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Clinical Efficacy of Targeted Biologic Agents as Second-Line Therapy of Advanced Thyroid Cancer

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Key Words. Thyroid cancer • Biologic agents • Second-line

Learning Objectives

List the therapeutic opportunities with tyrosine kinase inhibitors for advanced thyroid cancer, especially in the frontline setting.

Describe and discuss the current knowledge and experience with salvage therapy with biologic agents for thyroid cancer.

Abstract

Introduction. Targeted biologic agents showed clinically meaningful efficacy as front-line therapy for advanced radioiodine-refractory and medullary thyroid cancer. The clinical benefit of these agents beyond the front line has yet to be established.

Methods. We assessed the clinical benefit of targeted agents in patients with advanced differentiated and medullary thyroid cancer treated at a single academic cancer center. We determined efficacy and compared front-line and second-line benefit using biochemical and anatomic response, time to treatment failure, and progression-free survival (PFS). Statistical differences were assessed by *t* test and chi-square test. Survival curves were generated by the Kaplan-Meier method. Differences in survival were assessed using the log-rank test, and a *p* value <.05 was considered significant.

Results. We identified 39 patients with advanced differentiated and medullary thyroid cancer treated with targeted

biologic agents. Median age was 56.3 years. Overall, 25 men and 14 women participated. Histology showed 23% medullary and 77% differentiated cancer. Nineteen patients progressed on front-line therapy and subsequently received second-line therapy. Targeted agents conferred clinically meaningful benefit in the second-line setting in terms of biochemical response (13.3%), clinical benefit (83.3%), median time to treatment failure (4.0 months; 95% confidence interval: 2.6–8.2), and median PFS (4.6 months; 95% confidence interval: 3.2–8.2). Second-line benefit (median PFS) was more modest in comparison to the front-line setting in both genders (women: 3 months vs. 12.2 months; men: 6 months vs. 19.7 months), in differentiated cancers (4.1 months vs. 15.7 months), and with vascular targeting agents (4.4 months vs. 20.1 months).

Conclusion. Patients with advanced thyroid cancer derived meaningful clinical benefit from additional therapy with a biologic agent following disease progression on front-line targeted therapy. ***The Oncologist*** 2013;18:1262–1269

Implications for Practice: Significant benefit can be achieved in patients with iodine-refractory thyroid cancer treated with targeted agents in the first-line setting. It is currently unknown whether additional benefit would be obtained with the use of different biologic agents to treat patients after failing first-line therapy. We report our experience using biologic agents as second-line treatment for advanced thyroid cancer and show that patients derived additional benefit, albeit modest, in comparison to the front-line treatment. Our findings are relevant for the clinical management of patients and for future studies of second-line targeted therapy of thyroid cancer.

Introduction

Thyroid cancer is the most common endocrine malignancy in the United States, and its incidence continues to rise worldwide [1, 2]. The majority of cases of thyroid cancer are either follicular cell derived (papillary/follicular) or medullary. Despite the excellent initial outcome of surgery for the vast majority of patients, disease recurrence is frequently observed in a large proportion of patients [3, 4]. Therapeutic options are currently limited for patients with advanced differentiated

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Table 1. Demographics and clinical characteristics

Variable	Classification	Result, n (%)
Age, yr		56.28 (±15.11)[a]
Gender	Female	14 (35.9)
	Male	25 (64.1)
Cancer type	Differentiated	30 (76.9)
	Medullary	9 (23.1)
Front-line therapy	Everolimus	4 (10.5)
	Everolimus/pasireotide	6 (15.8)
	Lenalidomide/everolimus	1 (2.6)
	Octreotide	1 (2.6)
	Pasireotide	7 (18.4)
	Sorafenib	11 (28.9)
	Sunitinib	1 (2.6)
	Sunitinib/bortezomib	6 (15.8)
	Vandetanib	1 (2.6)
Second-line therapy	Everolimus	2 (10.5)
	Everolimus/pasireotide	7 (36.9)
	Sorafenib	8 (42.1)
	Sunitinib/bortezomib	1 (5.3)
	Vandetanib	1 (5.3)
Regimen		
Front-line	Multiple agents	13 (34.2)
	Single agent	25 (65.8)
Second-line	Multiple agents	8 (42.1)
	Single agent	11 (57.9)
Class of agent		
Front-line	Antiangiogenic	19 (50.0)
	Nonantiangiogenic	19 (50.0)
Second-line	Antiangiogenic	10 (52.6)
	Nonantiangiogenic	9 (47.4)

[a]Shown as mean plus or minus standard deviation.

thyroid cancer or medullary thyroid cancer that is not amenable to radioiodine therapy, surgical resection, or local therapy with external-beam radiation.

A better understanding of the role of altered signaling pathways in cancer development and progression has led to the evaluation and subsequent approval of biologically targeted therapies in various cancers such as breast cancer, renal cell cancer, lung cancer, and melanoma [5–8]. Multiple targeted kinase inhibitors and antiangiogenic agents including vandetanib, sorafenib, sunitinib, motesanib, cabozantinib, levantinib, and pazopanib have also been evaluated in small prospective phase II studies as first-line therapy for patients with metastatic thyroid cancer, with promising results [9–15]. These initial results have led to confirmatory phase III trials of these agents as well as widespread off-label use outside the clinical trial setting [16, 17]. Despite these promising results, the majority of patients progress within 12 months of therapy.

Based on the experiences with other cancer types where targeted agents have become standard treatment options, thyroid cancer patients who progress on front-line kinase inhibitor therapy are also likely to be treated with other biologic agents following progression. However, published reports of clinical studies or robust experiences from routine clinical care supporting such an approach in thyroid cancer patients are currently lacking. Consequently, we conducted a systematic analysis of our institutional experience with the second-line use of biologic-agent therapy for advanced thyroid cancer in order to provide a useful benchmark to guide future prospective trials in this setting.

MATERIALS AND METHODS

Enrollment

This retrospective study was approved by the Emory University institutional review board to review clinical records from patients with advanced thyroid cancer (medullary and differentiated tumors) treated at the Winship Cancer Institute of Emory University between 2006 and 2013. The primary study population consisted of advanced thyroid cancer patients treated with at least one line of targeted biologic agent during the period under review. Relevant clinical data including age, gender, ethnicity, date of diagnosis, type and duration of treatment, and treatment outcome were obtained from the electronic medical records.

Treatment Efficacy

Benefit from therapy was assessed in terms of anatomic response, biochemical response, and duration of benefit. A 50% or greater reduction in the level of standard tumor markers (thyroglobulin for differentiated cancers and calcitonin for medullary thyroid) compared with baseline measurement at the time of treatment initiation was considered as biochemical response. Best objective tumor response while on targeted agent therapy was determined by cross-sectional imaging obtained as part of the standard of care for the patients. Response assessment was categorized according to Response Evaluation Criteria In Solid Tumors version 1.1 in patients with appropriate anatomic lesions as complete response, partial response, stable disease, and progressive disease, as well as clinical benefit (complete response plus partial response plus stable disease).

Survival

The primary outcomes of interest included time to treatment failure (TTF), measured as the time interval from initiating a specific therapy until date of discontinuation for any reason, and progression-free survival (PFS), defined as the time interval from initiating treatment until objective disease progression or death. Differences in treatment efficacy were also assessed based on the known mechanism of action of the biologic agent, either as agents targeting tumor vasculature (antiangiogenic) or not targeting tumor vasculature (nonantiangiogenic). Similarly, the efficacy of single-agent biologic therapy was compared with that of combination therapy in both the front-line and second-line settings.

Statistical Analysis

The patients' categorical characteristics were summarized as frequency and proportions. Age was presented as mean and standard deviation. Chi-square test or Fisher's exact test was used to compare the categorical variables between patients in different treatment categories. McNemar's test was used to compare the response outcome between front-line and second-line treatment. The Kaplan-Meier method was used to generate survival curves and to

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Table 2. Anatomic and biochemical response with front-line and second-line therapy

Response type	Category	Front-line	Second-line	p value[a]
Anatomic response	Progressive disease	3 (8.11)	3 (16.67)	.337
	Partial response	4 (10.81)	0 (0)	
	Stable disease	30 (81.08)	15 (83.33)	
Biochemical response	Yes	15 (41.67)	2 (13.33)	.625
	No	21 (58.33)	13 (86.67)	

Data are presented as number of patients (column percentage).
[a]The p value is calculated by Fisher's exact test and McNemar's test for anatomic and biochemical response comparisons, respectively.

Table 3. Subset characteristics of front-line and second-line biochemical response

		Biochemical response		
		No	Yes	
Characteristic	Level	n = 21	n = 15	p value
Front-line				
Gender	Female	9 (42.86)	4 (26.67)	.319[a]
	Male	12 (57.14)	11 (73.33)	
Histology	Differentiated	14 (66.67)	14 (93.33)	.104[b]
	Medullary	7 (33.33)	1 (6.67)	
Regimen	Combination	7 (35)	5 (33.33)	.918[a]
	Single agent	13 (65)	10 (66.67)	
Class of agent	Antiangiogenic	9 (45)	9 (60)	.380[a]
	Nonantiangiogenic	11 (55)	6 (40)	
		No	Yes	
Characteristic	Level	n = 13	n = 2	p value[b]
Second-line				
Gender	Female	6 (46.15)	0 (0)	.486
	Male	7 (53.85)	2 (100)	
Histology	Differentiated	8 (61.54)	2 (100)	.524
	Medullary	5 (38.46)	0 (0)	
Regimen	Combination	6 (46.15)	1 (50)	1.000
	Single agent	7 (53.85)	1 (50)	
Class of drug	Antiangiogenic	6 (46.15)	2 (100)	.467
	Nonantiangiogenic	7 (53.85)	0 (0)	

[a]Chi-square test.
[b]Fisher's exact test.

estimate the survival rate. The log-rank test was used to compare survival between defined groups of interest.

The degree of benefit in the second-line setting was determined by comparing the primary survival outcomes of TTF and PFS associated with second-line therapy with the survival outcome with front-line therapy in the same group of patients with thyroid cancer. The impact of salient clinical factors, including gender, tumor histology (medullary vs. nonmedullary thyroid cancer), mechanism of drug action (antiangiogenesis vs. nonantiangiogenesis), and regimen (single agent vs. multiagent), was assessed by comparing front-line and second-line therapy using these factors as stratification factors. Separate subset analyses were conducted within the front-line and second-line patients to assess whether these factors (gender, histology, drug mechanism, and regimen) affect the efficacy of targeted agents. The significance p values were set

at .05 for all comparisons without adjusting for multiple comparisons, given the exploratory nature of the subset analysis. The SAS statistical package version 9.3 (SAS Institute, Inc., Cary, NC, http://www.sas.com) was used for data management and analyses.

RESULTS

Demographics

We reviewed the clinical records of 62 patients and identified 39 eligible patients with stage IV thyroid cancer who received targeted biologic agents for progressive disease. There were 9 patients with medullary thyroid cancer and 30 patients with differentiated thyroid cancer in the treatment group, 25 males and 14 females, with a median age at diagnosis of 56.3 years (Table 1). Nineteen patients re-
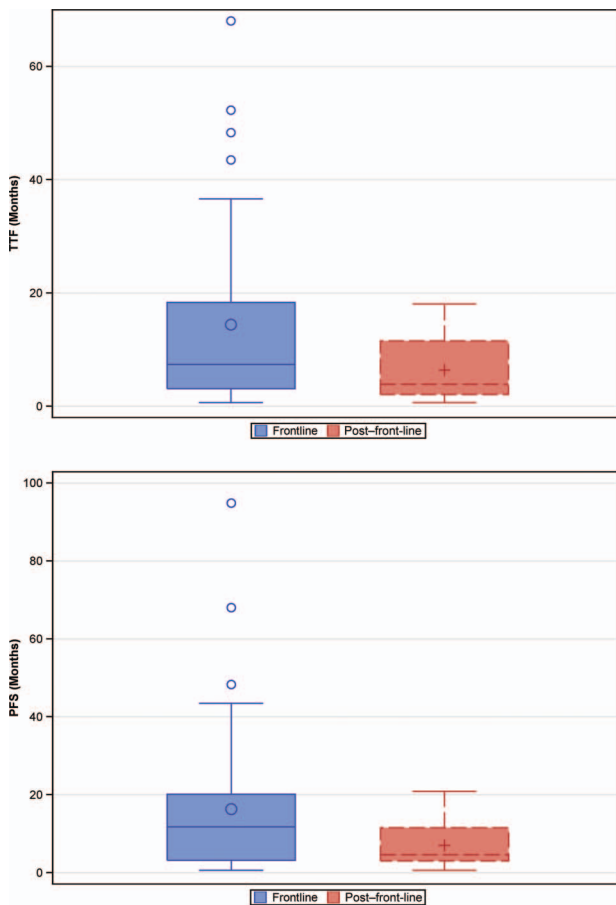
Figure 1. Box plots showing the median value and interquartile range for TTF (top) and PFS (bottom) associated with biologic therapy of advanced thyroid cancer in the front-line and second-line settings.

Abbreviations: PFS, progression-free survival; TTF, time to treatment failure.

Figure 2. TTF (top) and PFS (bottom) Kaplan-Meier survival curves for advanced thyroid cancer patients treated with biologic therapy in the front-line and second-line settings.

Abbreviations: PFS, progression-free survival; TTF, time to treatment failure.

ceived second-line therapy after progressing on the initial biologic agent therapy.

Therapy

Patients were treated with targeted biologic agents either as off-label therapy or through participation in ongoing clinical trials evaluating the safety and/or efficacy of these agents. Sorafenib was the most frequently administered treatment in both the front-line and second-line settings. A two-drug combination regimen was administered to 34% of the patients treated in the front-line setting and to 42% of the patients in the second-line setting [18, 19]. Agents targeting angiogenesis were administered to approximately 50% of the patient population in both the front-line and second-line settings. Full details of patient demographics, tumor characteristics, and treatment are presented in Table 1.

Biochemical and Anatomic Response

There was no significant difference in biochemical or anatomic response outcome when comparing front-line and second-line treatment, with a trend in favor of the front-line setting (biochemical response rate: 15 [41.7%] vs. 2 [13.3%]; $p = .625$; clinical benefit rate: 30 [81.1%] vs. 15 [83.3%]; $p = .337$) (Tables 2 and 3).
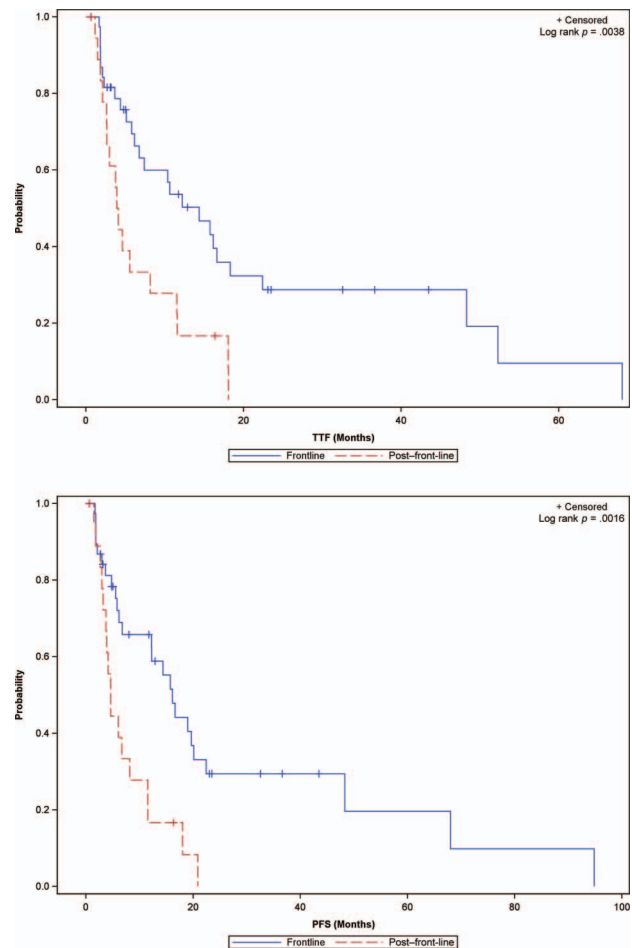
Overall Efficacy Assessment

The overall efficacy of second-line targeted therapy was more modest in comparison to the efficacy observed in the front-line setting: Median PFS comparing front-line and second-line therapy was 16.2 months (95% confidence interval [CI]: 6.8–22.4) versus 4.6 months (95% CI: 3.2–8.2), with a p value of .0016 (Figs. 1 and 2).

Efficacy by Gender

Front-line efficacy led to improved outcomes compared with second-line efficacy in both male and female patients: Median PFS was 19.7 months (95% CI: 6.8–48.3) versus 6 months (95% CI: 3.7–18) ($p = .0094$) in males and 12.2 months (95% CI: 1.8–16.2) versus 3 months (95% CI: 1.5–6.7) ($p = .0224$) in females (Fig. 3A).

Efficacy by Histology

There was a significant difference between front-line and second-line efficacy in differentiated cancers (median PFS: 15.7 months [95% CI: 6.1–22.4] vs. 4.1 [95% CI: 3–8.2]; $p = .0051$) and a similar but nonsignificant trend in medullary thyroid cancer patients (median PFS: 16.6 months [95% CI: 1.8–48.3] vs. 6 months [95% CI: 1.5–18]; $p = .1611$) (Fig. 3B).
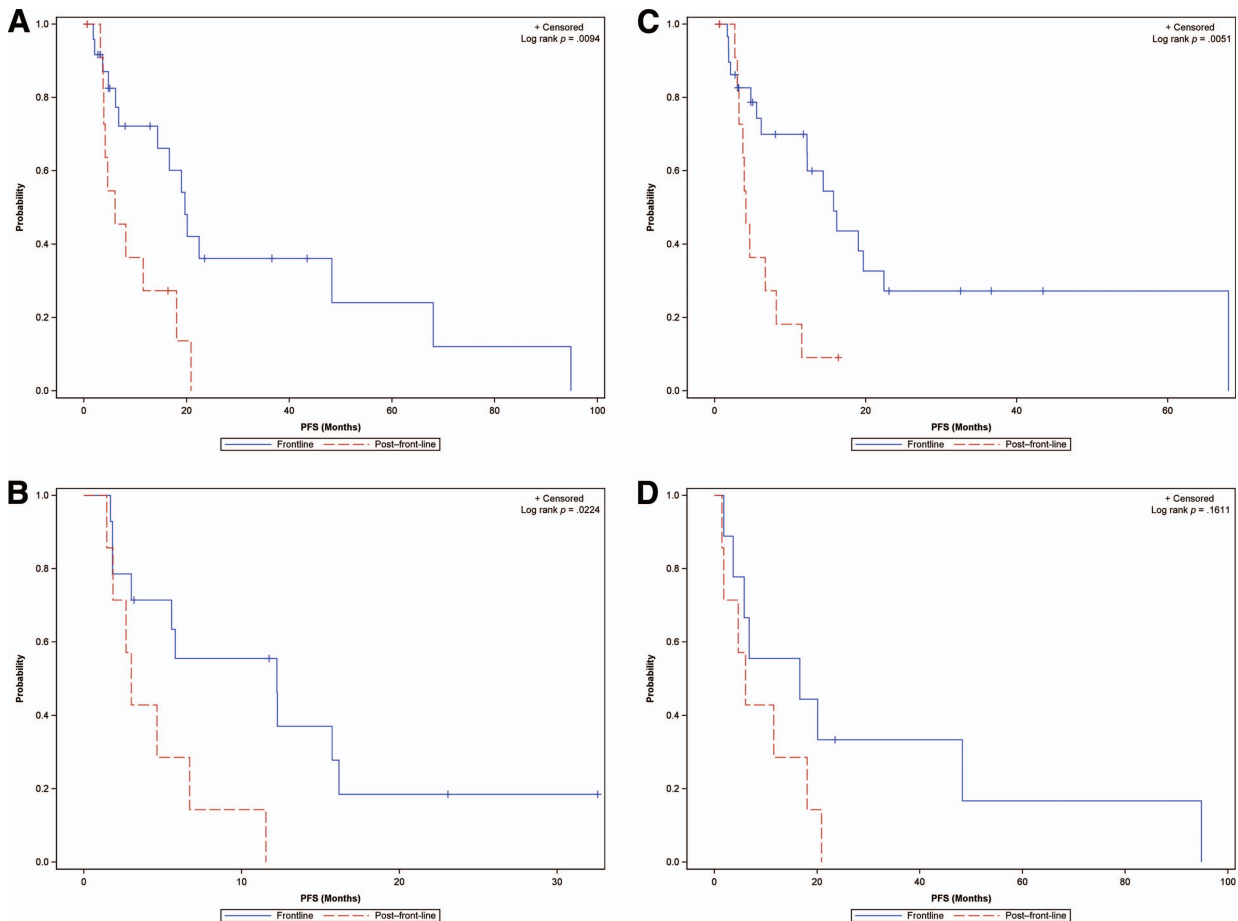
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Figure 3. Gender-based comparison of front-line versus second-line efficacy of targeted agents in male **(A)** and female **(B)** patients. PFS comparison of front-line and second-line therapy in patients with differentiated **(C)** and medullary **(D)** thyroid cancer.

Abbreviation: PFS, progression-free survival.

Efficacy by Treatment Regimen

Both single-agent and two-drug combinations of targeted agents demonstrated superior efficacy, as measured by PFS in the front-line setting versus the second-line setting: Median PFS was 19.7 months (95% CI: 5.6−68) versus 4.6 months (95% CI: 1.5−11.5) (p = .0147) and 14.4 months (95% CI: 5.8−20.1) versus 5.1 months (95% CI: 1.9−18) (p = .2287) (Fig. 4A). There was no significant difference in the efficacy of two-drug combination regimens when compared with single-agent therapy both in the front-line setting (median PFS: 14.4 months [95% CI: 5.8−20.1] vs. 19.7 months [95% CI: 5.6−68]; p = .3213) and in the second-line setting (median PFS: 5.1 months [95% CI: 1.9−18] vs. 4.6 months [95% CI: 1.5−11.5]; p = .8020).

Efficacy by Mechanism of Drug Action

The efficacy of agents targeting angiogenesis was superior in the front-line setting compared with the second-line setting (median PFS: 20.1 months [95% CI: 12.3−68] vs. 4.4 months [95% CI: 1.5−8.2]; p < .0001), whereas nonangiogenesis-targeting agents showed comparable efficacy whether as front-line or second-line therapy (median PFS: 6.1 months [95% CI: 2.1−94.8] vs. 6.4 months [95% CI: 1.9−20.9]; p = .8438) (Fig. 4B).

Exploratory Analysis

In order to exclude potential misestimation of PFS because of varying schedules of restaging scan in up to 45% of the patients who were not treated as part of a clinical trial, we repeated the efficacy analysis using TTF as the endpoint of interest and obtained similar results (data not shown). Furthermore, subset analysis performed separately within the front-line and second-line patient populations did not show any significant difference in efficacy outcome based on tumor histology, gender, class of drug, or treatment regimen (Table 4).

DISCUSSION

Vandetanib and cabozantinib recently received regulatory approval for the front-line treatment of advanced medullary thyroid cancer based on efficacy data from randomized phase III studies [14, 20]. The first registration trial of sorafenib as front-line therapy for differentiated thyroid cancer has just concluded [17, 21]. Treatment with sorafenib delayed disease progression by more than 5 months in comparison to survival [21]. Although these therapeutic advances are very encouraging, virtually all patients treated with targeted agents eventually progress and require additional therapy. There is no published report to date of a prospective study designed to assess whether the use of targeted agents beyond the front-line
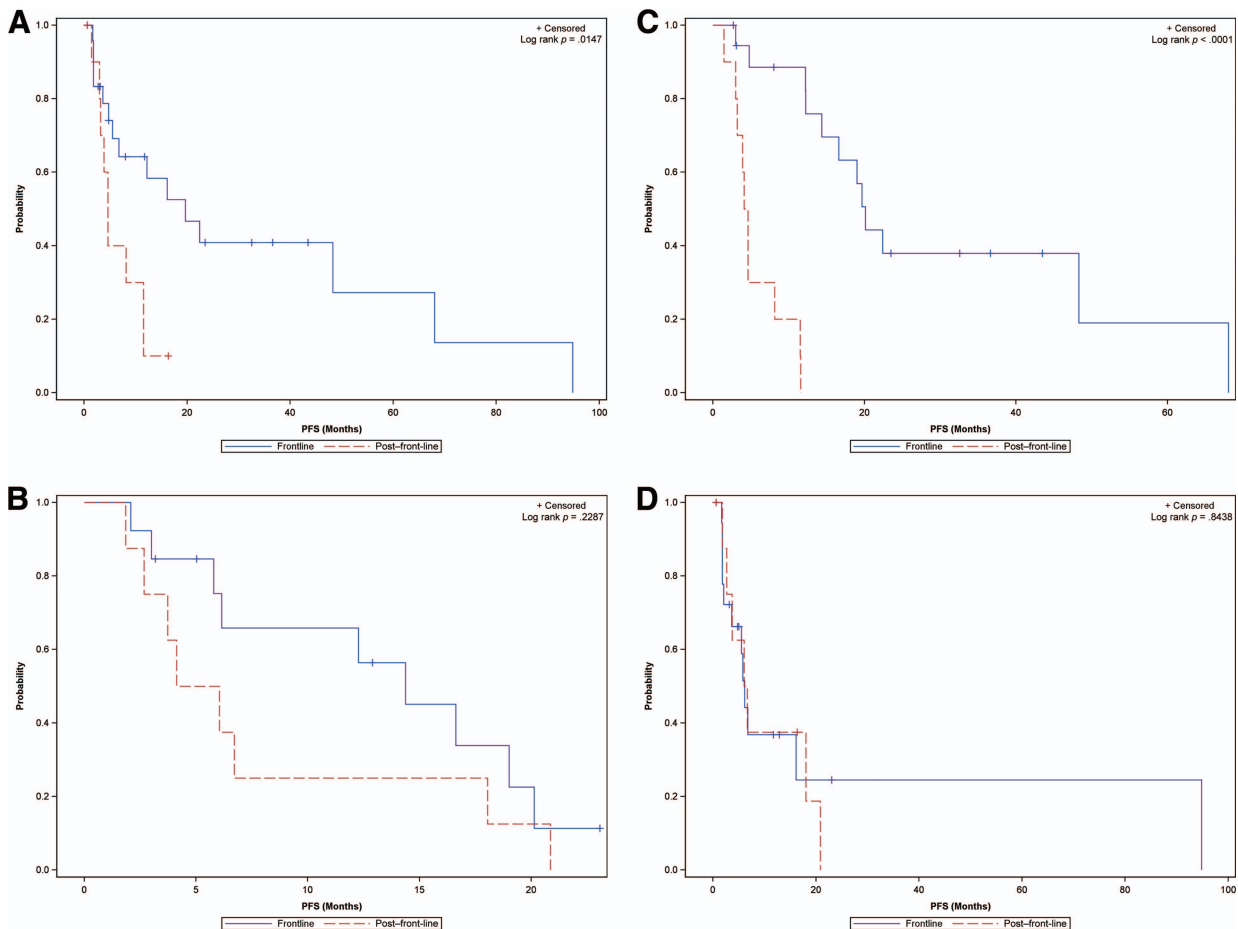
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Figure 4. Kaplan-Meier survival curves for PFS of showing comparison of front-line and second-line efficacy of biologic therapy in patients treated with a single-agent regimen **(A)** and a combination regimen **(B)**. Kaplan-Meier survival curves of PFS comparing front-line and second-line efficacy of vascular-targeting **(C)** and non-vascular-targeting **(D)** agents.

Abbreviation: PFS, progression-free survival.

setting is associated with meaningful clinical benefit. This retrospective study of patients with advanced thyroid cancer was conducted to bridge this knowledge gap and demonstrated that treatment with targeted agents beyond the front-line setting was associated with meaningful clinical benefit in a patient group for which therapeutic options are currently limited.

By comparing front-line efficacy and second-line efficacy in the same patient group treated in a single institution, we were able to reduce potential bias and confounding associated with retrospective observational studies and comparison across studies and patient populations. Similar to observations in the prospective phase II and registration phase III studies, objective anatomic responses were infrequent with the use of these agents; however, the majority of patients achieved durable control of disease. The duration of disease control observed with the front-line therapy in this observational study was comparable to results from prospective phase II studies [9–14]. As anticipated, the efficacy of targeted agents in the front-line setting was superior to the second-line setting. Nonetheless, the median PFS of 4.6 months achieved in the second-line setting by previously treated patients suggested that this approach may confer meaningful benefit to a significant number of patients.

The diminished second-line efficacy in comparison to the front-line setting is expected and is consistent with the experience of other cancer types for which therapeutic efficacy declines with an increasing number of prior lines of therapy [22–24]. A recent study reported comparable efficacy of second-line and first-line multiple kinase inhibitor therapy for differentiated thyroid cancer patients with a trend in favor of front-line therapy (median PFS: 6.7 month vs. 7.6 months; hazard ratio: 0.85 [95% CI: 0.45–1.61]; $p =$ .6) [25]. Interestingly, we observed efficacy diminution with the vascular-targeting class of agents, whereas treatment with nonantiangiogenic agents achieved comparable efficacy in the front-line and second-line settings. This intriguing observation may inform the appropriate sequencing of targeted agents in thyroid cancer and other cancer patient populations as well as the design of prospective clinical trials to evaluate second-line therapy.

The observation of greater benefit of targeted agents in male patients versus female patients, in both the front-line and second-line settings, has not been previously reported with any of the agents evaluated in this study. Although gender-based differences in efficacy resulting from altered pharmacodynamics and/or toxicity-induced treatment discontinuation may play a role, it is noteworthy that the large majority of patients in this analysis were treated with

Table 4. Subset analysis within the front-line and the second-line patient populations

Categories	Comparison	Time to treatment failure, median (95% CI)[a]	p value	Progression-free survival, median (95% CI)[a]	p value
Histology					
Front-line	Differentiated	14.4 (5.1–22.4)	.8246	15.7 (6.1–22.4)	.7896
	Medullary	10.6 (1.8–48.3)		16.6 (1.8–48.3)	
Second-line	Differentiated	3.9 (2.1–8.2)	.3811	4.1 (3–8.2)	.3400
	Medullary	5.6 (1.5–18)		6 (1.5–18)	
Gender					
Front-line	Female	5.8 (1.8–16.2)	.1410	12.2 (1.8–16.2)	.0727
	Male	16.6 (6.8–48.3)		19.7 (6.8–48.3)	
Second-line	Female	2.7 (1.2–4.6)	.0304	3 (1.5–6.7)	.0496
	Male	5.6 (2.6–18)		6 (3.7–18)	
Class of agents					
Front-line	Antiangiogenic	16.6 (7.4–48.3)	.1005	20.1 (12.3–68)	.1088
	Nonantiangiogenic	6.1 (1.9–52.3)		6.1 (2.1–94.8)	
Second-line	Antiangiogenic	4 (1.2–8.2)	.1670	4.4 (1.5–8.2)	.1753
	Nonantiangiogenic	4.6 (1.9–18.1)		6.4 (1.9–20.9)	
Treatment regimen					
Front-line	Combination	10.6 (5.1–18.3)	.4215	14.4 (5.8–20.1)	.3213
	Single agent	12.2 (4.4–52.3)		19.7 (5.6–68)	
Second-line	Combination	3.9 (1.9–18)	.6931	5.1 (1.9–18)	.8020
	Single agent	4.3 (1.2–11.5)		4.6 (1.5–11.5)	

[a]Months, second-line.
[b]p value is calculated by log-rank test.

sorafenib. Population-based pharmacokinetic studies did not show any gender-based differences in sorafenib handling [26]. Moreover, similar results were obtained using TTF or PFS endpoints as the basis for comparison and indicated that early treatment discontinuation because of increased toxicity was not responsible for this difference. Prospective assessment of this observation will be of interest in the future. We did not observe any significant difference in the clinical benefit of biologic agents based on tumor histology, consistent with other observational and prospective studies of biologic therapy in this patient population [11, 16].

Limitations of our study include the retrospective design and the relatively large number of targeted agents. Although a more homogenous population of patients treated with the same type of drug would have been more desirable, such a population of patients is very challenging to assemble at the present time because the choice of treatment agents is dictated by their availability as part of a clinical trial protocol or through a special access program. In addition, as a single-institution experience, the generalizability of these findings requires further replication and validation by other studies, especially prospective randomized studies. Moreover, we were not able to determine and control for the potential impact of driver mutations such as B-Raf or K-Ras, which have been shown to have prognostic implications in resected differentiated thyroid cancer [27–29]. Given the use of the same cohort of patients to assess efficacy in the front-line and second-line settings, any potential impact of

molecular differences between patients is unlikely to have confounded our analysis in this regard. Overall, the opportunity to use the same set of patients to compare the benefit of front-line and second-line use of biologic agents is a major strength of our study that enabled us to limit the some of the known drawbacks of a retrospective observational study.

CONCLUSION

This retrospective single-institution study provides the first systematic evidence supporting the use of targeted biologic agents beyond the front-line setting in advanced thyroid cancer patients. We expect that findings from this study will facilitate and inform the design of prospective studies of targeted biologic agents in the second-line setting in patients with advanced thyroid cancer.

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AUTHOR CONTRIBUTIONS
Conception/Design: Taofeek K. Owonikoko, Rajasree P. Chowdry
Provision of study material or patients: Taofeek K. Owonikoko
Collection and/or assembly of data: Taofeek K. Owonikoko, Rajasree P. Chowdry, Zhengjia Chen, Sungjin Kim
Data analysis and interpretation: Taofeek K. Owonikoko, Rajasree P. Chowdry, Zhengjia Chen, Sungjin Kim, Nabil F. Saba, Dong M. Shin, Fadlo R. Khuri
Manuscript writing: Taofeek K. Owonikoko, Rajasree P. Chowdry, Zhengjia Chen, Sungjin Kim, Nabil F. Saba, Dong M. Shin, Fadlo R. Khuri

Final approval of manuscript: Taofeek K. Owonikoko, Rajasree P. Chowdry, Zhengjia Chen, Sungjin Kim, Nabil F. Saba, Dong M. Shin, Fadlo R. Khuri

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