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Overview

Targeted therapy in patients with radioiodine-refractory differentiated thyroid cancer (DTC)

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Abstract

Papillary (PTC) and follicular (FTC) thyroid cancer (TC) belong to differentiated thyroid cancer (DTC). The initial treatment of DTC is surgery followed by radioiodine remnant ablation. Although the prognosis of DTC is generally good, approximately 10-15% of DTC patients will devolp advanced disease and their disease will become radioiodine refractory. Even in radioiodine refractory patients the natural history of disease can be slowly progressive or indolent.The expanded knowledge of the the biological basis of DTC has opened new opportunities in therapy – targeted therapy, aimed at inhibiting specific molecular targets and pathways in tumor proliferation, survival and progression. We rewieved different tageted therapies in DTC. Sorafenib was the first and only targeted drug approved by FDA for progressive and radiodine-refractory DTC. Also, lenvatinib had promising efficacy results in phase III trial, probably even better than sorafenib, but with more treatment-related deaths.

The timing of targeted therapy for DTC is of decisive importance. The potential benefit should be balanced with potential toxicity of targeted therapies.

INTRODUCTION

The incidence of thyroid cancer (TC) has been globally increasing over the last 30 years. This is attributed to an increase of diagnosing of small tumors (<2cm) by using high-frequency ultrasound probes and fine-needle aspiration (FNA) biopsies, and due to increased enviromental and medical radiation exposure, increased iodine intake, ethnic and genetic factors *(1)*. According to Croatian National Cancer Registry, 452 new thyroid cancers were diagnosed in 2011 *(2)*. Despite such a trend in incidence, the mortality, in western countries, has remained stable or is slowly decreasing *(3)*. Thyroid cancers are divided into four major histological types: papillary (85%), follicular (11%), medullary (35%), and anaplastic (1%). Papillary (PTC) and follicular thyroid cancer (FTC) are referred to as differentiated thyroid cancers (DTC). In general, 5-year survival rate of DTCs is more than 97% *(4)*. Tumors measuring less than 1 cm (thyroid microcarcinomas) have an excellent prognosis with 10-15 years disease-specific survival rates exceeding 99% *(5)*. Despite the general good prognosis of well differentiated TCs, some of them will develop a metastatic disease and cause a bad outcome. This has precluded the development of large body of trials to determine how patient characteristics and modalities of treatment affect the cause-specific mortality.

In addition to tumor size; age, completeness of resection, extrathyroidal extension, multicentricity, tumor grades are also prognostic factors that are used in many prognostic score systems for DTC. Prognostic scores caterogise patients into low-risk and high-risk groups based on stated variables *(6)*. The regional lymph node involment in determing DTC- specific survival remains controversial. Historically, the presence of lymph node metastases was belived to increase the reccurence without affecting survival, therefore the rutine lymph node dissection is often avoided. Large series and population-based studies suggest that lymph node involvement produces small but significant effect on survival *(7)*.

It is very important to recognise more agressive variants of DTCs such as tall-cell, columnar- cell, and diffuse-sclerosing subtype of DTC. Anaplastic thyroid cancers (ATC) are the least-differentiated and the most aggresive cancers of all. According to differentiation and prognosis, poorly differentiated thyroid cancers fall between the group of DTCs and ATCs. These tumors are insular and large-cell variants *(8)*. Pure FTC carries a worse prognosis in comparison to PTC. Mortality rate ranges from 5 to 15%, although survival extends as in PTC *(9)*. Hürthle cell or oncocytic tumor of thyroid arrises from the follicular epithelium and carries a worse prognosis compared with other DTCs *(10)*.

Recently, the data on genetic etiology of DTC has seen abundant growth (see Figure 1). Investigations into acquired genetic lesions that can distinguish carcinoma from benign thyroid nodule increased in the last decade. One of such markers is RET/PTC rearrangement. RET/PTC rearrangement represents a recombination of the promoter and N-terminal domain of a partner gene with the C-terminal region of the RET gene, resulting in a chimeric oncogene with a protein product containing a constitutively activated RET tyrosine kinase. At least 10 types of RET/PTC rearrangement have been identified. RET/PTC rearrangements are common in small, multifocal PTCs accompanied by an inflammatory infiltrates and are often seen in patients exposed to ionizing radiation (for example 70% of cancers found in Chernobyl survivors carried a RET/PTC rearrangement).

Another chromosomal translocation occurs in FTCs. The promoter region of the gene, encoding paired box 8 (PAX8) fuses with the coding sequence of the peroxisome proliferator-activated receptor-γ (PPARγ), was found in 35% of FTCs.

Most of the genetic alterations in thyroid cancer exert their oncogenic actions at least partially through the activation of the RET/PTC-RAS-RAF-MEK-ERK mitogen-activated protein kinase (MAP kinase) pathway.

Activation of this pathway is a common and important mechanism in the genesis and progression of human cancers through upregulating cell division and proliferation. When constitutively activated, the MAP kinase pathway leads to tumorigenesis. BRAF-activating missense point mutations in the kinase domain are clustered in exons 11 and 15 of the gene and the T1799A transversion mutation accounts for more than 80% of all the BRAF mutations. The T1799A mutation results in a V600E amino acid substitution in the protein product and subsequent constitutive activation of the BRAF kinase.

BRAF mutation is the most common genetic alteration in thyroid cancer, occurring in about 45% of PTCs, particularly in the relatively aggressive subtypes, such as the tall-cell PTC. *BRAF* mutation is mutually exclusive with *RET/PTC* rearrangement. This mutation is associated with a poorer clinicopathological outcome and is a novel independent molecular prognostic marker in the risk evaluation of thyroid cancer *(11)*.

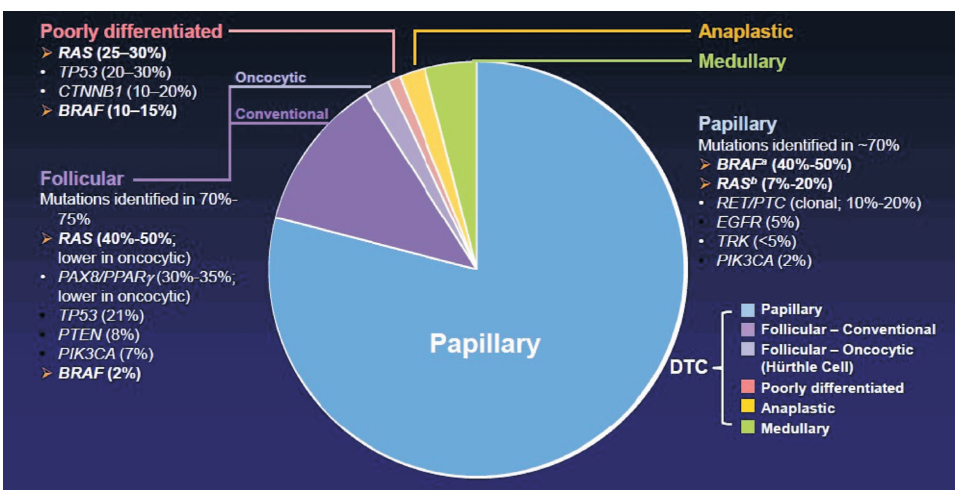


Figure 1. *Genetic etiology of thyroid cancer.*

The Ras proteins are plasma membrane GTPases activated by growth factor receptors. Mutations that result in constitutive activation of RAS lead to tumorogenesis. RAS mutations occur in 20% to 50% of follicular cancers *(12)*.

Initial treatment of differentiated thyroid cancer

The initial therapy of DTC should always be preceded by ultrasound exploration of the neck to access the neck lymph node status. The initial treatment for DTC is total or near-total thyroidectomy. Based on clinical recommendations (ESMO-European Society for Medical Oncology) and NCCN (Nation Comprehensive Cancer Network), the total thyroidectomy is surgical procedure of choice whenever the diagnosis is known before surgery (in most cases by FNA biopsy) and the thyroid nodule is ≥1 cm. The extent of thyroidectomy could be individualized for lower-risk PTC, but despite of clinical practice of some centers, the thyroid lobectomy is still a controversial issue. There are no randomized prospective trials comparing total thyroidectomy with thyroid lobectomy in low-risk TCs. Furthermore, radioactive iodine therapy for ablating microscopic disease becomes most effective when total thyroidectomy was performed or when small amount of thyroid remnant tissue is present. Multicentric tumors, with lower risk of recurrence in cervical lymph nodes, as well as easier long-term follow-up with thyroglobulin (Tg) determinations and whole-body 131-I imaging provide additional arguments for total thyroidectomy. The benefit of prophylactic central node dissection (level VI lymph nodes that include paratracheal, perithyroidal and precricoid lymph nodes) is another controversial topic related to the extent of initial surgery for DTC. Several studies support the concept that prophylactic central neck dissection is not necessary in case of postoperative radioactive iodine (RAI) ablation *(13, 14, 15)*.

Radiodine therapy (I-131) therapy is the standard adjuvant treatment after a total or near-total thyroidectomy aimed to ablate remnant thyroid tissue and microscopic residual disease. It is the first targeted therapy in oncological history and this procedure decreases the risk of locoregional recurrence (IA level of evidence according to ESMO Clinical Recommendations). As with the controversy over the extent of thyroidectomy, the benefit of RAI for low-risk patients remains unclear. There is no indication for RAI in very low-risk patients (those with unifocal T1 tumors, ≤1 cm in size, with favorable histology, no extrathyroidal extension or lymph node metastases). Some studies have shown an increase in the risk of developing secondary malignancies after RAI (hematological malignancies are the most common) *(16)*. Two large prospective trials (the ESTIMABL study and the HiLo trial) were performed to compare different activities for RAI ablation in patients with DTC *(17, 18)*. A meta-analysis including previously mentioned trials showed that there was no significant difference between the low and high dose regimen *(19)*. Recommended doses are (1100 to 3700 MBq or 30 to 100 mCi) for patients with lower risk and higher doses (3700 to 7400 MBq or 100 to 200 mCi) for patients with residual disease and more aggressive histological subtypes. Effective RAI requires the TSH concentrations at least as high as 30 mU/l to stimulate targeted (intracellular) uptake of I-131. The method of choice according to ESMO Clinical Recommendations for preparation for RAI is based on the administration of recombinant human TSH (rhTSH) while the patient is on levo-thyroxine (LT4) therapy. The traditional method is the withdrawal from thyroid replacement therapy (LT4) over 4-6 weeks to produce profound hypothyroidism.

Thyroxine suppression is another adjuvant approach in therapy of DTCs. TSH suppression is provided through the administration of supraphysiological doses of LT4. For high-risk patients LT4 doses should be initially titrated to a TSH of less than 0.1 mU/l, and for lower- risk patients between 0.1 to 0.5 mU/l. After few years of follow-up and in the absence of TC recurrence, TSH values can be returned to reference ranges *(12)*.

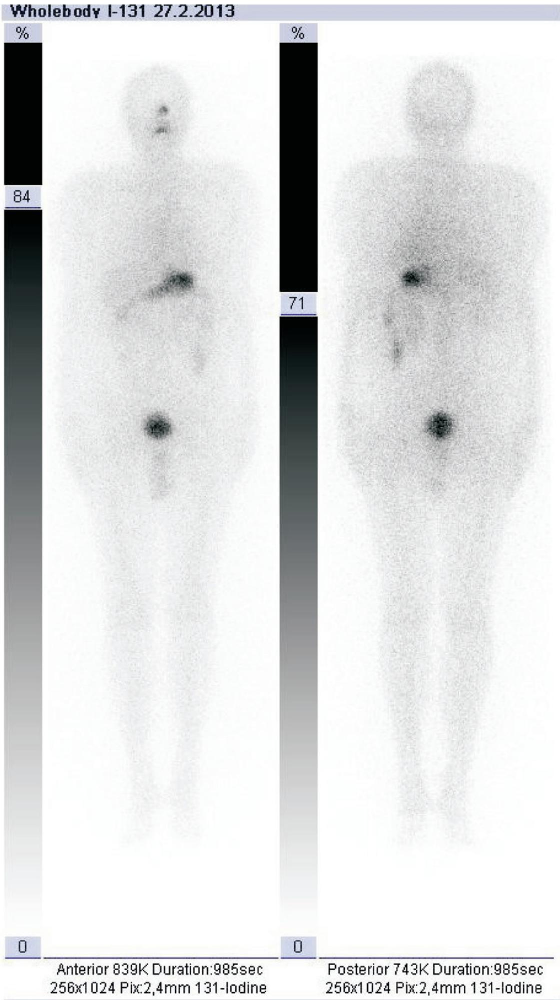
Conventional therapy for recurrent locoregional and metastatic TC

The most common sites of distant metastases from DTC are the lungs (50%) and bone (25%), followed by the brain, liver, kidneys, and muscles (5%). Two-thirds of patients who develop locoregional recurrence and one-third with distant metastases may achieve complete remission. Older patients have the worst prognosis (>45 years old) with metastatic disease. These patients have a 5-year survival rate of only ~30% to 40% *(20)*. Aggressive surgery, radioiodine therapy, and levothyroxine suppression therapy can improve overall survival and disease-specific survival in this subgroup of patients.

Treatment of locoregional recurrence is based on the combination of surgery and RAI.

External beam radiotherapy is reserved as an option, if surgery and RAI have been exhausted. Chemotherapy has not been largely evaluated for metastatic DTCs, but it is known to confer minimal effects (responses from 0% to 22% with the most used agent, doxorubicin) *(21)*.

In approximately 5%-15% of patients with thyroid cancer, the disease becomes refractory to RAI *(22)*. Resistance to RAI is defined by the presence of at least one tumor focus without any iodine uptake, by progression of the disease after RAI, and in patients with persistent disease after administration of cumulative dose of 600 mCi I-131 (see figure 2). RAI refractory disease occurs more often in older patients, in those with large metastases and those with positive FDG-PET scans. Median survival for patients with RAI-refractory DTC and distant metastases is estimated to be 2.5 – 3.5 years *(23)*.



However, metastatic DTC can be asymptomatically stable for long period of time. Progression rate of metastatic disease can be assessed by the doubling time of thyroglobulin and confirmed with morphological diagnostic methods *(22)*.

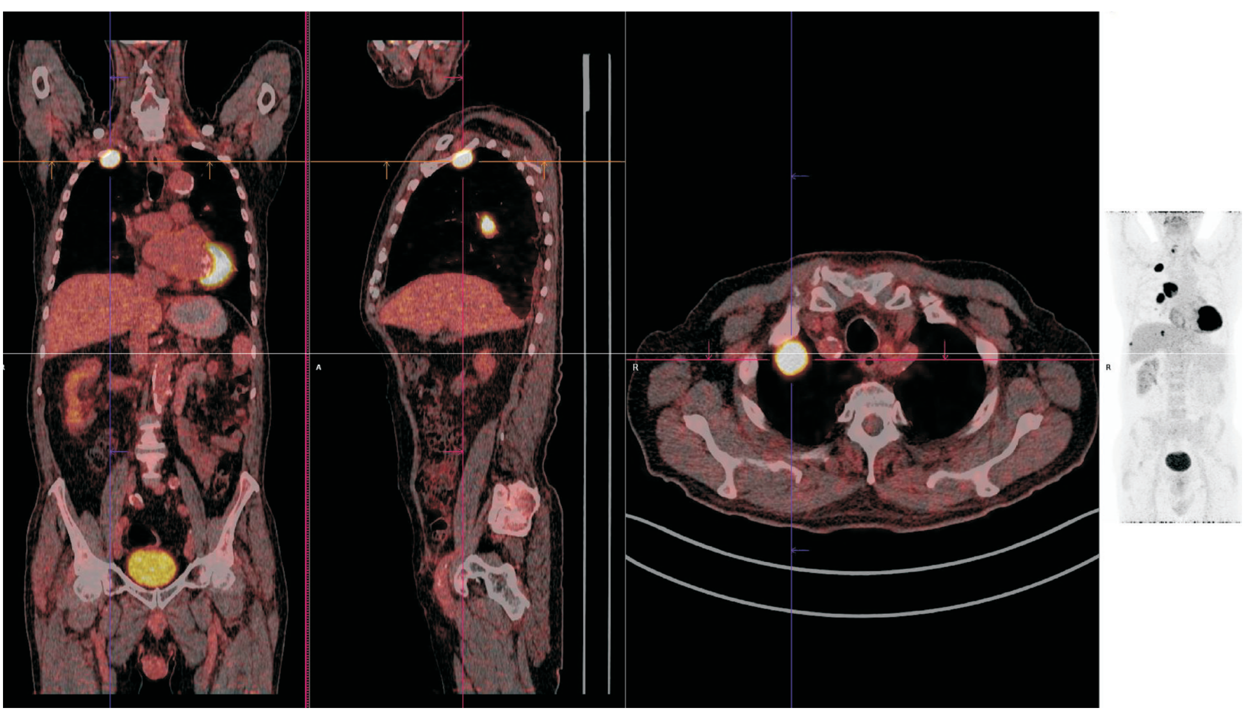
TARGETED THERAPY FOR DIFFERENTIATED THYROID CANCER

SORAFENIB is a small molecule that inhibits all Raf kinases (A-Raf, B-Raf and C-Raf),

Additionally, it targets a panel of angiogenic tyrosine kinase receptors such as vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptor β(PDGFRβ) and RET.

Since 2006, larger number of clinical studies has been conducted with sorafenib (Table 1), mostly phase II, but a Phase III study has recently been published, which resulted in that the US Food and Drug Administration (FDA) approved sorafenib for the treatment of RAI resistant metastatic DTC. The studies varied in the subtypes of DTCs that were included. All the studies have the unique peroral dose of sorafenib 400 mg/bid. Brose *et al. (37)* published randomized, double-blind, placebo-con-

Figure 2. *Shows radioiodine refractory metastases in patient with DTC; negative I-131 scan (image at the top) and intense fluorodeoxyglucose (FDG) uptake in lung metastases (PET-CT scan at the bottom).*



trolled phase III trial (DECISION), which comprised 417 patients. Patients assigned to the placebo group whose disease progressed during the trial could „cross over" and receive sorafenib. Median progression-free survival was significantly longer in the sorafenib group (10.8 months) than in the placebo group (5.8 months); hazard ratio (HR) 0.59. The objective response rate (ORR) was 24% in the sorafenib group and less than 1% in the placebo group. Overall survival (OS) did not differ between the patients treated with sorafenib and those who received a placebo. Stable disease (SD) ≥6 months in the sorafenib group was 41.8%. Among the patients with no objective response, nearly 42% in the sorafenib group had stable disease for at least 6 months after beginning the treatment, compared with 33.2% of those in the placebo group. Disease control rate (complete remission CR+ partial remission PR+SD) was significantly better for the sorafenib group in comparison to the placebo group (P<0.0001). Information on *BRAF* and *RAS* mutations in the patients' tumor tissue was available for 61% of all patients in the trial (126 patients in the sorafenib group and 130 patients in the placebo group). Mutations in these genes were not associated with longer progression-free survival in patients treated with sorafenib. The side effects were mainly low-grade and included hand-foot reaction, skin rash, fatigue, and hair loss. Nevertheless, nearly two-thirds of patients in the sorafenib group had their treatment temporarily halted or the drug dose reduced, and nearly 19% stopped the treatment altogether because of side effects. Approximately 37% of the patients in the sorafenib group and 26% of the patients in the placebo group had a serious adverse event (SAE). SAE in the sorafenib group included the development of a second primary cancer, breathing difficulties, and pleural effusion. One death, caused by a heart attack, was also attributed to sorafenib. The toxicity profile is acceptable and it is similar to the toxicity profile in hepatocellular carcinoma.

LENVATINIB is a synthetic, orally available inhibitor of VEGFR1-3 tyrosine kinase, fibroblast growth factor receptor (FGFR 1-4), PDGFRβ, RET and KIT resulting in inhibition of the VEGF receptor signal transduction pathway, resulting in decrease of vascular endothelial cell migration and proliferation, and vascular endothelial cell apoptosis. Lenvatinib showed promising results in thyroid cancer in Phase I *(38).* In phase II trial *(39)* lenvatinib induced a PR in 45% of 58 patients and SD in another 46% of patients. Median PFS was 13.3 months. In SELECT *(40),* global, randomized, double-blind, placebo-controlled phase III study 392 patients were enrolled. Upon progression, the patients receiving placebo could crossover to open-label lenvatinib. In the patients with RAI resistant DTC, lenvatinib significantly prolonged the median PFS by 14 months compared with placebo (lenvatinib median PFS: 18.3 months (95% CI 15.1-NR), the placebo median PFS (95% CI 2.2-3.7); HR 0.21 (99% CI, 0.14-0.31)). Response rate for lenvatinib and placebo, respectively, were: ORR: 65% vs 2% (with CR; 2% vs 0%). The median time to objective response to lenvatinib was 2.0 months (95% CI, 1.9-3.5 months). The median duration of response for lenvatinib has not been reached, but 75% of responders had an objective response >9.4 months. Median OS has not been reached. The 5 most common lenvatinib treatment-related adverse events of any grade were hypertension (68%), diarrhea (59%), appetite decreased (50%), weight loss (46%), nausea (41%). Lenvatinib grade ≥3 treatment-related adverse events (≥5%) were hypertension (42%), proteinuria (10%), weight loss (10%), diarrhea (8%), appetite decreased (5%). 6 of 20 lenvatinib treatment-emergent deaths were considered as treatment-related: pulmonary embolism (n=1), hemorrhagic stroke (n=1), general health deterioration (n=4).

VANDETANIB targets epidermal growth factor receptor (EGFR), VEGFR2 and 3, RET kinases. Based on ZETA (phase II/III randomized placebo-controlled trial) FDA approved vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer (MTC) in patients with unresectable, locally advanced or metastatic disease. Potentially serious cardiac effects (QT prolongation, torsades de pointes and sudden death) call for caution in prescribing this medication *(41).*

Improved PFS has been reported in a double-blind phase II study, where 45 patients with metastatic or locally advanced DTC were enrolled. The results showed longer PFS in the vandetanib group (11.1 months) with respect to the placebo group (5.9 months). The safety in this study was similar to previous studies of vandetanib *(42).*

MOTESANIB is a highly selective inhibitor of PDGFR, VEGFR 1-3 and c-KIT and inhibits cellular proliferation and angiogenesis. Trial II was conducted in patients with advanced RAI resistant DTC on motesanib phase *(43).* Median PFS of 40 weeks was achieved. Most common treatment-related adverse events were hypertension (56%), diarrhea (59%), fatigue (46%) and weight loss (40%).

AXATINIB targets PDGFR, VEGFR 1-3 and c-KIT. It is considered the most potent VEGFR2 inhibitor. In clinical studies patients suffering from DTC and MTC were randomized. PR was shown in 30% (18) patients and SD in 38% (23) patients. The most common adverse event was hypertension. In 3 patients grade 4 toxicity was diagnosed caused by hypertension, stroke and reversible posterior leukoencephalopathy *(44).*

SUNITINIB targets c-KIT, VEGFR-2, PDGFR, RET. Phase II study of sunitinib was conducted in refractory TC. The best response was PR 13% in 31 evaluable DTC patients, and SD 68%. The toxic profile was the same as seen in therapy of renal cancer (hypertension, thrombocytopenia, fatigue, neutropenia, palmar-plantar erythrodysestesia, and gastrointestinal symptoms *(45).* In

TABLE 1
Phase II studies of sorafenib for radioiodine resistant DTC.

studies	Thyroid cancer type numbers	Responses
Gupta-Abramson (24)	30 DTC	PR 23%, SD 53%, mPFS 79 weeks
Brose (25)	29 PTC, 18 FTC, 3 MTC, % PD/anaplastic	mPFS 84 weeks (DTC)
Kloos (26)	52 DTC/4 ATC	PR 15%, SD 56% (PTC), FTC no reponse, mPFS 15 months
Hoftijzer (27)	31 DTC	PR 25%, SD 34%
Ahmed (28)	MTC, DTC	PR 16%, SD 68%
Cepdevilla (29)	15 DTC, 12 MTC, 3 ATC	PR 19%, SD 50%, PFS 13.3 months, OS 23.6 months
Keefe (30)	47 DTC, 3 MTC, 5 ATC	PR 38%, SD 47%, PFS 96 weeks, OS 140.9 weeks
Schneider (31)	31 DTC	mPFS 18 months, mOS 34.5 months, PR 31%, SD 42%
Adili (32)	44 PD	Sorafenih vs placebo mOS 34 vs 9 months, PR 23% vs 12.5%, SD 62% vs 50%
Marotta (33)	17 DTC	30% PR, 41% SD
de la Fouchardiere (34)	45 DTC	PR 29%, mPFS 6.7 months
Chen (35)	9 PTC	PR 33%, SD 44%, mPFS 42 weeks
Cabanillas (36)	13 DTC	20% PD, mPFS 19 months

Abbreviations: DTC-differentiated thyroid cancer, PTC -papillary thyroid cancer, FTC -folicular thyroid cancer, ATC -anaplastic thyroid cancer, MTC – medullary thyroid cancer, PD – poorly differentiated thyroid canncer, PR – partial response, SD -stable disease, mPFS -mean progression free survival, mOS -mean overall survival

TABLE 2
Targeted therapy used in clinical trials in DTC.

drug	tumor type	study phase	No of pts	response	PFS	reference
lenvatinib	DTC	III	392	ORR 65%	18.3 vs 3.6 months	40
vandetanib	DTC	II	145	PR 1% SD 56% > 6 months	11.1 vs 5.9 months	42
motesanib	DTC	II	93	ORR 14%	40 weeks	43
axitinib	DTC	II	60	PR 30% SD 38% > 6 months	18 months	44
sunitinib	DTC	II	28	PR 29%		46
pazopanib	DTC	II	37	PR 49%	11.7 months	48
cabozatinib	DTC	I	15	PR 53% SD 66% >6 months		49
vemurafenib	DTC	II	51	PR 61% SD 66% >6 months	16 months	50

Abbreviations: DTC differentiated thyroid cancer; PFS progression free survival, ORR overall response rate, PR partial response, SD stable disease

the ASCO meeting 2008 THYSU study was presented with a small number of DTC patients, but the largest sunitinib phase II study published in 2010 enrolled 28 patients with DTC. CR was shown in 1 patient, PR in 28% and SD in 46% of patients *(46).*

CABOZATINIB is an oral inhibitor of multiple receptor tyrosine kinases including RET, MET, and VEGFR2. According to results of double-blind, randomized, placebo controlled phase III study (EXAM) FDA and EMA (European Medicines Agency) approved cabozatinib for the treatment of progressive, metastatic MTC *(47),* but the data for cabozatinib in DTC patients are very limited. Only one phase I study with promising results was reported on the ASCO meeting 2011 *(48).*

PAZOPANIB is a small-molecule inhibitor of VEGFR 1-3, FGFR 1-3, PDGFR, interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein kinase (Lck), c-Kit, and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). In a Phase II trial, pazopanib induced a PR 49% of 37 patients and lasted more than one year for the patients with RAI- refractory metastatic DTC. Interestingly, pazopanib is frequently more effective in follicular and Hürthle cell cancer than in PTC. Dose reduction was required in 43% of patients because of adverse events such as fatigue, skin and hair hypopigmentation, diarrhea, nausea, hepatotoxicity and hypertension. SAE were QT prolongation, thromboembolic events, and gastrointestinal perforation *(49).*

BRAF inhibitors

There are three kinds of Raf kinase proteins: A-Raf, B-Raf, and C-Raf. BRAF mutations results in signals for uncontrolled cellular proliferation. The most common is V600E mutation, in which valine is substituted with glutamic acid, and it is found in 40-50% of PTC, melanoma, and colon cancer *(11).*

VEMURAFENIB is an orally administered BRAF V600E inhibitor, but also other BRAF mutations such as V600K, and V600R. Vemurafenib was the first BRAF inhibitor approved by FDA and EMA for metastatic melanoma. In the phase II trial, 51 patients with progressive RAI refractory PTC were enrolled, and BRAF V600E mutation by cobas® 4800 V600 Mutation Assay was confirmed. Patients were assigned to either cohort 1 (TKI naive) or cohort 2 (if previously treated with TKIs). Median PFS was 15.6 months in cohort 1 and 6.8 months in cohort 2. The overall toxicity profile was consistent with that seen in melanoma trials. Common adverse events included rash, fatigue, weight loss and increased bilirubin *(50).*

DABRAFENIB is the second BRAF kinase inhibitor, also approved for metastatic melanoma. In a Phase I trial, patients with BRAF-mutant metastatic PTC had a 33% response rate *(51).*

The future direction would be to achieve a greater or durable response by utilizing combined targeted therapy. Sorafenib, as the first approved drug for progressive, RAI-refractory thyroid cancer, was combined with other TKIs. In phase II prospective trial tipifarnib, a farnesyl transferase inhibitor was combined with sorafenib. The tipifarnib trials results in PR of 4.5%, while SD was seen in 36% of DTC patients. Median PFS was 15 months, but the analysis included MTC participants. Sorafenib/tipifarnib toxicity was mostly grade 1-2, including rash, fatigue, and diarrhea *(52).*

A sorafenib/temsirolimus (intravenous mTOR inhibitor) showed 38% PR in the recurrent RAI-resistant DTC cohort that had not received previous systemic treatment *(53).* The same author reported a sorafenib/everolimus combination Phase II study with 28 RAI-resistant DTC of various histological subtypes and found PR between 33% and 50%. Cumulative grade 4 toxicities were seen in the form of one case each of hyperglycemia, pancreatitis, and elevation of aminotransferases *(54).*

CONCLUSION

In the vast majority of cases (90%) DTC is a curable disease. Even in metastatic setting, DTC has indolent, slowly progressive course, frequently cured by surgery, RAI and LT4 therapy. Two thirds of patients with metastases have RAI-resistant disease and, until recently, there were no therapy options for them. The knowledge of the biological basis of thyroid cancer was sufficiently increased, that induced the research on new targeted drugs, which aims to change the prognosis of patients with RAI-resistant metastatic DTC. The shown data are based primarily on Phase II trials, with only few on Phase III trials. We rewieved a wide variety of treatment strategies, but only sorafenib has been approved by FDA for progressive and RAI-refractory DTC so far. Also, lenvatinib had promising efficacy results in phase III trial, probably even better than sorafenib, but with more treatment-related deaths. For another rewieved drug, vandetanib, which was approved for MTC, the phase III trial for RAI- refractory DTC (VERIFY study) is being conducted, and the results are expected.

If the natural course of metastatic DTC it is a slowly progressing disease, the risk of adverse events outweigting the potential benefit of new drugs. Therefore, the patients must show at least a progressive disease within one year before the initiation of targeted therapy. The initiation of systemic therapy for DTC patients should preferably be coordinated in referral centres and patients should, if possible, be enrolled in clinical studies.

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