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FACTS ABOUT THYROID CANCER

Thyroid cancer is a malignancy that originates in the thyroid, a ductless gland composed of spheroidal follicles located over and on either side of the trachea (Fig. 1). Follicular cells in the thyroid gland synthesize and secrete thyroid hormone, which helps to regulate metabolism. Parafollicular cells (also called C cells) in the thyroid make calcitonin, a hormone that regulates how the body uses calcium. In addition to these two main cell types, the thyroid gland is also composed of lymphocytes and stromal cells. Different subtypes of thyroid cancer originate in the different cell types (Figs. 2 and 3).

Several types of neoplasia, not all of which are malignant, can develop in the thyroid. Thyroid malignancies currently account for 3.5% of cancers in women, who are affected disproportionately (Ferlay, J. et al., 2015). Furthermore, these tumors are rapidly increasing in prevalence worldwide due to the dual pressures of better diagnostic technology, which has led to increased diagnosis of indolent disease, as well as increased risk factors (La Vecchia, C. et al., 2015; Jasim, S. et al., 2014; Marcello, M.A. et al., 2014).
CLASSIFICATION

There are several types of thyroid cancer, most of which are grouped under the heading of differentiated cancers. In these cancers, which develop from thyroid follicular cells, the cells look very similar to normal thyroid tissue when seen under a microscope. The main types of differentiated thyroid cancer are (Venkat, R. and Guerrero, M.A., 2013):

- **Papillary carcinoma** (also called papillary cancer or papillary adenocarcinoma), which tends to grow very slowly and usually develops in only one lobe of the thyroid gland; it may spread to regional lymph nodes. There are several subtypes of papillary carcinoma. Of these, the follicular subtype (also called mixed papillary-follicular variant) occurs most often. The usual form of papillary carcinoma and the follicular subtype both have a favorable prognosis when diagnosed early. Other subtypes of papillary carcinoma (columnar, tall cell, insular and diffuse sclerosing) are not as common and tend to grow and spread more quickly. Papillary carcinomas account for 80% of all thyroid cancers.

- **Follicular carcinoma** (also called follicular cancer or follicular adenocarcinoma) accounts for approximately 10% of all thyroid cancers. It is more common in countries where people do not get enough iodine in their diet. These cancers usually do not spread to lymph nodes, but can metastasize to other parts of the body, such as the lungs or bones. The prognosis for follicular carcinoma is somewhat less favorable than that of papillary carcinoma.

- **Hürthle cell carcinoma** (also known as oxyphil cell carcinoma), a variant of follicular carcinoma, accounts for about 3% of thyroid cancers. The prognosis may not be as good as that of typical follicular carcinoma: this type is harder to identify and treat, because it is less likely to absorb radioactive iodine.

Other, less common thyroid cancers, which together account for the remaining 7% of all thyroid tumors, include:

- **Medullary thyroid carcinoma** (MTC), which accounts for approximately 4–5% of thyroid cancers (Griebeler, M.L. et al., 2013), develops from C cells in the thyroid gland. Both sporadic and familial forms of MTC exist. Because it cannot be detected using a thyroid scan, this cancer may spread to lymph nodes, lungs or the liver before a thyroid nodule is discovered.

- **Anaplastic carcinoma** (also called undifferentiated carcinoma) accounts for about 2% of all thyroid cancers. It is thought to sometimes develop from an existing papillary or follicular cancer. This cancer often spreads quickly into the neck and to other parts of the body, and has a very poor prognosis (Morrison, S.A. et al., 2014).

- **Thyroid lymphoma**, which develops from lymphocytes—the main cell type of the immune system—contained in lymph nodes in the thyroid gland.

- **Thyroid sarcoma**, a class of extremely rare cancers that originate in stromal cells, the supporting cells of the thyroid. They are often aggressive and difficult to treat.

RISK FACTORS

Like most thyroid diseases, thyroid cancer affects three times more women than men, and this difference is most pronounced after puberty. The reason for this imbalance remains unclear, although it suggests a role for estrogen in promoting thyroid cell growth (Xhaard, C. et al., 2014; Derwahl, M. and Nicula, D., 2014). This theory is supported by findings from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, in which conditions resulting in more prolonged exposure to endogenous hormones were associated with risk of postmenopausal thyroid cancer. These included older age at menopause, greater number of lifetime ovulatory cycles, greater number of live births, and history of uterine fibroids (Braganza, M.Z. et al., 2014). There is a lack of robust epidemiological evidence at this time, however, to support any specific reproductive or menstrual risk factor (Zamora-Ros, R. et al., 2015).

Increasing age (40–50 years in women, slightly older in men) is another risk factor, although thyroid cancer can also develop in children, and in fact the incidence rate in younger subjects has seen an upswing in recent decades (Marcello, M.A. et al., 2014), alongside the rate in adults.
In low- and middle-income countries, iodine deficiency remains an important risk factor for thyroid diseases, including follicular and papillary thyroid carcinoma (Choi, W.J. and Kim, J., 2014). In the developed world, where iodine supplementation of table salt and other foods is standard, iodine deficiency is infrequent. However, iodine supplementation can lead to iodine excess—which has been identified as a risk factor for papillary thyroid cancer—in populations consuming a high level of iodine-rich foods such as seafood. Particularly in women, iodine excess can alter levels of thyroid-stimulating hormone (TSH), contributing to carcinogenesis (Choi, W.J. and Kim, J., 2014; Marcello, M.A. et al., 2014).

The risk of thyroid cancer is elevated in people who are exposed to radiation from various sources, including therapeutic or diagnostic procedures, occupational exposures (Aschebrook-Kilfoy, B. et al., 2014), nuclear accidents, etc. This risk is most pronounced for those exposed to radiation during childhood or adolescence (Mathews, J.D. et al., 2013). In general, cancer risk is believed to exist with exposure to a radiation dose in excess of 100 mSv, and risk increases 0.05-fold for every 100 mSv increase in radiation dose (Miyakawa, M., 2014).

A personal history of Hashimoto’s thyroiditis, an autoimmune disease that causes hypothyroidism, is associated with an elevated risk of thyroid cancer. A characteristic feature of Hashimoto’s thyroiditis is infiltration of the thyroid gland by inflammatory cells; studies support an association between thyroid inflammation and carcinoma (Azizi, G. et al., 2014; Chen, Y.K. et al., 2013). Thyroid cancer risk has also been shown to be elevated in patients with Graves’ disease, another autoimmune thyroid disorder, particularly in the first three years after diagnosis (Chen, Y.K. et al., 2013).

A growing body of evidence supports obesity as a risk factor for some types of thyroid cancer. Data from more than 15,000 men and women undergoing a routine health checkup at the Asan Medical Center (Seoul, Korea) showed that obesity was linked to a higher prevalence of thyroid cancer. This association was not affected by serum TSH or insulin levels (Han, J.M. et al., 2013). In another study, Chinese researchers performed a meta-analysis of 32 observational studies including a total of 12.6 million individuals. Their analysis indicates that obesity increases the risk of papillary, follicular and anaplastic thyroid cancers; on the other hand, obesity was associated with a decrease in the risk of medullary thyroid cancer (Ma, J. et al., 2015). In a pooled analysis of case-control studies conducted in the U.S. and Europe, the risk of papillary thyroid cancer increased with certain anthropometric factors, including body mass index (BMI) and body fat percentage (Xu, L. et al., 2014).

Although smoking is an established risk factor for many types of cancer, studies in thyroid cancer patients (Marcello, M.A. et al., 2014), including at least one case-control study exclusively in men (Zivaljevic, V. et al., 2013), have failed to establish a role for smoking as a risk factor for this malignancy; in fact, some studies suggest that the practice may be associated with reduced risk (Kitahara, C.M. et al., 2012; Moura, M.A. et al., 2014). Studies have also suggested that alcohol consumption is inversely associated with risk of thyroid cancer (de Menezes, R.F. et al., 2013; Kitahara, C.M. et al., 2012).

**GENETICS**

Point mutations in the *BRAF* (V600E and K601E) and *RAS* genes are frequently detected in sporadic papillary thyroid cancer, and are thought to be induced by chemical carcinogens. Radiation exposure, on the other hand, contributes to intrachromosomal rearrangement of *RET* which generates the chimeric onogenes RET/PTC. Thyroid cancers with *BRAF* mutations are often more aggressive and invasive, and furthermore are increasing in frequency, whereas *RET/PTC* mutations are decreasing (Jung, C.K. et al., 2014; Alonso-Gordoa, T. et al., 2015) (Fig. 4). Other gene alterations implicated in thyroid cancer include *PTEN*, *P53* and *PIK3CA* mutations as well as *PAX8-PPARG* rearrangements (Yip, L., 2015).

![Fig 4. Mutation of the RET gene into the PTC oncogene.](image)
EPILOGUE

More than 296,000 cases of thyroid cancer were diagnosed in men and women worldwide in 2012, according to the International Agency for Research on Cancer (Globocan 2012 – International Agency for Research on Cancer, consulted March 4, 2015). The global age-standardized incidence rate in 2012 was 6.1 per 100,000 women and 1.9 per 100,000 men (La Vecchia, C. et al., 2015). The 1-year prevalence at the global level in 2012 was 255,828 and the 3- and 5-year prevalence was 741,316 and 1,206,075, respectively (Globocan 2012 – International Agency for Research on Cancer, consulted March 4, 2015). Epidemiology varies significantly between countries and regions of the world, however, with twofold higher incidence rates in high-income as compared to low- and middle-income countries (La Vecchia, C. et al., 2015) The highest incidence rate in the world is reported in Korea: 52.7 cases per 100,000 in 2010 (Oh, C.M. et al., 2014).

According to the American Cancer Society, about 62,450 new cases of thyroid cancer will be diagnosed in the U.S. in 2015. This includes 47,230 cases in women and 15,220 in men (Cancer facts & figures 2015 – American Cancer Society, 2015). The incidence of thyroid cancer has increased significantly in recent years; in fact, thyroid cancer is the most rapidly increasing cancer in the U.S. According to National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database, thyroid cancer incidence increased by 5.5% each year for the last 10 years, and currently accounts for 3.8% of all new cancer cases diagnosed in the U.S. (SEER stat fact sheets: Thyroid cancer – National Cancer Institute, consulted March 6, 2015). An analysis of SEER data from 1975–2009 suggests that much of this increase is the result of wider use of thyroid ultrasound, which can detect small thyroid nodules that might not have been diagnosed in the past (Davies, L. and Welch, H.G., 2014). Nonetheless, at least part of the increase corresponds to a greater number of large tumors being detected (Li, N. et al., 2013), indicating that risk factors are also contributing to the trend.

Thyroid cancer is the seventh most common malignancy diagnosed in Canada, and is increasing at a faster rate than any other malignancy in that country. In a population-based cohort study, the age-standardized incidence of thyroid cancer in the province of Manitoba, Canada, increased from 2.52 per 100,000 in 1970 to 9.37 per 100,000 in 2010. Age at diagnosis, gender distribution, tumor size, and initial tumor stage did not change significantly during the period evaluated, but the distribution of cancer subtypes did evolve, with an increasing number of papillary tumors and a decrease in the proportion of anaplastic carcinomas. The prevalence of thyroid cancer in this population increased by 373% from 1970 to 2010 (Pathak, K.A. et al., 2013). Another study reported that thyroid cancer incidence rates in Canadian women and men increased by 4.4% and 3.6%, respectively, between 1970 and 2007 (Kachuri, L. et al., 2013).

The incidence of thyroid cancer in Spain was 5.0 per 100,000 women and 1.9 per 100,000 men in 2013, equivalent to approximately 3% of all cancers reported (Trigo, J.M. et al., 2014). In contrast, thyroid cancer remains rare in the U.K., where it accounts for less than 1% of all malignancies. In 2011, there were 2,727 new cases of thyroid cancer diagnosed (Thyroid cancer statistics – Cancer Research UK, consulted March 4, 2015). In Wales, where a total of 1,747 cases of thyroid cancer were reported from 1985–2010, the age-standardized incidence rates in women and men were 2.8 and 1.2 per 100,000, respectively, and increased over time, particularly with respect to the incidence of papillary cancer (Amphlett, B. et al., 2013). The age-standardized incidence rate in the Nordic countries (2008–2012) was 5.9 per 100,000 per year in women and 2.1 per 100,000 in men. This rate has increased by 3.9% in women and by 4.5% in men over the last 10 years (Nordcan Project, consulted March 9, 2015).

Increases in thyroid cancer incidence have also been reported in two major Chinese cities. Based on data from local cancer registries, the age-standardized incidence rate increased by 3.1% and 3.8% per year on average, respectively, in Shanghai men and women during the period 1973–2009. Similarly, incidence increased by 2.2% and 2.7% per year on average, respectively, in Hong Kong men and women between 1983 and 2011 (Xie, S.H. et al., 2014). In the Zhejiang province of China, the incidence of thyroid cancer increased from 3.62 per 100,000 population in 2000 to 11.42 per 100,000 in 2009, an annual percent change (APC) of 16.32% (Song, K. et al., 2014). In Japan, the age-standardized incidence rate (both sexes) in 2010 was 6.3 per 100,000 population (Cancer statistics in Japan, consulted March 9, 2015).

For more epidemiology information, consult the Incidence and Prevalence Database (IPD):
IPD: Thyroid cancer.
MORBIDITY AND MORTALITY

Although thyroid cancer is becoming more prevalent, corresponding increases in mortality have not been reported. In fact, in most countries the age-adjusted mortality rates from thyroid cancer decreased between 2000 and 2010 (La Vecchia, C. et al., 2015). This is primarily due to the fact that the increase has been almost exclusively in the rate of papillary cancer, which is the least lethal subtype (Marcello, M.A. et al., 2014).

While the incidence of thyroid cancer in the U.S. nearly tripled from 1975 to 2009, the mortality rate remained constant at approximately 0.5 per 100,000 during the same period (Davies, L. and Welch, H.G., 2014). The American Cancer Society predicts that approximately 1,950 Americans (1,080 women and 870 men) will die from thyroid cancer in 2015 (Cancer facts & figures 2015 – American Cancer Society, 2015)). In the U.K., there were 373 deaths from thyroid cancer in 2012 (Thyroid cancer statistics – Cancer Research UK, consulted March 4, 2015). In Canada, the five-year relative survival ratio for thyroid cancer patients was 98% in 2011, and disease-specific survival improved by 10.2% from 1970–2010 (Pathak, K.A. et al., 2013).

A similar trend has been reported in Korea, where despite a 24.2% increase in incidence each year from 1999 to 2010, the mortality rate remained stable over the same period (Oh, C.M. et al., 2014). According to another Korean report, age-standardized mortality rates for thyroid cancer have actually been decreasing since 2000 (Choi, Y.M. et al., 2014).

Anaplastic thyroid cancer is a rare subtype with a very high mortality: the one-year survival rate is reported to be less than 10% (Morrison, S.A. et al., 2014).

COST

The lifetime cost associated with treatment of papillary thyroid cancer is estimated to be USD 34,723 per patient in the U.S., including USD 33,463 per patient without metastasis and USD 58,660 per patient with metastasis (Aschebrook-Kilfoy, B. et al., 2013). Based on a study of SEER data, Harvard researchers estimate that the overall societal cost in 2013 associated with the care of all U.S. patients diagnosed with well-differentiated thyroid cancer since 1985 was USD 1.6 billion (Lubitz, C.C. et al., 2014).

University of Chicago researchers predict that by 2019, papillary thyroid cancer will be the third most common malignancy diagnosed in U.S. females, and will incur a cost to the country in the range of USD 18–21 billion (Aschebrook-Kilfoy, B. et al., 2013).

Thyroid cancer was the fifth most prevalent cancer in Korea in 2010, with an associated societal cost of USD 1.7 billion (Lee, K.S. et al., 2014).

DIAGNOSIS

Thyroid nodules are typically encountered incidentally, either on physical examination or when a patient undergoes diagnostic imaging of the neck for other reasons (Trigo, J.M. et al., 2014; Morrison, S.A. et al., 2014). In such a case, further exploration should include a physical examination and review of the patient’s personal and familial medical history, followed by thyroid radionuclide scan and fine-needle aspiration biopsy (Bauer, A.J., 2014; Wienhold, R. et al., 2013). Proper preoperative diagnosis and risk stratification will eliminate the need for unnecessary diagnostic surgery (Cibas, E.S. and Ali, S.Z., 2009; Wienhold, R. et al., 2013).

Blood tests to evaluate levels of certain hormones (thyroid-stimulating hormone [TSH], calcitonin and thyroglobulin) are not diagnostic for cancer, but do provide useful information about the proper functioning of the gland. Serum TSH levels are checked first, and if higher than normal, a radionuclide thyroid scan should be performed (Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer—American Thyroid Association, November 2009).
Thyrotropin alfa, a highly purified recombinant form of human TSH, was launched in 1998 for use as an adjunctive diagnostic tool for the follow-up of patients with well-differentiated thyroid cancer. rhTSH is administered in lieu of thyroid hormone withdrawal—which can induce severe hypothyroidism—in order to enable serum thyroglobulin measurement. The test is not diagnostic for thyroid cancer, but is useful in follow-up of patients with residual disease following surgery and radioiodine ablation (Pellegriti, G. et al., 2003).

STAGING

Staging is used to determine the extent of the cancer, including the presence and location of metastases, and to guide treatment decisions. The TNM (tumor-node-metastasis) classification system, which is also used for other tumor types, is most commonly used for staging of thyroid cancer. This system describes both the anatomical extent of the primary tumor as well as regional lymph node involvement and distant metastases.

Following determination of the patient's TNM classification, the information is combined to assign a stage. Stage is expressed in Roman numerals, ranging from Stage I, in which carcinoma is contained within the thyroid gland, to Stage IV, in which the cancer has metastasized to distant sites (Thyroid cancer treatment (PDQ®)). Common sites of metastasis include the neck, chest, bone and brain (Trigo, J.M. et al., 2014).

DIFFERENTIAL DIAGNOSIS

A distinction must be made between benign thyroid nodules and malignant thyroid cancer (Bauer, A.J., 2014; Wienhold, R. et al., 2013). Other conditions to be considered in the differential diagnosis of thyroid carcinoma include goiter, toxic nodular goiter and Graves’ disease, as well as cancer of the parathyroid gland.

TREATMENT

The three main components of treatment for thyroid cancer are surgery, radioiodine ablation and chemotherapy. However, in spite of the existence of treatment guidelines, there is considerable variation among physicians regarding the best approach (Haymart, M.R. et al., 2013).

Thyroid cancer is an indolent tumor, and the risk of death remains elevated even decades after diagnosis and seemingly successful treatment. Long-term followup is therefore an essential aspect of treatment (Kim, T.Y. et al., 2014).

SURGERY

Surgery is the cornerstone of therapy for most patients with thyroid cancer. Total or near-total thyroidectomy is indicated for the resection of larger papillary thyroid tumors (>1 cm). In patients with small tumors (<1 cm), thyroidal lobectomy may be an option. Total thyroidectomy is also the preferred surgical approach for medullary thyroid cancer. In addition to open surgery, newer surgical options include minimally invasive surgery, video-assisted thyroidectomy, and endoscopic or robotic thyroidectomy (see Fig. 5 for the anatomy of mouth, nose and throat, and the location of thyroid, parathyroid and salivary glands) (Morrison, S.A. et al., 2014; Venkat, R. and Guerrero, M.A., 2013).

Although cervical lymph nodes (Fig. 6) are affected in approximately 50% of patients with papillary thyroid cancer, most of this involvement is microscopic (Morrison, S.A. et al., 2014). Both the American Thyroid Association and the European Thyroid Cancer Taskforce recommend prophylactic lymph node dissection in their treatment guidelines, although a meta-analysis failed to confirm that the procedure has any impact on patient survival, and there is hence a lack of agreement about whether or not it is warranted (Venkat, R. and Guerrero, M.A., 2013).
Thyroid hormone therapy should be initiated immediately after surgery in order to replace thyroid hormone while also preventing a surge of TSH that would stimulate the growth of any remaining cancer cells. Levothyroxine (T4) is the drug of choice for thyroid hormone replacement therapy (Pacini, F. et al., 2012).

**RADIOACTIVE IODINE**

Radioactive iodine (RAI) therapy has been used for the treatment of well-differentiated thyroid cancer since the 1940s (Esposito, G., 2014) and still forms a part of standard therapy for many patients. The procedure is based on preferential absorption of iodine by the thyroid gland, resulting in targeted delivery of radioactivity directly where it is needed (Worden, F., 2014). Following surgical removal of the tumor, RAI ablation is used to eliminate any remaining malignant cells, tissues or gross disease. With the exception of patients with advanced disease at time of diagnosis, local recurrence of disease that cannot be treated with surgery alone and/or distant metastases, a low dose of RAI is nearly always indicated. Patients at very low risk do not require RAI (Mayson, S.E. et al., 2014; Esposito, G., 2014). The therapy is not effective in treating medullary or anaplastic thyroid cancer (Perri, F. et al., 2015).

Uptake of RAI by thyroid cancer cells is improved through the elevation of TSH levels, resulting in enhanced treatment efficacy. Recombinant human TSH (thyrotropin alfa, rhTSH), previously marketed as a diagnostic agent, was approved as an adjunct to RAI remnant ablation in patients without distant metastases in Europe in 2005 and in the U.S. in 2007 (Robenshtok, E. and Tuttle, R.M., 2012).

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**Fig 5.** The anatomy of the mouth, nose and throat, and the location of thyroid, parathyroid and salivary glands.

**Fig 6.** Head and neck lymph glands.
CHEMOTHERAPY

Following surgery and radioactive iodine therapy, cytotoxic chemotherapy is indicated for the treatment of patients with progressive disease. As shown in Table I, very few drugs have been approved specifically for the indication of thyroid cancer. Standard chemotherapeutic drugs (doxorubicin, paclitaxel, cisplatin) are generally ineffective in treating thyroid tumors, but the introduction in recent years of targeted therapeutics has provided new treatment options for patients with RAI-refractory thyroid cancer (Worden, F., 2014; Jasim, S. et al., 2014).

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Organization</th>
<th>Year of first launch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer immunotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OK-432 (Picibanil)</td>
<td>Chugai</td>
<td>1975</td>
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<tr>
<td><strong>Cancer immunotherapy</strong></td>
<td></td>
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<tr>
<td>Sodium iodide I-131 (Hicon)</td>
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<tr>
<td><strong>Cancer immunotherapy</strong></td>
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<td><strong>Cancer immunotherapy</strong></td>
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<td>Vandetanib (Caprelsa)</td>
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<td>2011</td>
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<td><strong>Cancer immunotherapy</strong></td>
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<tr>
<td>Cabozantinib S-malate (Cometriq)</td>
<td>Exelixis</td>
<td>2013</td>
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<td><strong>Cancer immunotherapy</strong></td>
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<tr>
<td>Sorafenib (Nexavar)</td>
<td>Bayer/Amgen</td>
<td>2013</td>
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<tr>
<td><strong>Cancer immunotherapy</strong></td>
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<tr>
<td>Lenvatinib mesylate (Lenvima)</td>
<td>Eisai</td>
<td>2015</td>
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</table>

MULTIKINASE INHIBITORS

Targeted therapeutic agents for the treatment of radioactive iodine-refractory thyroid cancer typically act via one of two mechanisms: angiogenesis inhibition, or cell cycle inhibition, i.e. blockade of the processes of cell proliferation and survival (Worden, F., 2014).

The mitogen-activated kinase (MAP kinase) pathway is one of the most widely studied targets in thyroid cancer therapy, as disruptions in this pathway are implicated in approximately 80% of papillary thyroid cancers as well as a significant number of anaplastic thyroid cancers. Mutations in the gene encoding
for the upstream protein RET, a tyrosine kinase receptor, are frequently identified in thyroid tumors. The same is true for BRAF (V600E), another commonly found point mutation in thyroid cancer, and for RAS, which also intervene in the MAP kinase pathway (Perri, F. et al., 2015; Jasim, S. et al., 2014).

The multikinase inhibitor sorafenib inhibits several protein kinases with relevance in thyroid cancer, including BRAF, RET, VEGFR, PDGFR and c-KIT. In July 2013, the U.S. FDA granted approval of sorafenib for the treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment. In 2014 it was approved in the E.U., Canada and Japan for the same indication. In the U.S., approval of sorafenib followed a priority review and was based on the results from DECISION, an international, multicenter, placebo-controlled study in which 417 patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to RAI were randomized to receive sorafenib or placebo. Metastases were present in 96% of the patients: lung metastases in 86%, lymph node metastases in 51%, and bone metastases in 27% of subjects. Sorafenib significantly extended progression-free survival (PFS), the primary endpoint of the study. The median PFS was 10.8 months among patients treated with sorafenib compared to 5.8 months among patients receiving placebo. The most common adverse reactions reported for sorafenib- versus placebo-treated patients were palmar-plantar erythrodysesthesia syndrome (69 vs. 8%), diarrhea (68 vs. 15%), alopecia (67 vs. 8%), weight loss (49 vs. 14%), fatigue (41 vs. 20%), hypertension (41 vs. 12%), rash (35 vs. 7%), decreased appetite (30 vs. 5%), stomatitis (24 vs. 3%), nausea (21 vs. 12%), pruritus (20 vs. 11%) and abdominal pain (20 vs. 7%). Grade 3/4 adverse reactions were experienced by 65 vs. 30% of patients. Drug-related adverse reactions that resulted in treatment discontinuation were reported in 14% of sorafenib-treated patients compared to 1.4% of placebo-treated patients (Brose, M.S. et al., 2014).

Cabozantinib S-malate is an inhibitor of multiple receptor tyrosine kinases, including RET, MET, VEGFR-1, -2 and -3, TRKB, FLT-3, AXL and TIE-2, which are involved in both normal cellular function and pathological processes such as oncogenesis, metastasis, angiogenesis and maintenance of the tumor microenvironment. It was launched in the U.S. in 2013 for the treatment of progressive, metastatic medullary thyroid cancer (MTC). FDA approval was based on the results from EXAM, a randomized phase III trial involving 330 patients with progressive, metastatic MTC. The trial met its primary efficacy endpoint of improving progression-free survival and also showed a reduction in the size of tumors in some patients. Specifically, patients receiving cabozantinib lived an average of 11.2 months without tumor growth compared with an average of 4.0 months in patients receiving placebo (Elisei, R. et al., 2013).

Inhibition of angiogenesis—the process by which new blood vessels are formed from preexisting capillaries—is an effective treatment for thyroid tumors, which are highly vascularized (Worden, F., 2014). Tumors cannot grow without the formation of new blood vessels to provide them with nutrients. Angiogenesis is thus an integral element of tumor growth, progression, invasion and metastasis, and inhibition of angiogenesis is a promising antitumor strategy. Within the angiogenesis inhibitor class, drugs targeting the vascular endothelial growth factor (VEGF) pathway have been the most widely studied for this indication (Jasim, S. et al., 2014; Abdel-Rahman, O., 2015).

Vandetanib is an orally active vascular endothelial growth factor receptor-2 (VEGFR-2/KDR) tyrosine kinase inhibitor that was launched in 2011 for the treatment of medullary thyroid cancer. FDA approval for vandetanib was based on the results from the phase III ZETA study, a double-blind trial that randomized 331 patients with unresectable locally advanced or metastatic medullary thyroid cancer to the angiogenesis inhibitor or placebo. In the trial, participants receiving vandetanib showed a statistically significant improvement in progression-free survival versus those randomized to placebo. This difference reflects a 65% reduction in risk of disease progression. The median PFS was 16.4 months in the placebo arm and at least 22.6 months in the vandetanib arm (Thornton, K. et al., 2012). In spite of its efficacy in prolonging PFS, however, vandetanib has not been shown to improve overall survival. Furthermore, because of its potential for severe cardiovascular side effects and sudden death, use of the drug is restricted via a Risk Evaluations and Mitigation Strategy program (Cooper, M.R. et al., 2014).

Lenvatinib mesylate is a highly potent, orally active multikinase inhibitor that targets VEGFR-1, -2 and -3, PDGFRbeta, VEGFR-1 (Ft-1) and c-KIT. The drug was developed by Eisai and was approved and launched in the U.S. in 2015 as an oral treatment for progressive RAI-refractory differentiated thyroid cancer. The approval was based on data from the phase III trial SELECT (Schlumberger, M. et al., 2015), which achieved its primary endpoint of PFS improvement for oral lenvatinib compared to placebo in patients with radioiodine-refractory differentiated thyroid cancer. PFS was 18.3 and 3.6 months for
Lenvatinib and placebo, respectively. Tumor shrinkage was observed in 65% of the lenvatinib group compared to 2% of the placebo group. On disease progression, placebo-treated patients became eligible to receive lenvatinib. Treatment-related adverse events occurred in over 40% of the lenvatinib group. The most common were hypertension (67.8%), diarrhea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), weight loss (46.4%) and nausea (41.0%).

The mammalian target of rapamycin, or mTOR, is a downstream serine/threonine protein kinase of the PI3K-AKT pathway, also known as the PI3K-AKT-mTOR pathway. It also intervenes in other intracellular signal transduction pathways that regulate cell survival, hyperplasia and apoptosis or that otherwise contribute to tumorigenesis. mTOR has emerged in recent years as a potential target for thyroid cancer (Jasim, S. et al., 2014; Alonso-Gordoa, T. et al., 2015), including the difficult-to-treat form, medullary thyroid cancer (Manfredi, G.I. et al., 2015).

This continued to be an active area of research, as shown in Table II, which provides an overview of multikinase and targeted kinase inhibitors under active development for the treatment of thyroid cancer.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Organization</th>
<th>Mechanism of Action</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selumetinib sulfate</td>
<td>AstraZeneca</td>
<td>MEK1 Inhibitors/ MEK2 Inhibitors/ Extracellular-Regulated Kinase (ERK) Inhibitors/ Apoptosis Inducers/ Signal Transduction Modulators</td>
<td>Phase III</td>
</tr>
<tr>
<td>Anlotinib</td>
<td>Jiangsu Chia Tai Tianqing</td>
<td>Angiogenesis Inhibitors/ FGFR Inhibitors/ VEGF Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Dabrafenib mesylate</td>
<td>Ohio State University</td>
<td>Raf kinase B Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Novartis</td>
<td>FK506-Binding Protein 12 (Peptidyl-Prolyl Cis-Trans Isomerase FKBP12) Inhibitors/ Angiogenesis Inhibitors/ Mammalian Target of Rapamycin (mTOR; FRAP1) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>EORTC</td>
<td>Angiogenesis Inhibitors/ Breast Cancer-Resistant Protein (BCRP; ABCG2) Inhibitors/ FGFR1 Inhibitors/ FGFR3 Inhibitors/ P-Glycoprotein (MDR-1; ABCB1) Inhibitors/ VEGFR-1 (Flt-1) Inhibitors/ VEGFR-2 (FLK-1/KDR) Inhibitors/ PDGFRalpha Inhibitors/ VEGFR-3 (FLT4) Inhibitors/ PDGFRbeta Inhibitors/ Tyrosine Kinase Inhibitors/ Cytochrome P450 CYP3A4 Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Pazopanib hydrochloride</td>
<td>GlaxoSmithKline</td>
<td>Angiogenesis Inhibitors/ VEGFR-1 (Flt-1) Inhibitors/ KIT (C-KIT) Inhibitors/ VEGFR-2 (FLK-1/KDR) Inhibitors/ PDGFRalpha Inhibitors/ VEGFR-3 (FLT4) Inhibitors/ PDGFRbeta Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Ariad Pharmaceuticals</td>
<td>Ab1 Kinase Inhibitors/ Angiogenesis Inhibitors/ Bcr-Abl (Bcr-Abl1) Kinase Inhibitors/ FGFR Inhibitors/ Flt3 (FLK2/ STK1) Inhibitors/ KIT (C-KIT) Inhibitors/ Apoptosis Inducers/ PDGFR Family Inhibitors/ RET Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
TABLE II. MULTIKINASE AND TARGETED KINASE INHIBITORS IN DEVELOPMENT FOR THYROID CANCER

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Organization</th>
<th>Mechanism of Action</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib malate</td>
<td>National Cancer Institute (NCI)</td>
<td>Angiogenesis Inhibitors/ CSFIR (c-FMS) Inhibitors/ Flt3 (FLK2/STK1) Inhibitors/ VEGFR-1 (Flt-1) Inhibitors/ KIT (C-KIT) Inhibitors/ VEGFR-2 (FLK-1/KDR) Inhibitors/ VEGFR-3 (FLT4) Inhibitors/ PDGFRbeta Inhibitors/ RET Inhibitors/ Signal Transduction Modulators/ Leucine-Rich Repeat Kinase 2 (LRRK2; Dardarin) Inhibitors</td>
<td>Phase II</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
<td>Mammalian Target of Rapamycin (mTOR; FRAP1) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Roche</td>
<td>Raf kinase B Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Cediranib</td>
<td>National Cancer Institute (NCI)</td>
<td>Angiogenesis Inhibitors/ VEGFR-1 (Flt-1) Inhibitors/ VEGFR-2 (FLK-1/KDR) Inhibitors/ VEGFR-3 (FLT4) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Lapatinib ditosylate</td>
<td>National Cancer Institute (NCI)</td>
<td>EGFR (HER1; erbB1) Inhibitors/ HER2 (erbB2) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase I</td>
</tr>
<tr>
<td>Trametinib dimethyl sulfoxide</td>
<td>GlaxoSmithKline</td>
<td>MEK1 Inhibitors/ MEK2 Inhibitors/ Signal Transduction Modulators</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

VASCULAR DISRUPTING AGENTS

Tumor cells rely on the existence of a specialized vasculature for the oxygen and nutrients that they require in order to grow and survive. Targeting the tumor vasculature as a technique for inhibiting tumor growth was first attempted with angiogenesis inhibitors, which compromise the formation of new blood vessels. More recently a new class of drugs called vascular disrupting agents (VDAs) has been reported (Table III). Rather than preventing the formation of new blood vessels, VDAs target endothelial cells and pericytes in the already-established vascular network supporting the tumor. VDAs are designed to induce massive downstream tumor cell death in a tumor-specific manner, i.e. by shutting down the supporting vasculature (Hasani, A. and Leighl, N., 2011; Gridelli, C. et al., 2009).

TABLE III. VASCULAR DISRUPTING AGENTS IN ACTIVE DEVELOPMENT FOR THE TREATMENT OF THYROID CANCER

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Organization</th>
<th>Mechanism of Action</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosbretabulin disodium</td>
<td>OxiGene</td>
<td>Tubulin Polymerization Inhibitors/ Antimitotic Drugs/ Apoptosis Inducers/ Vascular Disrupting Agents (VDA)</td>
<td>Phase III</td>
</tr>
<tr>
<td>Crolibulin</td>
<td>National Cancer Institute (NCI)</td>
<td>Antimitotic Drugs/ Caspase Activators/ Apoptosis Inducers/ Signal Transduction Modulators/ Vascular Disrupting Agents (VDA)/ Microtubule Inhibitors</td>
<td>Phase I/II</td>
</tr>
</tbody>
</table>

Two subtypes of VDAs have been described: ligand-directed VDAs, which incorporate a targeting moiety linked to an effector moiety, and small molecules. Small-molecule VDAs, which include flavonoids and tubulin-binding agents, have several potential advantages over ligand-directed VDAs, including lower cost, greater specificity and reduced toxicity. Tubulin polymerization inhibitors disrupt the existing tumor vasculature through an interaction with the tubulin cytoskeleton, leading to altered
endothelial cell shape and destruction of intercellular junctions (Gridelli, C. et al., 2009; McKeage, M.J., 2011; Hasani, A. and Leighl, N., 2011). Flavonoid VDAs accentuate the pathological signals produced by cytokines, causing alterations in the actin cytoskeleton, increased vascular permeability and endothelial apoptosis (Baguley, B.C., 2011). Vascular disrupting agents are envisioned for use in combination with traditional chemotherapeutic agents, due to their complementary effects on different parts of the tumor and their synergistic activities in preclinical studies (McKeage, M.J., 2011), although the timing of their administration is an important consideration, i.e., disruption of the tumor vasculature may impede effective delivery of other antitumor agents (Baguley, B.C., 2011).

**AUTOPHAGY MODULATORS**

Autophagy is a specific type of programmed cell death whereby cellular contents (proteins and organelles) are captured in specialized membrane-bound vesicles and delivered to lysosomes, where they are digested and recycled in a process that sustains cellular metabolism. Two specific types of autophagy are known to exist: macroautophagy (i.e., the formation of a membrane containing target materials moving into the lysosome/vacuole) and microautophagy (i.e., the invagination of the lysosome/vacuole of target materials). Under normal physiological conditions, autophagy plays a vital role in cellular defense, quality control and energy metabolism. However, autophagy is also involved in tumorigenesis and cancer progression as well as treatment outcome. In recent years, biomedical researchers have begun to recognize the potential of autophagy modulation, i.e., harnessing this system to fight cancer (Yang, Z.J. et al., 2011; Claerhout, S. et al., 2011; Yi, H. et al., 2014).

Several known kinase inhibitors acting on the PI3K/mTOR and MAPK pathways have been shown to act as autophagy modulators, which may help to explain their efficacy in thyroid cancer, particularly as enhancers of radioactive iodine uptake (Yi, H. et al., 2014).

**HDAC INHIBITORS**

Histone deacetylase (HDAC) inhibitors are a newer class of targeted oncolytic drugs. Histone deacetylases alter chromatin structure and affect transcriptional regulation. Dysregulation of chromatin deacetylation is associated with cancer and inflammatory diseases. HDAC inhibitors act by inducing apoptotic cell death in cancer cells but not in normal cells, which are comparatively resistant to the apoptosis-inducing effects of these agents (Khan, O. and La Thangue, N.B., 2012). Histone deacetylase inhibitors—particularly those selective for HDAC-1, -2, -4 and/or -6—represent a promising approach to thyroid cancer therapy, especially when used in combination with other molecularly targeted drugs (Giaginis, C. et al., 2014; Russo, D. et al., 2013).

**CURRENT THYROID CANCER PIPELINE**

Consult Table I and Table IV for an overview of all products mentioned in this review, including drugs, biologics and diagnostic agents that have been marketed or are under active development for this indication. Tables may also include drugs not covered in the preceding sections because their mechanism of action is unknown or not well characterized.

**TABLE IV. DRUGS AND BIOLOGICS UNDER ACTIVE DEVELOPMENT FOR THE TREATMENT OF THYROID CANCER**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Organization</th>
<th>Mechanism of Action</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosbretabulin disodium</td>
<td>OxiGene</td>
<td>Tubulin Polymerization Inhibitors/ Antimitotic Drugs/ Apoptosis Inducers/ Vascular Disrupting Agents (VDA)</td>
<td>Phase III</td>
</tr>
<tr>
<td>Selumetinib sulfate</td>
<td>AstraZeneca</td>
<td>MEK1 Inhibitors/ MEK2 Inhibitors/ Extracellular-Regulated Kinase (ERK) Inhibitors/ Apoptosis Inducers/ Signal Transduction Modulators</td>
<td>Phase III</td>
</tr>
<tr>
<td>Afiblercept</td>
<td>National Cancer Institute (NCI)</td>
<td>Angiogenesis Inhibitors/ Placental Growth Factor (PGF) Inhibitors/ Vascular Endothelial Growth Factor (VEGF) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Organization</td>
<td>Mechanism of Action</td>
<td>Status</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>---------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Anlotinib</td>
<td>Jiangsu Chia Tai Tianqing Pharmaceutical</td>
<td>Angiogenesis Inhibitors/ FGFR Inhibitors/ VEGFR Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Buparlisib</td>
<td>Hospices Civils de Lyon</td>
<td>Phosphatidylinositol 3-Kinase alpha (PI3Kalpha) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Dabrafenib mesylate</td>
<td>Ohio State University</td>
<td>Raf kinase B Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Efututazone hydrochloride</td>
<td>Daiichi Sankyo</td>
<td>PPARgamma Agonists/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Novartis</td>
<td>FK506-Binding Protein 12 (Peptidyl-Prolyl Cis-Trans Isomerase FKBP12) Inhibitors/ Angiogenesis Inhibitors/ Mammalian Target of Rapamycin (mTOR; FRAP1) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>GT-111</td>
<td>Vascular Biogenics (d/b/a VBL Ther)</td>
<td>Angiogenesis Inhibitors</td>
<td>Phase II</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>EORTC</td>
<td>Angiogenesis Inhibitors/ Breast Cancer-Resistant Protein (BCRP; ABCG2) Inhibitors/ FGFR1 Inhibitors/ FGFR3 Inhibitors/ P-Glycoprotein (MDR-1; ABCB1) Inhibitors/ VEGFR-1 (Flt-1) Inhibitors/ VEGFR-2 (FLK-1/KDR) Inhibitors/ PDGFRalpha Inhibitors/ VEGFR-3 (FLT4) Inhibitors/ PDGFRbeta Inhibitors/ Tyrosine Kinase Inhibitors/ Cytochrome P450 CYP3A4 Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Novartis</td>
<td>Apoptosis Inducers/ Histone Deacetylase (HDAC) Inhibitors</td>
<td>Phase II</td>
</tr>
<tr>
<td>Pasireotide diaspartate</td>
<td>Novartis</td>
<td>Growth Hormone Release Inhibitors/ Somatostatin SRIFIA (sst2) Agonists/ Somatostatin SRIFIB (sst5) Agonists/ Somatostatin SRIF2A (sst1) Agonists/ Somatostatin srifIC (sst3) Agonists/ P-Glycoprotein (MDR-1; ABCB1) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Pazopanib hydrochloride</td>
<td>GlaxoSmithKline</td>
<td>Angiogenesis Inhibitors/ VEGFR-1 (Flt-1) Inhibitors/ KIT (C-KIT) Inhibitors/ VEGFR-2 (FLK-1/KDR) Inhibitors/ PDGFRalpha Inhibitors/ VEGFR-3 (FLT4) Inhibitors/ PDGFRbeta Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Pioglitazone hydrochloride</td>
<td>University of Michigan</td>
<td>PPARgamma Agonists/ Insulin Sensitizers/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Ariad Pharmaceuticals</td>
<td>Abl1 Kinase Inhibitors/ Angiogenesis Inhibitors/ Bcr-Abl (Bcr-Abl1) Kinase Inhibitors/ FGFR Inhibitors/ Fit3 (FLK2/STK1) Inhibitors/ KIT (C-KIT) Inhibitors/ Apoptosis Inducers/ PDGFR Family Inhibitors/ RET Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Organization</td>
<td>Mechanism of Action</td>
<td>Status</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Sunitinib malate</td>
<td>National Cancer Institute (NCI)</td>
<td>Angiogenesis Inhibitors/ CSFIR (c-FMS) Inhibitors/ Flt3 (FLK2/STK1) Inhibitors/ VEGFR-1 (Flt-1) Inhibitors/ KIT (C-KIT) Inhibitors/ VEGFR-2 (FLK-1/KDR) Inhibitors/ VEGFR-3 (FLT4) Inhibitors/ PDGFRbeta Inhibitors/ RET Inhibitors/ Signal Transduction Modulators/ Leucine-Rich Repeat Kinase 2 (LRRK2; Dardarin) Inhibitors</td>
<td>Phase II</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
<td>Mammalian Target of Rapamycin (mTOR; FRAP1) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Roche</td>
<td>Raf kinase B Inhibitors/ Signal Transduction Modulators</td>
<td>Phase II</td>
</tr>
<tr>
<td>yeast-CEA-6D</td>
<td>GlobeImmune</td>
<td></td>
<td>Phase II</td>
</tr>
<tr>
<td>68Ga-IMP-288</td>
<td>Universite de Nantes</td>
<td></td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Cediranib</td>
<td>National Cancer Institute (NCI)</td>
<td>Angiogenesis Inhibitors/ VEGFR-1 (Flt-1) Inhibitors/ VEGFR-2 (FLK-1/KDR) Inhibitors/ VEGFR-3 (FLT4) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Crolibulin</td>
<td>National Cancer Institute (NCI)</td>
<td>Antimitotic Drugs/ Caspase Activators/ Apoptosis Inducers/ Signal Transduction Modulators/ Vascular Disrupting Agents (VDA)/ Microtubule Inhibitors</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>TF-2</td>
<td>Immunomedics</td>
<td>Anti-CEACAM5 (CD66e)</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Lapatinib ditosylate</td>
<td>National Cancer Institute (NCI)</td>
<td>EGFR (HER1; erbB1) Inhibitors/ HER2 (erbB2) Inhibitors/ Signal Transduction Modulators</td>
<td>Phase I</td>
</tr>
<tr>
<td>Trametinib dimethyl sulfoxide</td>
<td>GlaxoSmithKline</td>
<td>MEK1 Inhibitors/ MEK2 Inhibitors/ Signal Transduction Modulators</td>
<td>Phase I</td>
</tr>
<tr>
<td>177Lu-PP-F11N</td>
<td>Universitaetsspitals Basel (USB)</td>
<td>CCK2 (CCKB/Gastrin) Receptor Ligands/ Signal Transduction Modulators</td>
<td>Preclinical</td>
</tr>
<tr>
<td>CP-4033</td>
<td>Translational Therapeutics</td>
<td></td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
TARGETS FOR THERAPEUTIC INTERVENTION

For an overview of validated therapeutic targets for this indication, consult Figure 7. The targetscape shows an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of the condition and their biological actions. An arrow indicates a positive effect; a dash indicates a negative effect. Gray or lighter symbols are targets that are not validated. For in-depth information on a specific target or mechanism of action, see the corresponding section in this report.

Fig 7. Thyroid cancer targetscape.
RELAT**E**D WEBSITES

American Cancer Society
http://www.cancer.org

American Thyroid Association (ATA)
http://www.thyroid.org/index.html

Endocrine Society
http://www.endocrine.org/

European Thyroid Association (ETA)
http://www.eurothyroid.com/index.html

Japan Thyroid Association
http://www.japanthyroid.jp/en/

National Cancer Institute
http://www.cancer.gov

Thyroid Foundation of Canada
http://www.thyroid.ca

SELECTED ONLINE PUBLICATIONS

Cancer facts & figures 2015 (American Cancer Society, 2015)

Thyroid cancer treatment (PDQ(R))
http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional

THYROID CANCER TREATMENT GUIDELINES


ACR appropriateness criteria®: Thyroid carcinoma (American College of Radiology, June 2014) http://www.oraloncology.com/article/S1368-8375(13)00772-0/pdf

2012 European Thyroid Association guidelines for metastatic medullary thyroid cancer (European Thyroid Association, 2012) http://www.karger.com/Article/FullText/336977


Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (European Society for Medical Oncology, 2012) http://annonc.oxfordjournals.org/content/23/suppl_7/vii110.full.pdf+html


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Jung, C.K.; Little, M.P.; Lubin, J.H.; Brenner, A.V.; Wells, S.A., Jr; Sigurdson, A.J.; Nikiforov, Y.E. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. J Clin Endocrinol Metab 2014, 99(2): E276.


Li, N.; Du, X.L.; Reitzel, L.R.; Xu, L.; Sturgis, E.M. Impact of enhanced detection on the increase in thyroid cancer incidence in the United States: Review of incidence trends by socioeconomic status
within the surveillance, epidemiology, and end results registry, 1980-2008. Thyroid 2013, 23(1): 103.


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• Identification of the current drug landscape, including tables of launched and development drugs
• An overview of the disease prevalence, etiology, diagnosis, prevention and treatments
• Multimedia and images depicting the current disease understanding and treatment processes
• On-going updates, with drug pipelines updated daily

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• 27 therapeutic areas

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