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Treatment of distant metastases from follicular cell-derived thyroid cancer

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Abstract

Distant metastases from thyroid cancer of follicular origin are uncommon. Treatment includes levothyroxine administration at suppressive doses, focal treatment modalities with surgery, external radiation therapy and thermal ablation, and radioiodine in patients with uptake of ^{131}I in their metastases. Two thirds of distant metastases will become refractory to radioiodine at some point, and when there is a significant tumor burden and documented progression on imaging, a treatment with a kinase inhibitor may provide benefits.

Introduction

Distant metastases occur in less than 10% of patients with differentiated follicular-derived thyroid carcinoma and are located mostly in lungs and bones. In contrast with the observed increasing incidence of small thyroid cancers, there is no evidence that their incidence changes with time. They are the main cause of thyroid cancer-related deaths, and mortality rates at 5 and 10 years after the diagnosis of metastasis are 65% and 75%, respectively [1–4].

In recent years, major therapeutic advances have been achieved for metastatic thyroid cancers: the aims of levothyroxine treatment have been clarified, thermal ablation is currently used, indications and limits of radioiodine treatment have been better defined, and new treatment modalities are available for radioiodine-refractory disease. This review is intended to describe these advances.

Treatment of distant metastases

Treatment of distant metastases includes levothyroxine treatment and focal treatment and systemic treatment (including radioiodine) and, in patients with radioiodine-refractory disease, the use of kinase inhibitors. No randomized clinical trial has demonstrated superiority of either radioiodine administration or thyroid-stimulating hormone (TSH) suppressive thyroid hormone treatment for patients with distant metastases. The use of these treatments is traditional and supported only by retrospective cohort studies, and modalities are presented according to author's practice, but there are broad variations in acceptable "standard of care" with respect to the aggressiveness of TSH suppressive therapy and to the frequency and amount of radioiodine to use.

The objective of levothyroxine treatment in these patients is to maintain serum TSH below 0.1 mIU/L in the absence of contraindications because TSH is a growth factor for thyroid cells and any increase in TSH level may stimulate cancer growth [5]. However, poorly differentiated thyroid cancers may progress even when serum TSH is undetectable. Also, the benefits of subclinical thyrotoxicosis have to be balanced in each patient with the risk of cardiovascular consequences.

In the past, focal treatment of bone metastases was based on surgery after embolization and external beam radiation therapy [2,6]. Thermal ablation (radiofrequency

ablation or cryoablation) and cement injection are currently used whenever possible because they are as effective, as but less aggressive than, surgery for the local control of the disease [7,8], and they may be combined with external beam radiation therapy. Focal treatment is indicated when there are neurologic or orthopedic complications or a high risk of such complications or when bone metastases are visible on computed tomography (CT) scan or magnetic resonance imaging (MRI), even in the presence of ^{131}I uptake, because in such cases radioiodine alone will not control the disease. In patients with a single or a few bone metastases, focal treatment may be performed with a curative intent [6]. In patients with brain metastases, surgery and stereotactic radiation therapy (rather than whole brain irradiation) may be indicated. In case of few and predominant lung metastases, thermal ablation or stereotactic radiation therapy may be used for local control.

Two thirds of patients with distant metastases have significant ^{131}I uptake and receive 100-200 mCi (3,700-7,400 MBq) every 4-6 months during the first 2 years and then at longer intervals. Activities based on weight—1-2 mCi (37-74 MBq) per kilogram of body weight—are given to children [9]. Between ^{131}I treatments, levothyroxine is used to maintain serum TSH level below 0.1 mIU/L. In one study, the radiation dose to the tumor tissue and outcome of ^{131}I therapy were correlated [10]. This is the rationale for using high activities of radioiodine either as standard activity or based on individual dosimetry. In patients with functioning metastases, positron emission tomography (PET) scanning with ^{124}I showed that, in a given patient, uptake may vary between metastases and also within a given metastasis [11]. Heterogeneity in the dose distribution is also observed at the cellular level and may explain pitfalls of ^{131}I treatment despite significant mean uptake on total body scan [12]. For treatment to be effective in this clinical setting, appropriate levels of TSH stimulation and absence of iodine contamination are essential. Excess iodine is eliminated 1 month after administration of an iodinated contrast CT scan [13]. Prolonged withdrawal usually induces higher uptake in neoplastic foci than injections of recombinant human TSH (rhTSH) and is the preferred method of TSH stimulation in patients with metastatic disease [14]. Similar short-term survival rates were observed in patients with distant metastases after ^{131}I treatment prepared with either withdrawal or rhTSH [15]. However, most patients with ^{131}I uptake in their metastases are alive at 5 years, and no data are available on long-term outcome after preparation with rhTSH. rhTSH-mediated therapy may be indicated in selected metastatic patients with underlying comorbidities, making iatrogenic hypothyroidism potentially risky, and in patients with pituitary disease who are unable to raise their serum TSH [16].

Efficacy of ^{131}I treatment is assessed by using functional parameters—serum thyroglobulin (Tg) level and quantitative ^{131}I uptake in metastases on post-therapy whole-body scan (WBS)—and tumor volume assessment on anatomical imaging with CT scan and MRI. Favorable responses are characterized by parallel decreases in tumor volume and in functional parameters (^{131}I uptake and serum Tg level). Disappearance of imaging abnormalities has been obtained overall in about 45% of the two out of three patients with distant metastases showing initial avidity for ^{131}I (who thus represent one third of all metastatic patients); median cumulative activity was 200 mCi, and almost all responses were achieved with a cumulative activity of 600 mCi [2]. Complete responses are more frequently achieved in younger patients, in those who had small pulmonary metastases, who had a well-differentiated cancer, and who had no or low fluorodeoxyglucose (FDG) uptake on PET scan [2,17–19]. When response was judged to have been complete after ^{131}I therapy, subsequent relapse occurred in less than 10% of patients, even though serum Tg levels were persistently detectable in some patients [2].

Definition of radioiodine-refractory thyroid cancer

Radioiodine-refractory thyroid cancer occurs in the two thirds of distant metastases that are not cured with radioiodine [2]. It is an uncommon condition, and the estimated incidence is four to five cases per million population (around 250 patients per year in France) [20,21]. Most patients with ^{131}I-refractory follicular-derived differentiated thyroid carcinoma fall into one of four categories: (a) Patients with metastatic disease that does not take up ^{131}I at the time of initial treatment. This group includes patients with structurally evident disease with no ^{131}I uptake on a diagnostic WBS, because in such patients ^{131}I uptake when present on post-therapy scans will not be sufficient to induce benefits [22]; (b) Patients whose tumors lose the ability to take up ^{131}I after previous evidence of uptake. This is due to the eradication by ^{131}I treatment of differentiated cells able to take up ^{131}I but not of less differentiated cells that do not take up ^{131}I and that are likely to progress; (c) Patients with ^{131}I uptake retained in some lesions but not in others. This is frequently seen in patients with multiple large metastases [10]. In all of these patients, progression is likely to occur in metastases without ^{131}I uptake (in particular when FDG uptake is present) [17–19]; (d) Patients with metastatic disease that progresses despite significant uptake of ^{131}I in the metastases and following a course of adequate radioiodine

treatment [23]. In patients with refractory disease, ^{131}I treatment does not provide benefits and should be abandoned.

Less clear is the situation for patients with persistent visible ^{131}I uptake in all lesions who are not cured despite several treatment courses but whose disease does not progress. For these patients, the probability of obtaining a cure with further ^{131}I treatment is low [2], and side effects, including the occurrence of secondary cancers and leukemias, may increase [24]. The decision to continue ^{131}I treatment in such patients (particularly after receiving more than 22 GBq-600 mCi of ^{131}I) is generally based on their response to previous treatment courses, persistence of a significant level of ^{131}I uptake on the previous post-therapy WBS, low FDG uptake in tumor foci, and absence of side effects [2]. Some patients may experience dissociated response to ^{131}I treatment with a tumor response in some lesions and progression in other lesions; in such patients, focal treatment modalities may be applied on progressive lesions, and ^{131}I treatment courses may be given according to the above-mentioned criteria.

Overall survival after the discovery of distant metastases is more favorable in young patients with well-differentiated tumors that take up ^{131}I and have metastases that are small when discovered [2]. When the tumor mass is considered, the location of the distant metastases, whether in the lungs or bones, has no independent prognostic influence. Small radio-avid bone metastases with no structural abnormalities respond to therapy [25], and the poor prognosis of most patients with bone metastases is linked to the large size of their lesions [1–3,5].

Patients with advanced disease who are refractory to ^{131}I treatment have a median life expectancy of 3-6 years [2]. Refractory disease occurs more frequently in older patients, in those with large metastases or with poorly differentiated thyroid cancer, and in those with high FDG uptake on PET scan [2,17–19]. Fortunately, major advances have been achieved in recent years for the treatment of these rare patients.

Treatment of refractory thyroid cancer

Once ^{131}I treatment is abandoned, levothyroxine treatment is maintained to suppress TSH secretion and focal treatment on metastases is performed whenever needed. Surveillance includes an FDG-PET/CT scan or a CT scan with contrast of the head, neck, chest, abdomen, and pelvis at an interval of 3-12 months that is dictated by the pace of prior disease progression. Most patients with refractory advanced disease have an aggressive course, but the disease can be asymptomatically stable for long periods of time, in particular in young patients with small lung metastases from a well-differentiated carcinoma who are maintained on levothyroxine treatment at suppressive doses, because in such patients the benefits of novel therapies may be largely outweighed by drug toxicities.

The decision to initiate systemic treatment in patients with radioiodine-refractory disease is based on several parameters, including tumor burden, disease progression, location of tumor foci, symptoms, or high risk of local complications. Progression rate can be evaluated by the doubling time of serum Tg [26] but should always be confirmed by imaging using response evaluation criteria in solid tumor (RECIST) [27]. Indeed, patients with multiple lesions of 1-2 cm and with progression within less than 12 months are considered for systemic treatment. In contrast, patients with few or small metastatic lesions less than 1 cm (or both) and those with no evidence of progression are considered for no treatment but for follow-up every 3-6 months [20,21]. Some patients with large tumor burden and lacking ^{131}I uptake and for whom there are no data on progression may be considered for systemic treatment on the basis of high uptake of FDG on PET scanning or even on primary tumor histology or when there is a high risk of local complications [17–19].

Bone-directed therapies

Two thirds of patients with bone metastases from a differentiated thyroid cancer (DTC) developed skeletal-related events within a year following the diagnosis of bone metastases [28]. Focal treatment modalities are used in patients with threatening or symptomatic bone lesions (or both) before initiation of systemic treatment. Unfortunately, bone progression commonly occurs during kinase inhibitor therapy and bone-directed therapy should be considered in patients with multiple progressing or symptomatic bone metastases (or both) even if kinase inhibitor therapy is intended or ongoing. In other solid tumors, bisphosphonates (especially intravenous infusion of zoledronic acid every 3 months) and the receptor activator of nuclear factor-kappa-B (RANK)-ligand-directed agent (monthly subcutaneous injection of denosumab, either on a routine basis or only in case of renal failure) have been shown to delay time to occurrence of skeletal-related events and to improve symptoms with similar efficacy [29,30]. Risks of these agents include hypocalcemia, prompting the concomitant use of supplemental calcium and vitamin D therapy, and non-healing oral lesions and jaw osteonecrosis indicating dental/oral surgical evaluation.

Cytotoxic chemotherapy

Cytotoxic chemotherapies provided low response rates (from 0-22% with the most frequently used agent, doxorubicin, at a dose of 60 mg/m^2 every 3-4 weeks),

and toxicity was high [31]. However, cytotoxic chemotherapy with recent drugs such as gemcitabine, oxaliplatinum, or taxanes may be used since they appeared to be effective in some patients [32,33].

Molecular-targeted therapy

Kinase inhibitors have been used for 10 years for the treatment of patients with refractory DTC. In most patients with DTC, an initiating carcinogenic event can be found and molecular targeted therapy could be given with a scientific rationale [20,34]. Gene rearrangements (*RET-PTC* and *NTRK*) or point mutations of the *RAS* and *BRAF* genes are found in two thirds of papillary thyroid cancers, resulting in the activation of the mitogen-activated protein (MAP) kinase pathway. Point mutations of the *RAS* genes are frequently found in follicular and poorly differentiated carcinomas. Angiogenesis is activated in thyroid cancers [35] by activation of the vascular endothelial growth factor receptor (VEGFR) pathway and other pathways, such as the fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) pathways. Up to now, most drugs used in refractory thyroid cancers are anti-angiogenic and some also target kinases in the MAP kinase pathway. The relative role of the inhibition of each target or of their combined inhibition on tumor growth is currently unknown.

With these agents, partial responses were observed in phase II trials in 0-59% of patients and long-term stable disease in at least another third. Table 1 reports targets of each drug and main results of each trial. Comparison of the outcomes among these compounds is at the present time not possible, but the response rates recently reported with pazopanib, lenvatinib, and cabozantinib (around 50% or even higher) seem higher than those previously reported [36–49]. It also appears that most drugs are more effective on metastases located in lymph nodes and lungs than in bones. Even more important is the benefit in progression-free survival (PFS) with these agents when compared with placebo as seen first in one phase II trial and then in two phase III trials. The lack of demonstrated improvement in overall survival might have been related to the crossover design of the studies.

The ZACTHYF Zactima in thyroid refractory cancer phase II randomized trial with vandetanib (300 mg/day) versus placebo on 145 patients with radioactive iodine (RAI)-refractory locally advanced or metastatic DTC that had progressed within the past 14 months produced a significant prolongation of the PFS (hazard ratio (HR) 0.63, P = 0.008; median 11.1 versus 5.9 months, respectively), but no partial response was observed [47].

The DECISION Study of Sorafenib in Locally Advanced or Metastatic Patients with RAI-Refractory Thyroid Cancer phase III trial was performed on 417 patients with RAI-refractory locally advanced or metastatic DTC that had progressed within the past 14 months [48]. Patients were randomly assigned 1:1 to either sorafenib (400 mg administered orally twice daily) or placebo. Sorafenib treatment significantly improved PFS compared with placebo (HR 0.587, 95% confidence interval [CI] 0.454 to 0.758; P <0.0001; median PFS 10.8 versus 5.8 months, respectively), and the partial response rate was 12%. The improvement in PFS was seen in all clinical subgroups. The safety profile of sorafenib was as expected, and most adverse events were grade 1 and 2. The most common treatment-emergent adverse events in the sorafenib arm were hand foot skin reaction (76%), diarrhea (69%), alopecia (67%), and rash/desquamation (50%). Toxicities led to dose reduction in 64% of patients and to drug withdrawal in 19%. These results led to the approval of sorafenib by the US Food and Drug Administration for advanced, refractory, and progressive DTC in November 2013 and by the European Medicines Agency in March 2014.

The SELECT Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid trial was performed on 392 patients with RAI-refractory locally advanced or metastatic DTC that had progressed within the past 13 months; progression was confirmed by independent radiological review [49]. Patients were randomly assigned 2:1 to either lenvatinib (24 mg/day) or placebo. Lenvatinib treatment significantly improved PFS compared with placebo (HR 0.21, 99% CI 0.14 to 0.31, P <0.001; median PFS 18.3 versus 3.6 months, respectively), and the objective response rate was 65% with complete responses in 2%. Similar benefits were observed in the 20% of patients who had received prior VEGF-targeted therapy. The improvement in PFS was seen in all clinical subgroups. Treatment-related adverse events were reported in all patients in the lenvatinib group. Most often, these were hypertension (68%), fatigue (64%), diarrhea (59%), and decreased appetite (50%). Proteinuria occurred in 32% and thrombo-embolic events in 11%. A total of 68% of the patients on lenvatinib required dose reduction, 82% required dose interruption, and 14% of patients were taken off the drug. In the active treatment arm, there were 20 fatalities compared with six in the placebo arm. Investigators attributed six fatalities (2%) directly to the use of lenvatinib. One person died from a pulmonary embolism, one died due to hemorrhagic stroke, and four others died due to general health deterioration.

In conclusion, both vandetanib and sorafenib improved median PFS by 5 months over placebo but with no or

Table 1. Kinase inhibitors used in patients with RAI refractory advanced thyroid differentiated cancer: targets and main results of reported trials. All these kinase inhibitors target VEGFR, and some also target the MAPkinase pathway

	VEGFR	Other targets	Number	PR, percentage	SD >6 months, percentage
Axitinib	+	RET, PDGFR, C-KIT			
Cohen *et al.* [38]			45	31	38
Locati *et al.* [39]			45	38	29
Cabozantinib	+	RET, C-MET	15	53	40
Cabanillas *et al.* [46]					
Lenvatinib	+	RET, FGFR, PDGFR, C-KIT	392	65	Median PFS: 18.3 versus 3.6 months
Schlumberger *et al.* (phase III versus placebo) [49]					
Motesanib	+	PDGFR, C-KIT, RET	93	14	33
Sherman *et al.* [36]					
Pazopanib	+	PDGFR, C-KIT	37	49	
Bible *et al.* [45]					
Sorafenib	+	RET, BRAF, PDGFR, C-KIT			
Kloos *et al.* [42]			58	5	58
Gupta *et al.* [40]			25	23	53
Hoftijzer *et al.* [41]			32	25	36
Ahmed *et al.* [43]			19	18	79
Capdevila *et al.* [44]			16	19	50
Brose *et al.* (phase III versus placebo) [48]			417	12	Median PFS: 10.8 versus 5.8 months
Sunitinib	+	RET, PDGFR, C-KIT			
Cohen *et al.* [38]			31	13	68
Carr *et al.* [37]			29	28	46
Vandetanib	+	RET, EGFR	145	0	Median PFS: 11.1 versus 5.9 months
Leboulleux *et al.* (phase II versus placebo) [47]					

BRAF, B-Raf proto-oncogene, serine/threonine kinase; C-KIT, Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, a transmembrane receptor for MGF (mast cell growth factor, also known as stem cell factor); C-MET, Mesenchymal epithelial transition factor, a transmembrane receptor for HGF (hepatocyte growth factor, also known as scatter factor); FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PR, partial response; RET, rearranged during transfection; SD, stable disease; VEGFR, vascular endothelial growth factor receptor.

few partial responses. Despite the absence of direct comparison, lenvatinib seems more effective with an almost 15 month improvement in median PFS over placebo and a response rate as high as 65%, with few complete responses. However, efficacy and toxicity of lenvatinib have to be evaluated in real life, outside the frame of a control trial, and this will permit clinicians to refine the indications for these drugs and also will determine the optimal initial dosage.

With any of these medications, the dose of levothyroxine treatment had to be increased in the majority of patients, and an increased need in calcium and vitamin D analog may also occur, particularly in patients treated for post-operative hypoparathyroidism.

Toxicities of kinase inhibitors included fatigue, diarrhea, hypertension, skin, renal toxicities, and cardio-vascular events, but there was no unexpected toxicity. However, toxicities were significant and led to dose reduction in 11-73% of patients and to drug withdrawal in 7-25%. This suggests that these treatments should be initiated only in patients with significant tumor burden and with documented progressive disease and managed by experienced teams.

Drugs directed against other targets

Oncogenic events that have been described in thyroid cancers have been studied in several trials. In the DECISION and SELECT trials, PFS was improved in all biomarker subgroups, irrespectively of *BRAF* and *RAS* mutation status [48,49].

The presence of *BRAF* mutation was an inclusion criteria in two phase II trials with a BRAF inhibitor: vemurafenib or dabrafenib [50]. Mutation in anaplastic lymphoma kinase (*ALK*) gene has been reported in few patients with refractory DTC and can be the target of an ALK inhibitor [51]. Other pathways, such as the PI3K-AKT pathway [52,53], are activated in follicular and poorly differentiated carcinoma, and trials with inhibitors of this pathway are ongoing.

Mutation screening should be performed on a routine basis in these patients because it may lead to the use of a specific inhibitor in the presence of a driver mutation.

However, larger series of patients are needed for defining the interest of this approach. Many data have been obtained on thyroid tumor tissues that were resected long before treatment, and analysis of the metastatic tumor tissue at the time of treatment would probably be more informative. In one study, the *BRAF* or *RAS* mutations found in the primary tumor were also present in the metastases, and additional mutations (*PIK3CA* or *AKT1*) may also be present in the metastatic tissue [54].

Another potential way of treating these patients is to restore the ability of radioiodine uptake in tumor cells and then to treat with radioiodine following a preparation with rhTSH stimulation: in a pilot study on 20 patients with metastatic differentiated thyroid carcinomas who had no significant radioiodine uptake in their metastases, lesional dosimetry with ^{124}I PET imaging was performed after rhTSH stimulation before and after 4 weeks of treatment with the MEK inhibitor, selumetinib. Twelve patients demonstrated increased tumoral ^{124}I uptake, and eight of these 12 patients achieved sufficient iodine reuptake to warrant treatment with ^{131}I: 5 achieved RECIST partial responses, and 3 had a stable disease. Of the 20 patients, 9 patients had tumors with the V600E BRAF mutation and 5 patients had tumors with NRAS mutations at codon 61. Interestingly, of the 8 patients with a major increased ^{124}I uptake, 5 were found to have NRAS mutations and one had a BRAF mutation [55]. This approach may be relevant in patients at high risk of recurrence in a post-operative adjuvant setting and also in patients with small metastases with a slow progression rate and with a baseline radioiodine uptake that is too low to allow significant radiation doses to be delivered. Immunological intervention may use two directions. One is guided by the increased number of tumor-associated macrophages (TAMs) in aggressive tumors that is most evident in anaplastic thyroid cancer [56,57]. It has recently been reported in transgenic mice that depletion of TAMs through inhibition of the colony-stimulating factor 1 (CSF1) pathway that attracts TAMs into the tumor impairs tumor progression [58]. Another one is the fact that some tumors evade immunosurveillance, possibly through changes over time of their immunological profile [59]. This can occur through an inhibitor of T-cell function, such as CTLA-4, PD-1, or PD-L1. There are no data showing that this mechanism may apply to refractory DTC, but this represents a new avenue of research in these patients.

Clinical practice and future developments

Predictive biomarkers are aimed to allow a better selection of patients for any treatment modality and also an early assessment of the tumor response to the drug. In patients treated with motesanib, decrease from baseline in serum placental growth factor after 1 week of treatment correlated with best tumor response, and a decrease in soluble VEGFR 2 after 3 weeks of treatment separated responders from non-responders. Lower baseline VEGF levels were associated with longer PFS [60]. Basal levels of other cytokines or angiogenic factors or changes in their serum level at 1-2 weeks have been associated with tumor response. These studies have shown the promise of using biomarkers in predicting drug efficacy, which needs to be refined before they can be used in clinical practice.

Comparison of FDG uptake on PET/CT at 1-2 weeks after treatment initiation with baseline FDG uptake has produced inconsistent results, and the interest of repeated FDG-PET/CT in the management of DTC patients during treatment with these new drugs is still unclear. During the treatment with sunitinib, a decrease in FDG uptake was associated with subsequent tumor response, and an increase with subsequent tumor progression [37]. However, in another study, no such relationship was observed [47].

At present, kinase inhibitors are the only drugs to be approved in some countries in patients with RAI-refractory DTC with significant tumor burden in whom progression has been documented and these drugs may be used as first line. Tumor responses were observed in only a small fraction of patients and most were partial and transient. Trial consideration should be given to all patients, even in countries where a drug is currently approved.

The duration of treatment is not yet validated and for this reason treatment is usually given as long as toxicities remain manageable and there is evidence of benefits. One unresolved question is when treatment should be stopped in case of progression or in case of dissociated response. Rapid progression has been reported after discontinuation of tyrosine-kinase inhibitor (TKI) treatment [61]. In patients who progress slowly during TKI treatment, the treatment may be maintained as long as there is evidence of benefits. Alternatively, patients may benefit from another anti-angiogenic drug that may produce significant benefits [62,63]. However, benefits of further treatments with subsequent lines with other anti-angiogenic drugs are questionable, and this may indicate that future studies should test cross-resistance between drugs and alternatively drugs targeted at abnormalities that are present in the tumor tissue. There is a need for trials, and recent trials performed in the frame of clinical networks have shown that inclusion of the expected number of patients with thyroid cancer to

reach statistically significant conclusions is possible in a limited period of time.

Abbreviations

ALK, anaplastic lymphoma kinase; CI, confidence interval; CT, computed tomography; DECISION, Study of Sorafenib in Locally Advanced or Metastatic Patients with RAI-Refractory Thyroid Cancer; DTC, differentiated thyroid cancer; FDG, fluorodeoxyglucose; HR, hazard ratio; MAP, mitogen-activated protein; MRI, magnetic resonance imaging; PET, positron emission tomography; PFS, progression-free survival; RAI, radioactive iodine; RECIST, response evaluation criteria in solid tumor; rhTSH, recombinant human thyroid-stimulating hormone; SELECT; TAM, tumor-associated macrophage; Tg, thyroglobulin; TKI, tyrosine-kinase inhibitor; TSH, thyroid-stimulating hormone; VEGF, vascular endothelial growth factor; WBS, whole-body scan.

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