Immunotherapy-Based Neoadjuvant Treatment of Advanced Microsatellite Instability–High Gastric Cancer: A Case Series

Louisa Liu, MD[1,2]; Yanghee Woo, MD[3]; Massimo D'Apuzzo, MD, PhD[4]; Laleh Melstrom, MD, MS[2]; Mustafa Raoof, MD, MS[4]; Yu Liang, MD, PhD[4]; Michelle Afkhami, MD[4]; Stanley R. Hamilton, MD[4]; and Joseph Chao, MD[2]

ABSTRACT

Despite the use of first-line therapies like fluoropyrimidine and platinum-based cytotoxic chemotherapy, gastric cancer (GC) continues to carry a poor prognosis. Recent subgroup analyses of first-line phase III trials have demonstrated that patients with microsatellite instability–high (MSI-H) metastatic GC derive significant improvement in survival rates when immune checkpoint inhibitors (ICIs) are combined with chemotherapy compared with chemotherapy alone. However, it remains to be seen whether the success of ICIs in the metastatic setting can be translated into earlier stages of GC with resectable disease. We report 6 cases of locally advanced, nonmetastatic MSI-H GC that all demonstrated favorable response following treatment with pembrolizumab in addition to neoadjuvant chemotherapy. With the exception of immune-related colitis in one patient, pembrolizumab was well-tolerated. To our knowledge, this is the first reported US case series of patients treated with an ICI in combination with neoadjuvant chemotherapy for advanced, nonmetastatic, resectable or unresectable MSI-H GC.

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[1]Department of Internal Medicine, University of California, Riverside School of Medicine, Riverside, California; and [2]Department of Medical Oncology and Therapeutics Research, [3]Division of Surgical Oncology, Department of Surgery, and [4]Department of Pathology, City of Hope Comprehensive Cancer Center, Duarte, California.

A meta-analysis of 1,556 patients with resectable gastric cancer (GC) identified 7.8% of cases as microsatellite instability–high (MSI-H).[1] This subset typically harbors a high tumor mutational burden (TMB) and favorable responses to immune checkpoint inhibitors (ICIs).[2–4]

In this case series, we aimed to characterize our experience on the efficacy and safety of neoadjuvant ICIs in patients with MSI-H GC. We also explored the relationship among methods for determining MSI status, including circulating tumor DNA (ctDNA).

Case Presentations

Case 1

A 92-year-old man presented with symptomatic anemia (Table 1). Esophagogastroduodenoscopy (EGD) revealed a friable mass occupying the entire antrum. Pathology noted poorly differentiated intestinal-type adenocarcinoma. The tumor was HER2-negative by immunohistochemistry (IHC). Endoscopic ultrasound staging was cT3N2MX. PET/CT demonstrated a hypermetabolic antral mass with mildly FDG-avid intrathoracic lymph nodes. Modified doses of FOLFOX (leucovorin/fluorouracil/oxaliplatin) were started given his comorbidities. After 8 cycles, PET/CT showed diminished size and metabolic activity of the mass but no change in FDG-avidity of the lymph nodes, favoring a reactive process. Repeat EGD re-demonstrated the antral mass and viable adenocarcinoma. Diagnostic laparoscopy showed no peritoneal metastasis. Molecular profiling with ctDNA via commercial Guardant360 assay (Guardant Health, Inc.) captured MSI-H status (Figure 1); tumor testing revealed high PD-L1 expression with combined positive score (CPS) of 50. He was switched to pembrolizumab, 200 mg every 3 weeks. Mismatch repair (MMR) IHC revealed heterogeneity for loss of MLH1 expression, with some tumor areas exhibiting retention and others loss of expression. After 3 cycles of pembrolizumab, restaging PET/CT demonstrated greater diminishment of the antral tumor and stable intrathoracic nodes.

The patient completed 4 cycles in total and tolerated treatment without immune toxicities. He then underwent

Table 1. Summary of Patient Characteristics, Treatments, and Responses

Patient	Age	Sex	Race/ Ethnicity	Site	Staging	MMR Protein Analysis	MSI PCR	PD-L1 CPS	Tissue NGS	Neoadjuvant Therapy	ypTNM	LNI
1	92 y	M	White	Antrum to pylorus	cT3N2M0	MLH1 heterogeneity	Not done	50 on first biopsy	Foundation (MSI, TMB indeterminate)	11 cycles of FOLFOX and 4 cycles of pembrolizumab	ypT0N0	0/15
2	79 y	M	Hispanic	Antrum	cT4bN1M0	PMS2 (−)	5/5	40 on first biopsy	GEM ExTra on surgery specimen (MSI-H, TMB 64 mut/Mb)	6 cycles of FOLFOX and 2 cycles of pembrolizumab	ypT3N0	0/36
3	80 y	F	Asian	Antrum	cT4aN1M0	MLH1 (−), PMS2 (−)	Not done	1 on first biopsy	GEM ExTra on surgery specimen (MSI-H, TMB 37 mut/Mb)	1 cycle of FOLFOX and 1 cycle of pembrolizumab	ypT3N0	0/29
4	52 y	F	Hispanic	Fundus to proximal body	cT4bN1M0	MSH2 (−), MSH6 (−)	4/5	50 on first biopsy	Not done	7 cycles of FLO and 4 cycles of pembrolizumab	ypT0N0	0/42
5	87 y	F	Asian	Antrum	cT4aN0M0	MLH (−), MSH6 (−), PMS2 (−)	Not done	10 on surgery specimen	GEM ExTra on surgery specimen (MSS, TMB 6 mut/Mb)	1 cycle of capecitabine and 1 cycle of pembrolizumab	ypT2(m)N0	0/40
6	87 y	M	Asian	Antrum	cT4bN2M0	PMS2 (−)	5/5	1 on first biopsy	GEM ExTra attempted on first biopsy but unable to be done	7 cycles of FOLFOX, 20 cycles of 5-FU/ LV, 26 cycles of pembrolizumab	ypT0N0	0/27

Abbreviations: 5-FU/LV, fluorouracil/leucovorin; CPS, combined positive score; F, female; FLO, fluorouracil/leucovorin/oxaliplatin; FOLFOX, leucovorin/ fluorouracil/oxaliplatin; LNI, lymph node involvement; M, male; Mb, megabase; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; mut, mutations; NGS, next-generation sequencing; TMB, tumor mutational burden.

distal gastrectomy with D1 lymphadenectomy. Final pathology revealed pathologic complete response (ypT0N0). Continued CT surveillance demonstrates stability of intrathoracic lymph nodes. Repeat Guardant360 testing revealed detectable putative ctDNA sequences (Figure 1) but no further detection of MSI-H fraction. Tumor-informed alternative ctDNA testing was pursued via the commercial Signatera assay, which reported no detectable ctDNA. The patient remains alive and well at last follow-up 20 months after surgery.

Case 2

A 79-year-old man presented with melena and weight loss (Table 1). EGD revealed a prepyloric ulcerated tumor. Pathology noted poorly differentiated adenocarcinoma that was HER2-negative. CT chest/abdomen/pelvis demonstrated an antral mass and lymphadenopathy invading the hepatic hilum. Diagnostic laparoscopy showed no peritoneal metastases but direct invasion of the pancreatic head, and the patient's disease was staged as cT4bN1M0. After one FOLFOX cycle, MMR IHC testing showed loss of

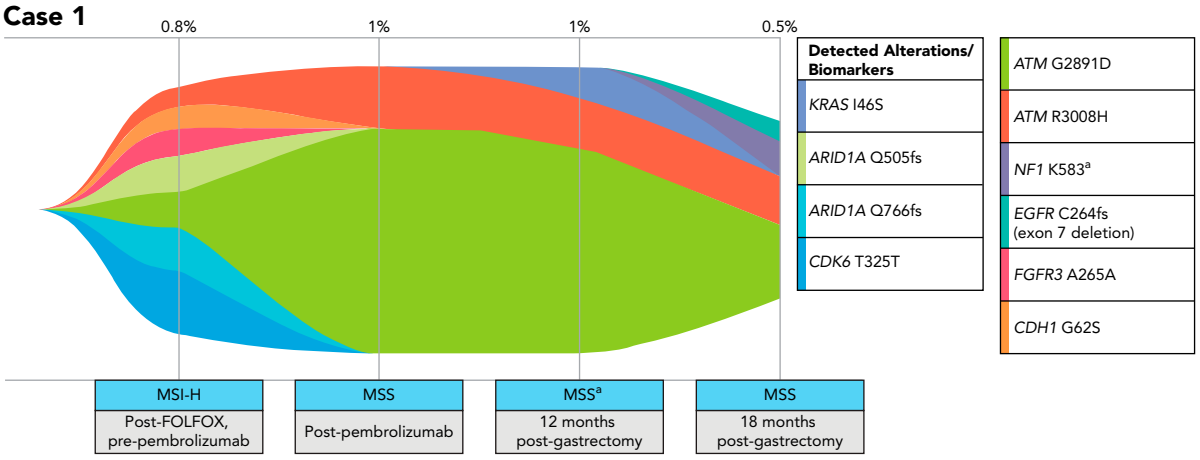

Figure 1. Serial ctDNA sequencing results for Case 1.
Abbreviations: ctDNA, circulating tumor DNA; FOLFOX, leucovorin/fluorouracil/oxaliplatin; MSI-H, microsatellite instability–high; MSS, microsatellite stable.
[a]ctDNA analysis via Signatera assay showing no detectable ctDNA (0.0 mean tumor molecules per milliliter of plasma).

PMS2 expression; follow-up MSI PCR analysis also detected MSI-H. Pembrolizumab, 400 mg every 6 weeks was added to ongoing FOLFOX.

Except for grade 1 fatigue and peripheral neuropathy, the patient tolerated treatment with no immune-related toxicity. Following 3 months of FOLFOX + pembrolizumab, CT demonstrated marked improvement of antral thickening. After multidisciplinary review and repeat surgical exploration confirmed that the tumor appeared resectable, he underwent distal gastrectomy with D2 lymphadenectomy. Final pathology revealed partial response (ypT3N0). Viable residual tumor tissue was sufficient to run whole-exome sequencing via the commercial GEM ExTra assay (Ashion Analytics),[5] which determined the residual tumor as still being MSI-H with TMB of 64 mutations per megabase. Minimal residual disease (MRD) assessment via Signatera measured no detectable ctDNA at 1, 4, and 6 months postresection. At last follow-up 9 months after surgery the patient remains alive without any disease.

Case 3

An 80-year-old woman presented with early satiety (Table 1). EGD revealed a large antral mass. Pathology noted poorly differentiated adenocarcinoma with loss of MLH1 and PMS2 expression and HER2-negative. PD-L1 CPS was 1. The Guardant360 assay also captured MSI-H status. PET/CT demonstrated hypermetabolic activity at the antrum without evidence of distant metastases. Diagnostic laparoscopy revealed no metastases, and therefore the patient's disease was staged as T4aN1M0. FOLFOX and pembrolizumab were started.

After one cycle, however, the patient tested positive on institutional QuantiFERON-TB screening (QIAGEN), raising concern for latent tuberculosis, and cancer treatment was paused. Bronchoalveolar lavage led to findings of *Mycobacterium abscessus*. However, she did not meet criteria for active *M abscessus* infection and instead was treated for latent tuberculosis. Due to ongoing symptomatic gastric outlet obstruction, she underwent subtotal gastrectomy with D1 lymphadenectomy. Final pathology revealed ypT3N0 disease. Repeat ctDNA assessment via Guardant360 assay no longer detected MSI-H and revealed significant reduction in ctDNA fraction after surgery (Figure 2). Per GEM ExTra, the residual tumor remained MSI-H with a TMB of 37 mut/Mb. The patient was last seen in follow-up at 22 months after surgery without any evidence of disease.

Case 4

A 52-year-old woman presented with dysphagia and abdominal pain (Table 1). EGD demonstrated a large ulcerated mass from fundus to proximal body. Pathology revealed poorly differentiated adenocarcinoma with loss of MSH2 and MSH6 expression and HER2-negative. PET/CT showed FDG-avid proximal stomach thickening, local invasion of pancreatic tail and splenic hilum, and mesenteric lymph nodes. Diagnostic laparoscopy showed no peritoneal metastasis but positive serosal involvement and perigastric lymphadenopathy, and therefore the patient's disease was staged as cT4bN1M0. Neoadjuvant FLOT (fluorouracil/leucovorin/oxaliplatin/docetaxel) was started. Due to significant diarrhea and oropharyngeal mucositis after one cycle, docetaxel was omitted. Additionally, pembrolizumab, 200 mg every 3 weeks was started given the deficient MMR (dMMR) result and MSI-H on PCR. Of note, Guardant360 was collected after she had already received one cycle of FLOT, revealing 0.1% ctDNA and no MSI-H detected (Figure 3).

Except for the development of grade 2 hypothyroidism corrected with levothyroxine therapy and grade 1 rash, the patient tolerated treatment well. After 2 months of chemotherapy and pembrolizumab, restaging CT showed decreasing gastric wall thickening and size of perigastric lymph nodes. She completed 2 additional months of therapy, though response plateaued and the primary tumor still appeared cT4b on imaging. Multidisciplinary discussion deemed repeat surgical exploration was warranted, and intraoperatively the tumor appeared resectable, which was not apparent by imaging. She subsequently underwent total gastrectomy, en bloc distal pancreatectomy, splenectomy, and D2 lymphadenectomy. Final pathology revealed pathologic complete response. Tumor-informed ctDNA via Signatera (Natera, Inc.) was undetectable at 1 month and remained so at 8 months following resection. The Guardant360 assay was repeated 4 months postresection, reporting no detectable ctDNA or MSI (Figure 3). The patient remained alive and well with no evidence of disease at 17 months after surgery.

Case 5

An 87-year-old woman presented with severe anemia (Table 1). EGD revealed a large antral ulcer. Pathology reported poorly differentiated adenocarcinoma with loss of MLH1, MSH6, and PMS2 expression and HER2-negative. PD-L1 CPS was 10. The Guardant360 assay revealed MSI-H status. CT chest/abdomen/pelvis demonstrated antral thickening, multiple gastrohepatic nodes, and subcentimeter hepatic lesions, but the liver biopsy was benign. Diagnostic laparoscopy showed no peritoneal metastasis and negative cytology on washings. Pembrolizumab and capecitabine were started due to the patient's older age and frailty. However, after one cycle, she was hospitalized for diarrhea. Colonoscopy demonstrated moderate ileocolonic inflammation. Biopsy showed lymphoplasmacytic inflammation and crypt abscesses, confirming immune-mediated colitis requiring high-dose steroids. Given intolerance to neoadjuvant therapy, she proceeded directly to surgery. Interestingly, repeat Guardant360 assay testing

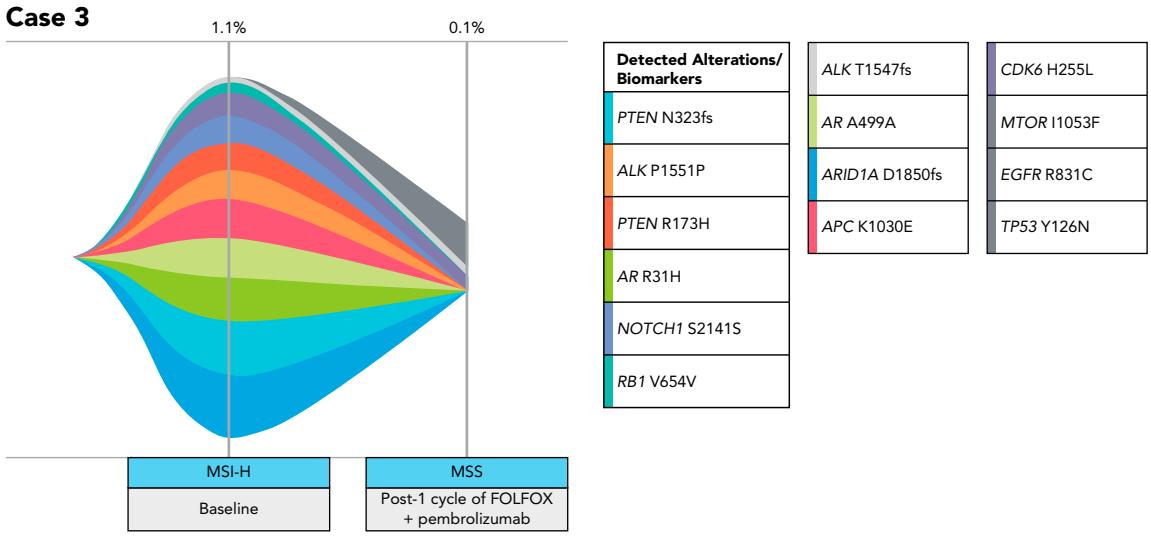

Figure 2. Serial ctDNA sequencing results for Case 3.
Abbreviations: ctDNA, circulating tumor DNA; FOLFOX, leucovorin/fluorouracil/oxaliplatin; MSI-H, microsatellite instability–high; MSS, microsatellite stable.

2 months after receiving pembrolizumab and capecitabine but prior to surgery reported no detectable ctDNA or MSI-H fraction (Figure 4). She underwent distal gastrectomy with D1 lymphadenectomy. Final pathology revealed ypT2(m)N0 due to the identification of 2 separate tumors in the surgical resection specimen. The first tumor exhibited no residual carcinoma and a tumor bed showing ulceration with granulation tissue, acellular mucin, and foamy histiocytes extending into the muscularis propria. The second tumor exhibited presence of a treatment effect with residual carcinoma cells and evident tumor regression. GEM ExTra reported the residual second tumor as microsatellite stable (MSS) and TMB 6 mut/Mb. MMR IHC was repeated on the surgical sample and confirmed now-intact expression of all 4 MMR enzymes. The patient was last seen in follow-up at 21 months after surgery with no evidence of disease.

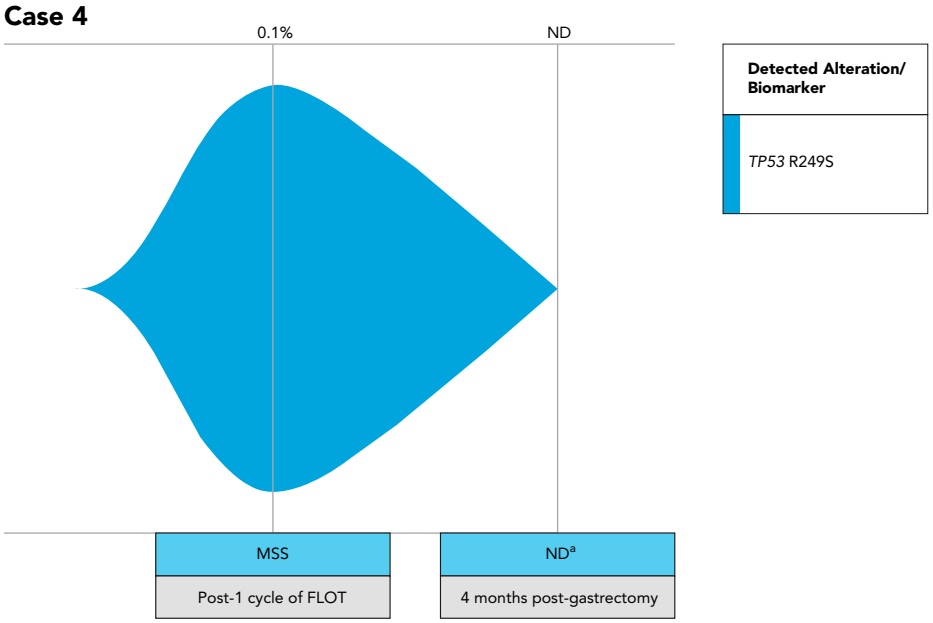

Figure 3. Serial ctDNA sequencing results for Case 4.
Abbreviations: ctDNA, circulating tumor DNA; FLOT, fluorouracil/leucovorin/oxaliplatin/docetaxel; MSS, microsatellite stable; ND, no ctDNA detected.
[a]ctDNA analysis via Signatera assay showing no detectable ctDNA (0.0 mean tumor molecules per milliliter of plasma).

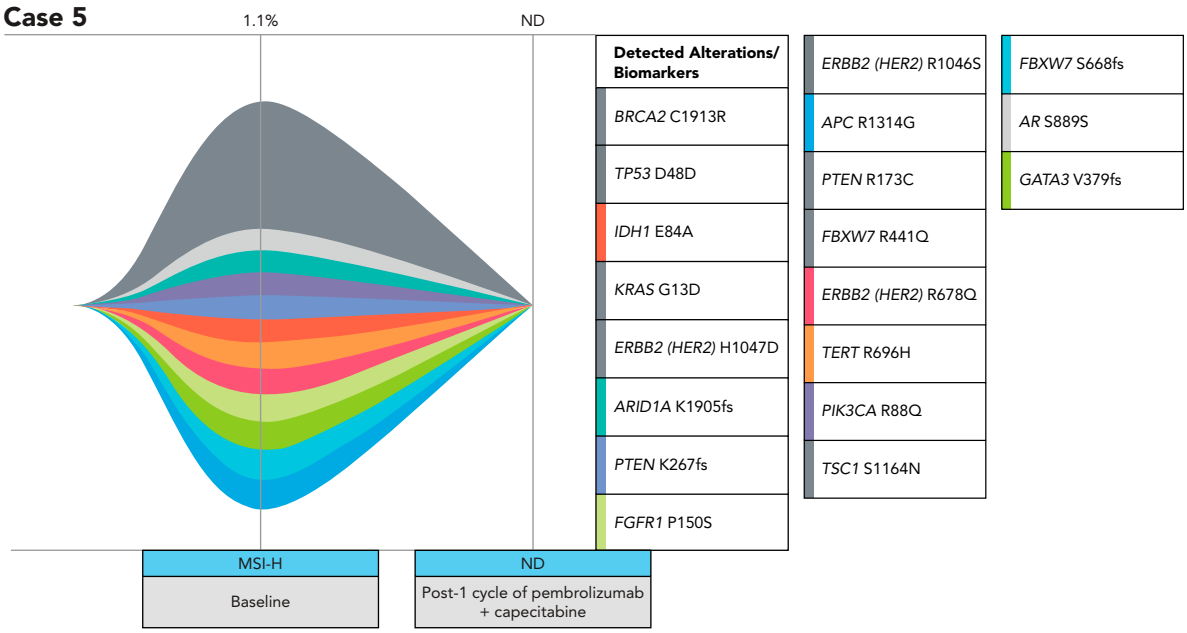

Figure 4. Serial ctDNA sequencing results for Case 5.
Abbreviations: ctDNA, circulating tumor DNA; MSI-H, microsatellite instability–high; ND, no ctDNA detected.

Case 6

An 87-year-old man presented with dyspepsia and weight loss (Table 1). EGD demonstrated a fungating antral mass. Pathology revealed poorly differentiated adenocarcinoma with loss of PMS2 expression. CT of the chest/abdomen/pelvis showed an irregular enhancing gastric mass. Diagnostic laparoscopy showed no peritoneal metastasis but posterior tumor extension into the pancreatic body, designating his disease stage as cT4b. PCR and Guardant360 assay testing also confirmed MSI. Given unresectable disease, FOLFOX every 2 weeks and pembrolizumab, 200 mg every 3 weeks were started. After 2 months of FOLFOX + pembrolizumab, restaging CT demonstrated decrease of the pyloric mass. After another 2 months and demonstration of stable CT findings, he was transitioned to maintenance 5-FU/leucovorin + pembrolizumab to avoid cumulative oxaliplatin neurotoxicity. Interestingly, the MSI-H ctDNA fraction on repeat Guardant360 testing had disappeared; however, persistent presumably tumor DNA remained (Figure 5). A Signatera assay was attempted to assess tumor-informed ctDNA detection, but the original tumor biopsy was insufficient to conduct whole-exome sequencing. After 20 months of maintenance therapy, his CEA level gradually increased without a CT imaging correlate of progression. Multidisciplinary review raised suspicion for resistant disease and a persisting MSS tumor clone to account for the ongoing ctDNA detection, and subsequently the patient underwent robotic distal gastrectomy with D1 lymphadenectomy, which revealed complete pathologic response. At last follow-up 8 months after surgery, the patient exhibited no evidence of disease recurrence.

Discussion

Emerging data suggest that the outcomes of patients with GC depend on molecular features as well as clinicopathologic factors.[6] Many efforts have been undertaken to study the MSI-H subgroup, which represents a small but clinically significant subset characterized by high TMB and responsiveness to ICIs. However, recent series have suggested that the degree of high TMB can be variable and possibly differentiate the heterogeneous response now well-recognized with single-agent PD-1 inhibitors in MSI-H GCs.[7,8]

MSI-H status may also portend better prognosis in resectable GC. In the meta-analysis of 4 landmark randomized controlled trials[9–12] by Pietrantonio et al,[1] MSI-H status in patients with resectable GC was associated with longer survival than their MSS counterparts. More provocative was the association of worsened survival in patients with MSI-H GC assigned to perioperative or adjuvant chemotherapy versus improved survival when treated with surgery alone. These findings remain hypothesis-generating but beg the question of whether ICIs should supplant chemotherapy in resectable disease. Zhang et al[13] recently reported a series of patients in China with advanced resectable dMMR/MSI-H gastrointestinal tumors (4 GCs, 2 colorectal cancers) treated with neoadjuvant ICIs, with 5 of their patients achieving

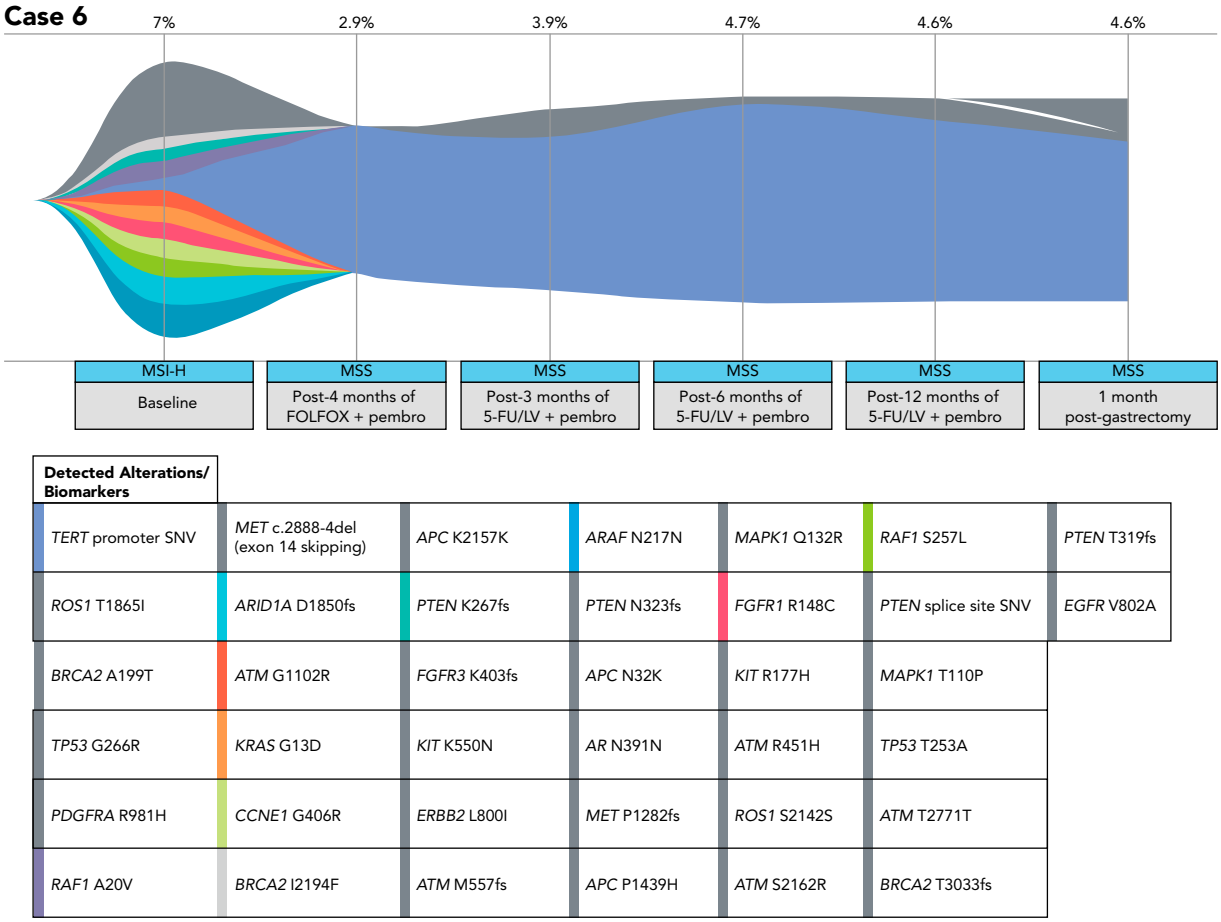

Figure 5. Serial ctDNA sequencing results for Case 6.
Abbreviations: 5-FU/LV, fluorouracil/leucovorin; ctDNA, circulating tumor DNA; FOLFOX, leucovorin/fluorouracil/oxaliplatin; MSI-H, microsatellite instability–high; MSS, microsatellite stable; pembro, pembrolizumab; SNV, single nucleotide variant.

complete pathologic responses. Unlike in the adjuvant setting, neoadjuvant immunotherapy with a primary tumor in place may better induce early formation of immunologic memory, contributing to the eradication of MRD/micrometastases that exist after surgery.[14–16]

In our series, tumor MSI status was predominantly determined using IHC, with some testing supplemented by tissue PCR. MSI-H phenotype was also assessed using Guardant360, given that ctDNA is emerging as a promising methodology for assessing TMB and detecting clinically significant MRD in GC.[2,17] When feasible, we also pursued a tumor-informed approach with the Signatera assay. Interestingly, all Signatera timepoints were without detectable ctDNA, although all sampling occurred after initiating therapy. In Guardant360 assays, cases 1, 3, 5, and 6 had detectable levels of ctDNA at baseline and evidence of MSI-H status. Case 4 without detectable MSI-H status may have had sensitivity impacted by having blood drawn after receiving FLOT.[18,19] However, case 2 did not have any detectable MSI-H fraction despite blood being drawn prior to starting therapy and concordance of MSI-H status by tissue IHC, PCR, and next-generation sequencing. Inherent lack of ctDNA shedding and issues of assay sensitivity may explain this discordance. It is also important to recognize that MSI determinations from ctDNA are heavily influenced by tumor fraction. In the setting of low tumor burden, the determination of MSI status can be inaccurate, and testing of tumor tissue remains the standard diagnostic method for assessing MSI/dMMR status.[20]

Decreasing ctDNA levels posttreatment have been correlated with greater clinical response to systemic therapy, including ICIs.[21,22] Our cases with baseline detectable ctDNA had disappearance of the MSI-H fraction post-pembrolizumab, although only case 5 had complete disappearance of ctDNA (Figures 1–5). However, case 5 still exhibited viable residual tumor, but now characterized as MSS on whole-exome sequencing. This likely represents tumor MSI heterogeneity, an increasingly described phenomenon in GC associated with poor response to ICIs.[2]

Likely, the first biopsy was taken from an MSI-H region, whereas the residual resected tumor represented a persistent MSS region after pembrolizumab therapy. Of the remaining cases with residual ctDNA, case 3 exhibited concordant viable tumor at surgery. However, cases 1 and 6 exhibited discordant pathologic complete responses, raising the question of physiologic clonal hematopoiesis confounding these patients' tumor-agnostic ctDNA analyses.[23]

In light of the MSI-H subset data from KEYNOTE-062,[3] we added pembrolizumab to neoadjuvant chemotherapy extrapolating from the high response rates observed for this subgroup with combination chemotherapy and pembrolizumab in the metastatic and locally advanced, unresectable disease setting.[24] Encouragingly, all 6 patients responded well to their treatment. To our knowledge, this is the first US-based case series combining neoadjuvant chemotherapy with ICIs in patients with advanced, nonmetastatic, both resectable and unresectable MSI-H GC. Our results align with the aforementioned findings by Zhang et al,[13] the abstract presentation of the phase II trial at MD Anderson Cancer Center showing high response rates to neoadjuvant PD-1 monotherapy in locally advanced MSI-H/dMMR gastrointestinal cancers,[25] and the recent abstract presentation of the NEONIPIGA trial reporting a pathologic complete response rate of 59% for MSI-H GC treated with neoadjuvant nivolumab + ipilimumab.[26]

In our cases, pembrolizumab was well-tolerated, except for case 5 developing immune-related colitis that resolved with steroids. Despite this, our patient achieved benefit with tumor downstaging. In CheckMate 142[27] that tested dual-ICI therapy in dMMR/MSI-H metastatic colorectal cancer, efficacy results remained consistent between patients who discontinued treatment due to immune-related adverse events (irAEs) and the overall population.[28] In fact, irAE onset has been regarded as a potential biomarker for ICI response, potentially predicting greater benefit compared with patients without irAEs.[29–31] Otherwise, no patients developed significant perioperative complications. Our observations appear consistent with other small prospective trials reported to date in which ICIs have been incorporated into perioperative chemotherapy for molecularly unselected patients with GC.[32–34] Ongoing phase III trials randomizing patients with GC receiving perioperative chemotherapy to the addition of an ICI or placebo may validate acceptable toxicities.[35,36]

Despite the dramatic responses to ICIs demonstrated in MSI-H tumors, the adoption of MSI/dMMR testing in the clinical setting remains a challenge. Given the relatively low MSI-H prevalence in GC,[37] MSI testing may not be routinely performed in patients with GC until the second-line or later-line setting. However, data from recent and ongoing studies corroborate the testing of MSI status up-front in advanced GC to identify individuals early on who may be candidates for immunotherapy. Collective post hoc subgroup analyses across the KEYNOTE-059, -061, and -062 trials examined the survival benefit of pembrolizumab in advanced GC with MSI-H status by line of therapy.[24] Not only does the use of pembrolizumab in the third line lead to a long-term survival benefit, its use in the second and even first line of therapy demonstrated improved overall survival compared with the use of chemotherapy. Furthermore, in the meta-analysis of 4 nonmetastatic trials by Pietrantonio et al,[1] MSI status was suggested to be predictive of lack of benefit from perioperative or adjuvant chemotherapy and have a positive prognostic role in MSI-H GC treated by surgery alone. These results, along with our own, seem to propose that the same benefits of ICIs in the metastatic setting can be translated to earlier stages of GC with resectable disease and support the addition of ICIs if neoadjuvant treatment is to be used. Accordingly, the data provide further validation to adopt up-front testing of MSI status in patients with all stages of GC.

The limitations of this study include those inherent to all case series and include selection bias, lack of a control group, and limited sample size and duration of long-term follow-up to fully inform survival outcomes. We acknowledge there is a degree of heterogeneity in neoadjuvant therapy among the patients, with some patients such as case 6 receiving much longer durations of neoadjuvant treatment than others. Furthermore, given the observational nature of our study, it is difficult to determine definitively whether our patients' responses were due to the combination of chemotherapy with immunotherapy or whether similar outcomes would have been derived from immunotherapy alone. At the time of our patients' treatment, perioperative chemotherapy remained the standard of care. We based our combinatorial approach on emerging data from KEYNOTE-062, in which the MSI-H GC subgroup with combination chemotherapy and pembrolizumab suggested the highest response rates and lowest rates of progressive disease as best response compared with the pembrolizumab or chemotherapy-only subgroups. Emerging datasets such as the NEONIPIGA trial have demonstrated encouraging chemotherapy-free neoadjuvant immunotherapy approaches, although there remains a discrete proportion of patients without any pathologic regression to immunotherapy alone.[38] In addition, it must be mentioned that several of our patients, specifically cases 2, 4, and 6, had undergone surgical resection in the setting of known clinical T4b disease. Multidisciplinary discussion was continually conducted for each patient to ensure the potential perioperative risks were justified. Moreover, although encouraging durable responses have been observed in the metastatic setting for MSI-H disease, such patients in GC datasets demonstrating

favorable survival of ≥3 years remain few compared with curative outcomes that can be derived with surgery in the absence of metastases. Data remain nascent, such as from the NEONIPIGA trial,[38] in which relatively high pathologic complete response rates to ICIs alone in MSI-H disease raises the question of whether surgery can be avoided. Newer trials, such as INFINITY,[39] which is examining the ICIs durvalumab and tremelimumab without chemotherapy initially as a neoadjuvant approach in MSI-H GC, will attempt to validate in a later cohort whether this approach can support nonoperative management. However, these studies remain ongoing, and there are currently limited prospective data from which we are able to validate the omission of surgery completely for these patients. Further understanding of the molecular and immune microenvironment diversity within MSI-H GC[7] to optimally and prospectively identify which patients can be treated with neoadjuvant immunotherapy alone, without the addition of chemotherapy or surgery, is certainly warranted. This can only be facilitated by more frequent MMR/MSI testing in the nonmetastatic setting and enrollment of these patients in ongoing neoadjuvant trials.

Conclusions

In this small case series, treatment of locally advanced MSI-H/dMMR GC using neoadjuvant ICIs combined with chemotherapy led to favorable responses. Assays utilizing ctDNA should be further developed as pharmacodynamic biomarkers.

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Correspondence: Joseph Chao, MD, Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010. Email: jchao@coh.org

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