Selected Summary

First-line immunotherapy: Hype rather than near reality in gastric cancer

Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, Wyrwicz L, Yamaguchi K, Skoczylas T, Bragagnoli AC, Liu T, Schenker M, Yanez P, Tehfe M, Kowalyszyn R, Karamouzis MV, Bruges R, Zander T, Pazo-Cid R, Hitre E, Feeney K, Cleary JM, Poulart V, Cullen D, Lei M, Xiao H, Kondo K, Li M, Ajani JA. (Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; Department of Medicine, Weill Cornell Medical College, New York, NY, USA; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Medicine, Johannes-Gutenberg University Clinic, Mainz, Germany; Department of Hemato-Oncology, Clinica San Carlos de Apoquindo, Pontificia Universidad Católica, Santiago, Chile; Department of Medical Oncology, Oncovida Cancer Center, Fundación Arturo López Pérez, Providencia, Chile; Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education/Beijing, Peking University Cancer Hospital and Institute, Beijing, China; Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warsaw, Poland; Department of Gastroenterological Chemotherapy, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; II Klinika Chirurgii Ogólnej, Gastroenterologicznej i Nowotworów Ukadu Pokarmowego, Medical University of Lublin, Lublin, Poland; Department of Medical Oncology, Fundacao Pio Xii Hosp Cancer De Barretos, Barretos, Brazil; Department of Medical Oncology, Zhongshan Hospital Fudan University, Shanghai, China; Department of Medical Oncology, Sfantul Nectarie Oncology Center, Dolj, Romania; Department of Internal Medicine, Oncology Unit, Universidad de La Frontera, Temuco, Chile; Hematology-Oncology, Oncology Center-Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; Instituto Multidisciplinario de Oncologia, Clinica Viedma SA, Viedma, Argentina; Department of Biological Chemistry and Laiko General Hospital Medical School, National and Kapodistrian University of Athens, Athens, Greece; Internal Medicine, Clinical Oncology, Instituto Nacional de Cancerología Empresa Social del Estado, Bogotá, Colombia; Department of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Düesseldorf, University Hospital of Cologne, Cologne, Germany; Department of Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza, Spain; Department of Chemotherapy, National Institute of Oncology, Budapest, Hungary; Department of Oncology, Haematology and Palliative Care, St John of God Murdoch Hospital, Murdoch, WA, Australia; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; Bristol Myers Squibb, Princeton, NJ, USA; Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.) 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.

SUMMARY

Chemotherapy with fluoropyrimidine and oxaliplatin has long been the standard of care for advanced gastro-oesophageal cancer. The CheckMate 649 trial by Janjigian *et al*. is a multicentre phase 3 randomized trial to evaluate the benefit of nivolumab along with fluoropyrimidine and oxaliplatin. The key inclusion criteria were patients who were >18 years of age, had untreated advanced unresectable gastric or gastro-oesophageal junction cancer with Eastern Cooperative Oncology Group (ECOG) performance score (PS) 0–1 and having measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, irrespective of previous curative therapy, while the key exclusion criteria were HER2-positive status, peripheral neuropathy more than grade 1, seropositive patients for HIV and hepatitis B or C.

Outcomes of patients randomized to two arms, namely nivolumab plus chemotherapy or chemotherapy alone in a 1:1 ratio are outlined in this article. Patients were stratified according to their first-line programmed cell death ligand (PD-L1) status, region of enrolment, ECOG PS and chemotherapy backbone. Patients were evaluated every 6 weeks for the first 48 weeks and then every 12 weeks till disease progression for the dual primary end-points of progression-free survival (PFS) and overall survival (OS) in patients with a PD-L1 combined positive score (CPS) of >4. Secondary end-points were OS in patients with a PD-L1 CPS of ≥1 and overall response rate (ORR), while exploratory end-points were duration of response, health-related quality of life (HRQOL), safety and tolerability and biomarkers potentially predictive of efficacy.

Between March 2017 and April 2019, a total of 789 patients were randomly assigned to the nivolumab plus chemotherapy arm, and 792 patients were assigned to the chemotherapy alone arm. After a median follow-up of 12.1 months, nivolumab plus chemotherapy statistically improved PFS from 6 to 7.7 months (hazard ratio [HR] 0.68; 98% confidence interval [CI] 0.56–0.81; p<0.0001) and OS from 11.1 to 14.4 months (HR 0.71; 98.4% CI 0.59–0.86; p<0.0001) in patients with a PD-L1 CPS of >4. While there was a numerical improvement in OS and PFS in patients with a PD-L1 CPS of >1 and all randomized patients, grade 3–4 treatment-related adverse events were more common in the immunotherapy arm (59% *v*. 44%), leading to more treatment discontinuation in the immunotherapy arm compared to the chemotherapy alone arm (36% *v*. 24%).

In this trial, Janjigian *et al*. showed a survival benefit of adding nivolumab to the fluoropyrimidine and oxaliplatin chemotherapy regimen, especially in patients with a PD-L1 CPS of >4.

COMMENT

Although these results indicate that nivolumab added to fluoropyrimidine and oxaliplatin chemotherapy increased OS in patients with a PD-L1 CPS of >4, a few issues with the trial need to be kept in mind.

First, the authors did not provide any information on the adverse events in both the subgroups of PD-L1 CPS of >4. The major issue with adding nivolumab in the Indian context will be added toxicity of immunotherapy, both physical and financial.

Almost one-third of patients discontinued the treatment in a trial setting, so the number could increase in the real-world setting. A retrospective study from our institute found that only 1.6% of the deserving patients could receive immunotherapy.[1]

Second, in the multicentre phase 3 KEYNOTE-062 study, patients with neither PD-L1 CPS of >1 nor 10 had the survival benefit of adding pembrolizumab to the same chemotherapy backbone.[2] Similarly, nivolumab in the ATTRACTION-4 trial failed to show a survival benefit in spite of a similar PFS benefit.[3] A major limitation of the trial is the change in the inclusion criteria to have patients only with a PD-L1 CPS of >4 after starting enrolment without explaining the basis of the cut-off of 4. The CPS of >4 is found in <40% of patients in some studies, so not many patients will be able to benefit from this combination in the real-world scenario,[4] where the experimental difference in OS shrinks compared to the ideal world of experimental environment.[5–7]

Third, the HRQOL did not improve in the nivolumab arm in spite of the improvement in the objective response rate and symptomatic benefit, points towards the toxicity in the combination arm which would have led to a decrement in HRQOL.

In the end, we appreciate the work done by Janjigian *et al*. in this controversial area. Although this trial has some limitations, a longer follow-up might help to clarify the benefit and duration of OS even in patients with a PD-L1 CPS of <4. A one-of-its-kind ongoing multicentre study initiated by our institute is trying to measure the impact of the addition of docetaxel to a fluoropyrimidine and oxaliplatin chemotherapy regimen on the OS in gastro-oesophageal cancer patients, and the results are eagerly awaited (CTRI/2020/03/023944).

Conflicts of interest. None declared

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PRABHAT BHARGAVA
Department of Medical Oncology

SHAILESH V. SHRIKHANDE
Department of GI and HPB Surgical Oncology
Homi Bhabha National Institute
Tata Memorial Centre
Parel, Mumbai, Maharashtra, India
shailushrikhande@hotmail.com

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