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CCR Translations

Commentary on Hayes et al., p. 2056

In Search of a Real "Targeted" Therapy for Thyroid Cancer

Marcia S. Brose

Over the past 5 years, patients with progressive radioactive iodine–refractory thyroid cancer have responded to "targeted" multikinase inhibitors, which inhibit angiogenesis and not the tumor cell. Here, selumetinib targets the mitogen-activated protein kinase pathway in papillary thyroid carcinoma and shows limited single-agent activity in the patients with tumors that harbor the $V600E$ BRAF mutation. *Clin Cancer Res*; 18(7); 1827–9. ©2012 AACR.

In this issue of *Clinical Cancer Research*, Hayes and colleagues report their findings from the phase II efficacy and pharmacogenomic study of selumetinib in ^{131}I -refractory papillary thyroid carcinoma (IRPTC) with or without follicular elements (1). The trial aimed to investigate the toxicity and efficacy of selumetinib and the possible relation of response to the presence of common mitogen-activated protein kinase (MAPK) pathway mutations, specifically BRAF and NRAS. Although not reaching the primary endpoint, this study captures our attention because it is the first report of an agent that selectively targets the MAPK pathway in thyroid cancer, and there is a subpopulation that may have fared better, namely the patients whose tumors carried the somatic $V600E$ BRAF mutation.

The 2 main points to consider in the current study are the basis for the lack of efficacy of selumetinib as a single agent and the identification of a population that did better, the patients whose cancers harbored the $V600E$ BRAF mutation.

First, the authors put their current study in the context of other phase II studies; however, we must consider the fact that, although patients entered on the selumetinib study were required to have progressed within the previous 12 months, the degree of progression required in that period was not specified. This information is important because in patients with radioactive iodine (RAI)–nonavid or –refractory cancer, tumors may grow at such a slow rate that systemic treatment and the associated toxicities accompanying it are not considered warranted. Thus, in more recent studies, including the ongoing phase III study of sorafenib in patients with RAI-refractory differentiated thyroid cancer (DTC; ref. 2), the additional requirement that the disease

meets progression by Response Evaluation Criteria in Solid Tumors (RECIST), in the preceding 12 to 14 months, has come to be an accepted criterion used in many of these studies for treating patients with systemic therapy. Thus, the population's rate of disease progression may have been significantly lower and may have taken up to 32 weeks to meet the criteria for disease progression by RECIST, with no treatment at all.

Interestingly, this issue may cut both ways. It is also possible that studies selecting for patients with DTC who are progressing rapidly, such as patients who were studied in the phase II trial of pazopanib that required progression by RECIST criteria within 6 months prior to study entry (3), may have identified a patient population that is more likely to have a greater response due to increased dependence on angiogenesis that is blocked by the multikinase inhibitors. Thus, the absence of a requirement for progression within 12 months prior to study entry may have increased or decreased our chances of seeing a response and points to another hazard in comparing outcomes across phase II studies. The fact that all of the patients had PTC made the treatment group more uniform than groups in prior studies and likely represents a trend for the next generations of trials in advanced thyroid cancer and will help with comparisons; however, because this clinical trial is the first to report on targeted therapy in just 1 histologic subtype, we have few studies with which we can compare these results.

As noted in the article, the trial failed to reach its primary endpoint, namely that 20% of the patients achieve a response (complete response or partial response). Yet, given the fact that most patients are asymptomatic even with metastatic disease, other endpoints, such as stable disease and progression-free survival (PFS), carry increased weight. Compared with other agents, the clinical benefit rate (complete response, partial response, and stable disease) of selumetinib of 57% is modest, as seen in several other previously published phase II studies (3–6). Unless the response rate in a larger study of patients with $V600E$ BRAF–positive PTC shows better activity, selumetinib as a single agent will not have a role in the first-line treatment of these patients, although a role in second- or third-line therapy cannot be ruled out.

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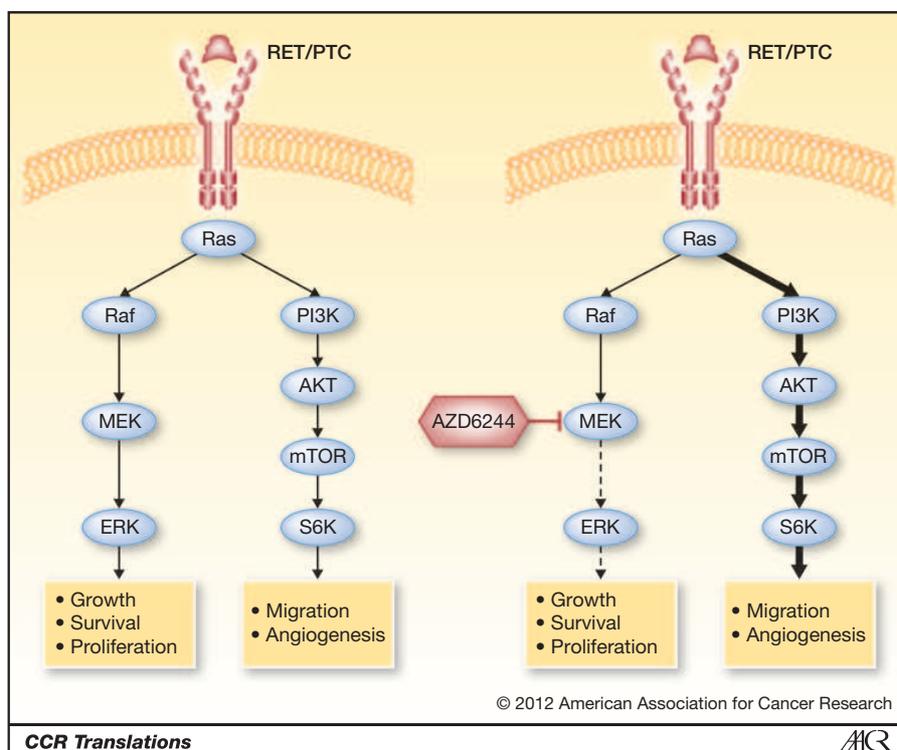


Figure 1. Selective targeting of MEK 1/2 in PTC. Intracellular-signaling pathway aberrancy is critical to the molecular pathophysiology of thyroid cancer tumorigenesis. In tumor cells (left), altered expression and mutation involving B-Raf, Ras, and Akt have been implicated in a wide variety of thyroid cancer cell types. In the tumor microenvironment, angiogenesis is also a critical step in tumor progression and metastasis. Angiogenesis is mediated primarily through VEGFR-2, which also signals through Raf and Akt. Inhibition of VEGFR-2 has proved to be a successful therapeutic strategy in thyroid cancer in which drugs such as bevacizumab, sorafenib, sunitinib, axitinib, and motesanib have activity as single agents. VEGFR-2 has been found to be expressed on tumor cells in thyroid cancer, raising the question of whether multikinase inhibitor therapy might also be exerting an effect on the tumor cells themselves.

The second issue to consider is the documented trend that patients with $V600E$ BRAF mutations may do better, raising the possibility that if this patient population were targeted, the results might be better and the presence of the $V600E$ BRAF mutation should be an eligibility criterion for future studies. Notably, a similar predictive effect was seen in early studies with sorafenib, which is primarily a VEGF receptor (VEGFR) inhibitor with weak BRAF inhibitory activity (7); however, larger numbers and longer follow-up failed to show that the improved outcome (in this case PFS) was statistically significant in subsequent analyses (M.S. Brose; unpublished data). Thus, even the data suggesting a trend for improved outcome in a $V600E$ BRAF patient cohort should be viewed with caution until additional studies with more patients can confirm the finding.

We know from preclinical data that thyroid cancer cells harboring $V600E$ BRAF mutations are sensitive to blockade with mitogen-activated protein (MAP)-extracellular signal-regulated kinase (ERK) kinase (MEK) inhibitors (8, 9). However, it is also known that RAI-refractory thyroid cancer may harbor second mutations in the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway,

and signaling through the PI3K/AKT/mTOR pathway also plays an important role in this disease (10, 11). Therefore, perhaps it is unreasonable to think that selective targeting of the MAP kinase pathway in these patients would be sufficient to block tumor growth as a single agent (Fig. 1). Preclinical studies suggest that blockade of both pathways is synergistic (12). Thus, given the low efficacy of single-agent selumetinib in this study, combination therapy is likely the best approach to consider in future studies (provided that the toxicity of the combination is tolerable), in addition to considering the BRAF mutation status of the patients being treated.

Although the toxicity of selumetinib seems in line with that of other multikinase inhibitors, it is worthwhile to pause a moment to consider what role it may play in the future treatment of the disease. VEGFR-targeted therapies that most likely inhibit the tumor vasculature have shown activity in multiple phase II trials, and phase III trials are ongoing. However, patients with thyroid cancer, unlike patients with other malignancies, have a good performance status, and although effective, these agents ultimately will lose their efficacy, and the majority of the treated patients will require additional therapies to treat

the resistant disease that evolves over time. Treatment strategies that embrace the identification of molecular cohorts may help in identifying treatment populations that will benefit from agents targeting molecular changes in the thyroid cancer cells directly, revealing activity that otherwise would escape detection. However, this study would suggest that the rational use of selumetinib, in combination with other agents to target both the MAPK and PI3K/AKT/mTOR pathways, may prove to be the best

use of an agent that selectively targets the MAPK pathway and has limited single-agent activity.

Disclosure of Potential Conflicts of Interest

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References

- Hayes DN, Lucas AS, Tanvetyanon T, Krzyzanowska MK, Chung CH, Murphy BA, et al. Phase II efficacy and pharmacogenomic study of selumetinib (AZD6244; ARRY-142886) in iodine-131 refractory papillary thyroid carcinoma (IRPTC) with or without follicular elements. *Clin Cancer Res* 2012;18:2056–65.
- Brose MS, Nutting CM, Sherman SI, Shong YK, Smit JW, Reike G, et al. Rationale and design of decision: a double-blind, randomized, placebo-controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory, differentiated thyroid cancer. *BMC Cancer* 2011;11:349.
- Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncol* 2010;11:962–72.
- Cohen EE, Rosen LS, Vokes EE, Kies MS, Forastiere AA, Worden FP, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *J Clin Oncol* 2008;26:4708–13.
- Gupta-Abramson V, Troxel AB, Nellore A, Puttaswamy K, Redlinger M, Ransone K, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol* 2008;26:4714–9.
- Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. *New Engl J Med* 2008;359:31–42.
- Brose MS, Troxel AB, Redlinger M, Harlacker K, Redlinger C, Chalian AA, et al., editor. Effect of BRAFV600E on response to sorafenib in advanced thyroid cancer patients. *J Clin Oncol* 2009;27:6002.
- Ball DW, Jin N, Rosen DM, Dackiw A, Sidransky D, Xing M, et al. Selective growth inhibition in BRAF mutant thyroid cancer by the mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244. *J Clin Endocr Metab* 2007;92:4712–8.
- Leboeuf R, Baumgartner JE, Benezra M, Malaguarnera R, Solit D, Pratilas CA, et al. BRAFV600E mutation is associated with preferential sensitivity to mitogen-activated protein kinase kinase inhibition in thyroid cancer cell lines. *J Clin Endocr Metab* 2008;93:2194–201.
- Ricarte-Filho JC, Ryder M, Chitale DA, Rivera M, Heguy A, Ladanyi M, et al. Mutational profile of advanced primary and metastatic radioactive iodine-refractory thyroid cancers reveals distinct pathogenetic roles for BRAF, PIK3CA, and AKT1. *Cancer Res* 2009;69:4885–93.
- Saji M, Ringel MD. The PI3K-Akt-mTOR pathway in initiation and progression of thyroid tumors. *Mol Cell Endocrinol* 2010;321:20–8.
- Jin N, Jiang T, Rosen DM, Nelkin BD, Ball DW. Synergistic action of a RAF inhibitor and a dual PI3K/mTOR inhibitor in thyroid cancer. *Clin Cancer Res* 2011;17:6482–9.