and will cover the actual number of subjects enrolled, shedding and exclusion of cases, demographics and other baseline characteristics, compliance, efficacy and safety analysis. The study is registered with ChiCTR.gov.cn (number ChiCTR2000034109).

## Discussion

The 5-year survival rate of gastric cancer patients in China is lower than that in Japan and South Korea, mainly because of the advanced stage of clinical diagnosis in China.<sup>28</sup> Therefore, tumor staging is one of the most important prognostic factors in patients with gastric cancer, which also lays the foundation of treatment decisions. The multimodal management of patients with advanced gastric adenocarcinoma is now recognized as an optimal treatment, including the combination of local and systemic treatment methods,<sup>29</sup> and is expected to achieve significant curative effects, and even lead to access to surgical conversion achieving a sufficient pathological response. Surgery is the cornerstone of therapeutic strategies, to achieve a curative effect or reduction of the tumor burden, while the addition of chemotherapy, anti-angiogenic or



other immune agents can decrease the rate of recurrence and prolong survival.

Results from the KEYNOTE-061 trial (NCT02370498) showed that PD-1 antibody could be used early in a specific subgroup of patients (ECOG PS 0, MSI-H/dMMR, EBVaGC, high tumor burden, PD-L1 CPS  $\geq 10$ ), with long-term survival benefits.<sup>19</sup> The randomized, phase III KEYNOTE-062 study (NCT02494583) was designed to compare the efficacy and safety of pembrolizumab alone or in combination with cisplatin plus a fluoropyrimidine with those of cisplatin plus a fluoropyrimidine as first-line therapy for PD-L1<sup>+</sup>/HER2<sup>-</sup> AGC/GEJC, suggesting that the efficacy of an immune checkpoint inhibitor (as monotherapy) in the first-line treatment of AGC/GEJC is not inferior to standard chemotherapy.<sup>20</sup> Furthermore, the ATTRACTION-04 study confirmed that an immune checkpoint inhibitor added to chemotherapy gave encouraging results, improving the ORR (up to 57.5%) and PFS (median survival time up to 10.45 months) for first-line treatment.<sup>30</sup> On the one hand, although the KEYNOTE-062 trial showed negative results, it also contributed to the application of immune checkpoint inhibitors in perioperative treatment of gastric cancer. On the other hand, the promising results obtained from the ATTRACTION-04 and CheckMate-649 trials, involving the first-line use of nivolumab, reveal bright prospects for the front-line use of PD-1 antibody in combination therapies.

However, successful immunotherapy requires not only the infiltration of immune cells, but also an immune-supported microenvironment to maintain T-cell proliferation and function. The team from Xinqiao Hospital Cancer Institute identified that angiogenesis, a negative correlation with the magnitude of the signature of cytotoxic function, was demonstrated particularly in patients with an inflamed TME.<sup>17</sup> The REGONIVO trial added regorafenib to nivolumab for advanced gastric and colorectal cancer, observing that the objective tumor response was as high as 40%, including 11 patients with gastric cancer (44%) and nine with colorectal cancer (36%); at the same time, the median PFS was 6.3 months, which was better than the historical control.<sup>31</sup> It seems that vascular normalization could provide such an immune-supported microenvironment for immunotherapy.<sup>27</sup> To further explore the mechanism behind this phenomenon, preclinical studies based on lung cancer and breast cancer models found that appropriate use of low-dose anti-angiogenic drugs could induce tumor vascular normalization, alleviate tumor

hypoxia, increase CD8<sup>+</sup> T-cell infiltration, hinder recruitment of tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), and decrease TGF- $\beta$ , suggesting a potential role of immunomodulation.<sup>23,26</sup> In turn, the activation of immune cells can promote vascular normalization, thus forming a positive feedback loop. Hence, apatinib is recognized to optimize the TME and potentiate the antitumor efficacy of PD-1/PD-L1 blockade in its immunomodulatory and normalization window of tumor vasculature effects at lower doses.<sup>17,18,23,27</sup> In a phase II clinical study of camrelizumab plus CapeOX sequential camrelizumab plus apatinib for first-line treatment of AGC/GEJC, initiated by Professor Lin Shen (NCT04609176) of Peking University Affiliated Cancer Hospital, the ORR and DCR of 46 evaluable patients reached 58.7% and 78.3%, respectively, indicating a manageable safety profile and encouraging antitumor activity. These findings provide a rationale for the potential combination of anti-angiogenic and immune agents, and further clinical investigations of combination therapies.

The research objective of our design is mainly aimed at patients with locally advanced or unresectable gastric/gastroesophageal junction cancer, who have missed the chance of R0 resection, a situation which is associated with worse outcomes. However, guidelines differ between countries and there is no universal standard of care.<sup>32,33</sup> With the introduction of multimodal methods during the critical perioperative period, the survival time of patients has been somewhat prolonged, but the perioperative safety issues have long been debated. Regarding perioperative therapy, the related outcomes demonstrated that patients had favorable response rates and tumor shrinkage following neoadjuvant S-1, oxaliplatin, apatinib (SOXA) and surgery, in research published in the past few years.<sup>34–37</sup> A report in the RESOLVE research found that a perioperative SOX regimen can improve the 3-year disease-free survival rate compared with postoperative XELOX for patients with locally advanced gastric cancer.<sup>34</sup> The other randomized controlled trials on AGC/GEJC revealed that the pathological response rate (pRR) was 56% in Chinese and 53.2% in Japanese patients.<sup>35,36</sup> The pRR of 89.7% in the present study is higher than that for the SOX regimen previously reported in Japan and China. This improvement may be attributed to the addition of apatinib to chemotherapy.<sup>36,37</sup> Based on the above research results, this topic has gradually aroused great interest in researchers in the front-line or even

perioperative treatment of gastric cancer with anti-angiogenic agents and immune checkpoint inhibitors, and the results are highly anticipated.

The management of patients with AGC/GEJC is multi-modal and individual. The timing of conversion therapy and perioperative methods for tumor control is becoming ever more critical in optimizing patient outcome by improving the effectiveness of systemic treatments. Our study combines low-dose apatinib with camrelizumab plus the SOX regimen in diagnosed potentially resectable and initially unresectable AGC/GEJC. To ensure the safety and efficacy of this combined therapy, this study is designed as a prospective, open-label, single-arm, dose escalation and extension phase Ib clinical trial, which is expected to function as a feasible and optimized first-line treatment option. In addition, this study will provide robust evidence and novel ideas for conversion therapy. As clinical trials continue to clarify and guide the roles of chemotherapy, targeted molecular agents and immunotherapy, we anticipate that all the related concerns about MDT-directed conversion therapy for AGC/GEJC will be resolved.

## Trial Status

The trial was registered at ChiCTR.gov.cn and the protocol version is ChiCTR2000034109. The clinical study will last for 32 months and run from June 2020 to December 2023. The first patient was recruited at Pukou Branch Hospital of Jiangsu Province Hospital and 42 patients will be included in this study in total.

## Ethical Statement

The ethics committee of Jiangsu Province Hospital approved the study (approval number 2020-SR-002). The trial protocol is conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (2013). All participants have to sign their informed consent before the trial.

## Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, agreed to the submitted journal, and agree to be accountable for all aspects of the work.

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## Disclosure

Kang-Xin Wang and Ting-Yun Cui are co-first authors, and Xiao-Feng Chen and Yue-Yu Fang are co-corresponding authors for this study. The authors have no conflicts of interests to disclose.

## References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359–86. doi:10.1002/ijc.29210
2. Isobe Y, Nashimoto A, Akazawa K, et al. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. *Gastric Cancer*. 2011;14(4):301–316. doi:10.1007/s10120-011-0085-6
3. van de Velde CJ, Peeters KC. The gastric cancer treatment controversy. *J Clin Oncol*. 2003;21(12):2234–2236. doi:10.1200/JCO.2003.91.138
4. Koizumi W, Takiuchi H, Yamada Y, et al. Phase II Study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX Study). *Ann Oncol*. 2010;21(5):1001–1005. doi:10.1093/annonc/mdp464
5. Kim GM, Jeung HC, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. *Eur J Cancer*. 2012;48(4):518–526. doi:10.1016/j.ejca.2011.12.017
6. Yamada Y, Higuchi K, Nishikawa K, et al. Phase III Study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. *Ann Oncol*. 2015;26(1):141–148. doi:10.1093/annonc/mdl472
7. Feng D, Leong M, Li T, Chen L, Li T. Surgical outcomes in patients with locally advanced gastric cancer treated with S-1 and oxaliplatin as neoadjuvant chemotherapy. *World J Surg Oncol*. 2015;13(1):11. doi:10.1186/s12957-015-0444-6
8. Satake H, Miki A, Kondo M, et al. Phase I Study of neoadjuvant chemotherapy with S-1 and oxaliplatin for locally advanced gastric cancer (Neo G-SOX PI). *ESMO Open*. 2017;2(1):e000130. doi:10.1136/esmoopen-2016-000130
9. Li J, Qin S, Xu J, et al. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. *J Clin Oncol*. 2016;34(13):1448–1454. doi:10.1200/JCO.2015.63.5995
10. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376(9742):687–697. doi:10.1016/S0140-6736(10)61121-X
11. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;29(13):1715–1721. doi:10.1200/JCO.2010.33.0597

12. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol.* **2018**;4(5):e180013.
13. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* **2017**;390(10111):2461–2471. doi:10.1016/S0140-6736(17)31827-5
14. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol.* **2018**;19(7):940–952. doi:10.1016/S1470-2045(18)30351-6
15. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med.* **2017**;377(20):1919–1929. doi:10.1056/NEJMoa1709937
16. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a Multicenter, Phase Ib Study. *J Clin Oncol.* **2017**;35(19):2117–2124. doi:10.1200/JCO.2016.71.6795
17. Feng Y, Dai Y, Gong Z, et al. Association between angiogenesis and cytotoxic signatures in the tumor microenvironment of gastric cancer. *Onco Targets Ther.* **2018**;11:2725–2733. doi:10.2147/OTT.S162729
18. Yi M, Jiao D, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. *Mol Cancer.* **2019**;18(1):60. doi:10.1186/s12943-019-0974-6
19. Shitara K, Ozguroglu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet.* **2018**;392(10142):123–133. doi:10.1016/S0140-6736(18)31257-1
20. Tabernero J, Bang YJ, Fuchs CS, et al. KEYNOTE-062: Phase III Study of pembrolizumab (MK-3475) alone or in combination with chemotherapy versus chemotherapy alone as first-line therapy for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. *J Clin Oncol.* **2016**;34(4 suppl):TPS185–TPS. doi:10.1200/jco.2016.34.4\_suppl.tps185
21. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet.* **2021**;398(10294):27–40.
22. Liu J, Blake SJ, Yong MC, et al. Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. *Cancer Discov.* **2016**;6(12):1382–1399. doi:10.1158/2159-8290.CD-16-0577
23. Zhao S, Ren S, Jiang T, et al. Low-dose apatinib optimizes tumor microenvironment and potentiates antitumor effect of PD-1/PD-L1 blockade in lung cancer. *Cancer Immunol Res.* **2019**;7(4):630–643.
24. Becker K, Reim D, Novotny A, et al. Proposal for a multifactorial prognostic score that accurately classifies 3 groups of gastric carcinoma patients with different outcomes after neoadjuvant chemotherapy and surgery. *Ann Surg.* **2012**;256(6):1002–1007. doi:10.1097/SLA.0b013e318262a591
25. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European organisation for research and treatment of cancer randomized trial 40954. *J Clin Oncol.* **2010**;28(35):5210–5218. doi:10.1200/JCO.2009.26.6114
26. Li Q, Wang Y, Jia W, et al. Low-dose anti-angiogenic therapy sensitizes breast cancer to PD-1 blockade. *Clin Cancer Res.* **2020**;26(7):1712–1724.
27. Zhou K, Zhang JW, Wang QZ, et al. Apatinib, a selective VEGFR2 inhibitor, improves the delivery of chemotherapeutic agents to tumors by normalizing tumor vessels in LoVo colon cancer xenograft mice. *Acta Pharmacol Sin.* **2019**;40(4):556–562. doi:10.1038/s41401-018-0058-y
28. Yang L, Zheng R, Wang N, et al. Incidence and mortality of stomach cancer in China, 2014. *Chin J Cancer Res.* **2018**;30(3):291–298. doi:10.21147/j.issn.1000-9604.2018.03.01
29. Stewart C, Chao J, Chen YJ, et al. Multimodality management of locally advanced gastric cancer-The timing and extent of surgery. *Transl Gastroenterol Hepatol.* **2019**;4:42. doi:10.21037/tgh.2019.05.02
30. Chen LT, Kang YK, Tanimoto M, Boku N. 777TiPATTRACTION-04 (ONO-4538-37): a randomized, multicenter, phase 2/3 study of nivolumab (Nivo) plus chemotherapy in patients (Pts) with previously untreated advanced or recurrent gastric (G) or gastroesophageal junction (GEJ) cancer. *Ann Oncol.* **2017**;28(suppl\_5):v266. doi:10.1093/annonc/mdx369.159
31. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer: an open-label, dose-escalation, and dose-expansion phase Ib trial (REGONIVO, EPOC1603). *J Clin Oncol.* **2020**;38(18):2053–2061. doi:10.1200/JCO.19.03296
32. Japanese Gastric Cancer Association. *Japanese Gastric Cancer Treatment Guidelines 2018*. 5th ed. Gastric Cancer; **2020**.
33. Qiu H, Zhou Z. [Updates and interpretation on NCCN clinical practice guidelines for gastric cancer 2017 version 5]. *Zhonghua Wei Chang Wai Ke Za Zhi.* **2018**;21(2):160–164. Chinese.
34. Ji J, Liang H, Xue Y, Shen L, Zhang X. Peri/post-operative chemotherapy of oxaliplatin combined with S-1 (SOX) versus post-operative oxaliplatin with capecitabine (XELOX) in locally advanced gastric cancer: RESOLVE Trial. *J Clin Oncol.* **2017**;35(15 suppl):e15519–e. doi:10.1200/JCO.2017.35.15\_suppl.e15519
35. Kobayashi K, Iwatsuki M, Orita H, et al. 670PPPhase II study of S-1 and oxaliplatin as neo-adjuvant chemotherapy for locally advanced gastric and esophago-gastric cancer (KSCC1601). *Ann Oncol.* **2018**;29(suppl\_8):viii225–viii226. doi:10.1093/annonc/mdy282.054
36. Zhao Q, Li Y, Huang J, Fan L, Liu Y. Short-term curative effect of S-1 plus oxaliplatin as perioperative chemotherapy for locally advanced gastric cancer: a Prospective Comparison Study. *Die Pharmazie.* **2017**;72(4):236.
37. Zheng Y, Yang X, Yan C, et al. Effect of apatinib plus neoadjuvant chemotherapy followed by resection on pathologic response in patients with locally advanced gastric adenocarcinoma: a single-arm, open-label, phase II trial. *Eur J Cancer.* **2020**;130:12–19. doi:10.1016/j.ejca.2020.02.013

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