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New approaches for patients with advanced radioiodine-refractory thyroid cancer

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Abstract

The cumulative evidence over the past decades has shown that the incidence of differentiated thyroid carcinoma (DTC) has exponentially increased. Approximately 10% of patients with DTC exhibit recurrent or metastatic disease, and about two-thirds of the latter will be defined as refractory to radioactive iodine (RAIR) treatment. Since this condition implies 10-year survival rates less than 10% after detection, using available treatments, such as systemic and targeted therapies, have become increasingly relevant. The initiation of these treatments aims to reach stabilization, tumor volume reduction, and/or symptom improvement and it should be decided by highly specialized endocrinologists/oncologists on the basis of patient's features. Considering that despite enlarged progression-free survival was proven, multikinase inhibitors remain non-curative, their benefits last for a limited time and the side effects potentially cause harm and quality of life reduction. In this context, molecular testing of cancer cells provides a promising spectrum of targeted therapies that offer increased compatibility with individual patient needs by improving efficacy, progression free survival, overall survival and adverse events profile. This review article aims to provide a summary of the current therapeutic strategies in advanced RAIR-DTC, including approved target therapies as well as those for *off-label* use, RAI resensitization agents, and immunotherapy.

Key Words: Advanced differentiated thyroid cancer; Radioactive iodine refractory thyroid cancer; Multikinase inhibitors; Systemic therapy; Target therapy

Core Tip: The incidence of differentiated thyroid carcinoma has increased due to the rising detection of low-risk small carcinomas. Nevertheless, approximately 10% of patients exhibit advanced disease and two-thirds of the latter will be defined as radioactive iodine (RAI) refractory. After detection, 10-year survival rates are less than 10%, therefore the role of systemic and targeted therapy in these patients has become increasingly relevant in recent years. This review article aims to provide a summary of the current therapeutic strategies in iodine-refractory thyroid cancer, including approved target therapies as well as those for off-label use, RAI resensitization agents, and immunotherapy.

INTRODUCTION

The cumulative evidence over the past decades has shown that the incidence of differentiated thyroid carcinoma (DTC) has increased exponentially, probably due to the rising detection of low-risk small carcinomas[1]. Nevertheless, approximately 10% of patients with DTC exhibit a more aggressive behavior in which persistent or recurrent distant metastatic disease is developed, and about two-thirds of them will be defined as refractory to radioactive iodine (RAI) treatment[2]. This condition cannot be defined by a single criterion, but it rather comprises a spectrum of scenarios included into any of the following: (1) Lack of initial RAI uptake in all or some of the metastatic foci in a whole-body scan (diagnostic or following a therapeutic dose) or lose of the ability to take up RAI after previous evidence of uptake; (2) Disease progression in a patient who has received RAI; (3) Disease progression in a patient who has received 600 mCi of ^{131}I of cumulative activity; and/or (4) Locally advanced disease for whom surgical resection is not feasible and RAI uptake status cannot be assessed[2]. After the detection of radioiodine refractory (RAIR) disease, 10-year survival rates may decrease to less than 10%[2]. Therefore, using second-choice treatments, such as systemic and targeted therapy, in these patients has become increasingly relevant in recent years. This review article aims to provide a summary of the current therapeutic strategies for patients with RAIR thyroid cancer, including approved target therapies as well as those prescribed for *off-label* use, RAI resensitization agents, and immunotherapy.

MOLECULAR PATHWAYS OF THYROID CANCER

The underlying carcinogenic molecular pathways of differentiated thyroid cancer have been well defined. The MAPK signaling pathway is one of the most extensively studied[3]. Driver mutations such as in *BRAF* and *RAS* oncogenes, as well as fusions involving tyrosine kinase receptors, lead towards a constitutive activation of the downstream events resulting in cell proliferation, dedifferentiation, and cancer cell survival. These mutations could be targeted with specific therapies which result in cell growth inhibition[3,4]. Meanwhile, multikinase inhibitors (MKIs) confer their anti-tumor effect in radioiodine-refractory metastatic thyroid cancer by other effects, mainly through their anti-angiogenic activity[4]. The main molecular signaling pathways involved in thyroid carcinogenesis and the most significant inhibitors are summarized in Figure 1.

INITIATION OF SYSTEMIC THERAPY

The initiation of health agencies approved systemic therapy or the enrollment of a patient in a clinical trial should be managed by highly specialized endocrinologists/oncologists. The aim of this treatment will be to reach stabilization, tumor volume reduction, and/or symptom improvement[2,4]. Nevertheless, it should be
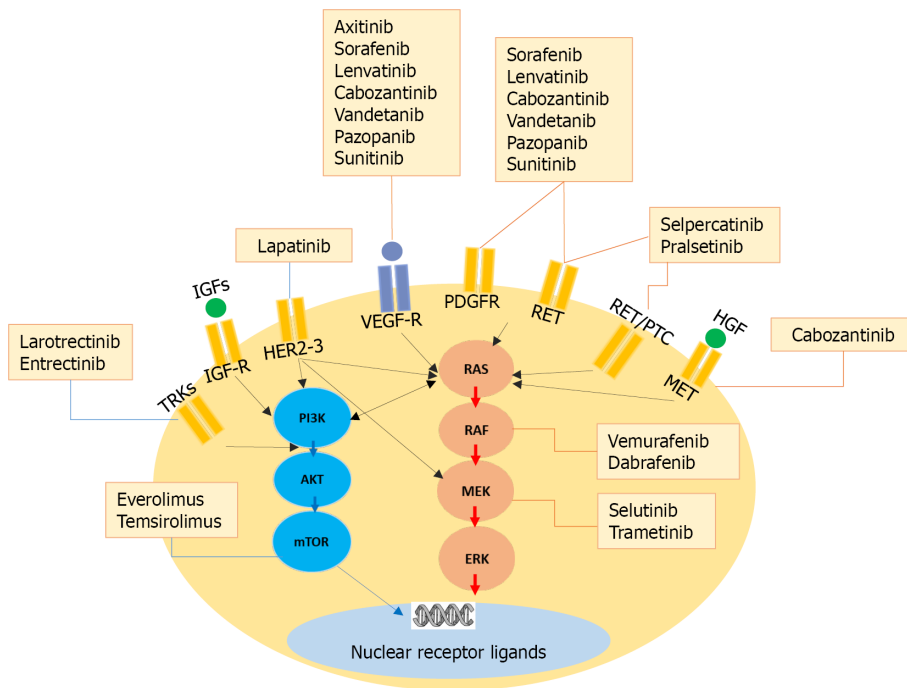
Figure 1 Major molecular signaling pathways involved in thyroid carcinogenesis and its most significant inhibitors.

decided on an individualized basis and under a coordinated decision taken together with patients, considering that target and multikinase inhibitor-based therapies remain non-curative and their benefits in terms of extending progression-free survival last for a limited time. Furthermore, the side effects of these therapies may have the potential to cause harm and significantly reduce the patient's quality of life[4]. Thus, the assessment of tumor burden, disease progression, symptoms, or a high risk of local complications is essential[2]. If available, genetic interrogation should be granted in order to initiate a selective TKI (either an approved drug or from clinical trials) in a patient with a progressive advanced RAIR-DTC that carries a specific target mutation [5]. If not genetic alterations are found, RAIR-DTC patients and those having tumor lesions in which the sum of diameter is larger than 2 cm and showing < 12-mo progression should be considered for multikinase inhibitors[2]. Additionally, all patients with DTC-related imminent symptoms and potentially symptomatic disease should be guaranteed treatment initiation[2]. This is a simplistic view but may help to decide the correct moment of treatment initiation when no other therapies are no longer amenable. A proposed decision-making algorithm for systemic therapy initiation in RAIR-DTC is shown in Figure 2. The main available agents studied in the treatment of RAIR-DTC are summarized in Table 1.

MULTIKINASE INHIBITORS (SORAFENIB AND LENVATINIB)

Multikinase inhibitors block several signaling pathways responsible for tumor prolif-eration and survival, with varying degrees of potency[2]. However, the main target for MKIs is the vascular endothelial growth factor receptor (VEGFR) and therefore the inhibition of tumor angiogenesis[3]. That is why they are also called antiangiogenic MKIs. These MKIs have demonstrated in phase III trials, an increase in the median progression free-survival (mPFS) from 11 to 18 mo, and objective responses of 12% to 64%[6,7]. We should consider that these drugs are usually tumoristatic and will eventually lose their effect due to *on-target* or *off-target* resistance, after which, another therapy will be needed. To date, only one *post-hoc* analysis of the SELECT study has demonstrated improved overall survival in a subgroup of patients receiving an Lenvatinib *vs* placebo[8].

Sorafenib

Sorafenib inhibits the VEGFR 1, 2, and 3, platelet-derived growth factor, RET, c-kit, and less potently, BRAF kinases[9]. In the phase III DECISION trial, patients treated with sorafenib (*n* = 207) had a significantly longer PFS over patients receiving placebo

Table 1 Available agents studied in the treatment of radioiodine refractory-differentiated thyroid carcinoma

Agent and national clinical trial number[1]	Molecular target	Phase	Dosage	Enrolled patients (*n*)	PR (%)	mPFS (mo)	Common AEs	Serious AEs (grade ≥ 3)	Withdrawal due to AEs
Sorafenib[6]; NCT00984282	VEGFR1–3, PDGFR, RET, c-kit, BRAF	III	400 mg orally twice daily	207	10.8	12.2	Hand–foot skin reaction (76%), diarrhea (69%), alopecia (67%), rash (50%)	Hand-foot skin reaction (20%), hypertension (10%), weight loss (6%)	19%
Lenvatinib[7]; NCT01321554	VEGFR1–3, FGFR1–4, PDGFR, RET, c-kit	III	24 mg per d in 28-d cycles	261	63.2; 65 (4 complete response + 165 partial response)	18.3	Hypertension (68%), diarrhea (59%), fatigue (59%), decreased appetite (50%), decreased weight (46%), nausea (41%)	Hypertension (42%), proteinuria (10%), decreased weight (10%), fatigue (9%), diarrhea (8%)	14%
Cabozantinib [28]; NCT01811212	VEGFR2, MET, FLT3, RET, c-kit	II	60 mg/d orally	25	40	12.7	Fatigue (44%), weight loss (36%), diarrhea (36%), hand– foot skin reaction (32%), hypertension (24%)	Hypophosphatemia (16%), lipase/amylase increase, neutropenia, fatigue, weight loss (12%)	
Axitinib[71]; NCT00094055	VEGFR, PDGFR, c-kit	II	5 mg twice daily	60	30	18.1	Fatigue (50%), diarrhea (48%), nausea (33%), anorexia (30%), hypertension (28%), stomatitis (25%), weight loss (25%), and headache (22%)	Hypertension (12%), proteinuria (5%), fatigue (5%)	
Vandetanib [72]; NCT00537095	VEGFR2/3, EGFR, RET	II	300 mg/d	72	8.3	11.1	Diarrhea (74%), hypertension (34%), acne (27%), asthenia, anorexia (26%), nausea, rash (25%), fatigue, QTc prolongation (23%)	QTc prolongation (14%), diarrhea (10%), asthenia (7%), fatigue (5%)	33%
Sunitinib[73]; NCT00381641	PDGFR, FLT3, c-kit, VEGFR, RET	II	37.5 mg/d orally	35	31	12.8	Neutropenia (34%), leukopenia (31%), fatigue (26%), HFS (26%), diarrhea (26%)	Neutropenia (34%), leukopenia (31%), diarrhea, hand/foot syndrome (17%), fatigue (11%)	11%
Pazopanib [74]; NCT00625846	VEGFR, PDGFR, c-kit	II	800 mg/d orally in 4-wk cycle	37	49	11.7	Fatigue (78%), skin and hair hypopigmentation (75%), diarrhea (73%), nausea (73%)	Raised alanine aminotransferase level (11%)	5%
Dovitinib[75]; NCT02964144	FGFR, VEGFR	II	500 mg/d orally for five days, followed by a 2-d rest every week	40	20.5	5.4	Diarrhea (54%), anorexia (36%), vomiting (26%), fatigue (23%), and nausea (21%)	Neutropenia (13%)	20%
Apatinib[31]; NCT03167385	VEGFR2, c-Kit, c-SRC	II	750 mg/d orally (*n* = 10, group I) - 500 mg/d orally (*n* = 10, group II)	20	90 (I); 70 (II)	18.4	Hand– foot skin reaction (95%), proteinuria (90%) and hypertension (80%)		
Lapatinib[76]; NCT01947023	HER2/3	I	750 mg initial dose, escalated to 500 mg daily; + Dabrafenib 150 mg twice daily	13	60	15		Lymphocytic toxicity (7%)	
Vemurafenib [58]; NCT01286753	BRAF V600E	II	960 mg orally twice daily	51	VEGFR naive: 39%; Previous VEGFR:	VEGFR naive: 18.8; Previous VEGFR:	Rash (73%), fatigue (69%), alopecia, dysgeusia (54%), creatinine increase, weight decrease	Skin squamous cell carcinoma (23.5%), lymphopenia, and increased γ-glutamyl-transferase (8%)	27%

					27%	8.9	(50%), arthralgia, anorexia, nausea, skin papilloma (46%)		
Dabrafenib [57]; NCT00880321	BRAF V600E	I	150 mg twice daily	13	29	11.3	Skin papillomas (57%), hyperkeratosis (36%), alopecia (29%)	Elevated lipase, elevated amylase, fatigue, febrile neutropenia and squamous cell carcinoma (7%)	0%
Selumetinib [66]; NCT00559949	MEK-1/2, RAS, BRAF V600E	II	100 mg twice daily for 28-d cycles	39	3	8	Rash (77%), fatigue (49%), diarrhea (49%), peripheral edema (36%)	Rash (18%), fatigue (8%)	15%
Larotrectinib [33]; NCT02122913	NTRK fusions	II	100 mg twice daily	153	129 (95%); 24 (16%) complete response	28.3	Fatigue (30%), cough, constipation (27%), dizziness, alanine aminotransferase increase (25%)	Anemia (10%), decreased neutrophil count (5%)	2%
Entrectinib [36]; NCT02097810 (STARTRK-1) NCT02568267 (STARTRK-2)	NTRK fusions	II	600 mg/d orally	54	50	10	Dysgeusia (47%), fatigue, constipation (28%), diarrhea (27%), edema peripheral, dizziness (24%)	Anemia (12%), weight gain (10%)	4%
Everolimus [62]; NCT01118065	mTOR	II	10 mg/d orally	33	3	12.9	Mucositis, acneiform rash, fatigue, cough	Fatigue (8%), weight loss, infection (6%)	
Temsirolimus [63]; NCT01025453	mTOR	II	Temsirolimus (25 mg IV weekly) + sorafenib (200 mg twice daily)	36	22	12		Hyperglycemia (19%), fatigue (13%), anemia (11%), oral mucositis, alanine aminotransferase increased (8%)	14%

[1]from ClinicalTrials.gov.

PR: Partial response; AE: Adverse event; VEGFR: Vascular endothelial growth factor receptor; NTRK: Neurotrophic tropomyosin receptor kinase.

(n = 209) (10.8 *vs* 5.8 mo, respectively; HR, 0.587; 95%CI: 0.45–0.76; P < 0.0001)[6]. The clinical benefit rate (CR + PR + SD > 6 mo) was 54%, with a PR rate of 12.2% and an SD > 6 mo of 41.8%[6]. The median duration of PR was 10.2 mo. An improvement in OS could not be demonstrated, probably because a large proportion of patients in the placebo arm (71%) crossed over to treatment[6]. In the last metanalysis that included 636 patients from 15 studies receiving sorafenib, 26% of patients (95%CI: 0.19-0.34) achieved a PR, and 44% (98%CI: 0.39-0.48) an SD[10]. PFS time ranged from 9 to 21.3 mo and OS ranged from 10 to 56 mo[10]. In an exploratory analysis of the phase III trial, patients who received open-label sorafenib after progression under the placebo arm achieved a comparable PFS to those receiving sorafenib from the beginning of the trial (9.6 *vs* 10.8 mo)[11]. This could suggest that delaying the initiation of sorafenib could not have a significant impact on the effectiveness. Also, in the same analysis, patients who continued receiving sorafenib after progression had a still longer PFS in comparison to patients who initially received placebo (6.7 *vs* 5.8)[11], meaning that sorafenib could still be an option in patients when an alternative drug is not available or not possible. In our real-life experience with sorafenib (n = 18), 72% had SD ≥ 6 mo and 11% demonstrated PR with a PFS of 16.5 mo[12].

The most frequent adverse events during sorafenib treatment were hand-foot skin reaction, diarrhea, fatigue, alopecia, weight loss, and rash[6,10,12]. HFS reaction and hypertension were the most frequent grade 3-4 AEs, reported from to and from to, respectively[6,10,12]. As reported with other MKIs, dose reductions and interruptions were frequent, however, drug withdrawal was uncommon[6,10,12]. The recommended initial dose of sorafenib is 400 mg twice a day[13]. In an exposure-response model, initial lower doses of sorafenib (600 or 400 mg/d) were associated with improved tolerability but reduced PFS. However, a strategy of 800 mg/d for an initial two cycles followed by dose reductions seemed likely to maintain efficacy while possibly mitigating some AEs[14]. The summary of the efficacy and safety of sorafenib in patients with thyroid cancer reported by clinical trials is shown in Table 2.

Table 2 Summary of the efficacy and safety of sorafenib in patients with thyroid cancer reported by clinical trials

Ref.	n	Type	PR, %	SD, %	Median PFS (mo)	Median OS (mo)	Most frequent AE	Most frequent grade 3-4 AE
Gupta-Abramson *et al* [77], 2008	27	DTC	26	59	19	-	HFS, 93%	Hypertension, 13%
Kloos *et al*[78], 2009	33	PTC	15	57	16	23	Fatigue, 85%	Fatigue, 16%
Hoftijzer *et al*[79], 2009	31	DTC	25	34	14.5	-	HFS, 66%	HFS, 18%
Cabanilas *et al*[59], 2010	13	DTC	20	60	19		HFS, 60%	-
Keefe *et al*[80], 2011	47	DTC/PD	38	47	22	32.4	-	-
Ahmed *et al*[81], 2011	19	DTC	16	-	-	-	Dermatology (other than HFS), 88%	HFS, 44%
Chen *et al*[82], 2011	9	DTC	33	44	10.5	-	Alopecia, 100%	-
Marotta *et al*[83], 2012	17	DTC	30	41	9	10	HFS, 88%	
Schneider *et al*[84], 2012	31	DTC	31	42	18	34.5	HFS, 71%	HFS, 22%
Capdevila *et al*[85], 2012	16	DTC	19	50	13.3	23.6	HFS and diarrhea, 62%	HFS, 23%
Brose *et al*[6], 2014	207	DTC	12	42	10.8	.	HFS, 73.6%	HFS, 20.3%
Benekli *et al*[86], 2014	14	DTC	-	43	21.3	-	-	HFS, 22%
Dadu *et al*[87], 2008	51	DTC	-	-	-	56	-	-
Luo *et al*[88], 2014	8	DTC	50	37	9.4	12.8	Alopecia, 75%	Hypocalcemia and serum amylase increased, 12.5%
Gallo *et al*[89], 2015	20	DTC	25	40	8.2	28.4	Fatigue, 95%	Gastrointestinal symptoms, 15%
Kim *et al*[90], 2018	98	DTC	25	37	9.7	-	HFS, 76%	HFS, 41%
Jerkovich *et al*[12], 2019	18	DTC	11	72	16.5	-	HFS, 67%	HFS, 14%

DTC: Differentiated thyroid carcinoma. PR: Partial response; PFS: Progression free survival; SD: Stable disease; OS: Overall survival; AE: Adverse event.

Lenvatinib

Lenvatinib inhibits FGFR1, -2, -3, -4, PDGFR, VEGFR1, -2, -3, RET, and KIT kinases [15]. In phase III clinical trial SELECT, median PFS was significantly longer in patients treated with lenvatinib in comparison to those receiving placebo (18.3 *vs* 3.6 mo, respectively; HR, 0.21; 99%CI: 0.14-0.31; *P* < 0.001)[7]. The response rate was 64.8% (CR 1.5% and PR 63.2%), with a median time to response of only 2 mo[7]. Real-life studies published afterward had reported PR from 31% to 69%, SD from 20% to 60%, and PFS from 10 to 13.8 mo[16-23]. This apparent lower efficiency of lenvatinib in observational data could be explained by the fact that these studies included patients with more than one prior MKI treatment, ECOG PS ≥ 3, more comorbidities, and patients who did not start with a full dose (24 mg per day). In fact, in our experience with lenvatinib (*n* = 22), when we excluded patients that would have not met the SELECT inclusion criteria, PR increased from 31.8% to 50% and PFS from 13.7 to 22 mo[23]. Hypertension was the most common adverse event (63%-83%) in almost all studies[7,16-19,21,23] and the most frequent grade 3-4 adverse event, occurring in 31%-42% of cases[7,23]. Other adverse effects include diarrhea, fatigue, decreased appetite, and decreased weight[7,16-23]. The recommended initial dose is 24 mg per day[13]. A lower initial dose and longer dose interruptions led to lower response rates and shorter progression-free survival[24,25]. A summary of the efficacy and safety of lenvatinib in patients with thyroid cancer reported by phase III clinical trial and real-life studies is shown in Table 3.

Cabozantinib

Cabozantinib is a RET, vascular endothelial growth factor receptor-2 (VEGFR2), and MET kinases inhibitor agent currently approved for the treatment of advanced medullary thyroid cancer[26]. However, it has also been studied in 15 patients with RAI-refractory DTC in a phase I clinical trial, with promising efficacy[27]. Ten of the

Table 3 Summary of the efficacy and safety of lenvatinib in patients with thyroid cancer reported by phase III clinical trial and real-life studies

Ref.	n	Patients with prior TKIs %	CR %	PR %	SD %	Median PFS (mo)	Median OS (mo)	Most frequent AE	Most frequent grade 3-4 AE
Schlumberger *et al*[7] 2015	261	25	1	63	23	18.3	-	Hypertension, 68%	Hypertension, 42%
Berdelou *et al*[16], 2017	75	68	0	31	51	10	-	Fatigue, 75%	Hypertension 35%
Jasim *et al*[17], 2017	25	31	0	50	28	-	-	Hypertension 64%	Hypertension 40%
Sugino *et al*[18], 2018	29	13	0	69	21	-	-	Hypertension 76%	-
Locati *et al*[19], 2019	94	64	0	36	41	10.8	23.8	Fatigue, 13%	Fatigue, 8%
Lee *et al*[20], 2019	57	89	0	38	60	5.1	19.3	General weakness 43%	
Masaki *et al*[21], 2019	42	10	0	62	24	13.8	-	Hypertension, 83%	Proteinuria, 36%
Aydemirli *et al*[22], 2020	39	77	2	33	37	9.7	18.3	Hypertension and fatigue, 64%	Hypertension, 28%
Jerkovich *et al*[23], 2020	22	59	4	32	32	13.7	-	Hypertension, 64%	Hypertension, 23%

TKIs: Tyrosine kinase inhibitors; CR: Complete response; PR: Partial response; SD: Stable disease; PFS: Progression free survival; OS: Overall survival; AE: Adverse event.

included patients were previously treated with VEGF inhibitors, mostly sorafenib. Cabozantinib was administered at a starting dose of 140 mg daily. A partial response was observed in 8 (53%) patients, 5 with prior VEGF inhibitors treatment. On the other hand, a phase II trial is currently ongoing, which involves a cabozantinib therapy in RAIR-DTC patients who experienced disease progression after second- or third-line VEGFR-targeted therapy[28]. Partial response was reached in 10 (40%) of the 25 enrolled patients, with a starting dose of 60-80 mg daily. The median PFS and OS were 12.7 and 34.7 mo, respectively[28].

Exelixis announced by the end of 2020 that, at a planned interim analysis, the phase III COSMIC-311 pivotal trial met the co-primary endpoint, demonstrating a significant reduction in the risk of disease progression or death of 78% of patients receiving cabozantinib compared to placebo (HR, 0.22, 96%CI: 0.13-0.36; $P < 0.0001$) in patients with RAIR differentiated thyroid cancer who have progressed after up to two prior VEGFR-targeted therapies. The safety profile was consistent with that previously observed for cabozantinib. In 2021, Exelixis® announced that the United States Food and Drug Administration (FDA) approved cabozantinib as a second/third line additional treatment for patients with RAIR thyroid cancer[29]. With this third MKI approved, there will surely be a change in defining first and second line of treatment according to the drug potency.

Apatinib

Apatinib, also known as rivoceranib, is a tyrosine kinase inhibitor that selectively inhibits the *VEGFR2*. Apatinib inhibits VEGF-mediated endothelial cell migration and proliferation thus blocking new blood vessel formation in tumor tissue. This agent also mildly inhibits c-Kit and c-SRC tyrosine kinases[30]. A recent phase II study performed in 20 patients with advanced thyroid cancer showed promising results with an objective response rate (ORR) of 80%, a median PFS of 18.4 mo (95%CI: 9.2-36.8 mo) and a median OS of 51.6 mo (95%CI: 29.2-not reached). The most common adverse events included palmar-plantar erythrodysaesthesia syndrome (19/20), proteinuria (18/20) and hypertension (16/20)[31].

SELECTIVE KINASE INHIBITORS

NTRK inhibitors (larotrectinib and entrectinib)

Neurotrophic tropomyosin receptor kinase (*NTRK*) fusions have been reported in
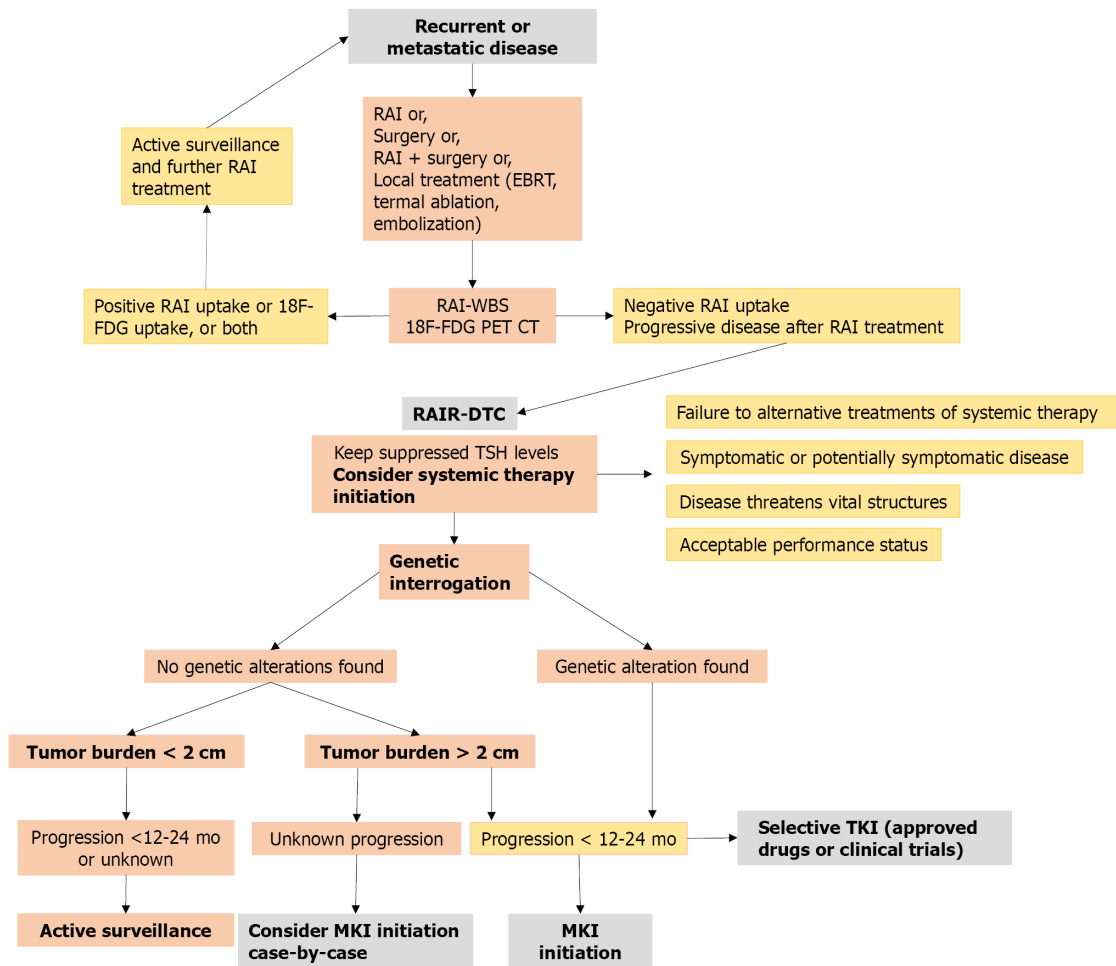
Figure 2 Proposed decision-making algorithm for systemic therapy initiation in radioiodine refractory-differentiated thyroid carcinoma.

variable percentages of patients with DTC (2%-25%)[32]. Larotrectinib and Entrectinib are highly selective inhibitors of *TRK* receptors and have been approved by the FDA for the treatment of any solid tumor-bearing an *NTRK1-3* fusion mutation (tumor-agnostic indication). Entrectinib also inhibit altered oncogenic expression of *ALK* and *ROS1*, which are much less frequent in DTC[32].

In a pooled analysis of three-phase 1/2 clinical trials, out of 24 patients with DTC bearing an *NTRK* fusion who received larotrectinib, 79% experienced an objective response[33]. This drug showed durable responses with a median time of 35 mo in the overall group of patients with solid tumors[33]. Also, larotrectinib seems to be active within the central nervous system (CNS)[33], which makes it an indispensable option when brain metastases are present in patients harboring this fusion, knowing that they have a worse outcome in patients with differentiated thyroid cancer[34]. Most frequent adverse events were primarily grade 1 and 2 and included fatigue (30%), cough, constipation (27%), dizziness (25%), and alanine aminotransferase increase (25%). The most common grade 3 or worse treatment-emergent adverse events (regardless of attribution) were anemia (10%) and decreased neutrophil count (5%)[33]. We recently showed our experience with Larotrectinib in a patient with RAIR DTC who had a rapid progression on MKI therapy (sorafenib and lenvatinib), and who had a complete response to treatment including the disappearance of multiple CNS metastasis[35].

Entrectinib also blocks *ROS1* and *ALK* and was specifically designed to have systemic activity and cross the blood–brain barrier. In an analysis of three-phase I or II trials, two out of four patients had a PR with entrectinib[36]. Most AE were grade 1-2 and included dysgeusia (47%), fatigue (28%), and constipation (28%). The most common grade 3 or 4 treatment-related AE were anemia (12%) and weight gain (10%) [36].

Resistance to larotrectinib and entrectinib

TRK fusion-positive cancers can develop resistance to *TRK* inhibition[37]. This resistance can be classified into *off-target* (new additional mutations that may occur in

the tumor) or *on-target* (within the same altered receptor, due point mutations that lead to amino acid substitutions in the solvent front, the gatekeeper residue or the *xDFG* motif)[38]. Mutations in the *NTRK* kinase domain cause resistance to *TRK* inhibitors by interfering with binding of the inhibitor, altering the kinase domain conformation or altering ATP-binding affinity[38].

New drugs are currently in development for those patients who develop *on-target* resistance, among them, selitrectinib and repotrectinib. Due to their small size, these low molecular weight molecules are able to engage the ATP-binding pocket while avoiding the steric penalties of kinase domain substitutions[39,40]. Selitrectinib is currently the drug with which the most experience has been gained. Thirty-one patients with solid tumors with *NTRK* fusions, previously treated with a *TRK* inhibitor (larotrectinib, entrectinib or PLX7486) with a median duration of prior therapy of 11 mo (range 2-30 mo) received treatment with selitrectinib. In patients with *TRK* kinase domain mutations (the majority of which involved the solvent front), the ORR was 45%[41].

Selective RET inhibitors (selpercatinib and pralsetinib)

RET/PTC rearrangements are present in 5%-25% of papillary thyroid carcinomas[42], although the occurrence of these mutations may be less frequent in advanced DTC [43]. Selpercatinib and pralsetinib, are kinase inhibitors that selectively target *RET* kinase, and were approved by the FDA for the treatment of advanced or metastatic *RET* fusion-positive thyroid cancer. In the phase 1/2 trial LIBRETTO-001, among 19 *RET* fusion-positive, non-medullary thyroid cancer patients, objective response was reported in 79%[44]. At 1 year, 71% of responses were ongoing, and 64% of the patients were free of progression[44]. The most common grade 3 or 4 adverse events included hypertension (21%), increased alanine aminotransferase (11%), increased aspartate aminotransferase (9%), hyponatremia (8%), and diarrhea (6%)[44].

In the phase 1/2 ARROW trial, praseltinib demonstrated objective responses in 75% (9/12), with a median duration of response of 14.5 mo, and 67% of responding patients continuing treatment[45]. Most treatment-related adverse events were grade 1-2, and included increased aspartate aminotransferase (31%), anemia (22%), increased alanine aminotransferase (21%), constipation (21%) and hypertension (20%)[45].

Mutation-specific kinase inhibitors -*RET* and *NTRK* inhibitors, as well as *BRAF* inhibitors-produced higher and durable objective responses[32,33,42,43]. Although prolongation of progression-free survival has not yet been demonstrated in phase III clinical trials, they seem to be promising options for RAIR thyroid cancer patients. In line with this, the implementation of molecular screening strategies seems to be necessary to improve the clinical course of these patients.

Resistance to selpercatinib and pralsetinib

Evidence on acquired resistance mechanisms to *RET*, both *on target* and *off-target*, is recently arising. Selpercatinib and pralsetinib were oriented to target gatekeeper mutations, such as *RET V804* and *S904F* which was associated with resistance to *RET*-targeted kinase inhibitors, as vandetanib[46]. Nevertheless, five *RET* kinase domain mutations at three non-gatekeeper residues were identified from selpercatinib and pralsetinib-resistant medullary thyroid cancer cell lines in a recent experimental study [47]. Information on acquired resistance to these drugs obtained from studies on non-small cell lung cancer (NSCLC) is slightly more extensive. For example, it was found acquired *RET G810R/C/S/V* mutations in *RET* fusion-positive tumors from patients who developed resistance to selpercatinib[48] and pralsetinib treatments[49]. Other reports of acquired selpercatinib resistance with *MET* amplification were demonstrated, in which probably this could be overcome by combing selpercatinib with crizotinib[50]. On the other hand, it was postulated that the combination of pralsetinib or selpercatinib with a selective *MET* inhibitor -such as capmatinib, savolitinib, or tepotinib- could offer acceptable tolerability and efficacy in NSCLC patients[51].

These experimental findings have shown the imperative need to develop next-generation targeted *RET* agents focused on both gatekeeper and non-gate keeper mutations for on- and off-target resistance in order to develop and validate combination therapies.

OFF-LABEL DRUGS FOR DIFFERENTIATED THYROID CARCINOMA

Considering the time-limited benefits of *FDA*-approved kinase inhibitors treatment in RAI-refractory thyroid cancer, it became necessary to develop additional new

therapeutic lines that would enhance compatibility with individual patient needs by improving efficacy and adverse events profile. Several targeting agents are being studied in advanced differentiated thyroid cancers, but none of them have been approved yet (Table 1). A summary of some relevant ongoing clinical trials for the treatment of advanced RAIR-DTC are shown in Table 4.

SELECTIVE BRAF INHIBITORS

Combination of dabrafenib-trametinib

BRAF oncogene mutations are present in approximately 50% of PTCs, while it has been observed that it rises to over 90% when an anaplastic transformation emerges from a prior history of PTC[52]. Under this premise, a clinical study using the combination dabrafenib 150 mg twice daily + trametinib 2 mg daily (selective inhibitors of *BRAF V600E* kinase and *MEK1-2* kinase, respectively) in 23 patients with locally advanced, unresectable, or metastatic ATC[53], prompted the rapidly FDA approval for these patients. This study showed an overall response rate of 61%, with complete and partial response rates of 4% and 57%, respectively. Progression free survival for at least 6 mo was seen in 64% of these patients and overall survival was 80% at 1 year. The most common adverse events were fatigue (44%), fevers (31%), and nausea (31%), and the most common grade 3 and 4 adverse event was anemia (13%) [53].

In our setting, where access to molecular tests and target therapies is not widely available yet, we have reported the cases of two patients with metastatic and locally unresectable ATC, in whom the use of dabrafenib-trametinib (D-T) provided a dramatic reduction of the cervical mass with a minimal residual loco-regional disease, and even allowed surgical resection on one of them. Besides, a partial and complete response to the pulmonary metastatic disease was also observed[54,55].

The combination of D-T was studied in a phase II clinical trial that included 53 patients with *BRAF* mutated RAIR-PTC with disease progression within the last year [56]. The participants were randomized to Arm A (dabrafenib 300 mg daily, *n* = 26) or Arm B (dabrafenib 150 mg daily + trametinib 2 mg daily, *n* = 27). Cross-over to Arm B was allowed at the time of progression. Out of 25% of patients had prior therapy with multi-kinase inhibitors. Preliminary results exhibited partial responses in 10 (38%) and 9 (33%) patients from Arm A and B, respectively. Progression-Free Survival for patients who received D-T was 11.4 mo, with a median follow-up of 13 mo. The treatment-related adverse events were similar to previously reported trials[56].

Dabrafenib and vemurafenib in RAIR-DTC

Dabrafenib and vemurafenib have been approved as single agents for the treatment of advanced melanoma, but they also have been evaluated in phase 2 trials in patients with *BRAF V600E*–mutated PTC[57,58]. Both *BRAF* inhibitors are effective also in papillary carcinoma, although the outcomes have not been as robust as for ATC, so neither are currently approved for this use. In general terms, objective responses were seen for up to half of patients treated with either vemurafenib or dabrafenib in different trials and clinical experiences[57-59]. Among them, a randomized, multi-institutional, open-label phase 2 trial was conducted over two arms of patients with *BRAF V600E*–mutated PTC[57]. Arm A employed dabrafenib as a single agent and arm B, the combination of dabrafenib with trametinib. Partial responses were reached in 10 of 26 patients (38%) from arm A, and 9 of 17 (33%) from arm B, with median PFS of 11.4 and 15.1 mo, respectively. Common adverse events included fever, diarrhea, anemia, fatigue, nausea, alopecia and skin reactions[57]. Meanwhile, a non-randomized, open-label, multicenter phase 2 vemurafenib trial was conducted in two cohorts of patients with *BRAF V600E*–mutated PTC. Cohort 1 was comprised of 26 patients who had never received multikinase VEGFR inhibitors, in which the best overall response (partial response) was reached in 12 patients (38%), with a median duration of PFS of 18.8 mo (14.2–26), and the median OS had yet to be reached. In cohort 2 were included 25 patients who previously received MKIs treatment. Partial response rates were seen in 27.3%, with a median PFS of 8.9 mo. The most common adverse events reported were rash, fatigue, weight loss, dysgeusia, and alopecia. Serious adverse events were seen in 62% and 68% of the patients in cohort 1 and 2, respectively, including benign and malignant skin lesions and cerebrovascular accidents, among others[58].

Table 4 Some relevant ongoing clinical trials for the treatment of advanced radioiodine refractory-differentiated thyroid carcinoma (thru March 11, 2021, from clinicaltrials.gov)

NCT number	Title	Status	Interventions	Characteristics	Population	Dates	Locations
NCT04554680	Clinical Trial in RAI-Refractory Thyroid Carcinoma Evaluating BRAF & MEK Blockade for Redifferentiation Therapy	Recruiting	Drug: Dabrafenib and trametinib	Study type: Interventional	Enrollment: $n = 5$	Study start: December 30, 2020	National University Hospital, Singapore, Singapore
				Phase: Phase 2	Age: 21-99 yr	Study completion: April 2022	
				Study design: Allocation: N/A; Intervention model: Single group assignment; Masking: None (open label); Primary purpose: Treatment outcome; Measures: The proportion of participants attaining at least one tumor lesion with lesional dosimetry of ≥ 2000 cGy with I-131 dose of =	Sex: All		
NCT01709292	Vemurafenib Neoadjuvant Trial in Locally Advanced Thyroid Cancer	Active, not recruiting	Drug: Vemurafenib (all groups)	Study type: Interventional	Enrollment: $n = 24$ Age: 18 yr and older	Study start: November 7, 2012	University of Texas MD Anderson Cancer Center, Houston, Texas, United States
			Drug: Vemurafenib (Post Surgery) - Group A + C Other: Post Surgery - Group B	Phase: Phase 2 Study design: Allocation: NonRandomized intervention; Model: Parallel assignment; Masking: None (open label); Primary purpose: Treatment outcome; Measures: Percent change in ERK (extracellular-signal regulated kinase) phosphorylation and tumor size, objective response rate	Sex: All	Study completion: November 30, 2020	
NCT03167385	Phase 2 Trial of Apatinib Mesylate in Locally Advanced/ Metastatic Differentiated Thyroid Carcinoma	Unknown	Drug: Apatinib mesylate	Study type: Interventional	Enrollment: $n = 20$ Age: 18 to 75 yr	Study start: March 22, 2017	Tianjin Medical University Cancer Institute and Hospital, Tianjin, Tianjin, China
				Phase: Phase 2 Study design: Allocation: N/A; Intervention model: Single group; assignment; Masking: None (open label); Primary purpose: Treatment outcome; Measures: Disease control rate, progression free survival, overall survival, objective response rate	Sex: All	Study completion: December 31, 2020	
NCT03753919	Durvalumab Plus Tremelimumab for the Treatment of Patients With Progressive, Refractory Advanced Thyroid Carcinoma - The DUTHY Trial	Recruiting	Drug: Durvalumab Drug: Tremelimumab	Study type: Interventional	Enrollment: 46 Age: 18 yr and older	Study start: April 2	Instituto Catalán de Oncología de Hospitalet, L'Hospitalet de Llobregat, Barcelona, Spain; Hospital Provincial de Castellón, Castelló, Valencia, Spain; Hospital Clínic Barcelona, Barcelona, Spain; Hospital Universitari Vall d'Hebron, Barcelona, Spain; MD Anderson Cancer Center, Madrid, Spain; Hospital Clínico San Carlos, Madrid, Spain; Hospital Universitario 12 de
				Phase: Phase 2 study Design: Allocation: N/A; Intervention model: Single group assignment; Masking: None (open label); Primary purpose: Treatment outcome; Measures: Progression-free survival rate at 6 mo, overall survival rate at 6 mo, overall response rate,	Sex: All	Study completion: July 2021	

			duration of response, median progression-free survival, incidence of treatment, emergent adverse events (safety and tolerability), median overall survival, response status after start of study treatment			Octubre, Madrid, Spain; Hospital Universitario HM Sanchinarro, Madrid, Spain; Hospital Universitario La Paz, Madrid, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; and 5 more
NCT00537095	Efficacy and Safety of Vandetanib (ZD6474) in Patients With Metastatic Papillary or Follicular Thyroid Cancer	Active, not recruiting	Drug: Vandetanib Other: Placebo	Study type: Interventional	Enrollment: n = 165 Age: 18 yr and older	Study start: September 29, 2007	Research Site, Brussels, Belgium; Research Site, Odense, Denmark; Research Site, Angers Cedex 9, France Research Site, Angers Cedex, France; Research Site, Bordeaux Cedex, France; Research Site, Caen Cedex 5, France; Research Site, Caen Cedex, France; Research Site, Lyon Cedex, France; Research Site, Lyon, France; Research Site, Marseille Cedex 9, France; and 12 more
				Phase: Phase 2	Sex: All	Study completion: December 2021	
				Study design: Allocation: Randomized; Intervention model: Parallel assignment; Masking: Double (participant, investigator); Primary purpose: Treatment outcome; Measures: Time to tumor progression, disease control rate at 6 mo, objective response rate, time to death			
NCT03602495	Donafenib in 131I-Refractory Differentiated Thyroid Cancer	Recruiting	Drug: Donafenib Drug: Placebo	Study type: Interventional	Enrollment: n = 204 Age: 18 yr and older	Study start: August 29, 2018	Peking Union Medical College Hospital, Beijing, Beijing, China
				Phase: Phase 3	Sex: All	Study completion: December 2021	
				Study design: Allocation: Randomized; Intervention model: Parallel assignment; Masking: Double (participant, investigator); Primary purpose: Treatment outcome; Measures: Progression-free survival, overall survival, objective response rate, disease control rate, time to disease progression			

Selective mTOR inhibitors (everolimus, temsirolimus)

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that exerts as an essential regulator of cell growth-related processes[60]. Everolimus and temsirolimus are two *mTOR* inhibitors that demonstrated clinical benefits in other cancers like advanced renal carcinoma, metastatic breast cancer, and pancreatic neuroendocrine tumors, in which they were approved by the FDA[61]. Since the mTOR pathway is over-activated in thyroid cancer, some studies have tested these agents' effects on advanced thyroid cancer, with promising outcomes[62,63].

Everolimus was evaluated in a single-arm, multicentric phase II study that included 31 patients with aggressive RAIR-DTC, among other thyroid tumor histologies. There was one PR (3%) but 27 patients (82%) had SD, for a clinical benefit rate of 84.8% and a median PFS for 12.9 mo. Median OS was not reached and 2-year OS was 73.5%[62]. For its part, a phase 2 study that enrolled 36 patients with metastatic RAIR-DTC evaluated the efficacy of the combination of oral sorafenib (200 mg twice daily) and intravenous temsirolimus (25 mg weekly)[63]. A partial response was reached in 8 patients (22%), while stable and progression disease was seen in 21 (58%) and 1 (2%) patients, respectively. The mPFS at one year was 30.5% and the most common toxicities included hyperglycemia, fatigue, anemia, and oral mucositis. The authors concluded that this combination appears to have better response rates in patients with RAI-refractory thyroid cancer who received no prior treatment, regardless of whether *RAS* or *RAF* mutation was present[63].

Redifferentiation agents

It has been well described that activating *BRAF* mutations induce loss of differentiated

features required for response to radioiodine treatment, while its blockade would restore radioiodine uptake in experimental models[64]. In patients with radioiodine-refractory differentiated carcinoma with somatic *BRAF* or *RAS* mutations, treatment with the specific targeted inhibitors may restore radioiodine responsiveness in up to two-thirds of patients, permitting iodine therapeutic administration leading to tumor shrinkage in up to one-third[57-59]. On the other hand, constitutive activation of MAPK pathway causes inhibition of a variety of thyroid genes, including NIS, leading to the investigation of selective MAPK blocking agents as Selumetinib, as redifferentiation agent[64,65].

Selumetinib

Selumetinib is a *MEK1–2*, *RAS* and *BRAF V600E* inhibitor which efficacy was evaluated in 32 RAIR-DTC patients enrolled in a multicenter, open-label, phase II trial [66]. There were 1 partial response (3%), 21 stable disease (54%), and 11 progressive diseases (28%). Median PFS was 32 wk, and it was seen that *BRAF V600E* mutants had a longer median PFS compared with patients with BRAF wild-type cancer (33 *vs* 11 wk, respectively). This suggest a potential beneficence of Selumetinib based on underlying genetic disorders. The most common adverse events included rash, fatigue, diarrhea, and peripheral edema[66]. A phase III trial is currently in progress which continues to explore selumetinib's redifferentiation benefits in a larger number of participants[66] (Table 2).

Immunotherapy

In recent years, there has been significant progress in the field of oncological immunotherapy. Several immunotherapeutic agents have now been approved by the FDA for the treatment of a variety of malignancies, including melanoma, non-small cell lung cancer, renal and breast carcinomas, among others[67]. In this line, several phase I studies research the use of immunotherapy in the treatment of advanced differentiated thyroid cancer focuses on restoring immune surveillance[68]. The recent identification of blocking antibodies of CTLA-4 and PD-1 to their corresponding ligands (CD80/86 and PD-L1/PD-L2 respectively) enhances the effector T cells and inhibits the regulatory suppressor cells. Thus, the evidence of PD-1 (+) T cell in thyroid tumors involved lymph nodes in PTC patients suggests the potential utility of immune checkpoint inhibitors like pembrolizumab (as a single agent or in combination with MKIs) for advanced thyroid cancers[68]. Only a few immunotherapy trials in patients with thyroid cancer have been published to date, but several trials are ongoing.

Pembrolizumab

Pembrolizumab is an anti–PD-1 monoclonal antibody that exhibits antitumor activity by blocking interaction between PD-1 and its ligands[68]. Patients with advanced thyroid cancer were enrolled in the nonrandomized, phase Ib KEYNOTE-028 trial conducted to evaluate its safety and antitumor activity in 22 patients with advanced papillary or follicular thyroid cancer. Pembrolizumab 10 mg/kg was administered every 2 wk up to 24 mo or until confirmed progression or intolerable toxicity. SD was achieved by 57% (4/7) of patients with follicular histology and 60% (9/15) of patients with papillary histology and two patients reached partial response for 8 and 20 mo. Median PFS was 7 mo and median overall survival was not reached. Diarrhea and fatigue were the most common adverse events[69]. This study suggests that pembrolizumab may be effective and have a favorable safety profile in PD-L1–positive thyroid cancer, providing a baseline for future research[69].

Other ongoing single-arm multicenter phase II study combine lenvatinib and pembrolizumab in patients with RAIR-DTC[70]. Patients were excluded if they had received previous VEGFR-directed multikinase therapy. The lenvatinib starting dose was 20 mg/d orally and pembrolizumab was 200 mg IV every 3 wk. The preliminary results showed that out of 29 evaluable patients, 18 (62%) had a partial response, 10 (35%) had stable disease and the clinical benefit rate was 97%. The PFS at 12 mo was 74%, and median PFS was not yet reached. The most common adverse events were hypertension (47%), weight loss (13%), maculopapular rash (13%), leukopenia (7%), diarrhea (7%), and oral mucositis (7%)[70]. While the results are promising, the continuation of this study will help determine the magnitude of the responses.

CONCLUSION

In conclusion, therapeutic options for patients with advanced radioiodine-refractory differentiated thyroid carcinoma have been increasingly evolving and fine-tuned. While the introduction of new therapies for multiple molecular targets has made it possible to extend progression-free survival, their impact on overall survival is still unclear. Based on the improving knowledge of the underlying molecular mechanisms in these patients, novel agents under study bring us a new scope for the near future. Thus, increasingly tailored therapy focused on critical molecular pathways will be offered, allowing to overcome drug evasion mechanisms, enhance efficacy, minimize adverse events, and finally achieve an overall survival improvement in these patients.

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