Targeted therapies and thyroid cancer: an update

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The treatment of metastatic, progressive thyroid cancer has evolved over recent years. New 'targeted' therapeutic approaches have been developed along with advances in the knowledge of thyroid carcinogenesis and the identification of tumor and endothelial targets. In recent years, results of targeted therapies have shown some benefit in refractory, progressive, differentiated, and medullary thyroid carcinomas but not, until recently, in undifferentiated thyroid carcinoma. We review here the different targeted therapies tested in thyroid cancers. ***Anti-Cancer Drugs*** **22:688–699 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The treatment of thyroid cancer has evolved significantly over recent years, especially in the setting of progressive advanced disease. New 'targeted' therapeutic approaches have been developed along with advances in the knowledge of thyroid carcinogenesis and the identification of tumor and endothelial targets. This overview will summarize the recent results of clinical trials and the new systemic strategies under investigation. We will focus on targeted therapies and their impact on the management of metastatic radioiodine-refractory differentiated thyroid carcinomas (DTCs), medullary thyroid carcinomas (MTCs), and undifferentiated or anaplastic thyroid carcinomas (ATCs).

The targets and signaling pathways (see Fig. 1)

Differentiated thyroid carcinomas

DTCs originate from the follicular epithelium. In the WHO classification, they are divided into different histological subtypes, with papillary and follicular carcinomas representing the vast majority of cases. Two other subtypes, Hürthle cell carcinoma and poorly differentiated carcinomas, are also important for identification because of their poorer prognosis. DTCs are the most common endocrine tumors; however, their frequency remains relatively low with 44 670 new cases in 2010 in the Unites States, as opposed to 207 090 new cases of breast cancer during the same period. As in other endocrine malignancies, surgery is the treatment of choice. Guidelines for patients with DTC have been published recently [1–4]. Total or near-total thyroidectomy is the preferred surgical procedure at the localized stage, whenever the diagnosis is made preoperatively and when the nodule is more than or equal to 1 cm. The indication for additional therapeutic lymph node dissection (in the central and lateral neck compartment) depends on initial clinical or ultrasound examination. Prophylactic (central or lateral) lymph node dissection is more controversial. When distant metastases are diagnosed synchronously, total thyroidectomy is mandatory before further radioiodine administration. Recently published guidelines recommend the use of postoperative radioiodine after total thyroidectomy, depending on the risk of persistent or recurrent disease, and separate the patients into three different risk groups [1]. Radioiodine treatment is considered the best method for destroying remnant normal thyroid cells and residual cancer cells. It is also recommended to detect locoregional or metastatic disease and to use serum thyroglobulin monitoring for patient follow-up [3,5]. The administration of ^{131}I requires thyroid stimulating hormone (TSH) stimulation to achieve sufficient ^{131}I uptake in normal and malignant thyroid cells. This stimulation is obtained by the withdrawal of L-thyroxine therapy or by recombinant TSH administration. Subsequent thyroxine treatment (L-thyroxine) restoring euthyroidism is also a way of preventing tumor progression or recurrence when administered at a suppressive level (TSH < 0.1 mUI/l).

With this three-step strategy (surgery, ^{131}I, and thyroxine-suppressive treatment), the overall prognosis of DTC is good with 90% 20-year survival [6]. Approximately 5% of the patients present distant metastases at diagnosis and less than 10% may develop these metastases metachronously [7]. The treatment of metastatic or recurrent disease is based on surgery, whenever feasible (especially in neck recurrences), and ^{131}I administration. Radioiodine treatment may be efficient in the case of distant metastases, especially in young patients with well-differentiated tumors and small lung metastases [8]. Remission

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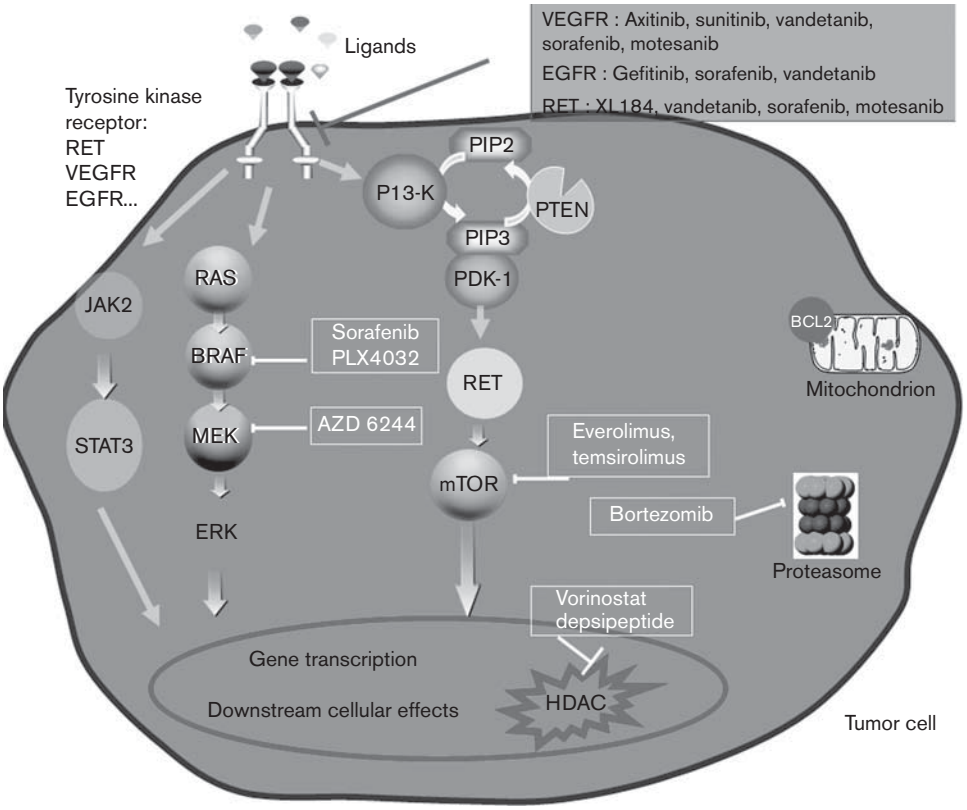
Fig. 1



The targets and signaling pathways. EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated protein kinase; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; PI3K, phosphatidyl-inositol-3 kinase; PTEN, phosphatase and tensin homolog; VEGFR, vascular endothelial growth factor receptor.

is then almost always obtained with less than 600 mCi cumulative dose. The management of bone metastases is more challenging, with sparse remissions after ^{131}I treatment and a frequent need for surgery, external beam therapy, and/or palliative treatments such as percutaneous cementoplasty, radiofrequency, or embolization. Biphosphonate administration should also be discussed [9].

Even if the vast majority of metastatic patients derive a benefit from ^{131}I, the treatment is not efficient in all cases. Indeed, approximately 10% of patients may experience disease progression despite well-conducted initial treatment, as a consequence of tumor dedifferentiation and consecutive loss of radioiodine uptake [10]. This situation may be shown by an elevated serum thyroglobulin concentration without evidence of disease on ^{131}I whole-body scan, by clinical evidence of disease progression or by signs of progressive disease despite persistent radioiodine uptake. In these cases, ^{18}FDG positron emission tomography (^{18}FDG-PET) is required, and often completed by a computed tomographic scan of the neck and chest and bone MRI (total spine, pelvis, and femurs). ^{18}FDG-PET has the double advantage of being a highly sensitive staging method and having prognostic significance. Indeed, ^{131}I and ^{18}FDG uptake are often inversely correlated, with a positive ^{18}FDG uptake indicating a likelihood of radioiodine resistance. For patients whose disease progresses despite ^{131}I therapy, therapeutic options are limited and prognosis is poor, decreasing to less than 15% survival at 10 years [8]. Surgery or radiofrequency ablation must be considered first, especially in patients with few lung lesions or bone metastases. External beam therapy is the next option, depending on the site of the metastatic lesion. Once surgery, radioiodine therapy, and irradiation have been ruled out, systemic therapies may be envisaged. Historically, chemotherapy is known to be insufficient for the treatment of DTCs, probably because of slow tumor growth and evolution, a spontaneous survival of several months (even after radioiodine refractoriness), and frequent overexpression of multidrug resistance transporters [11]. However, the evidence supporting this assertion derives from small, sometimes nonrandomized studies, not based on current tumor response evaluation criteria (Response Evaluation Criteria in Solid Tumors or RECIST), possibly leading to inadequate evaluation of treatment efficacy [3,12].

Furthermore, better management of adverse effects of chemotherapy with new antiemetic agents such as 5-hydroxytryptamine type 3 receptor or hematopoietic growth factors would probably have reduced toxicity. Some cytotoxic agents such as doxorubicin, taxanes, and probably also other drugs (pemetrexed, for instance) may have a role to play, especially in the case of symptomatic progressive disease, but their place in DTC management is currently not well established and must be discussed with a multidisciplinary team [12]. Targeted therapies have been available in DTC for several years and the number of presentations on the subject at the American Association of Clinical Oncology (ASCO) meeting has increased exponentially between 2004 and 2010. But none of these treatments has yet been approved in DTC and clinicians continue to enroll patients in clinical trials. The agents used so far in thyroid cancer are small molecules sharing the property to inhibit various tyrosine kinase receptors such as vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), rearranged during transfection (RET), or c-Met. In addition, some of them inhibit other kinases of the MAP kinase pathway. They are administered orally, with generally tolerable side effects. The results obtained in metastatic or locally advanced refractory DTC are currently available, showing the efficacy of these therapies in this indication.

Sorafenib (BAY 43-9006, Nexavar) is the drug whose development is most advanced in DTC. This inhibitor of BRAF, VEGFR-2 3, RET, and platelet-derived growth factor receptor-β (PDGFR-β) is currently being tested in a phase III double-blind, randomized, placebo-controlled trial (DECISION trial). The first report of its activity in DTC tested in a phase I trial was presented at the 2004 ASCO meeting [13]. Three phase II studies have now been published. The first one, published in the *Journal of Clinical Oncology* by Gupta-Abramson *et al.* and updated by M. Brose at the 2009 ASCO meeting [14,15], included 55 patients with progressive thyroid cancer including 52 nonmedullary carcinomas (papillary 26, follicular/Hürthle 19, and poorly differentiated/anaplastic 3/4). The patients were treated with standard doses of sorafenib (400 mg orally, twice a day). Fifty patients were evaluable for response at the time of analysis. Eighteen patients (36%) achieved partial response (PR) according to RECIST criteria. Twenty-three patients (46%) had stable disease (SD) as best response, with a clinical benefit (PR + SD) being achieved in 82% of the cases. All patients with DTC experienced a tumor reduction but this reduction was significant for only 18 patients who reached the 30% threshold defining PR according to the RECIST criteria. The patients with anaplastic or poor DTCs progressed. The median progression-free survival (mPFS) was 21 months. Adverse events were manageable but common and six patients (20%) had to discontinue therapy because of toxicity. Furthermore, dose reductions were frequent (47% of the treated population). The most common toxicities were palmar–plantar erythema, diarrhea, rash, fatigue, stomatitis/mucositis, weight loss, and musculoskeletal pain. Hypertension requiring treatment with more than one drug (grade 3) was seen in 13% of patients. An ancillary study has investigated the role of BRAF mutations in sorafenib efficacy. Preliminary results did not show a significantly longer PFS in patients with $BRAF^{V600E}$ than in those with $BRAF^{wt}$ tumors [14]. A second phase II study of sorafenib in advanced iodine-refractory DTC was published by Kloos *et al.* [16] in 2009. Among the 41 patients with advanced DTC treated in this study, six patients (15%) presented a PR and 23 patients (56%) had an SD for more than 6 months. The median duration of PR was 7.5 months (range 6–14) and the mPFS was 15 months [95% confidence interval (CI), 10–27.5]. Fifteen patients with non-DTC histology (follicular, Hurtle cell, and anaplastic carcinomas) were also included but no responses were observed in these tumor types. As seen in an earlier study, the most common grade 3 toxic effects were hand–foot skin reactions, musculoskeletal pain, and fatigue, and 52% of the patients needed dose reductions because of side effects [16]. A third study conducted in 31 patients with progressive metastatic radioiodine-refractory DTC investigated the impact of sorafenib on radioiodine uptake and tumor progression [17]. In this study, 19 patients (59%) had a clinical benefit, with eight patients having PR (25%) and 11 patients had SD (34%). No reinduction of radioiodine uptake was seen. Patients with bone metastases responded less favorably with only 9% PR and 13% SD (22% clinical benefit).

Motesanib diphosphate (AMG 706) is a small-molecule multikinase inhibitor that inhibits VEGFR 1–3, PDGFR-β, RET, and KIT. The results of a phase II trial in DTC were published in *The New England Journal of Medicine* in 2008 by Sherman *et al.* [18]. In this study, 93 progressive, radioiodine-resistant DTC patients were treated with AMG706 at 125 mg orally once daily. Only patients with a disease progression in the last 6 months were eligible for inclusion in the study. Thirteen patients achieved an objective response (14%, 95% CI: 7.7–22.7) and 67% had SD [longer than 6 months in 33 (35%) patients] leading to an 81% clinical benefit rate. The median duration of response was 8 months. The mPFS was estimated to be 40 weeks (95% CI: 32–50). No association between histological subtype, presence of $BRAF^{V600E}$ mutations, and clinical outcome or response rate was seen. The main adverse events were diarrhea, hypertension, fatigue, and weight loss, and 12 patients (13%) had to discontinue treatment because of toxicity. In this study, an exploratory analysis investigated circulating biomarkers of angiogenesis or apoptosis. An increase of serum PlGF after 1 week of treatment was shown to be correlated with PR. Similarly, an increase of caspase 3/7 activity and a decrease of sVEGFR2 (by 1.6 fold) distinguished responders from nonresponders.

Solely low-baseline VEGF plasma levels (< 671 pg/ml) were associated with better prognosis but not with a better response rate for motesanib treatment [19].

Sunitinib (SU011248, Sutent) is another orally available tyrosine kinase inhibitor (TKI) that preferentially targets VEGFR2, KIT, PDGFR-β, Fms-related tyrosine kinase (FLT-3), and also RET, fibroblast growth factor receptor 1 (FGFR-1), and the macrophage colony-stimulating factor receptor (MCSFR). Three phase II studies were reported at the 2008 ASCO meeting. All have shown interesting preliminary results [20–22]. Recently, Carr *et al.* reported the results of a phase II study in 28 patients with FDG-PET-positive, radioiodine-refractory DTC and seven metastatic MTC patients treated with sunitinib on a continuous schedule, at a 37.5 mg of daily dose. Eight of the 28 DTC patients achieved an objective response (28%) and one patient achieved a complete response. A total of 22 patients experienced disease control (78%). The median time to disease progression was 12.8 months and the median survival has not been reached after a median follow-up of 15.5 months (1–25.5). The main toxicities were fatigue, diarrhea, hand–foot syndrome, and neutropenia. Twenty-one of the 35 patients required sunitinib dose reductions to 25 mg daily and four patients discontinued treatment because of toxicity. Three patients developed bleeding problems, causing death in one patient. An exploratory analysis with FDG-PET was realized at baseline and after 7 days of sunitinib. The median average standard uptake value (SUV) and the SUV max (most avid lesion) were recorded. At baseline, the median average SUV was 7.9 (3.3–59.6) and the SUV max was 13 (3.8–67). Correlations between FDG-PET changes and the response rate by RECIST criteria showed that patients with response and SD had a significant decline in average SUVs compared with patients with progressive disease ($P = 0.02$ and 0.01). No significant correlation was found with time to progression or between thyroglobulin level decrease and objective response rate or clinical benefit [23].

Axitinib (AG-013736), another inhibitor of VEGR (1–3), also targets KIT and PDGFR-β. On the basis of encouraging phase I data, the drug has been tested in thyroid cancer in a phase II study, published in 2008 [24]. In a total of 60 patients who were enrolled, 45 had papillary or follicular thyroid carcinomas. No disease progression was required at randomization. The patients were pretreated with chemotherapy (15%), investigational therapy (8%), or others (16.6%). Fourteen PRs were seen in DTC patients (31%) and SD was observed in 19 patients (42%). The median PFS was 18.1 months (95% CI, 12.1, not estimable) but could hardly translate into a clinical benefit, as progression was not required at study entry. Hypertension was the most common grade (≥ 3) event but, as with other TKIs, fatigue, diarrhea, and nausea were common. Eight patients (13%) discontinued treatment because of toxicity.

Vandetanib (ZD6474, Zactima) is another orally available small-molecule inhibitor that targets VEGFR2-3, RET, and EGFR. On account of encouraging results in MTC and based on the knowledge of a RET activation in DTC, a randomized phase II study was initiated in 2007 in DTC. The first results were presented at the International Thyroid Cancer meeting in Paris in September 2010. Leboulleux *et al.* compared 145 patients treated with vandetanib (300 mg/day) versus placebo. Inclusion criteria were typically measurable, locally advanced or metastatic papillary or follicular thyroid carcinoma with progressive disease after radioiodine or patient unsuitable for radioiodine after surgery. PFS was significantly increased in the vandetanib arm (11.0 vs. 5.1 months) with a hazard ratio of 0.63 (95% CI: 0.43–0.92, two-sided $P = 0.017$). The objective response rate was 8.3% in the vandetanib arm and the disease control rate at 24 weeks was 56.9 versus 42.5% in the placebo arm ($P = 0.082$). Survival data were immature at the time of presentation. The most frequent adverse events were diarrhea (74%), hypertension (17%), rash (23%), and QTc prolongation (23%). Dose reductions were made in 22 (vandetanib) and 3% (placebo) of the patients and vandetanib was discontinued because of an adverse event in 33% [25].

Pazopanib (Votrient), a new oral antiangiogenesis inhibitor targeting VEGFR, PDGFR, C-kit, and RET, was recently approved for the treatment of metastatic renal cancer. First presented at the 2009 ASCO meeting, the results of a phase II study of 39 patients with metastatic, rapidly progressive (within 6 months before randomization) radioiodine-refractory DTC were published in *Lancet Oncology* in 2010 by KC Bible. Each patient received pazopanib at the dose of 800 mg daily, on a continuous schedule. Eighteen of the 37 assessable patients had confirmed PR. The mPFS at 1 year was 47% (35–68%), and the median duration of PFS was 11.7 months (range, 1– $\geq$ 23). This study yielded two attractive results: first, maximum pazopanib concentration in plasma is correlated with response and, second, the follicular subtype may be more responsive to pazopanib than papillary thyroid cancer. The main toxicities were fatigue (78%), skin and hair depigmentation (76%), diarrhea (73%), and nausea (73%). Sixteen of the 39 patients required pazopanib dose reductions to 600 or 400 mg daily and two patients discontinued treatment because of serious bleeding events. Two patients died during the study [26].

Other phase II studies with targeted therapies have been published in DTC patients. They will be only briefly reviewed because of disappointing results. Gefitinib (ZD1839, Iressa), a selective inhibitor of the EGFR tyrosine kinase domain has been tested in DTC because of the known overexpression of EGFR in normal and malignant thyroid tissues. An open-label phase II study in 27 patients with several thyroid tumor types, including papillary (41%), follicular (22%), anaplastic (19%), medullary (15%), and Hürthle cell carcinomas (4%), was

published in 2008. The patients were treated with gefitinib (250 mg/day). No PRs were seen according to RECIST criteria in the 25 assessable patients. Only 12% of the patients had SD at 12 months. The mPFS was 3.7 months and the median overall survival was 17.5 months, but as disease progression was not required at randomization, these results are questionable [27]. Thalidomide has been tested in a phase II clinical trial in 36 patients, including 29 patients with iodine-refractory progressive thyroid carcinomas. Of 28 patients assessable for tumor response, 18% achieved a PR, and 32% had SD, leading to disease control in 50% of the patients. But dose reductions were necessary in the majority of cases because of adverse events (e.g. neurological toxicity with fatigue and somnolence in 69% of patients and peripheral neuropathy in 53%) [28]. Lenalidomide (Revlimid), a recently developed immunomodulatory drug sharing the antiangiogenic and antitumor properties of thalidomide, has been evaluated in thyroid cancers. It seems to have a better toxicity profile than thalidomide and has shown promising results in a phase II study (22.5% PR and 44.5% SD) [29]. Rosiglitazone (Avandia), a peroxisome proliferator-activated receptor-γ(PPAR-γ) agonist, has been tested in a phase II trial to evaluate its ability to induce radioiodine uptake in radioiodine-refractory DTC. The PAX8/PPAR-γ rearrangements observed in FTC result in the loss of the tumor suppressor function of PPAR-γ. The rationale was to use an agonist of PPAR-γ in an attempt to restore the activity of the wild-type receptor. Twenty patients were treated with rosiglitazone. The patients were supposed not to have progressive disease before study entry; the second noteworthy point is the absence of precise information on initial disease evaluation (presence of target lesions by RECIST criteria). Results were disappointing with only short-term (8 weeks) radioiodine reinduction in five of 20 patients and no RECIST response. The expression level of PPAR-γ was studied for the first 10 patients but was not found correlated to radioiodine uptake after therapy [30].

Phase I studies in differentiated thyroid carcinomas

Vascular endothelial growth factor receptor inhibitor

E7080, a multikinase inhibitor, has shown potent inhibitory activity against several tyrosine kinase receptors including VEGFR1-3, PDGFR-β, and fibroblast growth factor receptor 1. A phase I study, has shown some antitumor activity in thyroid cancer [31]. The results of a recently completed phase II study in radioiodine-refractory DTC are pending.

BRAF inhibitors

PLX4032 is a TKI that selectively inhibits the V600E BRAF mutation. Preliminary results from a phase I study in metastatic malignant melanomas and DTC presented at the 2009 ASCO meeting have shown PRs and stabilization of disease in PTC patients [32].

XL281, a multiple Raf kinase inhibitor including wild-type (c-Raf, B-Raf) and activated mutant B-RafV600E, is also currently being tested in a phase I study in DTC. Preliminary results have shown some disease stabilizations in ^{131}I-refractory PTC tumors harboring BRAF V600E mutations [33].

As observed earlier with sorafenib, it is important to note that treatment with BRAF inhibitors can be complicated by the occurrence of skin lesions, including cutaneous keratoacanthomas and rarely squamous cell carcinomas, in approximately 20% of the treated patients [34].

Mitogen-activated protein kinase/extracellular signal-regulated kinase inhibitors

As mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK) is involved in the mitogen-activated protein kinase signaling cascade, immediately downstream of BRAF, it is a promising target for the ras–raf–MEK–ERK pathway inhibition. Furthermore, some preclinical data suggest that BRAF mutant tumors (in contrast to ras mutant tumors) would be particularly dependent on MEK activity, offering a therapeutic rationale for MEK inhibition in the subset of PTC with this mutation [35]. Several MEK inhibitors (AZD6244, PD0325901) have been tested in preclinical or phase I studies in DTC [36], but no mature results are yet available. At the 2010 ASCO meeting, the first results of a phase II study with AZD6244 (100 mg twice daily) in 39 patients with progressive radioiodine-refractory DTC were presented. The most common drug-related adverse events included rash (69%), fatigue (49%), diarrhea (49%), and peripheral edema (36%). Results in the 32 evaluable patients were one with a PR (3%), 21 with an SD(66%), and 10 with progressive disease (31%). Confirmation of these results is needed [37].

c-Mesenchymal–epithelial transition inhibitors

The tyrosine kinase receptor, mesenchymal–epithelial transition factor (MET), activated by its ligand, hepatocyte growth factor, induces migration and resistance to apoptosis or proliferation in many cellular types (epithelial, endothelial, or hematopoietic cells, neurons, hepatocytes). This oncogene, which is abnormally activated in many tumors (including thyroid carcinomas), initiates tumor growth and angiogenesis, and is known as an important prometastatic factor. MET has become an essential target in oncology and several strategies to counteract its activity have been developed. Among them is Foretinib (XL880), an orally bioavailable small-molecule inhibitor of MET, VEGF receptor (VEGFR2), Tie-2, PDGF, and Kit. The results of a phase I study in 40 patients (three thyroid cancers) have shown an interesting activity against medullary thyroid cancer. Dose-limiting toxicities were hypertension, fatigue, diarrhea, vomiting, proteinuria, and hematuria [38].

Histone deacetylase inhibitors

Histone deacetylase inhibitors act by direct inhibition of histone deacetylase (HDAC) enzymes, which regulate the acetylation status of histones. HDAC inhibitors have a large spectrum of antitumor effects. They induce alterations in gene expression, cell differentiation, cell cycle arrest and apoptosis, and antiangiogenic effects and depletion of several heat-shock protein 90-dependent oncoproteins. In thyroid cancer cell lines, HDAC inhibitors have been reported to enhance iodide uptake [39]. Several HDAC inhibitors have been tested in phase I or II studies including patients with DTC [40]. Vorinostat (Zolinza), already approved for the treatment of refractory cutaneous T-cell lymphoma, has been tested in 19 patients with thyroid cancer but no response has been observed [41]. Romidespin (formerly called depsipeptide or FK228) is another HDAC inhibitor evaluated in a phase II study for the treatment of DTC and ATC with the aim to re-sensitize dedifferentiated tumors to radioiodine therapy. Panobinostat (LBH589) is currently under investigation in metastatic medullary or differentiated thyroid cancers.

Mammalian target of rapamycin inhibitors

Among the signaling pathways involved in cancer progression, the phosphatidyl-inositol-3 kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway seems to play a central role by promoting both survival and proliferation. The inhibition of effectors of this pathway seems to be an interesting treatment strategy. The mTOR kinase is a key player acting downstream of PI3K activation. It has a major role in cell metabolism and control of mRNA translation. Recent data suggest that aberrant activations of the PIK3/AKT pathway and mTOR are involved in the development of thyroid cancer, particularly of anaplastic and follicular subtypes. A preclinical study with RAD001 (everolimus, certican) has shown interesting preclinical activity in two differentiated thyroid cancer cell lines [42]. It has been speculated that the combination of drugs targeting different signaling pathways would help increase response to treatment and prevent the development of resistance. A phase I study presented at the 2010 ASCO meeting has reported the first results of a combination therapy with sunitinib and bortezomib in seven patients with thyroid carcinomas (two medullary, three papillary, and two Hürthle carcinomas). This combination has been well tolerated (no dose-limiting toxicity) and has induced some tumor responses (2/6 PRs and 4/6 stabilizations of disease). A phase II trial of everolimus and sorafenib is ongoing in 35 patients with DTC who have progressed on sorafenib alone [43]. Finally, dual inhibition of MEK and mTOR has induced an apparently synergistic cytostatic effect both in-vitro and in xenograft tumors [3].

Off-label use of tyrosine kinase inhibitor

The M.D. Anderson experience of 'off-label' use of sorafenib or sunitinib in progressive metastatic DTC was published in 2009 [44,45]. The patients treated were not able or willing to participate in clinical trials. The results were similar to those of published phase II trials, with typical disease stabilizations in most patients (60%) and PRs in 20% patients, particularly in patients with lung metastases. Some interesting information could be derived from this 'close-to-life' study. First, it confirmed that there is no cross-resistance between TKI in DTC, and second that patients may have differential responses to TKI, especially patients with bone metastases, which could be more refractory to treatment, as suggested earlier by Hoftijzer [17].

Currently active trials in differentiated thyroid carcinomas (Table 1)

Conclusion for differentiated thyroid carcinomas

Until recently, treatment options for progressive radioiodine-refractory DTC patients were sparse. As of 2010, no targeted therapy has been validated for routine use but several drugs have shown promising results. However, we must not forget that improvement of overall survival and quality of life are the ultimate goal of these drugs and that patients still have to be enrolled in phase III trials. Furthermore, the introduction of molecular targeted therapies in radioiodine-refractory thyroid carcinomas has suggested a potential benefit of systemic therapy in these patients and has increased the number of patients with TC in phase I trials [46]. It will probably open the path for the development of new drugs and combinations.

Medullary thyroid carcinoma

MTC, a neuroendocrine carcinoma developed from the parafollicular C cells of the thyroid, accounts for 5–10% of all thyroid cancers. Its incidence is between one and five cases per million of population per year. In 60–70% of the cases, the disease is sporadic. In the other 30–40%, it occurs in patients with multiple endocrine neoplasia type 2 (MEN 2), an inherited autosomal dominant disease with an estimated prevalence of 0.2%. MTC is consistently present in all three forms of MEN2. The most common form is MEN 2A (Sipple's syndrome), which associates MTC to pheochromocytoma in 50% of cases and to primary hyperparathyroidism in 15–30% of the cases. MEN 2B (Gorlin's syndrome) is rare and is characterized by an aggressive course of MTC, a marfanoid habitus with neuromas of the tongue and lips and the absence of hyperparathyroidism. Familial MTC (FMTC) is a form of MEN2 including MTC without pheochromocytoma or hyperparathyroidism. The causal genetic defect in hereditary MTC is a germ-line mutation of the proto-oncogene RET (rearranged during transfection; 10q11.2), found in 98% of MEN 2A, 99% of MEN 2B and 95% of the FMTC cases. RET is a 60 kb oncogene consisting of 21 exons that encodes a tyrosine kinase receptor and is involved in the tumorigenesis of MTC. Germ line mutations of codon 634 (exon 11), particularly C634R, are the mutations most frequently found in

Table 1 Differentiated thyroid carcinoma and ongoing clinical trials (14 October 2010)

Drug	No NCT	Phase trial	Medical situation	Primary endpoint Principal investigator
Sorafenib vs. placebo	NCT00984282	Phase III	Progressive radioiodine-refractory DTC	**Progression-free survival** Bayer
Sunitinib + ^{131}I	NCT00668811	Phase II	Recurrent or progressive DTC disease after ^{131}I	**Clinical benefit rate** Kenneth D. Burman, Washington, USA
Bortezomib	NCT00104871	Phase II	Progressive radioiodine-refractory DTC	**Response rate** S. I. Sherman, M.D. Anderson, Houston, USA
Pazopanib	NCT00625846	Phase II	Progressive radioiodine-refractory DTC, MTC, or ATC	**Response rate** Keith C. Bible, Mayo Clinic, Rochester, Minnesota, USA
Temsirolimus + sorafenib	NCT01025453	Phase II	Progressive radioiodine-refractory DTC	**Response rate** Eric Sherman, MSKCC, New York, USA
LBH589 (histone deacetylase)	NCT01013597	Phase II	Progressive radioiodine-refractory DTC	**Response rate** Anne Traynor, University of Wisconsin, Madison, USA
Aflibercept	NCT00729157	Phase II	Recurrent and/or metastatic, radioactive iodine-refractory, DTC	**Response rate** David G. Pfister, MSKCC, New York, USA
AZD6244 (MEK inhibitor)	NCT00970359	Phase II	Progressive radioiodine-refractory DTC	**RAI uptake** Alan Ho, MSKCC, New York, USA
RAD001	NCT00936858	Phase II	Progressive radioiodine-refractory DTC, MTC, and ATC	**Progression-free survival** Jochen Lorch, Dana-Farber Cancer Inst., Boston, USA
Everolimus + sorafenib	NCT01141309	Phase II	Progressive radioiodine-refractory DTC	**Response rate** Eric Sherman, MSKCC, New York, USA
Everolimus	NCT01164176	Phase II	Radioiodine-refractory DTC	**Response rate** Byung Chul Cho, Yonsei University, Seoul, Korea
Everolimus	NCT01118065	Phase II	Unresectable recurrent or metastatic DTC, ATC, and MTC	**Response rate** E. Kapiteijn, Leiden University Medical Center, Leiden, Netherlands
Cediranib ± lenalidomide	NCT01208051	Phase I/II	Progressive radioiodine-refractory DTC	**Maximum-tolerated dose and response rate** Rebecca Brown, Chicago, USA
XL 281	NCT00451880	Phase I	Solid tumors including thyroid cancers	**Safety, tolerability, and maximum tolerated dose** Kanya Rajangam, Exelixis, San Francisco, USA

The primary endpoints are given in bold type.
ATC, anaplastic thyroid carcinoma; DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma; NCT, clinical trials.gov registry number.

MEN 2A (90% of cases). Other mutations generally affect codons 618, 611, and 609 in exon 10. Most MEN 2B patients carry a mutation in codon 918 in the intracellular tyrosine kinase domain of RET (M918T). In FMTC, mutations are distributed along the cysteine-rich region of RET. In sporadic MTC, somatic mutations of RET are acquired during tumorigenesis in approximately 50% of cases, mainly in the tyrosine kinase domain (codons 918 + + +, 804, and 768). The presence of a somatic RET mutation in codon 918 may have prognostic significance as it is associated with a high rate of metastasis and risk of death [47]. The search for somatic mutations of RET in tumor tissues of sporadic MTC is not currently recommended.

Complete surgical excision is the only curative treatment for MTCs. The intervention must include not only total thyroidectomy but also bilateral dissection of the central and lateral compartments of the neck. Successful surgery is reflected by an undetectable serum calcitonin level in the postoperative setting. Persistently elevated calcitonin levels after surgery predict clinical recurrence, though at unpredictable times. Synchronous distant metastases may be discovered in 7–23% of cases [48]. However, persistent or recurrent disease is not necessarily synonymous with poor short-term prognosis. As in other neuroendocrine malignancies, the pace of disease evolution is heterogeneous across patients. In patients with metastatic disease, treatment focuses on the relief of symptoms and especially on the control of diarrhea. Surgery, radio-frequency ablation and external beam therapy may sometimes be considered, especially in the case of neck recurrence or symptomatic bone lesions. When the metastatic lesions progress diffusely and rapidly (< 12 months), systemic treatment is discussed. As for DTC, publications regarding the use of chemotherapy are rare, with discouraging results. Indeed, analysis of the results would be improved by the use of standardized response criteria (RECIST), a higher number of treated patients and knowledge of the disease progression status. Furthermore, results are disappointing with 15–20% responses and 50% stabilizations, whatever the drug used. The

largest number of patients in the literature has been treated with 'neuroendocrine' polychemotherapy schedules based on 5-fluorouracil, DTC ± streptozotocin [49,50]. The use of doxorubicin with or without cisplatin does not seem to increase the response rate but seems more toxic. No experience with recent cytotoxic drugs such as taxanes, gemcitabine, oxaliplatin, or irinotecan has been reported. Targeted therapies have emerged and have shown impressive results. The agents used so far in MTC are, as in DTC, small molecules that inhibit several targets including VEGFR, kinases of the MAP kinase pathway, RET, c-Met, etc. The results obtained with these targeted agents are described later.

Vandetanib (ZD6474, Zactima) is the most advanced drug in MTC. It was first studied in hereditary MTC and a phase II study was presented in the *Journal of Clinical Oncology* in 2010. Wells *et al.* have treated 30 patients with hereditary MTC and RET germline mutation with vandetanib (300 mg) once daily. Their results have shown a 20% response rate and 53% SD at more than or equal to 24 weeks, yielding a disease control rate of 73%. The median duration of vandetanib treatment was 18.8 months (range, 0.6–38.4). Adverse events were mainly rash, diarrhea, fatigue, and nausea. Twenty-three percent of the patients discontinued vandetanib because of adverse events [51]. Another phase II trial with vandetanib (100 mg daily) in 19 patients with unresectable, measurable, locally advanced or metastatic hereditary MTC has recently been reported [52], with a PR rate of 16% (95% CI: 3.4–39.6). SD lasting 24 weeks or longer has been reported in 10 patients (53%), leading to a disease control rate of 68% (95% CI: 43.4–87.4). The results of a large international phase III trial of vandetanib (300 mg/day) versus placebo in 331 patients with progressive metastatic MTC have shown a 54% reduction in the rate of progression with the study drug compared with placebo (hazard ratio = 0.46, $P = 0.0001$) with a median PFS of 19.3 months for patients randomly assigned to placebo and not reached for patients receiving vandetanib. The objective response rate, a secondary endpoint of the study, was 45 versus 13% across the two groups ($P < 0.0001$) [53]. Since September 2010, the US Food and Drug Administration and the European Medicines Agency have accepted regulatory submissions for review of vandetanib in the treatment of patients with advanced MTC.

Sunitinib (SU011248, Sutent)

The activity of sunitinib in MTC has been reported in a phase II study published recently by Carr *et al.* [23]. In this study, seven of 35 patients had recurrent or metastatic MTC with increased metabolic activity on FDG-PET, but disease was not necessarily progressive according to the RECIST criteria. They were treated with sunitinib on a continuous schedule, at 37.5 mg daily dose, with a median follow-up of 15.5 months. Three of six evaluable patients achieved a PR. Two other patients presented a SD. The most common adverse events were fatigue, diarrhea, hand–foot syndrome, neutropenia, and hypertension. The preliminary results of two other phase II studies were reported at the 2008 annual ASCO meeting by Ravaud *et al.* and Cohen *et al.* Responses and stabilizations were described in MTC. Final results are pending [20,22,54]. Two other ways of using sunitinib in patients with MTC could be the neoadjuvant treatment of bulky cervical tumors [55] and combination with capecitabine (Xeloda) [56].

Axitinib (AG-013736)

The phase II study of axitinib published in 2008 by Cohen *et al.* [24] included 11 cases of MTC (18%). Two PRs and three SDs at more than or equal to 16 weeks were observed. As progression was not required at inclusion, results are difficult to analyze.

Sorafenib (BAY 43-9006, Nexavar) was tested in 21 patients with advanced MTC (five hereditary and 16 sporadic MTC) at the standard dose of 400 mg twice daily [57]. Progressive disease was not required for inclusion. In this study, 15 patients with sporadic MTC presented a reduction in the size of target lesions but this reduction was higher than the 30% needed to achieve a PR by RECIST criteria in only one patient (duration of 20.7 months at data cutoff point), and 15 patients achieved SD. In the arm of hereditary MTC, which was closed prematurely because of poor accrual, one PR and four SD were observed. One toxic death was encountered because of bowel perforation.

Motesanib diphosphate (AMG 706) has also been evaluated in a phase II trial in 91 progressive or symptomatic MTC patients. The study has shown a low response rate (2%) but 43% of the patients had disease stabilization for more than 24 weeks. The high frequency of diarrhea (66% at study entry) may explain these disappointing results [58].

XL184, a multikinase inhibitor targeting RET, MET, VEGFR2, and KIT, has been tested in patients with MTC and is currently used in a randomized phase III trial (XL184 versus placebo). A phase I study including 34 patients with MTC showed 15 PRs (10 confirmed) and 18 disease stabilizations. In contrast to expectations, the presence of RET mutations and efficacy were not strictly related [59,60].

E7080 has also been tested in a phase II study and results are pending [31].

EGFR tyrosine kinase domain inhibitors (imatinib, gefitinib) have been tested in MTC but have failed to induce tumor responses in phase II trials [27,61].

Other interesting phase I studies in medullary thyroid carcinoma

An interesting combination of sorafenib and tipifarnib (Zarnestra; farnesyltransferase inhibitor) has been tested

in a phase I study of 50 patients; six of eight MTC patients achieved a clinical benefit with three PRs (lasting 14, 16 + , and 26 + months) and three prolongations of disease (lasting 12–16 months). Five of these responders had a sporadic RET mutation. The most common adverse events were rash (dose limiting toxicity), hyperglycemia, and diarrhea. A phase II trial in MTC is planned [62].

Foretinib (XL880), a multitargeted inhibitor of c-Met, is a small molecule that also inhibits VEGF receptor (VEGFR2), Tie-2, PDGF and kit. The results of a phase I study of 40 patients (three thyroid cancers) have shown an interesting activity against MTC. Dose-limiting toxicities were hypertension, fatigue, diarrhea, vomiting, proteinuria and hematuria [38].

Currently active trials in medullary thyroid carcinoma (Table 2)

Conclusion for medullary thyroid carcinoma

MTCs are rare and complex tumors as they can develop in a context of inherited disease (MEN2). For patients with progressive, locally advanced and/or metastatic disease who are not amenable to surgery, targeted therapies have emerged and seem promising with a special emphasis on those targeting VEGFR and RET. For the moment vandetanib is the most effective drug with proven superiority over placebo, but further trials with other drugs or combinations (including chemotherapy) are ongoing.

Undifferentiated or anaplastic thyroid carcinoma

Undifferentiated cancers of the thyroid are rare. They represent 1.6% of all thyroid cancers according to a study of 15 698 cases by the US Surveillance and Epidemiology and End Results cancer registry [63]. Even in 2010, the outcome is fatal in most cases. The treatment of patients with localized disease combines, whenever possible, complete surgery, radiotherapy, and chemotherapy. In the metastatic setting, few options are available and palliative care should be rapidly initiated [64]. These cancers commonly have multiple genetic abnormalities and are in particular characterized by the presence of p53 mutations (55–70%), mitogen-activated protein kinase pathway activation (RAS and BRAF mutations), β-catenin and PIK mutations [3,65]. Some new strategies or targeted therapies have been tested but the results have been often disappointing. Targeted agents directed against VEGF-R such as axitinib (AG-013736) or against BRAF and VEGF-R such as sorafenib (Nexavar) have been tested in phase II trials including patients with multiple thyroid histologies [15,16]. The number of enrolled patients was low (two and four patients, respectively). One response was produced with axitinib and one stabilization with sorafenib. Another phase II study with sorafenib has been specifically conducted in ATC [66]. The results of 15 evaluable patients were presented at the 2009 ASCO meeting and showed two PRs and four SDs. Median time to progression was 1.5 months and median survival 3.5 months (range 1–26). Gefitinib, an anti-EGFR TKI, has been tested in five patients with ATC, with one disease stabilization lasting for more than or equal to 12 months [27]. Other studies on ATC cell lines may suggest that the combination of gefitinib and imatinib, anti-KIT, and PDGFR inhibitor could potentiate their antitumor effects [67]. Similarly, dual inhibition of MEK inhibitor and mTOR inhibitor may have a synergistic cytostatic effect both *in vitro* and in xenograft tumors [3]. Vascular disrupting agents as

Table 2 Medullary thyroid carcinoma and ongoing clinical trials (14 October 2010)

Drug	No NCT	Phase trial	Medical situation	Primary endpoint Principal investigator
XL184	NCT00704730	Phase III	Unresectable, locally advanced, or metastatic MTC	**Progression-free survival** Exelixis
Everolimus	NCT01118065	Phase II	Unresectable recurrent or metastatic differentiated, ATC and MTC	**Response rate** Ellen Kapiteijn, Leiden University Medical Center, Leiden, Netherlands
Vandetanib (Zactima) + bortezomib (Velcade)	NCT00923247	Phase I–II	Solid tumors with a focus on hereditary or sporadic, locally advanced or metastatic MTC	**Response rate** National Institutes of Health Clinical Center, Bethesda, USA
LBH589 (histone deacetylase)	NCT01013597	Phase II	Progressive radioiodine-refractory DTC and metastatic MTC	**Response rate** Anne Traynor, University of Wisconsin, Madison, USA
Sorafenib	NCT00654238	Phase II	Metastatic thyroid cancer including MTC	**Objective response rate and stable disease** Marcia Brose, Philadelphia, USA
Pazopanib	NCT00625846	Phase II	Progressive radioiodine-refractory DTC, MTC, or ATC	**Response rate** Keith C. Bible, Mayo Clinic, Rochester, Minnesota, USA
Everolimus	NCT01164176	Phase II	Locally advanced or metastatic thyroid cancer	**Response rate** Byung Chul Cho, Yonsei Univ, Seoul, Korea

The primary endpoints are given in bold type.
ATC, anaplastic thyroid carcinoma; DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma; NCT, clinical trials.gov registry number.

Table 3 Anaplastic thyroid carcinoma and ongoing clinical trials (14 October 2010)

Drug	No NCT	Phase trial	Medical situation	Primary endpoint Principal investigator
Sorafenib	NCT00126568	Phase II	Histologically confirmed ATC not amenable to definitive curative surgery or radiotherapy, progressive after prior cytotoxic chemotherapy	**Objective disease response** Panayiotis Savvides, Cleveland, Ohio, USA
Sorafenib	NCT00654238	Phase II	Metastatic thyroid cancer including ATC	**Objective response rate and stable disease** Marcia Brose, Philadelphia, USA
Avastin + doxorubicin	NCT00804830	Phase II	Cytologically or histologically verified ATC treated by radiochemotherapy and operated with R0 or R1 surgery	**Overall survival** Jan Tennvall, Lund University Hospital, Sweden
Pemetrexed + paclitaxel	NCT00786552	Phase II	Recurrent/advanced follicular, papillary or ATC	**Response rate** Joerg T Hartmann, Kiel, Germany
Pazopanib	NCT00625846	Phase II	Progressive radioiodine-refractory DTC, MTC, or ATC	**Response rate** Keith C. Bible, Mayo Clinic, Rochester, Minnesota, USA
Everolimus	NCT01118065	Phase II	Unresectable recurrent or metastatic differentiated, undifferentiated (anaplastic) and medullary thyroid carcinoma	**Efficacy** Ellen Kapiteijn, Leiden University Medical Center, Leiden, The Netherlands
Everolimus	NCT01164176	Phase II	Locally advanced or metastatic thyroid cancer	**Response rate** Byung Chul Cho, Yonsei University, Seoul, Korea

The primary endpoints are given in bold type.
ATC, anaplastic thyroid carcinoma; DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma; NCT, clinical trials.gov registry number.

Zybrestat (fosbretabulin, combretastatin A4 phosphate) have been evaluated in ATC because of their antiangiogenic and cytotoxic activity. The promising results obtained in vitro foreshadowed the clinical efficacy of the drug [68]. Then, the first results of combretastatin A4 phosphate as monotherapy in a phase II study were disappointing with no objective response but some 'long' (> 3 months) SDs in approximately 30% of the patients, leading to its further development in combination with chemotherapy [69,70]. At last, at the 35th European Society of Medical Oncology meeting, the preliminary results of a phase II–III study of Zybrestat in combination with chemotherapy in ATC were presented. In this study, 80 patients (of the 180 planned) were randomized to receive Zybrestat (IV once a week) in combination with chemotherapy (paclitaxel–carboplatin every 3 weeks) versus chemotherapy alone. For the first time in ATC, the median overall survival time was increased by the association (5.1 vs. 4.1 months for patients receiving chemotherapy alone) with a hazard ratio of 0.71 (0.42–1.22), representing a 29% reduction in the risk of dying for patients receiving Zybrestat and chemotherapy. At 1 year, 23% of patients treated with Zybrestat were alive compared with 9% of patients treated with chemotherapy alone. Subgroups analysis showed that patients of less than 60 years, IVc stage diseases and with greater than 6 cm tumor sizes may benefit also from this new treatment association. Toxicity seems manageable with myelosuppression and hypertension [71].

Currently active trials in anaplastic thyroid carcinoma (Table 3)

Conclusion for anaplastic thyroid carcinoma

Although the treatment of DTC and MTC has dramatically improved with the development of targeted therapies, patients with ATC currently derive little benefit from these treatments. As ATCs are rare and heterogeneous at diagnosis, clinicians must continue to develop collaborative studies to maximize the understanding of the molecular mechanisms of this disease and to improve the clinical results. Recently, positive results of trials combining chemotherapies and targeted therapies are appearing and may offer some hope to patients with ATC.

General conclusion

Targeted therapies have been developed in thyroid carcinomas for at least 5 years. As in other cancer types, their results seem promising. However, these systemic treatments are currently only used for patients with progressive DTC and MTC, refractory to conventional treatments. Evidence of their efficacy is emerging in ATC but research efforts need to be continued. While writing this review, several questions came to our minds. First, the widely used notion of 'clinical benefit' may be somewhat exaggerated. It is defined as the sum of PRs and SDs and it reflects the 'nonprogression' of disease rather than a true therapeutic benefit for the patient. In clinical trials, clinical benefit is also based on the '6-month nonprogression rate' or on the widely accepted 'waterfall plot' presentation, which allows counting minor responses as true responses. But the implications of these minor responses are unknown. Actually, the true benefit/risk ratio of these drugs is not clear because quality-of-life studies are lacking in clinical trials and because no one knows whether '6-month nonprogression' is a good surrogate marker of overall survival. Results of phase III trials are awaited. The role of ^{18}FDG uptake on PET scan should probably be investigated more extensively, may be as for gastrointestinal stromal tumors. And the prognostic

value of oncological markers, thyroglobulin for DTC and calcitonin for MTC, could also be assessed, even if it is known that RET blockade may lead to direct inhibition of calcitonin gene expression, independently of tumor volume variation [72].

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