# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## New Approaches to Thyroid Cancer

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**H&O** How common is thyroid cancer, and what is the prognosis for patients with this disease?

**EC** Thyroid cancer is not uncommon. Approximately 200,000 individuals within the United States have been diagnosed with thyroid cancer. The incidence is approximately 20,000 diagnoses per year. The sizeable difference between incidence and prevalence reflects the fact that most patients survive. The prognosis is excellent for the most part. For instance, the 5-year survival rate for papillary thyroid cancer is over 90%, and the prognosis for follicular thyroid cancer is close to that. There are, however, subtypes that carry a worse prognosis, the most notorious being anaplastic thyroid cancer. Fortunately, this entity makes up only 1–2% of all thyroid cancers.

**H&O** How are thyroid cancers categorized?

**EC** The largest category in this disease is differentiated thyroid cancer, which includes papillary, follicular, Hürthle cell, and all other variants that derive from the thyroid gland. Medullary thyroid cancer derives from the parafollicular cells (C cells) embedded in the thyroid gland. Those cells do not affect the thyroid gland or thyroid function; their normal function is to produce a hormone called calcitonin, which regulates calcium. The third category is anaplastic thyroid cancer, which likely derives from differentiated thyroid cancer and then dedifferentiates. It behaves so differently from differentiated thyroid cancer that it is categorized as a separate entity.

**H&O** What are some targets in thyroid cancer?

**EC** We knew much about thyroid cancer targets and biology before treatments were available. Thyroid cells are unique in that they are one of the few cell types in the body that concentrate iodine. Radioactive iodine, usually administered postoperatively, has been a mainstay for these patients. In a sense, it is a wonderfully targeted agent because only the normal thyroid cells take it up.

In differentiated thyroid cancer, 60% of patients carry the gene mutation *BRAF*, and approximately 10–20% carry a mutation in the *KRAS* or *NRAS* genes. These mutations appear to be mutually exclusive, so patients that carry a *BRAF* mutation do not have an *RAS* mutation and vice versa. Until recently, we did not have a mechanism with which to target these mutations. In medullary thyroid cancer, *RET* is often mutated. It is pathognomonic of genetic syndromes associated with medullary thyroid cancer, such as multiple endocrine neoplasia or familial medullary thyroid carcinoma. Those diseases must carry an *RET* mutation in order to make the diagnosis. Approximately 75–80% of sporadic medullary thyroid cancers also harbor an *RET* mutation. Lastly, in anaplastic thyroid cancer, these highly mutated cancers often have mutations in the p53 and PI3-kinase pathways, with a very complex genotype, which likely accounts for their aggressiveness and the difficulties with treatment.

**H&O** What are some recent data on multikinase inhibitors, *BRAF* inhibitors, and *RET* inhibitors?

**EC** Tyrosine kinase inhibitors (TKIs) have shown activity in thyroid disease, which was surprising because these agents do not target the genes or proteins previously mentioned, but in fact target vascular endothelial growth factor receptors (VEGFR), specifically VEGFR2. All of the TKIs that have shown activity in thyroid cancer inhibit VEGFR2, including sorafenib (Nexavar, Onyx), sunitinib (Sutent, Pfizer), axitinib (Inlyta, Pfizer), motesanib, and pazopanib (Votrient, GlaxoSmithKline). We have learned

that activity is fairly consistent throughout the class. Thyroid cancer is quite angiogenic, and likely depends on VEGFR2 signaling for its viability. These drugs are effective, producing a 20–30% response rate as defined by the Response Evaluation in Solid Tumors (RECIST) criteria. Moreover, an additional 30–50% of patients will achieve prolonged stable disease. These drugs have been used only in refractory patients or those with metastatic disease who have exhausted all other options. Even in that patient population, disease control or response occurs in the great majority.

There are now clinical trials of *BRAF* inhibitors, specifically vemurafenib (Zelboraf, Roche/Genentech), which was approved for metastatic melanoma patients with the *BRAF* V600E mutation. There is every indication that this drug will be active in *BRAF*-mutated thyroid cancer. We must await the data, but it is likely that vemurafenib will be active in thyroid cancer patients with a *BRAF* mutation, so this is an exciting prospect for the future.

The *RET* inhibitor vandetanib (Caprelsa, AstraZeneca) has been approved for medullary thyroid cancer. This agent also targets VEGFR and epidermal growth factor receptors (EGFR). The approval of vandetanib was based on the results of the phase III ZETA (Zactima Efficacy Study versus Tarceva) trial. In the study, patients randomized to vandetanib showed a statistically significant improvement in progression-free survival (PFS) as compared to those randomized to placebo (hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.24–0.53; $P<.0001$). This difference reflects a 65% reduction in risk of disease progression. Another agent that targets *RET* is cabozantinib (also known as XL184, Exelixis). The large phase III EXAM (Efficacy of XL184 in Advanced Medullary Thyroid Cancer) trial was recently completed, and the results show a significant improvement in PFS with cabozantinib versus placebo. Those data will be presented soon in abstract form. For medullary thyroid cancer, we have been able to translate what we know about the biology vis-à-vis *RET* mutations into a viable, approved therapy for these patients.

### H&O What are the biggest remaining challenges in thyroid cancer?

**EC** The biggest challenge and unmet need is how to treat patients with anaplastic thyroid cancer. This disease is so aggressive that it kills in just weeks or months. Fortunately, it is not common, but it is almost universally fatal. We must learn more about it and find treatment options. A second obstacle involves patients who progress during treatment with a VEGFR TKI. We must identify the mechanism of resistance and learn how to target and treat it. There is a clinical trial of a VEGFR inhibitor called cediranib (tentative trade name Recentin, AstraZeneca) with or without lenalidomide (Revlimid, Celgene). The hope is that we may be able to induce a response even in patients whose tumors are refractory to drugs like sorafenib and sunitinib, but it is clearly a challenge. The last obstacle involves patients with refractory disease who do not have metastatic disease. Many of these patients reach a point at which they can no longer undergo resection, especially after 4, 5, or even 6 surgeries. External beam radiation is often recommended, but it would be interesting to look at what a drug like sorafenib or pazopanib could achieve when combined with radiation in the context of locally advanced thyroid cancer. Such studies are worthy of consideration for the future.

## Suggested Readings

Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol*. 2012;30:134-141.

Clinicaltrials.gov. An international, randomized, double-blinded, phase 3 efficacy study of XL184 versus placebo in subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer. Identifier: NCT00704730. http://clinicaltrials.gov/ct2/show/ NCT00704730.

Perez CA, Santos ES, Arango BA, Raez LE, Cohen EE. Novel molecular targeted therapies for refractory thyroid cancer. *Head Neck*. 2011 [epub ahead of print].