

Updates on the Management of Thyroid Cancer

Authors

Katherine A. Araque^{1*}, Sriram Gubbi^{2*} , Joanna Klubo-Gwiezdzinska²

Affiliations

- 1 Endocrinology Department, Pacific Neuroscience Institute, John Wayne Cancer Institute, Santa Monica, CA, USA
- 2 Metabolic Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Bethesda, MD, USA

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Correspondence:

Joanna Klubo-Gwiezdzinska MD, PhD, MHSc
Acting Chief of the Thyroid Tumors and Functional Thyroid Disorders Section NIH-NIDDK
10 Center Drive Bldg 10 CRC, Room 9C-103
Bethesda
MD 20814
USA
Tel.: +1 301 496 5052, Fax: +1 301 451 5798
joanna.klubo-gwiezdzinska@nih.gov

ABSTRACT

The diagnostic modalities, stratification tools, and treatment options for patients with thyroid cancer have rapidly evolved since the development of the American Thyroid Association (ATA) guidelines in 2015. This review compiles newer concepts in diagnosis, stratification tools and treatment options for patients with differentiated thyroid cancer (DTC), medullary thyroid carcinoma (MTC) and anaplastic thyroid cancer (ATC). Newer developments apply precision medicine in thyroid cancer patients to avoid over-treatment in low risk disease and under-treatment in high risk disease. Among novel patient-tailored therapies are selective RET inhibitors that have shown efficacy in the treatment of MTC with limited systemic toxicity compared with non-specific tyrosine kinase inhibitors. The combination of BRAF and MEK inhibitors have revolutionized management of BRAF V600E mutant ATC. Several immunotherapeutic agents are being actively investigated in the treatment of all forms of thyroid cancer. In this review, we describe the recent advances in the diagnosis and management of DTC, MTC, and ATC, with an emphasis on novel treatment modalities.

Introduction

There have been several advances in the treatment of thyroid cancer over the past couple of decades. This has been possible due to improvements in diagnostic and therapeutic modalities and the advent of novel molecular targeted therapies. Thyroid cancers can be broadly classified based on their cell of origin. The cancers that arise from the endoderm-derived follicular cells comprise of differentiated thyroid cancer (DTC) [which in turn comprises of papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC)], anaplastic thyroid cancer (ATC), and poorly differentiated thyroid cancer

[1]. Medullary thyroid cancer (MTC) arises from the neural crest-derived C-cells [1]. Thyroid cancers can occur either sporadically, or as a part of a genetic or a familial condition [such as familial non-medullary thyroid cancer, multiple endocrine neoplasia (MEN) 2A and 2B, Cowden syndrome, Carney complex] [2]. Classification of the various forms of thyroid cancer and their genetic hallmarks is provided in ►Table 1.

The incidence of thyroid cancer has increased significantly in the United States and worldwide, driven predominantly by the increased annual incidence of DTC. The incidence of MTC has been relatively stable [3]. While increased DTC incidence has been attributed to sonographic detection of small PTCs, there is evidence of an increase of all stages of DTC [3, 4]. Despite this, the mortality

* KAA and SG are first co-authors.

► **Table 1** Classification of primary thyroid cancers and their genetic hallmarks.

A. Based on the cell of origin:

I. Endoderm-derived thyroid cancer:

1. Differentiated thyroid cancer (DTC)

- Papillary thyroid cancer (PTC)

Genetics (disease-causing variants): *BRAF V600E* (60 % of disease-causing variants), *RAS* (15 % of disease-causing variants), *RET*, *EIF1AX*, *PPM1D*, *CHEK2*, *NTRK* fusion, *ALK* fusion, *DICER1*.

- Follicular thyroid cancer (FTC, including Hurtle cell cancer)

Genetics (disease-causing variants): *RAS*, *PAX8-PPARγ* fusion gene.

2. Poorly differentiated thyroid cancer Genetics (disease-causing variants): *BRAF*, *RAS*, *TERT*, *EIF1AX*.

3. Anaplastic thyroid cancer (ATC)

Genetics (disease-causing variants): *BRAF*, *RAS*, *TERT*, *EIF1AX*, *TP53*, *CTNNB1*, *PIK3CA*, *PTEN*, *AKT1*. Other disease-causing molecular alterations are found in the SWI/SNF complex and histone methyltransferases.

II. Neural-crest C-cell derived thyroid cancer:

1. Medullary thyroid cancer (MTC) Genetics (disease-causing variants): *RET*, *RAS*, *STK11*.

B. Based on inheritance pattern:

I. Sporadic (non-inheritable).

II. Familial (inheritable):

1. Familial non-medullary thyroid cancer (DTC)

2. DICER1 syndrome (DTC)

3. Carney complex (DTC)

4. Multiple endocrine neoplasia type 4 (DTC)

5. Familial adenomatous polyposis (cribriform-morular variant of PTC)

6. Werner syndrome (mainly FTC)

7. PTEN hamartoma syndromes such as Cowden syndrome (mainly FTC)

8. Familial MTC

9. Multiple endocrine neoplasia type 2A (MTC)

10. Multiple endocrine neoplasia type 2B (MTC, mainly with *RET* M918T disease-causing variant)

DTC: Differentiated thyroid cancer. PTC: Papillary thyroid cancer. FTC: Follicular thyroid cancer. ATC: Anaplastic thyroid cancer. MTC: Medullary thyroid cancer. Data adapted from [1, 2].

rate has increased only slightly and has ranged from 0.4 to 0.5 per 100 000 people per year since 1980 [4]. Since the compilation of the American Thyroid Association (ATA) guidelines on the management of thyroid cancer in 2015, newer studies have focused on risk stratification and optimization of individualized therapeutic options in these groups of patients. The updated American Joint Committee on Cancer (AJCC) 8th edition published in 2017 has suggested new staging definitions to predict disease-specific survival in patients with thyroid cancer (www.cancerstaging.org) [5]. The application of newer targeted systemic therapies for subjects with advanced disease, shared decision-making process, and identification of the optimal timing for initiation of systemic therapy are being actively investigated. This review provides a comprehensive overview of the most recent updates in the management of thyroid cancer [6–8].

Differentiated Thyroid Cancer

About 85 % of all thyroid cancers are PTCs, while FTC and Hurtle cell cancers together make up to 5 % of all thyroid cancers [1]. Histologically, PTC has several variants, such as classical, tall-cell, follicular, cribriform-morular variants, among others. The encapsulated forms of follicular variants have been recently re-classified as non-

invasive follicular neoplasms with papillary-like nuclear features (NIFT-P) in an attempt to replace the term ‘carcinoma’ as this subset of tumors is indolent [1, 9]. Due to the indolent course of DTC in vast majority of patients, the main challenge is to balance the risks and benefits of therapies offered to these individuals to avoid over-treatment in low risk individuals and under-treatment in high-risk patients.

The genetic landscape of PTC is heterogeneous, made of mutually exclusive mutations involving the mitogen-activated kinase (MAPK) pathway [10]. Based on the driving somatic disease-causing variant present in the tumor, PTC can be classified as either *BRAF V600E*-like PTCs and *RAS*-like PTCs [10]. *BRAF V600E*-like PTCs contain *BRAF V600E* as the primary driving mutation (60 % of all disease-causing variants in PTC) and are defined as PTCs with classic papillary morphology and a high MAPK pathway signaling. *RAS*-like PTCs contain *RAS* as the primary disease-causing variant (~ 15 % of all PTCs) and are defined as PTCs with follicular morphology and low MAP kinase pathway signaling [1, 10]. Other novel driving disease-causing variants such as *NTRK* fusion genes, *RET*, *EIF1AX*, *PPM1D*, and *CHEK2* have been identified [10]. FTCs are associated with *RAS* and *PAX8-PPARγ* fusion disease-causing variants [11]. With the advent of targeted therapies with small molecules, several of

these molecular pathways are druggable targets and have been described in the upcoming sections.

Updates on DTC staging

The 8th edition of AJCC published in 2017 has implemented substantial changes in the staging of DTC. These changes include: (1) increased age cut-off from 45 to 55 years old at diagnosis, stratifying patients with metastatic disease to lower versus higher risk of death based on age; (2) changing the definition of T3 disease eliminating lymph node (LN) metastases and the minimal extra-thyroidal extension reported on histology, as microscopic extra thyroid extension is not an independent factor increasing the risk of death; (3) introducing new categories for T3 tumors – namely T3a (>4 cm tumors confined to the thyroid) and T3b (gross extra thyroidal extension into strap muscles); (4) N1 (metastasis to regional LN) disease no longer upstages to stage III or IV in patients over 55 years, all patients remain in stage II; (5) change in LN levels: level VII LNs are now classified as central neck LNs (N1a) along with level VI LNs; and (6) the presence of distant metastases in older patients with DTC is now considered stage IVB as opposed to stage IVC as per the previous classifications [5, 12]. The goal of the new staging model is to better reflect the DTC biology and to balance the patients' quality of life and the delivery of cost-effective treatments by down-staging of around 29–38 % of patients [13–16]. An online calculator to stratify patients based on these new recommendations can be found in the following website: <https://www.thyroid.org/professionals/calculators/thyroid-cancer-staging-calculator/>.

While the AJCC 8th edition assesses the risk of death, the ATA risk stratification system predicts the risk of persistence/recurrent disease. According to clinical, pathological and molecular characteristics, thyroid cancer is classified as either low, intermediate or high risk for recurrence. This risk stratification aids to individualize surveillance and treatment [17]. The modern risk stratification systems are dynamic and evolve during follow up, based on ongoing evaluation of the biochemical and structural response to therapy [6, 18]. The utility of newer models integrating artificial intelligence have been studied. These systems combine mortality and recurrence risk stratifications to provide optimal treatment recommendations in patients with DTC. However, software optimization and prospective data are needed. Retrospective reviews have demonstrated a suboptimal concordance rate (77 %) between artificial intelligence-based clinical decision systems and clinician-recommended management of DTC. The performance of this technology varies among various populations and the standard of practice in different countries [6, 19].

Treatment goals in DTC include minimization of the risk of persistent/recurrent symptomatic disease, reducing the risk of cancer-related death while maintaining an optimal quality of life and minimizing treatment-related morbidity. Given the ability of early disease detection with improved laboratory and imaging techniques, the main goal is to identify which patients benefit from active surveillance as the best treatment strategy and which individuals present with actionable disease requiring either surgical or medical intervention.

Novel laboratory techniques allows the identification of a molecular signature of thyroid cancer, particularly *BRAF V600E* somatic mutation, in circulating cell free DNA (cfDNA), also known as “liq-

uid biopsy” [20]. The pooled analysis of six studies involving a total of 438 thyroid cancer patients documented that the average proportion of patients who had both *BRAF V600E* disease-causing variant in the tumor, as well as circulating *BRAF V600E*, was relatively low (16.5 %) thus limiting its diagnostic utility [21]. However, some studies suggest an association between the level of *BRAF V600E*-mutated cfDNA and tumor aggressiveness [22]. This raises the potential of the peripheral detection of *BRAF V600E*-mutated cfDNA as a non-invasive marker of aggressive disease. In fact, the diagnostic and prognostic utility of liquid biopsy has been proven in the more aggressive MTC and ATC [23, 24]. Further understanding of the tumoral DNA natural history can refine the clinical utility of this promising non-invasive technique [25, 26].

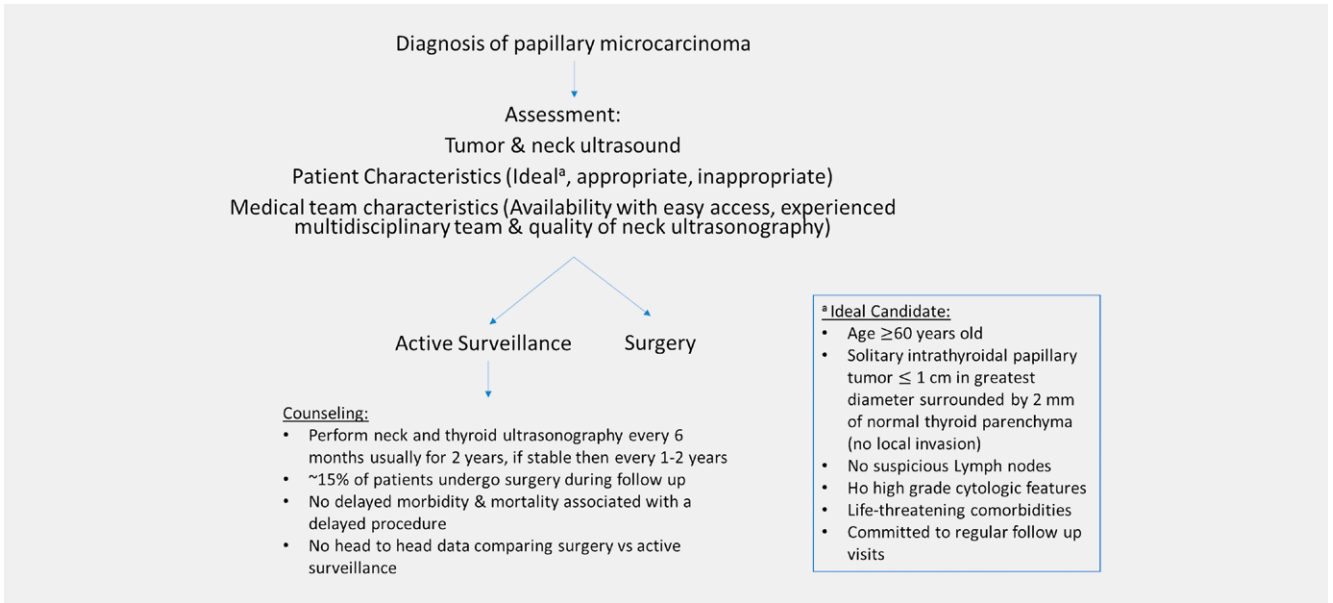
Current standard of care for DTC

Initial DTC treatment usually involves surgery. A personalized surgical approach is planned based on the disease burden. While surgical alternatives range from lobectomy/subtotal thyroidectomy for tumors not exceeding 4 cm to near total/total thyroidectomy with or without LN dissection for more advanced tumors, active surveillance without a surgical intervention is a reasonable option for very low risk patients with PTC [6]. Age, comorbidities and life expectancy should be considered when individualizing treatment, as total thyroidectomy for older adults with low risk PTC has been associated with higher incidence of complications and hospital readmissions [27]. In fact, a significant proportion of patients, specifically older individuals with low-risk tumors, may benefit from active surveillance without a surgical intervention.

In a large proportion of patients, PTCs are identified as either a papillary microcarcinoma (PMC) or a follicular variant thyroid microcarcinoma, both of which are defined as tumors of <1 cm in diameter with a favorable prognosis [1, 28]. Due to the indolent course of the disease, active surveillance is a strategy implemented by several centers for thyroid nodules up to 1.5 cm in diameter, depending on individual institutional protocols. Tumors larger than 1 cm and less than 1.5 cm (T1bN0M0) appear to have a similar course than tumors <1 cm (T1aN0M0) [29]. Conversely, a small subset of patients with PMC develop LN and even distant metastases warranting early surgical intervention.

The Memorial Sloan Kettering Cancer Center (MSKCC) provides a clinical decision-making framework in individuals with probable or proven PMC [30]. Based on this approach, cases are classified according to thyroid ultrasound findings, candidacy (ideal, appropriate, inappropriate) and team characteristics. For example, a patient older than 60 years of age who has a 1 cm thyroid nodule with well-defined borders with willingness to follow-up with an experienced multidisciplinary team within their health system at regular intervals would qualify as an ideal candidate for active surveillance. ► **Fig. 1** provides an algorithmic approach for clinical decision-making in PMC patients [31].

Active surveillance is defined based on the natural history of these tumors. Most PMCs grow slowly or remain stable over years, while some can even shrink over time. Disease progression has been inversely correlated with age at presentation, with younger patients being more likely to progress. None of the patients with low risk PMC showed distant metastasis or died from thyroid carcinoma during the active surveillance period [32]. Medical costs and ad-



► **Fig. 1** Risk stratified approach to decision making in papillary microcarcinoma. Adopted from Brito et al. (2016) [30], and Zanocco et al. (2019) [34].

verse events from surgery (recurrent laryngeal nerve injury, parathyroid gland damage and/or anesthetic complications) are higher in patients that undergo immediate resection. Contraindications for active surveillance include high risk features: presence of clinical LN or distant metastasis at diagnosis, signs or symptoms of invasion to the trachea or the recurrent laryngeal nerve and high grade malignancy on cytology, which includes tall cell variant and poorly differentiated carcinoma [33].

Transition from active surveillance to surgery should be considered when a thyroid nodule size increases in the greatest dimension by at least > 3 mm from initial measurement, in cases where a new suspicious metastatic LN disease shows cytological evidence for thyroid cancer, and when tumor volume increases by 50 % in three-dimensional measurements [32, 34]. The identification of tracheal invasion can be challenging, as ultrasound as standalone imaging may not provide a complete evaluation of tumors located at the dorsal side of the thyroid. Therefore, the use of computerized tomography (CT) can complement this evaluation. When a lesion is close to the trachea, clinicians should carefully examine the angle formed by the tumor surface and the tracheal cartilage. Acute angles are suitable for active surveillance while obtuse angles require surgical treatment [31]. In order to facilitate clinical decision making, “The Thyroid Cancer Treatment Choice”, an evidence-based tool has been designed [35]. A prototype is being tested in two health care systems in the United States. The goal is to understand the impact of this tool in the shared decision-making process and treatment decisions for patients with PMCs [35]. Active surveillance could be potentially advised as first line therapy in cases of PMC as it is safe, avoids side effects from surgery, and reflects a cost effective practice in health care systems [36]. The longest and largest experience from Kuma hospital in Japan demonstrated the safety of this conservative approach as well as a good quality of life of patients undergoing active surveillance [37].

Updates on Radioactive Iodine (RAI) therapy in DTC

RAI treatment is based on the principle of sodium iodide symporter (NIS) expressed by DTC cells having the ability of trapping RAI. There are 3 identified goals for the administration of RAI: 1. remnant ablation, to destroy residual presumably benign thyroid tissue, 2. adjuvant therapy, for suspected but not identified persistent disease, and/or 3. treatment of known residual or recurrent disease [17, 38]. The 2015 ATA guidelines recommend RAI therapy for all high-risk patients with RAI-avid disease due to a mortality benefit, for selected cases with intermediate risk disease, and does not recommend routine use for low risk patients. The selection of patients for adjuvant therapy needs to be based on careful multidisciplinary discussion with the patient [38]. It has been estimated that 10 % of patients with thyroid cancer develop advanced disease, which could become resistant to RAI (refractory disease). In these cases, the 5-year survival rate can be as low as 10 % in comparison with 56 % in cases of metastatic RAI-avid disease [39].

The standard treatment of empirically administered doses of RAI to treat metastatic DTC can lead to suboptimal dosing without tumoricidal effects but with increased risk of adverse effects. RAI-induced adverse effects include salivary gland damage, lacrimal duct obstruction, myelodysplastic syndrome and leukemia [6]. It is now clear that effectiveness of RAI therapy correlates with adequate lesional dosing. The implementation of lesional dosimetry utilizing Iodine-124 positron emission tomography/computed tomography (I-124 PET/CT) aids to individualize treatment. Currently, institutions in the United States (MSKCC and the National Institutes of Health) and in Germany are studying the utility of I-124 PET/CT in estimating the absorbed dose to individual tumoral lesions (ClinicalTrials.gov identifiers NCT03647358, NCT03841617 and NCT01704586).

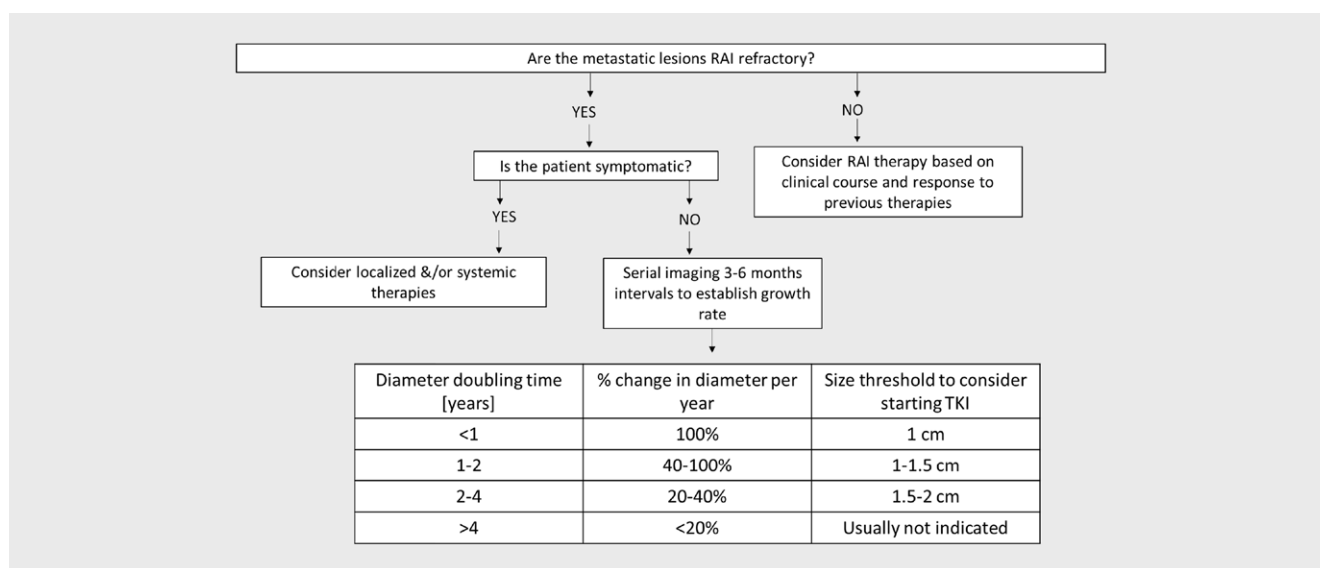
Treatment of RAI-refractory thyroid cancer

Over the past several years, researchers have developed an interest to restore and enhance RAI uptake in metastatic lesions in RAI-refractory metastatic thyroid cancer. These include therapy with lithium carbonate, retinoic acid, and more recently with MAPK/ERK kinase (MEK) inhibitors [40–42]. Activation of a MAP kinase signaling pathway by various oncogenes (RAS, BRAF and RET) reduces NIS expression, which is paramount in the iodine uptake process [43]. Mouse models have shown that inhibition of MEK signaling restores TSH receptor, thyroglobulin and NIS expression [44]. A landmark study documented that pretreatment with the MEK 1 and 2 inhibitor selumetinib induced RAI uptake to thresholds warranting therapeutic intervention as measured by I-124 PET/CT lesional dosimetry in 8 out of 20 patients in RAI non-avid DTC [45]. Selumetinib was particularly effective in patients with somatic N-RAS disease-causing variants in their tumors [45]. The SEL-I-METRY trial is a phase 2 open study, designed to assess the efficacy of selumetinib followed by RAI therapy in reversing RAI-refractory thyroid disease in patients with refractory DTC. It is expected that this study will lead towards defining a dose threshold for successful treatment, to individualize administered activity and to minimize toxicity [46, 47]. Treatment with trametinib, a second generation MEK inhibitor, followed by RAI therapy guided by I-124 PET/CT lesional dosimetry is also being investigated in a phase 2 clinical trial (NCT02152995). An individualized patient-tailored approach is being investigated by another trial where trametinib is given as pre-treatment for RAI in N-RAS-positive tumors and BRAF V600E inhibitor, dabrafenib, for BRAF-positive tumors (NCT03244956).

The identification of genetic landscapes and molecular pathways in thyroid cancer cells allowed development of newer therapies that improve progression-free survival (PFS) [48]. The Food and Drug administration (FDA) has approved two tyrosine kinase inhibitors (TKIs), sorafenib and lenvatinib, in the management of patients with RAI-refractory progressive DTC [49, 50]. The role of newer systemic agents has been incorporated by the National Com-

prehensive Cancer Network guidelines in the treatment of thyroid cancer, published in March 2019. Molecular testing can guide systemic treatment with novel small-molecule kinase inhibitors if a clinical trial is not available or if there is a contraindication to lenvatinib or sorafenib use. Dabrafenib/trametinib or vemurafenib off-label use in BRAF V600E positive status have been proposed. In addition, in cases with a positive neurotrophic tyrosine receptor kinase (NTRK) 1–3 or anaplastic lymphoma kinase (ALK) gene fusion, off-label use of axitinib, everolimus, pazopanib, sunitinib, vandetanib or carbozantinib have been described [51]. Prospective data describing patient's quality of life and resistance mechanisms can potentially allow to further establish of first- and second-line salvage treatments.

The optimal timing of the initiation of targeted therapies might be challenging. Lenvatinib and sorafenib were approved for progressive and/or symptomatic RAI-refractory thyroid cancer not amenable to localized therapies, including but not limited to external beam radiation, radiofrequency ablation, embolization or metastasectomy. However, the therapeutic intervention in patients with cancer-related symptoms might be already too late. Therefore, to identify the 'best timing' of systemic therapy initiation in otherwise asymptomatic patients, estimation of a time point called 'the inflection point' has been proposed [52]. The inflection point is a period of time where the structural disease progression is clinically significant, and it is the earliest time point where TKIs can be considered in asymptomatic patients with metastatic disease [52]. This time point can be obtained by integrating the maximal tumor diameter and the rate of doubling time of the maximal tumor diameter. Tumor volume doubling times can be calculated using freely available online calculators from either the American Thyroid Association (<http://www.thyroid.org/professionals/calculators/thyroid-with-nodules/>) or from the Kuma Hospital (<http://www.kuma-h.or.jp/english/about/doubling-time-progression-calculator/>) [52]. However, future clinical trials are required to evaluate whether initiation of TKIs at the inflection point is better or worse



► **Fig. 2** Practical assessment for cases with metastatic thyroid cancer and novel concepts for initiating multi-targeted kinase inhibitors in radioactive iodine refractory differentiated thyroid cancer. Adopted from Tuttle et al. (2017) [52]. RAI: Radioactive iodine; TKI: Tyrosine kinase inhibitor.

than initiating before or after that time point [52]. Tuttle et al. have proposed an algorithmic approach on management of metastatic DTC and the timing of initiation of TKIs based on tumor diameter doubling time and the percentage change in tumor diameter per year (► Fig. 2) [52].

Potential role of immunotherapy in DTC

DTC has been shown to be infiltrated by several immune cells, including natural killer cells, lymphocytes, and macrophages, with an enrichment in the expression of CTLA-4 and PD-L1. The intra-tumoral immune cell density correlates with *BRAF V600E* mutation and low thyroid differentiation scores [53]. PD-L1 positivity has been shown to correlate with LN metastasis, extra-nodal invasion, tumor recurrence and poor survival in thyroid cancer patients [53]. Data on utility of immunotherapy in DTC is currently lacking and there are several on-going clinical trials evaluating the role of immunotherapy in DTC. Recently, a non-randomized, phase 1b trial assessed the safety and efficacy of pembrolizumab, a PD-1 inhibitor in patients with advanced, PD-L1 positive DTC [54]. Among the 22 enrolled patients, the median progression-free survival was 7 months and the median overall survival was not reached. Two patients had confirmed partial response. Eighteen (82 %) patients experienced adverse events, diarrhea occurred in 7 patients and 4 patients experienced fatigue, one patient experienced a grade 3 adverse event (colitis), and no treatment discontinuation or treatment-related death occurred. Through large-scale gene expression profiling of PTC, a recent study classified the canonical *BRAF V600E*-like PTCs and *RAS*-like PTCs into 2 clusters: immunoreactive PTC (characterized by high immune-related gene expression and immune cell infiltration of the tumor), and immunodeficient PTC (characterized by low immune-related gene expression and low immune cell infiltration of the tumor) [55]. Potential future investigations could focus on immunotyping PTCs and targeting immunoreactive PTCs with immunotherapeutic agents.

On-going clinical trials

As of July 2019, a search for the term 'differentiated thyroid cancer' in ClinicalTrials.gov yielded 51 active clinical trials on DTC. Some of these trials have been listed in ► Table 2. Several TKIs are being investigated in phase 2 and 3 trials, with lenvatinib being the most studied TKI (NCT03573960, NCT03506048, NCT02702388, and NCT03139747 among others). TKIs are being studied either as monotherapy or in combination with immunotherapy (NCT03914300) or with mTOR inhibitors (everolimus; NCT01263951), or lenalidomide (NCT01208051). Immunotherapy also continues to be actively investigated. Some of these agents include pembrolizumab (NCT02973997), atezolizumab (NCT03170960), nivolumab (NCT03914300), and ipilimumab (NCT03914300). Several trials continue to investigate the optimization of RAI treatment either as monotherapy (NCT00415233) or in combination with TKIs (NCT03506048, NCT02393690), cytotoxic agents (NCT03387943), and *BRAF* + *MEK* inhibitors (NCT03244956). An open, phase 3, non-inferiority trial is currently comparing total thyroidectomy alone and a combination of total thyroidectomy and prophylactic central neck dissection to assess the outcomes in patients with low-risk DTC (NCT03570021).

Medullary thyroid cancer

Medullary thyroid cancer (MTC) accounts for ~3–5 % of all thyroid malignancies [7]. However, based on the Surveillance, Epidemiology, and End Results (SEER) database, the prevalence of MTC in the United States is in fact slightly lower (1–2 %), and this is attributed to the relative increase in the detection of PTC over the past 3 decades [56]. About 75 % of the cases of MTC are sporadic, while the remaining 25 % are hereditary [57]. The hereditary forms of MTC can occur as a part of one of the following syndromes: MEN2A, MEN2B, and hereditary MTC (FTMC) [57]. Unlike DTC, MTC is a form of neuroendocrine tumor which arises from the neural crest-derived parafollicular C-cells which produce calcitonin, a very specific tumor marker, as well as smaller quantities of several other peptides among which CEA is used as a non-specific tumor marker in surveillance of MTC patients [7]. The serum levels of both calcitonin and CEA are usually proportional to the C-cell mass in well differentiated MTC [7]. Pathogenic variants of *RET* (40–50 %), *RAS* (20 %), and *STK11* (10–20 %) genes are involved in the pathogenesis of sporadic MTC [58]. Interestingly, *RET* and *RAS* (*HRAS* and *KRAS*) disease-causing variants are usually mutually exclusive [59]. The somatic M918T disease-causing variant in the *RET* oncogene is the most common form of mutation seen with sporadic MTCs (> 75 % of *RET* disease-causing variants), and also a main germline disease-causing variant seen with MEN2B syndrome (► Table 1) [60, 61]. The sporadic forms of MTC are usually observed between the fourth and sixth decades of life [7]. In MEN2A patients, MTC can develop during childhood, but with MEN2B, MTC often develops during infancy and can follow a highly aggressive clinical course [7]. About 1–7 % of patients with presumed sporadic MTC cases in fact have hereditary disease [7, 62].

Current standard of care

The latest, revised ATA guidelines for diagnosis and management of MTC from 2015 provide several detailed algorithms for the work-up, treatment, and follow-up of these tumors [7]. Total thyroidectomy is performed in all patients, and cervical LN dissection is performed depending on serological, imaging and intra-operative findings [7]. External beam radiotherapy (EBRT) is provided to the neck if there is evidence of extensive local disease, residual disease or extra-thyroidal extension [7]. Targeted therapy with TKIs vandetanib or cabozantinib or enrollment into clinical trials is considered in patients with progressive symptomatic metastatic disease [7]. Local cryo-, thermo-, or chemo-ablation of liver metastases has been also successfully implemented. The 10-year overall survival in unselected MTC patients is about 75 %, but the survival rate is ≤ 40 % among those patients with locally advanced or metastatic disease [63].

The role of tyrosine kinase inhibitors

TKIs are small molecule inhibitors that specifically target and inhibit the action of tyrosine kinases [64]. As RET is a form of tyrosine kinase receptor, TKIs can inhibit the phosphorylation of RET protein leading to down-regulation of its downstream targets and consequent inhibition of tumor growth [64]. Over the past couple of decades, numerous TKIs have been evaluated in the treatment of MTC in phase 1, 2, and 3 clinical trials. Some of the examples include imatinib, gefitinib, motesanib, sunitinib, sorafenib, axitinib,

► **Table 2** List of currently investigated drugs in clinical trials for the treatment of differentiated thyroid cancer (registered under ClinicalTrials.gov).

Drug	Study phase	Study status	Location	NCT ID Number
I. Tyrosine kinase inhibitors:				
1. Vandetanib	Phase 3	Active, not recruiting	Multinational	NCT01876784
2. Apatinib	a. Phase 3	Recruiting	China	NCT03048877
	b. Phase 2	Recruiting	China	NCT03167385
3. Donafenib	Phase 3	Recruiting	China	NCT03602495
4. Cabozantinib	a. Phase 3	Recruiting	Multinational	NCT03690388
	b. Phase 1	Recruiting	Multinational	NCT03170960
	c. Phase 2	Recruiting	USA	NCT03914300
	d. Phase 2	Active, not recruiting	USA	NCT02041260
5. Lenvatinib	a. Phase 4	Recruiting	India	NCT03573960
	b. Phase 2	Recruiting	USA	NCT03506048
	c. Phase 2	Recruiting	Multinational	NCT02702388
	d. Phase 2	Recruiting	USA	NCT03139747
	e. Phase 2	Recruiting	USA	NCT02973997
	f. Phase 2	Recruiting	USA	NCT03630120
	g. Phase 2	Not yet recruiting	To be decided	NCT03732495
	h. Phase 1	Active, not recruiting	Multinational	NCT02432274
	i. Phase 3	Active, not recruiting	China	NCT02966093
6. Anlotinib	Phase 2	Active, not recruiting	China	NCT02586337
7. Sorafenib	a. Phase 2	Recruiting	USA	NCT03630120
	b. Phase 2	Active, not recruiting	USA	NCT01263951
8. Nintedanib	Phase 2	Active, not recruiting	Multinational	NCT01788982
9. Sulfatinib	Phase 2	Recruiting	China	NCT02614495
10. Sunitinib	Phase 2	Active, not recruiting	USA	NCT00381641
11. Cediranib	Phase 1	Active, not recruiting	USA, Canada	NCT01208051
12. Pazopanib	a. Phase 2	Active, not recruiting	Multinational	NCT00625846
	b. Phase 2	Recruiting	France	NCT01813136
II. Immunotherapy:				
1. Pembrolizumab	Phase 2	Recruiting	USA	NCT02973997
2. Ipilimumab	Phase 2	Recruiting	USA	NCT03914300
3. Nivolumab	Phase 2	Recruiting	USA	NCT03914300
4. Atezolizumab	Phase 2	Recruiting	Multinational	NCT03170960
III. mTOR inhibitors:				
1. Everolimus	Phase 2	Active, not recruiting	USA	NCT01263951
	Phase 2	Recruiting	USA	NCT03139747
2. Sirolimus	Phase 2	Recruiting	USA	NCT03099356
IV. Cytotoxic agents:				
1. Liposomal doxorubicin	Phase 2	Recruiting	China	NCT03387943
2. Cisplatin	Phase 2	Recruiting	China	NCT03387943
3. Cyclophosphamide	Phase 2	Recruiting	USA	NCT03099356
V. BRAF inhibitors:				
1. Dabrafenib	Phase 2	Recruiting	France	NCT03244956
VI. MEK inhibitors:				
1. Trametinib	a. Phase 2	Recruiting	France	NCT03244956
	b. Phase 2	Recruiting	USA	NCT02152995
2. Selumetinib	Phase 2	Recruiting	USA	NCT02393690

► Table 2 Continued.

Drug	Study phase	Study status	Location	NCT ID Number
VII. Radioactive iodine therapy:				
1.I-131	a. Phase 3	Recruiting	France	NCT01837745
	b. Phase 2	Recruiting	USA	NCT03506048
	c. Phase 2/3	Recruiting	UK	NCT01398085
	d. Phase 2	Recruiting	France	NCT03244956
	e. Phase 2	Recruiting	USA	NCT02393690
	f. Phase 2	Recruiting	USA	NCT02152995
	g. Unknown	Recruiting	Germany	NCT01704586
	h. Phase 2	Active, not recruiting	Korea	NCT02418247
	i. Phase 3	Active, not recruiting	UK	NCT00415233
VIII. Combination therapies:				
1. Everolimus + Sorafenib	Phase 2	Active, not recruiting	USA	NCT01263951
2. Liposomal doxorubicin + Cisplatin	Phase 2	Recruiting	China	NCT03387943
3. Lenvatinib + I-131	Phase 2	Recruiting	USA	NCT03506048
4. Cabozantinib + Nivolumab + Ipilimumab	Phase 2	Recruiting	USA	NCT03914300
5. Cyclophosphamide + Sirolimus	Phase 2	Recruiting	USA	NCT03099356
6. Everolimus + Lenvatinib	Phase 2	Recruiting	USA	NCT03139747
7. Trametinib + Dabrafenib + I-131	Phase 2	Recruiting	France	NCT03244956
8. Lenvatinib + Pembrolizumab	Phase 2	Recruiting	USA	NCT02973997
9. Cediranib + Lenalidomide	Phase 1	Active, not recruiting	USA, Canada	NCT01208051
10. Lenvatinib + Sorafenib	Phase 2	Recruiting	USA	NCT03630120
11. Cabozantinib + Atezolizumab	Phase 1/2	Recruiting	Multinational	NCT03170960
12. Selumetinib + I-131	Phase 2	Recruiting	USA	NCT02393690
13. Trametinib + I-131	Phase 2	Recruiting	USA	NCT02152995

apatinib, pazopanib, lenvatinib, vandetanib, and cabozantinib [63, 65–79]. Most of these studies are phase 2 studies, and the partial response rates of these drugs have been variable, ranging from 0–50 %, with many patients demonstrating prolonged stable disease [7]. Two TKIs, vandetanib (in 2011) and cabozantinib (in 2012) were approved by the FDA and the European Medicines Agency (EMA) for the treatment of advanced, progressive, metastatic MTC, based on the evidence of beneficial effects extending progression-free survival from well-designed phase 3 multicenter clinical trials [7]. As with other TKIs, the anti-tumor activity of these two drugs stems from their ability to simultaneously inhibit multiple, but functionally related kinases which would result in disruption of their associated pathways both in the parenchymal and stromal components of the thyroid gland [80]. The kinases inhibited by these drugs are: RET, VEGFR, EGFR for vandetanib, and RET, VEGFR, c-KIT and MET for cabozantinib [80].

However, therapy with TKIs is associated with significant adverse effects most likely due to wide-spread inhibition of RET at 'off-target' sites. Moreover, certain forms of RET disease-causing variants that affect the active enzymatic site of RET, such as V804L and V804M variants, can render all of the currently known non-specific RET inhibitors ineffective in treating MTC [80]. In fact, the V804 residue in the RET backbone also corresponds to the gate-keeper

position of several other kinases, including c-KIT, EGFR, PDGFR, and Abl [80]. Therefore, utilization of novel small molecules that selectively target RET rather than multiple kinases has been investigated in phase 2 clinical trials.

A highly selective, ATP-competitive small molecule RET inhibitor called LOXO-292 is being studied under phase 2 multinational clinical trials and patient recruitment is on-going (ClinicalTrials.gov identifiers NCT03157128 and NCT03899792). LOXO-292 demonstrates potent inhibitory effect on a diverse range of mutated RET proteins even at nanomolar concentrations. In a proof-of-concept study, orally administered LOXO-292 was utilized to treat a 49-year-old man with metastatic MTC who continued to have progression of disease in the liver, ascites, and severe tumor-related diarrhea, despite being on 6 MKI regimens [81]. The patient's initial surgical tumor specimen contained the founder M918T RET disease-causing variant, but over time acquired an additional RET V804M gate-keeper disease-causing variant. After initiation of the drug at 20 mg twice daily and step-wise escalation of the dose to 160 mg twice daily, the diarrhea, fatigue, and abdominal pain resolved, serum calcium and CEA levels drastically reduced, and there was up to 54% radiographic tumor response after 6.9 months of treatment. Moreover, analysis of circulating cfDNA revealed the suppression of both RET M918T and V804M variants after treatment. At the con-

clusion of the study, the patient continued to be on LOXO-292 and tolerated the medication well. All of the adverse events were grade 1 and none of these were attributed to LOXO-292 therapy.

A multi-national, open-label, phase 1/2 study of LOXO-292 is being carried out in patients with cancers harboring *RET* activating mutations (NCT03157128). As of 5th January 2018, the phase 1 study had been conducted in MTC patients with doses of 20–160 mg of oral LOXO-292 given in 28-day cycles [82]. Although the maximum tolerated dose was not achieved, adverse events were mainly of grade 1 or 2 (no grade 3 adverse events) and these events were fatigue, diarrhea, and dyspnea. Radiographic tumor reduction up to 45% was observed in 79% (11 out of 14) of MTC patients, including 1 patient who was treated previously with 3 TKIs and harbored a hereditary *RET* V804M gate-keeper disease-causing variant. A $\geq 50\%$ decrease in serum calcitonin levels was also observed in 79% of the patients. Another phase 1/2, multi-center clinical trial utilizing LOXO-292 is currently recruiting patients aged 6 months to 21 years of age with advanced solid or central nervous system tumors harboring *RET* disease-causing variants. Data on MTC patients is not yet available from this trial (NCT03899792). In addition to the promising preliminary results, LOXO-292 also possesses several favorable pharmacokinetic properties, such as high bioavailability, minimal drug interactions, predictable exposure and attainment of high central nervous system concentrations, which could potentially make it a powerful, novel therapy for MTC with *RET* disease-causing variants [81].

BLU-667 is a novel small molecule *RET* inhibitor that is currently being evaluated in a global phase I study on MTC and other *RET*-related solid tumors (ClinicalTrials.gov NCT03037385). BLU-667 has been designed to target oncogenic *RET* alterations, including *RET* fusions and *RET*-activating disease-causing variants such as M918T, C634W, V804L, and V804M [83]. When compared with non-*RET*-specific TKIs, BLU-667 has demonstrated more potent anti-tumor activity in *in vitro* experiments on *RET*-driven cancer cell lines and in *in vivo* murine *RET*-driven tumor models [83].

Clinically, BLU-667 has already demonstrated substantial beneficial effects in 2 patients with MTC [83]. The first patient was a 27-year-old with highly invasive TKI-naïve MTC which required emergent tracheostomy, total thyroidectomy, median sternotomy, total thymectomy and central and bilateral neck dissection from levels I through IV. TKIs were not considered due to the risk of VEGFR-related toxicities, predominantly fistula formation. The patient was enrolled in the BLU-667 clinical trial (NCT03037385) and started on 60mg once daily with an eventual dose escalation to 300mg once daily. After 28 days of BLU-667 therapy, the serum calcitonin levels dropped by $>90\%$. By 10 months, the patient had confirmed partial response with a 47% maximal tumor reduction. The clinical status of the patient improved, resulting in removal of tracheostomy tube and a return to the baseline body weight. At the time of this report, the patient continued to be on BLU-667 for over 11 months and remained progression free. Only a grade 1 adverse event of leukopenia was observed which spontaneously resolved. Under the same trial, another patient, a 56-year-old with MTC that progressed while on vandetanib was started on BLU-667 at 300 mg once daily dose. After 28 days of starting BLU-667, serum calcitonin and CEA levels were reduced by $>90\%$ and 75% respectively. After 8 weeks, there was radiographic evidence of tumor reduction

by 35% per RECIST 1.1. The *RET* 918T circulating cfDNA was undetectable after 56 days. The medication was well-tolerated with only grade 1 adverse events of nausea and hyperphosphatemia. At 8 months, a confirmed partial response with 47% maximum reduction was observed and the patient continued to be on the medication. In an initial data published from the above clinical trial, a 40% objective response rate was observed in 25 out of 29 MTC patients after a median treatment duration of 4.7 months [84]. Most adverse events were grade 1 and included hypertension, peripheral edema, elevated transaminases, fatigue and constipation [84, 85].

The role of immunotherapy in management of MTC

The role of immunotherapy in the treatment of MTC is yet to be fully explored. Previous studies have identified T-cell infiltration in the MTC tumors [86]. Dendritic cell vaccination strategies have been previously utilized in the treatment of MTC. Initial promising results were seen with administration of subcutaneous injections of calcitonin and CEA loaded dendritic cells into MTC patients [87]. During a mean follow-up of 13.1 months, 43% of the patients (3 out of 7) demonstrated favorable clinical response with reductions in serum calcitonin and CEA levels, and one of these patients demonstrated complete regression of liver metastases and substantial regression of pulmonary metastases. Another study was performed in a cohort of metastatic MTC patients who were treated with immunotherapy utilizing autologous dendritic cells loaded with tumor lysates derived from allogeneic MTC cell lines [88]. Three out of 10 patients had stable disease while the remaining showed progression of disease after a median follow-up of 11 months. In a phase 1 trial, a recombinant yeast-CEA (GI-6207) vaccine was utilized among patients with metastatic CEA-producing cancers to generate immune response to CEA resulting in anti-tumor activity [89]. However, the only MTC patient in this study was taken off the study at 3.5 months for a potential toxicity due to a strong immune response in the areas of metastatic disease. Currently, several immunotherapy drugs, including pembrolizumab (NCT03072160, NCT02721732), ipilimumab (NCT03246958), and nivolumab (NCT03246958) are being evaluated in phase 2 studies for the treatment of MTC.

Other novel therapeutic options for MTC

MTC, as a neuroendocrine tumor, is known to express somatostatin receptors (SSTRs) in a subset of tumors and peptide receptor radionuclide therapy may be of both diagnostic and therapeutic value. A phase 2 clinical trial evaluated the response, survival and long-term safety of systemic radiolabeled SSTR-2 analogue Y-90-DOTATOC in patients with metastatic MTC [90]. Out of the 31 patients, only 29% (9 patients) were responders (showed reduction in post-treatment calcitonin levels). Hematologic toxicity developed in 4 patients (12.9%) and renal toxicity was seen in 7 patients (22.6%). Responders had a significantly longer median survival when compared to non-responders (74.5 months vs. 10.8 months, respectively) from the time of treatment initiation [90]. In another trial, 7 MTC patients were treated with Lu-177-DOTATATE based on In-111-DTPA-octreotide uptake, out of which 3 patients had partial response, 3 patients had stable disease, and 1 patient had progressive disease [91]. A retrospective study on 10 consecutive patients treated with Lu-177-octreotate revealed stable dis-

ease in 4 patients and progressive disease in 6 patients [92]. Those patients with stable disease had a high uptake on In-111-DTPA-octreotide scan and an immunohistochemical evidence of SSTR-2 positivity. Radio-immunotherapy with bi-specific monoclonal antibodies, I-131-labeled bivalent hapten have shown initial promising results but their efficacy has not been tested in randomized, placebo-controlled trials [7]. The recent ATA guidelines on MTC recommend utilization of radio-immunotherapy only in selected patients in the setting of a well-designed clinical trial [7]. Radioiso-

tope therapy with I-131 MIBG has shown some evidence for partial response or stability of MTC, but ATA recommends utilization of radioisotope therapy only in the context of a clinical trial [7].

Future directions and on-going clinical trials for MTC

A list of on-going clinical trials for treatment of MTC are listed in ► **Table 3**. Some of the future considerations in the treatment of MTC include further evaluation of the utility of TKIs/MKIs and utilization of lower doses, combinations of these drugs or different

► **Table 3** List of currently investigated drugs in clinical trials for the treatment of medullary thyroid cancer (registered under ClinicalTrials.gov).

Drug	Study phase	Study status	Location	NCT ID Number
I. Tyrosine kinase inhibitors:				
1. Cabozantinib	a. Phase 4	Recruiting	Multinational	NCT01896479
	b. Phase 2	Recruiting	USA	NCT02867592
	c. Phase 2	Recruiting	USA	NCT03630120
	d. Phase 4	Active, not recruiting	Multinational	NCT00704730
	e. Phase 1	Active, not recruiting	USA, Canada	NCT01709435
2. Regorafenib	Phase 2	Recruiting	USA	NCT02657551
3. Sulfatinib	Phase 2	Recruiting	China	NCT02614495
4. Vandetanib	a. Phase 2	Recruiting	USA	NCT03630120
	b. Phase 1/2	Active, not recruiting	USA	NCT00514046
	c. Phase 3	Active, not recruiting	Multinational	NCT00410761
	d. Phase 4	Active, not recruiting	Multinational	NCT01496313
5. Nintedanib	a. Phase 2	Recruiting	USA	NCT03630120
	b. Phase 2	Active, not recruiting	Multinational	NCT01788982
6. Sorafenib	Phase 2	Active, not recruiting	USA	NCT00390325
7. Sunitinib	Phase 2	Active, not recruiting	USA	NCT00381641
8. Pazopanib	Phase 2	Active, not recruiting	Multinational	NCT00625846
9. Ponatinib	Phase 2	Not yet recruiting	To be decided	NCT03838692
II. RET inhibitors:				
1. LOXO-292	a. Phase 1/2	Recruiting	Multi-national	NCT03157128
	b. Phase 1/2	Recruiting	USA	NCT03899792
2. BLU-667	Phase 1	Recruiting	Multinational	NCT03037385
3. BOS172738	Phase 1	Recruiting	Belgium, France, and Spain	NCT03780517
III. Immunotherapy:				
1. Pembrolizumab	a. Phase 2	Recruiting	USA	NCT03072160
	b. Phase 2	Recruiting	USA	NCT02721732
2. Ipilimumab	Phase 2	Recruiting	USA	NCT03246958
3. Nivolumab	Phase 2	Recruiting	USA	NCT03246958
5. GI-6207 (CEA vaccine)	Phase 2	Active, not recruiting	USA	NCT01856920
IV. Gastrin analogues/Cholecystokinin-2 receptor agonists:				
1. 177Lu-PP-F11N	a. Phase 1	Recruiting	Switzerland	NCT02088645
	b. Phase 1	Recruiting	Switzerland	NCT03647657
2. 111In-CP04	Phase 1	Recruiting	Multinational	NCT03246659
IV. Anti-DLL3 antibody-drug conjugate:				
1. Rovalpituzumab	Phase 1/2	Active, not recruiting	USA	NCT02709889
VII. Combination therapies:				
1. Nivolumab + Ipilimumab	Phase 2	Recruiting	USA	NCT03246958

administration regimens to minimize systemic toxicity. Promising areas of research include the examination of the efficacy of novel therapies, including RET inhibitors such as LOXO-282 and BLU-667, as well as BOS172738 [93], immunotherapeutic agents such as pembrolizumab, nivolumab, and ipilimumab, gastrin analogues/cholecystokinin 2 agonists such as 177-Lu-PP-F11N and 111-In-CP04, CEA-vaccine (GI-6207), and rovalpituzumab, an anti-DLL3 antibody-drug conjugate (► Table 3).

Anaplastic thyroid carcinoma

Among all the thyroid malignancies, ATC is the most aggressive and carries the worst prognosis, with a median survival of 5–12 months and a 1 year survival rate of 20–40% [1, 8, 94]. Fortunately, ATC is rare and accounts for 1.7% of all thyroid malignancies in the United States and 3.6% of all thyroid malignancies world-wide (1.3–9.8% depending on the geographic region) [8]. The last robust set of guidelines for ATC management was generated and published by the ATA in 2012 and a new set of comprehensive guidelines is currently being prepared by the ATA [8]. The most recent version (8th edition) of the TNM classification of ATC was provided by the AJCC in 2017 [5]. All cases of ATC, regardless of the T, N or M, are classified as stage IV disease [5, 8]. Typically, ATC has a higher propensity to occur in a background of a pre-existing goiter or DTC [1, 8]. About 50% of the patients present with widely spread metastatic disease, 40% present with extrathyroidal extension/LN involvement and only 10% present with only intrathyroidal involvement [8]. About 20% of patients with ATC harbor a coexisting DTC in their thyroid glands [8].

Resectability of these tumors should be carefully assessed through imaging modalities such as thyroid US, CT, MRI, and PET scans [8]. If the tumor is deemed resectable and if there is no evidence of distant metastasis, the preferred modality of treatment is surgery followed by local/regional radiation with or without systemic chemotherapy [8]. For ATC confined to the thyroid, near-total or total thyroidectomy along with therapeutic LN dissection is performed and for ATC with extra-thyroidal extension, an en block resection is preferred, with a goal of achieving grossly negative margins [8]. In cases of unresectable tumors that are of local/regional confinement, the preferred initial treatment modality is radiation with or without systemic chemotherapy, and surgery can be considered if these tumors eventually become resectable [8]. Systemic chemotherapy involves the use of a combination of taxanes, anthracyclines, and platinum-based cytotoxic agents, but there has been no clear evidence for improvement in quality of life or survival with their use in ATC [8, 94]. Overall, the response rates for ATCs to standard systemic therapies are suboptimal, typically <15% [94]. Tubulin-binding compounds such as fosbretabulin, combretastatin, crolibulin, and TKIs/MKIs such as sorafenib, gefitinib, axitinib, and imatinib have been utilized in phase 1/2 studies with highly variable response rates [8, 95]. Favorable prognosis is associated with younger age (usually <60 years), smaller tumor size, female gender, disease confined to the thyroid gland, absence of distant metastasis, and complete resection of the primary tumor [8, 96, 97]. Due to the aggressive nature of the disease and poor prognosis, the ATA guidelines emphasize on the importance of multidisciplinary approach and a thorough discussion with the pa-

tients regarding surrogate decision making, advance directives, and code status [8].

The role of the combination of BRAF and MEK inhibitors

Molecular testing in ATC is a field that is being actively investigated. The 2012 ATA guidelines on ATC did not recommend molecular testing, but as more light is being shed on the commonly occurring molecular alterations in ATC there is increasing hope for utilization of targeted therapies [98]. ATCs harbor mutations in multiple genes, including *BRAF*, *RAS*, *TP53*, *EIF1AX*, *CTNNB1*, as well as genes involved in the AKT-mTOR pathway, the SWI/SNF complex, and histone methyltransferases (► Table 1). However *BRAF* and *RAS* are usually the main driving mutations. [1, 8]. Based on evidence of enhanced anti-tumor activity with combined inhibition of BRAF and MEK kinases in mouse models, and its subsequent success in treating melanoma and lung cancer, the safety and efficacy of combination therapy with dabrafenib (BRAF inhibitor; 150 mg twice daily) and trametinib (MEK inhibitor; 2 mg once daily) was evaluated in a phase 2, open-label trial, in 16 patients with ATC who had tried prior radiation and/or surgery and/or systemic therapy [94]. After a median follow-up of 47 weeks, the overall response rate was 69%, including 1 complete response. The most common adverse events (any grade) were fatigue (44%), pyrexia (31%), and nausea (31%), while anemia (13%) was the most frequent grade 3 and 4 adverse event. The 12-month Kaplan–Meier estimate of duration of response was 80% and the 12-month Kaplan–Meier estimate of overall survival was 90% (as compared to previous 12-month overall survival rates of 20–40% on other modes of therapy [94]). In a basket trial for non-melanoma cancers with *BRAF*V600 disease-causing variants, among the 7 enrolled ATC patients who had tried prior systemic therapies, one patient had a complete response and another patient had a partial response, and these responses were sustained for more than 12 months [99, 100]. Therefore, combination BRAF/MEK inhibitor therapy holds great promise in the treatment of ATC and was approved by the FDA for the management of *BRAF* V600E-positive ATC. Another BRAF inhibitor, vemurafenib, has also demonstrated favorable responses in isolated reports of ATC [99].

Other targeted therapies and on-going clinical trials

A list of on-going clinical trials on treatment of ATC is provided in ► Table 4. Apart from *BRAF* inhibitors and *MEK* inhibitors, several other classes of drugs have demonstrated efficacy and safety in the treatment of ATC.

The PI3K/AKT/mTOR pathway is activated in about 30–35% of ATCs and is another potential target for therapy [98]. Everolimus is by far the most extensively studied mTOR inhibitor in thyroid cancers. In a phase 2 clinical trial, everolimus (10 mg once daily) was evaluated in locally advanced or metastatic thyroid cancers of all histologic subtypes [101]. Among the 6 patients with ATC, the median progression-free survival was 10 weeks after a median follow-up of 11 months. Interestingly, one of the ATC patients demonstrated substantial reduction of tumor size (21% reduction after 4 weeks of treatment). Another phase 2 open label study evaluated everolimus (10 mg daily) in various forms of thyroid cancers [102]. In this study, (median follow-up of 10 months), 3 out of 5 ATC patients had disease progression, one patient had on-going disease

► **Table 4** List of currently investigated drugs in clinical trials for the treatment of anaplastic thyroid cancer (registered under ClinicalTrials.gov).

Drug	Study phase	Study status	Location	NCT ID Number
I. Tyrosine kinase inhibitors:				
1. Cabozantinib	Phase 2	Active, not recruiting	USA	NCT02041260
2. Lenvatinib	Phase 2	Active, not recruiting	Japan	NCT02726503
3. Sorafenib	Phase 2	Recruiting	China	NCT03565536
4. Pazopanib	a. Phase 2	Active, not recruiting	Multinational	NCT00625846
	b. Phase 2	Active, not recruiting	USA	NCT01236547
II. Immunotherapy:				
1. Pembrolizumab	a. Phase 2	Recruiting	USA	NCT02688608
	b. Phase 2	Active, not recruiting	USA	NCT03211117
2. Ipilimumab	Phase 2	Recruiting	USA	NCT03246958
3. Nivolumab	Phase 2	Recruiting	USA	NCT03246958
4. Durvalumab	Phase 1	Active, not recruiting	USA	NCT03122496
5. Tremelimumab	Phase 1	Active, not recruiting	USA	NCT03122496
6. Spatalizumab	Phase 1/2	Active, not recruiting	Multinational	NCT02404441
7. Atezolizumab	Phase 2	Recruiting	USA	NCT03181100
III. BRAF inhibitors:				
1. Dabrafenib	Phase 1	Not yet recruiting	USA	NCT03975231
2. Vemurafenib	Phase 2	Recruiting	USA	NCT03181100
IV. MEK inhibitors:				
1. Trametinib	Phase 1	Not yet recruiting	USA	NCT03975231
2. Cobimetinib	Phase 2	Recruiting	USA	NCT03181100
V. Cytotoxic agents:				
1. Paclitaxel	a. Phase 1	Recruiting	USA	NCT03085056
	b. Phase 2	Active, not recruiting	USA	NCT02152137
	c. Phase 2	Active, not recruiting	USA	NCT01236547
	d. Phase 2	Recruiting	USA	NCT03181100
2. Docetaxel	Phase 2	Active, not recruiting	USA	NCT03211117
3. Doxorubicin	Phase 2	Active, not recruiting	USA	NCT03211117
VI. m-TOR inhibitors:				
1. Sapanisertib	Phase 2	Recruiting	USA	NCT02244463
VII. PPAR γ agonists:				
1. Efatutazone	Phase 2	Active, not recruiting	USA	NCT02152137
VIII. ALK inhibitors:				
1. Ceritinib	Phase 2	Recruiting	USA	NCT02289144
IX. VEGF inhibitors:				
1. Bevacizumab	Phase 2	Recruiting	USA	NCT03181100
X. Combination therapies:				
1. Trametinib + Paclitaxel	Phase 1	Recruiting	USA	NCT03085056
2. Durvalumab + Tremelimumab + Stereotactic Body Radiotherapy	Phase 1	Active, not recruiting	USA	NCT03122496
3. Efatutazone + Paclitaxel	Phase 2	Active, not recruiting	USA	NCT02152137
4. Pembrolizumab + Docetaxel + Doxorubicin + Intensity-modulated radiotherapy + Surgery	Phase 2	Active, not recruiting	USA	NCT03211117
5. Sorafenib + External beam radiation + Surgery	Phase 2	Recruiting	China	NCT03565536
6. Dabrafenib + Trametinib + Intensity-modulated radiotherapy	Phase 1	Not yet recruiting	USA	NCT03975231
7. Paclitaxel + Pazopanib + Intensity-modulated radiotherapy	Phase 2	Active, not recruiting	USA	NCT01236547

► **Table 4** Continued.

Drug	Study phase	Study status	Location	NCT ID Number
8. Atezolizumab + Cobimetinib + Vemurafenib	Phase 2	Recruiting	USA	NCT03181100
9. Atezolizumab + Cobimetinib	Phase 2	Recruiting	USA	NCT03181100
10. Atezolizumab + Bevacizumab	Phase 2	Recruiting	USA	NCT03181100
11. Atezolizumab + Paclitaxel	Phase 2	Recruiting	USA	NCT03181100

stabilization, while another patient had achieved complete response that lasted for 18 months. Whole-exome sequencing in this patient revealed a somatic mutation in TSC-2 protein, a negative regulator of the mTOR pathway.

Analysis of immune markers in ATC samples have revealed extensive expression of PD-L1 in the tumor cells and PD-1 expression on inflammatory cells, thus making immunotherapy a potential targeted therapy in ATC [98, 103]. Nivolumab was administered along with vemurafenib to a 62-year-old male patient with ATC post-thyroidectomy, LN dissection and chemotherapy, who was treated with vemurafenib after his tumor was found to be PD-L1 positive [104]. Two months after nivolumab initiation, there was substantial regression of supraclavicular LNs and pulmonary nodules. The patient continued to be in complete remission 20 months into nivolumab therapy. In a retrospective analysis from MD Anderson Cancer Center, among the 12 patients treated with pembrolizumab and TKIs, 42 % achieved partial response, 33 % had stable disease, while 25 % experienced disease progression [105]. Common adverse events encountered with this combination included fatigue, anemia, and hypertension. Clinical trials are investigating several immunotherapeutic agents for the treatment of ATC. Examples include atezolizumab (NCT03181100), nivolumab (NCT03246958), ipilimumab (NCT03246958), pembrolizumab (NCT03211117), durvalumab (NCT03122496), tremelimumab (NCT03122496), and spartalizumab (NCT02404441). Other novel therapies considered for treatment of ATC include ALK inhibitors (ceritinib, NCT02289144), selective mTOR inhibitors (sapanisertib, NCT02244463), and efatutazone (PPAR γ agonist, NCT02152137). Several combination therapies consisting of cytotoxic agents, small molecule targeted therapies, and radiation, are also currently being investigated and are enlisted in ► **Table 4**.

Conclusions

Since the publication of the ATA 2015 guidelines in the management of thyroid carcinoma, several novel conceptual and evidence-based data have emerged. These new concepts allow for further optimization of risk-stratification of patients and individualization of care. Several novel therapeutic strategies, both single agents and combination therapies, are under various phases of clinical trials and are being utilized for different stages of thyroid cancer. Several studies have utilized artificial intelligence and machine learning and their findings have substantially added to the current knowledge of imaging, genetic, and molecular features of thyroid nodules and thyroid cancer [106–110]. The constant improvements in these technologies can give rise to more advanced meth-

ods which may potentially revolutionize the diagnosis and management of thyroid cancer. The advent of molecular stratification of thyroid cancers and development of targeted therapy based on the molecular landscape of thyroid cancers seems to hold a bright future in revolutionizing the care of thyroid cancer patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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