



Why should localized gastric adenocarcinoma patients fare poorly after adjunctive therapy compared to surgery alone?

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Hypermutated phenotype that is particularly caused by microsatellite instability (MSI) has been in focus and concepts surrounding it are changing rapidly. Not only many of these tumor respond dramatically to checkpoint inhibition, some patients with metastatic cancer are practically cured. In this regard, we found the report by Pietrantonio *et al.* is of considerable interest (1). Their painstaking work to collect individual patient data and consuming analyses are commendable. Their results are unexpected and inconsistent with those noted for colon cancer. Additionally, these results are contradictory with two gastric adenocarcinoma (GAC) cohorts included in their meta-analysis and also published separately (2,3). Re-strategizing the management of MSI localized GAC is worthy of discussion. However, we raise several issues with their analysis and make suggestions.

As acknowledged by the authors, the entire analysis is based on only 121 total MSI GAC patients derived from four trials. In each cohort, an entirely unique adjunct strategy was used with two trials lacking a surgery alone control (1). The method for MSI assessment was not uniform and not known for the ITACA-S trial. Various statistical methods were used to accommodate a number of shortcomings in patient populations, as shown in their table 2, disease-free survival (DFS) and overall survival (OS) in the category for MSI tumor patients have starkly wide 95% confidence intervals compared to those in the microsatellite-stable (MSS) categories, making their

observation less reliable and the conclusions weaker. The authors also did not explain why adjunctive systemic therapy would produce shorter DFS or OS for MSI GAC patients treated with adjunctive therapy. The MSI analysis of the CLASSIC trial (same 592 patients included in the Pietrantonio *et al.* report) showed no reduction in OS or DFS for MSI patients (3) and that of the ARTIST trial (almost the same patients included in the Pietrantonio *et al.* report) showed that MSI tumor patients actually fared better (the ARTIST trial lacked surgery alone control) (2). The Pietrantonio *et al.* report also uses the term predictive loosely to connote DFS/OS and many areas are confusingly presented (including, the * in table 2 is not explained, MSI-low can only be designated when polymerase chain reaction (PCR) is used to assess the MSI status) (1).

It is clear that MSI tumor patients (tumor type agnostically) have better prognosis when localized and in the advanced setting and have dramatic benefits from programmed-death-1 (PD-1) inhibition (4). Meaning, MSI tumors (despite their inherent heterogeneity) have rather uniform biologic/clinical characteristics. In this respect, we would like to think that if GAC patients fared poorly with adjunctive therapy, colon cancer patients should have experienced a disadvantage but that is not the case. The lack of benefit from certain adjunctive therapy in MSI tumor patients is a more consistent theme.

Finally, it is well known that the loss of function of tumor suppressor gene (TSG) (mutation/deletion, epigenomic

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silencing, or facilitation of TSG protein degradation) can result in upregulation of corresponding oncogenes (examples are TP53, CDH1, and ARID1A) (5). Work on mismatch repair TSGs is quite limited and needs to be expanded. Upregulation of oncogenes (when corresponding TSG protein function is lost) would make the cancer phenotypically aggressive and resistant to therapy (6). However, it is not likely to result in worse outcomes when cytotoxic agents are applied. Thus, we wonder if the conclusions of the current report should be moderated due to many limitations (small number of MSI tumor patients with wide confidence intervals for DFS and OS making the results/conclusions less robust, cohort heterogeneity, non-uniform therapeutic strategies, contradictory results published from two cohorts (one showing no detrimental effect on OS and another showing an advantage for MSI GAC patients), no validation of lack of benefit borne out in colon cancer studies which are cleaner and have large number of patients (7). We would also not agree that the localized MSI GAC patients should be stratified in empiric trials. We strongly suggest that these patients should not be included in generic trials but are in a need of unique strategies appropriate for their molecular/clinical behavior and some of these efforts are already underway (NCT04082572; NCT03832569). Such strategies will also afford a unique opportunity to study why nearly half of the MSI tumor patients do not benefit from PD-1 inhibition (is it the degree of MSI, neo-epitope load, neoantigen diversity/immunogenicity, T-cell diversity, quality of frame-shift-derived peptides, major histocompatibility complex-conformity/human leukocyte antigen diversity?). These MSI tumors are attractive targets for vaccines, cell therapies, simultaneous oncogene targeting therapies, and next generation of checkpoint inhibitors.

Finally, results of three new trials are worthy of mentioning. Chalabi *et al.* (8) reported a very novel strategy for MSI localized colon cancer patients who received preoperative nivolumab and ipilimumab and at surgery, many patients had complete pathologic response making this a viable future strategy. Ludford *et al.* reported another novel strategy in which patients with documented metastatic MSI colon cancer patients first received checkpoint inhibition (nivolumab) but later were taken to surgery to find complete pathologic response even though prior to surgery the CT scans were grossly abnormal in some patients (9). Finally on June 29, 2020, US Food and Drug Administration (www.fda.gov/) approved pembrolizumab as

first-line immunotherapy for patients with MSI metastatic colorectal cancer.

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Footnote

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