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 ≥ 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-a, 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 RAIR-DTC with disease progression during the 12 confirmed by an independent radiological assessment. The definition of RAIR 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 (≤ 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 (≥ 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 (≤ 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 ≥ 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 ≥3), diarrhea (59.4% of cases; 8% grade ≥3),

fatigue (59% of cases, 9.2% grade ≥3), loss of appetite (50.2% of cases, 5.4% grade ≥3) and weight loss (46.4% of cases, 9.6% grade ≥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 ≥3: 2.7%) and venous thromboembolic events (all grades: 5.4%, grade ≥3: 3.8%), acute renal failure (all grades: 4.2%, grade ≥3: 1.9%) and gastrointestinal fistulas (all grades: 1.5%, grade ≥3: 0.8%). The main biological side effects were: TSH increase (61.5%), proteinuria (32.2% of cases including 10% of grade ≥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 RAIR-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 RAIR-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 RAIR-DTC, these drugs, available for pts with melanomas, may be indicated in progressive RAIR 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 RAIR-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 ≥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 ^{131}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 redifferenciation 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 redifferenciation and from the immune checkpoint inhibitors, probably in combination with other treatments.

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Table 1: recommendations for adequate monitoring during kinase inhibitors treatment

When	What	Repetition during treatment
Before treatment (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

	Sorafenib (DECISION study) n=209	**Lenvatinib (SELECT study) n=261**
Patients characteristics		
Median age (years)	63 (24-82)	64
Previous TKI	Yes (3.4%)	Yes (25.3%)
Papillary thyroid cancer	57%	50.6%
Median cumulative radioiodine activity (mCi)	400	NA
- **Disease progression** - **Confirmation by an independent review**	Within 14 months no	Within 13 months yes
Cross-over	yes	yes
Efficacy parameters		
Median PFS (months)	**10.8** (vs 5.8)	**18.3** (vs 3.6)
HR **CI95%; p**	**0.49** 0·39–0·61; p<0·0001	**0.21** 0.14-0.31; P<0.001
Response rate	**12.2%**	**64.8%**
Median duration of treatment (months)	**10.6**	**13.8**
Median OS (months)	**NR**	**NR**
Tolerance		
Grade≥ 3 Adverse events	82.1%	75.9%
Dose interruptions	66.2%	82.4%
Dose reductions	64.3%	67.8%
Withdrawals	18.8%	14.2%
Toxic deaths (n/%)	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