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Case Report

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Curative Conversion of Metastatic Gastric Cancer After Pembrolizumab-Trastuzumab-Based Therapy in a PD-L1-Negative, HER2-Positive Patient: A Case Report and Literature Review

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Abstract

Introduction

Metastatic gastric cancer (mGC) is a challenging malignancy with poor survival outcomes. Immune checkpoint inhibitors (ICIs), including pembrolizumab, have shown promise in improving responses, particularly in Programmed Death-Ligand 1 (PD-L1)-positive and Microsatellite Instability (MSI)-high tumours. However, based on trial data, only patients with PD-L1-high (Combined Positive Score (CPS) ≥1) or microsatellite-unstable tumours are expected to derive benefit from ICIs.

Case Presentation

We report a 60-year-old male who presented with epigastric pain, early satiety, and significant weight loss. Esophagogastroduodenoscopy revealed an ulcerated gastric mass, and biopsy confirmed poorly differentiated gastric adenocarcinoma. Staging investigations demonstrated metastatic disease with omental, peritoneal, and distant nodal involvement (cT4N3M1). Immunohistochemistry showed strong HER2 positivity (IHC 3+), PD-L1 negativity (CPS <1), and proficient mismatch repair (pMMR). He was treated with pembrolizumab and trastuzumab-based chemotherapy. Following nine cycles, imaging revealed near-complete radiological response. The patient underwent radical total gastrectomy, splenectomy, omentectomy, and perigastric lymphadenectomy and pathological examination confirmed a complete pathological response (ypT0N0). The patient remains disease free at 28 months post-resection.

Discussion

This case demonstrates pembrolizumab's efficacy beyond PD-L1 expression, this is in keeping with previously reported responses in PD-L1-negative patients. The contribution of trastuzumab and cytotoxic agents to the observed response cannot be excluded, as pembrolizumab is not expected to confer benefit in CPS-negative disease per current trial evidence. Conversion surgery, facilitated by systemic therapy, exemplifies a promising approach to improving outcomes in advanced mGC.

Conclusion

The clinical course observed in this patient suggests that the incorporation of pembrolizumab alongside chemotherapy and targeted therapy may be associated with significant tumour downstaging in select cases of advanced metastatic gastric cancer, even in the setting of PD-L1–negative disease. While causal inference cannot be drawn from a single case, this observation highlights the need for further translational and clinical studies to better understand the biological factors that may underlie such atypical responses.

Keywords: Metastatic gastric cancer; Pembrolizumab; PD-L1 negative; HER2-positive; Complete pathological response; Conversion surgery; Immune checkpoint inhibitor; Trastuzumab

1. Introduction

Metastatic gastric cancer (mGC) remains a challenging condition with a poor prognosis [1] and is often diagnosed at an advanced stage. Despite advances in chemotherapy and targeted therapies, survival in advanced disease remains limited. Immune checkpoint inhibitors (ICIs), particularly pembrolizumab, have shown clinically meaningful activity in advanced gastric cancer, with benefit most evident in biomarker-selected populations, including patients with microsatellite instability-high (MSI-H) tumours and those with programmed death-ligand 1 (PD-L1) expression [2, 3]. The KEYNOTE-811 trial [4], together with the subsequent accelerated FDA approval [5], established pembrolizumab in combination with trastuzumab, fluoropyrimidine, and platinum-based chemotherapy as a frontline standard of care for HER2-positive mGC, with benefit concentrated in CPS ≥1 patients [4]. By contrast, patients with CPS <1 and proficient mismatch repair (pMMR) tumours represent a subset in whom ICI benefit is not anticipated based on current randomised evidence [4]. This case report illustrates the evolving role of immunotherapy-based treatment in stage IV gastric cancer, particularly its potential in selected responders to facilitate conversion from initially unresectable to resectable disease [6]. Conversion surgery, traditionally reserved for less advanced disease, is emerging as a multimodal strategy in the era of modern systemic therapy and immunotherapy [6]. As ICI therapies continue to shape treatment paradigms, understanding their impact on long-term survival and resectability in mGC is critical to optimising patient outcomes.

We present a case of a 60-year-old male with PD-L1-negative, HER2-positive mGC (cT4N3M1) who achieved complete pathological response (ypT0N0) after pembrolizumab-trastuzumab-based chemotherapy, followed by radical gastrectomy. We also reviewed similar cases in the literature to indicate the importance and management of such cases.

This case raises important questions about the mechanisms of response to ICIs in biomarker-negative patients, the relative contributions of individual agents, and the appropriate application of conversion surgery.

2. Case Presentation

2.1. History and Initial Presentation

A 60-year-old male with no significant past medical history presented in March 2022 with a four-week history of epigastric pain, early satiety, and unintentional weight loss of approximately 8 kg over that period. He denied dysphagia, haematemesis, or melaena. He was a non-smoker with no relevant family history of malignancy. On clinical examination, he appeared cachectic with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1. Abdominal examination revealed mild epigastric tenderness without palpable organomegaly or lymphadenopathy.

2.2. Diagnostic Workup

At initial diagnosis, he underwent esophagogastroduodenoscopy (OGD) which demonstrated a large, ulcerated lesion along the greater curvature of the stomach, involving the distal body, incisura and proximal antrum **(Figure 1).** Multiple biopsy specimens were obtained. Histopathological examination confirmed a poorly differentiated invasive gastric adenocarcinoma, Lauren-diffuse type. Immunohistochemistry (IHC) revealed HER2 strong positivity (IHC 3+), PD-L1 negativity (CPS <1) **(Figure 2),** and intact expression of all four mismatch repair proteins (MLH1, MSH2, MSH6, PMS2), consistent with proficient MMR (pMMR). Differential diagnoses at presentation included primary gastric lymphoma, gastrointestinal stromal tumour (GIST), and metastatic disease to the stomach, all of which were excluded based on histological and IHC findings.

Following endoscopic diagnosis, he underwent staging positron emission tomography (PET) scan, which showed extensive regional, left supraclavicular distant nodal metastases, omental caking and peritoneal metastases (stage cT4N3M1). No standard CT-CAP was performed prior to PET-CT, as our center proceeds directly to PET-CT for staging gastric cancer. Diagnostic laparoscopy was subsequently performed to confirm omental and peritoneal involvement.

2.3. Treatment

Following discussion at the multidisciplinary team (MDT) meeting, the disease was deemed incurable and palliative systemic therapy was commenced with the intention of reassessing for conversion surgery if a major response was achieved. At the time of treatment initiation (April 2022), pembrolizumab had received accelerated FDA approval for use in combination with trastuzumab and platinum/fluoropyrimidine-based chemotherapy in HER2-positive mGC, based on the interim analysis of KEYNOTE-811. This approval did not incorporate a CPS restriction at the time; accordingly, pembrolizumab was included in the frontline regimen. The regimen consisted of pembrolizumab 200 mg IV every 3 weeks, trastuzumab 6 mg/kg IV every 3 weeks (loading dose 8 mg/kg), cisplatin 60 mg/m^2 IV every 3 weeks, reduced by 20% in subsequent cycles, and fluorouracil by continuous intravenous infusion over 5 days every 3 weeks, initially at 4,000 mg/m^2 per cycle and subsequently reduced by 20% to 3,200 mg/m^2 per cycle. Due to significant neuropathy and bilateral high-frequency sensorineural hearing loss, cisplatin was discontinued on the eleventh cycle. No immunotherapy-related adverse events (irAEs) were observed throughout the course of treatment.

2.4. Treatment Response and Conversion Surgery

By the fifth cycle, a new computed tomography scan of the chest, abdomen and pelvis (CT-CAP) in August 2022 showed significant regression of the primary lesion, involving the distal gastric body, antrum and pylorus, from 9.3 mm to 2.8 mm;

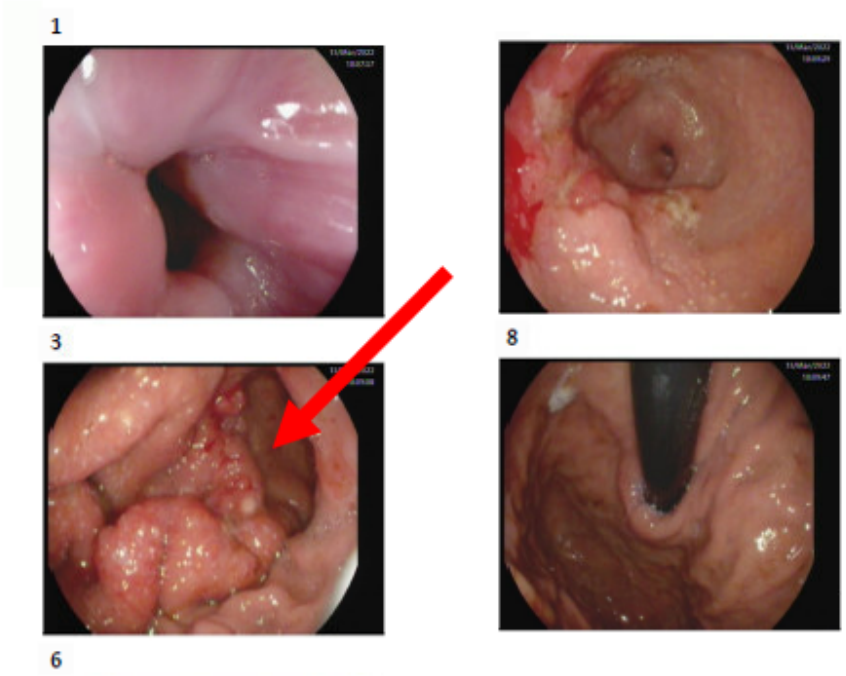

Figure 1: *Esophagogastroduodenoscopy (OGD) showing the ulcerated lesion (red arrow).*

there was also regression in all regional and metastatic lymph nodes **(Figure 3).** After nine cycles of treatment, a CT-CAP in October 2022 showed near "complete radiological response". Pembrolizumab, trastuzumab and fluorouracil were continued for a total of sixteen cycles, with trastuzumab being held in the sixteenth cycle due to a drop in ejection fraction to 50%. A PET scan performed in July 2023 confirmed near-complete metabolic and morphological resolution of the gastric lesions and lymphadenopathy in the abdomen, mesentery, retroperitoneum and left supraclavicular regions, with no new lesions. In August 2023, he underwent radical total gastrectomy, splenectomy, omentectomy and perigastric lymphadenectomy. The postoperative pathology report showed a complete pathological response, with no residual viable tumour cells identified in the gastric wall or any of the 24 lymph nodes examined (ypT0N0). R0 resection was confirmed.

2.5. Follow-up

The patient remains clinically well and free of cancer-related symptoms. Interval CT-CAP and PET scans performed in December 2025 showed no evidence of local recurrence or distant metastatic disease.
A clinical timeline of the patient from diagnosis to last follow-up is given in **Table 1**.

3. Discussion

Here we report on a 60-year-old male with HER2-positive mGC (cT4N3M1) who achieved, a complete pathological response (ypT0N0) after nine cycles of pembrolizumab, trastuzumab-based chemotherapy, followed by radical gastrectomy. The patient remains disease-free at 28 months post-resection.

3.1. Conversion Surgery in Metastatic Gastric Cancer

The role of conversion surgery in mGC has always been controversial. A phase 3 randomised controlled trial (REGATTA) demonstrated no survival benefit of gastrectomy followed by chemotherapy over chemotherapy alone in gastric cancer patients with a single non-curable factor (either liver, peritoneum, or para-aortic lymph nodes) [7]. However, this study has been noted to differ from the commonly adopted practice of initiating chemotherapy first, which may have influenced the reported survival outcomes. On the other hand, two recent studies, AIO-FLOT3 [8] and CONVO-GC-1 [9], reported median overall survival of 22.9 and 36.7 months, respectively, in patients with mGC following chemotherapy and surgery. Furthermore, a phase 3 trial (RENAISSANCE/AIO-FLOT5) of conversion surgery is ongoing for patients with retroperitoneal lymph node metastases with or without a single incurable organ site [10].
Traditionally, surgical resection in mGC has been limited to palliative interventions or select cases of oligometastatic disease [11]. However, emerging evidence suggests that conversion surgery, following significant tumour regression induced by systemic therapy, may improve long-term outcomes in advanced gastric cancer [12]. The role of conversion surgery in mGC has been demonstrated in a number of previous reports. A retrospective analysis demonstrated improved survival outcomes in patients undergoing conversion surgery for advanced gastric cancer [13]. The role of ICIs in enhancing complete response and

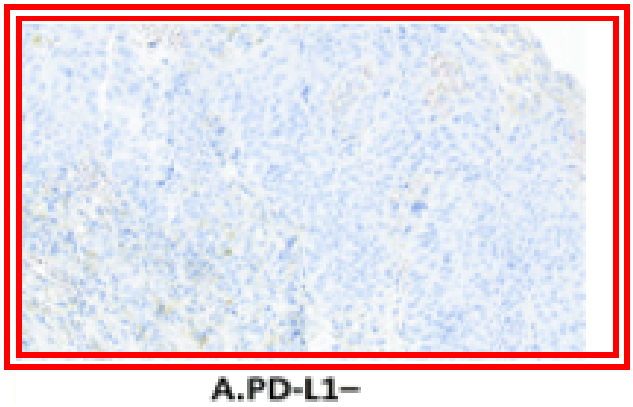

Figure 2: *PD-L1 IHC-staining patterns. PD-L1 immunohistochemistry demonstrating CPS <1. Only minimal staining is present, below the threshold for PD-L1 positivity. By comparison, PD-L1-high cases show more extensive staining in tumour and/or immune cells, producing a higher combined positive score.*

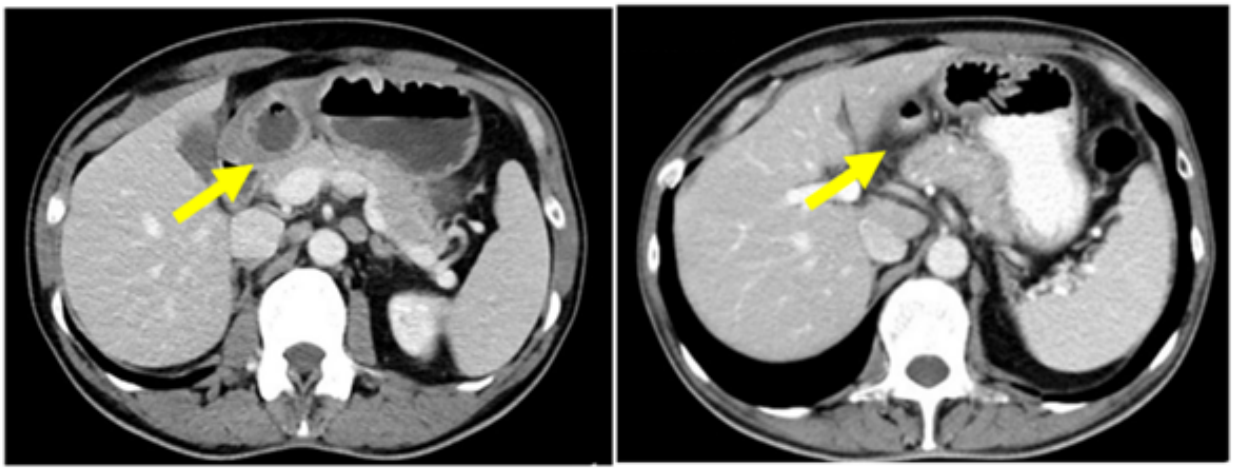

Figure 3: *Contrast-enhanced abdominal computed tomography images obtained approximately 6 months apart (9 March 2022 on the left and 2 August 2022 on the right), showing marked interval regression of the previously described distal gastric wall thickening involving the gastric body/antrum and pylorus following treatment.*

facilitating conversion surgery has been less studied. One recent retrospective analysis from Samsung Medical Centre reviewed 118 patients with mGC treated with chemotherapy and ICIs, reporting that 18% underwent successful conversion surgery, with complete pathological response linked to improved survival outcomes [14]. These data underscore the importance of identifying patients who can benefit from multimodal approaches, integrating systemic therapies and surgical resection. While conversion therapy offers a promising avenue for mGC management, patient selection remains key. For example, one retrospective cohort study of stage IV gastric cancer treated with immune checkpoint inhibitors and chemotherapy reported an objective response rate of 58.8%, with 42 patients undergoing conversion surgery and an R0 resection rate of 90.5% [15].

3.2. Pembrolizumab in PD-L1-Negative Gastric Cancer

At the time of the patient's diagnosis, pembrolizumab was incorporated into the treatment plan based on the initial interim analysis of the KEYNOTE-811 trial, which led to the accelerated FDA approval of pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic gastric cancer [4, 5]. Subsequent analyses revealed that the addition of pembrolizumab improved progression-free survival (PFS) to 10.1 months compared to 8.1 months with standard therapy (hazard ratio [HR] = 0.73). This benefit was predominantly observed in patients with a CPS ≥1 (10.9 vs 7.3 months, HR = 0.71), while no significant advantage was noted in those with CPS <1 (9.5 months in both groups, HR = 1.03) [4]. Despite these findings, emerging evidence suggests that pembrolizumab can elicit significant responses in patients with PD-L1-negative mGC. Against this background, we must acknowledge that the complete response observed in this patient may have been attributable to the

Table 1: A summary of the clinical timeline from diagnosis to last follow-up.

Date	Event	Clinical Finding / Decision
March 2022	Initial presentation and Esophagogastroduodenoscopy (OGD)	Large, ulcerated lesion, greater curvature; biopsy confirmed poorly differentiated gastric adenocarcinoma
March 2022	Staging PET-CT + laparoscopy	cT4N3M1: omental caking, peritoneal and left supraclavicular nodal metastases. IHC: HER2 3+, CPS <1, pMMR
April 2022 (Cycle 1)	Cisplatin + 5-FU + Trastuzumab + Pembrolizumab	ECOG PS 1 KEYNOTE-811-based regimen initiated: cisplatin 60 mg/m^2 q3w, and 5-FU continuous IV infusion over 5 days q3w; initial dose 4,000 mg/m^2/cycle, later reduced by 20% to 3,200 mg/m^2/cycle, pembrolizumab 200 mg q3w, trastuzumab 6 mg/kg q3w (8 mg/kg loading dose)
August 2022 (Cycle 5)	CT-CAP re-staging	Primary lesion regression from 9.3 mm to 2.8 mm; significant reduction in regional and distant lymphadenopathy
October 2022 (Cycle 9)	CT-CAP re-staging	Near-complete radiological response
December 2022 (Cycle 11)	Cisplatin discontinued	Grade 2 peripheral neuropathy and bilateral high-frequency sensorineural hearing loss; switched to non-platinum backbone
July 2023 (Cycle 16)	PET-CT re-staging	Near-complete metabolic and morphological resolution; no new lesions
August 2023	Radical total gastrectomy, splenectomy, omentectomy, D2 lymphadenectomy	R0 resection; ypT0N0M0; complete pathological response
December 2025	Follow-up CT-CAP + PET	No local recurrence or distant metastatic disease; disease-free at 28 months post-surgery

combination of trastuzumab and cytotoxic agents, rather than to pembrolizumab specifically. Strong HER2 positivity (IHC 3+) is itself associated with higher rates of response to trastuzumab-containing
patients with low PD-L1-expressing advanced solid tumours, although cross-disease extrapolation should be interpreted cautiously [16]. We therefore cannot claim that pembrolizumab was the driver of response on the basis of this case alone. Biomarker misclassification, for example due to a technically suboptimal PD-L1 IHC preparation leading to CPS underestimation, is another possibility that cannot be entirely excluded, although the IHC slide appeared adequate.

Several previously published cases have documented significant and durable responses to pembrolizumab-containing regimens in patients with PD-L1-negative, pMMR gastric cancer. A case report described a 46-year-old male with PD-L1-negative gastric cancer who achieved a complete response following pembrolizumab therapy, suggesting that PD-L1 negativity does not necessarily preclude responsiveness to this treatment [17]. Similarly, another case involved a 30-year-old male with HER2-negative, PD-L1-negative metastatic gastric adenocarcinoma who exhibited pseudoprogression followed by a spontaneous response after pembrolizumab administration, highlighting the potential for favourable outcomes irrespective of PD-L1 status [18]. In addition, a report described a patient with PD-L1-negative advanced gastric cancer, who experienced a prolonged response to PD-1 blockade after failure of prior systemic treatments, further supporting the possibility of benefit beyond PD-L1 expression [19]. These cases, along with this patient's clinical course, highlight the potential for substantial tumour regression in patients with mGC lacking PD-L1 expression. Summary of similar published cases is shown in **Table 2.**

The precise role of pembrolizumab in achieving complete responses in patients with PD-L1-negative disease, remains to be fully elucidated. Possible mechanisms underlying the ICI efficacy in PD-L1-negative disease include dynamic upregulation of PD-L1 following cytotoxic chemotherapy, tumour mutational burden independent of MSI status, infiltration by immune effector cells not captured by standard IHC-based scoring, and other uncharacterised immunological mechanisms. Comprehensive

molecular profiling, including tumour mutational burden, whole-exome sequencing, and multiplex immunofluorescence of the tumour microenvironment, was not performed in this patient, representing a limitation of this report. Future prospective studies incorporating these analyses in patients with exceptional responses, may help identify actionable biomarkers beyond PD-L1 CPS and MMR status.

3.3. Quality of Life Considerations

The patient tolerated the prolonged systemic therapy regimen reasonably well. Cisplatin was appropriately discontinued after cycle 11 due to cumulative neurotoxicity. No immunotherapy-related adverse events were documented. The patient underwent major abdominal surgery, namely total gastrectomy with splenectomy, following 16 cycles of systemic therapy and recovered to an ECOG PS of 0 within three months, with acceptable postoperative quality of life. Nutritional counselling and supplementation were provided in accordance with standard post-gastrectomy protocols.

Table 2: Summary of published cases of pembrolizumab responses in PD-L1-negative (CPS <1) metastatic gastric cancer.

Ref	Age Gender	Histology	Stage	PD-L1 CPS / MMR	Regimen	Response	Outcome
[17]	46/ Male	Gastric adenocarcinoma	Stage IV	CPS <1 / pMMR	Pembrolizumab monotherapy	Complete response	Durable response; published 2023
[18]	30/ Male	Metastatic gastric adenocarcinoma	Stage IV	CPS <1 / pMMR	Pembrolizumab-based	Pseudo-progression then spontaneous response	Sustained response; published 2018
[19]	N/A	Advanced gastric cancer	Stage IV	CPS <1 / pMMR	PD-1 blockade after prior systemic therapy	Prolonged response	Durable disease control; published 2021
Current case	60/ Male	Poorly differentiated gastric adenocarcinoma, HER2 3+	cT4N3M1 (omental + peritoneal + nodal)	CPS <1 / pMMR	Pembrolizumab 200 mg + Trastuzumab + Cisplatin + 5-FU (Cisplatin stopped cycle 11, 16 cycles total)	Complete pathological response ypT0N0	Disease-free 28 months post-surgery (Dec 2025)

4. Conclusion

This case illustrates the potential contribution of pembrolizumab in the management of metastatic gastric cancer (mGC), particularly when combined with chemotherapy and targeted therapies like trastuzumab. Despite the absence of PD-L1 expression in our patient, the complete pathological response observed suggests that meaningful tumour regression may occur, even in CPS-negative disease. Emerging evidence, including reports of significant responses in PD-L1-negative patients, suggests that benefit may occur beyond conventionally selected populations. Conversion surgery, when made feasible by effective systemic therapy, may represent a promising approach to improving long-term survival in mGC.
Future studies incorporating comprehensive molecular profiling, translational correlates, and prospective biomarker-stratified designs are needed to identify which PD-L1-negative patients may harbour biological features predictive of ICI benefit and to optimise multimodal treatment approaches in this challenging disease.

5. Declarations

Ethics Approval and Consent to Participate

Ethics approval and written informed consent were obtained.

Consent for Publication

Written informed consent for publication was obtained from the patient.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no competing interests.

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Author Contributions

IA and AA contributed to data collection and drafting of the manuscript. AS supervised the case management, contributed to the conception and revision of the manuscript, and approved the final version for submission. All authors read and approved the final manuscript.

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All medical content, clinical decisions, and interpretations are the sole responsibility of the authors.

AI Declaration

The authors confirm that no content in this manuscript was generated using artificial intelligence (AI) tools and the authors take full responsibility for the accuracy and integrity of the work.

6. Abbreviations

The following abbreviations are used in this manuscript:

mGC	Metastatic gastric cancer
ICIs	Immune checkpoint inhibitors
PD-L1	Programmed Death-Ligand 1
MSI	Microsatellite Instability
CPS	Combined Positive Score
HER 2	Human Epidermal growth factor Receptor 2
pMMR	proficient mismatch repair
ECOG PS	Eastern Cooperative Oncology Group Performance Status
MLH1	MutL Homolog 1
MSH2	MutS Homolog 2
MSH6	MutS Homolog 6
PMS2	Postmeiotic Segregation Increased 2
GIST	GastroIntestinal Stromal Tumour
PET	Positron Emission Tomography
CT-CAP	Computed Tomography – Chest, Abdomen, and Pelvis
OGD	Esophagogastroduodenoscopy
MDT	Multidisciplinary team
5-FU	5-fluorouracil
PFS	Progression-free survival

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