Differentiated Thyroid Cancer: Focus on Emerging Treatments for Radioactive Iodine-Refractory Patients

JOSHUA J. GRUBER, A. DIMITRIOS COLEVAS

Stanford Cancer Center, Stanford University Medical Center, Stanford, California, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Radioactive iodine refractory differentiated thyroid cancer • Papillary thyroid cancer • Follicular thyroid cancer • Tyrosine kinase inhibitors • BRAF inhibitors • MEK inhibitors

ABSTRACT

Background. The treatment of differentiated thyroid cancer refractory to radioactive iodine (RAI) had been hampered by few effective therapies. Recently, tyrosine kinase inhibitors (TKIs) have shown activity in this disease. Clinical guidance on the use of these agents in RAI-refractory thyroid cancer is warranted.

Materials and Methods. Molecular mutations found in RAI-refractory thyroid cancer are summarized. Recent phase II and III clinical trial data for TKIs axitinib, lenvatinib, motesanib, pazopanib, sorafenib, sunitinib, and vandetanib are reviewed including efficacy and side effect profiles. Molecular targets and potencies of these agents are compared. Inhibitors of BRAF, mammalian target of rapamycin, and MEK are considered.

Results. Routine testing for molecular alterations prior to therapy is not yet recommended. TKIs produce progression-free survival of approximately 1 year (range: 7.7–19.6 months) and partial response rates of up to 50% by Response Evaluation Criteria in Solid Tumors. Pazopanib and lenvatinib are the most active agents. The majority of patients experienced tumor shrinkage with TKIs. Common adverse toxicities affect dermatologic, gastrointestinal, and cardiovascular systems.

Conclusion. Multiple TKIs have activity in RAI-refractory differentiated thyroid cancer. Selection of a targeted agent should depend on disease trajectory, side effect profile, and goals of therapy. *The Oncologist* 2015;20:113–126

Implications for Practice: Tyrosine kinase inhibitors (TKIs) are now considered first-line therapies for differentiated thyroid cancer (DTC) refractory to radioactive iodine (RAI). In patients with BRAF V600E mutations, selective BRAF inhibitors should be considered, especially if patients are at high risk for serious antiangiogenic side effects. Careful documentation of disease progression and the presence of symptoms or impending organ impairment should prompt treatment; not every patient with RAI-refractory DTC needs therapy. TKI therapy is a chronic, life-long treatment that requires careful attention to quality of life and side effects. TKI side-effect profiles should play a role in selecting appropriate therapy. A second-line TKI often has benefit after failure of first-line TKI.

INTRODUCTION

The incidence of thyroid cancer in the U.S. is 12.9 per 100,000 per year, with a lifetime risk of 1.1%, making it the ninth most common malignancy in the U.S. [1]. The incidence rate has been climbing steadily since the 1990s at a rate of 6.5% yearly, although 5-year relative survival has held steady at ~95%. It is thought that overdiagnosis of previously clinically occult malignancy only partially accounts for the rising incidence [2]. The increasing incidence makes thyroid cancer the most rapidly increasing cancer in the U.S. It affects women more than men at a 3:1 ratio, most commonly in the fifth decade of life. It is estimated that approximately 500,000 persons in the U.S. are living with thyroid cancer [1].

Differentiated thyroid cancer (DTC) subtypes (papillary, follicular, Hurthle cell) make up ~93% of all thyroid cancers,

with medullary and anaplastic subtypes making up 4% and 2%, respectively [2]. Management of DTC typically consists of surgery followed by radioactive iodine (RAI) ablation of the thyroid remnant, followed by TSH suppression [3]. Only 3% of patients have metastasis at the time of presentation. Patients with distant metastatic disease at presentation have a 50% rate of 5-year survival mainly because of the sensitivity of metastatic disease to RAI therapy [1, 4]. Age at diagnosis has a strong effect on survival; patients aged <51 years have a >90% rate of 10-year survival, even with distant disease detected at time of diagnosis [5]. It is estimated that 20% of patients with locoregional disease at presentation will develop distant metastasis at some point in their lifetimes [6]. Distant metastasis most commonly occurs in lungs, followed by bones,

Correspondence: A. Dimitrios Colevas, M.D., Stanford Cancer Center, Stanford University Medical Center, 875 Blake Wilbur Drive, Stanford, California 94305-5826, USA. Telephone: 650-724-9707; E-Mail: colevas@stanford.edu Received August 15, 2014; accepted for publication December 1, 2014; first published online in *The Oncologist Express* on January 23, 2015. ©AlphaMed Press 1083-7159/2015/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2014-0313>

and less commonly in other sites. In the metastatic setting, serial treatments with RAI can render ~40% of patients free of disease over the course of 5 years, with a recurrence rate of only 7% [7]. However, patients whose tumors fail to respond adequately to RAI have a mere 19% rate of 5-year survival.

A dose-response relationship exists between the amount of radioactive iodine administered and the risk of second primary malignancies, including solid tumors and leukemias. Based on these and other risks (pulmonary fibrosis, xerostomia, lacrimal complications), it has been suggested that repeated RAI courses can be administered safely to a cumulative dose of 600 mCi, after which further RAI should be administered only on an individual basis with careful consideration of risks and benefits [7–10]. The repeated use of iodine 131 (^{131}I) should be restricted to patients who continue to respond to it [11].

There is no consensus definition of what constitutes RAI-refractory thyroid cancer. Clinical criteria endorsed by the American Thyroid Association (ATA) thyroid cancer guidelines point to indicators of poor response to RAI including lack of RAI avidity on diagnostic RAI scan and suboptimal prior response duration to RAI [12]. ^{131}I responses are also more likely to be poor in older patients (aged >40 years) and in patients with large tumor burden, poorly differentiated tumors, or lesions that are fluorodeoxyglucose (FDG) avid on position emission tomography (PET) [6, 13].

MATERIALS AND METHODS

Databases queried include PubMed and Embase, and conference proceedings of European Society for Medical Oncology, American Society for Clinical Oncology, American Association for Cancer Research, and ATA. Search terms were *differentiated thyroid cancer, follicular thyroid cancer, papillary thyroid cancer, axitinib, pazopanib, cediranib, lenvatinib, sorafenib, sunitinib, vandetanib, selumetinib, gefitinib, motesanib, vemurafenib, dabrafenib, everolimus, temsirolimus, vatalanib, bevacizumab, regorafenib, nintedanib, and cabozantinib*. Databases were queried with dates from 2005 to March 2014. A second search was performed using dates from 2009 to June 2014. The ClinicalTrials.gov website was also searched with the above terms. Only publications in English involving human subjects or human tissues were considered. Both abstracts and articles were considered.

MUTATIONAL SPECTRUM OF DTC

In theory, an understanding of the mutations prevalent in differentiated thyroid cancer could lead to the selection of targeted agents for this disease. The mutations associated with DTC have been extensively reviewed recently [14]. The most common known genetic abnormality in DTC is the BRAF V600E mutation, which is present in approximately 45% of papillary thyroid cancer (PTC) but is less common in follicular thyroid cancer (FTC) [15–18]. In contrast, RAS mutations are more common in FTC, with mutations in HRAS, NRAS, or KRAS detectable in approximately 40% of FTC [19–27]. Translocations involving the RET gene, so-called RET-PTC translocation, are present in 10%–87% of PTCs (median: ~30%) [28–30]. These translocations juxtapose the RET gene with a number of different translocation partners of which 10 have been characterized thus far, the most common being RET-PTC1

and RET-PTC3, in which RET is fused to the CCDC6 and NCPA4 genes, respectively. Other mutations detected less frequently include mutations in PIK3CA/B [19, 31, 32], IDH1 [33, 34], EGFR [35], and PAX8-PPAR γ translocation [36]. NDUFB/GRIM19 mutations are found in 15% of Hurthle cell thyroid cancers [37].

Numerous studies have highlighted that mutations affecting the MAPK pathway are often mutually exclusive in DTC. Soares et al. showed BRAF mutations in 46% of PTC and 0% of FTC [38]. RAS mutations were found in 33% of FTC and 7% of PTC. None of the PTCs with RAS mutations had a coexisting BRAF mutation. Furthermore, 18% of PTCs had RET-PTC mutations, all of which were negative for BRAF mutations. Similarly, Kimura et al. analyzed mutations in PTC, showing BRAF in 33%, RAS in 16%, and RET-PTC in 16%, all of which were mutually exclusive with each other [39]. This could indicate either similar function of all three classes of mutation or synthetic lethality of the mutations. It is unknown why RAS mutations tend to be more prevalent in FTC, whereas PTC is more likely to harbor BRAF and RET-PTC mutations.

There has been a more recent appreciation of the prevalence of PIK3CA/B mutations in DTC. The PIK3CA/B genes can undergo amplification events or activating mutations, both of which likely contribute to oncogenesis. PIK3C amplification is more prevalent than mutation. In FTC samples, 6% had PIK3CA mutations, whereas 45% had PIK3CA amplification and 45% had PIK3CB amplification [19]. Similarly, Abubaker et al. found PIK3CA copy number gain in 53% of PTC, with a PIK3CA mutation rate of only 1.9% [31]. PIK3CA mutations tend to be mutually exclusive with amplification events and mutually exclusive with RAS and PTEN mutations but not with BRAF mutations [20, 21].

Transcriptional activation of VEGFR has been shown to be a downstream effect of activation of the nuclear factor- κ B and RAS/RAF/ERK signaling cascades [40]. This has led to the targeting of VEGFR, specifically, to interfere with oncogenic signaling in DTC.

MECHANISM OF ACTION OF AGENTS STUDIED IN DTC

All TKIs available to date inhibit multiple kinases. The TKIs shown to have activity in RAI-refractory DTC (RAI-R-DTC) share a number of common targets but also have important differences in their target spectrums (Table 1). The shared targets include multiple VEGFRs and the related PDGFRs and FGFRs as well as RET. Axitinib has the highest affinity for VEGFRs with subnanomolar half-maximal inhibitory concentration (IC_{50}). All other TKIs with activity against DTC bind VEGFRs with IC_{50} ranging from 1 to 20 nM and high affinity, with the exception of vandetanib. TKIs that target RET include motesanib, pazopanib, sorafenib, sunitinib, and vandetanib; sorafenib has the lowest IC_{50} (2 nM). The most pleomorphic of the agents is sunitinib, which targets 38 kinases with submicromolar IC_{50} . Sorafenib is the only TKI with some inhibitory activity to BRAF (IC_{50} : 290 nM).

Everolimus and temsirolimus have specificity for mammalian target of rapamycin (mTOR); everolimus is much more potent. The selective BRAF inhibitors dabrafenib and vemurafenib inhibit both native and V600E mutant BRAF; however, both agents inhibit the mutant enzyme at lower IC_{50} . Selumetinib is a selective MEK inhibitor.

Table 1. Targets and potencies (IC₅₀) of agents with activity in radioactive iodine-refractory differentiated thyroid cancer

Agent	IC ₅₀ (nM) ^{a,b}												
	BRAF	BRAF V600E	CRAF	CSF-1R	FGFR-1	FGFR-3	FLT-3	Fms	ITK	Lck	MEK1	MET	mTOR
Tyrosine Kinase inhibitor													
Axitinib				73 [41]					1.7 [41]				
Cabozantinib			260 ^c [43]			14.4 [43]			4.6 [43]		390 [43]	1.8 [43]	
Cediranib				110 [45]	26 [45]								
Lenvatinib					46 [46]				100 [46]				
Motesanib									8 [47]				
Pazopanib					80 [48], 140 [49]	138 [48], 130 [49]		6 [48], 146 [49]	43 [50], 430 [49]	379 [48], 411 [49]			
Sorafenib	22 [51, 52], 290 [53]	38 [51, 52]	6 [51, 52], 110 [48]		64 [48], 580 [51, 52]	45 [48], 58 [51, 52]			68 [51, 52], 180 [53], 1,862 [48]				
Sunitinib				79 [54]	437 [48]	314 [48]	4 [48]	5 [48]	40 [48]	95, 410 [54]			
Vandetanib										370 [56]			
mTOR inhibitor													
Everolimus													5.3 [58]
Temsirolimus													1,760 [59]
BRAF inhibitor													
Dabrafenib	3.2 [44]	0.65 [92], 0.8 [44]	5 [44]										
Vemurafenib	39 [61]	8 [61]	16 [61], 48 [62]							217 [61]			
MEK inhibitor													
Selumetinib											14.1 [55]		

^aAll IC₅₀ values determined by biochemical assay unless otherwise specified.^bOnly agents with IC₅₀ ≤500 nM are included.^cAssay uses CRAF and its substrate MAP2K1. The inhibition observed is likely due to inhibition of MAP2K1.Abbreviations: CSF-1R, colony-stimulating factor 1 receptor; FGFR, fibroblast growth factor receptor; FLT-3, Fms-like tyrosine kinase 3; Fms, transmembrane glycoprotein receptor tyrosine kinase; IC₅₀, maximum inhibitory concentration; ITK, interleukin-2 receptor inducible kinase; KIT, stem cell factor receptor; Lck, leukocyte-specific protein tyrosine kinase; MEK1, MAPK/ERK kinase 1; MET, MNNG-HOSt transforming gene; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; RAF, rapidly accelerated fibrosarcoma; RET, glial cell line-derived neurotrophic factor receptor; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

COMPLETED CLINICAL TRIALS

As of June 2014, there have been 18 completed phase II or III clinical trials in RAI-refractory DTC, 8 of which evaluated tyrosine kinase inhibitors. One evaluated a MEK inhibitor and one evaluated gefitinib. Tables 2 and 3 outline trial parameters and outcomes for phase II and phase III trials, respectively. In summary, TKIs produce progression-free survival (PFS) of ~1 year with a range of 7.7–19.6 months. The most likely outcome of treatment with a tyrosine kinase inhibitor is stable disease (SD). Partial response (PR) rates of up to 50% by Response Evaluation Criteria in Solid Tumors (RECIST) were reported with trials of pazopanib and lenvatinib, although this increase in PR did not translate to an increase in PFS. The recent exception to this rule is the phase III randomized controlled trial SELECT, evaluating lenvatinib in RAI-R-DTC, in which PR by RECIST was 63.2% in the lenvatinib arm and there was a significant increase in PFS. Otherwise, it had been thought previously that RECIST might not capture the modest but potentially relevant clinical activity of TKI therapies. Waterfall plots examined throughout the trials show that patients whose best response is stable disease by RECIST often have shrinkage of target lesions by <30%. This has been quantified for each trial in Tables 2 and 3. Because of the indolent nature of differentiated thyroid cancer in most patients, even when RAI refractory, most of the trials lack endpoints that include overall survival (OS).

TKIs produce progression-free survival of ~1 year with a range of 7.7–19.6 months. The most likely outcome of treatment with a tyrosine kinase inhibitor is stable disease.

Complete responses (CRs) are rare. We have also learned that EGFR inhibition with gefitinib generally is not useful and perhaps detrimental because there were no PRs by RECIST, and the percentage of patients who achieved stable disease was lower than that achieved in the placebo control arm of other studies. Nevertheless, 36% of patients achieved tumor shrinkage with gefitinib [65].

The randomized phase II clinical trial with vandetanib, which stratified patients based on histology, seemed to suggest that papillary histology had a more favorable response rate to TKI than follicular or poorly differentiated thyroid cancer [79], but data across TKI trials to date are inadequate to state conclusively that histology is a predictor of response. The phase III trials of sorafenib and lenvatinib did not show that histological subtypes were predictors for PFS, despite the confirmation that histological type was prognostic [81, 82].

Two phase II trials evaluated axitinib with total enrollment of 112 patients (Table 2). Cohen et al. enrolled 60 patients with advanced DTC including medullary and anaplastic histologies that had no further response to RAI or RAI was not indicated [63]. This trial demonstrated median PFS of 18 months; OS could not be estimated. Locati et al. enrolled 52 patients with metastatic or locally advanced unresectable DTC (including medullary) and demonstrated median overall survival of 27 months with PFS of ~16 months and a 42% rate of serious adverse events (AEs) [64].

Sherman et al. evaluated lenvatinib in a phase II trial that enrolled 58 patients with DTC (including medullary) who had progressive disease by RECIST within the previous 12 months (Table 2). DTCs had to be RAI refractory as defined by lack of RAI uptake, progression despite RAI uptake, or >600 mCi of RAI administered with the last dose within the prior 6 months. This trial demonstrated median PFS of 12.6 months with a 50% partial response rate. OS was not reported. In addition, 29% of patients experienced grade 3 toxicity, and 9% had grade 4 toxicity.

The recently reported preliminary results of the SELECT phase III randomized controlled trial comparing lenvatinib and placebo were impressive (Table 3). This study enrolled 392 patients with documented disease progression in the prior 13 months. The trial met its primary endpoint of PFS; median PFS on lenvatinib was 18.3 months, compared with 3.6 months on placebo. Median OS, a secondary endpoint, was not reached, although crossover was allowed after progression, and 83% crossed over. There were four complete responses to lenvatinib (none on placebo). Partial responses by RECIST were seen in 63.2% on lenvatinib and 1.5% on placebo. The most common grade ≥3 treatment-related adverse events were hypertension, proteinuria, weight loss, diarrhea, and decreased appetite. Of particular interest is that, of the 25% of the patients who had received a TKI prior to enrollment, response rates and PFS in this subgroup were indistinguishable from those of the TKI-naïve patients.

The use of sorafenib in RAI-R-DTC has been studied in six clinical trials, including one phase III trial (Tables 2, 3). The phase III DECISION trial entry criteria required RAI-R-DTC, evidence of disease progression in the 14 months prior to entry, and patients who were TKI naïve. The trial demonstrated median PFS of 10.8 months in patients randomized to sorafenib versus 5.8 months for placebo, thus meeting its primary endpoint [81]. The most likely outcome was stable disease for >6 months in 42% of sorafenib-treated patients; 33% of placebo controls had SD >6 months. Twelve percent had PR to sorafenib by RECIST; there was only a rare PR on placebo. Common Terminology Criteria for Adverse Events (CTCAE) grade 3 events were experienced by 53% of sorafenib-treated patients compared with 23% of controls. CTCAE grade 4 events were experienced by 12% in the sorafenib arm and 7% of controls. It should be noted that this trial allowed for crossover after progression. Schlumberger et al. reported the results of quality-of-life analyses of patients treated in the DECISION trial. These analyses showed a small but significant detriment to quality of life in the sorafenib-treated arm compared with placebo [83].

The other trials with sorafenib enrolled between 9 and 56 patients in phase II studies (Table 2). One phase II trial enrolled 41 patients with metastatic PTC (not necessarily refractory to RAI) [71]. By RECIST, 15% had PR and 23% had SD >6 months. Median PFS was 15 months. Of 18 patients with evaluable thyroglobulin levels, 78% had a decline by >25%. Similarly, waterfall plots showed 87% with either SD or PR evinced by tumor shrinkage.

The remaining four trials with sorafenib showed median PFS ranging from 9 to 19.6 months, with stable disease the most likely outcome, ranging from 34% to 65%; partial response was 23%–25% by RECIST (Table 2). One study specifically evaluated patients with RAI-refractory pulmonary metastases from PTC, as

Table 2. Completed phase II trials in radioactive iodine-refractory DTC

Agent and design	Enrolled, <i>n</i> (evaluable for efficacy)	OS, months (95% CI)	PFS, months (95% CI)	RECIST response (%)				Tumor shrinkage (%)
				CR	PR	SD	PD	
Axitinib [63, 64]								
Single arm	60 (45)	NE (20.8–NE) ^a	18.1 (12.1–NE)	0	40	51	9	93
Single arm	52	27.4 (14.7–40.3)	16.2 (14.8–21.6)	NR	35	35	NR	NR
Gefitinib [65]								
Single arm	27	27.4 (10.5–NE ^a) ^b	3.9 (2.8–6.8) ^b	0	0	12 ^c	NR	38
Lenvatinib ^d [66]								
Single arm	58	NR	12.6 (10.4–14.1) ^e	NR	50	NR	NR	NR
Motesanib [67]								
Single arm	93	NE ^a	9.2 (7.4–11.5)	0	14	67	8	NR
Pazopanib ^d [68]								
Single arm	39 (37)	NE ^a	11.7 (range: 1 to >23)	0	49	NR	NR	86
Selumetinib [69, 70]								
Single arm	39 (32)	NR	7.4 (1.9–12.9)	0	3	54	28	62
Sorafenib [71–76]								
Multiarm	56 (50)							93
A: Chemo-naïve PTC	Arm A: 19	A: 23 (18–34)	A: 16 (8–27.5)		A: 15	A: 57	A: 12	
B: PTC with prior chemo or PTC with no tissue block	Arm B/C: 37	B: 37.5 (4–42.5)	B: 10 (4–28)		B: 13	B: 75	B: 12	
C: FTC or HTC		C: 24.2 (11–37.5)	C: 4.5 (2–16)		C: 0	C: 82	C: 9	
Single arm	30 (25)	NR	Overall: 18.2 (NR) DTC patients: 19.4 (NR)	0	23	53	3	88
Single arm	34	NE ^a	NE ^a	0	NR	65 ^f	NR	76
Single arm	32	NR	13.4 (10.9–15.7)	0	25	34	22	82
Single arm	9	NR	9.7 (6.8–12.4)	0	NR	NR	NR	NR
Sunitinib [77, 78]								
Single arm	43	NR	NR	0	13 ^g	68 ^g	10 ^g	NR
Single arm	35 (33)	NE ^a	NR	1 (3)	28	46	17	79
Vandetanib [79]								
RCT vs. PLC	145 VAN: 72 PLC: 73	NR	VAN: 11.1 (7.7–14.0) ^h PLC: 5.9 (4.0–8.9)	NR	VAN: 1 PLC: 0	VAN: 54 PLC: 36	VAN: 44 PLC: 65	54
Vemurafenib [80]								
A: TKI naïve	A: 26	NR	A: 15.6 (11–NR)	NR	A: 35	NR	NR	NR
B: Prior TKI	B: 25		B: 6.8 (5.4–NR)		B: 26			

^aNE due to high number of participants censored for survival or PFS.^bFor the subgroup of well-differentiated thyroid cancer patients.^cSD after 12 months of treatment.^dStudy is ongoing but not recruiting.^eBased on minimum 8-mo follow-up, with only 34% of events observed.^fRadiologic response at 12 months.^gIn 31 evaluable DTC patients who completed two 6-week cycles of treatment.^h*p* < .01

Abbreviations: chemo, chemotherapy; CI, confidence interval; CR, complete response; DTC, differentiated thyroid cancer; FTC, follicular thyroid cancer; HTC, Hürtle cell thyroid cancer; NE, not estimable; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PLC, placebo; PR, partial response; PTC, papillary thyroid cancer; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TKI, tyrosine kinase inhibitor; VAN, vandetanib.

defined by lack of uptake on RAI-uptake scan [72]. Nine patients were enrolled; by RECIST, 33% had PR and 44% had SD with median PFS of 42 weeks. Waterfall plot analysis was not included, but a mean 60% decrease in thyroglobulin levels was reported.

One trial evaluated motesanib in 93 DTC patients with radiographic evidence of progressive disease by RECIST in the prior 6 months and lesions that were not amenable to surgery or radiation or that were resistant to RAI [67] (Table 2). The trial demonstrated progression-free survival of ~9.3 months, with

Table 3. Completed phase III trials in radioactive iodine-refractory differentiated thyroid cancer

Agent	Trial name	Design	Enrolled (n)	OS, months (95% CI)	PFS, months (95% CI)	RECIST best response (%)				Tumor shrinkage by waterfall plot methods (%)
						CR	PR	SD	PD	
SOR	DECISION [81]	RCT vs. PLC	417; SOR: 207; PLC: 210	NE	SOR: 10.8 (9.1-12.9); PLC: 5.8 (5.3-7.8)	0	SOR: 12; PLC: 0.5	SOR: 42; PLC: 33	NR	SOR: 87.9; PLC: 26.7
LEN	SELECT [82]	RCT vs. PLC	392; LEN: 261; PLC: 131	NE	LEN: 18.7 (15.1-NE); PLC: 3.6 (2.2-3.7)	LEN: 1.5; PLC: 0	LEN: 63.2; PLC: 1.5	LEN: 15; PLC: 30	LEN: 7; PLC: 40	LEN: 98.6; PLC: 36.5

Abbreviations: CI, confidence interval; CR, complete response; LEN, lenvatinib; NE, not estimable; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PLC, placebo; PR, partial response; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOR, sorafenib.

14% PR and 67% SD; however, in patients with evaluable thyroglobulin levels, 81% had a decrease. Similarly, waterfall plots showed 87% had tumor shrinkage. Sixty percent suffered adverse events of grade ≥ 3 , although serious adverse events were uncommon.

Pazopanib has been evaluated in a phase II trial of 39 patients with RAI-R-DTC required to have radiographic evidence of progression by RECIST within 6 months of trial entry [68]. This trial demonstrated median PFS of 11.7 months, with 49% PR by RECIST 1.0 (Table 2). Waterfall plots showed only 2 patients with tumor growth as the best response; similarly, only 1 of 32 patients with evaluable thyroglobulin levels experienced an increase in thyroglobulin during treatment. Fifty-seven percent experienced grade 3 toxicity. Grade 4 toxicity was uncommon; however, two patients died during the trial of myocardial infarction and bowel perforation, both of which are associated with VEGF inhibition.

Sunitinib has been evaluated in two clinical trials that were both phase II (Table 2). Carr et al. enrolled 35 patients with FDG-avid, RAI-R-DTC and 7 patients with medullary thyroid cancer [77]. By RECIST, there was 1 CR, 28% had PR, and 46% had SD, and median time to progression was 12.8 months. Of 33 evaluable patients, 79% had tumor shrinkage, shown by waterfall plot analysis. Median OS was not reached. Response by PET, as measured by change in standardized uptake value, was also assessed and found to be modest (median change of -10% and -13.9% in patients with PR and SD, respectively). The second trial required patients to have RAI-R-DTC as shown by progression despite treatment with RAI or contraindication to RAI and evidence of radiological or biochemical progression in the prior 6 months [78]. SD was the most common response in 68%, whereas 13% had PR by RECIST. In both trials, toxicities were common, with 43%–53% experiencing at least CTCAE grade 3 toxicity.

Two drugs approved for medullary thyroid cancer, vandetanib and cabozantinib, are being explored in RAI-R-DTC. One randomized phase II trial evaluated vandetanib against a placebo control [79] (Table 2). Patients were required to have progression after RAI or have lesions without RAI uptake. Median PFS (the primary endpoint) was 11.1 months in the vandetanib arm versus 5.9 months in the placebo control arm. There were 38 grade 3 toxicities. Crossover to vandetanib after progression on placebo was allowed; no difference in OS was observed. Independent central review by RECIST showed only 1 PR in the vandetanib-treated group; however, by waterfall plot, 54% of

vandetanib-treated patients had lesions shrink, whereas this occurred for 27% of placebo-treated patients. Disease control (CR plus PR plus SD) was confirmed by independent review to favor vandetanib (56%) versus placebo (26%).

No data are available from phase II/III trials on cabozantinib; however, 15 patients with metastatic RAI-R-DTC who had progressed on standard therapies and had measurable disease were treated with cabozantinib in a phase I study looking at pharmacokinetic interactions with rosiglitazone, a CYP2C8 substrate [84]. Patients had been treated previously with a median of two prior regimens. By modified RECIST, 53% had PR and 40% had SD. Tumor shrinkage was noted in all patients that had at least one postbaseline scan (range: -9% to -55%). Median PFS and OS were not reached.

There are a handful of published experiences with the selective BRAF inhibitor vemurafenib in treating BRAF V600E mutant DTC. One publication detailed three patients that were enrolled in the initial expanded dose-escalation phase I trial of vemurafenib [85]. One patient had PR by RECIST, and the other two had stable disease, although shrinkage of target lesions in both patients was noted, by 9% and 16%. Time to progression was 11.7 months in the patient with PR and 13.2 and 11.4 months in the other two patients, respectively.

Dadu et al. reported a case series of 12 patients with BRAF V600E mutant PTC treated with vemurafenib outside of a clinical trial [86]. They found 25% had PR by RECIST and 75% had SD, of which 5 patients had a minor response, defined by shrinkage of target lesions by 10%–29%. Grade 3–4 CTCAEs included elevated lipase (1 patient), photosensitivity (2 patients), and hand-foot syndrome (HFS; 1 patient).

At the European Cancer Congress 2013, Brose et al. reported the results of a phase II trial in which 56 patients with RAI-refractory PTC with BRAF V600E mutations were treated with vemurafenib; of those, 25 had been treated previously with another TKI [80]. The PR rate by RECIST was 35% in TKI-native patients and resulted in 15.6-month PFS. Patients who had been treated previously with a TKI had a 26% PR rate and PFS of 6.8 months. Common AEs included rash, fatigue, weight loss, and hyperbilirubinemia.

The first-in-human phase I study of dabrafenib included 14 patients that had thyroid cancers with BRAF V600E mutations [87], 13 of which had previously received RAI and 9 of which had not received any systemic treatments apart from RAI. There were four partial responses (29%), and 64% had at least

Table 4. Drugs currently in clinical trials in RAI-refractory DTC

Agent	Phase	Design	Histology
Cediranib [89]	I/II	Randomized open label—cediranib; cediranib plus lenalidomide	Any DTC
Cabozantinib [90, 91]	II	Single arm	Any DTC
	II	Single arm	PTC, FTC
Dabrafenib [92]	II	Randomized open label—A: dabrafenib; B: dabrafenib plus trametinib	PTC, FTC
Everolimus [93–95]	II	Single arm	Any DTC, ATC, MTC
	II	Single arm	Any DTC, ATC, MTC
	II	Single arm	Any DTC, ATC, MTC
Everolimus plus sorafenib [96]	II	Single arm, following progression on sorafenib	DTC
Everolimus plus sorafenib [97]	II	Single arm	ATC excluded
Everolimus plus pasireotide [98]	II	Randomized open label—A: everolimus; B: pasireotide; C: everolimus plus pasireotide	DTC, MTC
Lenvatinib [99]	III	Randomized double-blind—lenvatinib; placebo	Any DTC
Pazopanib [100, 101]	II	Single arm	Any DTC, ATC, MTC
	II	Randomized open label—A: continuous; B: intermittent dosing	PTC, FTC, PDTC
Selumetinib [102]	II	Single arm	PTC
Sunitinib [103–105]	II	Single arm	DTC, MTC
	II	Single arm	Any DTC
	II	Single arm	DTC, MTC
Temsirolimus plus sorafenib [106]	II	Single arm	RAI refractory
Vandetanib [107]	III	Randomized double-blind—1: vandetanib; 2: placebo	Any DTC
Vemurafenib [108, 109]	II	Single arm	PTC
	II	Nonrandomized open label—A: presurgery vemurafenib plus postsurgery vemurafenib; B: presurgery vemurafenib; C: vemurafenib in patients not scheduled for surgical resection	PTC

Abbreviations: ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer; FTC, follicular thyroid cancer; MTC, medullary thyroid cancer; PDTC, poorly differentiated thyroid cancer; PTC, papillary thyroid cancer; RAI, radioactive iodine.

a 10% decrease in tumor size by RECIST. The median PFS was 11.3 months. There was one grade 4 elevated lipase. Grade 3 toxicities included elevated amylase, fatigue, febrile neutropenia, and cutaneous squamous cell carcinoma.

One phase II study evaluated everolimus in patients with progressive, locally advanced, or RAI-refractory thyroid cancer of any histology, including 28 patients with differentiated subtypes [88]. Responses were measured by RECIST 1.1. Of the patients with DTC, there were only two responses; however, 71% had tumor shrinkage, shown by waterfall plot. Median PFS was 10 months. Adverse events were as expected based on previous experience with everolimus, with grade 3 mucositis and diarrhea in 15% and 10%, respectively, of all patients. There was one grade 4 pneumonitis.

ONGOING CLINICAL TRIALS

Seventeen ongoing trials are currently listed in the ClinicalTrials.gov database, evaluating 12 drugs including cediranib, lenalidomide, cabozantinib, dabrafenib, trametinib, everolimus, lenvatinib, pazopanib, selumetinib, sunitinib, vandetanib, and vemurafenib (Table 4). Three trials are randomized controlled trials, and two are randomized against a placebo control (lenvatinib and vandetanib). The cediranib trial uses randomization with or without lenalidomide. All of these trials

have either PFS or response rate as the primary endpoint. Some address overall survival as a secondary endpoint.

SELECTION OF AGENTS BASED ON TUMOR MUTATIONS

Substantial work has aimed to understand whether prospective analysis of genetic mutations in thyroid cancers can dictate selection of targeted agents; however, outcomes of these analyses have not led to robust selection criteria.

Substantial work has aimed to understand whether prospective analysis of genetic mutations in thyroid cancers can dictate selection of targeted agents; however, outcomes of these analyses have not led to robust selection criteria.

A retrospective analysis of sequencing from formalin-fixed paraffin-embedded tumors of 18 patients treated with axitinib showed 22% had BRAF V600E mutations, 11% had KRAS mutations, 11% had HRAS mutations, and 1 sample had PIK3CA mutation [110]. There was no correlation of the mutations with response to axitinib, although the sample size was small.

A similar study evaluated BRAF and RAS mutations in patients in the DECISION trial who were treated with sorafenib;

30% had *BRAF* mutations, 19.5% had *RAS* mutations, and 47% had no genetic alteration detected [111]. In this study, neither *BRAF* nor *RAS* mutation predicted response to sorafenib, even though sorafenib inhibits *BRAF* directly, albeit weakly (Table 1). *RAS* mutation was associated with worse PFS compared with tumors with wild-type *RAS*. In contrast, *BRAF* mutation was associated with better PFS compared with patients lacking a *BRAF* mutation. In a separate study, papillary thyroid cancer cell lines made resistant to pazopanib in culture acquired a *KRAS* G13V mutation, and this was associated with more aggressive xenograft growth in animal models, further supporting a possible role for *KRAS* mutation driving a more aggressive disease course [112].

At the 2012 ASCO annual meeting, Ball et al. reported a retrospective analysis of *RAS* and *BRAF* mutations in 58 patients treated with lenvatinib, in which cytokine and angiogenic factors were also measured [113]. Results suggested that a combination of serum cytokine levels and mutation status could predict response to lenvatinib, although no external validation of this data set has been performed to date.

ADVERSE EVENTS AND TOXICITY

Clinical experience gleaned from using bevacizumab has taught us that the toxicity associated with VEGFR inhibition includes hypertension, proteinuria, delayed wound healing, bleeding, gastrointestinal (GI) perforation, fistulas, and thrombosis. Some, but not all, of the typical VEGFR inhibition adverse events have been noted with use of TKIs in RAI-R-DTC trials. Many of the agents have been approved by the U.S. Food and Drug Administration (FDA) for other indications and have existing adverse event data, including pazopanib, axitinib, sunitinib, sorafenib, vandetanib, vemurafenib, and dabrafenib. We have highlighted the most prevalent and important toxicities for each drug, as culled from trials in RAI-R-DTC (Table 5), and drawn parallels to existing AE data, as relevant.

Gastrointestinal side effects including anorexia, nausea, vomiting, stomatitis, and diarrhea are pervasive with these compounds and are the most likely side-effect class. Fortunately, grade 3 diarrhea affected <10% of patients. Weight loss affected a large proportion of patients with most agents (range: 24%–77%), with the exception of sunitinib and vandetanib, which did not report any weight loss. Tracheoesophageal fistula is a rare complication of antiangiogenic TKI therapy; patients with large invasive neck masses or prior neck radiation may be particularly at risk [116].

Fatigue is a pervasive side effect associated with all of these agents. It affects roughly 50% of treated patients, usually as grade 1 or 2.

Hypertension is associated with antiangiogenic TKIs and can be considered a marker of VEGF inhibition. Grade 3 hypertension ranged from 0%–25% in thyroid cancer trials, but any grade affected ~40%–60% of patients in these trials. It is generally managed with antihypertensive agents, although dose adjustments may be necessary. Adequate blood pressure control should be achieved prior to initiating TKI therapy.

Proteinuria is seen with axitinib, lenvatinib, and pazopanib but was not observed or recorded in DTC trials of motesanib, sorafenib, sunitinib, or vandetanib. Only ~5% of patients experience high-grade proteinuria. Sunitinib and sorafenib

have both been associated with proteinuria and, rarely, with nephrotic syndrome in other clinical settings [117]. Proteinuria was also seen in MTC trials of vandetanib.

To date, significant rates of venothromboembolism or arterial thrombosis have not been observed in RAI-R-DTC patients treated with these agents. Sorafenib has been associated with increased risk of cardiac ischemia or infarction in a small percentage of patients (2.7%–2.9% vs. 0.4–1.3% of placebo controls) in trials conducted in hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC); therefore, the extent to which the underlying disease versus the TKI influences thrombosis risk is unclear.

Hemorrhage has been reported with certain agents. One of the sunitinib trials reported a 14% rate of GI bleeding, including one grade 5 event [77]. Motesanib had 14% rate of hemorrhage including 4% grade ≥3. Only one of the eight DTC sorafenib trials reported hemorrhage as an adverse event. Sorafenib was associated with an increased risk of hemorrhage in the RCC clinical trials but not in HCC trials, suggesting that patient- or disease-specific factors may play a role. Pazopanib had a 16% rate of epistaxis, none grade ≥3.

Dermatologic toxicity, especially HFS, has been reported commonly with axitinib, sorafenib, and sunitinib but is especially prominent with sorafenib and can be dose limiting. The sorafenib package insert details suggested dose adjustments for HFS. Alopecia is observed with axitinib, pazopanib, and sorafenib in ≥50% of patients. Pazopanib causes skin and hair hypopigmentation in 76% of patients. Interestingly, this toxicity is associated with c-kit inhibition and may also be seen with sunitinib [118] and other agents.

Although not evident in the thyroid cancer data set thus far, the FDA prescribing instructions for pazopanib in renal cell carcinoma indicate that hepatotoxicity can be severe and fatal with this agent. Specific guidelines exist for liver function test (LFT) monitoring, and dose adjustments based on LFT levels available in the package insert. In RCC trials, 14% had grade 2 elevations in transaminases and 4% had grade 3 elevations. Similarly, sunitinib carries a black box warning for hepatotoxicity; in clinical trials outside of thyroid cancer, 0.3% suffered liver failure.

Vandetanib carries a black box warning for QTc prolongation, torsade de pointes, and sudden death and requires a risk-reduction prescriber program to administer the drug. In the RAI-R-DTC trial, 14% had at least grade 3 QTc prolongation. The vandetanib prescribing instructions also note that fatal cases of Stevens-Johnson syndrome and interstitial lung disease have occurred with this agent. It should also be noted that the FDA package insert for pazopanib indicates QT prolongation in <2% patients, and QT monitoring should be performed.

Sunitinib is contraindicated in patients with clinical congestive heart failure because the drug is associated with decline in ejection fraction, as observed in RCC, GI stromal tumor, and pancreatic neuroendocrine tumor trials. These trials excluded patients with cardiac events within the prior year from treatment, thus caution is advised in this setting, including baseline and periodic monitoring of left ventricular ejection fraction. Sunitinib also prolongs QT interval in a dose-dependent manner, and monitoring should be considered.

Table 5. Incidence of selected adverse events

Agent	Reference	Hypertension	Hand-foot-skin reaction	Diarrhea	Fatigue	Weight loss	AE, % any grade/grade ≥3				Elevated AP/ALT/AST	Hypopigmentation
							Proteinuria	QTc prolongation	Hemorrhage ^b	Mucositis/stomatitis		
Axitinib	[63]	28/12	15/0	48/3	50/5	25/3	18/5	NR	NR	Stomatitis: 25/0	NR	NR
	[64]	54/NR	12/NR	60/10	44/12	35/10	12/NR	NR	2/NR	Stomatitis: 12/NR	AP: 2/NR	NR
	[114]									Mucositis: 19/NR	AST: 4/NR	
Lenvatinib	[66] ^c	64/4	NR	45/5	55/7	43/4	39/7	NR	NR	NR	NR	NR
	[82]	68/42	32/3	60/8	49/9	16/10	31/10	NR	NR	NR	NR	NR
Motesanib	[67]	56/25	NR	59/13	46/4	40/5	NR	NR	14/1 ^d	NR	NR	NR
Pazopanib	[68]	49 ^e /3	5 ^e /0	70 ^e /3	78 ^e /0	24 ^e /3	22 ^e /0	NR	16 ^e /0	Mucositis ^f : 14 ^e /3	ALT: 27 ^e /11; AP: 14 ^e /0; AST: 38 ^e /3	76 ^e /0
Selumetinib	[70]	NR	NR	44 ^g /5	41 ^g /8	NR	NR	NR	NR	Stomatitis: 15 ^g /3	NR	NR
	[69]	5/0	NR	45/0	80/0	NR	NR	NR	NR	Mucositis: 35/0	NR	NR
Sorafenib	[73, 81, 115]	41/10	69/19	68/6	41/5	49/6	NR	NR	7/0	Stomatitis: 24/2	ALT: 59/4 AST: 54/2	NR
	[71]	39 ^e /4	55 ^e /7	71 ^e /4	66 ^e /16	77 ^e /5	NR	NR	NR	Stomatitis: 14 ^e /2	AP: 13 ^e /0; ALT: 39 ^e /0; AST: 47 ^e /0	NR
	[74]	30 ^g /13	83 ^g /10	73 ^g /7	60 ^g /3	50 ^g /10	NR	NR	3 ^e /0	Stomatitis/mucositis: 47 ^e /0	NR	NR
	[75] ^g	15 ^e /6	35 ^e /44	74 ^e /3	50 ^e /9	29 ^e /0	NR	NR	29 ^e /0	Mucositis: 18 ^e /9	AST: 23.5 ^e /0 ALT: 32.4 ^e /3	NR
	[76] ^g	41/15	66/22	50/0	NR	56/8	NR	NR	NR	Mucositis: 44/0	NR	NR
	[72] ^g	22 ^e /0	56 ^e /0	44 ^e /0	67 ^e /0	44 ^e /0	NR	NR	NR	NR	NR	NR
Sunitinib	[78]	42/16	53/14	56, 5	79/14	NR	NR	NR	NR	NR	NR	NR
	[77]	3/0	26/17	26/17	26/11	NR	NR	NR	GI bleed: 14/6 ^h , epistaxis: 6/0	Mucositis: 6/3	NR	NR
Vandetanib	[79] ⁱ	34/0	NR	74/10	23/5	NR	NR	23/14	NR	NR	NR	NR

^aAll AEs were considered treatment-related unless otherwise specified.^bIncludes epistaxis, gastrointestinal bleeding.^c9% experienced unspecified grade 4 events.^dAEs specified by the authors as being related AEs of interest.^eGrade 1–2.^fMucositis includes oral (8% and 3%), pharyngeal (3% and 0%), and small intestine (3% and 0%).^gNot specified as treatment related.^hIncluding one grade 5 event.ⁱCommon adverse events of any grade (≥20% incidence) and adverse events of grade 3.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GI, gastrointestinal; NR, not reported.

FIRST AND SECOND LINE FOR RAI-REFRACTORY DTC PATIENTS: WHICH TKI TO USE WHEN?

A number of studies have looked at sequencing of TKI administration or the use of TKIs in the second-line setting for RAI-refractory DTC in patients whose cancers have progressed while receiving first-line TKIs. In summary, these data seem to suggest that a second-line TKI can be as effective as TKI in the first-line setting regardless of the sequence. Although an agent with alternate molecular targets could be considered, the data do not suggest this is more efficacious than a TKI with similar molecular targets. Dadu et al. studied salvage TKI use after sorafenib failure in a retrospective analysis of 60 patients with metastatic RAI-refractory DTC [119]. Patients treated with sorafenib only and not offered a second-line TKI had OS of 24 months, whereas patients offered a second-line TKI had significantly improved overall survival of 63 months; however, in the second-line setting after sorafenib, treatment with sunitinib, pazopanib, cabozantinib, lenvatinib, or vemurafenib seemed to have equivalent effects on prolonging outcomes. Notably, in the second-line setting, there was actually a higher partial response rate of 41%, and 59% achieved stable disease. It is unclear whether this outcome represents differences in activity compared with sorafenib or other biological or patient-related factors.

Similarly, Massicotte et al. studied 62 patients with RAI-refractory DTC treated with a number of agents including sorafenib and sunitinib. In the first-line setting, these agents were associated with a 36% partial response rate by RECIST 1.1 and PFS of 6.7 months [120]. When used interchangeably in the second line, no partial responses were seen; however, progression-free survival was essentially the same at 7.6 months, suggesting that sequencing of the agents was not important.

One study suggested that patients with BRAF V600E mutations may benefit from first-line BRAF-targeted agents rather than other TKIs [80]. This phase II study enrolled 51 patients with RAI-R-DTC that harbored BRAF V600E mutations and treated them with vemurafenib. Patients were stratified by prior TKI exposure. TKI-naïve patients had a better response rate and PFS (35% and 15.6 months) compared with patients previously treated with TKI (25% and 6.8 months). Eighty-five percent of the patients previously treated with TKI had received sorafenib. Further studies will be needed to confirm whether vemurafenib in the first-line setting is truly superior to the second-line setting and whether the choice of first-line agent makes any difference.

INDUCING RAI UPTAKE IN RAI-R-DTC

Strategies to improve RAI uptake in RAI-refractory DTC have been explored recently. At the 2013 ASCO annual meeting, Rothberg et al. presented a study of seven patients with BRAF-mutant RAI-R-DTC treated with dabrafenib to induce iodine uptake on whole-body scan [121]. There were five evaluable patients, of which three had induced RAI uptake and went on to receive radioactive iodine treatment. All three also had increased thyroglobulin levels, suggesting redifferentiation in response to dabrafenib.

The MEK1/2 inhibitor selumetinib has also been evaluated for redifferentiation properties by PET scan in RAI-refractory

metastatic DTC [69]. Twenty patients were evaluated, eight received radioactive iodine therapy on the basis of PET scan, and five of those had *NRAS* mutations. Of eight treated patients, five had confirmed partial response and three had stable disease. One patient developed myelodysplastic syndrome that progressed to leukemia approximately 1 year after treatment, possibly highlighting the limitations of repeated RAI administrations.

DISCUSSION

The treatment of RAI-R-DTC is undergoing transformation. The number of agents with demonstrable anticancer activity has progressed from none to eight in the past 5 years and is expected to rise in coming years. Only sorafenib is FDA approved for RAI-R-DTC treatment; however, a number of other agents are on the market for other indications and should be considered for the treatment of this disease. Lenvatinib appears to be the most active agent but is not yet available, with a PFS versus placebo triple that of sorafenib and a RECIST response rate five times that of sorafenib in the phase III setting.

The present level of evidence does not support testing for the presence of specific tumor mutations to guide therapy. Low-level evidence shows that presence of a RAS mutation may portend a more aggressive clinical course. Given the specificity of the BRAF-targeted agents vemurafenib and dabrafenib, use of these agents should be restricted to tumors that harbor BRAF V600E mutations. Presently, data are insufficient to suggest routine testing for this mutation, at least in the first-line setting. Knowledge of a *BRAF* mutation may be useful in the second- or third-line setting or if patients have contraindications to an antiangiogenic TKI, as discussed more fully below.

An important consideration is the proper timing for initiating TKI therapy in patients with RAI-R-DTC. Because of the lack of survival data and the relatively indolent nature of DTC, the rationale for treatment and the expected treatment endpoints should be conceptualized clearly. Because DTC is an indolent disease, it is important to document that the disease is actually progressing when considering therapy and that progression is causing symptoms or is anticipated to cause symptoms shortly. Many of the trials discussed required evidence of progression as documented on interval cross-sectional imaging within the prior year or 6 months as an entry criterion. The concept is that documentation of RAI-refractory disease is not enough to merit treatment with TKIs in the absence of more robust data indicating that doing so will alter an important patient-related outcome. The worry is that because TKIs are life-long, chronic treatments, patients will be exposed to toxic drugs for a protracted period without meaningful clinical benefit, especially because stable disease is often the most likely treatment outcome. The results of the DECISION trial with sorafenib can be interpreted as demonstrating that there was no benefit to starting sorafenib earlier versus later, given that crossover was allowed and no difference in median OS was observed. In addition, quality of life evaluation suggested that patients receiving sorafenib had worse quality of life than patients on placebo. TKIs must be balanced with the use of localized treatments including radiation, cryoablation, and embolization in the proper clinical setting.

Once the decision to treat has been made, both efficacy and toxicity should be considered in choosing a first-line agent in RAI-R-DTC. Agents commercially available for the first-line setting include axitinib, cabozantinib, pazopanib, sorafenib, sunitinib, and vandetanib. The selective BRAF inhibitors vemurafenib and dabrafenib are also available and could be considered in the first-line setting, especially for patients at risk of TKI-related side effects, such as GI perforation, tracheoesophageal fistula, or other antiangiogenic side effects. We eagerly await approval of lenvatinib, which, based on the SELECT trial, greatly prolongs PFS compared with placebo; SELECT is the first trial to demonstrate PR rates by RECIST in >60% of patients.

Regarding efficacy, no OS data exists to guide us; however, PFS rates are generally similar, at ~1 year with all agents. A possible exception is increased PFS with axitinib and lenvatinib, although the axitinib trials did not specifically enroll patients with documented progressive disease. Pazopanib and lenvatinib have higher response rates of ~50% compared with 20%–40% with other agents. This indicates that if achieving a response is an important treatment objective, pazopanib (or lenvatinib, when available) may be the best choice. A patient with a symptomatic mass, for example, would benefit from treatment to shrink disease, improve symptoms, and improve quality of life.

Toxicity is an equally important consideration, and many agents have side-effect profiles that may limit use. Patients with cardiac issues will need careful consideration before treatment with vandetanib or sunitinib because of the risks of QT prolongation/sudden death and coronary heart failure, respectively. Patients with pre-existing liver disease would not be good candidates for pazopanib or sunitinib. Patients should be counseled about the prevalence of dermatologic toxicities; the hypopigmentation associated with pazopanib may be unacceptable to certain patients. Patients with propensity for bleeding or GI perforation may not be good candidates for TKI therapy in general, and BRAF inhibitors could be considered for first line in this setting if their disease harbors a BRAF V600E mutation. Patients with large invasive neck masses or prior neck radiation may be predisposed to tracheoesophageal fistula, thus antiangiogenic TKIs should be used judiciously in this setting.

At the current time, no overwhelming data strongly support the first-line selection of one agent over another. This may change when lenvatinib is approved. At the current time, we recommend individualized selection based on the intent of therapy, the expected side-effect profile, and patient input. Practically, FDA approval of sorafenib for RAI-R-DTC may make this agent the most appropriate first-line therapy in the near term, especially when considering the likelihood of insurance authorization. Axitinib or pazopanib are equally good choices in the first-line setting because of their efficacy and relatively tolerable side-effect profiles.

Data are currently insufficient to suggest that switching to an agent that inhibits a novel target in the second line will be any more effective than an agent of similar class. In the second-line setting after TKI, for example, the presence of a BRAF V600E mutation may suggest switching to a BRAF inhibitor;

however, this is not supported by current data. Further trials need to be performed before recommendations can be made in the second-line setting in RAI-R-DTC.

Data are currently insufficient to suggest that switching to an agent that inhibits a novel target in the second line will be any more effective than an agent of similar class.

In coming years, we can expect that more TKIs will progress toward approval for RAI-R-DTC. We also expect mTOR inhibitors and BRAF inhibitors may follow suit. Further questions to address in clinical trials involve the specific sequencing of agents and whether molecular characterization of tumor mutations is predictive of response, especially with the mTOR- and BRAF-targeted classes. In metastatic melanoma, MEK inhibitors have single-agent activity similar to BRAF inhibitors, and combined MEK/BRAF inhibition leads to improved PFS and response rates with decreased dermatologic toxicity [122, 123]. We hypothesize that the same might be true for DTC. In RAI-R-DTC, efforts thus far have been channeled toward improving RAI uptake with MEK inhibition, which appears feasible; however, it is possible that MEK inhibitor treatment may be effective in itself, without giving RAI. In other words, improving iodine uptake may be a marker of more indolent biology and may be a desirable outcome in itself, even if RAI is not given. An open phase II trial is evaluating the selective BRAF inhibitor dabrafenib with or without the MEK inhibitor trametinib in DTC (NCT01723202). More generally, combinations of targeted agents are a largely unexplored area that deserves further study.

CONCLUSION

Patients with RAI-R-DTC have an expanding suite of drugs available and in the pipeline that hold clinical promise. Selection of a targeted agent should depend on careful documentation of the patient's disease trajectory, consideration of side-effect profile, and realistic discussion of the goals of therapy.

ACKNOWLEDGMENTS

We thank Pam Foreman, Jeremy Altman, Jill Luer, and Lana Branscum at Percolation Communications for assistance with database searches and table preparation.

AUTHOR CONTRIBUTIONS

Conception/Design: Joshua J. Gruber, A. Dimitrios Colevas
Collection and/or assembly of data: Joshua J. Gruber, A. Dimitrios Colevas
Data analysis and interpretation: Joshua J. Gruber, A. Dimitrios Colevas
Manuscript writing: Joshua J. Gruber, A. Dimitrios Colevas
Final approval of manuscript: Joshua J. Gruber, A. Dimitrios Colevas

DISCLOSURES

A. Dimitrios Colevas: Bayer, Genentech, Exelixis (RF). The other author indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

- SEER stat fact sheets: Thyroid cancer. Available at <http://seer.cancer.gov/statfacts/html/thyro.html>. Accessed December 31, 2014.
- Enewold L, Zhu K, Ron E et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. *Cancer Epidemiol Biomarkers Prev* 2009;18:784-791.
- Byrd JK, Yawn RJ, Wilhoit CS et al. Well differentiated thyroid carcinoma: Current treatment. *Curr Treat Options Oncol* 2012;13:47-57.
- Nixon IJ, Whitcher MM, Palmer FL et al. The impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland. *Thyroid* 2012;22:884-889.
- Banerjee M, Muenz DG, Chang JT et al. Tree-based model for thyroid cancer prognostication. *J Clin Endocrinol Metab* 2014;99:3737-3745.
- Schlumberger M, Tubiana M, De Vathaire F et al. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 1986;63:960-967.
- Durante C, Haddy N, Baudin E et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: Benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab* 2006;91:2892-2899.
- Mandel SJ, Mandel L. Radioactive iodine and the salivary glands. *Thyroid* 2003;13:265-271.
- Kloos RT, Duvuuri V, Jhang SM et al. Nasolacrimal drainage system obstruction from radioactive iodine therapy for thyroid carcinoma. *J Clin Endocrinol Metab* 2002;87:5817-5820.
- Chen L, Shen Y, Luo Q et al. Pulmonary fibrosis following radioiodine therapy of pulmonary metastases from differentiated thyroid carcinoma. *Thyroid* 2010;20:337-340.
- Rubino C, de Vathaire F, Dottorini ME et al. Second primary malignancies in thyroid cancer patients. *Br J Cancer* 2003;89:1638-1644.
- Cooper DS, Doherty GM, Haugen BR et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19:1167-1214.
- Robbins RJ, Wan Q, Grewal RK et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[¹⁸F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. *J Clin Endocrinol Metab* 2006;91:498-505.
- Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nat Rev Cancer* 2013;13:184-199.
- Cohen Y, Xing M, Mambo E et al. BRAF mutation in papillary thyroid carcinoma. *J Natl Cancer Inst* 2003;95:625-627.
- Namba H, Nakashima M, Hayashi T et al. Clinical implication of hot spot BRAF mutation, V599E, in papillary thyroid cancers. *J Clin Endocrinol Metab* 2003;88:4393-4397.
- Xu X, Quiros RM, Gattuso P et al. High prevalence of BRAF gene mutation in papillary thyroid carcinomas and thyroid tumor cell lines. *Cancer Res* 2003;63:4561-4567.
- Fukushima T, Suzuki S, Mashiko M et al. BRAF mutations in papillary carcinomas of the thyroid. *Oncogene* 2003;22:6455-6457.
- Liu Z, Hou P, Ji M et al. Highly prevalent genetic alterations in receptor tyrosine kinases and phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinase pathways in anaplastic and follicular thyroid cancers. *J Clin Endocrinol Metab* 2008;93:3106-3116.
- Wang Y, Hou P, Yu H et al. High prevalence and mutual exclusivity of genetic alterations in the phosphatidylinositol-3-kinase/Akt pathway in thyroid tumors. *J Clin Endocrinol Metab* 2007;92:2387-2390.
- Hou P, Liu D, Shan Y et al. Genetic alterations and their relationship in the phosphatidylinositol 3-kinase/Akt pathway in thyroid cancer. *Clin Cancer Res* 2007;13:1161-1170.
- Ricarte-Filho JC, Ryder M, Chitale DA et al. Mutational profile of advanced primary and metastatic radioactive iodine-refractory thyroid cancers reveals distinct pathogenetic roles for BRAF, PIK3CA, and AKT1. *Cancer Res* 2009;69:4885-4893.
- Garcia-Rostan G, Zhao H, Camp RL et al. ras mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer. *J Clin Oncol* 2003;21:3226-3235.
- Basolo F, Pisaturo F, Pollina LE et al. N-ras mutation in poorly differentiated thyroid carcinomas: Correlation with bone metastases and inverse correlation to thyroglobulin expression. *Thyroid* 2000;10:19-23.
- Fukahori M, Yoshida A, Hayashi H et al. The associations between RAS mutations and clinical characteristics in follicular thyroid tumors: New insights from a single center and a large patient cohort. *Thyroid* 2012;22:683-689.
- Zhu Z, Gandhi M, Nikiforova MN et al. Molecular profile and clinical-pathologic features of the follicular variant of papillary thyroid carcinoma. An unusually high prevalence of ras mutations. *Am J Clin Pathol* 2003;120:71-77.
- Manenti G, Pilotti S, Re FC et al. Selective activation of ras oncogenes in follicular and undifferentiated thyroid carcinomas. *Eur J Cancer* 1994;30A:987-993.
- Rabes HM, Demidchik EP, Sidorov JD et al. Pattern of radiation-induced RET and NTRK1 rearrangements in 191 post-chernobyl papillary thyroid carcinomas: Biological, phenotypic, and clinical implications. *Clin Cancer Res* 2000;6:1093-1103.
- Santoro M, Thomas GA, Vecchio G et al. Gene rearrangement and Chernobyl related thyroid cancers. *Br J Cancer* 2000;82:315-322.
- Klugbauer S, Demidchik EP, Lengfelder E et al. Molecular analysis of new subtypes of ELE/RET rearrangements, their reciprocal transcripts and breakpoints in papillary thyroid carcinomas of children after Chernobyl. *Oncogene* 1998;16:671-675.
- Abubaker J, Jehan Z, Bavi P et al. Clinicopathological analysis of papillary thyroid cancer with PIK3CA alterations in a Middle Eastern population. *J Clin Endocrinol Metab* 2008;93:611-618.
- Santarpia L, El-Naggar AK, Cote GJ et al. Phosphatidylinositol 3-kinase/Akt and ras/raf-mitogen-activated protein kinase pathway mutations in anaplastic thyroid cancer. *J Clin Endocrinol Metab* 2008;93:278-284.
- Murugan AK, Bojdani E, Xing M. Identification and functional characterization of isocitrate dehydrogenase 1 (IDH1) mutations in thyroid cancer. *Biochem Biophys Res Commun* 2010;393:555-559.
- Hemerly JP, Bastos AU, Cerutti JM. Identification of several novel non-p.R132 IDH1 variants in thyroid carcinomas. *Eur J Endocrinol* 2010;163:747-755.
- Murugan AK, Dong J, Xie J et al. Uncommon GNAQ, MMP8, AKT3, EGFR, and PIK3R1 mutations in thyroid cancers. *Endocr Pathol* 2011;22:97-102.
- Kroll TG, Sarraf P, Pecciarini L et al. PAX8-PPARGgamma1 fusion oncogene in human thyroid carcinoma. *Science* 2000;289:1357-1360.
- Máximo V, Botelho T, Capela J et al. Somatic and germline mutation in GRIM-19, a dual function gene involved in mitochondrial metabolism and cell death, is linked to mitochondrion-rich (Hürthle cell) tumours of the thyroid. *Br J Cancer* 2005;92:1892-1898.
- Soares P, Máximo V, Sobrinho-Simões M. Molecular pathology of papillary, follicular and Hürthle cell carcinomas of the thyroid. *Arkh Patol* 2003;65:45-47.
- Kimura ET, Nikiforova MN, Zhu Z et al. High prevalence of BRAF mutations in thyroid cancer: Genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. *Cancer Res* 2003;63:1454-1457.
- Jo YS, Li S, Song JH et al. Influence of the BRAF V600E mutation on expression of vascular endothelial growth factor in papillary thyroid cancer. *J Clin Endocrinol Metab* 2006;91:3667-3670.
- Center for Drug Evaluation and Research, application no. 202324Orig1s000: Pharmacology review(s). Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202324Orig1s000PharmR.pdf. Accessed December 31, 2014.
- Hu-Lowe DD, Zou HY, Grazzini ML et al. Non-clinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. *Clin Cancer Res* 2008;14:7272-7283.
- Center for Drug Evaluation and Research, application no. 203756Orig1s000: Pharmacology review(s). Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203756Orig1s000PharmR.pdf. Accessed December 31, 2014.
- Center for Drug Evaluation and Research, application no. 202806Orig1s000: Pharmacology review(s). Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202806Orig1s000PharmR.pdf. Accessed December 31, 2014.
- Wedge SR, Kendrew J, Hennequin LF et al. AZD2171: A highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. *Cancer Res* 2005;65:4389-4400.
- Matsui J, Yamamoto Y, Funahashi Y et al. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. *Int J Cancer* 2008;122:664-671.
- Polverino A, Coxon A, Starnes C et al. AMG 706, an oral, multitargeted inhibitor that selectively targets vascular endothelial growth factor, platelet-derived growth factor, and kit receptors, potently inhibits angiogenesis and induces regression in tumor xenografts. *Cancer Res* 2006;66:8715-8721.
- Kumar R, Crouthamel MC, Rominger DH et al. Myelosuppression and kinase selectivity of

multikinase angiogenesis inhibitors. *Br J Cancer* 2009;101:1717–1723.

49. Center for Drug Evaluation and Research, application no. 22-465: Pharmacology review(s). Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000_PharmR.pdf. Accessed December 31, 2014.

50. Kumar R, Knick VB, Rudolph SK et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther* 2007;6:2012–2021.

51. Center for Drug Evaluation and Research, approval package for application no. NDA 21-923: Pharmacology review(s). Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021923_s000_Nexavar_PharmR.pdf. Accessed December 31, 2014.

52. Wilhelm SM, Carter C, Tang L et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004;64:7099–7109.

53. Kitagawa D, Yokota K, Gouda M et al. Activity-based kinase profiling of approved tyrosine kinase inhibitors. *Genes Cells* 2013;18:110–122.

54. Center for Drug Evaluation and Research, approval package for application no. NDA 21-938 (GIST), NDA 21-968 (MRCC): Pharmacology review (s). Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021938_s000_Sutent_PharmR.pdf. Accessed December 31, 2014.

55. Yeh TC, Marsh V, Bernat BA et al. Biological characterization of ARRY-142886 (AZD6244), a potent, highly selective mitogen-activated protein kinase kinase 1/2 inhibitor. *Clin Cancer Res* 2007;13:1576–1583.

56. Center for Drug Evaluation and Research, application no. 022405Orig1s000: Clinical pharmacology and biopharmaceutics review(s). Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022405Orig1s000ClinPharmR.pdf. Accessed December 31, 2014.

57. Wedge SR, Ogilvie DJ, Dukes M et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res* 2002;62:4645–4655.

58. Center for Drug Evaluation and Research, application no. 22-334: Pharmacology review(s). Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022334s000_PharmR.pdf. Accessed December 31, 2014.

59. Shor B, Zhang WG, Toral-Barza L et al. A new pharmacologic action of CCI-779 involves FKBP12-independent inhibition of mTOR kinase activity and profound repression of global protein synthesis. *Cancer Res* 2008;68:2934–2943.

60. Tafenlar (dabrafenib) [prescribing information]. Research Triangle Park, SC: GlaxoSmithKline; 2014.

61. Center for Drug Evaluation and Research, application no. 202429Orig1s000: Clinical pharmacology and biopharmaceutics review(s). Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202429Orig1s000ClinPharmR.pdf. Accessed December 31, 2014.

62. Bollag G, Hirth P, Tsai J et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature* 2010;467:596–599.

63. Cohen EE, Rosen LS, Vokes EE et al. Axitinib is an active treatment for all histologic subtypes of

advanced thyroid cancer: Results from a phase II study. *J Clin Oncol* 2008;26:4708–4713.

64. Locati L, Licitra L, Ou S-HI et al. Phase 2 trial of axitinib for advanced thyroid cancer: Preliminary activity results [abstract PP17]. *Eur Arch Otorhinolaryngol* 2012;269:1345.

65. Pennell NA, Daniels GH, Haddad RI et al. A phase II study of gefitinib in patients with advanced thyroid cancer. *Thyroid* 2008;18:317–323.

66. Sherman SI, Jarzab B, Cabanillas ME et al. A phase II trial of the multitargeted kinase inhibitor E7080 in advanced radioiodine (RAI)-refractory differentiated thyroid cancer (DTC). *J Clin Oncol* 2011;29(suppl):5503a.

67. Sherman SI, Wirth LJ, Droz JP et al. Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl J Med* 2008;359:31–42.

68. Bible KC, Suman VJ, Molina JR et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: Results of a phase 2 consortium study. *Lancet Oncol* 2010;11:962–972.

69. Ho AL, Grewal RK, Leboeuf R et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med* 2013;368:623–632.

70. Hayes DN, Lucas AS, Tanvetyanov T et al. Phase II efficacy and pharmacogenomic study of Selumetinib (AZD6244; ARRY-142886) in iodine-131 refractory papillary thyroid carcinoma with or without follicular elements. *Clin Cancer Res* 2012;18:2056–2065.

71. Kloos RT, Ringel MD, Knopp MV et al. Phase II trial of sorafenib in metastatic thyroid cancer. *J Clin Oncol* 2009;27:1675–1684.

72. Chen L, Shen Y, Luo Q et al. Response to sorafenib at a low dose in patients with radioiodine-refractory pulmonary metastases from papillary thyroid carcinoma. *Thyroid* 2011;21:119–124.

73. Brose MS, Nutting CM, Jarzab B et al. Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase III DECISION trial. *J Clin Oncol* 2013;31(suppl):04a.

74. Gupta-Abramson V, Troxel AB, Nellore A et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol* 2008;26:4714–4719.

75. Ahmed M, Barbachano Y, Riddell A et al. Analysis of the efficacy and toxicity of sorafenib in thyroid cancer: A phase II study in a UK based population. *Eur J Endocrinol* 2011;165:315–322.

76. Hoftijzer H, Heemstra KA, Morreau H et al. Beneficial effects of sorafenib on tumor progression, but not on radioiodine uptake, in patients with differentiated thyroid carcinoma. *Eur J Endocrinol* 2009;161:923–931.

77. Carr LL, Mankoff DA, Goulart BH et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. *Clin Cancer Res* 2010;16:5260–5268.

78. Cohen EE, Needles BM, Cullen KJ et al. Phase 2 study of sunitinib in refractory thyroid cancer. *J Clin Oncol* 2008;26(suppl):6025a.

79. Lebouleux S, Bastholt L, Krause T et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 2 trial. *Lancet Oncol* 2012;13:897–905.

80. Brose MS, Cabanillas ME, Cohen EEW et al. An open-label, multi-center phase 2 study of the

BRAF inhibitor vemurafenib in patients with metastatic or unresectable papillary thyroid cancer (ptc) positive for the BRAF V600 mutation and resistant to radioactive iodine. *Eur J Cancer* 2013;49(suppl 3):LBA28.

81. Brose MS, Nutting CM, Jarzab B et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 3 trial. *Lancet* 2014;384:319–328.

82. Schlumberger M, Makoto T, Wirth L et al. A phase 3, multicenter, double-blind, placebo-controlled trial of lenvatinib (E7080) in patients with 131I-refractory differentiated thyroid cancer (SELECT). *J Clin Oncol* 2014;32(suppl 5):LBA6008.

83. Schlumberger M, Jarzab B, Elisei R et al. Phase III randomized, double-blinded, placebo-controlled trial of sorafenib in locally advanced or metastatic patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) - exploratory analyses of patient-reported outcomes. *Thyroid* 2013;23:A-49–A-50.

84. Cabanillas ME, Brose MS, Holland J et al. A phase I study of cabozantinib (XL184) in patients with differentiated thyroid cancer. *Thyroid* 2014;24:1508–1514.

85. Kim KB, Cabanillas ME, Lazar AJ et al. Clinical responses to vemurafenib in patients with metastatic papillary thyroid cancer harboring BRAF (V600E) mutation. *Thyroid* 2013;23:1277–1283.

86. Dadu R, Shah K, Waguespack SG et al. Efficacy and tolerability of vemurafenib in BRAFV600E positive papillary thyroid cancer (PTC). *Thyroid* 2013;23:A-95–A-96.

87. Falchook GS, Millward M, Hong D et al. BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer. *Thyroid* 2014 [Epub ahead of print].

88. Lim SM, Chang H, Yoon MJ et al. A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes. *Ann Oncol* 2013;24:3089–3094.

89. Cediranib maleate with or without lenalidomide in treating patients with thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT01208051>. Accessed December 31, 2014.

90. Cabozantinib-S-malate in treating patients with refractory thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT01811212>. Accessed December 31, 2014.

91. A phase II trial of cabozantinib for the treatment of radioiodine (RAI)-refractory differentiated thyroid carcinoma (DTC) in the first-line setting. Available at <https://clinicaltrials.gov/ct2/show/NCT02041260>. Accessed December 31, 2014.

92. Dabrafenib with or without trametinib in treating patients with recurrent thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT01723202>. Accessed December 31, 2014.

93. RAD001 for patients with radioiodine refractory thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT00936858>. Accessed December 31, 2014.

94. Everolimus in treating patients with locally advanced or metastatic thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT01164176>. Accessed December 31, 2014.

95. Everolimus in treating patients with progressive or recurrent, unresectable, or metastatic thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT01180655>. Accessed December 31, 2014.

96. Study of everolimus and sorafenib in patients with advanced thyroid cancer who progressed on sorafenib alone. Available at <https://clinicaltrials.gov/ct2/show/NCT01263951>. Accessed December 31, 2014.
97. Evaluating the combination of everolimus and sorafenib in the treatment of thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT01141309>. Accessed December 31, 2014.
98. A trial of pasireotide and everolimus in adult patients with radioiodine-refractory differentiated and medullary thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT01270321>. Accessed December 31, 2014.
99. A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial of lenvatinib (E7080) in 131I-refractory differentiated thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT01321554>. Accessed December 31, 2014.
100. Pazopanib hydrochloride in treating patients with advanced thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT00625846>. Accessed December 31, 2014.
101. Phase II study of the optimal scheme of administration of pazopanib in thyroid carcinoma. Available at <https://clinicaltrials.gov/ct2/show/NCT01813136>. Accessed December 31, 2014.
102. AZD6244 in treating patients with papillary thyroid cancer that did not respond to radioactive iodine. Available at <https://clinicaltrials.gov/ct2/show/NCT00559949>. Accessed December 31, 2014.
103. Sunitinib in treating patients with thyroid cancer that did not respond to iodine I 131 and cannot be removed by surgery. Available at <https://clinicaltrials.gov/ct2/show/NCT00381641>. Accessed December 31, 2014.
104. Sutent adjunctive treatment of differentiated thyroid cancer (IIT Sutent). Available at <https://clinicaltrials.gov/ct2/show/NCT00668811>. Accessed December 31, 2014.
105. Sunitinib malate in treating patients with iodine-refractory recurrent or metastatic thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT00519896>. Accessed December 31, 2014.
106. Combination of temsirolimus and sorafenib in the treatment of radioactive iodine refractory thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT01025453>. Accessed December 31, 2014.
107. Evaluation of efficacy, safety of vandetanib in patients with differentiated thyroid cancer (VERIFY). Available at <https://clinicaltrials.gov/ct2/show/NCT01876784>. Accessed December 31, 2014.
108. A study of RO5185426 (vemurafenib) in patients with metastatic or unresectable papillary thyroid cancer positive for the BRAF V600 mutation. Available at <https://clinicaltrials.gov/ct2/show/NCT01286753>. Accessed December 31, 2014.
109. Vemurafenib neoadjuvant trial in locally advanced thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT01709292>. Accessed December 31, 2014.
110. Schechter RB, Nagilla M, Joseph L et al. Genetic profiling of advanced RAI-resistant differentiated thyroid cancer and correlation with axitinib response. *J Clin Oncol* 2013;31(suppl):6066a.
111. Brose MS, Nutting C, Shong YK et al. Association between tumor BRAF and RAS mutation status and clinical outcomes in patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) randomized to sorafenib or placebo: Sub-analysis of the phase III DECISION trial. *Eur J Cancer* 2013;49(suppl 2):O3155.
112. Isham CR, Netzel BC, Bossou AR et al. Pazopanib resistance induced by in vitro selection of BHP2-7 papillary thyroid cancer cells is associated with acquired KRAS mutation and more aggressive in vivo phenotype. *Thyroid* 2013;23:A-78.
113. Ball DW, Sherman SI, Jarzab B et al. Lenvatinib treatment of advanced RAI-refractory differentiated thyroid cancer (DTC): Cytokine and angiogenic factor (CAF) profiling in combination with tumor genetic analysis to identify markers associated with response. *J Clin Oncol* 2012;30(suppl):5518a.
114. Study of AG-013736 in patients with 131I-refractory thyroid cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT00389441>. Accessed December 31, 2014.
115. Nexavar (sorafenib) [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc; 2013.
116. Blevins DP, Dadu R, Hu M et al. Aerodigestive fistula formation as a rare side effect of antiangiogenic tyrosine kinase inhibitor therapy for thyroid cancer. *Thyroid* 2014;24:918–922.
117. Turan N, Benekli M, Ozturk SC et al. Sunitinib- and sorafenib-induced nephrotic syndrome in a patient with gastrointestinal stromal tumor. *Ann Pharmacother* 2012;46:e27.
118. Brzezniak C, Szabo E. Images in clinical medicine. Sunitinib-associated hair depigmentation. *N Engl J Med* 2014;370:e27.
119. Dadu R, Devine C, Hernandez M et al. Role of salvage targeted therapy in differentiated thyroid cancer patients who failed first-line sorafenib. *J Clin Endocrinol Metab* 2014;99:2086–2094.
120. Massicotte MH, Brassard M, Claude-Desroches M et al. Tyrosine kinase inhibitor treatments in patients with metastatic thyroid carcinomas: A retrospective study of the TUTHYREF network. *Eur J Endocrinol* 2014;170:575–582.
121. Rothenberg SM, McFadden DG, Palmer E et al. Re-differentiation of radioiodine-refractory BRAF V600E-mutant thyroid carcinoma with dabrafenib: A pilot study. *J Clin Oncol* 2013;31(suppl):6025a.
122. Flaherty KT, Infante JR, Daud A et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 2012;367:1694–1703.
123. Salama AK, Kim KB. MEK inhibition in the treatment of advanced melanoma. *Curr Oncol Rep* 2013;15:473–482.

CME

This article is available for continuing medical education credit at CME.TheOncologist.com.