CLINICAL INVESTIGATION

Tyrosine kinase inhibitors in differentiated thyroid carcinoma: a review of the clinical evidence

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Differentiated thyroid carcinoma (DTC) is a highly prevalent endocrine malignancy. The majority of DTCs are slowly progressive and, when identified at an early stage, frequently cured with adequate surgical management and radioactive iodine-131 ablation therapy. Metastatic DTC that has become inoperable or refractory to radioactive iodine-131, however, is associated with a poor survival. Results of conventional treatment modalities have been disappointing and, therefore, new therapies are needed. As a result of the increasing knowledge of the biologic basis for thyroid cancer, therapeutic agents that target involved biologic abnormalities have been identified. Multiple clinical trials have been initiated and performed in the past years. In this article conventional and new treatment modalities in differentiated advanced thyroid cancer are described, with the focus on kinase inhibitors.

Keywords: differentiated thyroid carcinoma • kinase inhibitors • radioactive iodine • redifferentiation • RET–RAS–RAF cascade • sodium–iodide symporter

Hendrieke C Hoftijzer[1], Ellen Kapiteijn[2], Tatiana Schneider[2], Guido C Hovens[1], Hans Morreau[3], Hans Gelderblom[2] & Johannes WA Smit[†1]

[1]Department of Endocrinology & Metabolic Diseases, Leiden University Medical Centre, PO Box 9600, 2300 RC, Leiden, The Netherlands
[2]Department of Clinical Oncology, Leiden University Medical Centre, The Netherlands
[3]Department of Pathology, Leiden University Medical Centre, The Netherlands
[†]Author for correspondence:
Tel.: +31 715 263 082
Fax: +31 715 248 136
E-mail: j.w.a.smit@lumc.nl

Thyroid carcinoma is the most prevalent endocrine malignancy and accounts for 94% of endocrine cancers. However it still has a low incidence of 2–10/100,000 persons per year. The incidence has increased during the last few decades, and this trend appears to be continuing [1–3, 201].

Thyroid cancer is a heterogeneous disease that is classified into differentiated thyroid carcinoma (DTC), medullary thyroid carcinoma (MTC) and undifferentiated (anaplastic) thyroid carcinoma (ATC). Differentiated thyroid carcinoma is most common (95%) and includes papillary thyroid carcinoma (PTC, 80%) and subtype follicular variant of PTC, follicular thyroid carcinoma (FTC, 10–15%) and Hürthle cell carcinoma. The mean age at diagnosis is between 45 and 50 years old [4]. The overall 10-year survival rates are approximately 90–95% [5]. This is because of a combination of the favorable biological behavior of the tumor (i.e., indolent) and the availability of effective therapies consisting of near-total thyroidectomy followed by radioactive iodide-131 (RaI) ablative therapy.

In the pathogenesis of thyroid carcinoma, it is believed that the genetic alterations lead to both proliferation via multiple pathways, and the loss of thyroid-specific proteins. The disappearance of the functional expression of thyroid-specific proteins is a complex chain of events, in which the mechanism is incompletely understood. Angiogenesis in the original tumor plays an essential role in the facilitation of distant metastasis. Once distant metastases have occurred, the prognosis of DTC becomes worse. Metastases are more prone for dedifferentiation of thyroid cancer cells. The subsequent loss of the ability to accumulate RaI leads to unresponsiveness to the only curative treatment option. Metastases are not always immediately life threatening, but may impair quality of life considerably. In this situation, only palliative treatment options remain and include external beam radiation therapy, resection of symptomatic metastasis or experimental therapies [6,7]. Recently,

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increasing knowledge in tumor biology has led to the identification of potential targets and novel treatment options with kinase inhibitors (KIs) [8,9]. These drugs show promising results in patients with progressive metastatic DTC, refractory for RaI.

Conventional treatment modalities in differentiated thyroid carcinoma

Initial therapy

Recent guidelines from the European Thyroid Association (ETA), the Latin American Thyroid Society (LATS) and the American Thyroid Association (ATA) give an up-to-date overview of the treatment strategies for DTC [10–12]. Initial therapy consists of near-total thyroidectomy in most patients. Only very low-risk patients (small [<1 cm] PTC, unifocal and intrathyroidal) may be treated with hemithyroidectomy. In other cases, a total thyroidectomy is recommended [13–17].

Controversy exists about the routine use of RaI ablative therapy for thyroid remnants. Arguments in favor are that RaI ablative therapy destroys the remaining normal thyroid tissue, which facilitates follow-up procedures [15,18]. The use of high-dose RaI permits postablative scanning to detect persistent carcinoma or metastatic disease [19,20] and RaI may destroy microscopic metastasis and carcinomas, thereby decreasing the risk of recurrence [21,22]. RaI ablation is not indicated in very low-risk patients, but is the treatment of choice in patients with a high risk of recurrence/mortality, gross extrathyroidal extension of the tumor, documented lymph node metastases, incomplete tumor resection and distance metastases as proposed by recent LATS, ATA and ETA guidelines [10–12]. Efficacy of RaI ablative therapy of thyroid remnants is comparable between thyroxine withdrawal and recombinant human thyroid-stimulating hormone (TSH) [23–26].

After initial therapy, DTC patients used to be treated with high doses of thyroxine aiming at suppressed TSH levels. Thyroid cancer cells express the TSH receptor on the cell membrane. A recent analysis indeed demonstrated that TSH levels are positively associated with thyroid cancer-associated death and relapse [27–31]. Long-term TSH suppression, however, may be associated with harmful effects on various systems including bone metabolism [32–34], glucose metabolism [35,36], cardiac function, including higher risk of ischemic heart disease and, increased risk of atrial fibrillation [37–39] and quality of life [40–42].

The European Consensus on thyroid cancer [43,44] and ATA thyroid cancer guidelines recommend that TSH suppression should be maintained only in high-risk and intermediate-risk thyroid cancer patients [10].

Conventional therapeutic strategies for recurrent or metastatic disease

Treatment strategies for local recurrence

In case of local recurrence, surgical management is the favored strategy. Therapeutic lateral and/or central neck dissection should then be performed. Radioiodine is also used adjunctively following surgical debulking if residual RaI avid disease is present [10].

External beam radiation therapy (EBRT) can be attempted as palliative therapy when airway obstruction is present. EBRT in addition to surgery, RaI ablation and TSH suppression has shown to increase the local relapse-free rate in patients with a high risk of relapse in the thyroid bed [45,46]. Patients with a high risk of recurrence include patients >40 years of age with invasive DTC, lymph node involvement and a macroscopically irradical resection, and patients harboring a BRAF mutation [47]. Although cases of complete remission have been described, local recurrence rate is high. In patients with recurrent disease which is inoperable or refractory to radioactive iodine therapy, EBRT can be used to lower the incidence of secondary relapses [46].

Treatment strategies for metastatic disease

Distant metastases, usually in the bones and lungs, occur in approximately 10–15% of patients with DTC. Lung metastases are most frequent in young patients with PTC. Metastatic thyroid cancer that has become inoperable or refractory to RaI therapy is associated with a poor 10-year survival of 5–10%. Owing to the indolent character of DTC, metastases are not immediately life threatening, but may impair quality of life considerably [48].

In case of metastases, surgery can be attempted when the lesion is accessible. In other cases high-dose RaI therapy will be given in patients that accumulate RaI. The remission rate in pulmonary metastases treated with RaI is approximately 50%, varying from 90% in patients with microscopic metastases to only 10% in macronodular disease. The remission rates of bone metastases are worse, varying between 7 and 20% [49]. The major problem in this category of patients is the dedifferentiation of thyroid cancer and, with that, reduced sodium–iodide symporter (NIS) expression and the diminished or lost ability to accumulate RaI. Only palliative treatment options remain. These include EBRT and chemotherapy, which have limited success [50].

External beam radiation therapy can be used as palliative therapy to reduce the pain of bone metastases or dyspnea in case of airway obstruction. No randomized trials have studied the possible benefit of EBRT, so its effectiveness can only be determined from retrospective studies [45,51].

Many conventional chemotherapeutic protocols have been tried in progressive thyroid carcinoma, with disappointing results overall [52]. The most frequently tested agent is doxorubicin. Doxorubicin alone or in combination with cisplatin and bleomycin may induce temporary remissions or stationary disease in approximately 30–50% of patients [50,53]. Furthermore, responses are typically short-lived and associated with a high degree of toxicity [54,55].

New therapeutic strategies for local recurrent & metastatic disease

Experimental treatments

A number of experimental treatments have been attempted in RaI refractory metastatic DTC. Some therapies are focused on redifferentiation in order to reintroduce NIS expression and, therefore, reintroduce RaI accumulation. Other studies focus on other strategies to improve RaI therapy in tumors that still accumulate iodide.

Redifferentiation therapies

When iodide uptake is completely lost, attempts to improve RaI targeted at reinduction of functional NIS expression have been performed.

Retinoids are derivates of vitamin A, and are important for growth, differentiation and morphogenesis in vertebrates [56]. Beneficial effects of retinoids have been reported *in vitro* in thyroid carcinoma [57–61]. A limited number of human studies have been performed on the effects of retinoids on RaI uptake and reported variable results [62–67]. The main conclusion, however, is that unfortunately retinoids are not able to restore susceptibility to RaI therapy.

Other mechanisms by which cells can block the expression of certain genes is by enzymes that methylate these genes or deacetylate the histones that envelope a particular gene. These mechanisms also play a role in the silencing of genes in cancer. Therefore, compounds that can reverse methylation or inhibit histone deacetylation may lead to the re-expression of genes that are silenced in cancer. The orally available histone deacetylase inhibitor vorinostat was studied in 16 DTC patients and three MTC patients. The study reported that the compound was able to reintroduce NIS mRNA expression. However no objective responses were reported and most patients discontinued therapy owing to adverse events [68].

Statins (e.g., lovastatin) have been shown to be potent inhibitors of the HMG–CoA reductase. In addition to their primary use, the anticancer activity of statins was intensively studied and *in vitro* studies have demonstrated an effect on growth and invasion of tumor cells [69,70]. At a dose of 25 μM, lovastatin was able to significantly increase iodine uptake [69]. This redifferentiating effect, which was observed at clinically achievable concentrations of lovastatin and troglitazone, may be highly beneficial in patients with DTC as iodine uptake can be lost in DTC metastases due to dedifferentiation.

Other experimental therapies

In tumors that still accumulate iodide, improving RaI therapy is essentially aimed at increasing the dose of RaI. Lithium has been associated with increased trapping of iodide by the thyroid gland, without impairing iodide uptake, thus enhancing RaI retention. However, despite an increase in RaI uptake in tumor deposits, there are no data that demonstrate a better outcome of patients treated with lithium as an adjunct to RaI therapy [71,72].

Peroxisome proliferator-activated receptor-γ (PPARγ) agonists have been introduced as antidiabetic agents. Their proposed mechanism is the differentiation of preadipocytes, thereby increasing the fatty-acid storing capacity of adipose tissue. Altered expression of PPARγ and *in vitro* beneficial effects of PPARγ agonists have been described in a number of malignancies. In general, a decreased PPARγ expression is observed in DTC [73]. Although PPARγ agonists showed promising results in preclinical models for thyroid cancer, they do not result in a clinically beneficial response [74].

Some drugs are capable of either inhibiting angiogenesis or disrupting tumor vasculature. Thalidomide is a glutamic acid derivate with an antiangiogenic effect. A Phase II trial was set up to study the effectiveness of thalidomide in patients with progressive, metastatic thyroid carcinoma. Overall, 18% achieved a partial response and 32% deomstrated stable disease. Partial response or durable stable disease was seen in 38% of DTC and 15% of MTC patients [75].

Lenalidomide (CC-5103) is a thalidomide derivate with a less toxic profile. Ain *et al.* performed a Phase II trial with lenalidomide in patients with rapidly progressive and iodine refractory DTC patients. Median overall survival was less than 11 months [76].

Expression of COX-2 mRNA is increased in thyroid cancer tissue, especially in those expressing RET/PTC mutations. In a Phase II trial, the efficacy of celecoxib, a selective COX-2 inhibitor, was investigated in patients with progressive metastatic DTC, however, with disappointing results [77].

Molecular pathogenesis in differentiated thyroid carcinoma & kinase inhibitors

Pathogenesis

In DTC, genetic alterations that have been identified involve kinase signaling pathways [78–80]. These include genetic defects involving the RET, RAS and RAF protein kinase signaling cascade (Figure 1). The RET–RAS–RAF

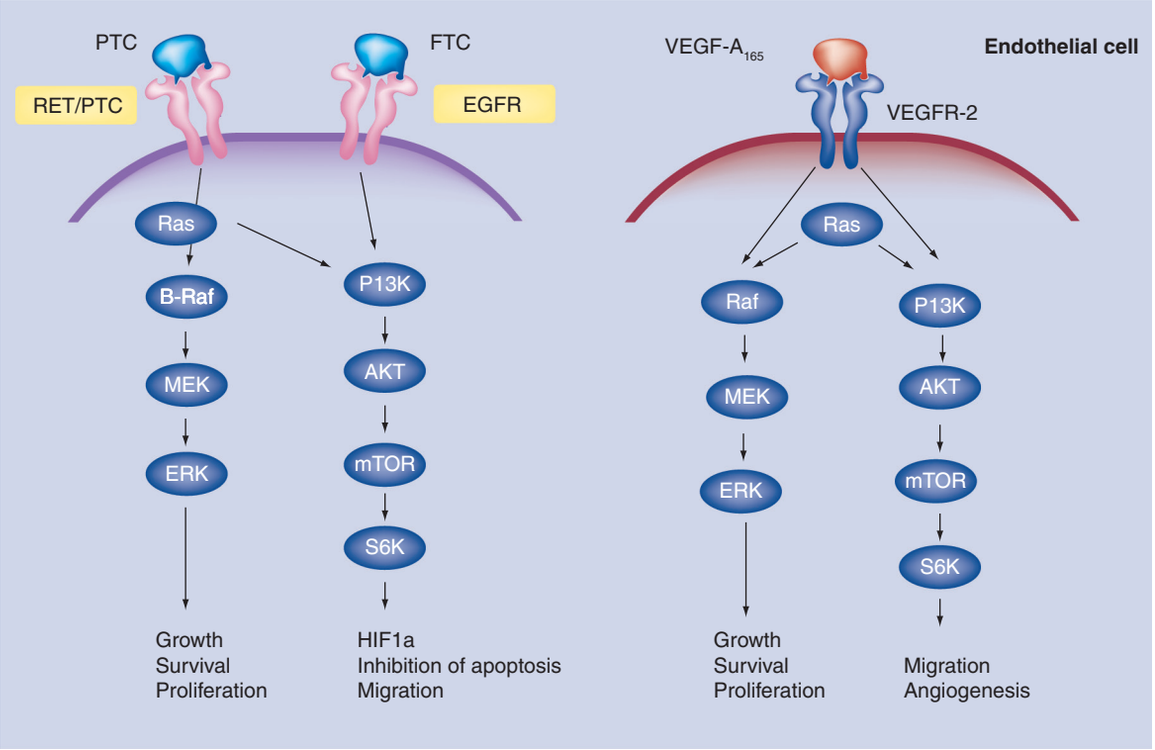

Figure 1. RET–RAS–RAF cascade.

pathway is interconnected with the EFGR-activated cascade that among others leads to VEGF and VEGF receptor (VEGFR) synthesis. Therefore, compounds targeting the activated RET–RAS–RAF pathway and beyond may be effective in non-RaI avid DTC. The RAF proteins are cytoplasmic serine/threonine protein kinases that are downstream effector molecules of RAS. Of these, BRAF is the most efficient at phosphorylating MAPK and is important in proliferative as well as apoptotic pathways [81]. The AKT pathway plays an important role in cell proliferation and survival and has been found by others to be aberrantly activated in thyroid tumors [82–85]. An important player in this pathway is the PI3KCA subunit that, in turn, is also regulated by RAS. In an interesting series of events unraveled by Hou *et al.*, a progressive activation of the PI3K/AKT pathway and associated methylation of PTEN, known to suppress this pathway, was found in thyroid adenomas, follicular and anaplastic thyroid cancers [86].

Based on evidence that BRAF is involved in the development of PTC and in the progression of anaplastic carcinoma, BRAF is an attractive target in thyroid cancer [87]. BRAF V600E can induce thyroid cell transformation *in vitro* and thyroid cancer *in vivo*, confirming that this mutation is an oncogene for thyroid cancer. The BRAF V600E mutation has been found in 29–69% of PTC [87–90]. It has been associated with aggressive features including extrathyroidal extension, advanced stage and VEGF overexpression, which, in turn, is associated with increasing tumor stage and invasiveness [91,92]. The incidence of BRAF V600E in anaplastic carcinomas is similar to that in early-stage well-differentiated tumors, suggesting that some anaplastic carcinomas develop from PTC and that BRAF signaling may be important in this process [93].

Another common genetic abnormality in PTC, occurring in 16–25% of cases, involves the RET proto-oncogene via rearrangements leading to the fusion of the tyrosine kinase domain to the 5′ end of other genes that are constitutively active in follicular thyroid cells [94,95]. This results in the generation of chimeric oncogenes and proteins denoted RET/PTC whose expression is under the control of promoters provided by the fused genes, leading to ligand-independent activation of RET in papillary thyroid cancer. To date, 12 of these chimeric RET/PTC proteins have been described [95,96].

Up to 50% of the FTC and 12% of Hürthle cell malignancies harbor mutations in one of the three RAS genes [97].

Other genetic alterations in FTC include PAX8–PPARγ rearrangement. This is a unique combination of genes that traditionally are associated with thyroid development (PAX8) and cell differentiation and metabolism (PPARγ) [98,99]. This chimeric protein

acts as a dominant negative competitor for PPARγ and is associated with more aggressive growth and propensity for invasion [98,99]. The follicular variant of PTC shares some of the molecular features of follicular tumors, but also less common BRAF mutations are reported [100]. Anaplastic carcinomas are frequently associated with mutations of the p-53 tumor suppressor gene [101].

Kinase inhibitors

Targeted cancer therapy with tyrosine kinase inhibitors (TKIs) has been of particular interest in anticancer drug development since the 1980s. At that time, available anticancer drugs acted on DNA only and these were unsuccessful in the cure of most solid cancers [102]. Targeted cancer therapies attempt to disrupt pathways that are inappropriately activated in cancer cells. The first notable successes have been with imatinib in chronic myeloid leukemia and in patients with gastrointestinal stromal tumors [78]. As a result of the increasing knowledge of the biologic mechanisms of thyroid cancer pathogenesis and progression, therapeutic agents that could target these mechanisms have been identified [103–107].

Sorafenib (BAY 43–9006) is the most promising TKI in DTC. It is an orally active KI targeting BRAF, VEGFR 1 and 2 and RET, conducting proapoptotic and antiangiogenic actions. In a Phase II study, Gupta-Arbramson *et al.* found a partial response rate of 23% and a stable disease rate of 53% mainly in patients with advanced DTC (n = 30). The median progression-free survival (PFS) was 79 weeks [8]. Kloos *et al.* examined the effect of sorafenib mainly in patients with metastatic PTC (n = 41). Of the PTC patients, 15% achieved a partial response, whereas 56% had stable disease for at least 24 weeks. The median PFS was 15 months [9]. Hoftijzer *et al.* performed a Phase II study investigating the efficacy and the question of whether sorafenib could increase or reintroduce radioiodine uptake in patients with iodine refractory recurrent or metastatic DTC. Although no reintroduction of radioiodine at metastatic sites was observed, a partial response rate was reported in 23% of patients and 39% had stable disease. The median PFS was 58 weeks [108]. Currently, a Phase III trial of sorafenib versus placebo is performed with the possibility of crossover in patients with advanced iodine refractory DTC.

Table 1 gives an overview of other relevant Phase II studies with TKIs in DTC.

Monotarget kinase inhibitors

Gefitinib (ZD1839) is an oral EGFR KI. The EGFR is highly expressed in malignant thyroid tissue and mutations of the *EGFR* gene have been described in thyroid cancer. Moreover, EGFR contributes to RET activation, signaling and growth stimulation and is associated with poor prognosis in DTC [109]. Pennell *et al.* studied the effectiveness of gefitinib in a Phase II trial with a mixed cohort of thyroid cancer patients. A total of 4% of patients demonstrated disease reduction; however this did not qualify as a partial response. Overall, 24% of patients acquired stable disease lasting at least 24 weeks. Median PFS was almost 16 weeks [110].

Axitinib (AG-013736) is an oral TKI that effectively blocks all of the VEGFRs. A Phase II trial by Cohen *et al.* studied the efficacy of axitinib in advanced or metastatic thyroid carcinoma of any histology (n = 60; of which 45 were DTC). A partial response was seen in 30% of the patients. Stable disease lasting at least 16 weeks was reported in 38% of the subjects. Objective responses were noted in all histologic subtypes with a partial response rate of 31% in patients with DTC. Median PFS was 18.1 months [111].

AZD6244 is a potent, selective, noncompetitive inhibitor of MEK1/2 that has been studied in a Phase I study and has shown interesting activity in two advanced thyroid cancer patients with stable disease for at least 5 months [112]. A multicenter Phase II trial is ongoing in advanced DTC patients.

Multikinase inhibitors

Motesanib diphosphate (AMG 706) is an oral KI targeting the VEGFR 1–3, RET and c-KIT. In a Phase I trial by Rosen *et al.*, a 50% overall response rate was observed in patients with advanced thyroid carcinoma [113]. Based on these results a multicenter Phase II trial was initiated, testing the efficacy of motesanib therapy in patients with progressive DTC and progressive or symptomatic MTC. A partial response was confirmed in 14% of the DTC patients, and another 35% of these previously progressive patients maintained stable disease for at least 24 weeks. The median response duration was 40 weeks [114].

Sunitinib (SU11248) is an oral KI of VEGFR 1–3, RET, and RET/PTC subtypes 1 and 3. A response rate of 8% in DTC patients was reported by Ravaud *et al.*, who performed a Phase II trial to determine the effect of sunitinib in refractory advanced thyroid carcinoma. Furthermore, 67% of DTC patients demonstrated disease stabilization [115]. In a second Phase II trial, Cohen *et al.* reported a 13% response rate and a 68% stable disease rate in patients with DTC [116]. Preliminary analysis from a third Phase II trial showed partial response or stable disease for at least 12 weeks in 17% of DTC patients [117].

Pazopanib (GW786034) is an orally bioavailable KI that targets VEGFR 1–3 and c-KIT. Its antitumor activity in advanced and progressive DTC was demonstrated in a Phase II trial. A total of 32 patients were enrolled. Partial responses were confirmed in 32% of patients, median PFS was 12 months [118].

Table 1. Literature on tyrosine kinase inhibitors in Phase II studies in differentiated thyroid carcinoma.

Drug	Target	Tumor type	Number of patients	Response rate (%)	Stable disease (%)	Progression free survival	Ref.
Monotarget tyrosine kinase inhibitors							
Gefitinib	EGFR–RET	DTC + MTC	18 + 4	0	24 (>24 weeks)	16 weeks	[110]
Axitinib	VEGFR	DTC	45	31	42	18 months	[111]
Multitarget tyrosine kinase inhibitors							
Motesanib	RET–PDGF–VEGFR–KIT	DTC	93	14	35 (>24 weeks)	40 weeks	[114]
Sunitinib	RET, VEGFR, PDGFR	DTC + MTC DTC DTC + MTC	8 + 4 37 26 + 7	8 13 32 (7 CR)	67 68		[115–117]
Pazopanib	VEGFR, PDGFR	DTC	32	32	65	12 months	[118]
Sorafenib	RET–RAS–RAF–VEGF– VEGFR–PDGF–c-KIT	DTC DTC DTC	41 30 31	15 23 25	56 (>24 weeks) 53 34	15 months 79 weeks 58 weeks	[8,9,108]

CR: Complete response; DTC: Differentiated thyroid carcinoma; EGFR: EGF receptor; MTC: Medullary thyroid carcinoma; PDGFR: PDGF receptor; VEGFR: VEGF receptor.

Small molecules

PLX 4032 is an orally administered small molecule that specifically inhibits the V600E mutant BRAF kinase, without appreciable impairment of wild-type BRAF or other RAF kinases. Three patients with PTC and documented V600E BRAF mutations have been treated in a Phase I study, with one of the three experiencing a partial response and the other two having prolonged stable disease [119]. No current Phase II trial is open.

XL880 is another orally bioavailable c-Met inhibitor that also blocks VEGFR 1–2 at a nanomolar level, and less potently PDGFR, KIT and FLT3. It has demonstrated promising activity against thyroid cancer patients in a Phase I clinical trial [120].

E7080 is also an inhibitor of multiple TKs, especially VEGFRs, c-KIT and PDGFR-β stem cell factor receptor. In animal studies, it has been shown to have potent antitumor activity against small cell lung cancer and breast cancer, most likely through inhibition of VEGFR 2 and 3 [121,122]. A Phase II, multicenter trial has been set up to evaluate the safety and efficacy of oral E7080 in medullary and refractory, unresectable DTC.

Differences in response to TKIs

The mechanism behind the differences in response rate between the multitargeted KIs is as yet unclear. Differences in IC_{50} for targets plays a role (Table 2). However, it has to be realized that these characteristics are derived from *in vitro* experiments. In addition, low IC_{50} values for wild-type kinase targets do not reflect efficacy in mutated targets: indeed, motesanib has affinity for RAF but not for mutated RAF. Sunitinib has a much lower efficacy in translocated RET than in wild type RET. Other phenomena (pharmacodynamics and pharmacokinetics) will also contribute to differences. In this respect, PLX 4032 (see earlier), that specifically inhibits the V600E mutant BRAF kinase is an interesting compound. In addition, comparison of the results of Phase II studies with different TKIs in DTC is hampered by differences in patient categories (including histologies, tumor stages, sites of metastases and tumor extent), study design and analytical methods [123].

Side effects of tyrosine kinase inhibitors

Although the toxicity of therapy with KIs is usually considered less serious than in conventional chemotherapeutic schedules, the side effects are by no means mild. The side effects in the study by Hoftijzer *et al.* [98], which are summarized in Table 3, are representative for most studies with KI in DTC. Doses had to be reduced in 56% of the patients to control toxicities and approximately one third of the patients discontinued treatment owing to side effects. The most prevalent side effect is the hand–foot syndrome, which occurs in the first few weeks of treatment and subsides in most after dose reduction and topical treatment. Most patients need nutritional support for weight loss. Diarrhea is a common cause of weight loss and also requires symptomatic treatment. Mineral deficiencies are treated with supplementation, whereas hypertension is treated with antihypertensive drugs. In order to maintain serum-free T4 levels and TSH levels at the required values, many patients will need an increase in thyroxine dose.

Conclusion & future perspective

In this article we have described conventional and new treatment modalities in differentiated advanced thyroid cancer. The large majority of patients with DTC can

be cured, and others may survive for decades despite persistent disease. Patients with asymptomatic, stable metastatic disease may be monitored closely on levothyroxine suppression therapy. However, DTC patients with progressive, radioiodine-resistant metastatic disease have a worse prognosis and the results of conventional treatment modalities have been disappointing. These patients should nowadays be considered for entry into clinical trials with new agents.

The large development in the treatment of advanced thyroid cancer is due to the unraveling of the carcinogenesis of thyroid cancer. Aberrations in RET/PTC–RAS–RAF–MAPK pathway are present in a high percentage of thyroid cancer, and there are also angiogenesis switch alterations and involvement of other receptor tyrosine kinases, such as EGFR or c-Met. Due to the oncogenic roles of activated BRAF, RET and RET/PTC kinases, the assumption was that specific targeting of these kinases could block tumor growth and induce senescence [124]. As can be shown from multiple clinical trials in thyroid cancer, these assumptions have appeared to be correct with considerable percentages of clinical responses.

In DTC, sorafenib seems a promising agent, since three Phase II trials have shown efficacy [8,9,108]. Several issues, however, need to be resolved.

The exact risk:benefit ratio of therapy with KIs in DTC can only be determined from Phase III studies. As indicated, KIs have considerable side effects. As most metastases in DTC are slowly progressive and many times not accompanied by invalidating symptoms, the balance between a gain in PFS at the cost of quality of life is extremely difficult to assess and requires a highly individualized approach. Currently, an international Phase III trial is underway in progressive metastatic DTC patients, who are randomized between sorafenib and placebo with the possibility of crossover. However, the search for new treatment agents will still be necessary, since patients eventually become progressive on sorafenib or do not tolerate sorafenib.

Selection of patients is another important issue. As yet, it is impossible to predict which category of patients will respond to KIs. Conventional pathological classifications of primary tumors do not predict responsiveness. Often, metastases are inaccessible to obtain tissue, and genetic analyses from primary tumors usually do not reflect metastases. Ideally, kinase profiles should be obtained from metastatic tissue to predict what kinase inhibitor profile would be optimal.

The timing of treatment and combined treatments is an important aspect. In most studies, patients with advanced DTC are included who have usually had a long history of ineffective conventional therapies. Therapy with KIs is based on the presumption that tumor proliferation is oncogene addicted, for example, driven by activated oncogenes. However, in advanced disease, this dependency is often lost, which makes therapies targeted to these oncogenes of limited use. Consequently, it should be considered to initiate KI therapy at a much earlier stage, in combination with RaI for high-risk patients with irradical thyroidectomy, metastasized disease with bone or macroscopic lung metastases, with limited RaI uptake.

Treatment schedules with KIs in DTC are not crystallized. In most patients, continuous treatment is used. As side effects may affect quality of life considerably, drug-holidays may be an option, but it has not been studied systematically in DTC.

For definitions of therapy response in patients with advanced thyroid cancer, the Response Evaluation Criteria in Solid Tumors (RECIST) criteria are applied

Table 2. IC_{50} values for the most important kinase inhibitors and different targets.

Compound	Targets						
	VEGFR 1 IC_{50} (nM)	VEGFR 2 IC_{50} (nM)	VEGFR 3 IC_{50} (nM)	RET IC_{50} (nM)	RET/PTC3 IC_{50} (nM)	BRAF IC_{50} (nM)	Other IC_{50} (nM)
Axitinib	1.2	0.25	0.29				c-Kit 1.7
Gefitinib							EGFR 33
Motesanib	2	3	6	59			c-Kit 8
Sorafenib		90	20	47	50	22	c-Kit 8
Sunitinib	2	9	17	41	224		
Vandetanib	1600	40	110	130	100		EGFR 500
XL184		0.035		4			c-Met 1.8
PLX4032						100	BRAF-V600E 31

VEGFR: VEGF receptor.
Adapted from [123].

Table 3. Adverse events of sorafenib.

Event	Number of patients (%)					
	Gefitinib [110]	Axitinib [111]	Motesanib [114]	Sorafenib [8]	Sorafenib [108]	Sorafenib [9]
Hand–foot syndrome		9 (15)		28 (93)	21 (66)	35 (63)
Fatigue		30 (50)	43 (46)	19 (63)		46 (82)
Asthenia			10 (11)			
Weight loss		15 (25)	37 (40)	18 (60)	18 (56)	46 (82)
Anorexia	3 (11)	18 (30)	25 (27)	6 (20)		23 (41)
Fever				2 (7)		
Diarrhea	11 (41)	29 (48)	55 (59)	22 (73)	16 (50)	42 (75)
Constipation				2 (7)		
Nausea	1 (5)	20 (33)	26 (28)	9 (30)		31 (55)
Vomiting		8 (13)	11 (12)			10 (18)
Abdominal pain			28 (30)			38 (68)
Alopecia				13 (43)	15 (47)	43 (77)
Rash	14 (51)	9 (15)		24 (80)	15 (47)	44 (78)
Musculoskeletal pain				17 (57)		50 (89)
Pruritus				4 (13)		42 (75)
Mucositis/stomatitis		15 (25)		14 (47)	14 (44)	9 (16)
Dry mouth			13 (14)			3 (0.5)
Hypertension		17 (28)	52 (56)	9 (30)	13 (41)	24 (43)
Headache		13 (22)	24 (26)	2 (7)		9 (16)
Anemia					8 (25)	
Thrombopenia					9 (28)	
Hypocalcemia					13 (41)	
Hypophosphatemia					9 (28)	
Hypothyroidism			11 (12)			
Myocardial infraction			1 (1)		1 (3)	
Heart failure					1 (3)	
Rhythm disorder						7 (13)
Dyspnoea				8 (27)		8 (15)
Proteinuria		11 (18)				

for the judgment of progression for the inclusion in trials and for follow-up scans to determine treatment effect. However, anatomical imaging alone using the RECIST criteria has limitations. Wahl *et al.* propose the PET Response Criteria in Solid Tumors (PERCIST) that can serve as a starting point for use in clinical trials and in structured quantative clinical reporting [125]. The premise of the PERCIST criteria is that cancer response, as assessed by PET, is a continuous and time-dependent variable, while RECIST uses unidimensional measurements of target lesions and classifies continuous data (tumor size) into four categories (complete remission, partial response, stable disease and progressive disease), with possible loss of information. However, the PERCIST criteria will need revisions and enhancements in validation studies in varying diseases and treatments. Until then, the RECIST criteria (version 1.1 [126]) are the best criteria we have and they should be applied in every clinical trial with dedicated radiologists using them.

Another issue is that a substantial proportion of patients (33–50%) have stable disease of varying duration as best response in several studies. Given the indolent natural history of many of these tumors, a report of stable disease might be of limited value. In this context, the determination of the primary end point in studies is sometimes difficult. The objective response rate gives information on progression, stabilization or shrinkage of tumors within a certain period of time, but does not correlate *per se* with overall survival. PFS or overall survival is not always the preferred primary end points in advanced thyroid cancer because of its indolent nature. Furthermore, the RECIST criteria may not be the best method for tumor evaluation in this tumor type, as was discussed previously. In any case, only patients with documented progressive disease should be included in clinical trials. However, if there are beneficial effects of therapy on tumor response, they must always be weighed against the side-effects of targeted therapies and hence its influence on quality of life.

In conclusion, the developments in the treatment of advanced thyroid cancer are intriguing. The unraveling of the molecular pathways in thyroid cancer has played a pivotal role in the development of targeted therapy for thyroid cancer.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Executive summary

- Thyroid cancer is a common endocrine malignancy.
- The incidence has increased during the last few decades.
- The overall 10-year survival is 90–95%, due to indolent behavior of the tumor as well as the availability of effective therapy.
- Once distant metastases have occurred, the prognosis of differentiated thyroid carcinoma (DTC) becomes worse as a result of dedifferentiation and subsequent loss of the ability to accumulate radioactive iodide-131 (RaI).
- Recently, increasing knowledge in tumor biology has led to the identification of potential targets and novel treatment options with tyrosine kinase inhibitors, including sorafenib and sunitinib.

Conventional treatment modalities in differentiated thyroid carcinoma

- In most cases initial therapy consists of near-total thyroidectomy and RaI ablative therapy followed by thyroid-stimulating hormone suppressive therapy.
- Conventional therapeutic strategies for metastatic disease, such as external beam radiation and chemotherapy, give disappointing results; effects are short-lived, with high toxicity and recurrence rates.
- Experimental therapeutic options like lithium, retinoids, proliferator-activated receptor-γ agonists and statins have led to promising *in vitro* results, but overall clinical results have been disappointing.

Kinase inhibitors in differentiated thyroid carcinoma

- New treatment modalities in thyroid carcinoma are based on the increasing knowledge of the pathological development and progression of thyroid carcinoma.
- Monotarget kinase inhibitors gefitinib and axitinib already demonstrated a promising response in DTC; however, multikinase inhibitors sorafenib and sunitinib have proven to be beneficial for patients with metastasized DTC, both in three Phase II studies.
- An international Phase III trial is currently being performed in progressive metastatic DTC patients, who are randomized between sorafenib and placebo.

Future perspective

- The risk–benefit balance of kinase inhibitors should be determined in Phase III studies.
- Strategies for patient selection and stratification for optimal treatment modalities should be developed.
- The efficacy of kinase inhibitors as an extended initial therapy in combination with RaI for high-risk patients should be explored.

Bibliography

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA* 295(18), 2164–2167 (2006).

2 Davies L, Welch HG. Thyroid cancer survival in the United States: observational data from 1973 to 2005. *Arch. Otolaryngol. Head Neck Surg.* 136(5), 440–444 (2010).

3 Jemal A, Siegel R, Ward E *et al.* Cancer statistics, 2009. *CA Cancer J. Clin.* 59(4), 225–249 (2009).

4 Schlumberger MJ. Papillary and follicular thyroid carcinoma. *N. Engl. J. Med.* 338(5), 297–306 (1998).

5 Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995. *Cancer* 83(12), 2638–2648 (1998).

6 Liu YY, Stokkel MP, Morreau HA *et al.* Radioiodine therapy after pretreatment with bexarotene for metastases of differentiated thyroid carcinoma. *Clin. Endocrinol. (Oxf.)* 68(4), 605–609 (2008).

7 Philips JC, Petite C, Willi JP, Buchegger F, Meier CA. Effect of peroxisome proliferator-

activated receptor γ agonist, rosiglitazone, on dedifferentiated thyroid cancers. *Nucl. Med. Commun.* 25(12), 1183–1186 (2004).

8 Gupta-Abramson V, Troxel AB, Nellore A *et al.* Phase II trial of sorafenib in advanced thyroid cancer. *J. Clin. Oncol.* 26(29), 4714–4719 (2008).

■■ **First Phase II trial that demonstrated the beneficial effect of sorafenib, the most potent kinase inhibiton in thyroid cancer treatment.**

9 Kloos RT, Ringel MD, Knopp MV *et al.* Phase II trial of sorafenib in metastatic thyroid cancer. *J. Clin. Oncol.* 27(10), 1675–1684 (2009).

10 Cooper DS, Doherty GM, Haugen BR *et al.* Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 19(11), 1167–1214 (2009).

■■ **Very well written and clear overview for clinicians.**

11 Pacini F, Schlumberger M, Dralle H *et al.* European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur. J. Endocrinol.* 154(6), 787–803 (2006).

12 Pitoia F, Ward L, Wohllk N *et al.* Recommendations of the Latin American Thyroid Society on diagnosis and management of differentiated thyroid cancer. *Arq. Bras. Endocrinol. Metabol.* 53(7), 884–887 (2009).

13 Baudin E, Travagli JP, Ropers J *et al.* Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. *Cancer* 83(3), 553–559 (1998).

14 DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J. Clin. Endocrinol. Metab.* 71(2), 414–424 (1990).

15 Mazzaferri EL, Kloos RT. Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. *J. Clin. Endocrinol. Metab.* 86(4), 1447–1463 (2001).

16 Katoh R, Sasaki J, Kurihara H *et al.* Multiple thyroid involvement (intraglandular metastasis) in papillary thyroid carcinoma. A clinicopathologic study of 105 consecutive patients. *Cancer* 70 (6), 1585–1590 (1992).

17 Russell WO, Ibanez ML, Clark RL, White EC. Thyroid carcinoma classification, intraglandular dissemination, and clinicopathological study based upon whole organ sections of 80 glands. *Cancer* 16 1425–1460 (1963).

18 Utiger RD. Follow-up of patients with thyroid carcinoma. *N. Engl. J. Med.* 337(13), 928–930 (1997).

19 Sherman SI, Tielens ET, Sostre S, Wharam MD Jr, Ladenson PW. Clinical utility of posttreatment radioiodine scans in the management of patients with thyroid carcinoma. *J. Clin. Endocrinol. Metab.* 78(3), 629–634 (1994).

20 Tenenbaum F, Corone C, Schlumberger M, Parmentier C. Thyroglobulin measurement and postablative iodine-131 total body scan after total thyroidectomy for differentiated thyroid carcinoma in patients with no evidence of disease. *Eur. J. Cancer* 32A(7), 1262 (1996).

21 Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. *Int. J. Radiat. Oncol. Biol. Phys.* 14(6), 1063–1075 (1988).

22 Tubiana M, Schlumberger M, Rougier P *et al.* Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer* 55 (4), 794–804 (1985).

23 Chianelli M, Todino V, Graziano FM *et al.* Low-activity (2.0 GBq; 54 mCi) radioiodine post-surgical remnant ablation in thyroid cancer: comparison between hormone withdrawal and use of rhTSH in low-risk patients. *Eur. J. Endocrinol.* 160(3), 431–436 (2009).

24 Haugen BR, Pacini F, Reiners C *et al.* A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J. Clin. Endocrinol. Metab.* 84(11), 3877–3885 (1999).

25 Ladenson PW, Braverman LE, Mazzaferri EL *et al.* Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. *N. Engl. J. Med.* 337(13), 888–896 (1997).

26 Taieb D, Sebag F, Cherenko M *et al.* Quality of life changes and clinical outcomes in thyroid cancer patients undergoing radioiodine remnant ablation (RRA) with recombinant human TSH (rhTSH): a randomized controlled study. *Clin. Endocrinol. (Oxf.)* 71(1), 115–123 (2009).

27 Goretzki PE, Frilling A, Simon D, Roeher HD. Growth regulation of normal thyroids and thyroid tumors in man. *Recent Results Cancer Res.* 118 48–63 (1990).

28 McGriff NJ, Csako G, Gourgiotis L *et al.* Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. *Ann. Med.* 34(7–8), 554–564 (2002).

29 Brabant G, Maenhaut C, Kohrle J *et al.* Human thyrotropin receptor gene: expression in thyroid tumors and correlation to markers of thyroid differentiation and dedifferentiation. *Mol. Cell Endocrinol.* 82(1), R7–R12 (1991).

30 Brabant G. Thyrotropin suppressive therapy in thyroid carcinoma: what are the targets? *J. Clin. Endocrinol. Metab.* 93(4), 1167–1169 (2008).

31 Hovens GC, Stokkel MP, Kievit J *et al.* Associations of serum thyrotropin concentrations with recurrence and death in differentiated thyroid cancer. *J. Clin. Endocrinol. Metab.* 92(7), 2610–2615 (2007).

■ **First study with proof of concept that thyroid-stimulating hormone values are associated with survival.**

32 Diamond T, Nery L, Hales I. A therapeutic dilemma: suppressive doses of thyroxine significantly reduce bone mineral measurements in both premenopausal and postmenopausal women with thyroid carcinoma. *J. Clin. Endocrinol. Metab.* 72(6), 1184–1188 (1991).

33 Franklyn JA, Betteridge J, Daykin J *et al.* Long-term thyroxine treatment and bone mineral density. *Lancet* 340(8810), 9–13 (1992).

34 Heemstra KA, Hamdy NA, Romijn JA, Smit JW. The effects of thyrotropin-suppressive therapy on bone metabolism in patients with well-differentiated thyroid carcinoma. *Thyroid* 16(6), 583–591 (2006).

35 Dimitriadis G, Mitrou P, Lambadiari V *et al.* Glucose and lipid fluxes in the adipose tissue after meal ingestion in hyperthyroidism. *J. Clin. Endocrinol. Metab.* 91(3), 1112–1118 (2006).

36 Yavuz DG, Yuksel M, Deyneli O *et al.* Association of serum paraoxonase activity with insulin sensitivity and oxidative stress in hyperthyroid and TSH-suppressed nodular goitre patients. *Clin. Endocrinol. (Oxf.)* 61(4), 515–521 (2004).

37 Biondi B, Palmieri EA, Fazio S *et al.* Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. *J. Clin. Endocrinol. Metab.* 85(12), 4701–4705 (2000).

38 Smit JW, Eustatia-Rutten CF, Corssmit EP *et al.* Reversible diastolic dysfunction after long-term exogenous subclinical hyperthyroidism: a randomized, placebo-controlled study. *J. Clin. Endocrinol. Metab.* 90(11), 6041–6047 (2005).

39 Botella-Carretero JI, Gomez-Bueno M, Barrios V *et al.* Chronic thyrotropin-suppressive therapy with levothyroxine and short-term overt hypothyroidism after thyroxine withdrawal are associated with undesirable cardiovascular effects in patients with differentiated thyroid carcinoma. *Endocr. Relat. Cancer* 11(2), 345–356 (2004).

40 Botella-Carretero JI, Galan JM, Caballero C, Sancho J, Escobar-Morreale HF. Quality of life and psychometric functionality in patients with differentiated thyroid carcinoma. *Endocr. Relat. Cancer* 10(4), 601–610 (2003).

41 Crevenna R, Zettinig G, Keilani M *et al.* Quality of life in patients with non-metastatic differentiated thyroid cancer under thyroxine supplementation therapy. *Support. Care Cancer* 11(9), 597–603 (2003).

42 Dagan T, Bedrin L, Horowitz Z *et al.* Quality of life of well-differentiated thyroid carcinoma patients. *J. Laryngol. Otol.* 118(7), 537–542 (2004).

43 Schlumberger M, Berg G, Cohen O *et al.* Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. *Eur. J. Endocrinol.* 150(2), 105–112 (2004).

44 Schlumberger M, Pacini F, Wiersinga WM *et al.* Follow-up and management of differentiated thyroid carcinoma: a European perspective in clinical practice. *Eur. J. Endocrinol.* 151(5), 539–548 (2004).

45 Brierley JD, Tsang RW. External-beam radiation therapy in the treatment of differentiated thyroid cancer. *Semin. Surg. Oncol.* 16(1), 42–49 (1999).

46 Tubiana M, Lacour J, Monnier JP *et al.* External radiotherapy and radioiodine in the treatment of 359 thyroid cancers. *Br. J. Radiol.* 48(575), 894–907 (1975).

47 Rovere RK, Awada A. Treatment of recurrent thyroid cancers – is there a light in the horizon? *Curr. Opin. Oncol.* 20(3), 245–248 (2008).

48 Durante C, Haddy N, Baudin E *et al.* Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J. Clin. Endocrinol. Metab.* 91(8), 2892–2899 (2006).

49 Pacini F, Agate L, Elisei R *et al.* Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic (131)I whole body scan: comparison of patients treated with high (131)I activities versus untreated patients. *J. Clin. Endocrinol. Metab.* 86(9), 4092–4097 (2001).

50 Haugen BR. Management of the patient with progressive radioiodine non-responsive disease. *Semin. Surg. Oncol.* 16(1), 34–41 (1999).

51 Brierley JD, Tsang RW. External beam radiation therapy for thyroid cancer. *Endocrinol. Metab. Clin. North Am.* 37(2), 497–509, XI (2008).

52 Sherman SI. Advances in chemotherapy of differentiated epithelial and medullary thyroid cancers. *J. Clin. Endocrinol. Metab.* 94(5), 1493–1499 (2009).

53 De Besi P, Busnardo B, Toso S *et al.* Combined chemotherapy with bleomycin, adriamycin, and platinum in advanced thyroid cancer. *J. Endocrinol. Invest.* 14(6), 475–480 (1991).

54 Shimaoka K, Schoenfeld DA, DeWys WD, Creech RH, DeConti R. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. *Cancer* 56(9), 2155–2160 (1985).

55 Williams SD, Birch R, Einhorn LH. Phase II evaluation of doxorubicin plus cisplatin in advanced thyroid cancer: a Southeastern Cancer Study Group Trial. *Cancer Treat. Rep.* 70(3), 405–407 (1986).

56 Smith MA, Parkinson DR, Cheson BD, Friedman MA. Retinoids in cancer therapy. *J. Clin. Oncol.* 10(5), 839–864 (1992).

57 Havekes B, Schroder van der Elst JP, van der Pluijm G *et al.* Beneficial effects of retinoic acid on extracellular matrix degradation and attachment behaviour in follicular thyroid carcinoma cell lines. *J. Endocrinol.* 167(2), 229–238 (2000).

58 Schmutzler C, Brtko J, Bienert K, Kohrle J. Effects of retinoids and role of retinoic acid receptors in human thyroid carcinomas and cell lines derived therefrom. *Exp. Clin. Endocrinol. Diabetes* 104(Suppl. 4), 16–19 (1996).

59 Schmutzler C, Kohrle J. Retinoic acid redifferentiation therapy for thyroid cancer. *Thyroid* 10(5), 393–406 (2000).

60 Van Herle AJ, Agatep ML, Padua DN III *et al.* Effects of 13 *cis*-retinoic acid on growth and differentiation of human follicular carcinoma cells (UCLA R0 82 W-1) *in vitro*. *J. Clin. Endocrinol. Metab.* 71(3), 755–763 (1990).

61 Schmutzler C, Schmitt TL, Glaser F, Loos U, Kohrle J. The promoter of the human sodium/iodide-symporter gene responds to retinoic acid. *Mol. Cell Endocrinol.* 189(1–2), 145–155 (2002).

62 Coelho SM, Corbo R, Buescu A, Carvalho DP, Vaisman M. Retinoic acid in patients with radioiodine non-responsive thyroid carcinoma. *J. Endocrinol. Invest.* 27(4), 334–339 (2004).

63 Liu YY, Stokkel MP, Pereira AM *et al.* Bexarotene increases uptake of radioiodide in metastases of differentiated thyroid carcinoma. *Eur. J. Endocrinol.* 154(4), 525–531 (2006).

64 Short SC, Suovuori A, Cook G, Vivian G, Harmer C. A Phase II study using retinoids as redifferentiation agents to increase iodine uptake in metastatic thyroid cancer. *Clin. Oncol. (R. Coll. Radiol.)* 16(8), 569–574 (2004).

65 Simon D, Kohrle J, Schmutzler C *et al.* Redifferentiation therapy of differentiated thyroid carcinoma with retinoic acid: basics and first clinical results. *Exp. Clin. Endocrinol. Diabetes* 104(Suppl. 4) 13–15 (1996).

66 Simon D, Koehrle J, Reiners C *et al.* Redifferentiation therapy with retinoids: therapeutic option for advanced follicular and papillary thyroid carcinoma. *World J. Surg.* 22(6), 569–574 (1998).

67 Simon D, Korber C, Krausch M *et al.* Clinical impact of retinoids in redifferentiation therapy of advanced thyroid cancer: final results of a pilot study. *Eur. J. Nucl. Med. Mol. Imaging* 29(6), 775–782 (2002).

68 Woyach JA, Kloos RT, Ringel MD *et al.* Lack of therapeutic effect of the histone deacetylase inhibitor vorinostat in patients with metastatic radioiodine-refractory thyroid carcinoma. *J. Clin. Endocrinol. Metab.* 94(1), 164–170 (2009).

69 Wang CY, Zhong WB, Chang TC, Lai SM, Tsai YF. Lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, induces apoptosis and differentiation in human anaplastic thyroid carcinoma cells. *J. Clin. Endocrinol. Metab.* 88(7), 3021–3026 (2003).

70 Zhong WB, Liang YC, Wang CY, Chang TC, Lee WS. Lovastatin suppresses invasiveness of anaplastic thyroid cancer cells by inhibiting Rho geranylgeranylation and RhoA/ROCK signaling. *Endocr. Relat. Cancer* 12(3), 615–629 (2005).

71 Koong SS, Reynolds JC, Movius EG *et al.* Lithium as a potential adjuvant to 131I therapy of metastatic, well differentiated thyroid carcinoma. *J. Clin. Endocrinol. Metab.* 84(3), 912–916 (1999).

72 Liu YY, van der PG, Karperien M *et al.* Lithium as adjuvant to radioiodine therapy in differentiated thyroid carcinoma: clinical and *in vitro* studies. *Clin. Endocrinol. (Oxf.)* 64(6), 617–624 (2006).

73 Liu YY, Morreau H, Kievit J *et al.* Combined immunostaining with galectin-3, fibronectin-1, CITED-1, Hector Battifora mesothelial-1, cytokeratin-19, peroxisome proliferator-activated receptor-{γ}, and sodium/iodide symporter antibodies for the differential diagnosis of non-medullary thyroid carcinoma. *Eur. J. Endocrinol.* 158(3), 375–384 (2008).

74 Kebebew E, Lindsay S, Clark OH *et al.* Results of rosiglitazone therapy in patients with thyroglobulin-positive and radioiodine-negative advanced differentiated thyroid cancer. *Thyroid* 19(9), 953–956 (2009).

75 Ain KB, Lee C, Williams KD. Phase II trial of thalidomide for therapy of radioiodine-unresponsive and rapidly progressive thyroid carcinomas. *Thyroid* 17(7), 663–670 (2007).

76 Ain KB, Lee C, Holbrook KM, Dziba JM, Williams KD. Phase II study of lenalidomide in distantly metastatic, rapidly progressive, and radioiodine-unresponsive thyroid carcinomas: preliminary results. *Proc. Am. Soc. Clin. Oncol.* 26, 6027 (2008).

77 Mrozek E, Kloos RT, Ringel MD *et al.* Phase II study of celecoxib in metastatic differentiated thyroid carcinoma. *J. Clin Endocrinol. Metab.* 91(6), 2201–2204 (2006).

78 Fagin JA. How thyroid tumors start and why it matters: kinase mutants as targets for solid cancer pharmacotherapy. *J. Endocrinol.* 183(2), 249–256 (2004).

■ **Interesting paper concerning the emerging field of targeted cancer therapies.**

79 Soares P, Sobrinho-Simoes M. Recent advances in cytometry, cytogenetics and molecular genetics of thyroid tumours and tumour-like lesions. *Pathol. Res. Pract.* 191(4), 304–317 (1995).

80 Sobrinho-Simoes M, Preto A, Rocha AS *et al.* Molecular pathology of well-differentiated thyroid carcinomas. *Virchows Arch.* 447(5), 787–793 (2005).

81 Puxeddu E, Durante C, Avenia N, Filetti S, Russo D. Clinical implications of BRAF mutation in thyroid carcinoma. *Trends Endocrinol. Metab* 19(4), 138–145 (2008).

82 Ringel MD, Hayre N, Saito J *et al.* Overexpression and overactivation of Akt in thyroid carcinoma. *Cancer Res.* 61(16), 6105–6111 (2001).

83 Miyakawa M, Tsushima T, Murakami H *et al.* Increased expression of phosphorylated p70S6 kinase and Akt in papillary thyroid cancer tissues. *Endocr. J.* 50(1), 77–83 (2003).

84 Vasko V, Saji M, Hardy E *et al.* Akt activation and localisation correlate with tumour invasion and oncogene expression in thyroid cancer. *J. Med. Genet.* 41(3), 161–170 (2004).

85 Kada F, Saji M, Ringel MD. Akt: a potential target for thyroid cancer therapy. *Curr. Drug Targets Immune. Endocr. Metabol. Disord.* 4(3), 181–185 (2004).

86 Hou P, Ji M, Xing M. Association of PTEN gene methylation with genetic alterations in the phosphatidylinositol 3-kinase/AKT signaling pathway in thyroid tumors. *Cancer* 113(9), 2440–2447 (2008).

87 Xing M. BRAF mutation in thyroid cancer. *Endocr. Relat. Cancer* 12(2), 245–262 (2005).

88 Dujardin F, Pages JC, Collin C *et al.* [BRAF V600E mutation in papillary thyroid carcinoma: prevalence and detection in fine needle aspiration specimens]. *Ann. Pathol.* 30(4), 252–262 (2010).

89 Tang KT, Lee CH. BRAF mutation in papillary thyroid carcinoma: pathogenic role and clinical implications. *J. Chin. Med. Assoc.* 73(3), 113–128 (2010).

90 Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. *Endocr. Rev.* 28(7), 742–762 (2007).

91 Riesco-Eizaguirre G, Gutierrez-Martinez P, Garcia-Cabezas MA, Nistal M, Santisteban P. The oncogene BRAF V600E is associated with a high risk of recurrence and less differentiated papillary thyroid carcinoma due to the impairment of Na+/I- targeting to the membrane. *Endocr. Relat. Cancer* 13(1), 257–269 (2006).

92 Espinosa AV, Porchia L, Ringel MD. Targeting BRAF in thyroid cancer. *Br. J. Cancer* 96(1), 16–20 (2007).

93 Begum S, Rosenbaum E, Henrique R *et al.* BRAF mutations in anaplastic thyroid carcinoma: implications for tumor origin, diagnosis and treatment. *Mod. Pathol.* 17(11), 1359–1363 (2004).

94 Nikiforov YE, Rowland JM, Bove KE, Monforte-Munoz H, Fagin JA. Distinct pattern of ret oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children. *Cancer Res.* 57(9), 1690–1694 (1997).

95 Nikiforov YE. RET/PTC rearrangement in thyroid tumors. *Endocr. Pathol.* 13(1), 3–16 (2002).

96 Mochizuki K, Kondo T, Nakazawa T *et al.* RET rearrangements and BRAF mutation in undifferentiated thyroid carcinomas having papillary carcinoma components. *Histopathology* 57(3), 444–450 (2010).

97 Segev DL, Umbricht C, Zeiger MA. Molecular pathogenesis of thyroid cancer. *Surg. Oncol.* 12(2), 69–90 (2003).

98 Kroll TG, Sarraf P, Pecciarini L *et al.* PAX8-PPARγ1 fusion oncogene in human thyroid carcinoma [corrected]. *Science* 289(5483), 1357–1360 (2000).

99 Nikiforova MN, Biddinger PW, Caudill CM, Kroll TG, Nikiforov YE. PAX8-PPARγ rearrangement in thyroid tumors: RT-PCR and immunohistochemical analyses. *Am. J. Surg. Pathol.* 26(8), 1016–1023 (2002).

100 Couto JP, Prazeres H, Castro P *et al.* How molecular pathology is changing and will change the therapeutics of patients with follicular cell-derived thyroid cancer. *J. Clin. Pathol.* 62(5), 414–421 (2009).

101 Vecchio G, Santoro M. Oncogenes and thyroid cancer. *Clin. Chem. Lab. Med.* 38(2), 113–116 (2000).

102 Powis G, Kozikowski A. Growth factor and oncogene signalling pathways as targets for rational anticancer drug development. *Clin. Biochem.* 24(5), 385–397 (1991).

103 Sherman SI. Targeted therapy of thyroid cancer. *Biochem. Pharmacol.* 80(5), 592–601 (2010).

■ **Well written overview of results of targeted therapy in differentiated thyroid carcinoma.**

104 Romagnoli S, Moretti S, Voce P, Puxeddu E. Targeted molecular therapies in thyroid carcinoma. *Arq. Bras. Endocrinol. Metabol.* 53(9), 1061–1073 (2009).

105 O'Neill CJ, Oucharek J, Learoyd D, Sidhu SB. Standard and emerging therapies for metastatic differentiated thyroid cancer. *Oncologist* 15(2), 146–156 (2010).

106 Pacini F, Brilli L, Marchisotta S. Targeted therapy in radioiodine refractory thyroid cancer. *Q. J. Nucl. Med. Mol. Imaging* 53(5), 520–525 (2009).

107 Milano A, Chiofalo MG, Basile M *et al.* New molecular targeted therapies in thyroid cancer. *Anticancer Drugs* 17(8), 869–879 (2006).

108 Hoftijzer H, Heemstra KA, Morreau H *et al.* Beneficial effects of sorafenib on tumor progression, but not on radioiodine uptake, in patients with differentiated thyroid carcinoma. *Eur. J. Endocrinol.* 161(6), 923–931 (2009).

109 Kogan EA, Rozhkova EB, Seredin VP, Paltsev MA. [Prognostic value of the expression of thyreoglobulin and oncomarkers (p53, EGFR, ret-oncogene) in different types of papillary carcinoma of the thyroid: clinicomorphological and immunohistochemical studies]. *Arkh. Patol.* 68(4), 8–11 (2006).

110 Pennell NA, Daniels GH, Haddad RI *et al.* A Phase II study of gefitinib in patients with advanced thyroid cancer. *Thyroid* 18(3), 317–323 (2008).

111 Cohen EE, Rosen LS, Vokes EE *et al.* Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a Phase II study. *J. Clin. Oncol.* 26(29), 4708–4713 (2008).

112 Banerji U, Camidge DR, Verheul HM *et al.* The first-in-human study of the hydrogen sulfate (Hyd-sulfate) capsule of the MEK1/2 inhibitor AZD6244 (ARRY-142886): a Phase I open-label multicenter trial in patients with advanced cancer. *Clin. Cancer Res.* 16(5), 1613–1623 (2010).

113 Rosen LS, Kurzrock R, Mulay M *et al.* Safety, pharmacokinetics, and efficacy of AMG 706, an oral multikinase inhibitor, in patients with advanced solid tumors. *J. Clin. Oncol.* 25(17), 2369–2376 (2007).

114 Sherman SI, Wirth LJ, Droz JP *et al.* Motesanib diphosphate in progressive differentiated thyroid cancer. *N. Engl. J. Med.* 359(1), 31–42 (2008).

115 Ravaud A, de la Fouchardiere C, Courbon F *et al.* Sunitinib in patients with refractory advanced thyroid cancer: the THYSU Phase II trial. *J. Clin. Oncol.* 26 (2008) (Abstract 6058).

116 Cohen EE, Needles BM, Cullen KJ *et al.* Phase 2 study of sunitinib in refractory thyroid cancer. *J. Clin. Oncol.* 26 (2009) (Abstract 6025).

117 Goulart B, Carr L, Martins RG *et al.* Phase II study of sunitinib in iodine refractory, well-differentiated thyroid cancer (WDTC) and metastastic medullary thyroid carcinoma (MTC). *J. Clin. Oncol.* 26 (2008) (Abstract 6062).

118 Bible KC, Smallridge RC, Maples WJ *et al.* Phase II trial of pazopanib in progressive, metastatic, iodine-insensitive differentiated thyroid cancers. *J. Clin. Oncol.* 27(Suppl. 15), (2009) (Abstract 3521).

119 Flaherty KT, Puzanov I, Sosman J *et al.* Phase I study of PLX4032: proof of concept for V600E BRAF mutation as a therapeutic target in human cancer. *J. Clin. Oncol.* 27(Suppl. 15) (2009) (Abstract 9000).

120 Eder JP, Heath E, Appleman L *et al.* Phase I experience with c-MET inhibitor XL880 administered orally to patients (pts) with solid tumors. *Proc. Am. Soc. Clin. Oncol.* 25(Suppl. 18), 3526 (2007).

121 Matsui J, Yamamoto Y, Funahashi Y *et al.* E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. *Int. J. Cancer* 122(3), 664–671 (2008).

122 Matsui J, Funahashi Y, Uenaka T *et al.* Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. *Clin. Cancer Res.* 14(17), 5459–5465 (2008).

123 Sherman SI. Tyrosine kinase inhibitors and the thyroid. *Best. Pract. Res. Clin. Endocrinol. Metab.* 23(6), 713–722 (2009).

124 Knauf JA, Fagin JA. Role of MAPK pathway oncoproteins in thyroid cancer pathogenesis and as drug targets. *Curr. Opin. Cell Biol.* 21(2), 296–303 (2009).

125 Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving Considerations for PET response criteria in solid tumors. *J. Nucl. Med.* 50(Suppl. 1) S122–S150 (2009).

■ **Study describing a new structured quantative clinical reporting system for tumor response.**

126 Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* 45(2), 228–247 (2009).

■ Website

201 Oncoline (2010) www.oncoline.nl