Editorial

Predictive markers in gastric cancer immunotherapy treatment—are we there yet?

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Immune checkpoint inhibitors (CPI) have become the standard of care in multiple lines of treatment in different settings in variety of cancers such as lung cancer, melanoma, renal cell carcinoma and some gastrointestinal cancers. In May 2017, Food and Drug Administration (FDA) provided the first tissue agnostic approval for pembrolizumab in mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) advanced solid tumors who have progressed on prior treatments or for which no other standard treatment exists (1). When dMMR or MSI-H gastric and gastroesophageal junction (GEJ) cancers were treated with single agent pembrolizumab, the overall response rate (ORR) was 60% (2). In the Phase II KEYNOTE-059 trial, programmed death-ligand 1 (PD-L1) positive advanced gastric and GEJ cancer patients treated with pembrolizumab after 2 prior lines of treatment showed an ORR 15.5% which led to its FDA approval in this subset of patients in September 2017 (3). Some other studies which have positive results but not yet led to FDA approvals are with nivolumab or combination of ipilimumab and nivolumab. In a phase III randomized trial of gastric and GEJ cancers refractory to standard treatment randomized 2:1 to nivolumab 3 mg/kg or placebo resulted in a significantly longer overall survival (OS) [5.26 versus 4.14 months; hazard ratio (HR) 0.63; P<0.0001] and progression-free survival (PFS) in nivolumab patients (4). In a phase I/II CheckMate-032 study in gastric and GEJ cancers, responses were observed with nivolumab and ipilimumab combination regardless of PD-L1 and MSI status. The ORR was 40% in PD-L1 positive and 24% in PD-L1 negative patients; similarly, ORR was 50% in MSI-H patients and 19% in non-MSI-H patients when treated with nivolumab 1 mg/kg and ipilimumab 3 mg/kg (5). The Cancer Genome Atlas (TCGA) defined a molecular classification of gastric cancers with MSI-H, Epstein-Barr virus (EBV) positive, genomically stable (GS) and chromosomal instability (CIN) subtypes (6). EBV positive tumors are identified with dense immune infiltrate and therefore studies have shown that these subtypes along with MSI-H are sensitive to CPIs (7).

In a recent study by Kim *et al.* published in Nature Medicine, the authors describe findings of a Phase II trial of pembrolizumab in 61 unselected gastric cancer patients for identification of response biomarkers (8). Of note, this study was conducted in Asia and only 13% of patients had cardia tumors unlike the trend we see in the Western world. The ORR in the unselected population was 24.6%, which is higher than previously reported in KEYNOTE-059 of 11.6% (3). The PD-L1 positivity rate was 51% in this study, which is similar to prior reports. The ORR reported in the Kim *et al.* study was 50%, which is significantly higher than previously reported. If MSI-H and EBV positive patients with PD-L1 positivity were excluded, the ORR was 13.3%. Thus, MSI-H and EBV positive status trumps PD-L1 positivity in terms of response prediction. MSI-H status does not imply an absolute response to CPI. In a recent study published in *JAMA Oncology*, the authors concluded that the reason for primary resistance to CPI in MSI-H colorectal cancers in misdiagnosis (9). There have also been

reports of tumor heterogeneity with certain areas in the tumor being MSI-H, while some being non-MSI-H. This begs the question, what should clinicians do when they see non-response to CPI in MSI-high tumors? Together this has promoted a thought of re-biopsy and even confirming status through pentaplex polymerase chain reaction testing.

Definition of PD-L1 positivity is also debatable. Most pembrolizumab studies have used the Dako 22C3 anti-PD-L1 antibody clone, while the 28-8 anti-PD-L1 antibody clone has been used in nivolumab studies. In addition, poor inter-reader concordance in reporting positive tests has been reported in the literature. While PD-L1 positivity has a significant bearing on ORR in pembrolizumab studies, that has not entirely been the case for nivolumab studies. In the ONO-4538-12 study, the ORR was 30% in gastric and GEJ cancers irrespective of PD-L1 status (4). Why is it that PD-L1 status has such an important bearing on ORR for some CPI, while not for others is currently unclear? Tumor mutational burden (TMB) has also been used as a marker for response to CPI. Most cases with high TMB are MSI-H tumors and have an ORR comparable to MSI-H gastric cancers. Even when categorized based on TCGA molecular subtypes, ORR in the genome stable (GS) and chromosomal instable (CIN) are much lower (5–12%) when compared to EBV and MSI-H subtypes. Several immune signatures have been studied as well. A 6-gene interferon-γ signature comprising *CXCL9*, *CXCL10*, *IDO1*, *IFNG*, *HLA-DRA*, and *STAT* have not correlated with ORR or PFS in KEYNOTE-012 or KEYNOTE-028 studies (10). Further an 18-genes T-cell inflamed gene expression profiling signature including *CCL5*, *CD27*, *CD274* (*PD-L1*), *CD-276* (*B7-H3*), *CD8A*, *CMKLR1*, *CXCL9*, *CXCR6*, *HLA-DQA1*, *HLA-DRB1*, *HLA-E*, *IDO1*, *LAG3*, *NKG7*, *PDCD1LG2* (*PD-L2*), *PSMB10*, *STAT1*, and *TGIT* had better correlation with ORR and PFS in the KEYNOTE-059 (3). The relationship with PD-L1 expression was not linear suggesting that there is more than PD-L1 expression that drives response to CPI in gastric and GEJ cancers.

It is well established in the oncology community that tumors do evolve over time and with various treatments including cytotoxic treatments and radiation. Serial biopsies would be one way to recapitulate this evolution. However, clinicians do understand that this may not be feasible in this population of patients due to their overall health in the advanced disease stage. Increasingly, we have now begun to use a circulating tumor DNA (ctDNA) based 73-gene commercial assay (Guardant360) that is a relatively non-invasive form of capturing the current mutational landscape of the tumor. Concordance studies of this test in lung cancer have shown concordance of 92–100% with tissue results (11). In recent studies multispectral immunohistochemical analysis are being increasing performed to evaluate the difference in immune infiltrates in tumors that predict response to CPI. In a Merkel Cell carcinoma study, immunohistochemistry (IHC) for CD8+ T cells, CD68+ macrophages, programmed cell death 1 (PD-1) and PD-L1 were performed simultaneously (12). In another study for melanoma, multispectral IHC with CD3, CD8, FoxP3, CD163 and PD-L1 increased the negative predictive value of the test to 100% (13). Such tests are yet to be developed for gastric and GEJ cancers.

So far, the breadth of CPI in gastric and GEJ cancers has heavily focused on cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), PD-1 and PD-L1 inhibitors. However, various checkpoints have been identified in cancer such as LAG-3, IDO1, TIM3, VISTA. In the future we can expect several other CPIs to be tested in gastric and GEJ cancers. Will these inhibitors be affected by PD-L1 or PD-1 expression or even PD-L2 expression is currently unclear? As it stands now, all advanced gastric and GEJ cancer patients should be tested for PD-L1 and MMR or MSI in tumor specimens. While EBV EBER-ish is not currently standard and FDA approved practice, it is highly encouraged to test patients for this as well. Concept of tumor heterogeneity should be borne in mind if dMMR or MSI-H patients are non-responders. While the role of longitudinal ct-DNA testing at this current time may be purely academic, it can potentially uncover some reliable biomarkers of response in this subset of patients.

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Footnote

Conflicts of Interest: Dr. R Mehta serves on the advisory board for Taiho Pharmaceutical. Dr. K Almhanna is a consultant for BMS and Merck and is a speaker for Eisai.

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