

Expert Answers to Clinician Questions on Caring for Patients With Advanced Gastric Cancer

Faculty Expert:

Steven Maron, MD

Assistant Attending Physician

Gastrointestinal Medical Oncology Service

Memorial Sloan Kettering Cancer Center

New York, New York

The text below is adapted from expert answers to healthcare professionals' questions submitted as part of the program, "Cases and Challenges in the Optimal Treatment of Advanced Gastric Cancer." To view downloadable slides associated with this program, please visit [here](#).

Cancer Biology

What is the mechanism by which Epstein-Barr virus (EBV) facilitates gastric cancer?

Despite nearly universal infection with EBV, only a small minority of people develop EBV-associated malignancies.^[Frappier 2021] EBV usually lives in B-cells and is unable to infect epithelial cells. While the mechanism remains unknown due to limited preclinical models, in some situations, EBV is able to invade carcinoma cells in a CD21-independent manner, which improves proliferation and survival, thus promoting malignant potential.^[Takada 2000]

These tumors are often recognizable by their lymphoepithelioma-like or medullary features upon hematoxylin and eosin staining. They also tend to have significant intratumoral lymphocyte infiltration.^[Vuong 2022; Lin 2021] Unsurprisingly, EBV-positive gastric cancers usually have very high PD-L1 scores.^[Lima 2022] EBV-positive gastric cancers exhibit focal amplifications of *CD274*, the gene encoding PD-L1, or activation of interferon gamma via IRF3 activation, which explains their high *CD274* expression and immune evasion.^[Nakano 2021]

Molecular Testing

Do you request biomarker testing with each progression of disease and how often do you see a change?

I do recheck biomarkers in patients who had an actionable target at baseline and/or who received targeted therapies. I also recheck in those who were positive at baseline for a novel target under investigation in clinical trials. Rechecking tells me which clones survived and helps guide what to target next. When safely possible, I retest with tissue testing because it provides a sample for both clinical testing and research prescreening, where applicable. Esophagogastric tumors are usually easily amenable to endoscopic biopsy. If the patient has significant disease burden, then I will also consider ctDNA testing, recognizing that absence of an actionable biomarker may reflect low tumor shedding into the bloodstream if disease burden is low.

As an example of how often biomarkers change, HER2 expression was reported to be lost in approximately 30% of patients with HER2-positive gastric cancers that progressed on first-line trastuzumab-based therapy.^[Seo 2019]



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In cases where the patient lacks actionable tumor biomarkers at baseline, I generally do not recheck biomarkers unless I am just trying to determine whether disease is present or absent. For example, if I have a patient with gastric cancer harboring a *CDH1* genomic mutation and a tumor mutation burden approaching zero, the probability of finding an actionable biomarker on later biopsy is exceedingly low.

Treatment Strategies

How long do you keep patients on pembrolizumab or nivolumab in the first-line setting?

To date, we only have robust clinical trial data through 2 years of treatment with first-line immune checkpoint inhibitor (ICI) therapy.^[Janjigian Nature 2021; Janjigian Lancet 2021] Unfortunately, few patients live long enough for treatment length to become an issue. When a patient in complete response (CR) does approach the 2-year point, I will have a discussion with them: Do they want to keep going? If they are experiencing 5-fluorouracil (5-FU)-related toxicities, should we stop the 5-FU? If they are not experiencing any immune-related toxicities, I will often just recommend continuing the ICI with or without concurrent 5-FU, while continuously reevaluating the risk/benefit ratio.

I do have a very low threshold to stop the 5-FU if there is evidence of toxicity or allow prolonged breaks once a deep response is achieved, with the understanding that we can always add back the ICI and/or 5-FU should patients progress later. For patients with microsatellite instability-high tumors, which generally do not respond to 5-FU monotherapy, I will have a much lower threshold for stopping oxaliplatin at 8 cycles to avoid neuropathy, as I expect the PD-1 inhibitor is accounting for the bulk of their benefit. When I stop the oxaliplatin, I generally also stop the 5-FU and continue nivolumab or pembrolizumab monotherapy.

Building on the previous question, if you have a patient in CR with some toxicity who is close to that 2-year mark, would you treat a little bit beyond depending on when that CR occurred? Is there any role for a PET at that point in time?

It really depends on the toxicity and whether we can clearly attribute it to disease vs therapy. If there is a diagnostic question as to whether CT reflects viable tumor or not, options include a liquid biopsy, measuring ctDNA, or a PET. However, absence of ctDNA detection or PET-avid lesions does not exclude presence of cancer, which is often misinterpreted by patients. Instead, it reflects a limit of detection for each assay, and so should be interpreted and emphasized as reassuring, but not remission/cure.

If there is no detectable cancer, then we have a risk-vs-benefit discussion about whether the patient prefers to stop or continue therapy. I worry that some of my patients will lose sleep if we stop therapy. That being said, I believe many patients do not actually need 2 years of therapy, and so there is no single answer.

How long should a patient stay on trastuzumab for advanced gastric cancer?

In my practice, I typically administer a quadruplet of FOLFOX (5-FU and oxaliplatin) every 2 weeks, pembrolizumab at 400 mg every 6 weeks, and trastuzumab every 2 weeks.^[NCCN Gastric] I usually stop the oxaliplatin after 8-12 cycles, depending on the patient's neuropathy, but continue the pembrolizumab, trastuzumab, and 5-FU for what can sometimes be many years. I have many patients on this for 3 or more years, including breaks, unless they are experiencing toxicity. Unless you are detecting cardiac toxicity in your quarterly cardiac imaging, significant cumulative toxicities from trastuzumab are exceedingly rare.

Adverse Event (AE) Management

How do you manage interstitial lung disease (ILD) with trastuzumab deruxtecan?

I want to first mention that we have long-term safety data now for trastuzumab deruxtecan in advanced gastric cancer.^[Shitara 2020; Yamaguchi 2022] Gastric cancer trials with trastuzumab deruxtecan were conducted after the initial ILD signal was detected in breast cancer trials of trastuzumab deruxtecan, and we saw a much lower ILD-related mortality rate in gastric cancer despite using higher doses than are used for breast cancer.^[Powell 2022] This is because study criteria emphasize early identification of ILD and intervention before patients even become symptomatic. That being said, DESTINY-Gastric01 reported grade 1/2 ILD in 12.8% of participants treated with trastuzumab deruxtecan, with grade 3/4 ILD in 2.4%.

The first step for ILD is early detection. Is your patient breathing well? Are they coughing more? Is this more likely to be a reversible, infectious cause (eg, RSV, rhinovirus, flu, COVID-19)? If you see changes in the lungs that do not look like infectious disease, test the patient with a broad respiratory panel. Be conscious that patients with worse renal function at baseline are more likely to develop ILD. If you suspect ILD, you need to consider drug toxicity.

For asymptomatic suspected ILD, I would hold therapy and recheck a high-resolution CT in about a month.^[Powell 2022; Trastuzumab deruxtecan PI] If the CT shows improvement, it is probably *not* the drug, and then I resume therapy. If I am still considering the drug as the cause, then I resume at a lower dose. However, if the CT shows that the suspect ILD is still there or worse, or if they are symptomatic, then I consider starting steroids, obtaining pulmonary function tests, and involving pulmonary early, once alternative etiologies are ruled out. If they have clinically significant, symptomatic toxicity, you start steroids and permanently discontinue the drug.

With this early-intervention approach, I have effectively managed ILD in my patients. I have also had patients with grade 1 ILD who, even without steroids, were able to resume on a lower dose without issues.

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