Editorial

# How to better select patients with advanced gastric cancer for immunotherapy

**Aziz Zaanan[1,2,3], Julien Taieb[1,2,3]**

[1]Department of Gastroenterology and Digestive Oncology, European Georges Pompidou Hospital, AP-HP, Paris, France; [2]Paris Descartes University, Sorbonne Paris Cité, Paris, France; [3]UMR-S1147, INSERM, Paris, France

*Correspondence to:* Dr. Aziz Zaanan. Department of Gastroenterology and Digestive Oncology, European Georges Pompidou Hospital, AP-HP, Paris, France. Email: aziz.zaanan@aphp.fr.

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Concomitantly to the development of biological agents in the treatment of gastric cancer, immunotherapy has revolutionized the oncology landscape by targeting the host immune system. The efficacy of immunotherapy seems to be related to the immune microenvironment of the tumor and its immunogenicity. Blocking immune checkpoint has already proven efficacy in several solid cancers (1). Based on phase II trials, the FDA has already approved the pembrolizumab (anti-PD-1 monoclonal antibody) for the treatment of patients with refractory advanced gastric cancer expressing PD-L1 [combined positive score (CPS) ≥1%] (2) or for the treatment of patients with refractory advanced solid tumors with dMMR/MSI (deficient mismatch repair/microsatellite instability) phenotype (3). However, different studies with immunotherapy have showed a rather wide range of tumor response rate in gastric cancer, highlighting the need to identify biomarkers to better select patients who might benefit most from immune checkpoint inhibitors.

In order to answer this question, Kim *et al.* have performed a molecular characterization from 61 patients with advanced gastric cancer treated by pembrolizumab monotherapy (ClinicalTrials.gov, NCT#02589496) (4). All patients underwent pretreatment tissue biopsy in order to assess the mutational load and molecular subtype of their gastric cancer, together with their MSI/MMR, PD-L1 and EBV status. In addition, patients were followed with serial collection of plasma-derived circulating tumor DNA (ctDNA).

All patients with advanced gastric cancer included in this monocentric phase 2 trial have been pretreated before inclusion with 1 (52.5%) or 2 (47.5%) lines of chemotherapy. Patients were all from Korea and a majority of them were men (70.5%) and in a good condition status (ECOG PS 1, 98.4%; PS 2, 1.6%). Six patients (9.8%) were confirmed to be EBV(+) and 7 (11.5%) with MSI tumors. Of the 55 patients for whom the tumor expression of PD-L1 was available (CPS cut-off value of 1%), 28 were considered PD-L1(+) (51%). After a median follow-up of 16.2 months, the objective response rate (ORR) was 24.6% for the 57 patients for whom the tumor response evaluations were available. According to the subtype of gastric cancer, authors demonstrated that patients with MSI or EBV(+) status showed the highest response rates. The PD-L1 status seemed to be less relevant to select patients who are most likely to benefit from pembrolizumab treatment. Indeed, the ORR was 50.0%, 85.7% and 100% in PD-L1(+), MSI and EBV(+) gastric cancer patients, respectively.

For PD-L1 status, the KEYNOTE-059 phase II study has suggested that PD-L1(+) (CPS ≥1) could be a predictive marker for efficacy of pembrolizumab monotherapy in patients with refractory advanced gastric cancer (2). However, in two recent published phase III studies (ATTRACTION 02 and JAVELIN 300 trials), the PD-L1(+) (CPS ≥1) status had no predictive value for efficacy of nivolumab (anti-PD-1 monoclonal antibody) and avelumab (anti-PD-L1 monoclonal antibody) in the

treatment of refractory advanced gastric cancer patients (5,6). Interestingly, in the phase III KEYNOTE-061 study, negative for its primary endpoint (improvement in overall survival) in second-line treatment with pembrolizumab versus paclitaxel in the population of patients with PD-L1(+) (CPS ≥1), patients who expressed high level of PD-L1(+) (CPS ≥10) seemed to benefit from pembrolizumab (7). Taken together, these data suggest that still more work is needed on the methodology used and the standardization of PD-L1 assessment and that future validation in large prospective trials remains necessary before having this test ready for daily use.

For EBV status, this study provides the first clinical evidence showing that EBV(+) tumors could be a strong marker for efficacy of immunotherapy. Indeed, all EBV(+) gastric cancer patients in this study (n=6; 9.8%) achieved a complete or partial response. These results are very encouraging and need to be validated prospectively in the future on larger series of advanced gastric cancer patients. The rationale for this potential efficacy of immunotherapy is possibly linked to the high tumor immune cell infiltration and overexpression of PD-L1 and PD-L2 in EBV(+) gastric cancer previously described. Interestingly, this predictive value of EBV(+) for efficacy of pembrolizumab was independent of the tumor mutational load, PD-L1, and MSI status. As previously observed, EBV(+) and MSI gastric cancer are mutually exclusive. The EBV(+) gastric cancer had a high prevalence of DNA-methylation but lacked the *MLH1* promoter hypermethylation that is a characteristic of MSI tumor associated with CIMP phenotype (8). Unlike some Asian countries, the EBV test for gastric cancer is not routinely performed in western countries and these results should motivate western counties to assess EBV at least through translational research projects.

For MMR status, authors showed that among the 7 patients with MSI gastric cancer, 6 achieved major responses (3 complete response and 3 partial response), while one patient progressed rapidly. For this patient who was refractory to pembrolizumab [26-year-old woman, PD-L1(–) and low mutational load tumor], authors showed that protein expression of MLH1 in IHC staining was heterogeneous with both positive and negative area within the gastric tumor. Moreover, MLH1 IHC positive and negative regions were confirmed as MSS and MSI, respectively, by pentaplex PCR. In metastatic colorectal cancer (mCRC), dMMR/MSI status seems to be a major predictive biomarker for the efficacy of immune checkpoint inhibitors (3,9). However, a recent publication suggested that the rare primary resistance of dMMR/MSI mCRC to immune checkpoint inhibitors is mainly due to misdiagnosis of their dMMR/MSI status (10). In the study of Kim *et al.*, the results of IHC and MSI status were concordant but showed heterogeneous intratumoral distribution of dMMR/MSI in the same patient. The MMR deficiency occurs via three main mechanisms: (I) somatic hypermethylation of the *MLH1* gene promoter; (II) an inherited germline mutation in one of the MMR genes (Lynch syndrome); and (III) double somatic mutations in MMR genes (11). Thus, in order to examine a potential molecular mechanism of heterogeneous MMR status distribution, it will be interesting to complete analysis on normal and tumor tissues by next-generation sequencing (NGS) and multiplex ligation-dependent probe amplification (MLPA) analysis of MMR genes, including methylation of *MLH1* gene promoter, and by constitutional analysis for Lynch syndrome screening (especially for this young patient). Another question is to know whether the chemotherapy could modify the results of MMR assay, which would highlight the interest of analyzing the tumor at the time of diagnosis in patients naïve of any anti-cancer medical treatment.

As already showed, the overexpression of PD-L1 is preferentially observed in dMMR/MSI and EBV(+) tumors, and there is also a strong correlation between dMMR/MSI status and the mutational load tumor. In this study, authors showed that among the 8 patients with high mutational load tumor, 6 were MSI, 1 was EBV(+) and 1 was MSS/EBV(–). Among these patients, all of them achieved a complete or partial response, except one patient who was MSS/EBV(–).

Taken together, these data suggest that EBV(+) and MSI status seem to be very relevant to select GC patients for immune checkpoint blockers. Nevertheless, it would be interesting to know the results of efficacy in terms of progression-free and overall survivals in these patients. Further explorations are needed to assess response to immunotherapy in MSS and EBV(–) gastric cancer patients according to the mutational load tumor and the level of PD-L1 tumor expression.

All the biomarkers discussed above required tumor biopsies that can be considered as invasive explorations. Given this limitation and the fact that gastric cancer could exhibits significant spatial and temporal tumor heterogeneity, authors hypothesized that ctDNA may be an effective tool to select patients for immunotherapy. The ctDNA analysis at baseline may effectively reflect the mutational load in the tumor, and its early variation after

 

treatment start, may predict the efficacy of immunotherapy. Interestingly, the authors showed that (I) the mutational tumor load evaluated by ctDNA at baseline (73-gene sequencing panel—NGS) was predictive of response to pembrolizumab; (II) and its decrease 6 weeks after treatment was associated with efficacy of immunotherapy in terms of tumor response and progression free survival. These interesting results on ctDNA as an early dynamic predictive marker, which have been already shown in mCRC treated with chemotherapy (12), are very promising and need to be validated in larger studies. However, this approach of ctDNA is not able to identify EBV(+) patients (who generally exhibit a low mutational load), and despite the development of innovative detection techniques, some patients do not have detectable ctDNA (12).

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## Footnote

*Conflicts of Interest:* A Zaanan has participated in consulting and/or advisory boards for Roche, Merck Serono, Amgen, Sanofi, Servier and Lilly. J Taieb has received honoraria for speaker and/or advisory role from Merck, Roche, Amgen, Eli Lilly, Sanofi, Celgene, Servier, and Sirtex.

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