Toward predictive biomarkers of response to kinase inhibitor therapies in differentiated thyroid cancer

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Small-molecule kinase inhibitors have emerged as effective therapies for patients suffering from progressive, metastatic, radioiodine-refractory (RAIR) differentiated thyroid cancer (DTC) [1]. Sorafenib and lenvatinib are now subject to regulatory approval in the United States and European Union for this indication [2, 3], with other agents—including sunitinib, pazopanib, axitinib, vandetanib, and cabozantinib—also approved for other cancer indications and showing evidence of benefit in RAIR DTC based on phase 2 trial data [1]. These kinase inhibitors are thought to demonstrate efficacy principally through their actions on vascular endothelial growth factors (VEGFRs), but they also inhibit many other kinases. Moreover, these systemically administered therapeutics are expected to inhibit targets not only in tumor, but also in host tissues, with potential therefore for their efficacies to be affected not only by tumor-specific, but also by host-specific, alterations [1].

Accordingly, in their small preliminary study, Marotta et al. [4] posed the question of whether specific germline single-nucleotide polymorphisms (SNPs) of the VEGF-A and VEGFR-2 genes (dominant angiogenic regulators potentially capable of altering sensitivities to VEGFR-targeted kinase inhibitors) might correlate with response to sorafenib treatment in patients with RAIR DTC. Six SNPs were selected for analysis based on previous reported

studies in cancers other than thyroid (other solid tumors and lymphoma). Seventeen patients were assessed, with median follow-up of 17 months. The majority of patients (eight, 47%) attained stable disease as assessed by RECIST response, with six (35%) enjoying partial responses (PRs) and three (18%) experiencing progressive disease as best responses to sorafenib therapy; median progression-free survival (PFS) was 12 months.

All six assessed SNPs were successfully genotyped in all patients. Statistical significant associations were reported for two VEGF-A SNPs located in the promoter of the gene (−2578 C>A and −460 T>C), and for a VEGFR-2 SNP located in the coding region for the extracellular domain of the receptor (+1719 T>A), each associated with greater probability of PR and longer PFS relative to other assessed corresponding SNPs. No assessments of associations with overall survival were possible, however, as no patients died during the study period.

The study by Marotta et al. [4] importantly targeted identification of possible predictive biomarkers of response to sorafenib therapy in RAIR DTC, an area yet to be fully explored. To date, searches for predictive biomarker of kinase inhibitor response in RAIR DTC have, however, almost exclusively examined somatic (tumor) mutations/alterations [5], with attempts to elucidate germline SNP predictors of response largely ignored. The investigation of the possibility that heterogeneity of germline VEGF/VEGFR SNPs might predict response to sorafenib therapy is thus an especially provocative aspect of the study of Marotta et al. [4], as any identified positive association—if robust—might be used to individualize therapy even in the absence of interrogation of tumor tissue and without the need for biopsy. Such an approach has potential to aid in better selection of patients for sorafenib treatment, sparing

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patients with lesser probability of response undesirable side effects, potentially seeding them instead to clinical trials or therapy based on their somatic tumor mutations (e.g., BRAFV600E).

The concept that altered angiogenic activity associated with VEGF pathway SNPs may yield predictive biomarkers of VEGFR-inhibitor response seems a credible and complementary approach to biomarker identification to supplement the alternative approach of interrogation of tumor-specific alterations. Although provocative, reported data require validation in larger studies due to the extremely high frequency of SNPs in the general population and the possibility of detecting random non-causal associations. The veracity of true SNP associations (SNP-specified disease or of a true SNP predictive biomarker of response to therapy [TKI]) can only be confirmed with a sufficiently large validation sample of advanced thyroid cancer patients subjected to kinase inhibitor therapy, a prerequisite of robust genetic association studies. Moreover, it will be important to define whether any confirmed correlation(s) might be useful to predict class-specific, as opposed to sorafenib-specific, effects.

In addition to the approach taken by Marotta et al. [4], other germline biomarkers might alternatively be sought in the form of explorations of whether pharmacogenomics heterogeneity of SNPs of relevance to metabolism might also contribute to differential response to kinase inhibitor therapy in RAI R DTC. Continued research into the

elucidation of candidate predictive germline markers of therapeutic response is much needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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