CORRESPONDENCE

Comment on 'Testing for BRAF fusions in patients with advanced BRAF/NRAS/KIT wild-type melanomas permits to identify patients who could benefit of anti-MEK targeted therapy'

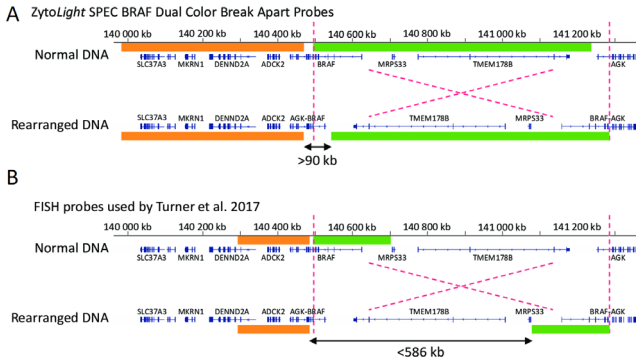

Figure 1 The choice of FISH probes might be critical for the detection of the *AGK-BRAF* fusion. Cartoons shown to scale illustrating the binding of the Zyto*Light* SPEC BRAF Dual Color Break Apart Probes (A) or the FISH probes used by Turner *et al*[5] (B) on normal and rearranged DNA resulting from an *AGK-BRAF* fusion. FISH, fluorescence *in situ* hybridisation.

We read with great interest the article from Le Flahec and colleagues encouraging the testing for *BRAF* fusions in patients with advanced *BRAF/NRAS/KIT* wild-type melanomas.[1] As emphasised in the article, the only viable therapeutic option currently available for patients lacking *BRAF* point mutations is immunotherapy. However, despite unprecedented efficacy gain, combined immune checkpoint inhibitors therapy only achieves long-lasting response in a third of the patients.[2] Thus, considering that *BRAF* fusions are the most common oncogenic rearrangements in melanoma and that they are clinically actionable, we agree with the authors that their detection in *BRAF/NRAS/KIT* wild-type tumours is of theranostic importance. To further support the detection of *BRAF* fusions in melanoma, we would like to comment on some of the conclusions in the light of our recently published article on the subject.[3]

Our discovery that the nature of the fusion partner can influence the biology of the fusions and its drug response adds another level of complexity to the clinical management of patients with *BRAF* fusion-driven tumours.[3] Indeed, the presence of a dimerisation domain in the fusion partner promotes the paradoxical activation of the MAPK signalling pathway and overproliferation in response to αC-out RAF inhibitors such as vemurafenib or dabrafenib and to a lesser extent to sorafenib-like molecules. Similarly, a high expression level of the fusion driven by the promoter of the 5′ partner and/or copy number gain may drive resistance to targeted therapies. Our *in vivo* data suggest that *BRAF* fusion-driver tumours would respond better to a combination of αC-in/DGF-OUT RAF inhibitors of new generation (eg, LY3009120 or lifirafenib) and MEK inhibitors.

Thus, if the use of break-apart fluorescence *in situ* hybridisation (FISH) presents the advantages of being fast, easy to implement in a pathology lab and relatively inexpensive, it presents the limitation of not allowing the identification of the fusion partner. Further, our review of the published cases of melanocytic tumours harbouring *BRAF* fusions identified the *AGK-BRAF* fusion, joining exon 2 of *AGK* to exon 8 of *BRAF*, as the most recurrent.[3] As we previously reported, the proximity of the two genes on chromosome 7 may impair the proper resolution of the fusion by break-apart FISH.[4] On that matter, Zyto*Light* SPEC BRAF Dual Color Break Apart Probes are apart from 66 kb when binding normal DNA, a distance that only increases to a maximum of 90 kb after *AGK-BRAF* rearrangement which is likely not sufficient for the calling of rearrangement (figure 1A). It is thus likely that the frequency of *BRAF* fusions reported by Le Flahec and colleagues might be underestimated as the *AGK-BRAF* fusion is recurrent in melanoma. Noticeably, Turner and colleagues[5] were able to detect the same *AGK-BRAF* fusion by FISH by using a shorter distal probe (196 vs 699 kb for the Zyto*Light*) that increases the break-apart after rearrangement and may favour the detection of the fusion (figure 1B).

In conclusion, break-apart FISH can be of use for the detection of *BRAF* fusions, but the choice of probes is an important parameter to consider. This is particularly true for the detection of the *AGK-BRAF* fusion which is the most recurrent *BRAF* fusion in melanoma and that we have shown to be clinically actionable using sorafenib or MEK inhibitors.[4 6] Considering the potential therapeutic impact in patients with melanoma lacking *BRAF* point mutations who failed to respond to immunotherapy, RNA sequencing should be preferred for fusion detection. It remains the gold standard in terms of sensitivity, identification of partner genes and will be the most informative to guide the therapeutic management of patients whose melanomas are driven by *BRAF* fusions.

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