



## **The medical treatment of radioiodine-refractory differentiated thyroid cancers in 2019. A TUTHYREF® network review**

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# The medical treatment of radioiodine-refractory differentiated thyroid cancers in 2019. A TUTHYREF® network review.

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## Abstract

Patients with radioiodine-refractory (RAIR) differentiated thyroid carcinoma (DTC) represent a challenging subgroup of DTC because they are at higher risk of cancer-related death. Multidisciplinary discussions can assess the role and the nature of local treatments, but also determine the optimal timing for first-line antiangiogenic therapy as some of these patients can be followed for several months or years without any treatment. In this review, we will examine the definition of RAIR-DTC, the different treatment options and finally some of the most recent cancer research breakthroughs for RAIR-DTC.

**Keywords:** Radioiodine-refractory differentiated thyroid carcinoma Target therapy Antiangiogenic Network Tuthyref Molecular biology

At the opposite of the majority of differentiated thyroid cancers (DTC) patients (pts), who are successfully treated with surgery, with or without postoperative RAI treatment and thyroid hormone substitution, a small proportion will exhibit persistent or recurrent local and/or metastatic disease which can be refractory to RAI therapy. These pts with radioiodine-refractory (RAIR) differentiated thyroid cancer (RAIR-DTC) have a reduced life expectancy and represent the main cause of thyroid cancer deaths [1,2]. Although they benefit now from antiangiogenic treatments, as demonstrated in two randomized phase III studies, [3,4], several questions remain unanswered such as the best timing for treatment initiation, the selection of the pts who benefit the most from treatment and the optimal treatment after first-line failure ? Furthermore, besides antiangiogenic treatments other strategies such as redifferentiation or immunotherapy are now present in the therapeutic

landscape. We will review the definition of RAIR-DTC, the different treatment options and finally some of the most recent cancer research breakthroughs for RAIR-DTC.

First discussions about RAIR DTC have been initiated in the late 2000s and coincided with encouraging results from phase II trials of sorafenib in patients with DTC [5,6]. The authors involved in these clinical trials defined RAI refractoriness when, at least, one lesion did not take up RAI on whole-body scan or when clinical evidence indicated that further RAI administrations would no longer benefit to the patient [7]. These criteria were later refined and are currently cited in the 2015 American Thyroid Association guidelines, as follows “(a) metastatic disease that does not concentrate RAI at the time of the first RAI treatment, (b) ability to take up RAI lost after previous evidence of uptake, (c) RAI uptake retained in some lesions but not in others, or (d) metastatic disease that progresses despite substantial uptake of RAI” [2,8]. These criteria have been used in all clinical trials in RAIR-DTC and widely applied in routine even if controversial, especially for the last criteria regarding the definition of the “substantial” dose which was set to 600 mCi (22.2 GBq) [1,9]. Some authors tend also to consider pts with bulky unresectable thyroid carcinomas often uptaking FDG as RAIR even if never treated with RAI [10,11]. Furthermore, pts can be classified as RAIR based on one or several criteria but have a different prognosis in terms of survival, those with lesions without any RAI uptake having a worse prognosis than those with initial RAI uptake and progression despite RAI administrations [12]. After establishing a patient being RAIR, further administration of RAI is no more indicated but initiation of antiangiogenic therapy is not systematic. The decision for initiating antiangiogenic treatment should take into account several criteria including tumor burden, i.e. the size ( $<$  or  $\geq$  1 or 2 cm) and of target lesions, tumor growth rate, localization of metastatic sites and the presence of symptoms [8]. The thyroglobulin doubling time, used in the management of pts with DTC, has not been

specifically evaluated in RAIR tumors to add informations for treatment decision [13,14]. When a pt with non-progressive RAIR-DTC is not symptomatic, surveillance includes an FDG-PET/CT-scan and/or a CT-scan of the neck, chest, abdomen and pelvis with contrast every 6 to 12 months. It is also recommended to perform a spine bone and cerebral MRI, especially when the thyroglobulin is increasing without any change of target lesions on CT-scan or to better evaluate bone metastases. In pauci-metastatic diseases, a local treatment such as surgery, stereotaxic radiation or thermal ablation (radiofrequency and cryoablation) can be advised for brain, lung, liver and/or bone metastases. These local treatment modalities should be considered prior to the initiation of a systemic treatment when the metastases are symptomatic or at high risk of local complications but also to delay the initiation of systemic treatments in case of solitary metastatic lesions and/or slowly-progressive diseases [15,16]. The discussion on the optimal timing and the choice of the local treatment method should be should take place within a multidisciplinary team.

Two different drugs have been approved by FDA and EMA for the RAIR progressive metastatic or locally advanced thyroid cancers. Sorafenib, an oral treatment inhibiting several kinases (BRAF, VEGFR1-3, PDGFR, RET and c-kit), was approved following the randomized phase III DECISION trial results [3]. Inclusion criteria comprised a locally advanced or metastatic RAIR-DTC (papillary, follicular (including Hürthle cell), or poorly differentiated) with measurable progressive target lesions defined according to Response Evaluation Criteria in Solid Tumors (RECIST v1.0). Among other important inclusion criteria, pts were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 and a serum thyroid stimulating hormone (TSH) <0.5 mIU/l. Patients were randomized (1/1) to receive either sorafenib 400 mg (2×200 mg tablets) twice daily or matching placebo, until disease progression, unacceptable toxicity, noncompliance, or

withdrawal of consent. Results showed that pts demographics and baseline clinical characteristics were well balanced between the treatment groups with a median age of 63 years and an ECOG-PS of 0 (62%) or 1 (34%). The progression-free survival (PFS) of patients treated with sorafenib was significantly increased to 10.8 months versus 5.8 months with placebo. The risk of progression was decreased by 41% (HR = 0.59, 95% CI: 0.45-0.76,  $p < 0.0001$ ). Median overall survival was not achieved at the time of analysis (August 31, 2012) and the difference between the 2 groups was masked by cross-over from placebo to sorafenib in pts with progression (HR = 0.802, 95% CI: 0.539 -1.194,  $p = 0.138$ ) [3]. Neither BRAF nor RAS mutations were predictive of sorafenib benefit in terms of PFS. The additional analysis of demographic baseline or disease-related patient characteristics showed that papillary histology, low tumour burden, and sites of metastases (absence of bone metastases and presence of lung-only metastases) were independent predictive factors for a longer PFS [17]. Furthermore, the disease-related symptoms at baseline (including dyspnea, pleural effusion, dysphagia, hemoptysis, chest, bone or tumor pain, spinal cord compression) did not influence the PFS in a post-hoc analysis [17]. Thus, based on these exploratory analyses, experts have considered patients with maximum tumor size  $< 1.5$  cm to be good candidates for a "watch and wait" attitude [2]. One year later, lenvatinib also showed positive results in prolonging PFS versus placebo in progressive RAIR-DTC pts [4]. Lenvatinib is a tyrosine kinase inhibitor (TKI) targeting VEGFR1-3, FGFR 1-4, PDGFR- $\alpha$ , RET and c-kit. In preclinical studies, lenvatinib had been shown to inhibit migration and tumor invasion in different cell lines, with inhibition of VEGFR1-3 but also FGFR 1-4 [18,19]. In addition, studies of crystallography showed that lenvatinib might have a mode of VEGFR2 binding different from other angiogenic agents possibly explaining its clinical efficacy [20]. From the preclinical studies till the phase I-II trials, lenvatinib had shown a remarkable activity in DTC [21,22].

Following these results, a phase III clinical trial was initiated [4]. The SELECT study was a multicenter randomized phase III study with a 2/1 randomization evaluating the lenvatinib at a dose of 24 mg/day versus placebo. It included 392 patients RAI-R-DTC with disease progression during the 12 confirmed by an independent radiological assessment. The definition of RAI-R was conventional. The randomization was stratified by geographical region (Europe, North Carolina and other), by the previous administration of an antiangiogenic treatment (patients could have received one previous anti-VEGF/VEGFR treatment) and age ( $\leq$  or  $>$  65 years). The main objective was to demonstrate a prolongation of PFS with lenvatinib over placebo, progression being qualified by independent radiological evaluation, according to the RECIST criteria. The secondary endpoints were the overall response rate (ORR) and overall survival (OS). A cross-over was allowed in case of disease progression for placebo-treated patients. 392 patients were randomized to receive either lenvatinib 24 mg /day (n = 261) or placebo (n = 131). Their baseline characteristics were well balanced between the two groups. Most of them were Europeans (49.7%), anti-angiogenic treatment naive (76.3%) and with a median age of 63 years. 51% of patients had papillary carcinoma of the thyroid, 19% a follicular one, 18% with Hürthle cells and 12% a poorly differentiated cancer. The median RAI cumulative activity administered before inclusion was 350 mCi (12.95 GBq). Metastatic sites were in order of frequency, lungs in 89% of patients, nodes (51%), bones (39%), liver (18%), pleura (16%) and brain (4.1%). The results were impressive with a statistically significant increase of PFS by lenvatinib (HR = 0.21, 99% CI [0.14-0.31], p <0.001). The median PFS was 18.3 months with lenvatinib versus 3.6 months on placebo. The treatment effect was comparable in all subgroups regardless of age ( $\geq$  65 years or <65 years), sex, race, histological subtype, geographical area and previous treatment with anti-angiogenic agents. The benefit of lenvatinib was not different in pts with RAS and BRAF-

mutant tumors. For patients treated with placebo but who received lenvatinib at progression, the median PFS was 10.1 months (95% CI 8.3-NR). Similarly, lenvatinib significantly increased ORR (64.8% vs 1.5% on placebo) with a median delay of 2 months to objective response (95% CI [1.9-3.5 months]). Robinson et al. published an analysis of the tumor response during lenvatinib treatment, showing the tumor regression was rapid and important (-25%) in the first 8 weeks of treatment and then, more slowly but continuous with an average of -1.3% per month [23]. The importance of tumor shrinkage at 2 months was correlated with PFS. In the first analysis, overall survival was no different between the 2 treatment arms (HR 0.73, 95% CI 0.5-1.07; p 199 = 0.10). However, it should be noted that the median survival was not reached and that the cross-over, affecting 83% of the pts in the placebo group (n=109 patients), could have erased the difference between both groups. In 2015, a statistical analysis taking into account the cross-over (RPSFT for Rank Preserving Structural Failure Time analysis) showed a significant difference between the 2 arms (HR = 0.53; IR 95% 0.34-0.82, p=0.0051) [24]. Median survival was not reached in the lenvatinib arm and was 19.1 months in the pts from the placebo arm who benefited from cross-over (95% CI 14.3- not estimable). No effect of age ( $\leq 65$  or  $> 65$  years) on the efficacy of lenvatinib was observed in a prespecified sub-group analysis, suggesting that age should not be a limit for lenvatinib prescription [25]. Of note, a higher toxicity was observed in patients aged over 65 years. Almost all patients treated with lenvatinib (97.3%) reported adverse events (AE), 75.9% of which were grade 3 or higher. An increased toxicity was observed in older patients with a higher proportion of grade  $\geq 3$  treatment-related adverse events (89% vs 67%;  $P < .001$ ). Six pts over twenty treated with lenvatinib (2.3%) died from treatment-related side effects according to investigators. Among the most common AEs were hypertension (69.3% of cases, 42.9% grade  $\geq 3$ ), diarrhea (59.4% of cases; 8% grade  $\geq 3$ ),



fatigue (59% of cases, 9.2% grade  $\geq 3$ ), loss of appetite (50.2% of cases, 5.4% grade  $\geq 3$ ) and weight loss (46.4% of cases, 9.6% grade  $\geq 3$ ). Other effects like nausea, stomatitis, dysgeusia, dysphonia or myalgia have also been frequently reported by patients. Less common side effects, but more serious and classically associated with anti-angiogenics, have been reported, such as arterial (all grades: 5.4%, grade  $\geq 3$ : 2.7%) and venous thromboembolic events (all grades: 5.4%, grade  $\geq 3$ : 3.8%), acute renal failure (all grades: 4.2%, grade  $\geq 3$ : 1.9%) and gastrointestinal fistulas (all grades: 1.5%, grade  $\geq 3$ : 0.8%). The main biological side effects were: TSH increase (61.5%), proteinuria (32.2% of cases including 10% of grade  $\geq 3$ ) and hypocalcemia (6.9%). QTc prolongation was found in 8% of patients. Side effects typically occurred early, between 3 and 12 weeks after the lenvatinib 's initiation [26]. A dose reduction was needed in 67.8% of patients (with a median time to the first dose reduction of 3 months (95% CI 2.7-3.7)), an interruption in 82.4%, and a definitive stop in 14.2% of the pts. It has led to a post-approval FDA-mandated phase II clinical trial asking the impact of starting lenvatinib with a lower dose (18 mg vs 24 mg) on efficacy and tolerance (NCT02702388). Trying to show a relationship between toxicity and efficacy, Wirth et al recently reported a significant correlation of hypertension (HTN) with median PFS, being 18.8 months in pts with HTN and 12.9 months in those without (HR=0.59; 95% CI [0.39-0.88]; p=0.0085) [27].

Without a direct comparison between the 2 drugs, it is difficult to favour lenvatinib or sorafenib in the first-line setting in RAI-DTC. However, when analyzing both drugs results (Table 2), we propose to promote lenvatinib use in pts with a large tumor mass and/or rapidly progressive disease due to its activity profile (high tumor response rate and rapid response).

Other anti-angiogenic treatment have been evaluated in RAI-DTC in phase II studies, like vandetanib [28], cabozantinib [29,30], pazopanib [31] or sunitinib [32]. The question of drug holidays has also been questioned in the randomized phase II PAZOTHYR study of which results are awaited (NCT01813136). Furthermore, kinase inhibitors targeting other molecular targets identified in thyroid tumorigenesis have been studied like everolimus [33,34] a mammalian target of rapamycin (mTOR) inhibitor, or buparlisib targeting phosphatidylinositol 3-kinase (PI3K) pathway [35]. However, their results were disappointing. More interesting, BRAF inhibitors like vemurafenib or dabrafenib have been evaluated in phase II clinical trials in BRAF-mutant papillary thyroid cancers (PTC) showing high response rates (38.5% and 50% respectively) [36,37]. Although not approved in RAI-DTC, these drugs, available for pts with melanomas, may be indicated in progressive RAI BRAF mutant TC.

Denosumab, a RANK-ligand inhibitor, can be used in bone metastases from thyroid cancer as from other cancers with a special attention for the jaw necrosis risk, especially in case of concurrent anti-angiogenic treatment [38,39]. Global palliative care services could also be provided early in the disease, alongside with kinase inhibitors or in case of treatment failure or discontinuation, according to the American Society of Clinical Oncology (ASCO) Practice Guideline [40].

The question of a second- or third-line therapy remains open and few prospective data existed until recently. In the SELECT study, 73 pts were pretreated with a tyrosine kinase inhibitor (n=66 in the lenvatinib arm, n=27 in the placebo arm) and their results were similar than patients who had not received previous treatment with a median PFS of 15.1 months. Some retrospective data confirmed these point of view [41]. Following exciting results in a

phase II study, cabozantinib is currently evaluated in a randomized phase III clinical trial and will provide interesting prospective data of tumor response and survival benefit for pts having progressed on a first-line antiangiogenic treatment [30,42]. One of the options, especially after progression during first-line antiangiogenic therapy is to look for druggable molecular targets by a tumor genotype. Until recently, few real solutions resulted from this attitude [43]. However, beside BRAF mutations that could be efficiently targeted in RAI-DTC (see above), some recurrent gene fusions (NTRK) or gene rearrangements (RET) are present in thyroid cancers and are potentially amenable to pharmacological inhibition [44]. Although rare, these abnormalities can predict high response rates with their inhibitors showing impressive results in small cohorts of phase I trials : for example, 100% overall response rate (n=5/5; 1 CR and 4 PR) observed in DTC pts treated with larotrectinib and 83% (n = 5/6) in metastatic RET fusion papillary carcinoma with the RET inhibitor LOXO-292, [45,46].

Patient's education and management before and during kinase inhibitors is surely the best way to avoid part of adverse events and the reduction or interruptions of the anticancer treatment. The suitability of the patient for the lenvatinib or sorafenib treatment should be assessed almost like he was a candidate for a clinical trial [47]. The performance status must be correct, between 0 and 2. The age is not an *a priori* exclusion criterion even if there are limited data on the use of TKI in patients aged  $\geq 75$  years [25,48]. As hypertension is the most common AE seen with antiangiogenic treatments, pts should be pre-assessed for cardiovascular risk factors and monitored 2 to 4 weeks before starting for the therapy blood pressure (BP) levels. Pts should also be asked to try to modify their lifestyle if necessary (increase physical activity, reduce or stop smoking etc.). After the beginning, a close monitoring of BP is recommended during the first 4–6 weeks on treatment. Of note, the 2017 American College of Cardiology/American Heart Association hypertension guidelines

recommend ambulatory or home BP measurement to evaluate patients with suspected “white coat” hypertension [49,50]. The diarrhea should also be treated as early as possible, to avoid weight loss, dehydration and metabolic disorders (like hypokalemia). Dietary measures (avoiding high-fibre, spicy foods and lactose containing products and drinking 1.5 to 2 liters of water per day) and loperamide use (2 mg after each bowel movement up to a maximum of 16 mg a day) must be explained to the patient from the first visit. Dermatological adverse effects can also be decreased by early special attention. The pts must be informed of the antiangiogenic treatment skin toxicity, and educated to skin cares (wear cotton socks, avoid extended walking and jogging, use topical moisturizers (urea-creams) and sunscreens). A multidisciplinary approach and a good collaboration between different specialties facilitate the management of kinase inhibitors such as the nursing staff assessing regularly by phone calls the patient’s overall condition. The minimal treatment follow-up must be stringent and has been summarized in table 1.

The hypothesis of being capable of a RAI resensitization in RAIR-DTC has been suggested in the late 2000s, after the recognition that DTCs with BRAF mutations were more likely to be FDG positive [51] followed by a preclinical study showing that BRAF or MEK inhibitors could restore RAI incorporation in mouse thyroid cancers with BRAF mutation [52]. Subsequently, several phase II clinical studies studying the role of BRAF- or MEK-directed targeted agents on radioactive iodine uptake were published [53–56]. The results showed a significant restoration of radioactive iodine uptake in more than half of the pts (60-62%), allowing some of them to receive further <sup>131</sup>I treatments and revealed also partial tumor responses (20-33%). Few data on PFS or overall survival are available until now. Prospective larger trials are

ongoing to prove the long-term benefit of the redifferentiation with trametinib alone or in combination with dabrafenib (NCT03244956, NCT02152995), with vemurafenib alone or in combination with an anti ERb3 antibody (NCT02145143, NCT02456701), with selumetinib (NCT00970359).

At last, immunotherapy has been evaluated in thyroid cancer cohorts. The first results with pembrolizumab a PD-1 inhibitor showed in the 22 pts enrolled in the KEYNOTE-028 study (NCT02054806), an ORR of 9.1% [95% CI, 1.1-29.2] and a 54.5% of stable disease rate [95% CI, 32.2-75.6] [57]. It led to a thyroid cancer cohort in the KEYNOTE-158 study (NCT02628067) whose results are awaited. Of note immunotherapy results were impressive in MSI cancer pts including 2 thyroid carcinomas [58]. Combining anti-angiogenics and checkpoint inhibitors could be synergistic and this hypothesis sustained a clinical trial, currently evaluating the combination of lenvatinib with pembrolizumab (NCT02973997) and the combination of cabozantinib with azetolizumab (NCT03170960)

In conclusion, RAIR-DTC has benefited from the antiangiogenic treatments (sorafenib and lenvatinib) which allowed pts to live longer with their disease. Clinicians have also learnt to watch and wait small burden diseases before introducing a treatment with toxicities outweighing the benefit. In parallel, local treatments such thermal ablation (RFA and cryoablation) and radiotherapy made concrete progresses. In 2019, tumor molecular genotype aims to identify somatic mutations (BRAF V600E and RAS especially), gene fusions or rearrangements (RET, NTRK) affecting rare but precious subgroups of pts that could be offered very precise targeted therapies. Furthermore, great expectations are awaited from redifferentiation and from the immune checkpoint inhibitors, probably in combination with other treatments.

## References

- [1] Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, 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* 2006;91:2892–9.
- [2] Schlumberger M, Brose M, Elisei R, Leboulleux S, Luster M, Pitoia F, et al. Definition and management of radioactive iodine-refractory differentiated thyroid cancer. *Lancet Diabetes Endocrinol* 2014;2:356–8.
- [3] Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014;384:319–28.
- [4] Schlumberger M, Tahara M, Wirth LJ. Lenvatinib in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015;372:1868.
- [5] Gupta-Abramson V, Troxel AB, Nellore A, Puttaswamy K, Redlinger M, Ransone K, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol* 2008;26:4714–9.
- [6] Brose MS, Troxel AB, Redlinger M, Harlackner K, Redlinger C, Chalian AA, et al. Effect of BRAFV600E on response to sorafenib in advanced thyroid cancer patients. *JCO* 2009;27:6002–6002.
- [7] Brose MS, Smit J, Capdevila J, Elisei R, Nutting C, Pitoia F, et al. Regional approaches to the management of patients with advanced, radioactive iodine-refractory differentiated thyroid carcinoma. *Expert Rev Anticancer Ther* 2012;12:1137–47.
- [8] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26:1–133.
- [9] Pacini F. Which patient with thyroid cancer deserves systemic therapy and when? *Best Pract Res Clin Endocrinol Metab* 2017;31:291–4.
- [10] Sabra MM, Dominguez JM, Grewal RK, Larson SM, Ghossein RA, Tuttle RM, et al. Clinical outcomes and molecular profile of differentiated thyroid cancers with radioiodine-avid distant metastases. *J Clin Endocrinol Metab* 2013;98:E829–836.
- [11] Van Nostrand D. Radioiodine Refractory Differentiated Thyroid Cancer: Time to Update the Classifications. *Thyroid* 2018;28:1083–93.
- [12] Wassermann J, Bernier M-O, Spano J-P, Lepoutre-Lussey C, Buffet C, Simon J-M, et al. Outcomes and Prognostic Factors in Radioiodine Refractory Differentiated Thyroid Carcinomas. *Oncologist* 2016;21:50–8.
- [13] Pacini F, Sabra MM, Tuttle RM. Clinical relevance of thyroglobulin doubling time in the management of patients with differentiated thyroid cancer. *Thyroid* 2011;21:691–2.
- [14] Rössing RM, Jentzen W, Nagarajah J, Bockisch A, Görges R. Serum Thyroglobulin Doubling Time in Progressive Thyroid Cancer. *Thyroid* 2016;26:1712–8.

- [15] Cazzato RL, Bonichon F, Buy X, Godbert Y, de Figuereido BH, Pointillart V, et al. Over ten years of single-institution experience in percutaneous image-guided treatment of bone metastases from differentiated thyroid cancer. *Eur J Surg Oncol* 2015;41:1247–55.
- [16] Cazzato RL, Garnon J, Koch G, Shaygi B, Tsoumakidou G, Caudrelier J, et al. Current role of interventional radiology in the management of visceral and bone metastases from thyroid cancer. *Gland Surg* 2018;7:80–8.
- [17] Schlumberger M, Elisei R, Pacini F. Prognostic and predictive factors correlated with treatment outcomes for radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC) patients receiving sorafenib or placebo on the phase III DECISION trial. 84th annual meeting of the American Thyroid Association, Colorado, USA. *Thyroid* 2014;24:P-1.
- [18] Boss DS, Glen H, Beijnen JH, Keesen M, Morrison R, Tait B, et al. A phase I study of E7080, a multitargeted tyrosine kinase inhibitor, in patients with advanced solid tumours. *Br J Cancer* 2012;106:1598–604.
- [19] Tohyama O, Matsui J, Kodama K, Hata-Sugi N, Kimura T, Okamoto K, et al. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. *J Thyroid Res* 2014;2014:638747.
- [20] Okamoto K, Ikemori-Kawada M, Jestel A, von König K, Funahashi Y, Matsushima T, et al. Distinct binding mode of multikinase inhibitor lenvatinib revealed by biochemical characterization. *ACS Med Chem Lett* 2015;6:89–94.
- [21] Cabanillas ME, Schlumberger M, Jarzab B, Martins RG, Pacini F, Robinson B, et al. A phase 2 trial of lenvatinib (E7080) in advanced, progressive, radioiodine-refractory, differentiated thyroid cancer: A clinical outcomes and biomarker assessment. *Cancer* 2015;121:2749–56.
- [22] Hong DS, Kurzrock R, Wheler JJ, Naing A, Falchook GS, Fu S, et al. Phase I Dose-Escalation Study of the Multikinase Inhibitor Lenvatinib in Patients with Advanced Solid Tumors and in an Expanded Cohort of Patients with Melanoma. *Clin Cancer Res* 2015;21:4801–10.
- [23] Robinson B, Schlumberger M, Wirth LJ, Dutcus CE, Song J, Taylor MH, et al. Characterization of Tumor Size Changes Over Time From the Phase 3 Study of Lenvatinib in Thyroid Cancer. *J Clin Endocrinol Metab* 2016;101:4103–9.
- [24] Guo M, Sherman S, Wirth L, Schlumberger M, Dutcus C, Robinson B, et al. 2805 Overall survival gain with lenvatinib vs. placebo in radioactive iodine refractory differentiated thyroid cancer (RR-DTC): An updated analysis. *European Journal of Cancer* 2015;51:S559. Doi: 10.1016/S0959-8049(16)31549-0.
- [25] Brose MS, Worden FP, Newbold KL, Guo M, Hurria A. Effect of Age on the Efficacy and Safety of Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer in the Phase III SELECT Trial. *JCO* 2017;35:2692–9.
- [26] Haddad RI, Schlumberger M, Wirth LJ, Sherman EJ, Shah MH, Robinson B, et al. Incidence and timing of common adverse events in Lenvatinib-treated patients from the SELECT trial and their association with survival outcomes. *Endocrine* 2017;56:121–8.
- [27] Wirth LJ, Tahara M, Robinson B, Francis S, Brose MS, Habra MA, et al. Treatment-emergent hypertension and efficacy in the phase 3 Study of (E7080) lenvatinib in differentiated cancer of the thyroid (SELECT). *Cancer* 2018;124:2365–72.

- [28] Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. *Lancet Oncol* 2012;13:897–905.
- [29] Cabanillas ME, Brose MS, Holland J, Ferguson KC, Sherman SI. A Phase I Study of Cabozantinib (XL184) in Patients with Differentiated Thyroid Cancer. *Thyroid* 2014;24:1508–14.
- [30] Brose MS, Shenoy S, Bhat N, Harlackner AK, Yurtal RK, Posey ZA, et al. A phase II trial of cabozantinib (CABO) for the treatment of radioiodine (RAI)-refractory differentiated thyroid carcinoma (DTC) in the first-line setting. *JCO* 2018;36:6088–6088.
- [31] Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncol* 2010;11:962–72.
- [32] Ravaud A, de la Fouchardière C, Caron P, Doussau A, Do Cao C, Asselineau J, et al. A multicenter phase II study of sunitinib in patients with locally advanced or metastatic differentiated, anaplastic or medullary thyroid carcinomas: mature data from the THYSU study. *Eur J Cancer* 2017;76:110–7.
- [33] Schneider TC, de Wit D, Links TP, van Erp NP, van der Hoeven JJM, Gelderblom H, et al. Everolimus in Patients With Advanced Follicular-Derived Thyroid Cancer: Results of a Phase II Clinical Trial. *J Clin Endocrinol Metab* 2017;102:698–707.
- [34] Hanna GJ, Busaidy NL, Chau NG, Wirth LJ, Barletta JA, Calles A, et al. Genomic Correlates of Response to Everolimus in Aggressive Radioiodine-refractory Thyroid Cancer: A Phase II Study. *Clin Cancer Res* 2018;24:1546–53.
- [35] Borson-Chazot F, Dantony E, Illouz F, Lopez J, Niccoli P, Wassermann J, et al. Effect of Buparlisib, a Pan-Class I PI3K Inhibitor, in Refractory Follicular and Poorly Differentiated Thyroid Cancer. *Thyroid* 2018;28:1174–9.
- [36] Brose MS, Cabanillas ME, Cohen EEW, Wirth LJ, Riehl T, Yue H, et al. Vemurafenib in patients with BRAF(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016;17:1272–82.
- [37] Shah MH, Wei L, Wirth LJ, Daniels GA, De Souza JA, Timmers CD, et al. Results of randomized phase II trial of dabrafenib versus dabrafenib plus trametinib in BRAF-mutated papillary thyroid carcinoma. *JCO* 2017;35:6022–6022.
- [38] Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer* 2012;48:3082–92.
- [39] Orita Y, Sugitani I, Takao S, Toda K, Manabe J, Miyata S. Prospective Evaluation of Zoledronic Acid in the Treatment of Bone Metastases from Differentiated Thyroid Carcinoma. *Ann Surg Oncol* 2015;22:4008–13.
- [40] Osman H, Shrestha S, Temin S, Ali ZV, Corvera RA, Ddungu HD, et al. Palliative Care in the Global Setting: ASCO Resource-Stratified Practice Guideline. *JGO* 2018:1–24.



- [41] Massicotte M-H, Brassard M, Claude-Desroches M, Borget I, Bonichon F, Giraudet A-L, et al. Tyrosine kinase inhibitor treatments in patients with metastatic thyroid carcinomas: a retrospective study of the TUTHYREF network. *Eur J Endocrinol* 2014;170:575–82.
- [42] Cabanillas ME, de Souza JA, Geyer S, Wirth LJ, Menefee ME, Liu SV, et al. Cabozantinib As Salvage Therapy for Patients With Tyrosine Kinase Inhibitor-Refractory Differentiated Thyroid Cancer: Results of a Multicenter Phase II International Thyroid Oncology Group Trial. *J Clin Oncol* 2017;35:3315–21.
- [43] de la Fouchardiere C, Oussaid N, Derbel O, Decaussin-Petrucci M, Fondreville M-E, Wang Q, et al. Does Molecular Genotype Provide Useful Information in the Management of Radioiodine Refractory Thyroid Cancers? Results of a Retrospective Study. *Target Oncol* 2016;11:71–82.
- [44] Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol* 2018;15:731–47.
- [45] Drilon AE, Subbiah V, Oxnard GR, Bauer TM, Velcheti V, Lakhani NJ, et al. A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers. *JCO* 2018;36:102–102.
- [46] Wirth L, Drilon A, Albert C, Farago A, Wel-Diery, Ma P, et al. Larotrectinib Is Highly Active in Patients With Advanced Recurrent TRK Fusion Thyroid (TC) and Salivary Gland Cancers (SGC). *International Journal of Radiation Oncology\*Biophysics* 2018;100:1318.
- [47] Capdevila J, Mayor R, Mancuso FM, Iglesias C, Caratù G, Matos I, et al. Early evolutionary divergence between papillary and anaplastic thyroid cancers. *Ann Oncol* 2018;29:1454–60.
- [48] Gosain R, Alexander JS, Gill A, Perez C. Radioactive Iodine-Refractory Differentiated Thyroid Cancer in the Elderly. *Curr Oncol Rep* 2018;20:82.
- [49] Melville S, Byrd JB. Out-of-Office Blood Pressure Monitoring in 2018. *JAMA* 2018;320:1805–6.
- [50] Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;71:e127–248.
- [51] Ricarte-Filho JC, Ryder M, Chitale DA, Rivera M, Heguy A, Ladanyi M, et al. Mutational profile of advanced primary and metastatic radioactive iodine-refractory thyroid cancers reveals distinct pathogenetic roles for BRAF, PIK3CA, and AKT1. *Cancer Res* 2009;69:4885–93.
- [52] Chakravarty D, Santos E, Ryder M, Knauf JA, Liao X-H, West BL, et al. Small-molecule MAPK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation. *J Clin Invest* 2011;121:4700–11.
- [53] Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, et al. Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer. *N Engl J Med*. 2013 Feb 14;368(7):623-32.
- [54] Rothenberg SM, McFadden DG, Palmer EL, Daniels GH, Wirth LJ. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. *Clin Cancer Res* 2015;21:1028–35.

- [55] Cabanillas ME, Dadu R, Waguespack SG, Sherman SI, Jaber T, Busaidy NL, et al. Targeted Therapy in Advanced Thyroid Cancer to Resensitize Tumors to Radioactive Iodine. *The Journal of Clinical Endocrinology & Metabolism* 2018;103:3698–705.
- [56] Dunn LA, Sherman EJ, Baxi SS, Tchekmedyian V, Grewal RK, Larson SM, et al. Vemurafenib Redifferentiation of BRAF Mutant, RAI-Refractory Thyroid Cancers. *J Clin Endocrinol Metab.* 2019 May 1;104(5):1417-1428.
- [57] Mehnert JM, Varga A, Brose M, Aggarwal RR, Lin C-C, Prawira A, et al. Pembrolizumab for advanced papillary or follicular thyroid cancer: preliminary results from the phase 1b KEYNOTE-028 study. *JCO* 2016;34:6091–6091.
- [58] Diaz LA, Marabelle A, Delord J-P, Shapira-Frommer R, Geva R, Peled N, et al. Pembrolizumab therapy for microsatellite instability high (MSI-H) colorectal cancer (CRC) and non-CRC. *JCO* 2017;35:3071–3071

Table 1: recommendations for adequate monitoring during kinase inhibitors treatment

When	What	Repetition during treatment
<b>Before treatment</b> (within 2 weeks prior starting treatment)	-ECG (QTc) + Echocardiogram (LVEF)	Every 6 months
	-Blood pressure (BP) monitoring	Every week during the first 6 weeks
	-Blood test	Once a month for the first 3 months and then every 3 months if everything is OK
	-Urine test (proteinuria)	
	-General clinical exam	
	-CTscan	Every 2 to 3 months

Table 2: Results of DECISION and SELECT studies

	<b>Sorafenib (DECISION study) n=209</b>	<b>Lenvatinib (SELECT study) n=261</b>
<b>Patients characteristics</b>		
<b>Median age (years)</b>	63 (24-82)	64
<b>Previous TKI</b>	Yes (3.4%)	Yes (25.3%)
<b>Papillary thyroid cancer</b>	57%	50.6%
<b>Median cumulative radioiodine activity (mCi)</b>	400	NA
- <b>Disease progression</b>	Within 14 months	Within 13 months
- <b>Confirmation by an independent review</b>	no	yes
<b>Cross-over</b>	yes	yes
<b>Efficacy parameters</b>		
<b>Median PFS (months)</b>	<b>10.8</b> (vs 5.8)	<b>18.3</b> (vs 3.6)
<b>HR</b>	<b>0.49</b>	<b>0.21</b>
<b>CI95%; p</b>	0.39–0.61; p<0.0001	0.14-0.31; P<0.001
<b>Response rate</b>	<b>12.2%</b>	<b>64.8%</b>
<b>Median duration of treatment (months)</b>	<b>10.6</b>	<b>13.8</b>
<b>Median OS (months)</b>	<b>NR</b>	<b>NR</b>
<b>Tolerance</b>		
<b>Grade≥ 3 Adverse events</b>	82.1%	75.9%
<b>Dose interruptions</b>	66.2%	82.4%
<b>Dose reductions</b>	64.3%	67.8%
<b>Withdrawals</b>	18.8%	14.2%
<b>Toxic deaths (n/%)</b>	1/0.5%	6/2.3%

PFS = PROGRESSION-FREE SURVIVAL

CI95% CONFIDENCE INTERVAL 95%

OS = overall survival

TKI = TYROSINE KINASE INHIBITORS

HR=HAZARD RATIO

NR = not reached

mCi= MILLICURIES