Editorial Commentary

Challenges and prospects of LAG-3 inhibition in advanced gastric and gastroesophageal junction cancer: insights from the RELATIVITY-060 trial

Sofie Seghers[1,2]^, Andreas Domen[1,2], Hans Prenen[1,2]^

[1]Department of Medical Oncology, University Hospital Antwerp, Edegem, Belgium; [2]Center for Oncological Research (CORE), University of Antwerp, Wilrijk, Belgium

Correspondence to: Hans Prenen, MD, PhD. Department of Medical Oncology, University Hospital Antwerp, Drie Eikenstraat 655, 2650 Edegem, Belgium; Center for Oncological Research (CORE), University of Antwerp, Wilrijk, Belgium. Email: hans.prenen@uza.be.

Comment on: Hegewisch-Becker S, Mendez G, Chao J, *et al.* First-Line Nivolumab and Relatlimab Plus Chemotherapy for Gastric or Gastroesophageal Junction Adenocarcinoma: The Phase II RELATIVITY-060 Study. J Clin Oncol 2024;42:2080-93.

Keywords: Cancer; gastro-intestinal cancer; lymphocyte-activation gene 3 (LAG-3); programmed death-1 (PD-1); relatlimab; nivolumab

Submitted Oct 04, 2024. Accepted for publication Dec 04, 2024. Published online Dec 27, 2024.
doi: 10.21037/jgo-24-757
View this article at: https://dx.doi.org/10.21037/jgo-24-757

Gastric cancer (GC), including gastroesophageal junction cancer (GEJC), remains a significant global health challenge, being the fifth leading cause of cancer-related mortality worldwide (1). The prognosis for patients with metastatic disease is somber, with a 5-year relative survival rate of 10% or less (2). The current standard of care for metastatic GC and GEJC relies on chemotherapy in combination with targeted therapy (e.g., trastuzumab) and immune checkpoint inhibitors (ICI) (e.g., pembrolizumab) depending on the presence of clinical actionable targets and molecular characteristics. Despite the integration of targeted therapy and ICI into first-line treatment, survival outcomes remain limited, and new strategies are needed to further improve prognosis in this population.

While programmed death-1 (PD-1) blockade has become a standard of care (3), the role of lymphocyte-activation gene 3 (LAG-3) is under investigation. LAG-3, or CD223, is a critical immune checkpoint molecule implicated in T cell exhaustion and is expressed on a variety of immune cells such as $CD4^+$ T cells, $CD8^+$ T cells, natural killer (NK) cells and regulatory T cells (4). LAG-3 negatively regulates T cell activity, particularly in the context of chronic tumor antigen exposure (4,5). PD-1 and LAG-3 are frequently co-expressed on T cells in a state of exhaustion (6). Therefore, simultaneous targeting of both LAG-3 and PD-1 offers the potential to revitalize the exhausted T cells. This approach has been validated in the RELATIVITY-047 trial in advanced melanoma, which showed that combining nivolumab with relatlimab (a LAG-3 inhibitor) more than doubled the progression-free survival (PFS) compared to PD-1 inhibition alone (7). The success of RELATIVITY-047 has prompted investigations into this combination for other malignancies, including GC/GEJC.

The RELATIVITY-060 trial (NCT03662659) was a phase II, open-label, multicenter study designed to evaluate the efficacy and safety of adding relatlimab to nivolumab and chemotherapy in the first-line treatment of advanced GC/GEJC (8). A total of 274 patients with unresectable or metastatic GC/GEJC were randomized to receive either the triplet of nivolumab, relatlimab, and chemotherapy or the doublet of nivolumab and chemotherapy. Standard chemotherapy regimens, XELOX, FOLFOX and SOX, were used in combination with either nivolumab alone or the fixed-dose combination of nivolumab and relatlimab. The primary endpoint was the objective response rate (ORR) in patients with LAG-3 expression ≥1%. Secondary

^ ORCID: Sofie Seghers, 0000-0002-2438-4155; Hans Prenen, 0000-0001-8802-7352.

endpoints included PFS, overall survival (OS), duration of response (DOR), and safety.

Unfortunately, the trial did not meet its primary endpoint. Patients in the triplet arm demonstrated a lower ORR compared to the doublet arm (48% *vs.* 61%, P=0.0711). Moreover, the median DOR, OS, and PFS were also shorter in the triplet group (DOR: 5.7 *vs.* 10.1 months; OS: 13.5 *vs.* 16.0 months; PFS: 7.0 *vs.* 8.3 months). These findings raise important questions about the role of LAG-3 inhibition in this setting, particularly given the success of dual checkpoint blockade in melanoma. Notably, the disease control rate (DCR) was higher in the triplet arm (92% *vs.* 85%), but the rates of complete response (6% *vs.* 10%) and partial responses (42% *vs.* 51%) were lower, suggesting that the addition of relatlimab may not be enhancing the depth of response. It is also important to consider the lower cumulative chemotherapy dose intensity in the triplet arm, which may have confounded the results.

Subgroup analyses revealed some interesting findings. Patients with LAG-3 expression ≥5% (n=37) appeared to derive greater benefit from the triplet regimen, with a trend toward improved PFS [13.1 *vs.* 6.9 months, hazard ratio (HR) =0.75]. Additionally, patients with LAG-3 expression ≥1% and programmed cell death ligand 1 (PD-L1) combined positive score (CPS) between 1 and 5 (n=41) had a higher median OS (15 *vs.* 11.2 months, HR =0.66). While these results are exploratory, they suggest that higher LAG-3 expression may identify a subgroup of patients who could benefit from dual LAG-3/PD-1 blockade. However, it is important to note that LAG-3 expression was not predictive of benefit in the RELATIVITY-047 trial, underscoring the need for better biomarkers.

The safety profile of the triplet regimen was consistent with other immunotherapy trials, with higher rates of grade 3/4 treatment-related adverse events in the triplet arm (69% *vs.* 61%). Discontinuation rates were also higher (42% *vs.* 36%), with peripheral neuropathy being the most common reason for discontinuation in both arms. Notably, three treatment-related deaths occurred in the triplet arm compared to one in the doublet arm.

The RELATIVITY-060 trial is part of a broader effort to explore LAG-3 inhibition in various cancers. Other RELATIVITY trials, such as the pivotal RELATIVITY-047 in previously untreated advanced melanoma (7), RELATIVITY-123 in microsatellite-stable metastatic colorectal cancer (9) and RELATIVITY-104 in non-small cell lung cancer tumors (10), are investigating the potential of LAG-3 blockade in different tumor types. Despite the disappointing results in GC/GEJC, these studies may provide insights into the contexts in which LAG-3 inhibition is most effective.

A major challenge in extending dual checkpoint blockade strategies to GC/GEJC is the highly heterogenous tumor microenvironment (TME), which can contribute to resistance to various treatment strategies (11). GC/GEJC is characterized by diverse immune infiltrates, including tumor associated macrophages and neutrophils, T cells, NK cells, all of which play critical roles in shaping the immune response (11). Besides, LAG-3 expression in GC/GEJC is complex and demonstrates differences in the TME among various clinicopathological parameters and main histological and molecular subtypes of GC, as demonstrated by Ulase *et al.* (12). The RELATIVITY-060 did not provide any information on Epstein-Barr virus (EBV) and microsatellite instability (MSI) status of patients, while LAG-3+ immune cell density is associated with sex, tumor location, Lauren phenotype, HER2, and PD-1/PD-L1 status, as well as EBV and MSI status. Also, cancer-specific survival was found to be significantly longer for GC patients with high LAG-3 expression based on biological cut-offs. Increased numbers of LAG-3+ cells within GC tissue could therefore be a sign of crosstalk between cancer and immune cells rather than a sign of exhausted, dysfunctional T cells. Ulase *et al.* conclude that LAG-3 may have different, stage-based functional roles within the TME of GC despite the postulated immunosuppressive role of LAG-3 within the TME of solid tumors (12). As such, the role of LAG-3 in GC is more complex than anticipated. In a LAG-3 comparative transcriptomic expression patterns across malignancies (13), high-level LAG-3 RNA-expression was higher in melanoma compared to GC (i.e., 50% *vs.* 16%); however, the difference was not significant due to the small number of patients. Nonetheless, high LAG-3 expression was significantly and independently associated with high expression of PD-1/PD-L1 and CTLA-4, as well as high tumor mutational burden (TMB) ≥10 mutations/megabase, a marker for immunotherapy response (13), providing a potential rationale for the observed differential organ-specific outcome of LAG-3 inhibition in melanoma and GC.

Immunotherapy has recently demonstrated substantial benefits in GC/GEJC. Several landmark global phase III trials, including KEYNOTE-859, CheckMate-649, and RATIONALE-305, have firmly established the role of PD-1 inhibitors in combination with chemotherapy as a standard first-line treatment for advanced HER2-negative GC/GEJC (14-16). In the KEYNOTE-859, pembrolizumab combined

with chemotherapy led to significantly improved OS, PFS and ORR compared to chemotherapy alone. Importantly, the survival advantage was most pronounced in patients with a CPS of 10 or higher (HR =0.64), with intermediate benefit in CPS 1–9 (HR =0.83) and no benefit in CPS <1 (HR =0.92) (14). In the CheckMate-649, nivolumab plus chemotherapy improved both OS and PFS for patients with untreated advanced HER2-negative GC/GEJC and esophageal adenocarcinoma compared to chemotherapy alone, particularly in those with a PD-L1 CPS of 5 or higher (HR =0.71) (15). Similarly, the RATIONALE-305 trial demonstrated that tislelizumab plus chemotherapy provided a significant improvement in OS for tumor area positivity (TAP) 5% (HR =0.74) (16). These findings are consistent with a pooled Food and Drug Administration (FDA) meta-analysis that included KEYNOTE-859, CheckMate-649, and RATIONALE-305, showing a similar pattern of benefit stratified by PD-L1 expression [OS HR =0.91 for PD-L1 (CPS/TAP) <1, HR =0.88 for PD-L1 1–4, HR =1.01 for PD-L1 5–9, and HR =0.64 for PD-L1 10+ in proficient mismatch repair GC/GEJC] (17). While other trials such as ATTRACTION-4 and ORIENT-16 have shown favorable outcomes within specific populations (respectively Asian and Chinese cohorts), their relevance to global practice is more limited due to geographical and population-specific considerations (18,19). Overall, these trials emphasize the importance of biomarker-guided (here PD-L1) decisions in immunotherapy for GC/GEJC. The potential of dual checkpoint blockade in GC/GEJC, while not fully realized in RELATIVITY-060, may still exist in highly selected patient populations based on biomarker expression.

In conclusion, the RELATIVITY-060 trial underscores the complexity of finding novel therapeutic strategies for advanced GC/GEJC. While the addition of relatlimab to nivolumab and chemotherapy did not improve outcomes, the exploratory analyses in patients with high LAG-3 expression suggest that further research is warranted. Future studies should focus on spatial and prognostic heterogeneity of LAG-3 in GC and refining patient selection and developing better biomarkers to predict response to dual checkpoint blockade. Ultimately, overcoming the heterogeneity of the TME in GC/GEJC may require more innovative combinations, including agents targeting other components of the TME, to fully unlock the potential of ICI in this difficult-to-treat disease.

Acknowledgments

Funding: This work was supported by the University Research Fund (BOF) of the University of Antwerp, Antwerp, Belgium (No. FFB220225 to S.S). The funders played no role in study design, data collection, analysis and interpretation of data, or the writing of this manuscript.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology*. The article has undergone external peer review.

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-757/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-757/coif). The authors have no 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. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229-63.
2. Li Y, Feng A, Zheng S, et al. Recent Estimates and Predictions of 5-Year Survival in Patients with Gastric Cancer: A Model-Based Period Analysis. Cancer Control 2022;29:10732748221099227.
3. Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33:1005-20.
4. Andrews LP, Marciscano AE, Drake CG, et al. LAG3

(CD223) as a cancer immunotherapy target. Immunol Rev 2017;276:80-96.
5. Chocarro L, Blanco E, Zuazo M, et al. Understanding LAG-3 Signaling. Int J Mol Sci 2021;22:5282.
6. Park Y, Seo AN, Koh J, et al. Expression of the immune checkpoint receptors PD-1, LAG3, and TIM3 in the immune context of stage II and III gastric cancer by using single and chromogenic multiplex immunohistochemistry. Oncoimmunology 2021;10:1954761.
7. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med 2022;386:24-34.
8. Hegewisch-Becker S, Mendez G, Chao J, et al. First-Line Nivolumab and Relatlimab Plus Chemotherapy for Gastric or Gastroesophageal Junction Adenocarcinoma: The Phase II RELATIVITY-060 Study. J Clin Oncol 2024;42:2080-93.
9. Feeney K, Joubert WL, Bordoni RE, et al. RELATIVITY-123: A phase 3, randomized, open-label study of nivolumab (NIVO) + relatlimab (RELA) fixed-dose combination (FDC) versus regorafenib or trifluridine + tipiracil (TAS-102) in later-line metastatic colorectal cancer (mCRC). J Clin Oncol 2023;41:TPS278.
10. Morgensztern D, Chaudhry A, Iannotti N, et al. 1359TiP RELATIVITY-104: First-line relatlimab (RELA) + nivolumab (NIVO) with chemotherapy vs nivo with chemotherapy in stage IV or recurrent non-small cell lung cancer (NSCLC): A phase II, randomized, double-blind study. Ann Oncol 2021;32:S1030.
11. Yasuda T, Wang YA. Gastric cancer immunosuppressive microenvironment heterogeneity: implications for therapy development. Trends Cancer 2024;10:627-42.
12. Ulase D, Behrens HM, Krüger S, et al. LAG3 in gastric cancer: it's complicated. J Cancer Res Clin Oncol 2023;149:10797-811.
13. Adashek JJ, Kato S, Nishizaki D, et al. LAG-3 transcriptomic expression patterns across malignancies: Implications for precision immunotherapeutics. Cancer Med 2023;12:13155-66.
14. Rha SY, Oh DY, Yañez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2023;24:1181-95.
15. 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.
16. Qiu MZ, Oh DY, Kato K, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial. BMJ 2024;385:e078876.
17. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. FDA Briefing Document "Immune checkpoint inhibitors in patients with metastatic or unresectable HER2-negative gastric adenocarcinoma". September 26, 2024. Available online: https://www.fda.gov/media/182138/download [visited 21/11/2024].
18. 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.
19. Xu J, Jiang H, Pan Y, et al. Sintilimab Plus Chemotherapy for Unresectable Gastric or Gastroesophageal Junction Cancer: The ORIENT-16 Randomized Clinical Trial. JAMA 2023;330:2064-74.

Cite this article as: Seghers S, Domen A, Prenen H. Challenges and prospects of LAG-3 inhibition in advanced gastric and gastroesophageal junction cancer: insights from the RELATIVITY-060 trial. J Gastrointest Oncol 2024;15(6):2735-2738. doi: 10.21037/jgo-24-757