

Artificial immortalization, number of therapy lines, and survival of patients with advanced gastric and esophagogastric adenocarcinoma

Letter

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Letter to the Editor regarding 'Impact of the number of therapy lines on survival in advanced gastric and esophagogastric adenocarcinoma - a real-world retrospective analysis from Croatia', published in Neoplasma 2024; 71: 201–208. https://doi.org/10.4149/neo_2024_231209N633

Dear Editor,

With great interest, we have read the article by Bišof et al. [1] reporting improved overall survival (OS) in patients with advanced gastric and esophagogastric adenocarcinoma treated with multiple treatment lines. The authors of this real-world study have rightfully highlighted the relevance of the ratio of patients receiving multiple lines of therapy and the importance of the availability of effective compounds in this clinical context. However, we would like to point out that a significant proportion of patients included in the study by Bišof et al. [1] in each therapy line had progressive disease (44.9% in first-, 54.2% in second-, and 74.3% in third-line) with median OS being 11 months for the overall cohort, but only 5.9 and 5.4 months from the start of second- and third-line therapy, respectively. Therefore, the authors' conclusion regarding improved OS with more therapy lines could be misleading and may rather represent immortalization bias, as patients experiencing second- and third-line treatments and coded as such are guaranteed to live long enough to reach later treatment lines during survival analysis. The presented statistical artifact is unfortunately common in cancer research and, when wrongly interpreted, may lead to erroneous conclusions, i.e. when studies suggest a potential favorable prognostic impact of a late-occurring drug-related side-effect on patient survival [2]. In the study by Bišof et al. [1], this effect can also be depicted in Figure 3 of the original manuscript where the median OS of patients on second- and third-line therapies are approximately 12 and 20 months, with visible plateaus at the start of each curve corresponding to the guaranteed immortalization period. This contrasts the aforementioned reported low OS when being calculated from the start of second- and third-line treatment.

We congratulate the authors on providing valuable insights into real-world clinical outcomes of patients with advanced gastric and esophagogastric adenocarcinoma. Instead of emphasizing

improved patient OS with more therapy lines, we would rather argue that using novel and more effective agents in the first-line treatment of patients with advanced gastric and esophagogastric adenocarcinoma may be the most rational approach to improve patient outcomes.

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