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New systemic therapies for locally advanced and metastatic thyroid cancer

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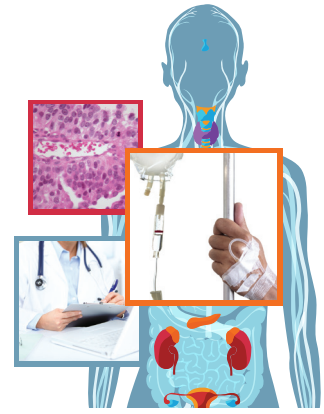
REVIEW



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New systemic therapies for locally advanced and metastatic thyroid cancer

Cynthia J Herrick*[,1] & Jeffrey F Moley[2,3]

Practice points

- Thyroid cancer is increasing in incidence, and, while it generally has a good prognosis, there have been limited therapeutic options for patients with advanced disease.
- The MAPK and PI3K pathways are important for cell growth and contain multiple potential drug targets, including RAS, BRAF, and RET among others. BRAF and TERT promoter mutations portend a poorer prognosis in papillary thyroid cancer.
- Sorafenib and lenvatinib are now US FDA approved for progressive, locally advanced or metastatic radioactive iodine refractory differentiated thyroid cancer. Sorafenib doubled progression-free survival (PFS) time versus placebo, and median PFS was five times longer for lenvatanib than for placebo with a >50% partial response rate in the treatment group.
- Vandetanib and cabozantinib are FDA approved for locally advanced or metastatic medullary thyroid cancer. Both drugs significantly prolonged median PFS over placebo (1.5-3 times), and cabozantinib was tested in patients with recent progression.
- Many other agents are under study for progressive, locally advanced or metastatic radioactive iodine refractory differentiated thyroid cancer (vandetanib, motesanib, pazopanib and selumetinib, axitinib, sunitinib, cabozantinib and dovitinib), and advanced medullary thyroid cancer (sorafenib, motesanib, pazopanib, axitinib, lenvatinib and sunitinib).
- No significant improvement in anaplastic thyroid cancer survival has been seen with tyrosine kinase inhibitors to date.
- Off target effects are common with tyrosine kinase inhibitors, including cardiovascular, gastrointestinal, dermatologic, and ophthalmologic complications. TSH also rises on tyrosine kinase inhibitor therapy.
- Rare severe adverse events have included GI perforation and fistula, major hemorrhage, and QTc prolongation.

Thyroid cancer affects one in 100 people over their lifetime. Differentiated and medullary thyroid cancer, refractory to traditional therapy, respond poorly to chemotherapeutic agents. However, tyrosine kinase inhibitors provide new hope for stabilizing disease in patients with advanced progressive disease. There are multiple tyrosine kinase inhibitors under study for thyroid cancer and currently four drugs that are US FDA approved. Nonetheless, use of these drugs should be selective given a significant adverse event profile and diseases with a typically indolent course. This review will cover molecular mechanisms in thyroid cancer as they are relevant to targeted therapies and review available evidence for the safety and efficacy of therapies currently approved and under study for thyroid cancer.

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KEYWORDS
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Thyroid cancer is the most common endocrine malignancy and the incidence has been increasing. According to the Surveillance, Epidemiology and End Results (SEER) database, there were an estimated 62,980 new cases of thyroid cancer diagnosed in 2014 with 1890 deaths, comprising 3.8% of all new cancer cases and 0.3% of cancer deaths. From 2009 to 2011 data, 1.1% of the population will be diagnosed with thyroid cancer during their lifetime, and rates of new thyroid cancer diagnosis have been rising 5.5% per year with death rates rising approximately 0.8% per year over the last 10 years [1].

Differentiated thyroid cancer (DTC) arises from the thyroid follicular epithelial cells and comprises 90% of all thyroid cancers. Papillary thyroid cancer (PTC) accounts for 85% of these cases, follicular thyroid cancer (FTC) accounts for 10%, and Hurthle cell, oxyphil and poorly differentiated subtypes account for the remainder [2]. While some histologic subtypes (tall cell, columnar cell, diffuse sclerosing variant, insular, trabecular, solid) have a worse prognosis, papillary and follicular cancers generally have an excellent 5-year survival rate exceeding 95%. However, 10–20% of patients with DTC develop distant metastases, with half of these patients no longer responding to radioactive iodine (RAI) or TSH suppression. Long-term survival for patients with stage IV DTC is approximately half that of those with stage I DTC (43 vs 86%) and drops to less than 10% in patients with radioactive iodine (RAI) refractory disease [3].

Medullary thyroid cancer (MTC) is a neuroendocrine tumor arising from the parafollicular C cells of the thyroid, accounting for approximately 4% of thyroid cancer cases. Seventy-five percent of cases are sporadic with 25% of cases associated with hereditary syndromes (multiple endocrine neoplasia [MEN] 2A, 2B; familial medullary thyroid cancer [FMTC]). Ten-year disease-specific survival for medullary thyroid cancer is 75%, but again is stage dependent, as 10-year survival for stage IV disease is 21% compared with 100% for stage I disease [4]. In contrast to DTC where less than 5% of cases present with distant metastases, up to 23% of MTC cases present with distant metastases [5]. In both DTC and MTC, traditional chemotherapy is not particularly effective, with tumor response rates typically less than 20% [5]. Anaplastic thyroid carcinoma (ATC) is a highly aggressive form of thyroid cancer, comprising 2% of all cases, occurring mostly in older patients, with a very poor prognosis and median survival of 3–5 months from diagnosis [6].

While the majority of thyroid cancer is not aggressive and is well treated with conventional therapies (surgery, RAI and TSH suppression for DTC and surgery for MTC), there is a clear need for additional treatment options for the cancers most likely to result in death: locally advanced or metastatic RAI refractory DTC, progressive metastatic MTC and anaplastic thyroid cancer. Increasing understanding of the molecular mechanisms underlying thyroid cancer in recent years has opened possibilities for targeted therapies in these cases.

This review has three principle goals: illustrate existing knowledge regarding molecular pathways involved in thyroid cancer and the mechanisms of available targeted therapies; appraise existing literature on the efficacy of US FDA approved and investigational systemic therapies for each thyroid cancer type and highlight ongoing clinical trials; discuss data regarding the safety profiles of these systemic agents. We will then synthesize this information to make recommendations regarding the use of these new drugs in clinical practice and speculate on future directions in this field.

Molecular mechanisms in thyroid cancer

Mutations in pathways important for cell growth, proliferation and angiogenesis are particularly promising targets. For example, mutations in the *RET* gene are important in MTC, as *RET* is highly expressed in the C cells, but *RET* is also involved in the pathogenesis of some PTC through a gene rearrangement. *RET* encodes a tyrosine kinase receptor, that when activated, initiates signal transduction through the MAPK and PI3K pathway that regulate cell growth [7]. The PI3K-AKT-mTOR pathway also regulates apoptosis, proliferation and cell migration [8]. Similarly, VEGFs and their receptors (VEGFR-1, VEGFR-2) are overexpressed in thyroid cancer tissue, activate the MAPK pathway, and are critical in tumor angiogenesis. The EGFR and PDGFR activate the MAPK pathway as well. As such, all of these receptors and pathways represent potential drug targets.

In 80% of PTC, activating mutations have been discovered in the MAPK pathway, including *RET*/PTC re-arrangements (up to ~40% of PTCs, most common in classical type), *RAS* mutations (10–20% of PTCs, most commonly

in the follicular variant) and *BRAF* point mutations (V600E; 40–50% of PTCs, more frequent in tall cell variant with rates up to 70% in de-differentiated PTC) [5,7]. Furthermore, *TERT* promoter point mutations (C228T) have been associated with particularly aggressive PTC variants and increase risk for recurrence independently and when combined with *BRAF* V600E mutations [9]. In a retrospective review of 507 patients, tumor recurrence was seen in 25.8 versus 9.6% of *BRAF* mutation positive versus negative patients, 47.5 versus 11.4% of *TERT* mutation positive versus negative patients and 68.6 versus 8.7% of those with both mutations versus those with neither mutation [9]. FTCs have *RAS* mutations in 20–35% of cases and *Pax8-PPAR-γ* rearrangements in 30% of cases. As mentioned above, most hereditary MTC contain germline *RET* mutations, and somatic *RET* mutations are present in 30–50% of sporadic MTC cases. PI3K activation may occur in PTC, but is more frequent in FTC, poorly differentiated and anaplastic thyroid cancers. *p53* mutations are found in ATC and poorly differentiated thyroid cancers. In addition to using targeted therapies to halt tumor growth and angiogenesis, re-induction of sodium iodide symporter (NIS) expression to re-establish tumor sensitivity to RAI has been proposed [5].

There are a number of tyrosine kinase inhibitors (TKI) currently on the market or in development that block various components of the above pathways **(Figure 1)**. *RET* and the VEGFR are the most common targets, and the overwhelming effect of currently approved therapies relates to their anti-angiogenic properties. Drugs targeting *RET* include sorafenib, vandetanib, cabozantinib, motesanib, lenvatinib and sunitinib. Drugs targeting one or more of the VEGFR include sorafenib, cabozantinib, vandetanib, motesanib, axitinib, lenvatinib, sunitinib, dovitinib and pazopanib. The PDGFR is inhibited by sorafenib, motesanib, axitinib, lenvatinib, sunitinib, dovitinib and pazopanib while the EGFR is inhibited by vandetanib [10]. Sorafenib and vemurafenib inhibit *BRAF*. *C-KIT*, an oncogene involved in signal transduction from *RET* to *RAS* is another commonly targeted molecule, inhibited by sorafenib, motesanib, axitinib, lenvatinib, sunitinib, dovitinib and pazopanib. Selumetinib selectively inhibits MEK-1/2, a protein kinase in the MAPK pathway. Because of the involvement of the PI3K-AKT-mTOR pathway, everolimus which targets mTOR is under investigation for thyroid cancer, and nuclear targets involved in DNA methylation and histone modification, vorinostat and romidepsin, are in early stages of investigation [8].

Defining tumor response to therapy

All of the trials that we will review in the next sections utilize the Response Evaluation Criteria in Solid Tumors (RECIST) system for reporting tumor response. This set of criteria, available since 2000 and revised in 2009, provides a standardized way of assessing radiologic tumor burden response to therapy. Measureable lesions at baseline are those measuring at least 10 mm on CT in the longest diameter with measurable malignant lymph nodes being those measuring at least 15 mm in the short axis. At baseline, target lesions are defined as up to five measurable lesions (with a maximum of two per organ) and are chosen by those that are the largest, most representative and most easily amenable to repeated measurement. Nontarget lesions are also measured and recorded at baseline. Response groups designated are: complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD). A CR requires the disappearance of all target and nontarget lesions, reduction of lymph node short axis to less than 10 mm and normalization of tumor markers. A PR requires at least a 30% decrease in the sum of diameters of target lesions. PD is at least a 20% increase in the sum of diameters of target lesions and an absolute increase in the sum by 5 mm or the appearance of any new lesions. SD is any change in the sum of diameters of target lesions that does not meet CR, PR or PD criteria [11]. Some trials will also report data on tumor marker and biochemical response or tumor response on radiographic modalities such as PET scan. Also, criteria for entry into most trials discussed required that patients have a good functional status according to the European Cooperative Oncology Group (ECOG) performance status scale (ECOG 0–2) [12].

• Differentiated thyroid cancer

Sorafenib is the first FDA approved targeted therapy for metastatic or locally advanced RAI refractory DTC, approved in November 2013. Its approval was based on the results of the Phase III DECISION trial, which was a multicenter, randomized, double-blind, placebo-controlled trial, enrolling 417 patients (207 sorafenib 400 mg b.i.d., 210 placebo) **(Table 1)** [13]. Median age in

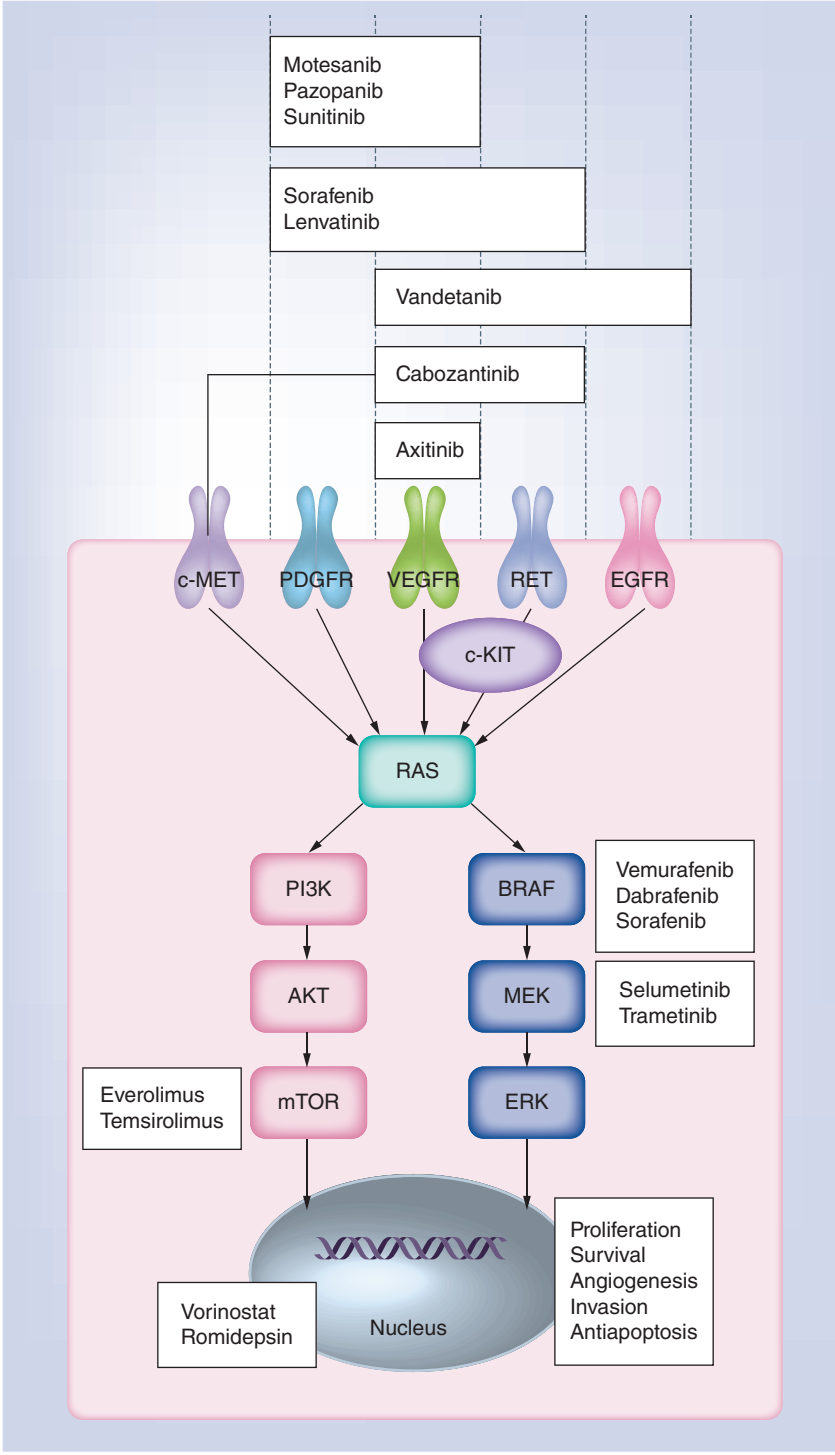

Figure 1. Targeted therapies assessed in clinical trials for advanced radioactive iodine refractory differentiated thyroid cancer.
Reproduced with permission from [8].

both groups was 63 and the trial population was approximately 60% white and 50% female with the majority of patients having PTC. Sorafenib approximately doubled PFS (10.8 vs 5.8 months; HR: 0.59; 95% CI: 0.45–0.76; $p < 0.0001$). The median overall survival (OS) end point was not reached.

Patients in the treatment group had a PR rate of 12.2% (as compared with 0.5% in the placebo group), with a median duration of response of 10.2 months (95% CI: 7.4–16.6), and SD rate of 41.8% (as compared with 33.2% in the placebo group), resulting in a significantly higher disease control rate of 54.0% (vs 33.7%) in the sorafenib group. Interestingly, *BRAF* and *RAS* mutation status predicted prognosis (*BRAF* mutation groups had longer PFS than wild-type and *RAS* wild-type had longer PFS than mutation groups), but *BRAF* and *RAS* status did not predict response to therapy in this trial. Subgroups that did not show significant benefit included North American patients, non-Hurthle cell follicular and poorly differentiated subtypes, those with negative FDG uptake on PET, and those with less than five measurable lesions at baseline [13].

Multiple open label single-arm Phase II trials of sorafenib preceded the DECISION trial, all with sample sizes less than 50 and median age in the 50s–60s [15–18]. PR rates in these trials ranged from 15 to 26% with SD rates ranging from 34 to 56%. Median PFS was slightly longer than in the Phase II trials, ranging from approximately 13.5 to 20 months. One trial demonstrated proof of mechanism, showing that pVEGFR, pERK and pAKT activity were reduced after drug administration [17]. Another trial demonstrated that there was no re-induction of radioactive iodine uptake after sorafenib administration [18]. While thyroglobulin declined in most patients on therapy in these trials, there were conflicting findings in how this biochemical marker correlated with radiographic response [15,18]. Further comparison of these sorafenib trials can be found in **Supplementary Table 1**.

A single-center retrospective review of off-label sorafenib use in patients with progressive RAI refractory DTC, including patients with worse functional status (ECOG 3–4), demonstrated a PR in 30% and SD in 41% of patients. Median PFS was 9 months (95% CI: 5.8–12.2) and median OS was 10 months, both significantly correlated with baseline ECOG status. In this study, there was a correlation between baseline thyroglobulin, thyroglobulin response and PFS. Early assessment with PET scan after 15 days of therapy correlated with PR and SD but not with PFS [19]. A small trial, using a lower

dose of sorafenib (200 mg b.i.d.) in nine Chinese patients with RAI refractory pulmonary metastases from PTC, found similar PR and SD rates (33 and 44%, respectively). Mean PFS was 42 weeks (95% CI: 29.5–53.9) in this study. While rates of adverse events in this trial were similar to other trials, they did appear less severe (no grade 3, 4) and required no further dose adjustments or discontinuations on the lower dose [20].

In summary, sorafenib is indicated in RAI refractory locally advanced or metastatic DTC because it significantly increased PFS, with disease control rates >50%, though no CR or OS benefit has been reported.

Lenvatinib was recently approved by the FDA based on data from the Phase III SELECT trial. This was a multicenter, randomized, double-blind, placebo-controlled trial in RAI refractory locally advanced or metastatic disease with documented progression in the last 13 months **(Table 1)** [14]. Median age was 63 and approximately half of the population was female, half had PTC and the majority had distant metastases. Approximately 25% had tried another VEGF therapy prior to trial inclusion. Three-hundred and ninety-two patients were randomized (261 lenvatinib 24 mg daily vs 131 placebo) with a median PFS of 18.3 months (95% CI: 15.1-NE) versus 3.6 months (95% CI: 2.2–3.7; HR: 0.21; 95% 0.14–0.31; p < 0.0001). There was also a high PR rate of 63.2% in the treatment group versus 1.5% in the placebo group, with 1.5% CR rate in the treatment group. No OS benefit was shown.

In conclusion, lenvatinib is also indicated in progressive RAI refractory locally advanced or metastatic DTC because it significantly increased PFS. While PFS and response rates in the lenvatinib group were higher in the SELECT trial than those seen in the DECISION trial for sorafenib, there has been no head-to-head comparison to support the use of one therapy before another.

Table 1. US FDA-approved therapy: locally advanced and metastatic radioactive iodine refractory differentiated thyroid cancer.

Drug	Sorafenib (400 mg b.i.d.) [13]	Lenvatinib (24 mg daily) [14]
Phase III studies		
Trial	Phase III (DECISION)	Phase III (SELECT)
Includes non-DTC patients?	No	No
Design	Multicenter, randomized, placebo controlled, double blind	Multicenter, randomized, placebo controlled, double blind
Inclusion criteria	Age >18 years Locally advanced or metastatic Progression in previous 14 months RAI refractory ECOG 0–2	Age ≥18 years Locally advanced or metastatic Progression in previous 13 months RAI refractory ECOG 0–3
Patients:		
– Number	417 (207 sorafenib vs 210 placebo)	392 (261 lenvatinib vs 131 placebo)
– Age (years); median (range)	63 (24–82) vs 63 (30–87)	64 vs 61
– White (%)	59.4 vs 61.0	
– Female (%)	49.8 vs 54.8	52.1 vs 42.7
–Distant mets (%)	96.6 vs 96.2	91 vs 97
– PTC (%)	57.0 vs 56.7	50.6 vs 51.9
Outcomes:		
– Median duration of treatment	10.6 vs 6.5 months	13.8 vs 3.9 months
– Median PFS	10.8 vs 5.8 months HR: 0.59; 95% CI: 0.45–0.76; p < 0.0001	18.3 months (95% CI: 15.1–NE) vs 3.6 months (95% CI: 2.2–3.7) HR: 0.21; 95% CI: 0.14–0.31; p < 0.0001
– Median OS	Not reached HR: 0.80; 95% CI: 0.54–1.19; p = 0.14	Not reached
– Partial response (%)	12.2 vs 0.5; p < 0.0001	63.2 vs 1.5 (also CR 1.5 vs 0)
– Stable disease (6 months) (%)	41.8 vs 33.2	15.3 vs 29.8
– Disease control rate (PR + SD 6 months) (%)	54.0 vs 33.7; p < 0.0001	80.1 vs 31.3

For all patient characteristics and outcomes, treatment group listed first and placebo group (if applicable) listed second.
Disease control rate = clinical benefit rate.
CR: Complete response; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; PTC: Papillary thyroid cancer; RAI: Radioactive iodine; SD: Stable disease.

• Medullary thyroid cancer

There are two FDA-approved therapies for MTC at present, vandetanib and cabozantinib. Vandetanib was approved on data from the Phase III ZETA trial in 2011. This was a multicenter, double-blind randomized placebo-controlled trial enrolling patients with either hereditary or sporadic medullary thyroid cancer that was locally advanced or metastatic with calcitonin ≥500 pg/ml and good functional status **(Table 2)**. Out of the 331 patients randomized (231 vandetanib 300 mg/day and 100 placebo), mean age was approximately 50, slightly less than half were female, and the large majority had sporadic disease with distant metastases [21]. Median PFS in the treatment group was not met at the time of data analysis but was projected to be 30.5 vs 19.3 months in the placebo group (HR: 0.46; 95% CI: 0.31–0.69; p < 0.001). Median OS was not reached. The objective response rate (PR + CR) was significantly higher in the treatment group (45 vs 13%; p < 0.001), but rates of SD were not significantly different between groups (42 vs 58%). Calcitonin and CEA response was significantly better in the vandetanib group. Also of note, while all patients received benefit, objective response rates appeared higher in patients with sporadic *RET* M918T mutations (54.5 vs 30.9%) [21].

Preceding the Phase III trial, there were two Phase II trials of vandetanib in patients with hereditary MTC (MEN2a, MEN2b or FMTC) **(Supplementary Table 2)**. The first was a single-arm open-label multicenter trial enrolling 30 patients with hereditary MTC that had a documented germline *RET* mutation with locally advanced or metastatic disease. Patients received vandetanib 300 mg daily. This sample was predominantly female with distant metastases. The median PFS was similar to ZETA at 27.9 months (95% CI: 19.4–NE). The PR rate was lower at 20% (95% CI: 8–39) with similar stable disease rates (53%). Even if patients did not meet RECIST criteria for response, 83% of patients in the sample had a measurable reduction in tumor size and there was no specific association between the type of *RET* mutation and tumor response [23]. The other Phase II trial was also open label and single arm, enrolling 19 patients with locally advanced or metastatic hereditary MTC to receive vandetanib 100 mg daily. Mean age was 45 years and this sample was predominantly male with distant metastases. Median PFS and OS were not calculated. PR and SD rates were similar to the other Phase II trials (16 and 53%, respectively) with no association between *RET* mutation and response. While calcitonin and CEA response were variable among those with PR, there were consistent increases in these markers in those with PD [24]. A final study examined vandetanib with locally advanced or metastatic medullary thyroid cancer specifically in 16 children and adolescents with MEN2B, finding an objective response rate of 44% (95% CI: 20–70) with the best tolerated dose being 100 mg/m^2 (equivalent ~180 mg/day in an adult) [25].

In brief, vandetanib is indicated in locally advanced and metastatic MTC, extending PFS beyond 2 years and resulting in disease control rates exceeding 50% in most trials, though again no OS benefit has been reported.

Cabozantinib is the second FDA-approved therapy for locally advanced or metastatic MTC. Approval was based on a multicenter double-blind randomized placebo-controlled Phase III trial of 330 patients (219 cabozantinib [140 mg/day] and 111 placebo) with locally advanced or metastatic hereditary or sporadic MTC **(Table 2)** [22]. Median age was 55 and the population was predominantly male with primarily sporadic disease. PFS was lower in both treatment and placebo groups than that seen in the vandetanib trials at 11.2 months in the cabozantinib group as compared with 4 months in the placebo group (HR: 0.28; 95% CI: 0.19–0.40; p < 0.001). This may have been because entry into the trial was predicated on observed progression in the 14 months prior. Median OS was not reached. PR rate was 28% in the treatment group versus 0% in the placebo group (0 < 0.001), however, 94% of patients in the treatment group had measurable reduction in tumor size [22]. A Phase I multicenter, single-arm, open-label dose escalation trial of cabozantinib in locally advanced or metastatic MTC enrolled 37 patients, with median age 55, who were predominantly male and about 60% had sporadic disease **(Supplementary Table 2)**. It found a 29% partial response rate and 43% stable disease rate. There was no clear association between *RET* mutation and response in this trial, but reduction in calcitonin and CEA did parallel radiographic response. This study also documented expected changes in placental growth factor, VEGF-A, VEGFR-2 and MET [26].

In short, cabozantinib is indicated in progressive locally advanced and metastatic, hereditary or sporadic, MTC because it nearly triples PFS in comparison to placebo.

Table 2. FDA approved therapy: locally advanced and metastatic medullary thyroid cancer.

Drug	Vandetanib (300 mg/day) [21]	Cabozantinib (140 mg/day) [22]
Trial	Phase III (ZETA)	Phase III
Includes patients w/o MTC?	No	No
Design	Multicenter, randomized, placebo controlled, double blind	Multicenter, randomized, placebo controlled, double blind
Inclusion criteria	Hereditary or sporadic (did not have to have *RET*) Locally advanced or metastatic Calcitonin ≥ 500 pg/ml ECOG 0–2	Locally advanced or metastatic Progression in previous 14 months
Patients:		
Number	331 (231 vandetanib, 100 placebo)	330 (219 cabozantinib, 111 placebo)
– Age (years)	50.7 vs 53.4 (mean)	55.0 (20–86) vs 55.0 (21–79) (median)
– Female (%)	42.0 vs 44.0	31.1 vs 36.9
– Sporadic (%)	87.9 vs 95.0	87.2 vs 84.7
– Distant mets (%)	93.9 vs 97.0	
Outcomes:		
– Median duration of treatment	90.1 vs 39.9 weeks	204 vs 105 days
– Median PFS	30.5 vs 19.3 months	11.2 vs 4.0 months
	HR: 0.46; 95% CI: 0.31–0.69; p < 0.001	HR: 0.28; 95% CI: 0.19–0.40; p < 0.001
– Median OS	Not reached	Not reached
	HR: 0.89; 95% CI: 0.48–1.65; p = NS	HR: 0.98; 95% CI: 0.63–1.52; p = NS
– Objective response rate (CR + PR) (%)	45.0 vs 13.0; OR: 5.48; 95% CI: 2.99–10.79; p < 0.001	28.0 vs 0.0; p < 0.001 (PR)
– Stable disease at 6 months (%)	42.0 vs 58.0	
– Disease control rate (PR + SD 6 months) (%)	87.0 vs 71.0; OR: 2.64; 95% CI: 1.48–4.69; p = 0.001	
– Calcitonin response	69.0 vs 3.0%; OR: 72.9; 95% CI: 26.2–303.2; p < 0.001	45.2% decrease vs 57.3% increase; p < 0.001
– CEA response	52.0 vs 2.0%; OR: 52.0; 95% CI: 16.0–320.3; p < 0.001	23.7% decrease vs 88.7% increase; p < 0.001

For all patient characteristics and outcomes, treatment group listed first and placebo group (if applicable) listed second.
Disease control rate = clinical benefit rate.
CEA: Carcinoembryonic antigen; CR: Complete response; MTC: Medullary thyroid cancer; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; SD: Stable disease.

• Differentiated thyroid cancer

There are numerous drugs in various phases of development for differentiated thyroid cancer **(Table 3)**.

Vandetanib at 300 mg per day has been tested in a Phase II multicenter randomized placebo-controlled trial for RAI refractory locally advanced or metastatic DTC [27]. One-hundred and forty-five patients were randomized (72 vandetanib vs 73 placebo). Median age was in the mid 60s with slightly less than half of the population being female. About 40% had PTC and the majority had distant metastases. Median PFS was similar to that seen in the DECISION trial with sorafenib (11.1 months vandetanib [95% CI: 7.7–14.0] vs 5.9 months placebo [95% CI: 4.0–8.9], HR: 0.63 [95% CI: 0.43–0.92; p = 0.017]). PR rates were low and did not significantly differ between groups, and while there was a trend toward higher overall disease control in the vandetanib group, this was also not significantly different. More improvement was seen in the PTC subgroup but this did not reach significance. There was no correlation between radiologic response and thyroglobulin levels or PET scans in this trial [27].

A number of other single arm, open label Phase II trials have been published investigating other multi-kinase inhibitors in RAI refractory locally advanced or metastatic DTC [28–34]. The full details of these trials are summarized in **Table 3**. Among those in which progression in the last 6–12 months was required for study entry (motesanib, pazopanib, selumetinib and dovitinib), median progression-free survival ranged from approximately 6 to 11 months, consistent with findings on treatment in larger trials. PR rates varied significantly but overall disease control rate over 6 months was in the range of 40–60% [20,28–30]. While there was no difference in response according to *BRAF* status in the motesanib trial, there appeared to be a trend

Table 3. Investigational therapies: locally advanced and metastatic radioactive iodine refractory differentiated thyroid cancer.

	Drug							
	Vandetanib (300 mg daily) [27]	**Motesanib (125 mg daily)** [28]	**Pazopanib (800 mg daily)** [29]	**Selumetinib (100 mg b.i.d.)** [30]	**Axitinib (5–10 mg b.i.d.)** [31]	**Axitinib (5–10 mg b.i.d.)** [32]	**Sunitinib (37.5 mg daily)** [33]	**Dovitinib (500 mg daily)** [34]
Differentiated thyroid cancer†								
Trial	Phase II	Phase II 2	Phase II	Phase II	Phase II	Phase II	Phase II	Phase II
Includes non-DTC patients?	No	No	No	No	Yes	Yes	Yes	Yes
Design	Multicenter, randomized, placebo controlled, double blind	Multicenter, nonrandomized, single arm, open label	Single center, nonrandomized, single arm, open label	Multicenter, nonrandomized, single arm, open label	Multicenter, nonrandomized, single arm, open label	Multicenter, nonrandomized, single arm, open label	Nonrandomized, single arm, open label	Nonrandomized, single arm, open label
Progression?/ ECOG	No/0–2	Yes in last 6 months/0–2	Yes, in last 6 months/0–2	Yes, in last 12 months/0–2	No/0–1	No/0–1	No/0–3	Yes, in last 12 months/0–2
Patients:								
– Number	145 (72 vandetanib vs 73 placebo)	93	37	39	45 with DTC	45 with DTC	28 DTC	28 DTC
– Age (years)‡	63 (29–81) vs 64 (23–87) median (range)	62 (36–81) median (range)	63 (23–79) median (range)	64 (37–86) median (range)	59 (26–84) median (range)	57.6 (28–81) mean (range)	61 (34–73) median (range)	60 (31–81) median (range)
– White (%)‡		91.4		87.2	78.3	84.6	82.8	
– Female (%)‡	45.8 vs 46.6	47.3	48.6	33.3	41.7	46.2	51.4	55.0
Outcomes:								
Median duration of Rx	192 days vs 175.5 days	35 weeks (0.4–56)	48 weeks (12 4-week cycles)	13 weeks (0.3–98)	4.8 months (0.07–24.5 months)	12.9 months (0.07–56.2)	8.5 months	3.4 mo
Median PFS	11.1 months (95% CI: 7.7–14.0) vs 5.9 (95% CI: 4.0–8.9) HR: 0.63, 95% CI: 0.43–0.92; p = 0.017	40 weeks (~9 months) (95% CI: 32–50)	11.7 months (1->23)	32 weeks (~7.5 months) (95% CI: 8.4–56)	18.1 months (95% CI: 12.1–NE) (includes non-DTC)	15.2 months (14.5–21.2)		PTC 6.3 months (95% CI: 1.8–10.7) FTC 3.2 months (95% CI: 1.1–9.9)
Partial response (%)	8.3 vs 5.5 (OR: 1.57, 95% CI: 0.42–5.81 p = 0.501)	14.0 (95% CI: 7.7–22.7)	48.6 (95% CI: 35–68)	2.6	31.1 (14/45 DTC patients)	37.8 (17/45 DTC patients)	25.0 (7/28 DTC); 3.6 CR (1/28 DTC)	17.4 (4/23 PTC); 40.0 (2/5 FTC)
Disease control rate (PR + SD 6 months) (%)	56.9 vs 42.5 (OR: 1.79, 95% CI: 0.93–3.46; p = 0.082)	49.5		38.6	73.3 (33/45 DTC patients) (defined at ≥ 16 weeks)	66.7 (30/45 DTC patients) (defined at ≥16 weeks)	78.6 (22/28 DTC)	65.2 (15/23 PTC); 60.0 (3/5 FTC)

For all patient characteristics and outcomes, treatment group listed first and placebo group (if applicable) listed second.
Disease control rate = clinical benefit rate.
†All DTC trials included adults ≥ 18 with locally advanced/metastatic/RAI refractory disease.
‡Patient characteristics are reported for whole trial if information on PTC, FTC, MTC subgroups is not available.
CR: Complete response; FTC: Follicular thyroid cancer; MTC: Medullary thyroid cancer; PFS: Progression-free survival; PR: Partial response; PTC: Papillary thyroid cancer; RAI: Radioactive iodine; SD: Stable disease.

toward improved median PFS in *BRAF*-positive patients in the selumetinib trial, though this did not reach statistical significance, possibly because of inadequate power.

Two multicenter single-arm trials of axitinib at doses titrated up to 10 mg b.i.d., each including 45 patients with PTC or FTC found median PFS in the range of 15–18 months, PR rates approximately 30%, and overall disease control rates of approximately 70%. However, these trials were both done in patients with excellent functional status (ECOG 0–1), and one trial had only 50% of patients with distant metastases (whereas all other trials mentioned have had >90% of patients with distant metastases) [31–32]. A Phase II trial of sunitinib 37.5 mg daily including 28 patients with PTC and FTC did not comment on PFS or OS but found an overall response rate of 28.6% (with one CR) and a 50% SD rate leading to a high overall disease control rate of 78.6%. This study was also interesting in that it demonstrated a significant association between percent SUV change on PET and RECIST radiographic response as well as time to progression, raising the possibility that an early PET scan may help determine likely responders and thus potentially limit exposure to drug toxicity in those less likely to respond [33]. Cabozantinib has also been tested in a Phase I trial of 15 patients with locally advanced or metastatic RAI refractory DTC, with most having received one other systemic agent prior to the trial, finding that 53% had PR and 27% had SD for more than 6 months. Median PFS and OS were not reached. Adverse events in this trial were similar to other trials [35].

Overall, TKI currently under investigation for use in progressive RAI refractory locally advanced or metastatic DTC have shown similar PFS and similar or better disease control rates than FDA-approved therapies, and vandetanib has the best quality evidence from a Phase II randomized controlled trial.

Novel mechanisms: RAI uptake re-induction

In addition to using multi-kinase inhibitors to directly treat advanced DTC, their use has also been proposed to re-induce RAI uptake in previously refractory metastases. There is preclinical evidence that activation of the MAPK pathway, via gene mutations observed in thyroid cancers, inhibits the sodium-iodide symporter and thyroid peroxidase. Hence, it is reasonable to postulate that inhibiting the MAPK pathway could allow for improved expression of the sodium-iodide symporter. Sorafenib was not demonstrated to be effective in this regard; however, selumetinib, which selectively inhibits MEK 1/2 in the MAPK pathway, has shown promise in re-inducing radioiodine sensitivity [18,36]. A single center trial, enrolling 24 patients (of whom 20 could be evaluated), evaluated thyrotropin stimulated I-124 PET CT at baseline and after 4 weeks of selumetinib 75 mg b.i.d. If there was adequate response on the second I-124 PET CT, dosimetry was used to calculate RAI dose for therapy. Median age was 61, 45% were female, 45% had a *BRAF* mutation and 25% had an *NRAS* mutation. Sixty percent had an increase in radioactive iodine uptake after selumetinib, and 40% received radioactive iodine treatment, including all of the patients with *NRAS* mutations. Out of those who were treated with radioactive iodine, 62.5% had a PR and 37.5% had SD [36].

Re-induction of RAI sensitivity using TKI therapy may be a novel way to achieve disease control and limit toxicity, as there were no grade 3 or higher adverse events noted in the selumetinib trial.

Novel mechanisms: selective BRAF inhibition

While most therapies discussed above affect multiple kinases, vemurafenib is a selective *BRAF* inhibitor, which has been used with success in melanoma. A Phase I trial demonstrated a maximum tolerable dose of 960 mg b.i.d.. Treatment of three patients with locally advanced metastatic PTC and a *BRAF* mutation with doses escalated to 720 mg b.i.d. resulted in one partial response and two stabilizations of disease with overall survival of at least 15–31 months [37]. Another case report of a patient with RAI refractory metastatic PTC with a *BRAF* mutation receiving 960 mg b.i.d. reduced to 480 mg b.i.d., demonstrated a PR sustained at 23 months on vemurafenib [38].

Novel mechanisms: chemotherapy sensitization

Romidepsin, a histone deacetylase inhibitor, has targets in the nucleus instead of the tyrosine kinase signaling cascade. It has been studied in a single institution nonrandomized Phase II open label trial enrolling 20 patients with locally advanced or metastatic, progressive, RAI refractory DTC. Median age in this trial was 64 (30–78), 50% of patients were women

and 40% of patients had PTC. Sixty-five percent of patients had SD, but there were no RECIST responses. Median overall survival was 33.2 months (range 1–71). Two of twenty patients had re-induction of radioactive iodine avidity. Authors concluded that this agent may be useful as a chemotherapy sensitizing agent in the future but not likely as a single agent [39].

Salvage therapy after failure of one TKI

Finally, sunitinib, pazopanib, cabozantinib, lenvatinib and vemurafenib have been examined as salvage therapy in patients failing sorafenib in a retrospective review out of MD Anderson [40]. Twenty-five patients who received salvage therapy after sorafenib were compared with 35 patients receiving sorafenib alone. Mean age was 54 and about 47% of the population was female. Groups were well matched with the exception that the salvage group had a higher percentage of FTC and a higher rate of sorafenib discontinuation for progression than the comparison group. Median overall survival in the salvage group was 58.4 months (95% CI: 33.4–NA) vs 28.8 mo (95% CI: 33.4–NA) in the sorafenib alone group (p = 0.013). In the subgroup that received salvage therapy, 13% achieved PR on sorafenib and 41% achieved PR on salvage therapy while 67% had SD on sorafenib and 59% had SD on salvage therapy. Interestingly, patients with PD on sorafenib achieved PR with another agent and some patients who had treatment limiting toxicity on sorafenib were able to tolerate sunitinib, suggesting that failure of one TKI should not preclude trial of another [40].

• Medullary thyroid cancer

A number of the agents discussed for DTC are also under investigation for locally advanced or metastatic MTC **(Table 4)**. Sorafenib has been studied for this indication in two Phase II nonrandomized open label trials with small numbers of patients [15,41]. While the PR rate at 6 months was low (6–13%), the SD rate was quite high (~87% in both trials) leading to high rates of disease control and 1- and 2-year PFS and OS over 80%. Interestingly, in one trial, the PR rate increased from 13.3% at 6 months to 25% at 12 months [15]. A case report also demonstrated complete response to sorafenib in metastatic MTC with PET/CT becoming negative after 8 months and remaining negative at 6 months follow-up [42].

Pazopanib, motesanib and lenvatinib have also been studied in multicenter nonrandomized single-arm open-label trials in locally advanced or metastatic MTC with recent progression [43–44,46]. The 35 patients in the pazopanib trial were found to have a median PFS of 9.4 months and median OS of 19.9 months with a PR rate of 14.3% and SD rate of 57.1%. There was a median reduction in CEA and calcitonin from baseline, and longer PFS was associated with a CEA decrease ≥25% [43]. A trial of 91 patients using motesanib found a median PFS of approximately 11 months and a very low PR rate of 2% with SD rate at 48%. The majority of patients had a decrease in calcitonin and CEA but this was sustained over time in only 1–2% of patients [44]. In the lenvatinib trial, median PFS was 9 months with median OS of 16.6 months, PR was 35.6% and SD rates were 28.8% [46]. PFS was generally lower in these trials than in the vandetanib study, possibly because they required progression within the last 6–12 months for study entry.

Phase II trials on axitinib and sunitinib included small subgroups of patients with advanced or metastatic MTC and demonstrated variable PR and SD rates (PR: 0–18.2% for axitinib, 42.9% for sunitinib; SD: 27.3–83% for axitinib; 28.6% for sunitinib). Median age in these trials was in the late 50s to early 60s, approximately half of patients were female and greater than 75% were white [31–33]. A preclinical study has suggested that sunitinib and cisplatin may have synergy in inhibiting cell growth and inducing apoptosis in MTC cell lines expressing *RET* M918T [47]. A Phase II study of dovitinib, enrolling 12 patients with MTC, median age 60 found median PFS to be 4.5 months (95% CI: 2.3–6.6). PR rate was 16.7% and SD rate was 58.3% yielding a 75% disease control rate in this study [34]. A small trial of 15 patients with advanced MTC receiving imatinib found no PR and a very low SD rate of 26.7% without significant decline in CEA or calcitonin, confirming that although this drug inhibits *RET*, the necessary concentrations for this inhibition cannot be safely reached in humans [45].

In summary, Phase II trials for drugs under investigation for progressive, locally advanced, metastatic MTC have had variable results and have generally included small numbers of patients, often part of larger trials including patients with DTC.

Novel mechanisms: radio-immunotherapy

Another novel approach in rapidly progressive metastatic MTC is radio-immunotherapy.

Table 4. Investigational therapies: locally advanced and metastatic medullary thyroid cancer.

Medullary thyroid cancer[†]										
	Drug									
	Sorafenib (400 mg b.i.d.) [41]	**Sorafenib (400 mg b.i.d.)** [15]	**Pazopanib (800 mg daily)** [43]	**Motesanib (125 mg daily)** [44]	**Axitinib (5–10 mg b.i.d.)** [31]	**Axitinib (5–10 mg b.i.d.)** [32]	**Sunitinib (37.5 mg daily)** [33]	**Imatinib (600–800 mg daily)** [45]	**Lenvatinib (24 mg daily)** [46]	**Dovitinib (500 mg daily)** [34]
Trial	Phase II	Phase II	Phase II	Phase II	Phase II	Phase II	Phase II	Phase II	Phase II	Phase II
Includes patients w/o MTC?	No	Yes	No	No	Yes	Yes	Yes	No	No	Yes
Design	2 centers, nonrandomized, 2 arms (A:hereditary, B:sporadic), open label	Single center, non-randomized, single arm, open-label	Multicenter, non-randomized, single arm, open label	Multicenter, non-randomized, single arm open label	Multicenter, non-randomized, single arm, open label	Multicenter, non-randomized, single arm, open label	non-randomized, single arm, open label	non-randomized, single arm, open label	Multicenter, non-randomized, single arm open label	Non-randomized, single arm, open label
Progression?/ ECOG	No/0–2	Yes, in last 12–18 months/0–1	Yes, in last 6 months/0–2	Yes, in last 6 months/0–2	No/0–1	No/0–1	No/0–3	No/0–2	Yes, in last 12 months/0–2	No/0–2
Patients:										
– Number	A: 5, B: 16	15 with MTC	35	91	11 MTC	6 MTC	7 MTC	15	59	12 with MTC
– Age (years)[‡]	A: 49 (21–70), B: 60 (39–72) median (range)	55.0 (21–78) median (range)	60.0 (26–83) median (range)	49.0 (18–77) median (range)	59 (26–84) median (range)	57.6 (28–81) mean (range)	61 (34–73) median (range)	50 (32–69) median (range)	51.6	60 (31–81) median (range)
– Female (%)[‡]	A 0.0, B 31.2	44.1	20.0	35.1	41.7	46.1	51.4	33.3	37.3	55.0
– White (%)[‡]	A 100.0, B: 81.2		80.0	94.5	78.3	84.6	82.8		93.2	
– Sporadic (%)[‡]				83.5				73.3		
Outcomes:										
– Median duration of Rx	15 months (1–28.2)	16.5 months	~8 months	38 weeks (0.9–50 weeks)	4.8 months (0.07–24.5)	12.9 months (0.07–56.2)	8.5 months	4 months	264 days (13–547)	3.4 months (0.5–22.9)
– Median PFS	B: 17.9 months (95% CI: 8.0–NR)	Not reached	9.4 months	48 weeks (95% CI: 43–56)	18.1 months (95% CI: 12.1–NE) (includes non-MTC)	Not calculated for MTC alone		Not assessed	9.0 months (95% CI: 7.0–NE)	4.5 months (95% CI: 2.3–6.6)
– Objective response rate (CR + PR) (%)	B: 6.3 (PR)	13.3 (2/15 MTC) (PR)	14.3 (90% CI 5.8–27.7) (PR)	2.2 (95% CI: 0.3–7.7) (PR)	18.2 (PR) (2/11 MTC)	0.0	42.9 (PR) (3/7 MTC)	0.0	35.6 (95% CI: 24–49) (PR)	16.7 (PR) (2/12 MTC)
– Disease control rate (CR + PR + SD 6 months) (%)	B: 93.8	100.0		50.5	45.5 (5/11 MTC)	83.3 (5/6 MTC)	71.5 (5/7 MTC)	26.7	64.4	75.0 (9/12 MTC)

For all patient characteristics and outcomes, treatment group listed first and placebo group (if applicable) listed second.

Disease control rate = clinical benefit rate.

[†]All MTC trials included adults ≥ 18 with locally advanced/metastatic disease.

[‡]Patient characteristics are reported for whole trial if information on PTC, FTC, MTC subgroups not available.

CR: Complete response; FTC: Follicular thyroid cancer; MTC: Medullary thyroid cancer; PFS: Progression-free survival; PR: Partial response; PTC: Papillary thyroid cancer; SD: Stable disease.

A Phase II trial using a bispecific monoclonal antibody (humanized anti-CEA × murine anti-DTPA) and I-131 di-DTPA indium bivalent hapten to target radiotherapy to CEA expressing cancer cells demonstrated promising results. Among the 42 patients in this open label trial, median age was 54 (23–80) and 40% were women, all with distant metastatic disease and disease progression. CR was seen in 2.4% and durable SD in 73.8% with median PFS of 13.6 months (1.9–78.1) and median OS of 43.9 months (3.1–78.2). PFS and OS were both significantly better among patients with ≥100% increase in calcitonin or CEA doubling time after therapy. The main toxicity with this therapy is hematologic with 54.7% of patients experiencing grade 3–4 toxicity [48].

• Anaplastic thyroid cancer

As discussed above, anaplastic thyroid cancer is a rare but very aggressive disease for which there is little effective therapy. As such, some investigators have begun to look at targeted therapies in this patient population, unfortunately with little success.

A Phase II single arm trial of pazopanib 800 mg in patients age 18 or older with progression within 6 months of enrollment of advanced ATC with good functional status (ECOG 0–2) enrolled 15 patients with median age 66 (45–77), of whom 67% were female and 80% were Caucasian. Most had received radiation and some prior systemic therapy. While there were no CR or PR, 11/15 patients had SD after one cycle of therapy; however, median time to progression was 62 days with median OS of 111 days, which is not significantly different than would be expected in the natural history of disease [49].

In a Phase II trial of sorafenib in ATC, enrolling 20 patients with median age of 59 (28–79), 65% male and 100% white, all with prior chemotherapy and most with radiation or surgery, 10% (95% CI: 3–30%) experienced a PR and 25% had SD. Those with a PR had a previous history of progressive PTC or focal areas with papillary features. Median PFS was 1.9 months (95% CI: 1.3–3.6 months) and median OS was 3.9 months (95% CI: 2.2–7.1 months) [6].

Finally, a Phase II study of imatinib 400 mg b.i.d. in anaplastic thyroid cancer enrolling 11 patients, median age 65 (53–79), 45% female, 64% with distant metastases and all having received prior surgery and/or chemoradiation, found PR in 25% and SD in 50% of evaluable patients. Six-month PFS was 27% (95% CI: 7–54%) and 6-month OS was 46% (95% CI: 17–71%). Those that achieved PR had locally advanced, rather than metastatic disease [50]. A case report documented disease stability for approximately 1 year in a 58-year-old woman receiving sunitinib after radiation and multiple previous courses of chemotherapy [51].

While some of these therapies may be promising as part of multimodal regimens for patients with ATC, it is too soon to draw conclusions given small numbers of patients from current trials.

• Trials with ongoing recruitment

There are a number of ongoing trials utilizing both new drugs and established drugs for new purposes. Trametinib, a specific inhibitor of MEK 1/2 is being investigated to determine its effect in re-inducing radioactive iodine sensitivity in RAI refractory DTC. Vemurafenib is also being examined for this indication in *BRAF* mutant RAI refractory thyroid cancers. Ponatinib, an inhibitor of Bcr-Abl as well as VEGFRs and FGFRs is under investigation for use in advanced MTC. Everolimus, a potent mTOR inhibitor in the PI3K pathway, is under investigation as a single agent in all types of advanced thyroid cancer and as an adjunct in patients with advanced DTC who progressed on sorafenib. A unique use of pioglitazone is being studied in RAI refractory or metastatic FTC or follicular variant of papillary thyroid cancer (FV-PTC) with the *Pax8-PPAR-γ* translocation. Finally, crolibulin, a microtubule inhibitor, is being studied in conjunction with cisplatin in ATC.

Adverse events

One of the primary concerns with use of targeted therapy for thyroid cancer is the toxicity of these agents. Specific toxicity rates for the FDA-approved drugs discussed above, drawn from Phase III trials, are summarized in **Table 5**. For the purposes of rating event severity, grade 1 is considered mild, grade 2 moderate, grade 3 severe, grade 4 life threatening or disabling and grade 5 fatal. Notably, almost all patients report some toxicity on therapy and rates of severe (grade 3 or higher) adverse effects range from 1/3 to 2/3 of patients on therapy. There have been cardiovascular, dermatologic, ophthalmologic, gastrointestinal, hematologic and

Table 5. Adverse events with US FDA approved targeted therapies

	Drug			
	Sorafenib (data from DECISION) [13]	**Lenvatinib (data from SELECT)** [14]	**Vandetanib (data from ZETA)** [21]	**Cabozantinib (data from Phase III)** [22]
Rate of all AEs (%)	98.6 vs 87.6	97.3 vs 59.5		
Rate of severe AEs (grade 3/4/5) (%)	37.2 vs 26.3	75.9 vs 9.9		69.1 vs 33.0
Dose interruption (%)	66.2 vs 25.8	82.4 vs 18.3		65.4 vs 17.4
Dose reduction (%)	64.3 vs 9.1	67.8 vs 4.6	35.0 vs 3.0	79.0 vs 9.2
Medication withdrawal (%)	18.8 vs 3.8	14.2 vs 2.3	12.0 vs 3.0	16.4 vs 8.3
Most common reactions (%) (rate >30% in treatment arm)	Hand–foot skin reaction (76.3 vs 9.6) Diarrhea (68.6 vs 15.3) Alopecia (67.1 vs 7.7) Rash (50.2 vs 11.5) Fatigue (49.8 vs 25.4) Weight loss (46.9 vs 13.9) HTN (40.6 vs 12.4) Anorexia (31.9 vs 4.8)	HTN (67.8 vs 9.2) Diarrhea (59.4 vs 8.4) Fatigue (59.0 vs 27.5) Decreased appetite (50.2 vs 11.5) Decreased weight (46.4 vs 9.2) Nausea (41.0 vs 13.7) Stomatitis (35.6 vs 3.8) Hand–foot skin reaction (31.8 vs 0.8) Proteinuria (31.0 vs 1.5)	Diarrhea (56.2 vs 26.2) Rash (45.0 vs 11.1) Nausea (33.3 vs 16.2) HTN (31.6 vs 5.1)	Diarrhea (63.1 vs 33.0) Hand–foot skin reaction (50.0 vs 1.8) Decreased weight (47.7 vs 10.1) Decreased appetite (45.8 vs 15.6) Nausea (43.0 vs 21.1) Fatigue (40.7 vs 28.4) Dysgeusia (34.1 vs 5.5) Hair color changes (33.6 vs 0.9) HTN (32.7 vs 4.6)
Life threatening/fatal reactions reported		PE/hemorrhagic stroke	Prolonged QTc (14.3 vs 1.0)†	GI perforation, hemorrhage, fistula formation

For all categories, treatment group listed first and placebo group listed second.
†No torsades.
AE: Adverse event.

endocrine adverse effects reported for this class of medications. Fatigue is also extremely common. Given that their use is intended to be long-term in patients with a disease that often does not progress quickly, careful consideration must be given to risks and benefits. Many of these agents are metabolized in the liver via the CYP3A4, so awareness of drug–drug interactions is paramount.

Hypertension is the most common cardiovascular side effect and may actually be a marker of efficacy, as survival benefit correlates with development of hypertension. This can typically be managed with anti-hypertensive agents [52]. One of the most concerning serious adverse events is QTc prolongation. This has been reported with vandetanib, sunitinib and pazopanib. In a meta-analysis of nine trials with 2188 patients on vandetanib, the incidence of all-grade QTc prolongation was 18% (10.7–28.6%) and high-grade QTc prolongation was 12.0% (4.5–28.0%) among thyroid cancer patients. This was significantly higher than rates among nonthyroid cancer patients and controls [53]. Recommendations for monitoring include echocardiogram, ECG, potassium, calcium, magnesium and TSH before therapy and ECG, electrolytes and TSH at 1, 3, 6 and 12 weeks of therapy and every 3 months for 1 year. Therapy should not be started in individuals with QTc >450 ms and should be interrupted once started for QTc ≥500 ms [54]. Vandetanib can currently only be prescribed through a Risk Evaluation Management Strategy (REMS) in the USA. Congestive heart failure has also been reported with sunitinib, sorafenib and pazopanib [52].

Dermatologic complications are also common with TKIs targeting the VEGFR and EGFR. The mechanism for this relates to the importance of the EGFR in keratinocyte survival, proliferation, differentiation and attachment. Types of skin reactions commonly seen are: rash, erythema, pruritus, acne, paronychia, telangiectasia, stomatitis, changes in hair growth or pigment, discoloration, xerosis, photosensitivity and a hand–foot skin reaction. The frequency of different reactions varies by drug. The hand–foot skin reaction, most commonly seen with sorafenib and cabozantinib, involves impairment of vascular repair mechanisms through inhibition of the VEGFR and PDGFR.

Hand–foot skin reaction can be prevented using urea cream or ammonium lactate or other heavy moisturizer, and mild-to-moderate toxicity can be treated with urea and clobetasol with the potential addition of topical lidocaine. Avoiding sun exposure and wearing sunscreen can prevent photosensitivity, and mild-to-moderate reactions can be treated with topical steroids and oral antihistamines. There is agreement that treatment should be interrupted for any grade 3 or higher toxicity and restarted at a lower dose with improvement of the reaction to grade 1 or better [55].

A systematic review and meta-analysis of trials using vandetanib in different cancers found that patients on vandetanib were more than twice as likely to develop a rash than controls [56]. Also, corneal abnormalities are an uncommon but significant effect of vandetanib, related to its EGFR inhibitory properties. These occurred in 5.6% of patients on vandetanib (vs 1% of placebo) and included corneal edema, corneal opacity, corneal dystrophy, corneal pigmentation, keratopathy, arcus lipoides, corneal deposits, and acquired corneal dystrophy [57].

Gastrointestinal complications include diarrhea, nausea, mucositis, stomatitis, dysgeusia, anorexia, abdominal pain and weight loss. Many can be managed with symptomatic therapy, dose interruption and dose reduction. Gastrointestinal perforation, bleeding and fistula development are rare, but serious and sometimes fatal reported side effects, related to VEGF inhibition. Hepatic toxicity (both transaminitis and hyperbilirubinemia) and pancreatitis are also possible [52]. Hematologic toxicity can include mucosal bleeding and more severe hemorrhage. Neutropenia, lymphopenia, anemia and thrombocytopenia are also reported, and myelosuppression from previous RAI and external beam radiation is a concern in this patient population. A small series of patients on sunitinib demonstrated similar rates of hematologic toxicity as other cancers and generally responded well to dose reduction [52,58].

Particularly relevant to the use of TKIs in thyroid cancer is the development of hypothyroidism on therapy. While patients with metastatic differentiated thyroid cancer have typically had a complete thyroidectomy and are on suppressive levothyroxine therapy, a rising TSH has been documented in numerous trials. Documented prevalence of hypothyroidism on sunitinib, vandetanib and axitinib may be more than 80% [59]. This complication can be managed reasonably with increasing the dose of levothyroxine, but it is important to be aware of this potential side effect when starting a TKI. TSH should be followed monthly as TSH suppressive therapy is important for suppressing tumor growth in DTC as well.

Conclusion

TKIs offer a treatment for a very small subset of thyroid cancer patients. They offer promise in a disease that has not responded well to traditional chemotherapy. Those most likely to benefit have advanced, rapidly progressive, metastatic, RAI refractory DTC or MTC that has been refractory to more established first line therapies. They may also have a role in treating widely disseminated disease while the patient is undergoing local control procedures such as ethanol ablation or debulking surgery, radiation for bone metastases or chemotherapy. Furthermore, during TKI therapy, TSH suppression for DTC should be maintained as long as tolerated by the patient. Targeted therapies consistently prolong PFS and produce reasonable PR and SD rates. There is also evidence that lack of response to one targeted therapy does not preclude response to a different targeted therapy. However, CR is exceedingly rare. Moreover, median OS is often not significantly different or not reached at the time of publication. Since most trials have a stipulation to allow the placebo group to receive drug after a certain time point, it is unclear that OS benefit will be demonstrated. Finally, because most of these medications affect multiple components of cell signaling pathways, there are numerous off-target effects that limit their tolerability. Hence, they should only be considered in patients with good functional status and rapidly progressive disease (progression within 6 months). Patients on therapy should be monitored closely for side effects with therapy, and interruption and dose reduction or permanent discontinuation is indicated for serious adverse effects. With continued investigation in this area, therapies may be refined for more selective benefit with less toxicity.

Future perspective

As more is discovered regarding the underlying molecular mechanisms of thyroid cancer, we will likely see more targeted therapies for refractory thyroid cancer, particularly as this disease does not respond well to cytotoxic

chemotherapy. Drugs that have more specific targets, such as the MEK inhibitor trametinib and the *BRAF* inhibitor vemurafenib, may be further developed so as to minimize off-target effects. Drugs that re-induce tumor radioactive iodine sensitivity may also leverage TKIs for benefit while minimizing side effects. Since patients refractory to one targeted therapy may respond to another, determining an ideal algorithm for use of each kinase inhibitor based on tumor molecular characteristics may be an area of future research inquiry. Finally, combination therapy may be investigated to block multiple pathways involved in tumorigenesis or sensitize patients to chemotherapy.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/ije-2015-0002

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