



OPEN ACCESS

EDITED BY

Stavros P. Papadakos,
Laiko General Hospital of Athens, Greece

REVIEWED BY

Maria Davern,
Dana–Farber Cancer Institute, United States

*CORRESPONDENCE

Xianlei Cai

✉ lhlcaxianlei@nbu.edu.cn

Weiming Yu

✉ lhlyuweiming@nbu.edu.cn

RECEIVED 11 October 2025

REVISED 25 November 2025

ACCEPTED 03 December 2025

PUBLISHED 17 December 2025

CITATION

Cai X, Xiao X, Zhang C and Yu W (2025)
Perioperative immunotherapy in gastric
cancer: walking a fine line between
hope and caution.
Front. Immunol. 16:1722749.
doi: 10.3389/fimmu.2025.1722749

COPYRIGHT

© 2025 Cai, Xiao, Zhang and Yu. This is an
open-access article distributed under the terms
of the [Creative Commons Attribution License
\(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction
in other forums is permitted, provided the
original author(s) and the copyright owner(s)
are credited and that the original publication
in this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Perioperative immunotherapy in gastric cancer: walking a fine line between hope and caution

Xianlei Cai*, Xia Xiao, Congcong Zhang and Weiming Yu*

Department of Gastrointestinal Surgery, The Affiliated Lihuili Hospital of Ningbo University (Ningbo Medical Center Lihuili Hospital), Ningbo, Zhejiang, China

Perioperative immunotherapy has emerged as an important strategy in the management of resectable gastric and gastroesophageal junction adenocarcinoma. Phase II and III studies combining immune checkpoint inhibitors with chemotherapy have shown higher pathological response rates and improvements in event-free outcomes, particularly in molecularly selected groups such as HER2-positive and MSI-H or dMMR tumors. MSI-H and dMMR cancers show marked sensitivity to immune treatment, often achieving high rates of pathological complete response. Combinations that include HER2-directed therapy and immunotherapy have also produced encouraging antitumor activity. However, the results in broader, unselected populations remain variable, and reliable predictive markers such as PD-L1 are still lacking. While safety profiles are generally acceptable, some treatment regimens, especially those involving antiangiogenic agents or dual checkpoint blockade, call for careful perioperative evaluation. Importantly, despite improvements in pathological and early clinical outcomes, the impact on overall survival has been limited so far, and longer follow-up is needed to clarify the true survival benefit. Future progress will depend on better patient selection through integrated molecular and immune markers, more thoughtful sequencing of therapies, and the development of combination strategies that can enhance the durability of response. These findings highlight both the promise of perioperative immunotherapy and the need for continued efforts to achieve meaningful survival gains.

KEYWORDS

perioperative immunotherapy, gastric cancer, clinical trial, biomarkers, pathological response rate

Introduction

Gastric cancer remains a significant global health burden (1), with conventional perioperative chemotherapy regimens such as FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) demonstrating limited efficacy in preventing recurrence (2). Immunotherapy has fundamentally reshaped the therapeutic landscape for advanced gastric cancer, establishing a new standard of care in the metastatic setting (3–5). The

integration of immune checkpoint inhibitors (ICIs) into perioperative treatment strategies has emerged as a promising approach to improve outcomes for patients with resectable gastric and gastroesophageal junction (G/GEJ) adenocarcinoma. This paradigm shift is supported by robust evidence from metastatic settings, where immunotherapy has substantially improved survival (6). The unique immunological microenvironment of gastric cancer, particularly in subtypes with microsatellite instability-high (MSI-H) or programmed death-ligand 1 (PD-L1) positivity, provides a strong rationale for incorporating ICIs in earlier disease stages. This review synthesizes recent advancements from key phase II and III clinical trials investigating perioperative immunotherapy, highlighting efficacy endpoints, biomarker exploration, and safety profiles (Table 1). Furthermore, it examines specialized approaches for HER2-positive and dMMR/MSI-H subgroups, discusses predictive biomarkers, and outlines future research directions aimed at personalizing treatment and overcoming resistance mechanisms.

Perioperative immunotherapy combined with chemotherapy in gastric cancer: phase III clinical research progress

The phase III MATTERHORN trial represents a landmark study evaluating the addition of durvalumab to FLOT chemotherapy in resectable G/GEJ adenocarcinoma (7). This multinational, double-blind, randomized trial demonstrated a significant improvement in event-free survival (EFS) with durvalumab plus FLOT compared to FLOT alone (67.4% vs. 58.5% at 2 years; HR 0.71). The pathological complete response (pCR) rate was substantially higher in the durvalumab group (19.2% vs. 7.2%), and overall survival (OS) also favored the experimental arm (75.7% vs. 70.4% at 2 years) (7). These findings establish a new benchmark for perioperative immunotherapy in unselected populations.

Similarly, the KEYNOTE-585 trial investigated pembrolizumab combined with cisplatin-based chemotherapy or FLOT (8). While it met its primary endpoint for pCR (12.9% vs. 2.0%), the improvement in EFS did not reach statistical significance (HR 0.81), suggesting that not all immunotherapy combinations yield equivalent benefits (8). The contrasting outcomes between MATTERHORN and KEYNOTE-585 may be attributed to differences in chemotherapy backbones, patient selection, or immunotherapy agents.

The DRAGON IV/CAP 05 trial explored a novel combination of camrelizumab (anti-PD-1), rivocecanib (VEGFR-2 inhibitor), and chemotherapy (SOX) (9). This regimen significantly improved pCR rates compared to chemotherapy alone (18.3% vs. 5.0%), indicating that dual targeting of PD-1 and VEGF pathways may provide synergistic antitumor effects (9).

For adjuvant therapy specifically, the ATTRACTION-5 trial evaluated nivolumab plus chemotherapy after D2 gastrectomy in

stage III gastric cancer (10). Contrary to expectations, the addition of nivolumab did not improve relapse-free survival (HR 0.90), highlighting the potential differences between neoadjuvant and adjuvant immunotherapy approaches (10). This suggests that the immunosuppressive microenvironment following surgery may limit the efficacy of adjuvant immunotherapy, or that patient selection criteria need refinement.

These phase III trials collectively demonstrate that while perioperative immunotherapy shows promise, its benefits are not uniform across all regimens and patient populations. The MATTERHORN regimen has emerged as a potential new standard of care, while other combinations require further optimization.

Perioperative immunotherapy combined with chemotherapy in gastric cancer: phase II clinical research progress

Phase II trials have been instrumental in exploring diverse immunotherapy combinations and identifying responsive patient subsets. The MONEO trial evaluated avelumab plus FLOT, demonstrating a pCR rate of 21.1% and a major pathological response (MPR) rate of 28.9% (11). Importantly, responses were more pronounced in patients with PD-L1 combined positive score (CPS) ≥ 10 (33.3% vs. 21.1%), providing early evidence for biomarker-driven patient selection (11).

Several studies have investigated PD-1 inhibitors with chemotherapy backbones commonly used in Asian populations. A phase II trial of sintilimab plus FLOT in HER2-negative G/GEJ cancer showed a pCR rate of 17.2% and MPR rate of 55.2% (12). The NEOSUMMIT-01 trial demonstrated that toripalimab plus SOX/XELOX significantly improved tumor regression grade (TRG) 0/1 rates compared to chemotherapy alone (44.4% vs. 20.4%) (13). Similarly, tislelizumab plus SOX in the NEOSUMMIT-03 trial achieved an MPR rate of 50.0% and pCR rate of 25.0% (14).

The combination of immunotherapy with antiangiogenic agents has also shown promise. A randomized phase II trial found that camrelizumab and apatinib combined with chemotherapy (nab-paclitaxel plus S-1) significantly improved MPR rates compared to chemotherapy alone (33.3% vs. 17.0%) (15). This approach targets multiple pathways simultaneously and may benefit patients with immunosuppressive tumor microenvironments.

For radiotherapy combinations, the Neo-PLANET trial evaluated camrelizumab with concurrent chemoradiotherapy, demonstrating a pCR rate of 33.3% (16). This suggests that radiotherapy may enhance the immunogenicity of tumors and synergize with immunotherapy, though this approach requires further validation.

These phase II trials collectively indicate that perioperative immunotherapy combinations can achieve pCR rates of 15-30% and MPR rates of 30-55% in unselected populations. The variability in responses highlights the need for better patient selection strategies and the importance of biomarker development.

TABLE 1 Characteristics of key phase II and III neoadjuvant/perioperative immunotherapy ± chemotherapy trials in resectable gastric and gastroesophageal junction cancer.

Year	Study name/ identifier	Phase	Experimental/ control arm (n)	Experimental regimen	Control regimen	MPR rate (%)	pCR rate (%)	R0 (%)	EFS/DFS/PFS	OS	Grade 3–4 adverse events (%)
Unselected											
2025	MATTERHORN	Phase III, double-blind, randomized, international	533/530	Durvalumab + FLOT	Placebo + FLOT	33 vs 24	19 vs 10	93 vs 93	24-mo EFS: 67.4% vs 58.5%, HR:0.71; 95%CI: (0.58-0.86)	3-year OS: 68.6% vs 61.9% HR:0.78; 95%CI: (0.63-0.95)	71.6 vs 71.2
2024	KEYNOTE-585	Phase III, randomized, double-blind, multicenter	503/498 (Cohort D: pemb + FP); 280/279 (Cohort F: pemb+ CAPOX)	Pemb + chemo (FP or CAPOX)	Placebo + chemo (FP or CAPOX)	28 vs 15 (FP cohort); 24 vs 12 (CAPOX cohort)	13 vs 5 (FP); 10 vs 3 (CAPOX)	91 vs 90	mEFS 44.4m vs 25.7m; HR:0.81; 95%CI: (0.67-0.98)	mOS 71.8m vs 55.7m; HR:0.86; 95%CI: (0.71-1.06)	71 vs 68
2025	DRAGON IV/ CAP-05	Phase III, randomized, multicenter	180/180	Camrelizumab + rivoceranib + SOX (SOXRC)	SOX	51.1 vs 37.8	18.3 vs 5.0	99 VS 94	N/A	N/A	34 vs 17
2025	MONEO	Phase II	40	Avelumab + FLOT4:	None	28.9	21.1%	N/A	3-year DFS: 66%	3-year OS: 69%	80
2024	N/A	Phase II	32	Sintilimab + FLOT	None	55.2	17.2	93.1	3-year EFS: 71.4	3-year OS: 70.9	59.4
2024	NEOSUMMIT-01	Phase II, randomized	54/54	Toripalimab + SOX/ XELOX	SOX/XELOX	44.4 vs 20.4	22.2 vs 7.4	N/A	N/A	N/A	35.2 vs 29.6
2025	NEOSUMMIT-03	Phase II	32	Tislelizumab + SOX	None	50.0	28.1	96.9	N/A	N/A	31.2
2024	NCT04195828	Phase II, multicenter, randomized	51/53	Camrelizumab + Apatinib + nab-Paclitaxel + S-1	nab-Paclitaxel + S-1	33.3 VS 17.0	N/A	94.1	N/A	N/A	33.3 vs 26.4
2022	Neo-PLANET	Phase II	36	Camrelizumab + concurrent chemoradiotherapy	None	44.4	33.3	91.7	2-year PFS: 66.9%	2-year OS: 76.1%	75.0
2024	PANDA	Phase II	21	Atezolizumab + docetaxel + oxaliplatin + capecitabine	None	70	45	100	N/A	N/A	10
2025	NCT03288350	Phase II	51	Avelumab+ docetaxel + cisplatin + 5-fluorouracil	None	18	14	N/A	2-year DFS: 67.5%	N/A	40
2024	WuhanUHGI001	Phase II	49	Tislelizumab + SOX	None	49.0	26.5	N/A	2-year PFS: 69.4%	2-year OS: 81.2%	12.2
2024	NCT05602935	Phase II	29	Camrelizumab + SOX	None	69.0	10.3	96.6	N/A	N/A	0

(Continued)

TABLE 1 Continued

Year	Study name/ identifier	Phase	Experimental/ control arm (n)	Experimental regimen	Control regimen	MPR rate (%)	pCR rate (%)	R0 (%)	EFS/DFS/PFS	OS	Grade 3–4 adverse events (%)
Her2+											
2025	ChiCTR2200058732	Phase II	22	Sintilimab + Trastuzumab)+ chemotherapy	None	55	50	N/A	N/A	N/A	27
2025	NCT04661150.	Phase II, randomized	21/21	Atezolizumab + Trastuzumab + XELOX	Trastuzumab + XELOX	N/A	38 VS 14	N/A	N/A	N/A	57 VS 67
2025	NCT03950271	Phase II	25	Camrelizumab + Trastuzumab + CapOx	None	30.4	21.7	100	3-year DFS: 78.3	N/A	36
MSI-H/dMMR											
2023	NEONPIGA	Phase II	32	Nivolumab + Ipilimumab	None	N/A	58.6	100	N/A	N/A	19
2025	INFINITY	Phase II	18	Tremelimumab + Durvalumab	None	80	60	N/A	2-year PFS: 85	2-year OS: 92	17
2025	NICE	Phase II	16	Toripalimab + CapeOX	None	93.3	80	100	N/A	N/A	37.5

HER2-positive gastric cancer: perioperative immunotherapy combined with targeted therapy

HER2-positive gastric cancer represents a distinct subtype where dual blockade of HER2 and immune checkpoints may yield synergistic effects. A phase II trial evaluating sintilimab (PD-1 inhibitor) plus trastuzumab and chemotherapy demonstrated impressive results, with 55% of patients achieving MPR and 50% achieving pCR (17). These response rates substantially exceed those historically observed with trastuzumab and chemotherapy alone, suggesting that immune activation may enhance the antitumor effects of HER2 blockade.

Similarly, a randomized phase II trial compared atezolizumab plus trastuzumab and XELOX versus trastuzumab and XELOX alone (18). The addition of atezolizumab significantly improved pCR rates (38% vs. 14%), particularly in patients younger than 65 years, males, and those with intestinal-type histology (18). This study provides further evidence that immune checkpoint inhibition can augment the efficacy of HER2-targeted therapy.

The single-arm phase II trial of camrelizumab plus trastuzumab and CapOx showed a pCR rate of 21.7% and near-pCR rate of 30.4% (19). Importantly, no patients achieving pCR experienced recurrence during follow-up, suggesting that pathological response may serve as a surrogate for long-term outcomes in this population (19).

Mechanistic studies have revealed that HER2-targeted therapy may enhance antigen presentation and T-cell infiltration, potentially creating a more favorable microenvironment for immunotherapy (17, 18). However, resistance mechanisms involving regulatory T cells have been identified, suggesting that additional immunomodulatory strategies may be needed for complete responses (17).

These findings position immunotherapy plus HER2-targeted therapy as a promising approach for HER2-positive gastric cancer, with several regimens demonstrating superior pathological response rates compared to historical controls. Ongoing trials are further exploring this combination and seeking to identify optimal patient selection criteria.

dMMR/MSI-H gastric cancer: perioperative immunotherapy and non-operative management

Deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) gastric cancers exhibit exceptional sensitivity to immune checkpoint blockade due to their high tumor mutational burden and abundant neoantigen presentation. The NEONIPIGA phase II study evaluated neoadjuvant nivolumab plus ipilimumab (CTLA-4 inhibitor) in locally advanced resectable dMMR/MSI-H G/GEJ adenocarcinoma (20). This chemo-free regimen achieved a remarkable pCR rate of 58.6% among patients who underwent

surgery, demonstrating that immunotherapy alone can induce substantial tumor regression in this molecular subset (20).

The INFINITY study took a more ambitious approach by investigating non-operative management for dMMR/MSI-H tumors achieving clinical complete response (cCR) after tremelimumab plus durvalumab (21). In cohort 1 (neoadjuvant), the pCR rate was 60%, while in cohort 2 (non-operative management), 13 of 17 assessable patients achieved cCR and avoided surgery (21). With a median follow-up of 11.5 months, the 12-month gastrectomy-free survival was 64.2%, providing preliminary evidence that selected patients may be spared surgical morbidity without compromising outcomes (21).

The NICE trial reported exceptional pathological complete response rates of 80% in dMMR/MSI-H patients treated with neoadjuvant toripalimab plus CapeOX, yet such dramatic responses in molecularly enriched populations may not reflect outcomes in broader patient groups (22).

These findings challenge the traditional paradigm of mandatory surgical resection for localized gastric cancer and suggest that organ preservation may be feasible in dMMR/MSI-H patients achieving complete response to immunotherapy (20, 21). However, longer follow-up is needed to confirm the durability of these responses and establish reliable criteria for patient selection. The exceptional response of dMMR/MSI-H tumors to immunotherapy underscores the importance of universal molecular testing in gastric cancer patients. These results also provide a strong rationale for upfront immunotherapy in this population, potentially avoiding the toxicity of chemotherapy while achieving superior outcomes.

Biomarkers and efficacy prediction

Identifying reliable biomarkers to predict response to perioperative immunotherapy remains a critical research focus. PD-L1 expression, as measured by combined positive score (CPS), has shown variable predictive value across studies (11, 23). While the MONEO trial observed better responses in patients with CPS ≥ 10 (11), other studies found no correlation between PD-L1 status and pathological response (12, 24), suggesting limited utility as a standalone biomarker.

MSI-H/dMMR status consistently predicts exceptional response to immunotherapy (20, 21), though this molecular subtype represents only a small proportion of gastric cancers. Beyond MSI status, multi-omics approaches have identified several potential predictive biomarkers. Transcriptomic analyses have revealed that regulatory T cell infiltration is associated with resistance to dual PD-1/HER2 blockade (17), while M2-tumor-associated macrophage proliferation correlates with lack of response (24).

A prospective phase II trial identified intestinal subtype by Lauren classification as a key predictor of sensitivity to neoadjuvant immunochemotherapy (25). Mechanistically, intestinal-type tumors exhibited increased DNA damage repair-active cancer cells and enrichment of CLEC9A+ dendritic cells in the tumor microenvironment (25). Based on these findings, a machine

learning model integrating transcriptomic features of both epithelial and immune compartments was developed to accurately predict treatment response (25).

Peripheral immune markers have also shown promise. The WuhanUHGI001 trial found that preoperative circulating tumor cells combined with pathological responses helped in prognosis assessment (26). Additionally, T downstaging, lymphocyte-to-monocyte ratio, and CD3+ T cells were independent factors affecting progression-free survival (26).

Emerging biomarkers beyond conventional markers show promise in refining patient selection. Tumor microenvironment characteristics, including the presence of PDPN+ cancer-associated fibroblasts, have been associated with reduced likelihood of pathological response to immunotherapy (27). Similarly, CD8A expression and PGF levels have demonstrated predictive value for treatment response in gastric cancer patients receiving neoadjuvant immunotherapy (28). Multimodal biomarker approaches incorporating circulating tumor DNA, immune cell infiltration patterns, and transcriptomic signatures may further enhance patient selection (26, 29). The development of validated predictive models integrating clinical, pathological, and molecular variables represents an essential step toward personalized perioperative immunotherapy (26).

These emerging biomarkers reflect the complex interplay between tumor cells and the immune microenvironment. While no single biomarker has yet been validated for routine clinical use, multi-parameter models incorporating tumor and immune characteristics show promise for personalizing perioperative immunotherapy approaches.

Safety management and treatment-related adverse events

The safety profile of perioperative immunotherapy combinations is generally manageable, with most adverse events being attributable to the chemotherapy component. In the phase III MATTERHORN trial, the incidence of grade 3-4 adverse events was similar between the durvalumab and placebo groups (71.6% vs. 71.2%) (7). Similarly, the KEYNOTE-585 trial reported comparable rates of grade 3 or higher adverse events between pembrolizumab and placebo arms (78% vs. 74%) (8).

Common immunotherapy-related adverse events include immune-mediated toxicities such as rash, thyroid dysfunction, and hepatitis, which are generally manageable with corticosteroids and treatment interruption (19, 30). The incidence of these events varies across studies, with some reporting grade 3-4 immune-related adverse events in approximately 10% of patients (23).

Surgical safety is a particular concern in the perioperative setting. Most trials have reported no significant increase in surgical complications or mortality with the addition of immunotherapy (7, 13, 14). For instance, the NEOSUMMIT-01 trial found comparable surgical morbidity between toripalimab plus

chemotherapy and chemotherapy alone groups (11.8% vs. 13.5%) (13).

However, specific combinations may present unique safety considerations. The integration of immunotherapy into perioperative treatment protocols introduces unique safety considerations that extend beyond those observed in metastatic disease. Patients undergoing multimodality therapy for locally advanced gastric cancer face compounded toxicities from combined surgical stress, chemotherapy, and immune activation (31). The addition of antiangiogenic agents to immunotherapy and chemotherapy can increase the risk of hypertension, proteinuria, and wound healing complications (9, 15). Immune-related adverse events, including myocarditis, hepatitis, pneumonitis, and rare manifestations such as ureteritis/cystitis, present particular challenges in the preoperative period, potentially delaying curative surgery or complicating postoperative recovery (32, 33).

The perioperative period represents a physiologically vulnerable state characterized by surgical stress, transient immunosuppression, and metabolic alterations that may modulate both the efficacy and toxicity of immunotherapy (29, 34). This altered immune context raises legitimate concerns about potentially exacerbating irAEs during surgical recovery (32). Furthermore, the VESTIGE trial demonstrated that adjuvant nivolumab/ipilimumab actually resulted in worse disease-free survival compared to chemotherapy in high-risk patients (ypN+ and/or R1) following neoadjuvant chemotherapy and resection, highlighting that immune interventions are not universally beneficial even in settings of minimal residual disease (33). This sobering result emphasizes that the perioperative immune environment may differ fundamentally from that of advanced disease, necessitating careful risk-benefit assessment for each patient.

These findings highlight the importance of careful patient selection, proactive monitoring, and multidisciplinary management when implementing perioperative immunotherapy. While the toxicity profile is generally acceptable, specific combinations may require additional precautions and specialized management approaches.

Conclusion and future perspectives

Perioperative immunotherapy has fundamentally transformed the treatment landscape for resectable gastric cancer, with phase III trials demonstrating improved pathological responses and survival outcomes (7, 9). The integration of immune checkpoint inhibitors with chemotherapy has established a new standard of care, particularly for microsatellite stable tumors (7). For molecularly selected populations, including HER2-positive and dMMR/MSI-H subgroups, targeted combinations and chemo-free approaches have shown remarkable efficacy.

Current evidence shows that perioperative immunotherapy can improve pCR and EFS in patients with advanced gastric cancer, but the overall survival benefit remains limited. Because OS is the most meaningful outcome for patients, these earlier improvements

should be viewed with caution. Several reasons may explain the modest impact on OS, including relatively short follow-up, the biological diversity of gastric cancer, the use of additional treatments after recurrence, and the fact that a better pathological response does not always translate into long-term survival gains.

Future research should focus on several key areas. First, optimizing patient selection through validated biomarkers remains paramount. While PD-L1 and MSI status provide some guidance, more comprehensive biomarkers incorporating tumor and immune microenvironment characteristics are needed. Second, the sequencing and duration of perioperative therapy require refinement, particularly regarding the role of adjuvant immunotherapy after achieving pathological complete response. Third, novel combinations targeting complementary pathways, such as VEGF or LAG-3, may benefit patient subsets with inherent resistance to PD-1/PD-L1 blockade (15, 35).

The exploration of non-operative management for exceptional responders represents another frontier (21). While preliminary data from the INFINITY study are encouraging, longer follow-up and larger cohorts are needed to validate this approach (21). Finally, understanding and overcoming resistance mechanisms through translational research will be crucial for further improving outcomes (17).

In conclusion, perioperative immunotherapy has ushered in a new era for gastric cancer treatment, offering unprecedented response rates and survival benefits for selected patients. Through continued research and biomarker development, these approaches will become increasingly personalized and effective, ultimately improving outcomes for patients with this challenging disease.

Author contributions

XC: Validation, Investigation, Conceptualization, Writing – original draft, Formal Analysis, Visualization. XX: Visualization,

Validation, Writing – original draft. CZ: Writing – original draft. WY: Conceptualization, Writing – review & editing.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The authors declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Cai XL, Li XY, Zhang MZ, Dong ZB, Weng YH, Yu WM. RBM15 promotes lipogenesis and Malignancy in gastric cancer by regulating N6-Methyladenosine modification of ACLY mRNA in an IGF2BP2-dependent manner. *Biochim Et Biophys Acta-Molecular Cell Biol Lipids*. (2025) 1870:159580. doi: 10.1016/j.bbalip.2024.159580
- Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. (2019) 393:1948–57. doi: 10.1016/S0140-6736(18)32557-1
- Lote H, Chau I. Immunotherapy in gastrointestinal cancers. *Cancer Treat Res*. (2024) 192:277–303. doi: 10.1007/978-3-031-61238-1_14
- Xu J, Jiang H, Pan Y, Gu K, Cang S, Han L, et al. Sintilimab plus chemotherapy for unresectable gastric or gastroesophageal junction cancer: the ORIENT-16 randomized clinical trial. *Jama*. (2023) 330:2064–74. doi: 10.1001/jama.2023.19918
- Qiu MZ, Oh DY, Kato K, Arkenau T, Tabernero J, Correa MC, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial. *BMJ*. (2024) 385:e078876. doi: 10.1136/bmj-2023-078876
- Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, 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) 398:27–40. doi: 10.1016/S0140-6736(21)00797-2
- Janjigian YY, Al-Batran SE, Wainberg ZA, Muro K, Molena D, Van Cutsem E, et al. Perioperative durvalumab in gastric and gastroesophageal junction cancer. *New Engl J Med*. (2025) 393:217–30. doi: 10.1056/NEJMoa2503701
- Shitara K, Rha SY, Wyrwicz LS, Oshima T, Karaseva N, Osipov M, et al. Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): an interim analysis of the multicentre, double-blind, randomised phase 3 study. *Lancet Oncol*. (2024) 25:212–24. doi: 10.1016/S1470-2045(23)00541-7
- Li C, Tian Y, Zheng Y, Yuan F, Shi Z, Yang L, et al. Pathologic response of phase III study: perioperative camrelizumab plus rivoceranib and chemotherapy versus chemotherapy for locally advanced gastric cancer (DRAGON IV/CAP 05). *J Clin Oncol*. (2025) 43:464–74. doi: 10.1200/JCO.24.00795
- Kang YK, Terashima M, Kim YW, Boku N, Chung HC, Chen JS, et al. Adjuvant nivolumab plus chemotherapy versus placebo plus chemotherapy for stage III gastric or gastro-oesophageal junction cancer after gastrectomy with D2 or more extensive lymph-node dissection (ATTRACTION-5): a randomised, multicentre, double-blind,

- placebo-controlled, phase 3 trial. *Lancet Gastroenterol hepatology*. (2024) 9:705–17. doi: 10.1016/S2468-1253(24)00156-0
11. Alsina M, Villacampa G, de Andrea C, Vivancos A, Ponz-Sarvisse M, Arrazubi Y, et al. A phase II study of perioperative avelumab plus chemotherapy for patients with resectable gastric cancer or gastroesophageal junction cancer - the MONEO study. *Clin Cancer Res*. (2025) 31:2890–8. doi: 10.1158/1078-0432.CCR-25-0369
 12. Li N, Li Z, Fu Q, Zhang B, Zhang J, Wan XB, et al. Efficacy and safety of neoadjuvant sintilimab in combination with FLOT chemotherapy in patients with HER2-negative locally advanced gastric or gastroesophageal junction adenocarcinoma: an investigator-initiated, single-arm, open-label, phase II study. *Int J Surg (London England)*. (2024) 110:2071–84. doi: 10.1097/JS9.0000000000001119
 13. Yuan SQ, Nie RC, Jin Y, Liang CC, Li YF, Jian R, et al. Perioperative toripalimab and chemotherapy in locally advanced gastric or gastro-oesophageal junction cancer: a randomized phase 2 trial. *Nat Med*. (2024) 30:552–9. doi: 10.1038/s41591-023-02721-w
 14. Nie RC, Yuan SQ, Ding Y, Chen YM, Li YF, Liang CC, et al. Perioperative tislelizumab plus chemotherapy for locally advanced gastroesophageal junction adenocarcinoma (NEOSUMMIT-03): a prospective, nonrandomized, open-label, phase 2 trial. *Signal Transduct Target Ther*. (2025) 10:60. doi: 10.1038/s41392-025-02160-8
 15. Lin JX, Tang YH, Zheng HL, Ye K, Cai JC, Cai LS, et al. Neoadjuvant camrelizumab and apatinib combined with chemotherapy versus chemotherapy alone for locally advanced gastric cancer: a multicenter randomized phase 2 trial. *Nat Commun*. (2024) 15:41. doi: 10.1038/s41467-023-44309-5
 16. Tang Z, Wang Y, Liu D, Wang X, Xu C, Yu Y, et al. The Neo-PLANET phase II trial of neoadjuvant camrelizumab plus concurrent chemoradiotherapy in locally advanced adenocarcinoma of stomach or gastroesophageal junction. *Nat Commun*. (2022) 10.1038/s41467-022-34403-5
 17. Nie RC, Chen XJ, Liang CC, Zhao BW, Wang W, Zhang FY, et al. Safety and efficacy of perioperative dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Cell Rep Med*. (2025) 6:102190. doi: 10.1016/j.xcrm.2025.102190
 18. Peng Z, Zhang X, Liang H, Zheng Z, Wang Z, Liu H, et al. Atezolizumab and trastuzumab plus chemotherapy for ERBB2-positive locally advanced resectable gastric cancer: A randomized clinical trial. *JAMA Oncol*. (2025) 11:619–24. doi: 10.1001/jamaoncol.2025.0522
 19. Ma Y, Li Z, Wei C, Zhang J, Fu Q, Zhang Z, et al. Neoadjuvant camrelizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastroesophageal junction adenocarcinoma: a single-arm, phase 2 trial. *Gastric Cancer*. (2025) 28:652–61. doi: 10.1007/s10120-025-01606-w
 20. André T, Tougeron D, Piessen G, de la Fouchardière C, Louvet C, Adenis A, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: the GERCOR NEONIPIGA phase II study. *J Clin Oncol*. (2023) 41:255–65. doi: 10.1200/JCO.22.00686
 21. Raimondi A, Lonardi S, Murgioni S, Cardellino GG, Tamperi S, Strippoli A, et al. Tremelimumab and durvalumab as neoadjuvant or non-operative management strategy of patients with microsatellite instability-high resectable gastric or gastroesophageal junction adenocarcinoma: the INFINITY study by GONO. *Ann Oncol*. (2025) 36:285–96. doi: 10.1016/j.annonc.2024.11.016
 22. Zhao L, Liu H, Yu J, Yuan S, Liang H, Wang W, et al. Efficacy and safety of neoadjuvant toripalimab plus chemotherapy in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma (NICE): a multicentre, single-arm, exploratory phase 2 study. *EClinicalMedicine*. (2025) 87:103421. doi: 10.1016/j.eclim.2025.103421
 23. Verschoor YL, van de Haar J, van den Berg JG, van Sandick JW, Kodach LL, van Dieren JM, et al. Neoadjuvant atezolizumab plus chemotherapy in gastric and gastroesophageal junction adenocarcinoma: the phase 2 PANDA trial. *Nat Med*. (2024) 30:519–30. doi: 10.1038/s41591-023-02758-x
 24. Alcindor T, Tankel J, Fiset PO, Pal S, Opu T, Strasser M, et al. Phase 2 trial of perioperative chemo-immunotherapy for gastro-oesophageal adenocarcinoma: The role of M2 macrophage landscape in predicting response. *Cell Rep Med*. (2025) 6:102045. doi: 10.1016/j.xcrm.2025.102045
 25. Wang L, Sun M, Li J, Wan L, Tan Y, Tian S, et al. Intestinal subtype as a biomarker of response to neoadjuvant immunochemotherapy in locally advanced gastric adenocarcinoma: insights from a prospective phase II trial. *Clin Cancer Res*. (2025) 31:74–86. doi: 10.1158/1078-0432.CCR-24-2436
 26. Sun X, Lyu J, Yang M, Lin Y, Wu K, Liu K, et al. Two-year outcomes and biomarker analysis of locally advanced gastric and gastroesophageal junction adenocarcinoma after neoadjuvant chemotherapy and immunotherapy from the phase II wuhanUHGI001 trial. *Ann Surg Oncol*. (2024) 31:8157–69. doi: 10.1245/s10434-024-16041-x
 27. Jian M, Yang Z, Tang Y, Jiang F, Cai L, Liu A, et al. PDPN+ cancer-associated fibroblasts correlate with the neoadjuvant immunotherapy response in gastric cancer. *APL bioengineering*. (2025) 9:036115. doi: 10.1063/5.0250475
 28. Zhang C, Wang T, Yuan J, Wang T, Ma B, Xu B, et al. Potential predictive value of CD8A and PGF protein expression in gastric cancer patients treated with neoadjuvant immunotherapy. *BMC Cancer*. (2025) 25:674. doi: 10.1186/s12885-025-14046-7
 29. Ji Z, Wang X, Xin J, Ma L, Zuo D, Li H, et al. Multiomics reveals tumor microenvironment remodeling in locally advanced gastric and gastroesophageal junction cancer following neoadjuvant immunotherapy and chemotherapy. *J immunotherapy cancer*. (2024) 12:e010041. doi: 10.1136/jitc-2024-010041
 30. Zhong WJ, Lin JA, Wu CY, Wang J, Chen JX, Zheng H, et al. Efficacy and safety of camrelizumab combined with oxaliplatin and S-1 as neoadjuvant treatment in locally advanced gastric or gastroesophageal junction cancer: A phase II, single-arm study. *Cancer Med*. (2024) 13:e7006. doi: 10.1002/cam4.7006
 31. Yu Z, Liang C, Xu Q, Yuan Z, Chen M, Li R, et al. The safety and efficacy of neoadjuvant PD-1 inhibitor plus chemotherapy for patients with locally advanced gastric cancer: a systematic review and meta-analysis. *Int J Surg (London England)*. (2025) 111:1415–26. doi: 10.1097/JS9.0000000000002056
 32. Ji J, Lai CH, Zhang X, Hu H. Immune-related adverse events with renal colic as the main manifestation: a case report of sintilimab-induced ureteritis/cystitis treated by ureteral stent and review of the literature. *Front Immunol*. (2024) 15:1501415. doi: 10.3389/fimmu.2024.1501415
 33. Lordick F, Mauer ME, Stocker G, Cella CA, Ben-Aharon I, Piessen G, et al. Adjuvant immunotherapy in patients with resected gastric and oesophagogastric junction cancer following preoperative chemotherapy with high risk for recurrence (ypN+ and/or R1): European Organisation of Research and Treatment of Cancer (EORTC) 1707 VESTIGE study. *Ann Oncol*. (2025) 36:197–207. doi: 10.1016/j.annonc.2024.10.829
 34. Sun F, Gao X, Li T, Zhao X, Zhu Y. Tumor immune microenvironment remodeling after neoadjuvant therapy in gastric cancer: Update and new challenges. *Biochim Biophys Acta Rev cancer*. (2025) 1880:189350. doi: 10.1016/j.bbcan.2025.189350
 35. Kelly RJ, Landon BV, Zaidi AH, Singh D, Canzoniero JV, Balan A, et al. Neoadjuvant nivolumab or nivolumab plus LAG-3 inhibitor relatlimab in resectable esophageal/gastroesophageal junction cancer: a phase Ib trial and ctDNA analyses. *Nat Med*. (2024) 30:1023–34. doi: 10.1038/s41591-024-02877-z