Encouraging results for PD-1 inhibition in gastric cancer

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The prognosis for advanced gastric cancer is poor: less than 10–15% of patients with metastases live for more than 2 years. Trastuzumab and ramucirumab have resulted in modest improvements in overall survival for patients with HER2-positive gastric cancer and in the second-line setting, respectively (1–2). However, these drugs are notable for their success in a field in which there have been many failures (1–4). Within this challenging therapeutic context, the results of the KEYNOTE-012 study by Kei Muro and colleagues (5) are promising.

In KEYNOTE-012, patients with PD-L1-positive advanced gastric cancer were treated with pembrolizumab, an anti-PD-1 antibody, until progression or intolerable adverse events. 65 (40%) of 162 patients screened were PD-L1-positive, and 39 (24%) patients were enrolled in this international phase 1b study. Impressively, 17 (53%) of 32 patients with at least one post-baseline tumour assessment had evidence of tumour regression, and eight (22%) of 36 evaluable patients had a confirmed partial radiological response. Consistent with immunotherapy trials in other cancers, these responses were sustained; the median duration of response was 40 weeks and four (11%) of 36 evaluable patients who had a response had not progressed at the time of reporting. Toxicity was as expected, with immune-related adverse events occurring in nine (23%) patients. No patients discontinued therapy due to an immune-mediated adverse event; this result compares favourably with second-line chemotherapy trials in which treatment discontinuation due to adverse events ranges from 11% to 30% (4,6). Muro and colleagues show that in KEYNOTE-012, survival was similar between Asian and non-Asian patients, a reassuring finding given that recent international gastric cancer trials have been affected by regional variations in survival (3,4).

Screening for KEYNOTE-012 was done with a prototype immunohistochemistry assay for PD-L1. To be eligible to participate, patients needed at least 1% PD-L1 expression in tumour cells, immune cells, or both cell types. PD-L1 status was then reassessed with a different assay. The results of the second assay suggest that PD-L1 expression on immune cells, but not tumour cells, is associated with response to pembrolizumab in gastric cancer. Secondly, eight of the 35 patients with assessable biopsies were classified as PD-L1-negative on repeat testing. These results are a testament to the complexity of PD-L1 analysis in general, and gastric cancer biomarker assessment in particular. This discordance could be due to dynamic

changes in PD-L1 expression following treatment, assay variability, or gastric cancer heterogeneity. Consequently, it is unclear whether the radiological responses that have been reported in seemingly PD-L1-negative patients treated with anti-PD1 therapies in non-biomarker selected trials are indicative of underlying heterogeneity of biomarker expression or a true absence of association between the biomarker and response (7). Further exploration will be needed to identify the best method to assess PD-L1 and whether it is a true predictive biomarker for immunotherapy in gastric cancer. The authors also presented preliminary results with their interferon γ gene expression signature, as a tissue-of-origin independent predictive biomarker, which, if validated, could be helpful in the future to circumvent these immunohistochemistry assay-related challenges.

KEYNOTE-012 presents several thought-provoking results that cannot be definitively resolved by this small study. First, the interaction between previous chemotherapy treatment and the efficacy of pembrolizumab is unclear. Although several patients with a response had received one or fewer lines of chemotherapy prior to pembrolizumab, encouragingly, most (63%) responding patients had received two or more prior anticancer therapies. However, a small early phase trial such as KEYNOTE-012 cannot take into account the short life expectancy of many advanced gastric cancer patients, which might make the relatively slow response rates and occasional pseudoprogression associated with immunotherapy challenging to adopt. The optimum setting in which to treat patients with gastric cancer with immunotherapy will be established by several ongoing trials. Second, although microsatellite unstable gastric cancer should, theoretically, be an easy target for immunotherapy, this hypermutated phenotype predicted response in only half of the patients with microsatellite instability treated with pembrolizumab in KEYNOTE-012. This subset represents up to 22% of patients with gastric cancer and merits further investigation (8). Finally, the metrics by which the success of immunotherapy clinical trials for gastric cancer should be assessed require careful consideration. The proportion of patients achieving a response in KEYNOTE-012 is smaller than that in the RAINBOW trial of the combination of paclitaxel and ramucirumab—in fact, by a purely statistical definition KEYNOTE-012 is a negative trial. Neither do the unremarkable progression-free survival results account for the substantial overall survival benefi t for patients who responded to treatment (5). Attention to each of these issues is warranted in ongoing randomised clinical trials.

Trials of anti-CTLA-4 and anti-PD-1 therapy have been extremely successful in melanoma, which risks making the results of KEYNOTE-012 seem less impressive by comparison. However, gastric cancer causes three times as many deaths as melanoma does each year worldwide, arguably making these results more important (9). The results of the current study are an encouraging first step towards the development of a therapy that can result in long-term remission for a disease that, for most patients, currently has no realistic hope for a cure.