About *HER2* monitoring using liquid biopsies in patients with gastric cancer

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To the Editor,

Shoda et al. recently reported that they monitored the *HER2* copy number status of circulating tumor DNA in patients with gastric cancer by droplet digital PCR [1]. Preoperative *HER2* tumor status based on tumor samples was found to be well correlated with the *HER2* plasma ratio, albeit with some discrepant results. In the postoperative follow-up, 7/13 cases presented high plasma *HER2* ratios despite having an initial *HER2*-negative status. The authors concluded that analyzing the *HER2* ratio in circulating DNA permits the detection of a *HER2*-positive conversion and facilitates the identification of alternative treatment choices in initially *HER2*-negative patients [1]. Here, we comment on the relevance of their *HER2* ratio and potential alternative methods of monitoring *HER2* status in liquid biopsies.

HER2 status must be checked in patients with advanced gastric cancer to determine if trastuzumab anti-*HER2* protein targeted therapy is applicable. The first-line test is immunohistochemistry, to distinguish between tumors with major *HER2* overexpression (score 3+), which can be treated with trastuzumab, and tumors with no or a low level of expression (score 0 or 1+), which cannot. In equivocal

cases of *HER2* protein overexpression (score 2+), in situ hybridization analyses are required to identify *HER2*-amplified cancers [i.e., those with a *HER2*(17q12)/chromosome 17 ratio >2 or with clusters of *HER2* signals] that can be treated with trastuzumab. Thus, it is worth determining both the *HER2* expression level and the *HER2*(17q12)/chromosome 17 ratio in order to establish *HER2* status and identify appropriate treatment choices.

The *RPPH1* reference gene chosen by Shoda et al. is not located on chromosome 17 but on chromosome 14 (14q11.2) [1]. Given that gastric cancer can involve chromosomal imbalances, notably in chromosomes 17 and 14, elevation of the *HER2/RPPH1* ratio (i.e., the 17q12/14q11.2 ratio) could also reflect chromosome 17 polysomy or a loss of the *RPPH1* locus on chromosome 14, not just *HER2* amplification [2]. We believe that it would be more appropriate to use a reference gene located on chromosome 17 instead of *RPPH1* to check for *HER2* amplification, as performed in in situ hybridization tests and in liquid biopsies from patients with breast cancers [3].

An analysis of circulating DNA will not reflect the level of expression of the *HER2* protein. An increased copy number of a given gene may not be correlated with increased expression of the corresponding protein, which is a prerequisite for the corresponding targeted therapy to be efficient. An alternative liquid biopsy method of monitoring patients with advanced gastric cancer could involve searching for circulating tumor cells rather than circulating tumor DNA. Highly sensitive methods are now available to detect and isolate these rare cells in blood samples, and *HER2* protein expression analyses of these cells could be performed using immunocytochemistry and in situ hybridization methods [4, 5].

We agree with Shoda et al. that liquid biopsies offer new and interesting opportunities to monitor tumor

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development in patients with gastric and other cancers according to a personalized medicine strategy. Further studies are needed to compare the advantages and drawbacks of circulating tumor DNA analysis to those of circulating tumor cell analysis in gastric cancer.

Compliance with ethical standards

Conflict of interest The author declares no conflict of interest in this work.

Research involving human participants and/or animals Not applicable.

Informed consent Not applicable.

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