LETTER TO THE EDITOR

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Comment on 'High MET expression is an adverse prognostic factor in patients with triple-negative breast cancer'

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Sir,

In their recent article, Zagouri *et al* (2013) show that high c-Met expression is associated with a worse outcome in triple-negative (TN) breast cancer, however the authors state that they 'did not include further markers such as basal cytokeratins and/or EGFR that may identify a group of tumours that have a distinct adverse prognosis'. This is a surprising omission, as data from several studies indicate that TN tumours that express basal markers are distinct from those that do not, and that these 'Core Basal' tumours have a worse outcome (Blows *et al*, 2010). Whether c-Met contributes to this poorer prognosis would therefore appear to be an important question to address.

In our own immunohistochemical (IHC) analysis, we identified 38 TN tumours from a cohort of 182 patients with invasive breast cancer. We divided the TN group into 'Core Basal' (CB, $n=31$) and basal marker negative (referred to as 'Unclassified' (U), $n=7$) using a panel of antibodies to basal markers (Rakha *et al*, 2009; Blows *et al*, 2010): CK5/6, CK14, CK17 and EGFR (with a cut-off of 10% tumour reactivity to denote positivity). Positivity for any of the basal markers placed the tumour in the CB group. The sections were stained for c-Met (CVD13, Invitrogen) and the staining was scored semi-quantitatively (0–3 for intensity and 0-4 for area of tumour reactivity to give a sum score of 0–7). Both the cytoplasmic and membranous scores were combined to give a total c-Met score between 0 and 14. Analysing c-Met expression as a continuous variable (Figure 1), CB tumours had a significantly higher median total c-Met score of 8.4 (interquartile range (IQR) = 7.0-10.3) compared with 6.0 (IQR = 5.7-7.0) for U tumours (Mann–Whitney test, $P=0.008$). By comparison, it is very possible that the high c-Met expressing tumours in the study by Zagouri *et al* (2013) were predominantly CB tumours, and this raises the possibility that patients with CB tumours may derive more benefit from anti-c-Met therapy.

Knowledge of EGFR status may be of further clinical relevance. There is growing evidence that c-Met and EGFR can crosstalk in a variety of cancers (Lai *et al*, 2009). Amplification of the *MET* gene has been described in Gefitinib/Erlotinib-resistant non-small-cell lung cancer (NSCLC) cell lines, leading to persistent signalling via the PI3K pathway (Bean *et al*, 2007; Engelman *et al*, 2007). Moreover, treatment with a combination of a c-Met tyrosine kinase inhibitor (PHA-665752) and Gefitinib resulted in reduced PI3K/AKT signalling and growth inhibition in Gefitinib-resistant NSCLC cells (Engelman *et al*, 2007). Similarly, in the presence of Gefitinib, EGFR phosphorylation in the breast cancer cell line SUM229 has been shown to be mediated by a c-Met/c-Src-dependant pathway (Mueller *et al*, 2008). These studies suggest that c-Met and EGFR have a compensatory relationship, whereby inhibition of one receptor tyrosine kinase

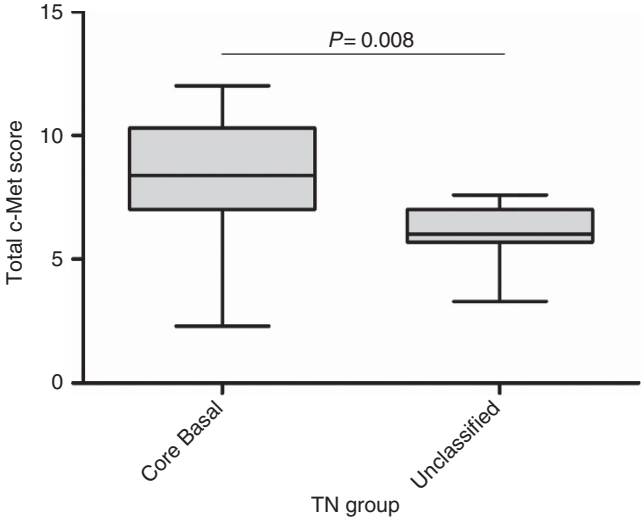

Figure 1. Box plot showing total c-Met scores for the Core Basal and Unclassified groups of TN tumours. The whiskers represent the minimum and maximum values (Mann–Whitney test, $P=0.008$).

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(RTK) may result in the activation of the other, thus maintaining downstream signalling (Lai *et al*, 2009). In our own analysis, we found a positive correlation between c-Met and EGFR expression (Spearman's correlation coefficient = 0.290, $P < 0.001$), indicating that compensation may be possible in these tumours. While several of the c-Met kinase inhibitors currently in clinical trials have activity against multiple RTKs, it would seem appropriate to consider EGFR expression (and other RTKs) when investigating the clinical significance of c-Met; these data would be of clear benefit in clinical trial design and patient selection.

In summary, the study by Zagouri *et al* (2013) provides further evidence of the involvement of c-Met in breast cancer progression, but the clinical impact of the study would have been enhanced by addressing the expression of basal markers, including EGFR, and this further supports the recognition of CB tumours as a distinct subset of TN cancers.

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