Replica: ‘Comments on Stromal disrupt effects of nab-paclitaxel in pancreatic cancer’

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Sir,

In response to Boeck et al

We read with interest the comments made by Boeck et al (2014) about our study. We appreciate their attention to the units used to report CA19.9 levels, which indeed should have been U ml-1 and not U dl-1 as stated. We certainly agree that a high level of CA19.9 at diagnosis may be an indication of advanced disease and that this should be considered in the selection criteria in preoperative studies. Indeed in our study, with small sample size, one patient with very high CA19.9 level who actually progressed during chemotherapy skewed that average level of CA19.9. This patient was not operated and therefore does not affect the tissue results. As Boeck et al mention, levels of CA19.9 should be either a selection criteria or a stratification factor in outcome-oriented preoperative studies that should also include better imaging methods to determine responses and histological, rather than cytological, diagnosis. In our study, however, as the goals were to determine the effects of Nab-paclitaxel in tumour tissue, this criterion was not part of the eligibility criteria. We agree, however, that future controlled studies to confirm our observations should exclude patients with elevated CA19.9 and plan to do so.

In clinical practice, however, one of the goals of preoperative treatment is to identify patients with more advanced or resistant disease who can be

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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LETTERS TO THE EDITOR

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In response to Ramirez et al

We read with great interest the recent comments made by Ramirez et al (2014) in which they highlight the importance of tumour stroma in pancreatic cancer (PDAC) and the role of ‘pancreatic stellate cells’ in the development of tumour stroma. The current data, while with still some inconsistencies, show that in preclinical models of PDAC, the combination of gemcitabine and Nab-paclitaxel (PTX) increases the delivery of gemcitabine to the tumour. Mechanistically, this has been explained by a decrease in the expression of the gemcitabine catabolism enzyme cytidine deaminase and hence increasing the intracellular retention time of the active gemcitabine metabolites or by elimination of the PDAC stroma (Von Hoff et al, 2011; Frese et al, 2012). In the only clinical study available so far, we have shown that Nab-PTX markedly alters the PDAC stroma and decreases the number of CAF (Alvarez et al, 2013).

The precise mechanisms underlying these observations remain obscure. Selective binding of albumin-coated Nab-PTX to SPARC-positive cells or uptake of nutrient-rich drug by cancer cells by pynocytosis have been proposed and are the subject of specific studies. The role of SPARC has been studied in the MPACT randomised clinical trial and we hope to have these results available in the near future (Von Hoff et al, 2013). As these authors propose, the effects of Nab-PTX on cancer stroma could be a consequence of the direct elimination of cancer cells and interruption of the cancer cell–stroma interactions. Certainly, additional preclinical and translational clinical studies are needed to determine the precise mechanism of action of this, otherwise, clinically effective regimen.

Sir,

We read with great interest the recent publication by Heinzerling et al (2013), demonstrating intra-patient heterogeneity of BRAF mutation status between tumours in 10 of 53 (18.9%) patients. However, we have great concern that the results of the study may reflect the (less than 100%) sensitivity of the results of the study may reflect the (less than 100%) sensitivity of the current molecular techniques employed and/or an incorrect assumption that the primary melanoma was the source of the metastatic disease rather than true intra-patient BRAF heterogeneity.

Potentially, the results of the study by Heinzerling et al could have tremendous clinical importance, as accurate determination of a patient’s BRAF mutation status is critical when planning treatment for melanoma patients with advanced stage disease. Targeting the mitogen-activated protein kinase (MAPK) pathway in patients with BRAF-mutant metastatic melanoma has vastly improved clinical outcomes; however, BRAF inhibitors may paradoxically activate the MAPK pathway in wild-type BRAF melanomas and therefore adversely affect survival if such patients are treated with BRAF inhibitors. Thus, if intra-patient melanoma BRAF heterogeneity exists and treatment decisions are made on the basis of mutation assessment of a single tumour, potentially effective treatment may not be offered in a significant proportion of patients, or alternatively, treatment may be administered that is potentially detrimental.

Although the results of the study by Heinzerling et al are in keeping with other recent reports of heterogeneity in 15% and 13.5% of patients (Colombino et al, 2012; Saint-Jean et al, 2014), two recent studies (Boursault et al, 2013; Menzies et al, 2013) demonstrated very little heterogeneity of BRAF status within metastatic melanoma patients. Several factors may have influenced the results of these studies. First, the techniques used to determine BRAF status were different in the ‘higher’ and ‘lower’ discordance studies. The latter studies used a highly sensitive and specific immunohistochemical technique (the anti-BRAF V600E VE1 antibody) that enables determination of the BRAF status in all individual cells by direct visualisation and at the same time confirmation that they are in fact tumour cells. This technique is not reliant on a certain percentage of tumour cells being present. In contrast, the former studies used molecular methods such as pyrosequencing, allele-specific PCR, and Sanger sequencing, all of which may have false-negative results when samples contain low tumour content. A recent study highlighted the problem of false-negative mutation tests by molecular techniques. Discordant BRAF V600E status was identified in 5 of 97 specimens; subsequent molecular retesting both confirmed an initial molecular misdiagnosis in 4 of the 5 cases and the greater accuracy of BRAF protein immunohistochemistry (Long et al, 2013).

Another factor that may have resulted in heterogeneity is the assumption that any given primary melanoma is the culprit tumour from which the metastatic disease was derived. Ten per cent of patients with metastatic melanoma have a history of multiple primary melanomas (Murali et al, 2012). Even in patients with a history of only a single known primary melanoma, sometimes the site of locoregional metastasis is not in keeping with the ‘stage’ or site of the presumed primary melanoma, or it does not occur within a plausible time period, suggesting that an occult primary melanoma may have led to the metastatic disease. In this situation, close scrutiny of a patient’s clinical history is required to ensure accurate assignment of the ‘culprit’ primary melanoma (Murali et al, 2012).