



Lymph node-only metastatic gastric/gastroesophageal junction cancer and efficacy of immunotherapy

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Dear Editor,

We read with great interest the paper by Chen et al. reporting the 2-year update analysis of the ATTRACTION-2 trial [1]. At 2 years of follow-up, nivolumab was confirmed to confer an overall-survival (OS) benefit over placebo in heavily pretreated advanced gastric or gastroesophageal junction (G/GEJ) cancer patients (10.6% vs 3.2%) and this was regardless of the presence of potential predictors such as PD-L1 positivity. Radiologic response, however, seemed to be associated with prolonged survival in the nivolumab arm. Other clinical features were not associated with treatment efficacy as shown in a forest plot provided in the supplementary material. In particular, no interaction with the presence of liver or peritoneal metastasis was demonstrated. However, presence of lymph-node metastasis was not included in the subgroup analysis. Lymph-node metastases have been found to be particularly responsive to immune checkpoint inhibitors (ICIs) [2, 3] and also the three complete responses reported in the ATTRACTION-2 were in patients with predominantly lymph node-based metastatic disease.

We recently reviewed 57 patients with mGC treated in second-line with ICIs [4]. Herein we report that patients with lymph node-only metastatic disease had a significantly longer median overall survival as compared to other

metastatic patterns (mOS 20.6 vs 4.8 months, HR 0.28, 95% CI 0.12–0.63, p 0.001, see Figure S1). Progression free survival (PFS) and objective response rate (ORR) were similarly significantly improved in the lymph node-only subgroup (mPFS 11 vs. 2 months, HR 0.43, p 0.01 and ORR 33% vs 11%, p 0.05, respectively). Presence of lymph node-only metastasis was confirmed to be an independent prognostic factor in a multivariate cox-regression analysis including gender, primary tumor location, age, Lauren's subtype, PD-L1 expression, resection of the primary, number of metastatic sites and ECOG performance status (Fig. S1).

Lymph node-only metastatic disease might represent a biologically and phylogenetically distinct entity with peculiar prognosis and response to treatment [5]. Moreover, it can be hypothesized that the increased density and infiltration of lymphocytes in the lymph-node tissue might favor an enhanced ICI-induced immune response against cancer cells metastasizing to the lymph nodes.

We suggest the inclusion of specific metastatic patterns in future subgroup analyses of ICIs in G/GEJ cancer, and in particular we suggest the assessment of the effect of exclusive or predominant nodal metastatic disease in terms of interaction with immunotherapy efficacy.

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Compliance with ethical standards

Conflict of interest No conflict of interest has to be declared.

Ethical standard All procedures reported herein were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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