Editorial Commentary

Nivolumab plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastroesophageal junction cancer—regional differences in efficacy

Rutika Mehta[1], **Manish A. Shah**[2]

[1]Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA; [2]Gastrointestinal Oncology Program, Weill Cornell Medicine, New York, NY, USA

Correspondence to: Manish A. Shah, MD. Professor of Medicine, Weill Cornell Medicine, 1305 York Avenue, 12th Floor, New York, NT 10021, USA. Email: mas9313@med.cornell.edu.

Comment on: Kang YK, Chen LT, Ryu MH, *et al.* Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2022;23:234-47.

Submitted Jul 15, 2022. Accepted for publication Sep 05, 2022.
doi: 10.21037/apm-22-851
View this article at: https://dx.doi.org/10.21037/apm-22-851

It is estimated that 47,020 individuals will be diagnosed with gastroesophageal cancers in the United States in 2022 (1). The 5-year survival of patients with this type of cancer is about 5% (2), highlighting the unmet need for continued drug development. The mainstay of treatment for untreated or recurrent unresectable disease has been chemotherapy for many years. Doublet chemotherapy regimens with fluoropyrimidine and cisplatin or oxaliplatin are the preferred regimens (3). In patients with HER2-positive cancer, it is recommended to add trastuzumab to chemotherapy (4), and more recently there is evidence of an improved response rate with the addition of immunotherapy as well (5). In spite, the median overall survival of these patients with treatment was about 1 year.

In the recent years with the advent of checkpoint inhibitors targeting PD-1 and PD-L1, several trials have been conducted testing the efficacy of the combination of chemotherapy with immunotherapy in the front-line setting (6-8). Certain chemotherapeutic drugs such as platinum can improve antigenicity of tumor cells and makes them more sensitive to immune effector cells. Fluoropyrimidines can help with the elimination of immunosuppressive immune cells. While these mechanisms influence the immune system to contain its immunosuppressive nature, the addition of immunotherapy can help enhance the anti-tumor immune response, thus leading to synergistic actions in favor of tumor death (9-11). There have been concurrent trials with different checkpoint inhibitors across the world some of which are heavily dominated by Western world patients, while some are purely Asian studies. There are some differences in gastric cancers seen among Asian versus Western patients. An important difference is the location of the tumor. While in the Western world, majority of the gastric cancer cases are limited to the proximal third of the stomach, Asian patients more frequently are diagnosed with distal gastric cancer (12). In a meta-analysis, Asian patients with advanced or metastatic gastric and gastroesophageal junction (GEJ) cancers were found to have better survival outcomes than Western patients (13). The results of ATTRACTION-4 suggest that these differences as well as differences in study design could have played a significant role in the study outcome (14).

The ATTRACTION-4 study is a Phase III randomized placebo-controlled trial conducted in Asia in front-line metastatic HER-2 negative gastric and GEJ cancer patients (14). The trial was conducted across 130 centers in Japan, South Korea, and China (Taiwan). This was a double-blind placebo-controlled study and patients were randomized 1:1 to receive chemotherapy plus nivolumab versus chemotherapy plus placebo. The chemotherapy

Table 1 Comparison of ATTRACTION-4 and CheckMate-649 studies

Study or patient related factors	ATTRACTION-4 (14)	CheckMate-649 (6)
Type of study	Phase 3 double-blinded randomized	Phase 3 open label randomized
Geographic location	Asia [Japan, South Korea, China (Taiwan)]	Asia [including China (mainland, Hong Kong, Taiwan), Japan, Singapore, South Korea], United States, Canada, rest of the world
Chemotherapy backbone	S-1/oxaliplatin or capecitabine/oxaliplatin	5-fluorouracil/oxaliplatin or capecitabine/oxaliplatin
Primary endpoints	PFS by independent review and OS	PFS or OS by independent review in patients with PD-L1 positive (CPS ≥5) patients
Gastric cancer/GEJ cancer (%)	65/9	70/16
Diffuse type histology	51%	33%
Peritoneal metastases (yes)	47%	24%
MSI-high patients	Not reported	3%
Treatment-related Grade 3–4 AEs	18% in study arm; 9% in control arm	59% in study arm; 44% in control arm
Received subsequent therapy	71%	40%

PFS, progression free survival; OS, overall survival; CPS, combined positive score; GEJ, gastroesophageal junction; MSI, microsatellite instability; AE, adverse event.

options included oxaliplatin with either S-1 or capecitabine. The primary endpoints of the study were centrally assessed progression free survival (PFS) and overall survival (OS). Therefore, patients were required to have at least 1 measurable lesion per RECIST v1.1 at the time of enrollment. The secondary endpoints were PFS as assessed by site investigators, objective response rate (ORR); disease control rate (DCR) and best overall response as assessed both centrally and by site investigators; duration of response and time to response assessed centrally; and maximum percentage change in the sum of diameters of target lesions assessed by site investigators. In addition to adverse events, quality of life (QoL) measures using EQ-5D-3L and FACT-Ga scales were also evaluated. Seven hundred twenty-four patients were randomized between March 23, 2017 and May 10, 2018. Interim PFS analysis was performed at data cutoff on October 31, 2018 at which time median follow up period was 11.6 months. Primary OS analysis was performed at data cutoff on January 31, 2020 at which time median follow-up period was 26.6 months. At interim analysis, PFS was longer in the study arm than the control arm (10.45 *vs.* 8.34 months; HR 0.68; P=0.0007). At final data cutoff, PFS continued to remain significantly longer in the study arm (10.94 *vs.* 8.41 months; HR 0.70; P=0.0005). The median OS was not significantly different with 17.45 months in the chemotherapy plus nivolumab arm and 17.15 months in the chemotherapy plus placebo arm (HR 0.90; P=0.26). Similar percentages of patients in both groups went on to receive subsequent anti-cancer treatment (72% *vs.* 73%). Since this was a double-blind study, 23% patients in the chemotherapy plus nivolumab group and 19% patients in the chemotherapy plus placebo was unblinded for selection of subsequent anti-cancer therapy. A higher proportion of these patients in the control arm (68%) went on to receive subsequent checkpoint inhibitors than that in the study arm (17%). Treatment related grade 3–4 adverse events occurred in 18% of patients on the chemotherapy plus immunotherapy and 9% of patients on chemotherapy plus placebo. Deaths due to drug toxicity were noted in 3 patients on the study arm and 4 in the control arm. There was no significant difference in time to symptom deterioration or improvement when comparing the two arms. Thus, QoL scores were not substantially different in the two groups (14).

The safety and QoL data from ATTRACTION-4 were in line with other similar studies combining chemotherapy and immunotherapy. However, while the PFS improvement with the addition of immunotherapy to chemotherapy was significant, this study failed to meet one of its primary endpoints, OS. In comparison, CheckMate-649 a similar study conducted in the same population of patients not only showed improved PFS and ORR, but also significantly longer OS with chemotherapy plus nivolumab (6). Some of the differences in the two studies are shown in *Table 1*.

Some important differences between CheckMate-649 and ATTRACTION-4 include geographic location of the trial (all over the world with 25% patients from Asia versus 100% patients from Asia), higher percentage of patients on the ATTRACTION-4 study with diffuse type histology (51% *vs.* 33% on CheckMate-649), higher proportion of patients with peritoneal disease on ATTRACTION-4 (46% *vs.* 24%). There are some other differences with study design including statistical considerations, sample size, chemotherapy backbone which may also partly explain some differences in results. The ATTRACTION-4 study did not report how many patients were mismatch repair deficient or microsatellite instability high (MSI-high) or positive for Epstein Barr virus (EBV) which biologically has important implications to sensitivity to chemotherapy versus immunotherapy. Per the Asian Cancer Research Group (ACRG) molecular classification of gastric cancers; about 50% of patients can be classified as MSI-high or EBV+ which are typically immunologically active and therefore more sensitive to immunotherapy (15). If ATTRACTION-4 consisted of these patients reflective of ACRG classes, then treatment with chemotherapy over time may have led to loss of benefit from immunotherapy. It can be postulated that tumors that are immunologically rich may not need the chemotherapy for substantially longer periods of time for sensitization of tumor cells to immune cells. Moreover, with continued use of chemotherapeutic drugs, it is plausible that there is destruction of immune effector cells as well thus blunting the effect of immunotherapy eventually. Further, there was greater crossover to immunotherapy in ATTRACTION-4 (66% with ATTRACTION-4 *vs.* 39% with Checkmate-649). If there were a greater proportion of immunologically sensitive malignancies in ATTRACTION-4, and a greater proportion received subsequent line immunotherapy, that could explain the reduced OS benefit, while maintaining the PFS benefit in the first line treatment setting.

It is also unclear how the chemotherapy backbone plays a role in affecting survival. While the CheckMate-649 study used either 5-fluorouracil or capecitabine in combination with oxaliplatin as chemotherapy backbone (6), the ATTRACTION-4 study used S-1 or capecitabine with oxaliplatin (14). About 1/3rd of patients on ATTRACTION-4 received capecitabine based chemotherapy as opposed to 50% on CheckMate-649. The median OS in Asian patients receiving chemotherapy in the CheckMate-649 study was 12.5 months which is substantially lower than 17.15 months seen in ATTRACTION-4. More than 3/4ths of patients on ATTRACTION-4 went on to receive subsequent treatment while less than half ended up receiving subsequent treatment on CheckMate-649 which may explain some of these differences. The distribution of tumor PD-L1 expression was similar across both studies (16% with tumor PD-L1 ≥1). Therefore, biomarker selection does not explain the survival differences. The ORRs were similar in both studies with chemotherapy plus nivolumab (58%) however, the median duration of response was substantially longer in ATTRACTION-4 (12.91 months) than in CheckMate-649 (8.5 months). Lastly, ATTRACTION-4 was a double-blinded study, while CheckMate-649 was an open-label study. The knowledge of treatment that a patient receives may have implications in making decisions about benefit from that treatment.

The authors conclude that regional variations in molecular classes of gastric cancer can exist which can influence overall benefit of different treatments. There are differences in approved treatments, practices of treatment, and disease burden that can influence patient survival. Chemotherapy in combination with immunotherapy is now the new standard of care for HER-2 negative recurrent, unresectable, metastatic gastric and GEJ cancer patients and was FDA approved for use in United States in April 2021. It is also clear that chemotherapy plus immunotherapy combination in HER-2 negative patients has a greater magnitude of benefit in tumors with higher PD-L1 expression. We think that ATTRACTION-4 has been an important study to add to our current knowledge of chemotherapy plus immunotherapy treatments for upper gastrointestinal cancers and forces us to define patient populations that are expected to have proportionately higher benefits from the treatment thereby pushing the needle of survival for this cancer higher and higher.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Palliative Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-851/coif).

RM has received consulting fees from Eli Lilly; and has served on speaker bureau for Natera and Daiichi Sankyo; and has accepted compensation for a talk from Foundation Medicine; and has served on advisory board for Eli Lilly, BMS, Astellas and Boston Gene and is a volunteer advisory board member for Debbie's Dream Foundation. MAS has received grants or contracts from Merck, Bristol Meyers Squibb, and Oncolys Biopharma, all to the institution; and he serves on the Data Safety Monitoring Board for Zymeworks, and has a Leadership role as a volunteer for the ASCO Leadership Council and the Degregorio Foundation for Upper GI Malignancies. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Society AC. Cancer Facts & Figures 2022.
2. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 8 Registries, Nov 2021 Sub (1975-2019) - Linked To County Attributes - Time Dependent (1990-2019) Income/Rurality, 1969-2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program [Internet]. National Cancer Institute. 2022.
3. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36-46.
4. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
5. Janjigian YY, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature 2021;600:727-30.
6. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398:27-40.
7. Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer: The KEYNOTE-062 Phase 3 Randomized Clinical Trial. JAMA Oncol 2020;6:1571-80.
8. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398:759-71.
9. Ramakrishnan R, Huang C, Cho HI, et al. Autophagy induced by conventional chemotherapy mediates tumor cell sensitivity to immunotherapy. Cancer Res 2012;72:5483-93.
10. Vacchelli E, Aranda F, Eggermont A, et al. Trial Watch: Chemotherapy with immunogenic cell death inducers. Oncoimmunology 2014;3:e27878.
11. Zitvogel L, Galluzzi L, Smyth MJ, et al. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. Immunity 2013;39:74-88.
12. Shim JH, Song KY, Jeon HM, et al. Is gastric cancer different in Korea and the United States? Impact of tumor location on prognosis. Ann Surg Oncol 2014;21:2332-9.
13. Zhang Z, Liu Z, Chen Z. Comparison of Treatment Efficacy and Survival Outcomes Between Asian and Western Patients With Unresectable Gastric or Gastro-Esophageal Adenocarcinoma: A Systematic Review and Meta-Analysis. Front Oncol 2022;12:831207.
14. Kang YK, Chen LT, Ryu MH, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal

junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2022;23:234-47.

15. Heo YJ, Park C, Yu D, et al. Reproduction of molecular subtypes of gastric adenocarcinoma by transcriptome sequencing of archival tissue. Sci Rep 2019;9:9675.

Cite this article as: Mehta R, Shah MA. Nivolumab plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastroesophageal junction cancer—regional differences in efficacy. Ann Palliat Med 2022;11(10):3371-3375. doi: 10.21037/apm-22-851

